New heteroatom-rich ring systems from *N,N*-dialkyl-*N'*-chlorosulfonyl chloroformamidines

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DOI: http://dx.doi.org/10.3998/ark.5550190.p009.629

Abstract

N,N-Dialkyl-*N'*-chlorosulfonyl chloroformamidines constitute a class of readily available and very versatile bis-electrophiles. This Account describes the application of these unusual $^{\delta+}C{=}N{-}S^{\delta+}$ building blocks for construction of a cornucopia of previously unknown or uncommon heterocyclic ring systems. Regioselectivity encountered during heterocycle formation and some properties and chemistry of the newly-formed ring systems are also discussed.

Keywords: *N,N*-Dialkyl-*N'*-chlorosulfonyl chloroformamidines, heterocycle, synthesis, bis-electrophile, bis-nucleophile, regioselectivity

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1. Introduction

Nitrogen-containing heterocycles are the building blocks of life and central to the chemical reactions that occur in all organisms.[1] Nitrogen-containing rings are also common fragments of the majority of marketed drugs[2-4] and the reason for this is that identification of effective therapeutic treatments is usually based on mimicking nature but "fooling" it in a very subtle way. Because heterocycles are core elements of a wide range of natural products such as nucleic acids, amino acids, vitamins, and alkaloids, medicinal chemistry discovery efforts often evolve around simulating such structural motifs.[2]

Heterocycles also play a larger role in medicinal chemistry. The strategic inclusion of a heterocyclic moiety into a drug candidate molecule can allow the modulation of properties[2,3,5-9] such as potency and selectivity (through bioisosteric replacements), lipophilicity, polarity, aqueous solubility, electronic distribution, hydrogen bond basicity, and metabolic stability. Replacement of carbo-aromatic rings with hetero-aromatic rings and inclusion of fused ring systems rather than individual rings tends to confer reduced lipophilicity and greater aqueous solubility, resulting in improved properties.[7-9]

Interestingly, a recent systematic study of the behavior of compounds containing individual heteroaromatic rings in solubility, protein binding, and CYP450 inhibition screens, found that the 5 best performing rings (of 19 rings studied) all contained two nitrogen atoms – pyridazine, pyrazine, imidazole, pyrazole, and 1,3,4-oxadiazole.[7] Three of these rings contain N-N bonds and it is well known that there are very few examples of naturally occurring pyridazines[5] and pyrazoles,[10,11] probably due to the difficulty in the construction of N–N bonds by living organisms. The situation with 1,3,4-oxadiazoles appears to be similar.[12] Therefore, the availability of such compounds is predicated upon synthetic methods. Additionally, a recent analysis of the frequency of nitrogen heterocycles among U.S. FDA-approved pharmaceuticals found that 4 of the 10 most commonly used nitrogen heterocycles also contain a sulfur atom.[4]

It has been widely concluded that the number of ring systems in drugs and bioactive space is currently very small and distributed in sparsely populated islands.[3] The historical exploration of chemical space by synthetic chemists has been exceptionally uneven and unsystematic. Around half of all known compounds are based on just 0.25% of the known molecular scaffolds and this uneven exploration is also reflected in small molecule screening collections.[13] A recent analysis by Pitt and co-workers found that fewer than 10 novel small heteroaromatic ring systems are published each year.[14]

In light of all of the above, we were encouraged to continue our program of compound library enrichment and diversification by emphasizing the construction of new or unusual nitrogen and sulfur-containing rings. New ring systems can provide scaffolds and building blocks for exploration of uncharted chemical space, free of patent competition.

We preferred a diversity-oriented synthesis strategy with the aim of generating both skeletal and appendage diversity[15] and were attracted to the so-called "build couple pair" approach (Figure 1).[13]

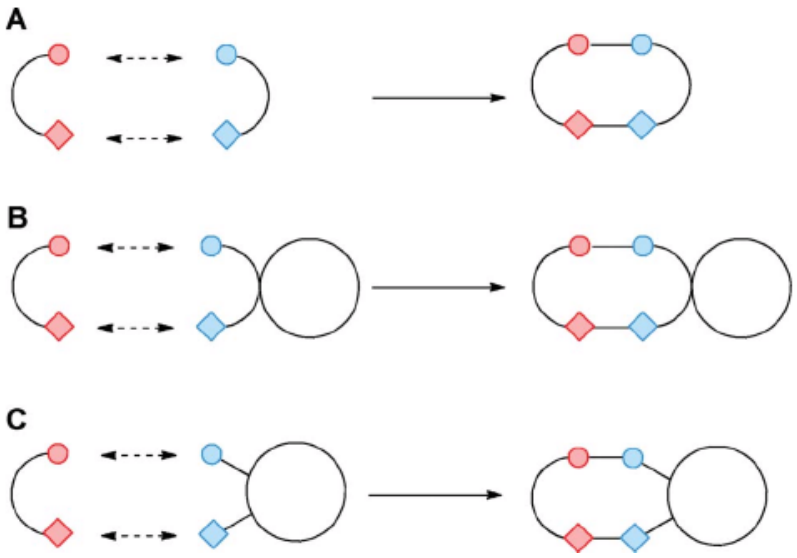
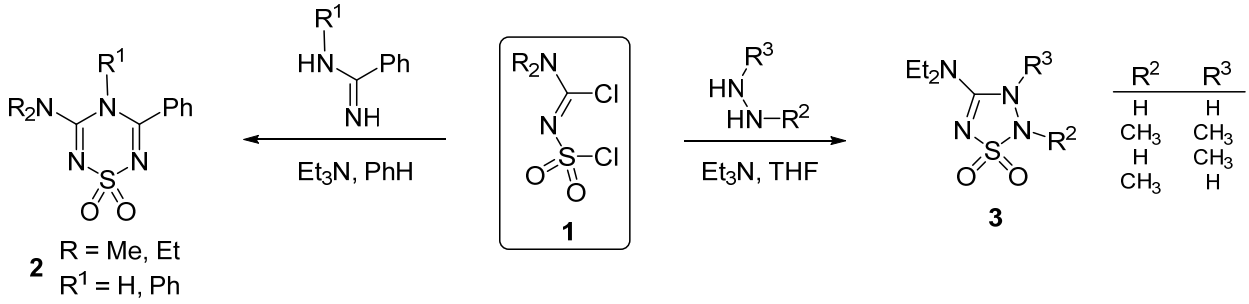


Figure 1. Synthesis of small molecule scaffolds from pairs of bifunctional building blocks. The approach may be used to prepare monocyclic scaffolds (Panel A), or, by using cyclic buildingblocks, spirocyclic (Panel B) or fused (Panel C) scaffolds. *Reproduced from reference 13*.

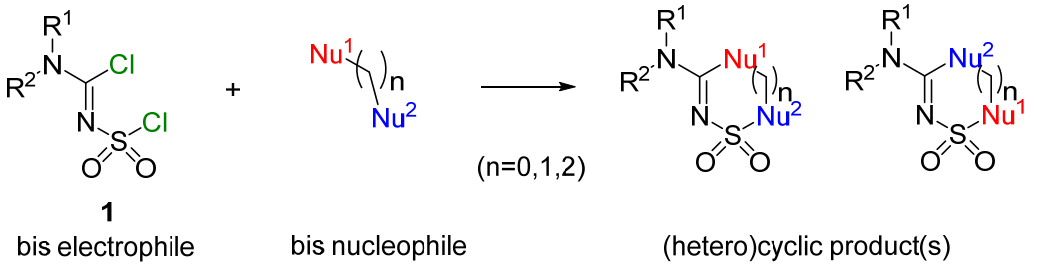
In this context, we noted that certain readily accessible *N,N*-dialkyl-*N*'-chlorosulfonyl chloroformamidines **1**[16,17] had been reacted with benzamidines and with some simple hydrazines to form thiatriazines **2**[18] and thiatriazoles **3**,[19] respectively (Scheme 1).



Scheme 1

We also noted that in each of these isolated reports, only a small number of examples were described and it appeared to us that these studies had overlooked much of the potential offered by a versatile intermediate which promised many additional opportunities for the synthesis of new or uncommon heterocycles.

We considered the dichlorides **1** to be an ideal type of bis-electrophile for participation in reactions with bis-nucleophiles in a simple version of the "build couple pair" approach, which would allow the convenient synthesis of new and unusual heterocyclic ring systems. The approach is outlined in Scheme 2.

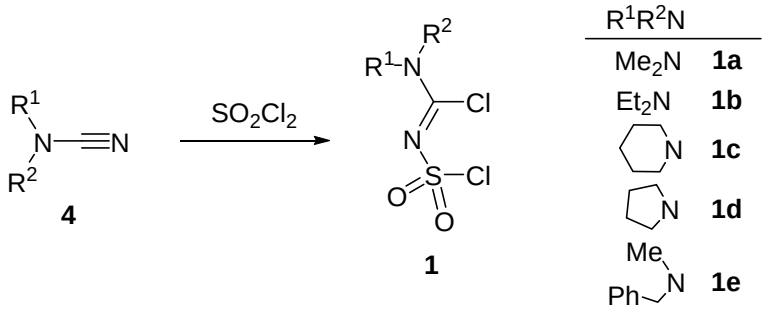


Scheme 2

This reagent-based approach enables the generation of skeletal diversity through construction of distinct molecular scaffolds from bis-electrophiles **1** by varying the type of bis-nucleophilic partner reactant. This Account discusses our studies of reactions of dichlorides **1** with a variety of bis-nucleophilic systems to produce new or uncommon heteroatom-rich nitrogen/sulfur heterocyclic ring systems. The regioselectivity of heterocycle formation and some properties and reactions of the newly-formed ring systems are also described.

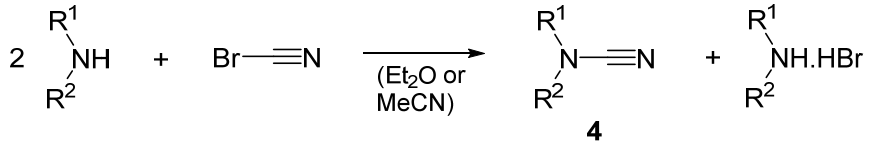
2. Synthesis of *N,N*-Dialkyl-*N'*-Chlorosulfonyl Chloroformamidines

N,N-Dialkyl-*N'*-chlorosulfonyl chloroformamidines **1** are readily formed from the reaction between dialkylcyanamides **4**[20] and sulfuryl chloride (Scheme 3).[16,17,21] Simply stirring a mixture of the appropriate dialkylcyanamide with an excess (1.5 to 2 molar equivalents) of sulfuryl chloride at ambient temperature overnight followed by removal of the excess of sulfuryl chloride by evaporation provides a crude product suitable for use without further purification. It was found that the deterioration of dichlorides **1** and substantial losses during attempted purification outweighed the benefits of increased purity. Samples of dichlorides **1** could be satisfactorily stored under nitrogen at room temperature for many months and we noted only gradual decreases in yields of condensation products from these samples over time.

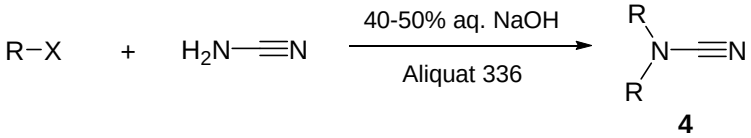


Scheme 3

Dimethylcyanamide **4a**, diethylcyanamide **4b**, piperidine-1-carbonitrile **4c**, and pyrrolidine-1-carbonitrile **4d**, are commercially available, which allows convenient use of these compounds, but other dialkylcyanamides **4** are readily prepared from either the reaction between cyanogen bromide and various secondary amines, such as *N*-benzyl-*N*-methylcyanamide **4e** (Scheme 4),[22,23] or by the direct alkylation of cyanamide with various alkyl halides (Scheme 5).[23,24]



Scheme 4



Scheme 5

It should be noted that the latter method is suitable only for generating symmetrical dialkylcyanamides, whereas the former provides access to compounds **4** in which R^1 and R^2 are different to one another, but is dependent upon the availability of a suitable secondary amine.

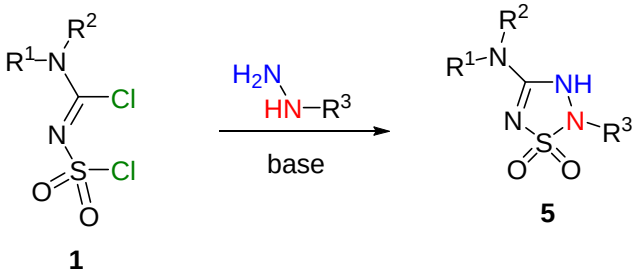
3. Synthesis of Heterocyclic Ring Systems from *N*,*N*-Dialkyl-*N*'-chlorosulfonyl Chloroformamidines

3.1 Five-membered rings from 1,2-bis-nucleophiles

3.1.1 N-N 1,2-bis-nucleophiles. In the 1980s, Knollmüller and Kosma[19] examined the reactions of *N*,*N*-diethyl *N*'-chlorosulfonyl chloroformamidine with hydrazine, *N*-methylhydrazine and 1,2-dimethylhydrazine to furnish [1,2,3,5]thiatriazole derivatives **3** (Scheme 1). Unambiguous structural elucidation of products from the asymmetric hydrazine proved difficult by spectroscopic means. Structures were assigned based on literature precedent for chemical shifts of a sulfamide NH which was expected to be higher than that for the NH group at N3, further from the sulfur atom. The major product was presumed to arise from an initial attack by the CH_3NH moiety upon the sulfamoyl chloride group.[19]

Some early literature on dichlorides **1** suggests, on the basis of infrared and NMR spectroscopy, a greater susceptibility of the sulfamoyl chloride moiety in **1** towards nucleophilic attack by secondary amines (such as morpholine and piperidine)[18] and simple hydrazines.[19] However, the opposite regioselectivity in the reaction of **1** with secondary amines has also been proposed from an analysis of fragmentation in mass spectrometry experiments.[25]

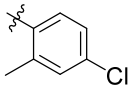
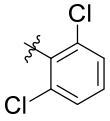
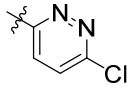
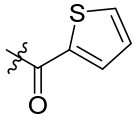
In an expansion of the work by Knollmüller and Kosma,[19] the reactions of compounds **1** with a range of hydrazine derivatives in the presence of various bases and solvents were studied with the dual aim of assessing the scope of the reaction and determining the regiochemistry of thiatriazole formation. The reactions involving various aryl hydrazines, hydrazides, and carbazates, conducted under a variety of conditions, all afforded 2-substituted [1,2,3,5]thiatriazoles **5** regioselectively (Scheme 6). A selection of these products is shown in (Table 1).[26]



1 **5**

Scheme 6

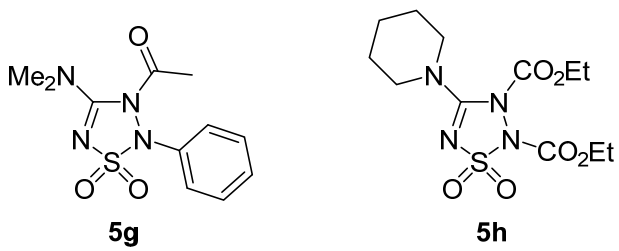
Table 1. [1,2,3,5]thiatriazole products **5**

Product	R^1R^2N	R^3	Method	Yield (%)
5a	Me_2N	CO_2t-Bu	A	50
5b	Me_2N		B	85
5c	Me_2N		C	50
5d	Et_2N		B	61
5e			A	24
5f		Ph	D	41

Method A = Na_2CO_3(aq.)/DCM; Method B = Et_3N / CH_2Cl_2; Method C = Cs_2CO_3 / EtOAc/cat. *n*-Bu_4NBr; Method D = excess of hydrazine/Et_2O.

The structures of compounds **5** were unequivocally elucidated by X-ray crystallography of two representative compounds, **5b** and **5e**, derived from an aryl- and an acyl-hydrazine respectively. The results confirmed that in each case the cyclisation had proceeded via reaction of the unsubstituted nitrogen atom of the hydrazine derivative at the amidinyl carbon of **1** and reaction of the substituted nitrogen at the sulfamoyl chloride. In general, monosubstituted acyl and aryl hydrazines react with most electrophiles at the unsubstituted amino group,[27,28] so the regioselective formation of 2-substituted thiatriazoles **5** suggested that the amidinyl carbon of **1** may be the more electrophilic site.

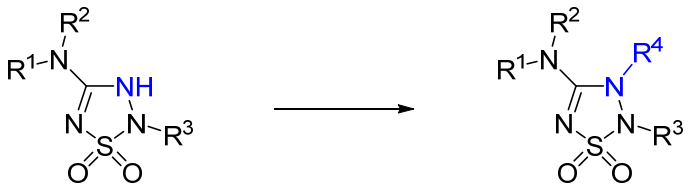
1-Acetyl-2-phenylhydrazine and 1,2-dicarbethoxyhydrazine were also successfully employed in analogous reactions with **1** to afford products **5g** and **5h**, respectively (Figure 2). The structure of **5g** was confirmed by X-ray crystallography.[26]



5g **5h**

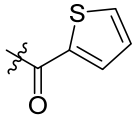
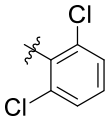
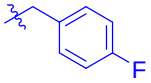
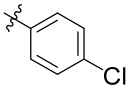
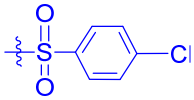
Figure 2. Products obtained from 1,2-bis-substituted hydrazines.

Thiatriazoles such as **5a-5f**, which were formed from a monosubstituted hydrazine, possess an NH moiety at the 3-position and thus have potential for the introduction of various substituents at this site. The nucleophilic nature of such thiatriazoles was confirmed by acylation and alkylation of several analogues. This resulted in the expected products **5i-5l** shown in (Scheme 7) and (Table 2).



Scheme 7

Table 2. [1,2,3,5]thiatriazole products **5i-5l**

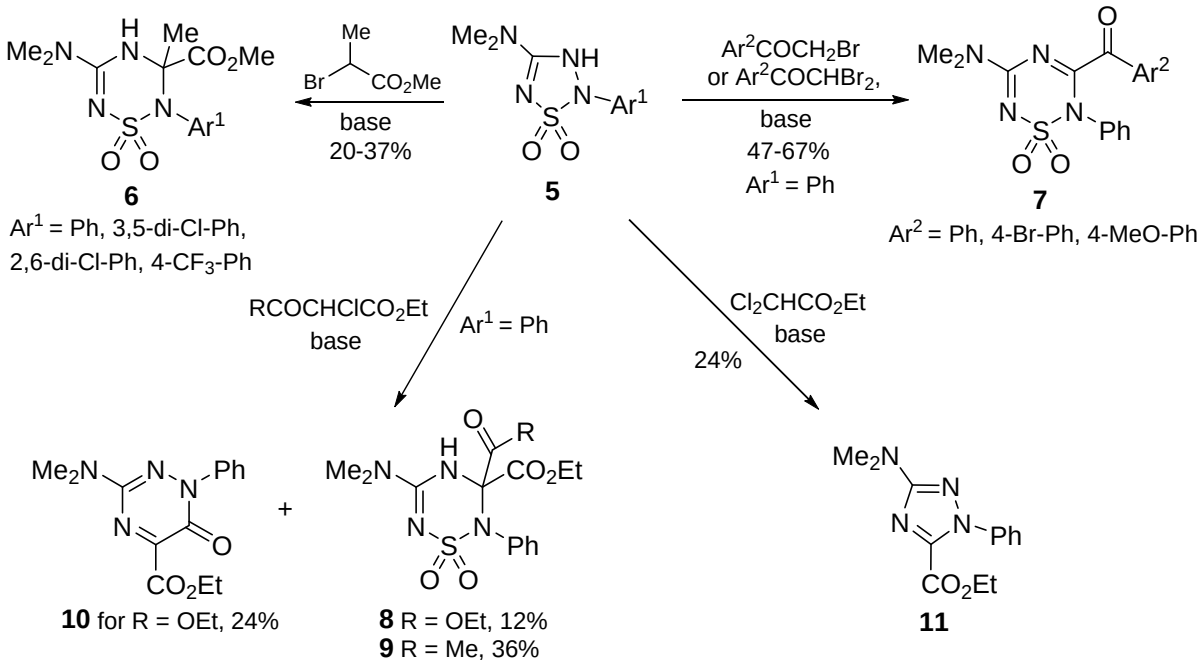
Product	R^1R^2N	R^3	R^4	Method	Yield (%)
5i			Me	A	45
5j	Me_2N			B	67
5k	Me_2N		COMe	C	79
5l		Ph		D	91

Method A = MeI/Na_2CO_3/acetone; Method B = 4-F-BnBr/K_2CO_3/EtOAc/cat. *n*-Bu_4NBr; Method C = Ac_2O/py; Method D = 4-Cl-$PhSO_2Cl$/Na_2CO_3/PhH.

The structural assignments were made on the basis of literature precedent,[19] where the methylation of closely related thiatriazoles was reported to occur exclusively at N3.

In the course of these investigations, the thiatriazole **5** (R^3=3,5-di-Cl-Ph) was treated with methyl 2-bromopropanoate in the presence of K_2CO_3, with the expectation of producing the simple N^3-alkylated product. Surprisingly, the major product from this reaction was a ring-expanded compound. X-ray crystallographic analysis confirmed that the product was a derivative of the relatively rare 5-amino-[1,2,4,6]thiatriazine 1,1-dioxide system, **6** (Scheme 8).[29] The scope

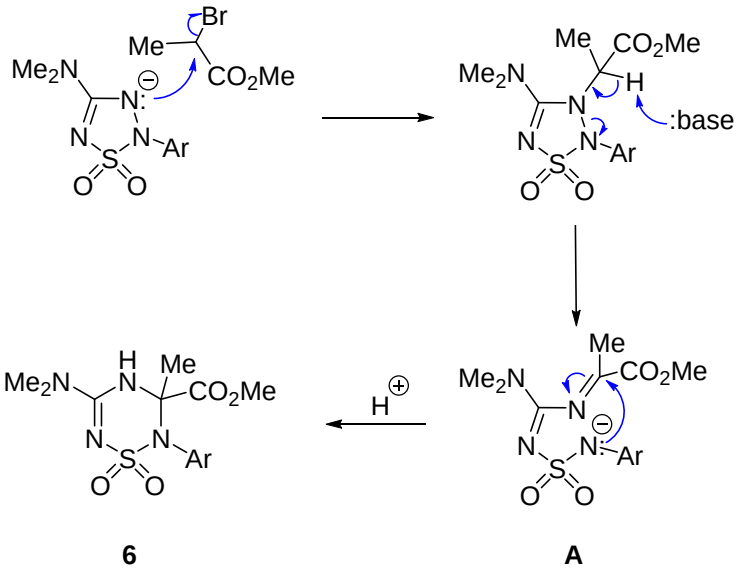
of this novel base-promoted ring expansion reaction was investigated. Additional examples of **6** with differently substituted N^2-phenyl groups were prepared (Scheme 8). Similar alkylation of **5** with a phenacyl bromide followed by ring expansion and aerial oxidation afforded **7**. Diethyl chloromalonate and ethyl 2-chloroacetoacetate likewise produced the ring expanded products **8** and **9**, respectively; the chloromalonate reaction also gave the triazinone **10**.[29]



Scheme 8

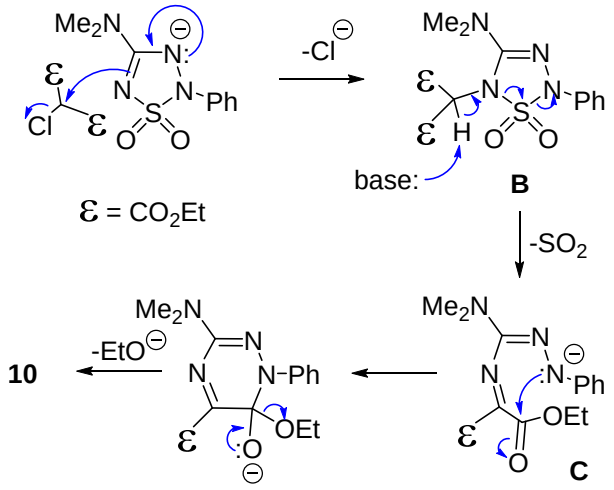
Reaction of **5** with 2,2-dibromo-4-methoxyacetophenone afforded the ring-expanded product **7** directly in 67% yield (Scheme 8), whereas the reaction with ethyl dichloroacetate gave the triazole **11**. Related electrophiles, including 2-chloroamides, 2-chlorosulfonamides, and bromomethyl phenylsulfone, did not react.[29]

Reaction mechanisms for the above transformations were proposed, based on studies reported three decades earlier by Bartholomew and Kay[30] on related reactions of [1,2,3,5]thiatriazol-4-ones. Presumably, treatment of **5** with methyl 2-bromopropanoate and potassium carbonate initially gives the N^3-alkylated product, which upon deprotonation of the activated methylene group and rupture of the N-N bond, affords the sulfamide anion **A**. Ring closure at the imine-type carbon of **A**, followed by protonation, would provide the ring expanded product **6** (Scheme 9).[29]



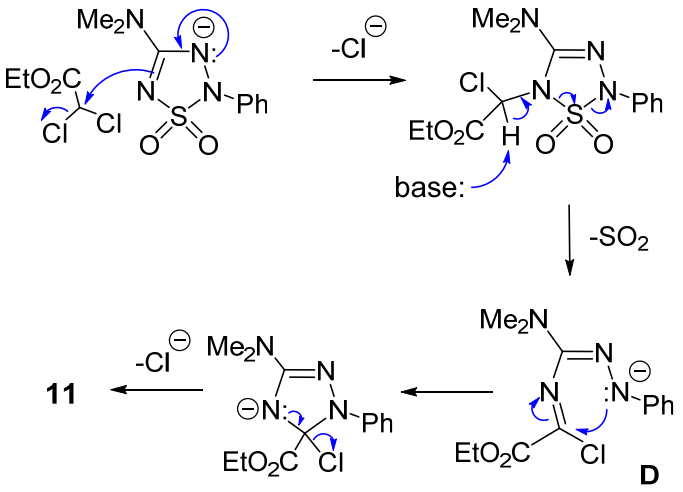
Scheme 9

The formation of the triazinone **10** likely involves initial alkylation at N^5 and SO_2 expulsion (Scheme 10).[29] A distinguishing feature of this mechanism is the initial alkylation of *N*-5 rather than *N*-3 to give intermediate **B**. The action of base on this intermediate would lead to ring-opening and expulsion of SO_2, to give the highly delocalised anion **C**. Ring closure by attack on an ester moiety would lead to the observed triazinone **10**.[29]



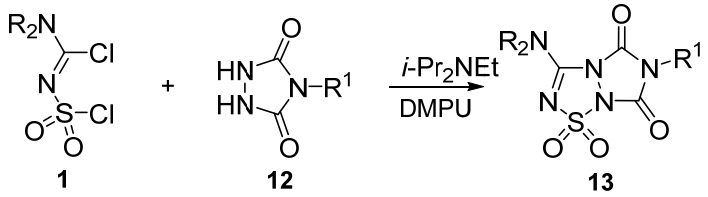
Scheme 10

The formation of the triazole **11** probably proceeds via initial alkylation of *N*-5 and ring closure at the chloro-imine carbon in preference to the carbonyl carbon of the ester moiety of anion **D** (Scheme 11).[29]



Scheme 11

The reaction of dichlorides **1** with 4-substituted urazoles **12** in 1,3-dimethyl-3,4,5,6-tetrahydro-2(*1H*)-pyrimidinone (dimethylpropylene urea, DMPU), in the presence of Hünig's base, readily gave [1,2,4]triazolo[1,2-*b*][1,2,3,5]thiatriazoles **13**, the first reported representatives of this ring system, as the sole isolated product (Scheme 12, Table 3).[31]



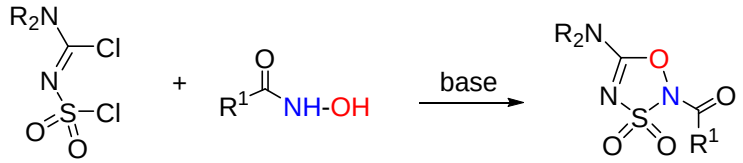
Scheme 12

Table 3. Synthesis of the [1,2,4]triazolo[1,2-*b*][1,2,3,5]thiatriazoles **13**

Product	R_2N	R^1	Yield (%)
13a	Me_2N	Ph	50
13b	Et_2N	Ph	31
13c		Ph	60
13d	Me_2N	4-Cl-Ph	54
13e		3-Cl-Ph	73
13f		1-naphthyl	55
13g	Me_2N	cyclohexyl	29
13h	Me_2N	*i*-Pr	16

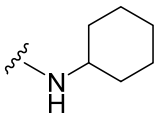
The fused [1,2,3,5]thiatriazoles **13** were isolated in high purity after simple precipitation from the DMPU-based reaction mixture by the addition of ethyl acetate and water. The relatively low yields of diethylamino derivative **13b** and alkyl-substituted compounds **13g** and **13h** were attributed to their greater solubility in organic solvents. The structural assignments for **13a-h** were confirmed by X-ray crystallographic analyses of **13e** and **13h** as typical representatives.[31]

3.1.2 N-O 1,2-bis-nucleophiles. The reactions of dichlorides **1** with hydroxylamine derivatives, in particular hydroxamic acids, as bis-nucleophiles, generated derivatives of the very rare heterocycle, [1,3,2,4]oxathiadiazole **15** (Scheme 13, Table 4). X-ray crystallographic analysis of **15d** confirmed that attack by the more nucleophilic oxygen atom of **14** had occurred at the amidine carbon atom while the nitrogen atom of the hydroxamic derivative reacted with the sulfamoyl chloride moiety of **1**. A selection of products **15** is shown in (Table 1).[26]



Scheme 13

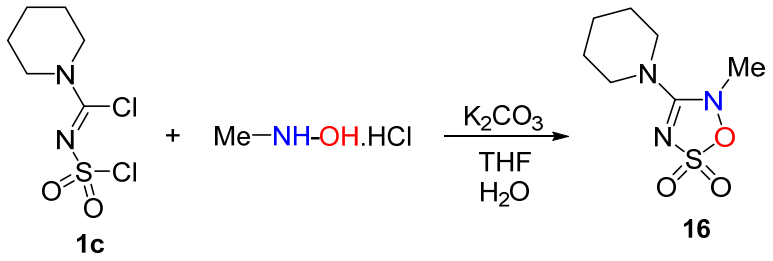
Table 4. Synthesis of the [1,3,2,4]oxathiadiazoles **15**

Product	R_2N	R^1	Method	Yield (%)
15a	Me_2N	3-Cl-Ph	A	95
15b	Me_2N	2-Cl-Ph	B	27
15c		2-PhO-Ph	B	34
15d		*t*-BuO	A	83
15e			B	38

Methods: A = Cs_2CO_3/EtOAc/cat. *n*-Bu_4NBr; B = *i*-Pr_2NEt/DMPU.

Interestingly, the reaction between dichloride **1c** and *N*-methylhydroxylamine (a bis-nucleophile with reversed relative nucleophilicities in comparison to hydroxamic acids) afforded

a derivative of the isomeric ring system, the [1,2,3,5]oxathiadiazole **16** (Scheme 14). The structure of **16** was confirmed by X-ray crystallography.[26]



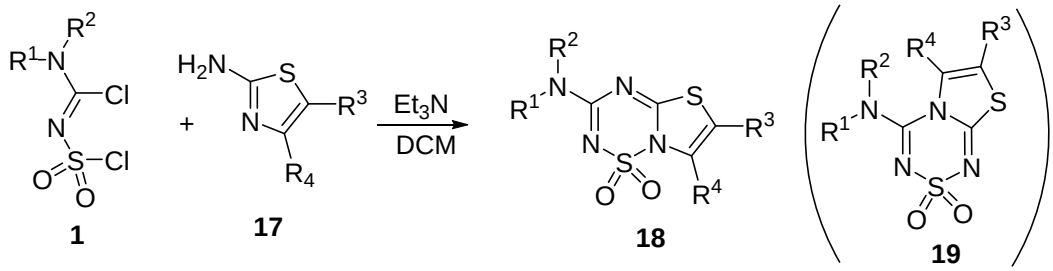
Scheme 14

Deprotection of N^2-Boc derivatives such as **15d** to deliver oxathiadiazoles bearing an NH group in the 2-position proved more difficult than expected. Surprisingly, bubbling anhydrous hydrogen chloride gas through a solution of the Boc-derivative in dichloromethane only returned starting material, while concentrated hydrochloric acid led to *N*-Boc deprotection with additional decomposition. Curiously, when neat formic acid or trifluoroacetic acid was used, conversion to the corresponding 2-*N*-*t*-butyl analogue occurred, presumably as a result of trapping of the *t*-butyl cation during deprotection. The use of methanesulfonic acid in the presence of 4-*t*-butylthiophenol as a scavenger appeared to be effective.[32]

3.2 Six-membered rings from 1,3-bis-nucleophiles

3.2.1 N-C-N 1,3-bis-nucleophiles. Given the results described in the previous section and the reported reactions of dichlorides **1** with benzamidines to form [1,2,4,6]thiatriazines **2**,[18] it was apparent that analogous cyclizations might be effected between **1** and suitable 1,3-dinucleophiles to furnish routes to 6-membered heterocycles. 2-Amino-1-azaheterocycles are well known to manifest the characteristics of a 1,3-dinucleophilic system and we envisaged that such compounds could enable the synthesis of fused [1,2,4,6]thiatriazines.

Treatment of the dichlorides **1** with 2-aminothiazole derivatives **17** in the presence of triethylamine afforded thiazolo[3,2-*b*][1,2,4,6]thiatriazine dioxides **18** (Scheme 15, Table 5). The possible isomeric thiazolo[2,3-*c*][1,2,4,6]thiatriazine dioxides **19** were not observed.[33]

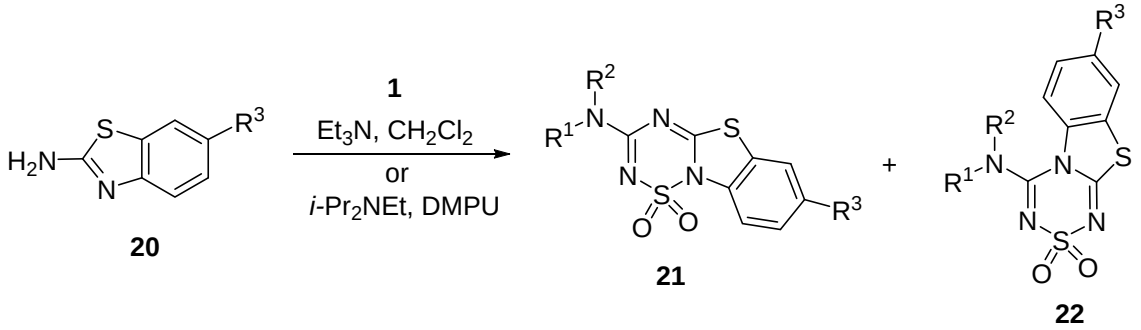


Scheme 15

Table 5. Synthesis of the thiazolo[3,2-*b*][1,2,4,6]thiatriazine dioxides **18**

Product	R^1R^2N	R^3	R^4	Yield (%)
18a	Me_2N	H	CH_2CO_2Et	15
18b	Et_2N	Me	Me	14
18c		Me	Me	41
18d		Me	Me	44

Similar reaction of the dichlorides **1** with 2-aminobenzothiazole derivatives **20**, using either the above conditions or *N,N*-diisopropylethylamine in DMPU, gave benzo[4,5]thiazolo[3,2-*b*][1,2,4,6]thiatriazine dioxides **21** as major products and sometimes also the isomeric benzo[4,5]thiazolo[2,3-*c*][1,2,4,6]thiatriazine dioxides **22** as a minor product (Scheme 16, Table 6).[33]



Scheme 16

Table 6. Synthesis of the benzo[4,5]thiazolo-fused [1,2,4,6]thiatriazine dioxides **21** and **22**

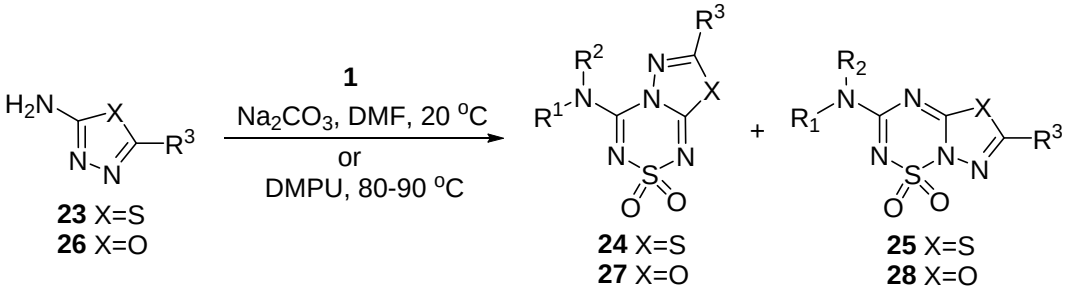
Product(s)	R^1R^2N	R^3	Yield(s) (%)
21a		Cl	12
21b (+**22b**)		OEt	33 (+4)
21c		H	38

Each of compounds **18**, **21** and **22** represent novel heterocycles.

The lack of contiguous NMR-responsive nuclei in the core heterocyclic systems of these products meant that spectroscopic studies failed to provide convincing structural assignments and consequently unequivocal determination of structures was based on X-ray crystallographic structural studies.[33] Such a scenario was common when dealing with bicyclic ring-condensed products generated from dichlorides **1** and X-ray crystallography was critical in confirming the exact connectivity of the atoms constituting the heterocyclic cores.

The major cyclization products formed from a reaction of the amino group of **17** or **20** with the amidinyl chloride moiety of **1** and reaction of the ring nitrogen with the sulfamoyl chloride group.

Related reactions between dichlorides **1** and 2-amino-[1,3,4]thiadiazoles **23** in either Na_2CO_3/DMF or DMPU (without added base) provided [1,3,4]thiadiazolo[2,3-*c*][1,2,4,6] thiatriazine dioxides **24** as the major products with the isomeric [1,3,4]thiadiazolo[3,2-*b*][1,2,4,6]thiatriazine dioxides **25** occasionally isolated as minor products (Scheme 17, Table 7). The analogous reactions of **1** with 2-amino[1,3,4]oxadiazoles **26** in DMPU led to similar outcomes with [1,3,4]oxadiazolo[2,3-*c*][1,2,4,6]thiatriazine dioxides **27** as the major products and the isomeric [1,3,4]oxadiazolo[3,2-*b*][1,2,4,6]thiatriazine dioxides **28** as the minor product in at least one instance (Scheme 17, Table 7).[33]



Scheme 17

Table 7. Synthesis of the fused [1,2,4,6]thiatriazine dioxides **24**, **25**, **27**, and **28**

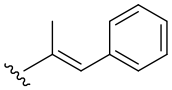
Product(s)	R^1R^2N	X	R^3	Yield(s) (%)
24a	Me_2N	S	Et	13
24b	Me_2N	S	*t*-Bu	31
24c (+25c)	Me_2N	S	SEt	42 (+10)
24d (+25d)	Et_2N	S	Me	23 (+4)
24e		S	Et	29
24f		S	SEt	29
27a	Me_2N	O	Bn	80
27b	Me_2N	O	4-*t*-Bu-Ph	23
27c	Me_2N	O		27
27d (+28d)	Et_2N	O	Bn	37 (+5)
27e	Et_2N	O	Thien-2-yl	48

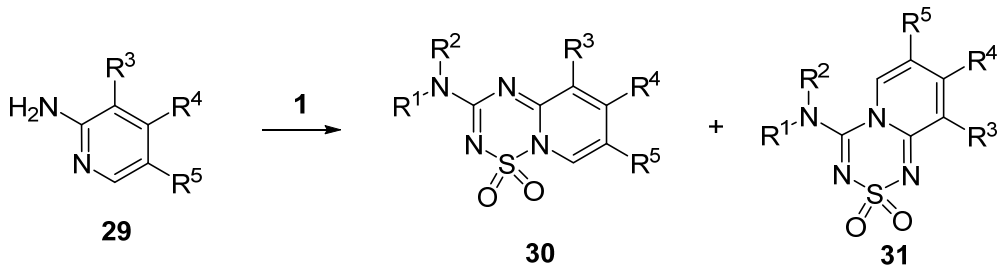
Table 7. Continued

Product(s)	R^1R^2N	X	R^3	Yield(s) (%)
27f		O	Ph	85
27g		O	4-*t*-Bu-Ph	72

Assignment of structures was based on X-ray crystallographic analyses of representative compounds, solubility properties, and behavior during thin layer chromatography. In both series of reactions, the major products **24** and **27** were less soluble (and less mobile during TLC) than the respective minor products **25** and **28** and this allowed selective precipitation of the major products directly from the reaction mixture. The minor products **25** and **28** were isolated from the mother liquors.[33]

The major reaction pathway involved reaction of a ring nitrogen of the amino-thiadiazole **23** or the amino-oxadiazole **26** with the amidine carbon atom of **1** and concomitant reaction of the amino group with the sulfamoyl chloride moiety. Curiously, this is the opposite regioselectivity from that observed in the thiazole series. However, it is known that the exocyclic nitrogen atom of 2-aminothiazoles is the preferred site of reaction with sp^2C electrophiles (e.g. acid chlorides, formimidates)[34,35] while the N-3 atom of 2-amino[1,3,4]thiadiazoles has greater nucleophilicity than the exocyclic nitrogen atom,[36] so the findings described above provide consistent evidence that the chloro-substituted amidine carbon atom of **1** is the more electrophilic site.

The reactions of dichlorides **1** with 2-amino-1-azaheterocycles to form fused thiatriazines was extended to amino compounds containing 6-membered rings. Reaction of **1** with an excess of 2-aminopyridines **29** in dichloromethane provided 3-dialkylamino-pyrido[1,2-*b*][1,2,4,6]thiatriazines **30** as well as the isomeric 4-dialkylamino-pyrido[2,1-*c*][1,2,4,6]thiatriazines **31** as a minor product (Scheme 18, Table 8).[37] Carrying out the reaction with a slight excess of the dichloride **1** in DMF in the presence of Hünig's base resulted in the production of significant amounts of both isomeric products **30** and **31** with a slightly greater proportion of **31**. Compounds **30** and **31** are new derivatives of very rare ring systems.



Scheme 18

Table 8. Synthesis of the pyrido-fused [1,2,4,6]thiatriazine dioxides **30** and **31**

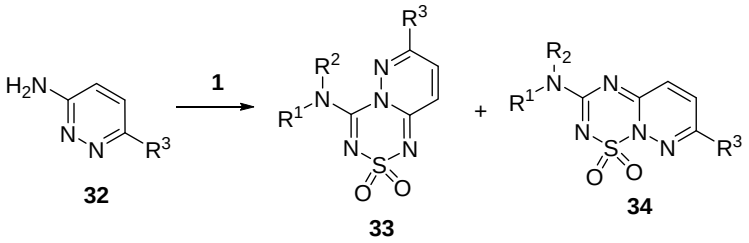
Product(s)	R^1R^2N	R^3	R^4	R^5	Method	Yield(s) (%)
30a	Me_2N	H	H	Cl	A	41
30b	Et_2N	H	H	H	A	49
30c		H	H	H	A	33
30d (+31d)	Me_2N	H	Me	H	A	37 (+9)
30e		H	Me	H	A	16
30e (+31e)					B	17 (+28)
30f (+31f)		H	H	Me	B	9 (+10)
30g (+31g)	Me_2N	Cl	H	Cl	C	18 (+3)*

Method A = excess of **29** in CH_2Cl_2; Method B = *i*-Pr_2NEt/DMF; Method C = DMPU/80 ^oC
also 33% starting aminopyridine recovered

Unequivocal determination of structures was based on X-ray crystallographic analyses of representative compounds. Consistent trends in relative solubilities and behavior during chromatography were useful in differentiating between the isomers. The more soluble, more TLC-mobile isomers were the pyrido[1,2-*b*][1,2,4,6]thiatriazine dioxides **30**, which were formed from a reaction of the exocyclic amino group of **29** with the amidinyl chloride moiety of **1** and reaction of the ring nitrogen with the sulfamoyl chloride moiety, while the relatively less soluble, less TLC-mobile isomers were the pyrido[2,1-*c*][1,2,4,6]thiatriazine dioxides **31**, formed by bonding of the ring nitrogen of **29** to the amidine carbon atom of **1** and the amino group reacting with the sulfamoyl chloride moiety.

The regioselectivity of the reaction could be modified by variation of the reaction conditions. Use of dichloromethane with excess of the 2-aminopyridine (as both reactant and base), or with a slight excess of dichloride **1** in DMPU without added base, resulted in predominant formation of pyrido[1,2-*b*][1,2,4,6]thiatriazines **30** whereas similar reactions in DMF in the presence of excess of Hünig's base, resulted in predominant formation of pyrido[2,1-*c*][1,2,4,6]thiatriazines **31**.[37]

The analogous reaction between dichlorides **1** and 3-aminopyridazines **32** in DMPU (with or without added base) provided 4-dialkylamino-pyridazo[3,2-*c*][1,2,4,6]thiatriazine dioxides **33** and also the isomeric 3-dialkylamino-pyridazo[2,3-*b*][1,2,4,6]thiatriazine dioxides **34** as a minor product in at least one instance (Scheme 19, Table 9).[37] Both **33** and **34** are new heterocyclic systems.



Scheme 19

Table 9. Synthesis of the pyridazo-fused [1,2,4,6]thiatriazine dioxides **33** and **34**

Product	R^1R^2N	R^3	Method	Yield (%)
33a	Me_2N	Cl	A	20
			B	36
33b (+34b)	BnMeN	Cl	A	54 (+5)
33c	Me_2N	*n*-PrS	A	35
			B	45
33d		*n*-PrS	A	21
33e	Me_2N	*n*-PrO	A	17

Method A = DMPU/80 ºC; Method B = *i*-Pr_2NEt/DMPU/80 ºC.

The addition of Hünig's base to these reactions improved yields. Unequivocal determination of structures was based on X-ray crystallographic analysis of representative compound **33e**.[37]

The relatively low solubility of compounds **33** allowed selective precipitation directly from the reaction mixture, simply achieved by the addition of ethyl acetate and water to the vigorously stirred reaction mixture. The product often precipitated and settled out at the interface between the organic and aqueous phases. This simple and convenient workup of reactions conducted with Hünig's base in DMPU was frequently employed and filtration and washing often afforded the product in high purity. As a result, the Hünig's base/DMPU system often became the conditions of choice in the synthesis of fused ring systems from dichlorides **1**

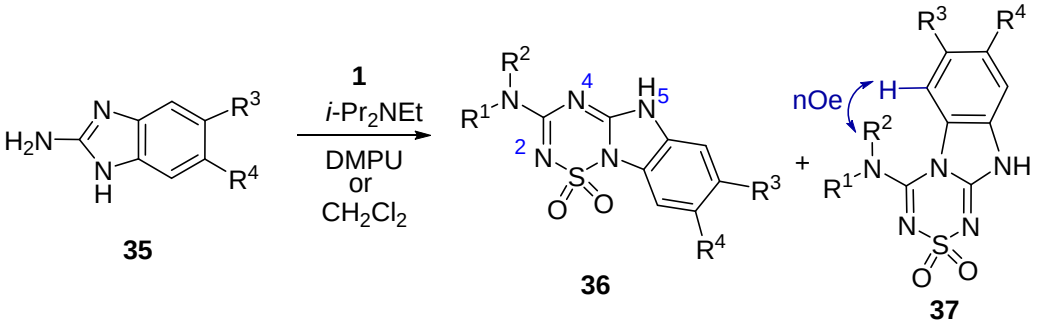
Predominant formation of pyridazo[3,2-*c*][1,2,4,6]thiatriazine dioxides **33** resulting from bonding of the ring nitrogen of the aminopyridazine to the amidine carbon atom of **1** and the exocyclic amino group reacting with the sulfamoyl chloride moiety is consistent with the known greater nucleophilicty of ring nitrogen N-2 compared to the exocyclic amino group of 3-aminopyridazines.[38-41] Our observations are that the chloro-substituted amidine carbon atom of **1** is the more electrophilic site in response to nitrogenous nucleophiles.[37]

In addition to the interest inherent in the chemical attributes of the novel fused [1,2,4,6]thiatriazine products described above, testing for possible biological activity seemed appropriate. In the absence of reactive NH moieties (amenable to substitution reactions) in these

ring systems, opportunities for structural variations were limited. Accordingly, we extended the present synthetic methodology to generate new or uncommon fused [1,2,4,6]thiatriazines bearing an NH group, which would then allow subsequent substitution and diversification within the pool of available test compounds.

Reactions of dichlorides **1** with derivatives of 2-aminobenzimidazole (a representative 2-amino-1*H*-azaheterocycle) were expected to deliver ring-fused [1,2,4,6]thiatriazine dioxides bearing an NH moiety, thus offering prospects for *N*-substitution.

Treatment of 2-aminobenzimidazoles **35** with **1** in the presence of Hünig's base, provided benzo[4,5]imidazo[1,2-*b*][1,2,4,6]thiatriazine dioxides **36**, and, on occasion, benzo[4,5]imidazo[2,1-*c*][1,2,4,6]thiatriazine dioxides **37** (Scheme 20, Table 10).[42]



Scheme 20

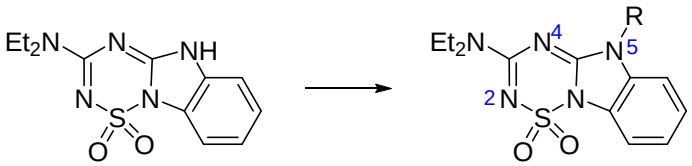
Table 10. Synthesis of the benzimidazo-fused [1,2,4,6]thiatriazine dioxides **36** and **37**

Products	R^1R^2N	R^3	R^4	Method	Yield (%)
36a + 37a	Me_2N	H	H	A	45 + 16
				B	30 + 19
36b	Et_2N	H	H	A	37
36c		H	H	B	30
36d + 37d		H	H	A	40 + 15
36e	Me_2N	Me	Me	B	33
36f	BnMeN	Me	Me	B	43
36g	Me_2N	tetrahydrobenzo	fused	B	27
36h	Et_2N	benzo	fused	B	29

Method A=*i*-Pr_2NEt in CH_2Cl_2; Method B= *i*-Pr_2NEt in DMPU.

Determination of structures was based on X-ray crystallographic analyses of compounds **36b** and **36c** and aided by consistent trends in relative solubilities, behaviour during chromatography, and ^{1}H NMR spectroscopic properties. Of particular note, the ^{1}H NMR signals due to the alkyl groups on the amine in compounds **36a** and **36d** resonated downfield relative to the corresponding signals for compounds **37a** and **37d**. In the spectra of compounds **37a** and **37d**, nuclear Overhauser effects were observed between the resonances described above and the hydrogen between R^3 and the ring junction (see Scheme 20).[42]

In both crystal structures **36b** and **36c**, a single tautomeric form was clearly evident, with the hydrogen atom residing on the imidazole ring nitrogen atom (N5) (for numbering, see Scheme 20). The nucleophilic nature of N5 was confirmed by acylation, alkylation, and sulfonylation of **36b**, which resulted in the expected products (**38a**–**e**) shown in Scheme 21 and Table 11. The reaction site was confirmed by X-ray crystallographic analyses of an acylated (**38b**) and an alkylated product (**38c**). No isomeric products (substituted at either N2 or N4) were isolated.[42]

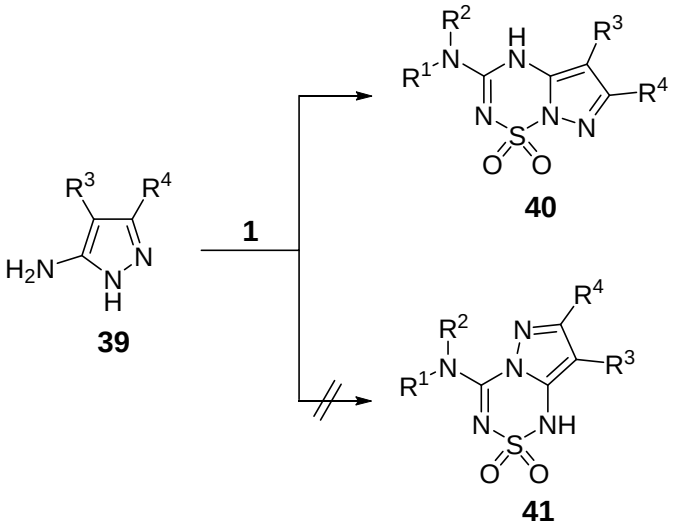


Scheme 21

Table 11. Synthesis of the 5-substituted benzimidazo-fused [1,2,4,6]thiatriazine dioxides **38**

Product	Method	R	Yield (%)
38a	$(CH_3CO)_2O$, pyridine, 100 °C	$COCH_3$	92
38b	PhCOCl, pyridine, 20 °C	COPh	72
38c	4-Cl-BnBr, cat. *n*-Bu_4NBr, K_2CO_3, CH_3CN, 20 °C	4-Cl-$C_6H_4CH_2$	84
38d	$PhSO_2Cl$, pyridine, 20 °C	SO_2Ph	78
38e	4-Cl-$PhSO_2Cl$, pyridine, 20 °C	4-Cl-$C_6H_4SO_2$	46

Reactions of dichlorides **1** with 3-aminopyrazole derivatives **39** were examined under a variety of conditions: (a) heating at 80 °C in a polar, aprotic solvent, DMPU; (b) in DMPU at ambient temperature in the presence of an organic base; (c) a two-phase system (aqueous/non-polar organic solvent) containing an inorganic base; and (d) a homogeneous system using a non-polar, organic solvent with an organic base (see Table 12). These reactions all provided pyrazolo[1,5-*b*][1,2,4,6]thiatriazines **40** (Scheme 22, Table 12).[43]



Scheme 22

Table 12. Synthesis of pyrazolo[1,5-*b*][1,2,4,6]thiatriazine 1,1-dioxides **3**

Product(s)	R^1R^2N	R^3	R^4	Method	Yield (%)
40a	Me_2N	H	H	C	39
40a				D	76
40b	Et_2N	H	H	D	64
40c		H	H	D	28
40d	Me_2N	H	Ph	B	93
40e	Et_2N	H	Ph	B	82
40e				A	53
40f		H	Ph	B	68
40f				A	36
40g	Me_2N	H	Thien-2-yl	B	88
40h	Et_2N	H	Thien-2-yl	A	42
40h				B	79
40h				C	24
40h				D	40
40i	Me_2N	CO_2Et	H	B	28

Table 12. Continued

Product(s)	R^1R^2N	R^3	R^4	Method	Yield (%)
40i				D	26
42a				C	24
42b	Et_2N	CO_2Et	H	B	54
42b +**43/44**				D	21 + 7
40j	Me_2N	H	Me	D	79
40k	Me_2N	H		D	90
40l		H		D	30

Method A = DMPU / 80 °C; Method B = *i*-Pr_2NEt / DMPU; Method C = $KHCO_3$(aq.) / C_6H_6 / *n*-Bu_4HSO_4; Method D = Et_3N/CH_2Cl_2.

The core ring structure of compounds 4**0** was confirmed by X-ray crystallographic analyses of several examples. No other ring-fused products, such as the isomeric pyrazolo[5,1-*c*][1,2,4,6]thiatriazines **41**, were isolated.

3-Amino-4-carbethoxypyrazole was slow to react compared to the other aminopyrazoles, suggesting the electron withdrawing group at C4 reduces the reactivity of the amino substituent. Pyrazolo-thiatriazine **40i** was obtained (in modest yield) from the reaction with dichloro compound **1a** using methods B and D. Employing the same starting materials using method C produced a bis-pyrazole product **42a** (Figure 3), confirmed by X-ray crystallography, which showed ring nitrogen N1 had reacted at each electrophilic site of dichloride **1a**. Apparently, the intermediate compound from the reaction of N1 with the bis-electrophile is incapable of cyclising because the other ring nitrogen N2 is not sufficiently reactive. Instead, another aminopyrazole molecule reacts at the remaining electrophilic site to form the bis-adduct **42a**. Interestingly, only compound **42b** was obtained from the diethylamino-dichloro compound **1b**. In the method D experiment, using dilute conditions, with the aim of reducing bis-pyrazole product formation and facilitating ring-fused product formation, a mixture of "partly reacted" products **43** and **44** was also isolated in low yield. Attempted reactions of 3-amino-4-phenyl pyrazole with the dichloro compounds **1** did not afford any detectable formation of pyrazolo-thiatriazines **40**. These results suggested that steric hindrance also retarded reaction of the exocyclic amino group with the dielectrophile **1**, especially in the case of diethylamino-substituted **1b**.[43]

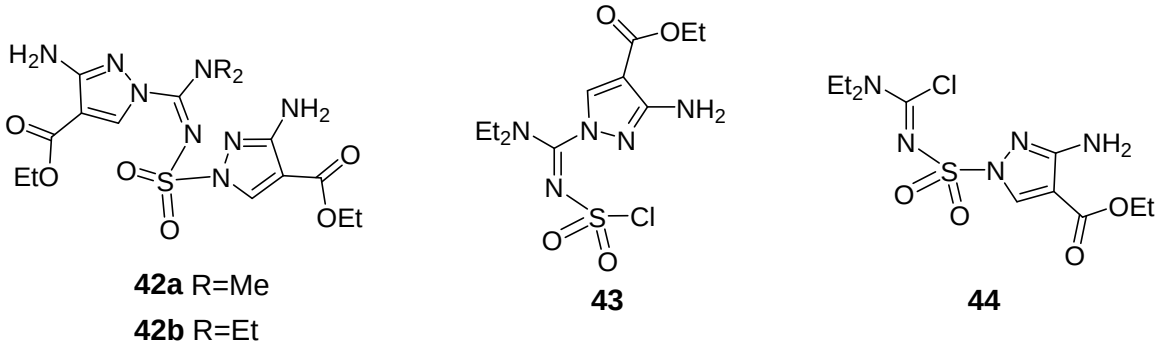
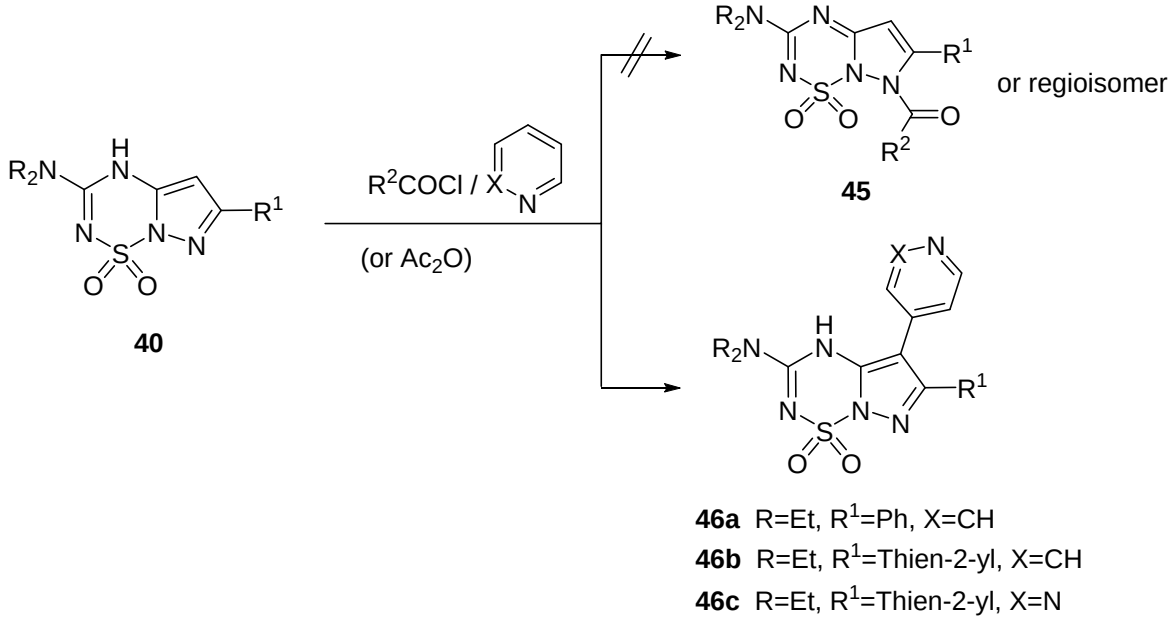


Figure 3. Structures of bis-pyrazole adducts **42** and other minor products **43** and **44**.

In order to confirm the nucleophilic nature of the NH moiety of compounds **40**, representative **40e** was treated with benzoyl chloride in pyridine (such acylation conditions were successful with related compounds **38**[42]); however, neither the expected N-benzoyl derivative **45** (Scheme 21), nor the N2- or N4-benzoylated regioisomers, was observed. The only isolated product, in 51% yield, was the bright yellow, crystalline, 5-(pyridin-4-yl) derivative **46a** (Scheme 23), confirmed by X-ray crystallography.[43]

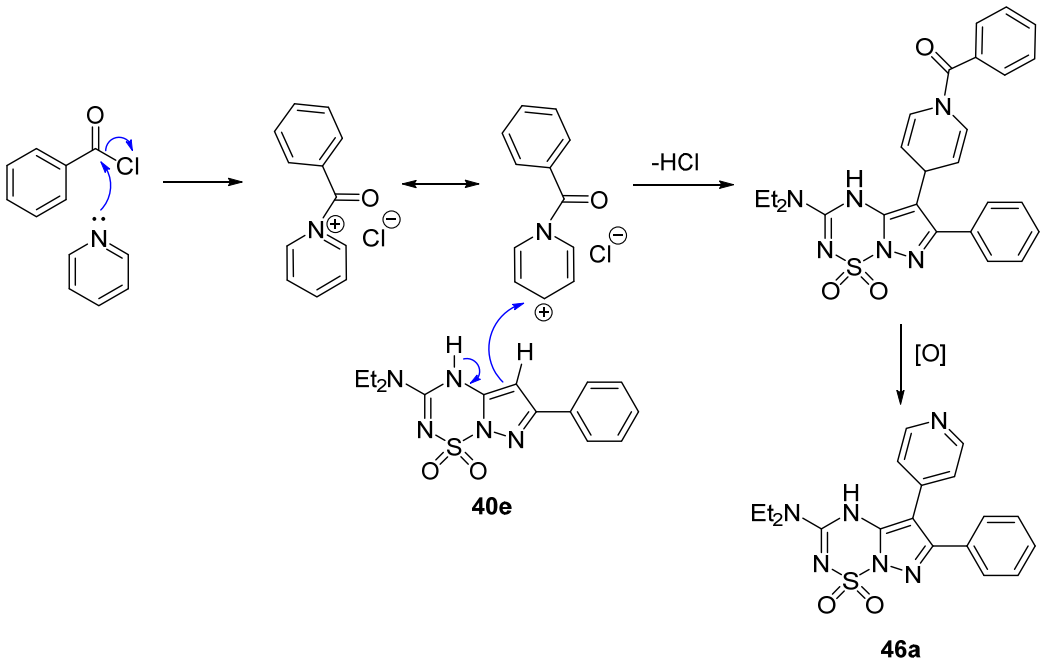


Scheme 23

A plausible mechanism for the formation of compound **46a** is shown in (Scheme 24). Unexpectedly, C5 of the pyrazolo-thiatriazine ring system appears to be more nucleophilic towards the *N*-acylpyridinium species than any of the ring nitrogen atoms.

This type of reaction with pyrazole-[44,45] or imidazole-[46] fused ring systems had been reported earlier, with ethyl chloroformate as the favoured reagent for such transformations.

However, in the previously reported reactions, a discrete oxidation step was required to re-aromatize the pyridine substituent.



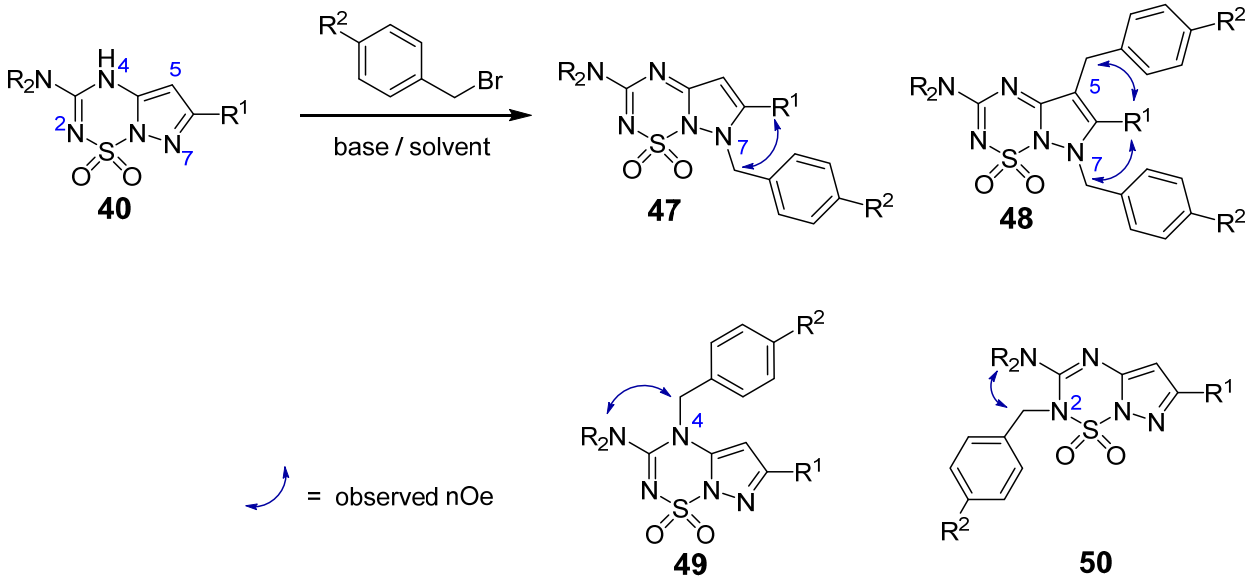
Scheme 24

The reaction of 6-(thien-2-yl) compound **40h** with benzoyl chloride in pyridine afforded the 5-(pyridin-4-yl) derivative **46b** in 70% yield. Compound **46b** was also obtained (68% yield) from **40h** by treatment with methyl chloroformate and pyridine in acetonitrile. Similarly, **40h** with methyl chloroformate and pyridazine afforded the 5-(pyridazin-4-yl) derivative **46c** (55% yield). Substituting acetyl chloride for methyl chloroformate provided **46c** in 46% yield. Analogous reactions with acetic anhydride were much less efficient. From these results, it appeared that use of the chloroformate offered no advantage over acetyl or benzoyl chloride. Similar experiments with 4-methylpyridine, 2,6-dimethylpyridine, and quinoline resulted in >90% recovery of starting material.[43]

Further experiments were conducted to test the nucleophilicity of the NH moiety of the novel heterocyclic system **40** towards acylation. These involved the use of acetyl or benzoyl chloride in the absence of pyridine or with a non-nucleophilic base, or Friedel-Crafts conditions employing $BF_3.OEt_2$ as a Lewis acid catalyst, as well as carbodiimide/activated ester coupling methodology with simple carboxylic acids. No useful reactions were observed under a variety of conditions.[43]

Despite the lack of reactivity of **40** towards *N*-acylation, it was readily alkylated. Treatment of compounds **40** with a benzylic halide in the presence of a base, afforded the N7-alkylated regioisomer **47** as the major product in every case (Scheme 25). The regioselectivity was not greatly influenced by solvent or choice of base, or by the substituent on the pyrazole ring.

Pyrazole carbon C5 also reacted as a nucleophile to afford bis-benzylated compounds **48**. Minor proportions of 4-benzylated products **49** and 2-benzyl compounds **50** were isolated in several cases (Table 13).[47]



Scheme 25

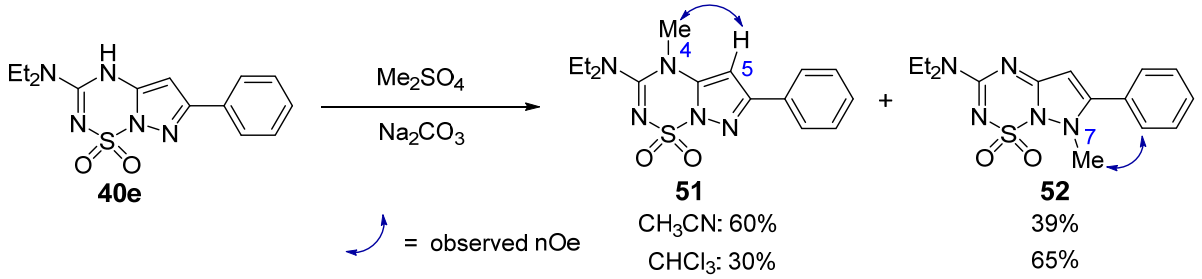
Table 13. Synthesis of benzylated pyrazolo[1,5-*b*][1,2,4,6]thiatriazine dioxides **47-50**

R_2N	R^1	R^2	Method	Product(s)	Yield(s) (%)
Me_2N	Ph	Cl	A	**47a**	49
			B	**47a** + **48a**	60 + 15
Et_2N	Ph	Cl	C	**47b** + **48b**	86 + 1
			D	**47b** + **48b** + **49b**	73 + 10 + 1
Me_2N	Thien-2-yl	Cl	B	**47c** + **48c** + **49c** + **50c**	46 + 13 + 4 + 1
			C	**47c** + **48c** + **49c**	77 + 13 + 3
Et_2N	Thien-2-yl	Cl	C	**47d** + **48d** + **49d**	72 + 20 + 1
Et_2N	Thien-2-yl	H	C	**47e** + **48e** + **49e**	69 + 14 + 2
			D	**47e** + **48e** + **49e**	72 + 6 + 12
Me_2N	Me	H	C	**47f** + **48f** + **49f** + **50f**	60 + 11 + 6 + 2
Et_2N	Thien-2-yl	OMe	C	**47g** + **48g** + **49g** + **50g**	44 + 8 + 16 + 4

Methods: A=K_2CO_3, cat. *n*-Bu_4NBr, CH_2Cl_2; B=Et_3N, THF; C=K_2CO_3, cat. *n*-Bu_4NBr, MeCN; D=K_2CO_3, cat. *n*-Bu_4NBr, MeCN, microwave irradiation, 50 °C.

Structural assignments for products **47-50** were based on the key nOe interactions shown in (Scheme 25), combined with X-ray crystallographic analyses of representative compounds **48c** and **49c**, and consistent trends in TLC mobilities, NMR chemical shifts, and solubilities.[47]

The 4-methyl derivative **51** and the 7-methyl derivative **52** were obtained from the reaction of pyrazolo-thiatriazine **40e** with dimethyl sulfate (Scheme 26).[47]

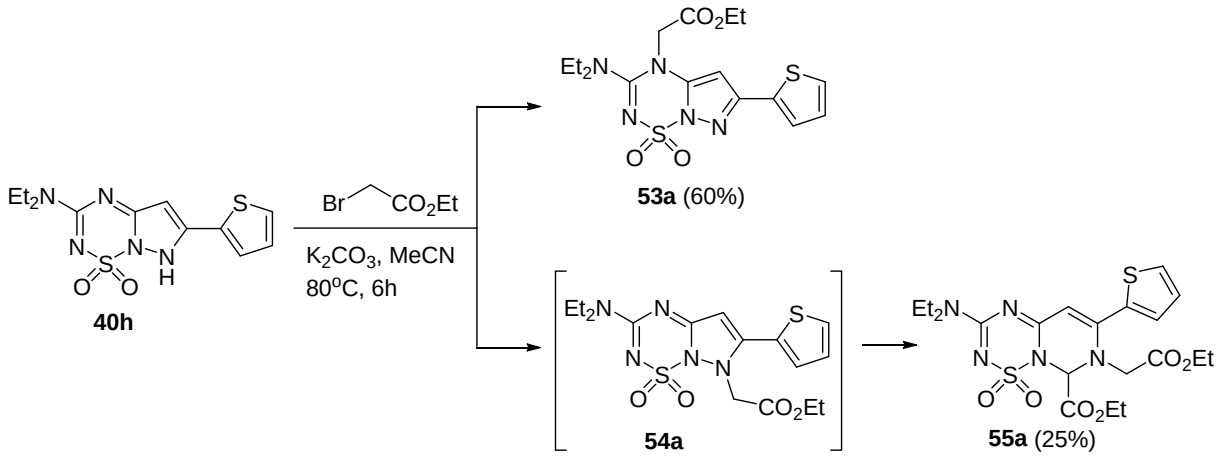


Scheme 26

Interestingly, the choice of solvent had a major influence on the regioselectivity of the methylation reactions. The 4-methyl derivative **51** was the major product in the polar aprotic solvent acetonitrile, whereas the use of chloroform as solvent favoured formation of the 7-methyl product **52**. This solvent dependence stands in contrast to the benzylation experiments summarized in Table 13, in which the product ratio was apparently independent of solvent.[47]

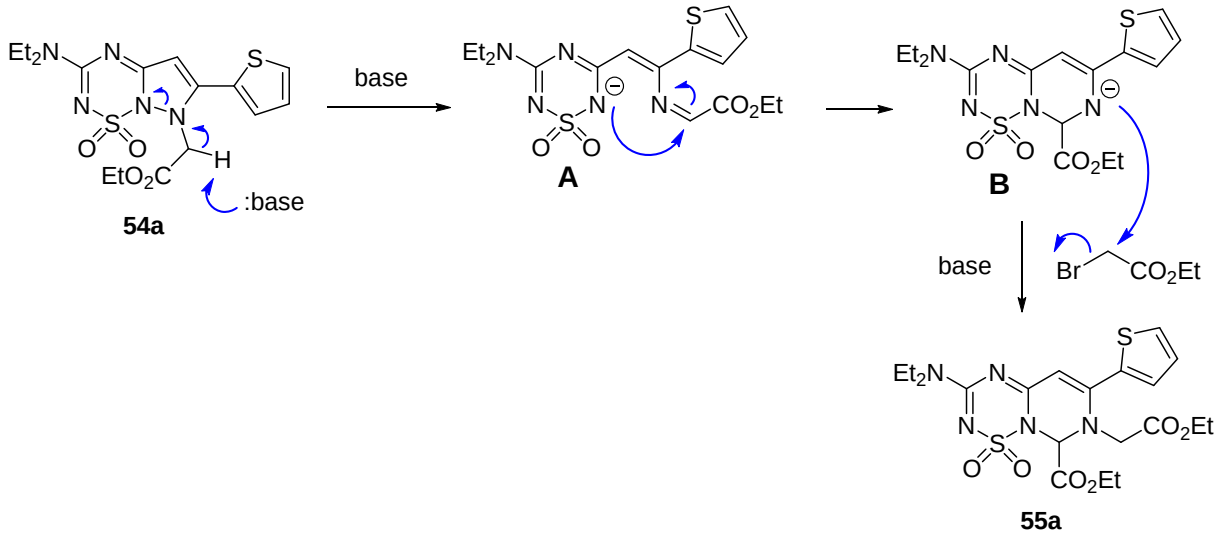
Attempts to alkylate compounds **40** with iodomethane, iodoethane, or 1-bromobutane using similar conditions resulted in no reaction.[47]

An unexpected result occurred from an experiment aimed at *N*-alkylation of pyrazolo-thiatriazine **40h** with ethyl bromoacetate and potassium carbonate in acetonitrile. In addition to a 60% yield of the expected N4-alkylated product **53a**, a second product containing two ethoxycarbonylmethyl substituents was isolated from this reaction in 25% yield. X-ray crystallographic analysis revealed the pyrimido-thiatriazine structure **55a**, presumably formed from ring expansion of the pyrazole moiety of N7-alkylated compound **54a** (Scheme 27).[47]



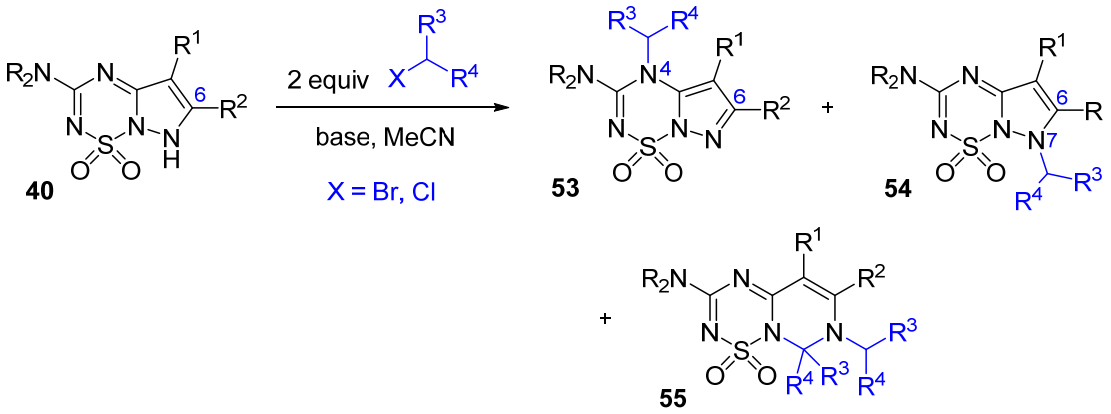
Scheme 27

Compound **55a** represents the first reported example of the pyrimido[1,6-*b*][1,2,4,6]thiatriazine ring system and the first reported ring expansion of a pyrazole moiety by means of an alkylating agent and appears related to the ring expansion reactions of [1,2,3,5]thiatriazoles described in Section 3.1.1. By analogy with the mechanism proposed for these reactions, a mechanism for formation of **55a** is suggested in Scheme 28. The electron withdrawing nature of the ester group flanking the alkyl substituent on N7 of **54a** contributes to the acidic nature of the α-proton which is removed under basic conditions to form an imine, with concomitant cleavage of the pyrazole ring to form sulfamide anion **A**. The sulfamide nitrogen of anion **A** then adds to the imine carbon to form intermediate **B** which is alkylated to provide the fused pyrimidine **55a**.[47]



Scheme 28

This unusual result prompted investigations into the scope of this rare ring-expansion reaction; results are summarised in Scheme 29 and Table 14.



Scheme 29

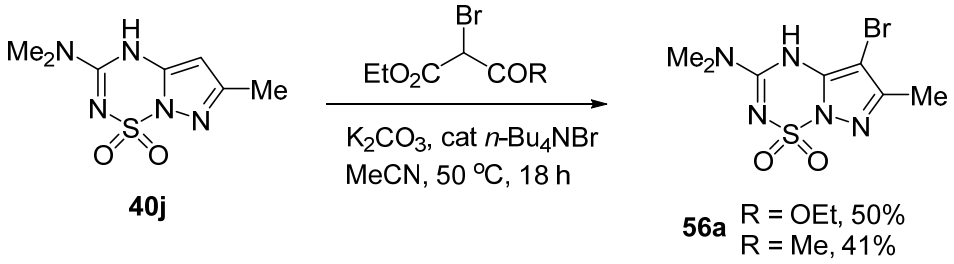
Table 14. Synthesis of *N*-alkylated pyrazolo[1,5-*b*][1,2,4,6]thiatriazine dioxides (**53** and **54**) and dihydropyrimido[1,6-*b*][1,2,4,6]thiatriazine dioxides (**55**)

R_2N	R^1	R^2	R^3	R^4	Conditions†	Product(s)	Yield(s) (%)
Et_2N	H	Thien-2-yl	CO_2Et	H	K_2CO_3, cat. *n*-Bu_4NBr, 80 °C	**53a + 55a**	60 + 25
Me_2N	H	H	CO_2Et	H	K_2CO_3, cat. *n*-Bu_4NBr	**53b + 54b + 55b**	25 + 4 + 31
					K_2CO_3, cat. *n*-Bu_4NBr, 80 °C	**53b**	25
Me_2N	H	Me	CO_2Et	H	K_2CO_3, cat. *n*-Bu_4NBr	**53c + 55c**	24 + 40
					i-Pr_2NEt	**53c + 55c**	40 + 33
Me_2N	CO_2Et	H	CO_2Et	H	K_2CO_3, cat. *n*-Bu_4NBr	**53d + 54d + 55d**	12 + 1 + 34
Me_2N	H	cyclopropyl	CO_2Et	H	K_2CO_3, cat. *n*-Bu_4NBr	**53e + 55e**	40 + 31
Me_2N	H	H	4-bromo phenacyl	H	K_2CO_3	**53f**	18
Me_2N	H	Me	CO_2Me	CO_2Me	K_2CO_3, cat. *n*-Bu_4NBr	**55g**	25

Reactions performed in MeCN at 50 °C, unless otherwise specified.

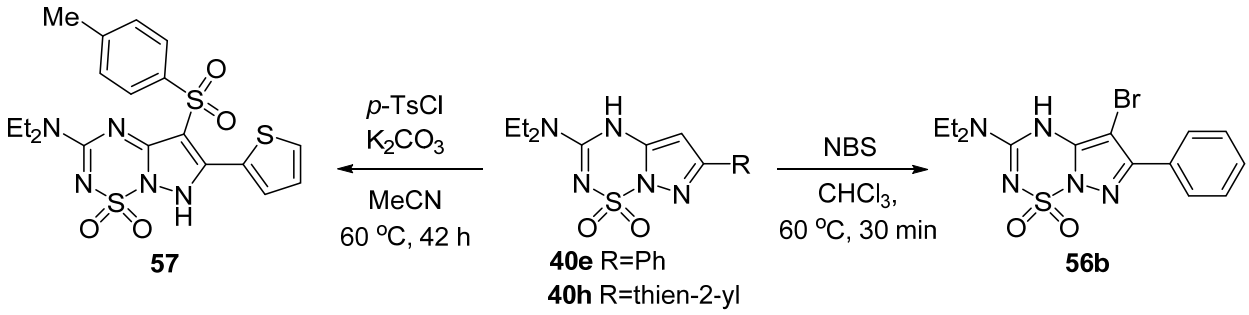
Substrates lacking a bulky substituent at C6 resulted in the ring-expanded compound being the major product, whereas substrates with bulky substituents at C6 led to a greater proportion of alkylation at thiatriazine nitrogen N4, presumably due to steric hindrance at N7. 2-Chloroacetamide, 2-bromoacetamide, ethyl 2-bromobutyrate, ethyl 2-chloroacetoacetate, and ethyl 2,2-dichloroacetate were unreactive towards compounds **40** over long periods of time with potassium carbonate in acetonitrile or DMF at 60-80 °C.[47]

Treatment of **40j** with either diethyl bromomalonate or ethyl 2-bromoacetoacetate did not result in alkylation or ring expansion. Curiously, a bromine atom was introduced to the pyrazole carbon C5 to afford the unstable bromide **56a** (Scheme 30).[47]



Scheme 30

Bromination by diethyl bromomalonate is known;[48,49] however, the present results are the first reported examples of diethyl bromomalonate and ethyl 2-bromoacetoacetate acting as brominating agents for the pyrazole ring and further highlight the considerable nucleophilicity of the C5 atom of pyrazolo-thiatriazines **40**. Accordingly, a 5-bromo substituent was introduced into **40e** in high yield by treatment with *N*-bromosuccinimide (NBS) in hot chloroform (Scheme 31).[47]

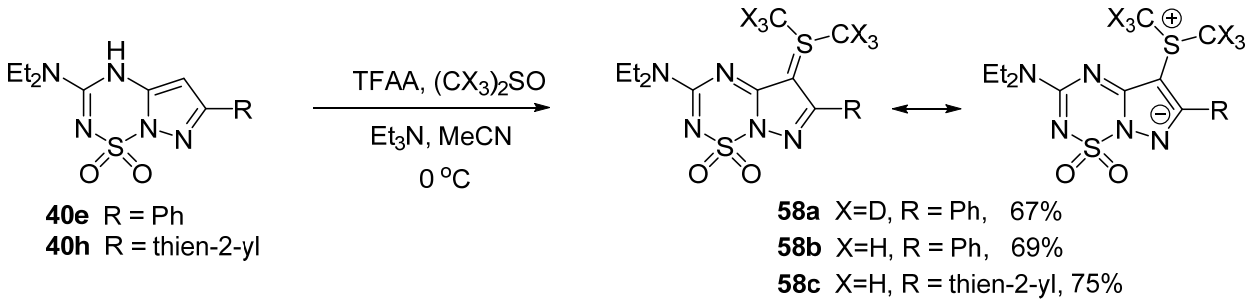


Scheme 31

The 5-tosyl derivative **57** was obtained in 48% yield by treatment of **40h** with tosyl chloride and potassium carbonate in acetonitrile (Scheme 31). Interestingly, the only product isolated resulted from selective reaction at C5 of the pyrazolo-thiatriazine ring system, rather than reaction at N2, N4, or N7.[47]

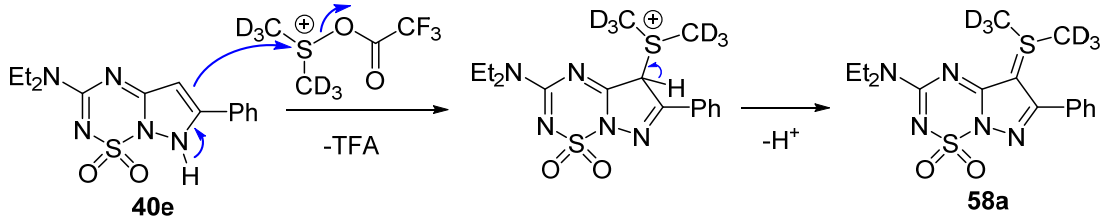
The bromo-compounds **56** and the tosyl-compound **57** were considered as potential substrates for further chemistry, such as Suzuki-couplings and related transformations; however, these compounds proved to be unstable in solution and to chromatography, making them unsuitable as synthetic intermediates.

During the course of attempted acylation experiments with **40e** using trifluoroacetic anhydride and triethylamine, in one instance, the 5-dimethylsulfonio derivative **58a** was isolated in 67% yield (Scheme 32). The structure of **58a** was confirmed by X-ray crystallography. This unexpected product was traced to the presence of residual DMSO-d_6 in a contaminated sample of compound **40e**.[50]



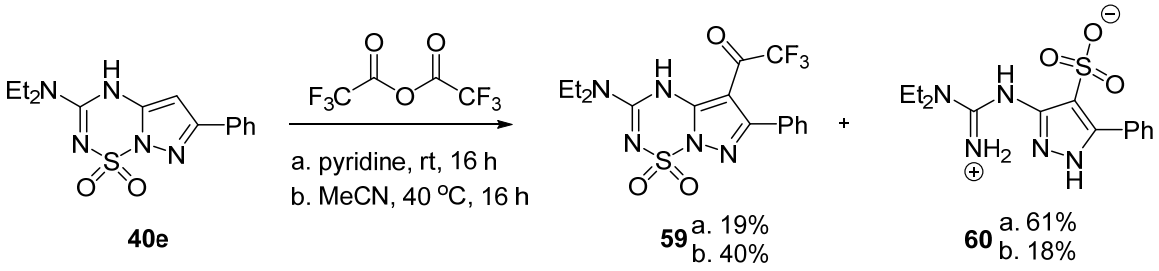
Scheme 32

A plausible mechanism involves the activation of DMSO-d_6 by TFAA to generate an electrophilic salt which reacted at the nucleophilic pyrazole carbon C5 (Scheme 33).[50]



Scheme 33

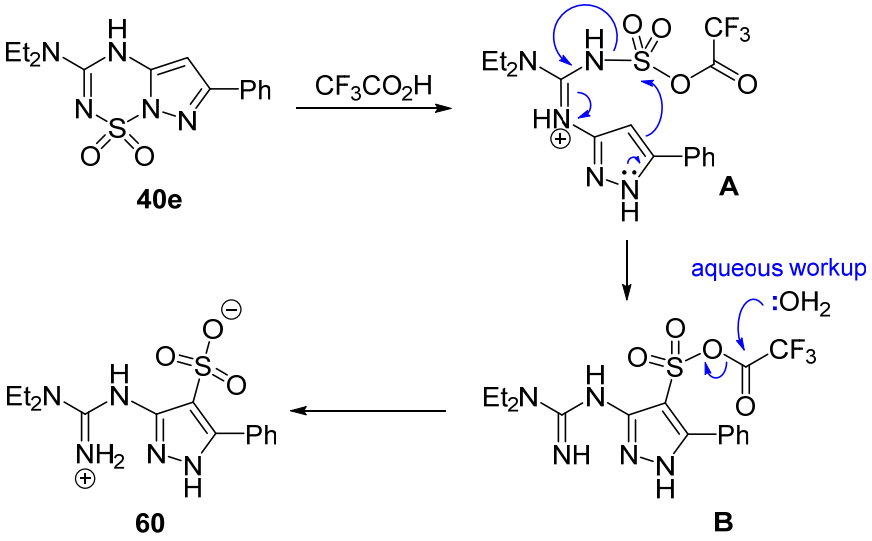
This isolation of **58a** prompted the synthesis of analogues **58b** and **58c** (Scheme 32).[50] Treatment of pure samples of **40e** with TFAA in acetonitrile or pyridine afforded the C5 trifluoroacetylated product **59**. No NH acylated products were isolated, confirming the significant nucleophilicity of C5 in this ring system. Interestingly and unexpectedly, the guanidino-pyrazolesulfonic acid **60** (Scheme 34) was isolated in major proportion from the reaction in pyridine. The structure of **60** was elucidated by X-ray crystallography.[50]



Scheme 34

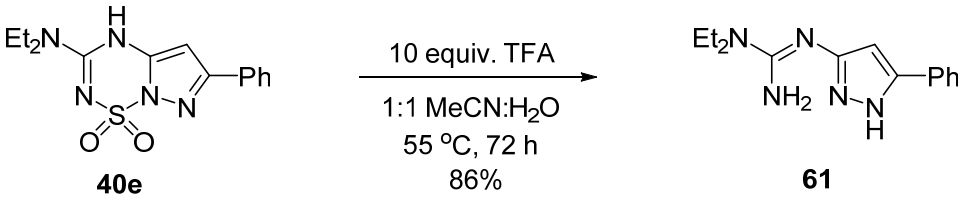
A possible mechanism for the formation of compound **60** is outlined in Scheme 35. Trifluoroacetic acid in the mixture could facilitate the cleavage of the sulfamide S-N bond, as is

observed in similar acid-catalysed reactions of related ring systems,[51] followed by the nucleophilic pyrazole carbon of intermediate **A** reacting with the sulfur atom of the "mixed anhydride" moiety. The nature of the reaction mixture would have the guanidine moiety protonated (even in the presence of pyridine, a weak base), causing it to be a better leaving group than trifluoroacetate, resulting in transfer of the anhydride moiety to the pyrazole carbon atom, forming intermediate **B**. Hydrolysis of the anhydride moiety of **B** during aqueous workup would liberate the sulfonic group, producing the isolated compound **60**.



Scheme 35

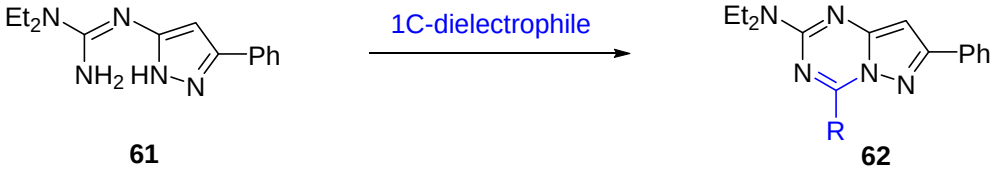
The desulfonated compound **61** could be prepared efficiently using aqueous acidic conditions, most conveniently with excess of TFA in a water/acetonitrile mixture (Scheme 34). Presumably, water intercepts the pathway to formation of the sulfonic acid **60** by hydrolysis of the mixed anhydride moiety of intermediate **A** in (Scheme 33).[50]



Scheme 36

The pyrazolo-guanidine **61** proved to be a useful synthetic precursor to derivatives of the uncommon pyrazolo[1,5-*a*][1,3,5]triazine ring system, which has been proposed as an isostere of purine.[52-54] A small set of 4-substituted pyrazolo-triazines **62** was prepared from one-carbon di-

electrophiles, most conveniently with either orthoesters or carboxylic anhydrides (Scheme 37, Table 15).[47]



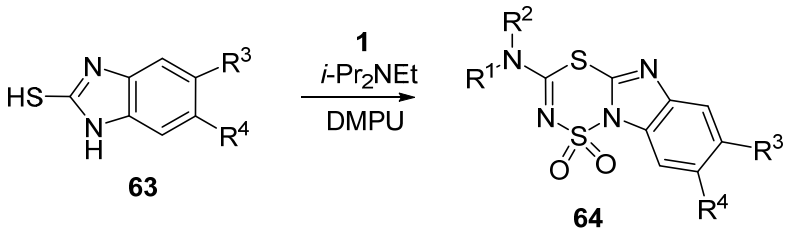
61 **62**

Scheme 37

Table 15. Synthesis of pyrazolo[1,5-*a*][1,3,5]triazines **62**

R	Conditions	Product	Yield (%)
H	$HC(OMe)_3$ (neat), reflux, 43 h	**62a**	94
Me	$MeC(OMe)_3$ (neat), 10mol% MsOH, reflux, 16 h	**62b**	71
Me	$POCl_3$, DMA, 50 °C, 23 h	**62b**	33
Me	Ac_2O, *i*-Pr_2NEt, DMF, 70 °C, 15 h	**62b**	42
Et	$(EtCO)_2O$, *i*-Pr_2NEt, DMF, 100 °C, 18 h	**62c**	66
Ph	BzCl, *i*-Pr_2NEt, DMF, 100 °C, 4.5 h	**62d**	31
Ph	$(PhCO)_2O$, NEt_3, DMF, 100 °C, 39 h	**62d**	60
Ph	$(PhCO)_2O$, *i*-Pr_2NEt, DMF, 100 °C, 42 h	**62d**	71

3.2.2 S-C-N 1,3-bis-nucleophiles. 2-Mercapto-1*H*-azaheterocyclic compounds display the characteristics of S-C-N 1,3-dinucleophilic systems and 2-mercaptobenzimidazoles **63** embody readily available representatives. The reactions of **63** with dichlorides **1** provided derivatives of the previously unreported ring system benzo[4,5]imidazo[1,2-*b*][1,4,2,6]dithiadiazine **64** (Scheme 38, Table 16).[51]



63 **64**

Scheme 38

Table 16. Synthesis of benzo[4,5]imidazo[1,2-*b*][1,4,2,6]dithiadiazine dioxides **64**

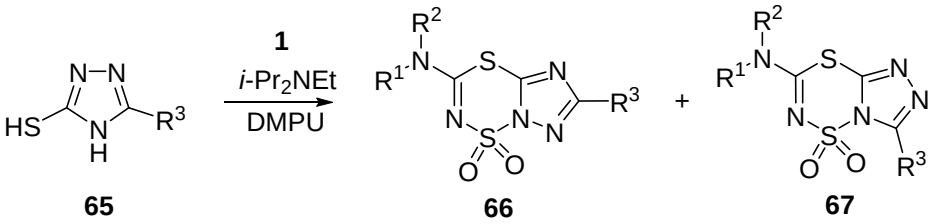
Product	R^1R^2N	R^3	R^4	Yield (%)
64a	Me_2N	H	H	79
64b	Et_2N	H	H	27
64c		H	H	50
64d		H	H	52
64e	BnMeN	H	H	27
64f	Me_2N	Cl	Cl	76
64g	Et_2N	Cl	Cl	59
64h	Et_2N	benzo	fused	43
64i		benzo	fused	76
64j (R^3=Cl, R^4=H)	Me_2N	Cl	H	19
64k (R^3=H, R^4=Cl)				18
64l (R^3=H, R^4=OMe)	Et_2N	OMe	H	11
64m (R^3=OMe, R^4=H)				13
64n (R^3=H, R^4=OMe)		OMe	H	11
64o (R^3=OMe, R^4=H)				13

Often the benzo[4,5]imidazo[1,2-*b*][1,4,2,6]dithiadiazine dioxides **64** were selectively precipitated from the reaction mixture in high purity and generally in good yield. The reactions were highly regioselective and no isomeric products were isolated after purification of the mother liquors.[51]

In cases of asymmetric mercaptobenzimidazoles **63** where R^3 and R^4 are different, another source of regioisomerism exists. In these reactions, similar quantities of the two possible isomers were formed (see Table 16, **64j-64o**).[51]

Unequivocal determination of structures **64** was based upon X-ray crystallographic analyses of four representative compounds and was aided by consistent trends in ^{1}H NMR chemical shifts of the three aromatic hydrogen atoms in compounds **64l-o**.[51]

The efficient construction of ring-fused [1,4,2,6]dithiadiazines **64** encouraged the investigation of an analogous reaction with 3-mercapto[1,2,4]triazoles **65**. Indeed, such a reaction gave [1,2,4]triazolo[1,5-*b*][1,4,2,6]dithiadiazines **66** and, on occasion, the isomeric [1,2,4]triazolo[4,3-*b*][1,4,2,6]dithiadiazines **67** (Scheme 39, Table 17).[51] Compounds **66** represent derivatives of a unique heterocyclic system and there is only one report[55] of the ring system of **67**.



Scheme 39

Table 17. Synthesis of [1,2,4]triazolo[1,5-*b*][1,4,2,6]dithiadiazines **66** and [1,2,4]triazolo[4,3-*b*][1,4,2,6]dithiadiazines **67**

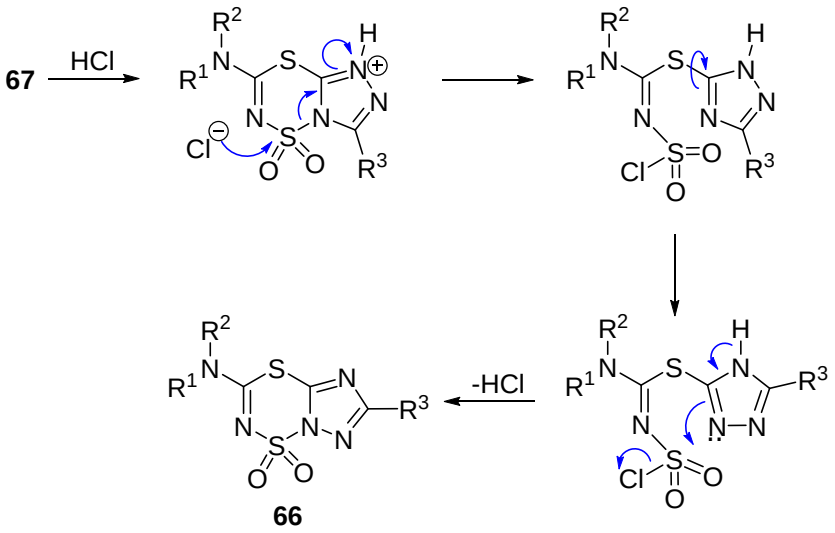
Product(s)	R^1R^2N	R^3	Yield(s) (%)
66a (+67a)		H	30 (+21)
66b (+67b)	Et_2N	*i*-Pr	15 (+23)
66c		*t*-Bu	63
66d		Ph	49
66e	Me_2N	4-*t*-Bu-Ph	53
66f (+67f)	Et_2N	4-*t*-Bu-Ph	29 (+10)
66g		4-*t*-Bu-Ph	43
66h		4-*t*-Bu-Ph	47
66i	Me_2N	4-Py	65
66j	Et_2N	4-Py	35
66k		4-Py	54
66l	BnMeN	4-Py	35

Assignment of structures for dithiadiazines **66** and **67** was based on X-ray crystallographic analyses of representative compounds and consistent relative behavior during thin layer chromatography.[51]

The usually major products **66** result from bonding of the sulfur atom of **65** to the amidine carbon atom of **1** (as was the case with mercaptobenzimidazoles **63**) and N-2 reacting with the sulfamoyl chloride moiety. The minor isomers **67** were formed by reaction of N-4 with the sulfamoyl chloride moiety of **1**. Others have reported that 5-phenyl-3-mercapto[1,2,4]triazoles

react with ambident electrophilic reagents such as α-haloketones and 2-chloromethyloxirane firstly via the mercapto group and subsequently at N-2, rather than N-4, to afford bicyclic products.[56,57] This suggests an order of nucleophilicity for these mercaptotriazoles of S > N-2 > N-4. Our observations in the current work are consistent with the above and suggests the likelihood that the previously reported[55] compounds apparently possessing the ring system of **67** may actually contain the isomeric ring system of **66**. The selective formation of fused [1,4,2,6]dithiadiazines **64**, **66**, and **67** also provides further evidence that the chloro-substituted amidine carbon atom of **1** is the more reactive site in the bis-electrophile.

An interesting HCl-induced isomerization of the minor products [1,2,4]triazolo[4,3-*b*][1,4,2,6]dithiadiazines **67** to the major products, [1,2,4]triazolo[1,5-*b*][1,4,2,6]dithiadiazines **66** occurred at room temperature in NMR samples stored in $CDCl_3$. A possible mechanism for this interconversion is outlined in (Scheme 40).[51]



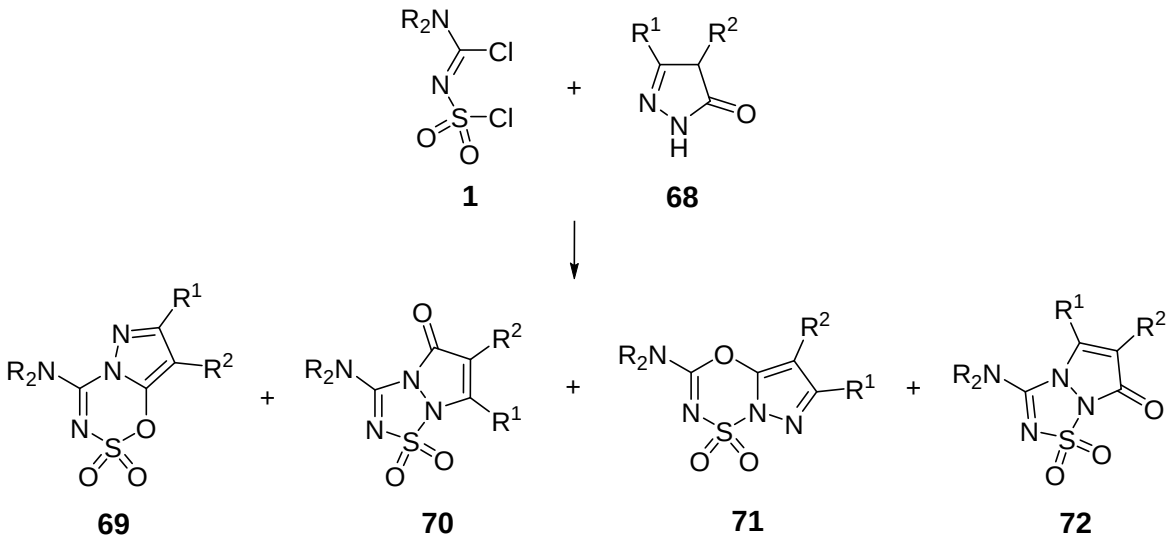
Scheme 40

The proposed mechanism involves HCl-induced cleavage of the triazole-N(4)—SO_2 bond followed by rotation of the triazole group and subsequent attachment of the triazole-N(2) to the SO_2 moiety.[51]

3.2.3 O-C-N 1,3-bis-nucleophiles. An extension of the methodology for creating six-membered rings, described in the previous two sections, is the employment of 2-hydroxy-1*H*-azaheterocycles in similar reactions to produce fused oxathiadiazine derivatives. Pyrazol-3-ones **68** represent a suitable candidate 2-hydroxy-1*H*-azaheterocyclic system, since these compounds have been shown to act as 1,3-O-C-N bis-nucleophiles in reactions with bis-electrophiles to produce cyclic products.[58,59]

The reactions of dichlorides **1** with pyrazol-3-ones **68** were examined under the same broad range of conditions used in the studies involving 3-aminopyrazoles **39** – see (Scheme 22) and

(Table 12) in section 3.2.1. Usually, such reactions provided pyrazolo[2,3-*e*][1,2,3,5]oxathiadiazines **69** and pyrazolo[3,2-*b*][1,4,3,5]oxathiadiazines **71**, and frequently, one or both of pyrazolo[1,2-*b*][1,2,3,5]thiatriazoles **0** and **72** (Scheme 41, Table 18).[21]



Scheme 41

Table 18. Synthesis of the fused heterocycles **69**, **70**, **71** and **72**

R_2N	R^1	R^2	Method	Products **69**	**70**	Yields (%) **71**	**72**
Me_2N	Me	H	A	**69a** (22)	-	**71a** (29)	
	Me	H	A	**69b** (14)	**70b*** (3)	**71b** (22)	
Me_2N	*n*-Pr	H	B	**69c** (24)	**70c** (2)	**71c** (34)	
Et_2N	*n*-Pr	H	C	**69d** (8)	**70d** (2)	**71d** (60)	
	*n*-Pr	H	B	**69e***[60] (2)	**70e** (2)	**71e** (13)	
Me_2N	Me	Me	B	**69f*** (7)		**71f*** (52)	**72f** (11)
Et_2N	Me	Me	A	**69g** (13)		**71g***[61] (26)	-
Me_2N	$-(CH_2)_4-$		A	**69h*** (17)	**70h*** (6)	**71h*** (23)	**72h***[62] (17)
			C	-	-	**71h*** (40)	-
Et_2N	$-(CH_2)_4-$		B	**69i*** (2)		**71i*** (37)	**72i*** (17)
Et_2N	Ph	H	B	**69j** (1)	-	**71j*** (47)	-
			C	**69j** (1)		**71j*** (58)	

Table 18. Continued

R_2N	R	R^2	Method	**69**	Products **70**	Yields (%) **71**	**72**
	PhH		D	**69k** (2)		**71k*** (16)	

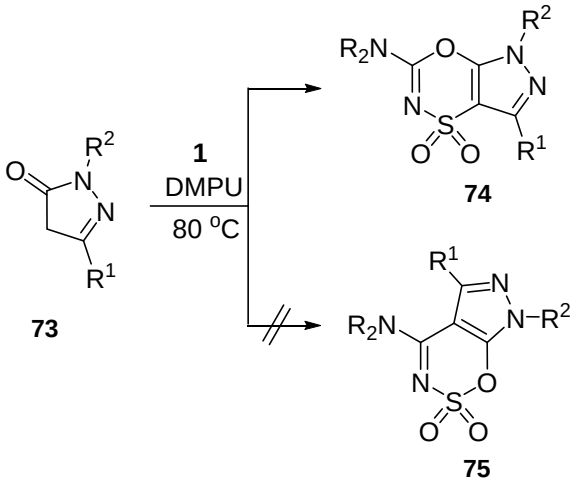
*X-ray crystal structure obtained.
Method A = DMPU / 80 °C; Method B = *i*-Pr_2NEt / DMPU; Method C = $KHCO_3$(aq.) / C_6H_6 / *n*-Bu_4NHSO_4; Method D = Et_3N/CH_2Cl_2

Under all conditions employed, the pyrazolo[3,2-*b*][1,4,3,5]oxathiadiazine **71** was the major product, with the pyrazolo[2,3-*e*][1,2,3,5]oxathiadiazine **69** usually appearing as a significant product in the absence of base. The other two products, pyrazolo[1,2-*b*][1,2,3,5]thiatriazoles **70** and **72**, were sometimes also isolated.[21]

The ring systems of compounds **69** and **71** have not been previously reported.
The four isomeric products from these reactions reflect the numerous tautomeric forms available to *N*-unsubstituted pyrazol-3-ones. Ring formation to produce the major products **71** proceeds such that the oxygen atom of **68** bonds with the amidine carbon atom of **1** and N2 reacts with the sulfamoyl chloride moiety. The other significant reaction product **69** results from N2 of the pyrazolone bonding with the amidine carbon atom of **1** and the oxygen reacting with the sulfamoyl chloride moiety. The minor products, thiatriazoles **70** and **72**, arise from a 1,2-N-N mode of reaction via both nitrogen atoms of the pyrazole ring of **68** in each possible orientation.[21]

3.2.4 O-C-C 1,3-bis-nucleophiles. It was of interest to attempt to alter the course of the reaction between pyrazol-3-ones and dichlorides **1** so as to obtain fused cyclic products involving C-substitution. Employment of N^1-substituted pyrazol-5-ones **73**, which are substituted at the nitrogen atom directly adjacent to the carbonyl group, was expected to block both of the 1,2-N-N and 1,3-N-C-O modes of reaction and ensure 1,3-O-C-C dinucleophilic substitution.[10,63,64]

Treatment of pyrazolones **73** with dichlorides **1** at 80 °C in DMPU indeed effected a regioselective 1,3-O-C-C dinucleophilic substitution to form 3-dialkylamino-pyrazolo[4,3-*e*][1,4,3]oxathiazine dioxides **74** (Scheme 42, Table 19).[31] These compounds are the first reported representatives of the pyrazolo[4,3-*e*][1,4,3]oxathiazine ring system.



Scheme 42

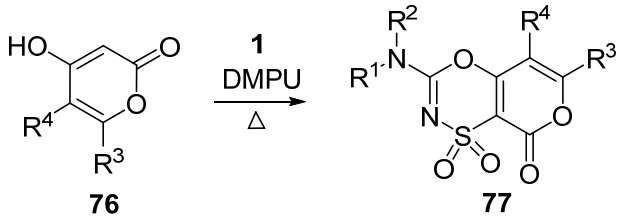
Table 19. Synthesis of the pyrazolo[4,3-*e*][1,4,3]oxathiazines **74**

Product	R_2N	R^1	R^2	Yield (%)
74a	Me_2N	Me	Ph	61
74b		Me	2-Cl-Ph	72
74c		Me	2-Cl-Ph	56
74d		Et	Ph	37
74e	Me_2N	Me	^{t}Bu	20
74f	Et_2N	Me	^{t}Bu	26
74g	Me_2N	CF_3	Me	59
74h	Et_2N	CF_3	Me	34
74i		CF_3	Me	50

Usually, the pyrazolo[4,3-*e*][1,4,3]oxathiazines **74** were precipitated from the reaction mixture in high purity by the favoured ethyl acetate/water workup procedure. X-ray crystallographic analyses of representative compounds confirmed the structural assignments. No isomeric products, such as **75**, were isolated. In the case of compound **74a**, analysis of the whole reaction mixture did not reveal the presence of any isomeric products.[31]

The reactions of dichlorides **1** with 4-hydroxy-2-pyrone derivatives **76**, a representative class of cyclic 1,3-dicarbonyl compounds and a known 1,3-dinucleophilic (:O-C-C:) system, were studied. Heating mixtures of **1** and **76** in DMPU selectively provided 3-dialkylamino-

pyrano[3,4-*e*][1,4,3]oxathiazine dioxides **77**, representatives of a previously unknown heterocyclic system (Scheme 43, Table 20).[65]



76 **77**

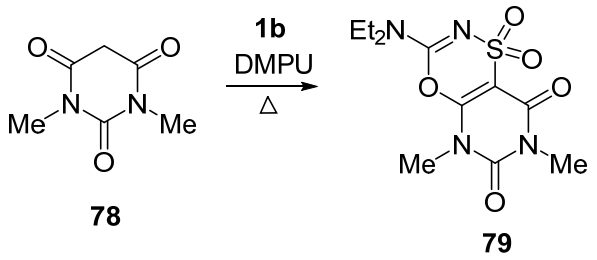
Scheme 43

Table 20. Synthesis of the 3-dialkylamino-pyrano[3,4-*e*][1,4,3]oxathiazine dioxides **77**

Product	R^1R^2N	R^3	R^4	Yield (%)
77a	Me_2N	Me	H	20
77b	Et_2N	Me	H	10
77c	BnNMe	Me	H	30
77d	Et_2N	$PhCH_2CH_2$	H	15
77e	Me_2N	benzo	fused	24
77f	Et_2N	benzo	fused	28
77g	Me_2N	$-(CH_2$	$CH_2)_2-$	11
77h	BnNMe	$-(CH_2$	$CH_2)_2-$	26

The procedural simplicity and ease of work up partly compensated for the modest yields. Structural assignments were confirmed by X-ray crystallographic studies on **77f** and **77g**.[74]

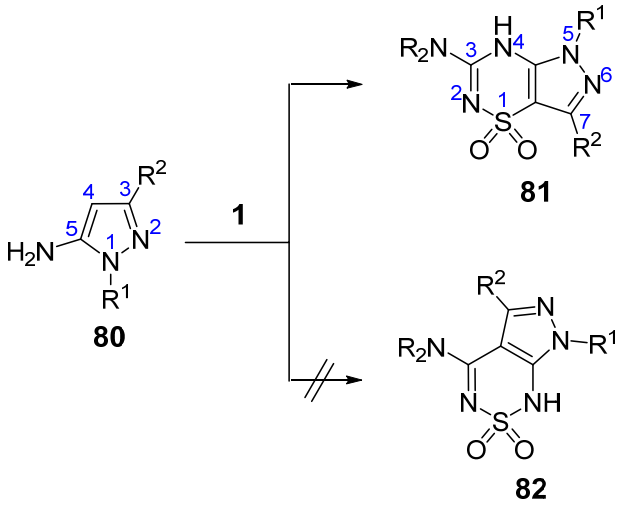
It is apparent that this methodology can be extended to reactions with other 1,3-dicarbonyl systems to produce related [1,4,3]oxathiazines. For example, treatment of 1,3-dimethylbarbituric acid **78** with dichloro compound **1b** in DMPU provided the tetraoxopyrimido[5,4-*e*][1,4,3]oxathiazine **79** (Scheme 44), representing another new ring system.[65]



Scheme 44

3.2.5 N-C-C 1,3-bis-nucleophiles. In a similar strategy to that used to alter the course of the reaction between pyrazol-3-ones and dichlorides **1**, the employment of N^1-substituted 5-aminopyrazoles **80** (in place of *N*-unsubstituted 3-aminopyrazoles **39** - see section 3.2.1, Scheme 22) in reactions with **1** was studied. Aminopyrazoles **80** are substituted at the nitrogen atom directly adjacent to the exocyclic amino group, which blocks the 1,3-N-C-N and 1,2-N-N modes of reaction and enables 1,3-N-C-C dinucleophilic substitution, via the exocyclic amino group and C4, which is a known nucleophilic site,[10,64,66] leading to pyrazole-fused thiadiazines.

The reactions of dichlorides **1** with 1-substituted 5-aminopyrazoles **80** were examined under a range of conditions, but regardless of the conditions chosen, only the pyrazolo[3,4-*e*][1,2,4]thiadiazines **81** (Scheme 45, Table 21) were isolated.[67] Compounds **81** are derivatives of a very rare ring system.[68-71]



Scheme 45

Table 21. Synthesis of the 3-dialkylamino-pyrazolo[3,4-*e*][1,2,4]thiadiazines **81**

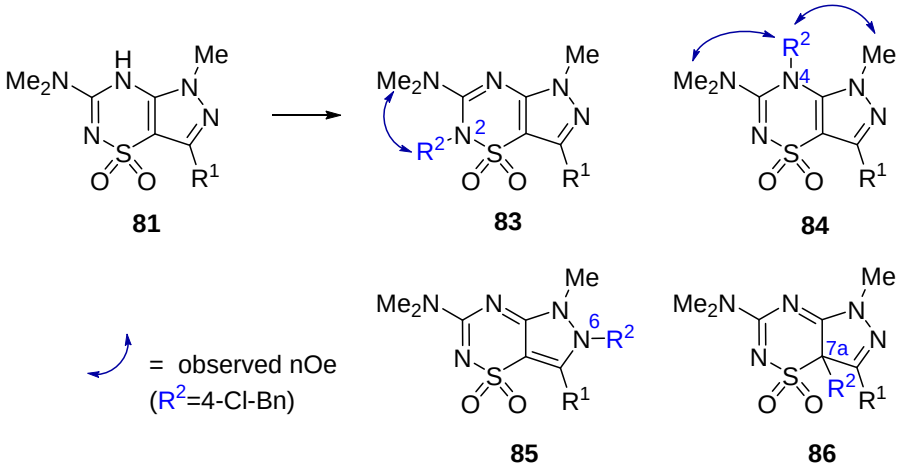
Product	R_2N	R^1	R^2	Method	Yield (%)
81a	Me_2N	Me	H	C	78
81b#	Me_2N	Me	Me	A	60
81b#				B	71
81c		Me	Me	B	15 (21*)
81c				C	36 (51*)
81d	Me_2N	Ph	Me	B	14 (19*)
81d				C	42 (56*)
81e	Me_2N	Me	Ph	B	44
81f		Me	Ph	D	49 (60*)
81g	Me_2N	Me	Thien-2-yl	B	44
81g				D	70
81h#	Me_2N	Me	*t*-butyl	B	12
81h#				D	33

#X-ray crystal structure obtained. *Based on consumed starting material.
Method A = DMPU/80 °C; Method B = *i*-Pr_2NEt/DMPU; Method C = Et_3N/CH_2Cl_2/20 °C;
Method D = Et_3N/MeCN/20 or 50 °C

No other ring-fused products, such as the isomeric pyrazolo[3,4-*c*][1,2,6]thiadiazines **82**, were isolated, indicating that the favoured mechanistic pathway involved reaction of the exocyclic amino group at the amidinyl carbon of **1** and cyclisation at C4.[67] The regiochemical outcome of these reactions is in accord with our other studies with dichlorides **1**, where carbon nucleophiles typically reacted at the sulfamoyl group (see previous section 3.2.4).

Compounds **81** contain an NH moiety in the newly formed ring system which has tautomeric forms with the NH group present at positions 2, 4, or 6. Thus, each of these sites has potential for the introduction of substituents. In order to determine the relative nucleophilicity of the nitrogen atoms in compounds **81**, some representatives were treated with a variety of electrophilic reagents.

Representative pyrazolo-thiadiazines **81** were treated with dimethyl sulfate or a benzylic halide following conditions successfully employed with pyrazolo[1,5-*b*][1,2,4,6]thiatriazines (see Table 13, Schemes 25 and 26) and the results are summarized in (Scheme 46 and Table 22).[67]



Scheme 46

Table 22. Synthesis of alkylated pyrazolo[3,4-*e*][1,2,4]thiadiazine 1,1-dioxides **83-8**

R^1	R^2	Method	Product(s)	Yield (%)
Me	Me	Me_2SO_4, K_2CO_3, MeCN, reflux	**83a** + **84a** + **85a**	14 + 15 + 65
Thien-2-yl	Me	Me_2SO_4, K_2CO_3, MeCN, reflux	**83b** + **84b** + **85b**	30 + 30 + 21
Me	4-Cl-Bn	4-Cl-BnBr, K_2CO_3, cat. *n*-Bu_4NBr, MeCN, 60°C	**83c** + **84c**+ **86c**	47 + 5 + 31
Thien-2-yl (**3h**)	4-Cl-Bn	4-Cl-BnBr, K_2CO_3, cat. *n*-Bu_4NBr, MeCN, 40°C	**83d** + **84d** + **86d**	67 + 16 + 7

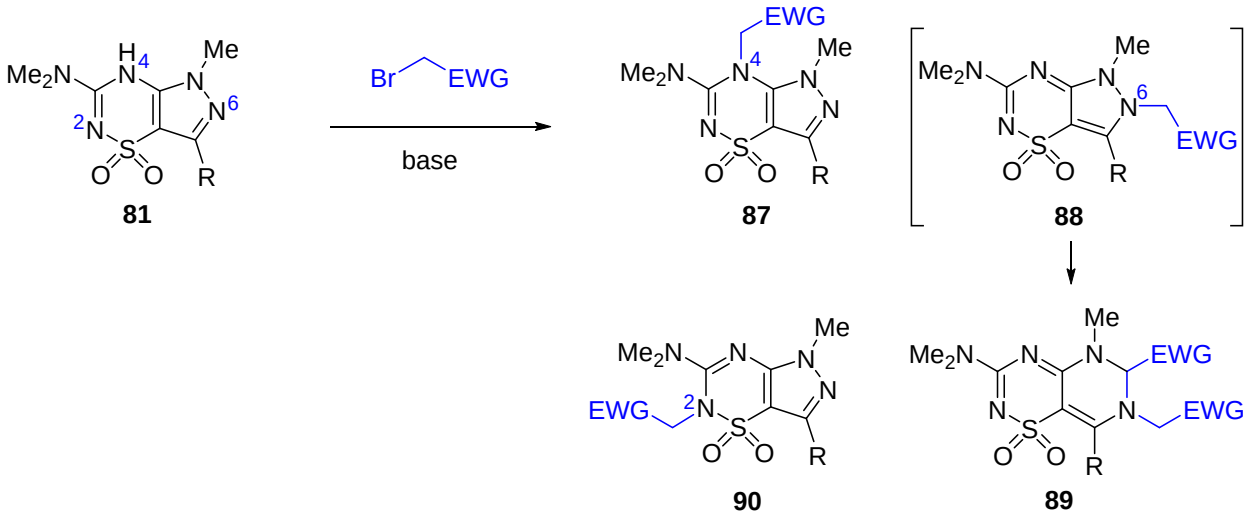
Methylation of **81b** and **81h** was not very selective and a mixture of products was obtained in each case; however, methylation of substrate **81b**, with a (relatively small) methyl substituent at C7, resulted in a higher yield of N6 methylated product **85a** (65%) than with substrate **81h**, with a 7-(thien-2-yl) substituent (**85b**; 21%).[67]

NOe data could not be used to effectively elucidate regioisomers of the methylated compounds owing to the methyl groups in *N*-methylated products **83a-85b** not being in sufficiently close proximity to the other substituents; therefore, an X-ray crystal structure of an example of each of **83**, **84**, and **85** was solved.[67]

Alkylation of **81b** and **81h** with 4-chlorobenzyl bromide occurred at N2 and N4; preferentially at N2, providing products **83**, and to a lesser extent at N4, giving **84**. The structural assignments of these products were based on key nOe interactions shown in Scheme 49. Interestingly, benzylation also occurred at the ring junction carbon C7a, adjacent to the SO_2 moiety, affording compounds **86**. Initially, the N6-alkylated structure **85** was assigned to compounds **86c** and **86d**, but the NMR data were not compatible with structure **85**. The data were consistent with structure **86**, which bears a benzyl substituent on an asymmetric, quaternary carbon C7a. As might be expected, the compound with less steric hindrance at C7 produced a

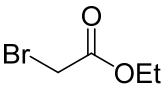
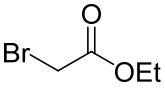
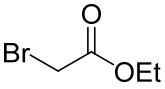
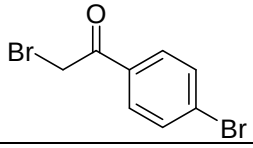
greater proportion of alkylation at C7a, furnishing isomers **86** (**86c**; 31%, compared with **86d**; 7%).[67]

Alkylation of compounds **81** with ethyl bromoacetate occurred at both N4, to give compounds **87**, and N6, affording **88**, but the latter derivatives apparently underwent a pyrazole ring expansion to afford pyrimido[4,5-*e*][1,2,4]thiadiazine derivatives **89** (Scheme 47, Table 23). However, the reaction of compound **81a** with 4-bromo-phenacyl bromide furnished only the N4 alkylated product **87**. Heating **81a** with dimethyl chloromalonate, methyl 2-bromopropionate, or ethyl dichloroacetate in DMF largely returned the starting materials.



Scheme 47

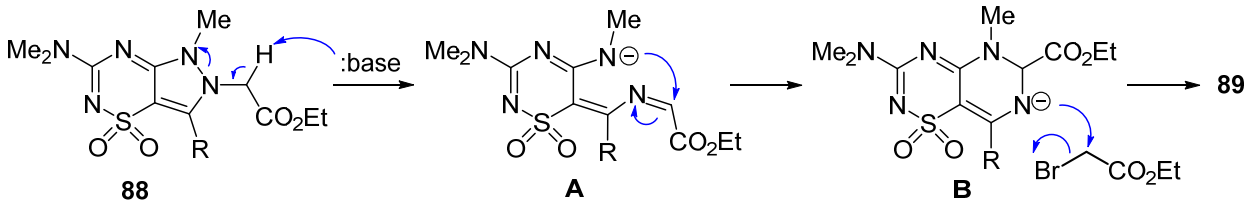
Table 23. Reactions of pyrazolo-thiadiazines **81** with ethyl bromoacetate and 4-bromophenacyl bromide

Electrophile	R	Method	Product(s)	Yield (%)
	H	A	**87a + 89a**	11 + 39
	Me	B	**87b + 89b**	5 + 53
	Ph	A	**87c + 90c**	62 + 3
	Me	C	**87d**	24

Method A = K_2CO_3, *n*-Bu_4NBr, DMF, 60 °C; Method B = K_2CO_3, *n*-Bu_4NBr, MeCN, 55 °C; Method C = i. $NaHCO_3$ ii. K_2CO_3, DMF, 20 °C.

Structural assignments of compounds **87** and **89** were established by X-ray crystallographic studies on representative compounds **87c** and **89b**.[67]

Presumably, the ring expansion reaction affording compounds **89** follows a similar mechanism to that of the pyrazolo-thiatriazine ring expansion described earlier (see Section 3.2.1, Scheme 28). A proposed mechanism is shown in (Scheme 48).



Scheme 48

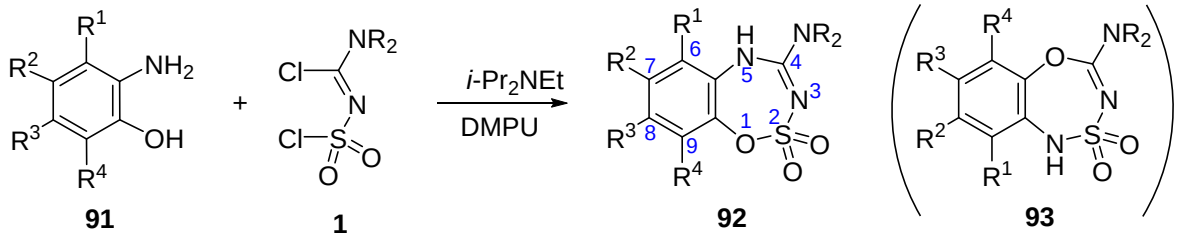
Under the basic reaction conditions, the acidic α-proton of the ester-containing substituent on N7 is removed, with concomitant pyrazole ring opening to form anion **A**, which presumably is extensively stabilised by delocalisation throughout the dioxothiadiazine ring. Anion **A** affords the pyrimidine ring via reaction of the exocyclic nitrogen anion at the imine carbon to form intermediate **B** which is subsequently alkylated to provide the isolated product **89**.[67]

Substrates **81** with little steric bulk around the pyrazole ring to hinder N6-alkylation, gave rise to appreciable quantities of the ring expanded material **89**. One example with a (bulky) phenyl group at C7, from which mostly N4-alkylated product **87** and a little N2-alkylated product **90** were isolated, demonstrated the steric influence of the C7 substituent on the regioselectivity of N-alkylation.[67]

Compounds **81** were unreactive toward common acylating agents. Experiments with acetyl chloride (or anhydride) or trifluoroacetic anhydride under various conditions resulted in >90% of the starting materials being recovered.[67]

3.3 Seven-membered rings from 1,4-bis-nucleophiles

3.3.1 O-C-C-N 1,4-bis-nucleophiles. Reaction of dichlorides **1** with 2-aminophenols **91** in DMPU in the presence of Hünig's base provided 4-dialkylaminobenzo[*f*][1,2,3,5] oxathiadiazepine dioxides **92** (Scheme 49, Table 24),[72] examples of a new ring system.



Scheme 49

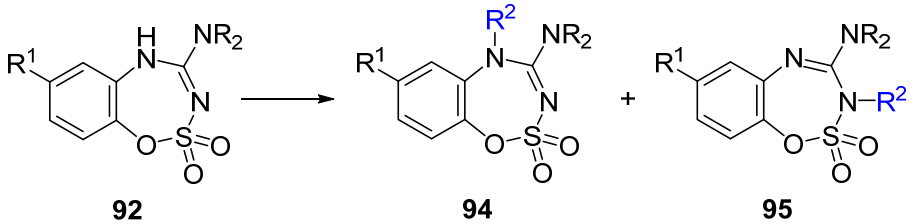
Table 24. Synthesis of the 4-dialkylaminobenzo[*f*][1,2,3,5]oxathiadiazepine dioxides **92**

Product	R_2N	R^1	R^2	R^3	R^4	Yield (%)
92a	Me_2N	H	H	H	H	48
92b		H	H	H	H	69
92c		Me	H	H	H	23
92d	Me_2N	H	Me	H	H	53
92e		H	Me	H	H	24
92f	Me_2N	H	H	Me	H	71
92g	Et_2N	H	H	Me	H	53
92h	Me_2N	H	Cl	H	Cl	31
92i	Et_2N	H	Cl	H	Cl	48
92j	Et_2N	H	tetrahydrobenzo	fused	H	54

The possible regioisomeric products **93** (Scheme 49) were not isolated.[72]

The ring structure of benzoxathiadiazepines **92** was established by X-ray crystallographic studies of *N*-acylated and *N*-alkylated derivatives (*vide infra*). Ring formation to produce compounds **92** proceeds such that the amino group of **91** bonds with the amidine carbon atom of **1** and the hydroxyl group reacts with the sulfamoyl chloride moiety. This mode of reaction further confirms the greater electrophilicity of the amidinyl chloride moiety, relative to the sulfamoyl chloride group, in dichlorides **1**.[72]

The nucleophilic nature of the NH moiety of the oxathiadiazepine ring of **92** was confirmed by acylation and alkylation of **92b** and **92d**. The reactions of **92b** and **92d** with acetic anhydride and the reaction of **92b** with benzoyl chloride all occurred selectively at *N*5 to give the acylated products **94a-94c** (Scheme 50, Table 25).[72]



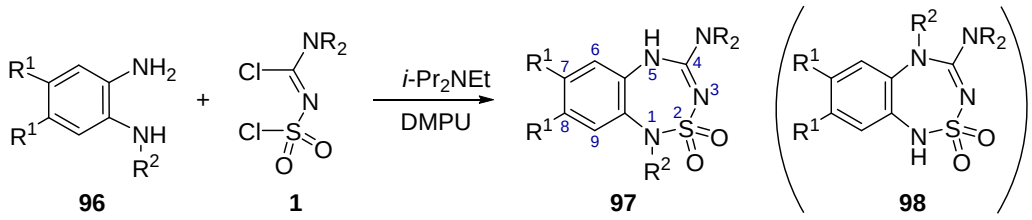
Scheme 50

Table 25. Synthesis of the benzoxathiadiazepine dioxides **94** and **95**

R_2N	R^1	R^2	Method	Product(s)	Yield(s) (%)
	H	$COCH_3$	$(CH_3CO)_2O$, py, 120 ºC	**94a**	77
Me_2N	CH_3	$COCH_3$	$(CH_3CO)_2O$, py, 120 ºC	**94b**	77
	H	COPh	PhCOCl, py, 20 ºC	**94c**	50
	H	4-Cl-Bn	4-Cl-BnBr, cat. *n*-Bu_4NBr, K_2CO_3, CH_3CN, 20 ºC	**94d** + **95d**	32 + 49

Alkylation of **92b** with 4-chlorobenzyl bromide was not selective and a mixture of benzylated products **94d** and **95d** was obtained (Scheme 50, Table 25). The structural assignments for **94a-95d** were based on X-ray crystallographic analyses of the acylated product **94c** and benzylated compound **95d**.[72]

3.3.1 N-C-C-N 1,4-bis-nucleophiles. Inspired by the construction of the benzo[*f*][1,2,3,5]oxathiadiazepine ring from dichlorides **1** and 2-aminophenols **91**, we envisaged an analogous reaction with 1,2-diaminobenzenes **96**. Indeed, such reactions gave 4-dialkylaminobenzo[*e*][1,2,4,7] thiatriazepine 2,2-dioxides **97** and, on occasion when $R^2 \neq H$, the isomeric compounds **98** as a minor product (Scheme 51, Table 26).[72] These compounds are new derivatives of a rare[73,74] ring system.



Scheme 51

Usually, the benzothiatriazepines **97** were precipitated from the reaction mixture in high purity by the ethyl acetate/water (pH 3) workup method. Structural assignments for compounds listed in Table 28 were based upon X-ray crystallographic analyses of compounds **97f** and **97g**.[72]

Table 26. Synthesis of the 4-dialkylaminobenzo[*e*][1,2,4,7] thiatriazepine 2,2-dioxides **97** and **98**

R_2N	R^1	R^2	Product(s)	Yield(s) (%)
Me_2N	H	H	**97a**	55
	H	H	**97b**	33
Me_2N	Cl	H	**97c**	66
Me_2N	Me	H	**97d**	52
Et_2N	Me	H	**97e**	52
Me_2N	H	4-Cl-Bn	**97f**	48
	H	Me	**97g + 98g**	43 + 2

Interestingly, in the solid state, the thiatriazepine heterocycle exists in a pseudo boat conformation, for which there are two enantiomorphic configurations (A and B, Figure 4). In the solid state, **97f** crystallizes in the non-centrosymmetric space group $P2_12_12_1$ and the crystal analysed contained only one configuration (A) whilst **97g**.H_2O had both configurations A and B due to the inversion symmetry present in the centrosymmetric space group $P2_1/c$.[72]

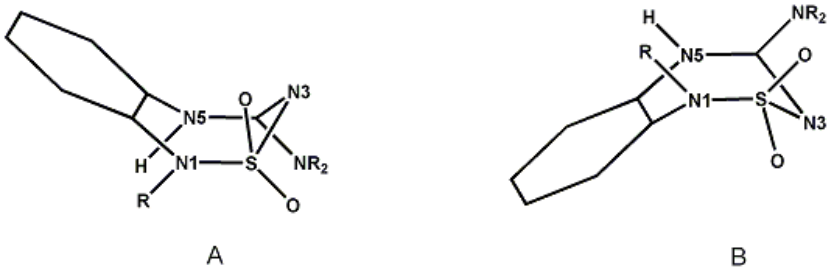
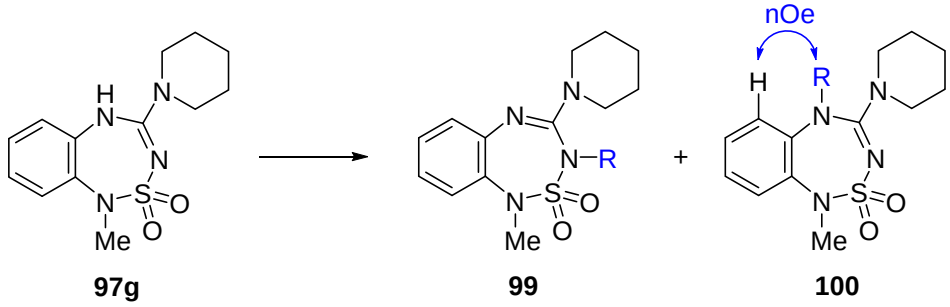


Figure 4. Enantiomorphic forms of the thiatriazepine ring of **97** found in the solid state.

The nucleophilic nature of the nitrogen atoms of the thiatriazepine ring was confirmed by acylation and alkylation of **97g**. Acylation of the 1-methyl thiatriazepine **97g** with acetic anhydride or benzoyl chloride occurred preferentially at *N*3 (Scheme 52, Table 27) to afford the 3-acetyl- and 3-benzoyl- derivatives **99a** and **99b**, respectively. The structural assignments were confirmed by X-ray crystallographic study of the benzoyl derivative **99b**. Alkylation of **97g** with 4-chlorobenzyl bromide also proceeded predominantly at *N*3 to give **99c** as the major product, but also occurred at *N*5, affording **100c** as a minor product (Scheme 52, Table 27).[72]



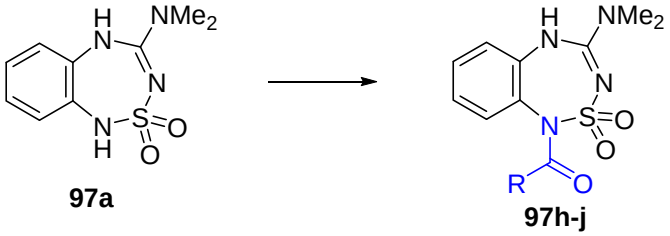
Scheme 52

Table 27. Synthesis of the benzothiatriazepine dioxides **99** and **100**

R	Method	Product(s)	Yield(s) (%)
$COCH_3$	$(CH_3CO)_2O$, py, 90 ºC	**99a**	64
COPh	PhCOCl, py, rt	**99b**	38
4-Cl-$C_6H_4CH_2$	4-Cl-BnBr, cat. *n*-Bu_4NBr, K_2CO_3, CH_3CN, 20 ºC	**99c +100c**	70 + 18

The 500MHz gradient-selected NOESY 2D ^{1}H NMR spectrum of **100c** showed a relatively strong nOe between the resonance due to the benzylic methylene group and the resonance due to the *ortho*-hydrogen (relative to *N*5) of the benzo moiety (Scheme 52).[72]

The reactions of **97a** with acetic anhydride, benzoyl chloride, and *p*-tolyl isocyanate all occurred selectively at *N*1 to give the acylated products **97h-j** shown in Scheme 53 and (Table 28).[72]



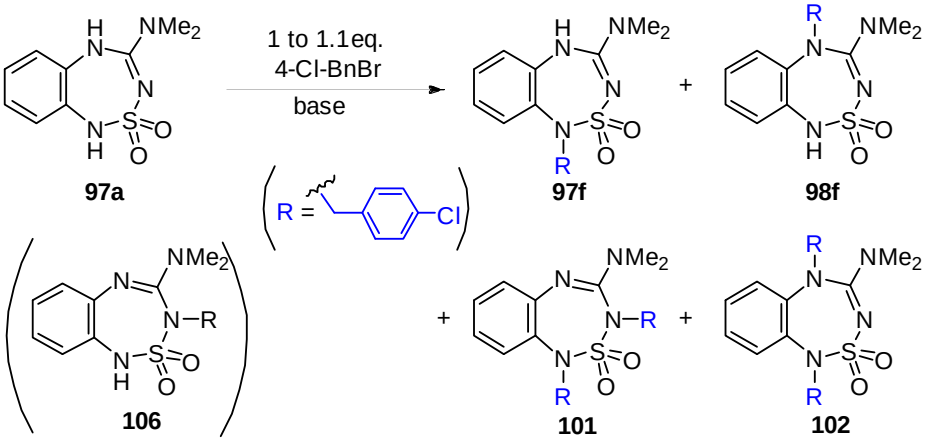
Scheme 53

Table 28. Synthesis of the acylated benzothiatriazepine dioxides **97h-j**

R	Method	Product	Yield (%)
CH_3	$(CH_3CO)_2O$, pyridine, 20 ºC	**97h**	69
Ph	PhCOCl, pyridine, 20 ºC	**97i**	49
4-CH_3-C_6H_4NH	4-CH_3-C_6H_4NCO, cat. NEt_3, CH_2Cl_2, 20 ºC	**97j**	76

The structural assignments were based on X-ray crystallographic analyses of the benzoylated product **97i** and the isocyanate adduct **97j**. As with **97f** (above), **97j** crystallises in a non-centrosymmetric space group $P2_12_12_1$ and has only the one enantiomorph (A in Figure 4) present in the crystal.[72]

Alkylation of **97a** with 1 to 1.1 molar equivalents of 4-chlorobenzyl bromide under basic conditions was not selective and mixtures of mono- and di-alkylated products were obtained from a variety of reaction conditions (Scheme 54, Table 29). Aqueous sodium hydroxide, dichloromethane, and a phase transfer catalyst resulted in predominant formation of the 1,3-bis(4-chlorobenzyl) product **101** along with minor proportions of the 1,5-bis(4-chlorobenzyl) product **102** and the *N*1 monosubstituted derivative **97f**. Potassium carbonate in DMF afforded a similar product mixture, with an additional product, the *N*5 monosubstituted derivative **98f**, being isolated in very low yield. Formation of an *N*-anion with 1.1 molar equivalents of sodium hydride in THF/DMF, followed by addition of 4-chlorobenzyl bromide, resulted in the *N*1 monosubstituted derivative **97f** as the major product, along with a significant proportion of the 1,3-bis substituted product **101**, and minor proportions of **98f** and **102**.[72]



Scheme 54

Table 29. Alkylation products from the benzothiatriazepine dioxide **97a**

Method	Product		Yields (%)	
	97f	**98f**	**101**	**102**
NaOH, cat. *n*-Bu_4NBr, CH_2Cl_2, H_2O, 20 ºC	4	-	41	2
K_2CO_3, cat. *n*-Bu_4NBr, DMF, 20 ºC	8	4	36	2
NaH, THF/DMF (2:1), 20 ºC	31	5	23	3

These results suggest that initial alkylation probably occurs at *N*1 and that the resulting compound **97f** is more susceptible to alkylation than the starting material **97a**.

The structural assignments for **98f**, **101**, and **102** were made on the basis of their ^{1}H NMR spectra and insights gained from other alkylation experiments; specifically the distinctive chemical shifts of the benzylic methylene group resonances.[72]

Successful construction of the benzo[*f*][1,2,3,5]oxathiadiazepine and benzo[*e*][1,2,4,7]thiatriazepine rings from 2-aminophenols and 1,2-diaminobenzenes, respectively, encouraged an investigation of the analogous reaction with 2-aminothiophenols. However, reaction of dichloride **1a** with 2-aminothiophenol (Hünig's base/DMPU) afforded a complex mixture of products. The only compound isolated from chromatographic purification was the known 2-(*N,N*-dimethylamino)benzo[*d*]thiazole.[75]

4. Properties of Heterocyclic Ring Systems from the Dichlorides 1

4.1 Stability and physical properties

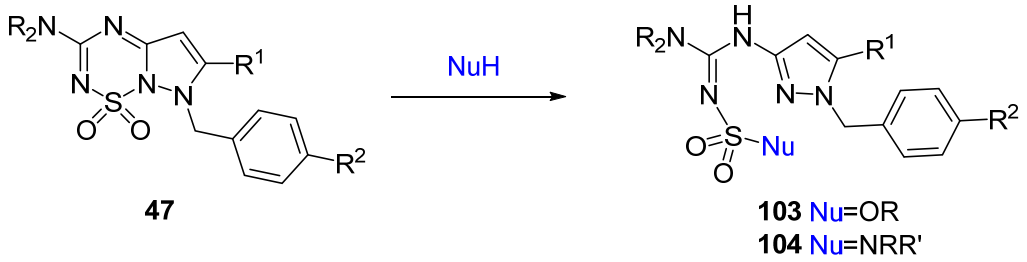
Generally, the heterocyclic systems generated from dichlorides **1** were stable, colorless, crystalline solids. Samples of many of these compounds showed no signs of decomposition after being stored for months, or in some cases years, at room temperature.

In general, the compounds had moderate solubility in chloroform and dichloromethane, but much lower solubility in either ethyl acetate or diethyl ether. Amongst the products most soluble in organic solvents were the pyrazolo-oxathiadiazine dioxides **69** and **71** (Section 3.2.3, Scheme 41) and the fused dithiadiazine dioxides **64**, **66**, and **67** (Section 3.2.2, Schemes 38 and 39). Amongst the least soluble ring systems were the pyrano-oxathiazine dioxides **77** (Section 3.2.4, Scheme 43) and the pyridazo-thiatriazine dioxides **33** (Section 3.2.1, Scheme 19). Derivatives of some ring systems bearing small substituents showed significant water-solubility; for example, *N*-methylated pyrazolo-thiadiazines **84** and **85** (Section 3.2.5, Scheme 46).[67]

The crystallinity of the majority of these ring systems allowed convenient production of high quality crystals for X-ray crystallographic analysis; a fortunate feature, since structural elucidation via conventional spectroscopic analysis proved ambiguous.

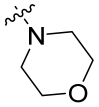
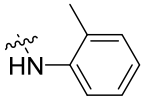
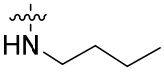
In the vast majority of cases, the products were unaffected by recrystallization from boiling alcohols. However, there were some exceptions. Chloro-substituted pyrido-thiatriazines **30a**, **30g**, and **31g** (Section 3.2.1, Scheme 18, Table 8) showed some signs of partial decomposition during recrystallization trials. After repeated cycles of dissolution and evaporation involving heating in various solvents, some additional signals appeared in the ^{1}H NMR spectra of these three compounds.[37] Similar observations were made with [1,2,4]triazolo[4,3-*b*]-[1,4,2,6]dithiadiazines **67**.[51] Urazole adducts, [1,2,4]triazolo[1,2-*b*][1,2,3,5]thiatriazoles **13** (Section 3.1.1, Scheme 12), were not stable to attempted recrystallization from methanol or ethanol. After boiling in these solvents, significant decomposition was observed by NMR spectroscopy. Nevertheless, recrystallization to analytical purity was possible from isopropanol or isopropanol/acetone mixtures.[31]

7-Substituted-pyrazolo[1,5-*b*][1,2,4,6]thiatriazines **47** displayed a strong tendency for cleavage of the thiatriazine ring by alcoholysis to produce sulfamate derivatives **103** (Scheme 55).[50] Results are summarized in (Table 30).



Scheme 55

Table 30. Formation of sulfamates **103** and sulfamides **104** via thiatriazine ring cleavage

Product	R	R^1	R^2	Nu	Conditions	Yield (%)
103a	Et	Thien-2-yl	OMe	EtO	EtOH, rt, 16h	65
103b			Cl	EtO	EtOH, rt, 25h	71
103c		Ph	Cl	EtO	MeOH, rt, 21h	70
103d	Me	Me	H	MeO	MeOH, rt, 21h	99
104a	Et	Ph	Cl		1.5 equiv. morpholine, MeCN, reflux, 1h	42
104b			Cl		2 equiv. o-toluidine, MeCN, reflux, 2h	66
104c		Thien-2-yl	Cl		1.5 equiv. *n*-butylamine, MeCN, 50 °C, 45min	71

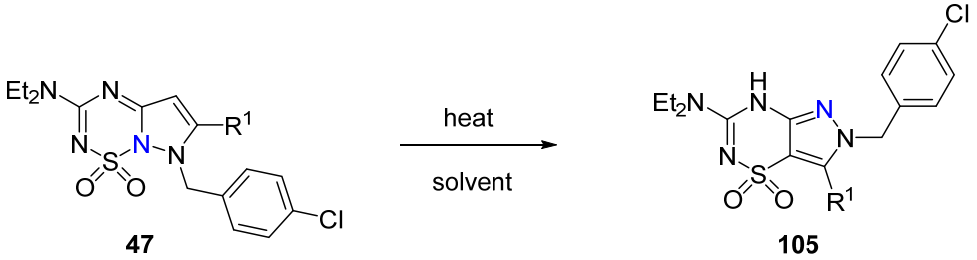
The susceptibility of the sulfamide group in compounds **47** to nucleophilic attack was further demonstrated by reactions with amine nucleophiles. Sulfamides **104a-c** were produced from treatment of N7-benzyl substrates **47** with primary and secondary amines in acetonitrile (Scheme 55, Table 30). The structures of these compounds were confirmed by X-ray crystallography of **104a**.[50]

The susceptibility of *N*7-benzyl-pyrazolo[1,5-*b*][1,2,4,6]thiatriazines **47** to alcoholysis was discovered during attempted cleavage of the benzyl group using hydrogen and catalytic amounts of activated palladium in alcohols. Ethyl acetate as an alternative solvent afforded the debenzylated pyrazolo-thiatriazines **40**, except with substrates containing a thiophene moiety, which appeared to poison the palladium catalyst.[76,77] Hydrogenolysis of **47** to **40** was also achieved in *tert.*-butanol;[50] presumably the tertiary alcohol was too sterically hindered for

alcoholysis of the thiatriazine ring. The reaction rate was faster than in ethyl acetate, consistent with literature reports[78] describing the lower efficiency of H_2 uptake in ethyl acetate compared to alcohols.

[1,2,4]Triazolo[4,3-*b*][1,4,2,6]dithiadiazines **67** were not stable under acidic conditions and isomerized to the more stable isomeric ring system, [1,2,4]triazolo[1,5-*b*]-[1,4,2,6]dithiadiazines **66**, via dithiadiazine ring cleavage (see Section 3.2.2, Scheme 40). The N7-benzylated pyrazolo[1,5-*b*][1,2,4,6]thiatriazines **47** were also not stable to acidic conditions, under which extrusion of the SO_2 moiety occurred to afford pyrazolo-guanidines.[43,47,50] The parent pyrazolo[1,5-*b*][1,2,4,6]thiatriazines **40** required more forcing acidic conditions (heating) to cleave the thiatriazine ring and furnish pyrazolo-guanidines (Scheme 36).[50]

7-Substituted-pyrazolo[1,5-*b*][1,2,4,6]thiatriazines **47** were not stable to heat and thermally decomposed, except in the case of compounds bearing *both* 6-aryl and 7-benzyl substituents, which underwent a clean thermal rearrangement reaction to produce 7-aryl-6-benzyl-pyrazolo[3,4-*e*][1,2,4]thiadiazines **105** in high yield (Scheme 56). This unusual reaction was studied in a range of solvents (Table 31).[50]



Scheme 56

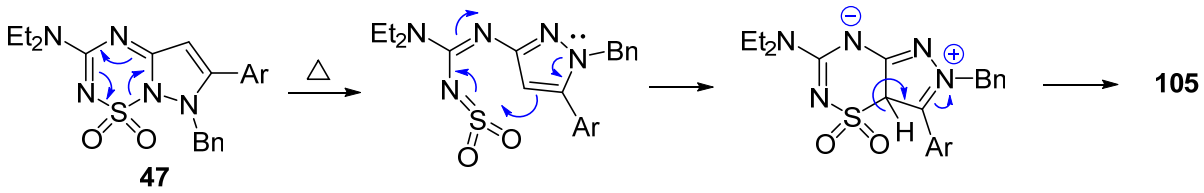
Table 31. Thermal rearrangement of 7-benzylated pyrazolo[1,5-*b*][1,2,4,6]thiatriazines **47** to 6-benzylated pyrazolo[3,4-*e*][1,2,4]thiadiazines **105**

Entry	R^1	Conditions	Product	Yield (%)
1	Thien-2-yl	Dioxane, reflux, 4 h	**105a**	99
2		MeCN, reflux, 14.5 h	**105a**	82
3		Toluene, reflux, 46 h	**105a**	79
4		EtOAc, reflux, 44 h	**105a**	74
5	Ph	Dioxane, reflux, 8 h	**105b**	88
6		EtOAc, reflux, 48 h	**105b**	83

There did not appear to be a clear correlation between product yields and solvent polarity; however, higher solubility of the starting material did enable shorter reaction time (Entries 1, 2,

and 5).[50]

The rearrangement was only observed with substrates which contained *both* N7-benzyl *and* C6-aryl groups, indicating that cleavage of the sulfamide bond in pyrazolo-thiatriazines **47** is facilitated by this substitution pattern. A possible mechanism for formation of compounds **105** is presented in Scheme 57.[50]



Scheme 57

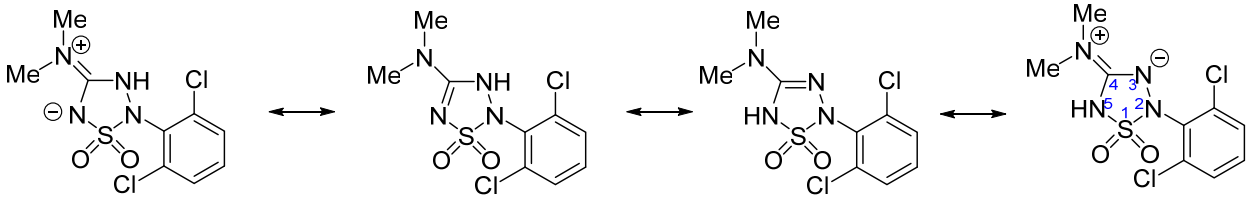
Interestingly, the 4-substituted isomers **49** and the unsubstituted pyrazolo[1,5-*b*][1,2,4,6]thiatriazines **40** were stable to heating.[50]

Products resulting from pyrazole ring expansion, pyrimido[1,6-*b*][1,2,4,6]thiatriazine dioxides **55** (Scheme 29, Table 14) and pyrimido[4,5-*e*][1,2,4]thiadiazine dioxides **89** (Scheme 47, Table 23), gradually decomposed when stored in solution or in air. Heating (and lengthy reaction times during synthesis) accelerated the decomposition of the ring-expanded compounds, which were also not stable under acidic conditions.[47,67]

4.2 Spectral properties

A frequent observation throughout this body of work was a differentiation between, or significant broadening of, the ^{1}H NMR signals attributable to the methyl or methylene groups flanking the nitrogen atom of the dialkylamino substituent on the newly formed ring. In some cases, these phenomena were accompanied by a significant broadening, or occasionally a virtual absence, of the ^{13}C NMR signals attributable to these groups. These effects are most likely to be a consequence of relatively slow (on the NMR time scale) tautomerism as well as contribution from zwitterionic species which restricts free rotation of the exocyclic dialkylamino substituent.

An example of such tautomeric forms, for 4-dimethylamino-[1,2,3,5]thiatriazole **5c**, is shown in (Scheme 58).[26]



Scheme 58

Variable temperature NMR spectroscopic studies on **5c** supported this conclusion. The ^{1}H NMR spectrum showed a sharpening of the Me_2N signal at higher temperatures (55 °C) and resolution into two distinct singlets upon cooling (-13 °C). In compounds where there is no N-H moiety on the thiatriazole ring, as in analogues **5g-l**, strong and distinct resonances for the methyl or methylene groups adjacent to the nitrogen substituent at C4 were observed.[26]

There was a consistent trend in ^{1}H NMR spectroscopic properties that helped to distinguish between the isomer pairs, pyrido-thiatriazines **30**/**31** and pyridazo-thiatriazines **33**/**34**. The alkyl groups of the exocyclic dialkylamino function were non-equivalent in all derivatives **30** and **34**, while the same alkyl groups in compounds **31** and **33** were equivalent.[37]

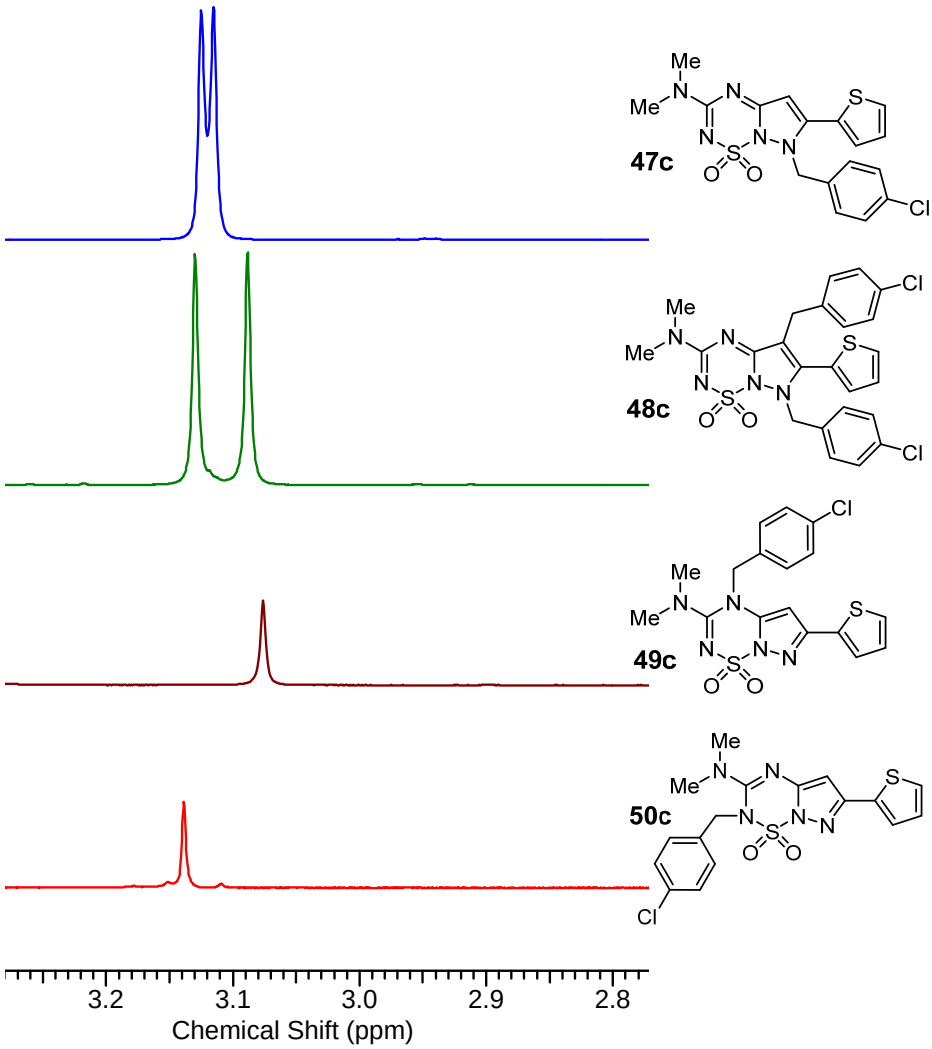


Figure 5. Dimethylamino resonances in the 400 MHz ^{1}H NMR spectra of **47-50c**.[47]

A consistent trend between the site of benzylation and the NMR signals corresponding to the protons on the exocyclic dialkylamino substituent was observed in pyrazolo-thiatriazines **47-**

50 (Figure 5). Products **47** and **48** which contain benzyl groups on the pyrazole ring showed different NMR environments for each alkyl group of the dialkylamino moiety. Products containing benzyl substituents on N4 and N2 positions (compounds **49** and **50**) presented single, broad signals for the two alkyl groups, representing an average of two environments. These trends were used to assist with structural assignment.[47]

Compound **34b** (Figure 6) showed interesting behaviour during a study by NMR spectroscopy. In the ^{1}H NMR spectrum initially recorded in $CDCl_3$ solution at 25 ºC, two separate sets of resonances attributable to each of the two aromatic hydrogens on the pyridazine ring, the benzylic methylene group, and the *N*-methyl group were observed. This twin resonance effect was observed in $CDCl_3$, DMSO-d_6, C_6D_6, and acetone-d_6, but the integration ratios differed between solvents. The ^{13}C NMR spectrum in $CDCl_3$ also contained additional resonances. These observations led to the presumption that compound **34b** exists as two conformers that interconvert very slowly (on the NMR timescale).[37]

Variable temperature 500 MHz ^{1}H NMR studies of a solution of **34b** in DMSO-d_6 were undertaken in an attempt to clarify this presumption. However, the twin resonance phenomenon persisted at higher temperatures (up to 105 ºC) while further heating to 125 ºC and beyond caused chemical change.[37]

A 500 MHz gradient-selected NOESY two-dimensional 1H NMR spectrum of **34b** recorded in C_6D_6 was informative. Through-space mutual relaxations (NOEs) were observed between the pyridazine hydrogen resonances at δ 5.70 and 5.40 and also between those at δ 5.53 and 5.33, between the benzylic methylene resonance at δ 4.33 and the *N*-methyl resonance at δ 2.47 as well as the benzylic methylene resonance at δ 4.20 and the *N*-methyl resonance at δ 2.57. Exchange effects were observed between the pyridazine hydrogen resonances at δ 5.70 and 5.53, and between those at δ 5.40 and 5.33, between the benzylic methylene resonances at δ 4.33 and 4.20, and between the *N*-methyl resonances at δ 2.57 and 2.47. These exchange effects indicate chemical equivalence between the pairs of resonances (and therefore the protons themselves) but environmental (conformational) non-equivalence, with interconversion occurring between the two conformations in solution.[37]

In the ^{1}H NMR spectra of benzimidazo-fused dithiadiazines **64** (Figure 6), differentiation between the resonances attributable to the methyl or methylene groups flanking the nitrogen atom of the dialkylamino substituent was observed. In the case of the (*N*-methyl)benzylamino derivative **64e**, which is not symmetrical about the exocyclic C–N bond, two sets of *N*-methyl and benzylic methylene signals were observed in the ^{1}H NMR spectrum recorded in either $CDCl_3$ or DMSO-d_6 at 25 ºC. When the spectrum of **64e** was recorded in DMSO-d_6 at 100 ºC, both pairs of resonances coalesced to single signals. On cooling to 20 ºC, the resonances reverted to twin signals. The ^{13}C NMR spectra in $CDCl_3$ and DMSO-d_6 also contained additional resonances.[51]

Similarly, in the ^{1}H and ^{13}C NMR spectra of pyrano-oxathiazine **77c** (Figure 6), there were two separate resonances (of approximately equal integration) attributable to each of the vinylic, benzylic, pyrone-methyl, and *N*-methyl moieties. When the spectra were recorded at 140 ºC, all

of these resonances coalesced to single signals. Upon cooling to 20 ºC, the resonances reverted to twin signals (along with additional, minor resonances indicating some thermal decomposition). Similar behaviour was observed in the NMR spectra of **77h** and benzimidazo-fused thiatriazine **36f** (Figure 6), which also possess an *N*-methyl benzylamino moiety.

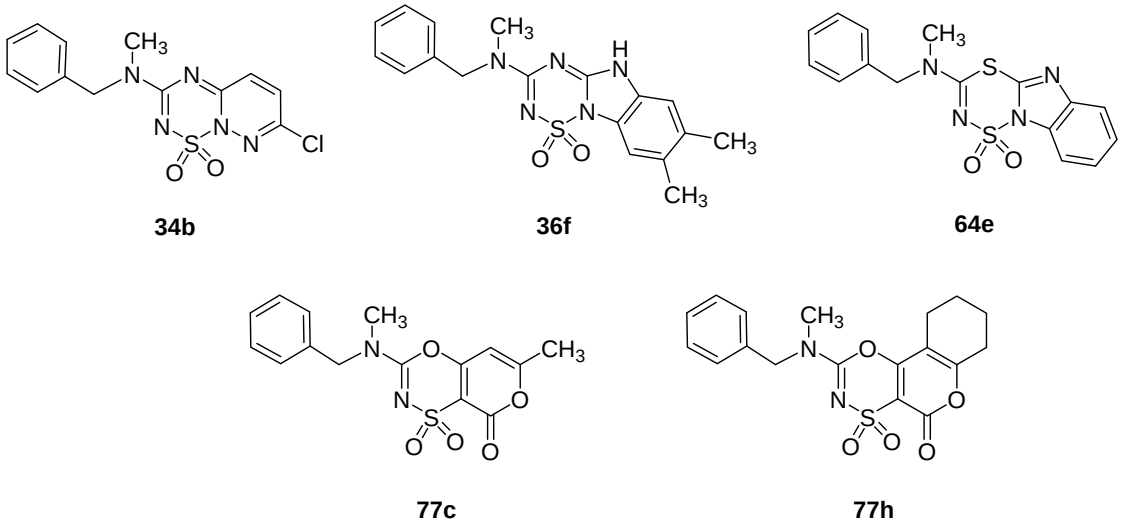


Figure 6. Structures of (*N*-methyl)benzylamino compounds **34b**, **36f**, **64e**, **77c**, and **77h**.

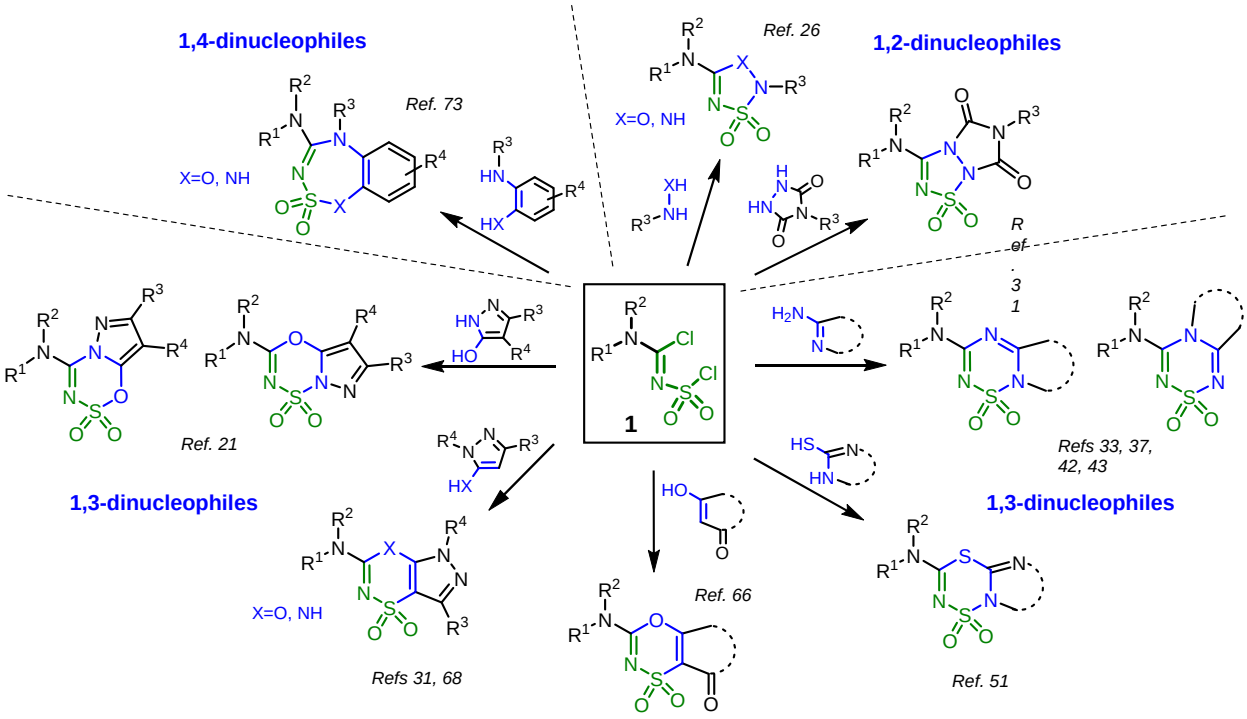
All of these observations indicated that the *N*-methyl benzylamino compounds **34b**, **36f**, **64e**, **77c**, and **77h** all exist as two conformers which interconvert slowly (on the NMR timescale) by rotation of the *N*-methyl benzylamino substituent.[42,65] The effect was most striking in the *N*-methyl benzylamino compounds, but occurred widely throughout the work, including compounds with a symmetrical exocyclic dialkylamino substituent.

5. Summary and Conclusions

The body of research described in this Account demonstrates the facility with which *N,N*-dialkyl *N*′-chlorosulfonyl chloroformamidines **1**, readily available 1,3-bis-electrophiles, act as versatile intermediates for the convenient synthesis of a cornucopia of new and uncommon nitrogen/sulfur heterocyclic ring systems. An overview of the types of ring systems produced from these unusual $^{\delta+}C{=}N{-}S^{\delta+}$ building blocks is presented in Scheme 59.

Dichlorides **1** have been shown to react with 1,2-dinucleophilic species to give new five-membered ring products[26] or with various 1,3-dinucleophilic species to provide a variety of novel or very rare fused [1,2,4,6]thiatriazines,[33,37,42,43] [1,4,2,6]dithiadiazines,[51] [1,2,3,5]- and [1,4,3,5]oxathiadiazines,[21] [1,4,3]oxathiazines,[31,65] and [1,2,4]thiadiazines.[67] Similar reactions of dichlorides **1** with 1,4-dinucleophiles afforded new seven-membered ring products.[72] Generally these compounds were stable, colorless, crystalline solids. Assignment of structures was based

on a combination of X-ray crystallographic analyses of representative compounds, 2D NMR experiments, and consistent trends in solubility properties and chromatographic behavior.



Scheme 59. Overview of ring systems produced from dichlorides **1**.

The regioselectivity of heterocycle formation was usually determined by the more nucleophilic site of the bis-nucleophile reacting with the amidinyl chloride moiety of **1** and the other nucleophilic atom bonding to the sulfamoyl moiety. Such outcomes clearly establish the amidinyl chloride moiety of **1** as the more reactive electrophilic site and provide a basis for prediction of the likely regioselectivity in reactions of **1** with other bis-nucleophiles.

Several of the ring systems produced from **1** bear one or more NH moieties which can undergo substitution reactions and most of these reactions were highly regioselective. For example, [1,2,3,5]thiatriazoles **5** and benzo[4,5]imidazo[1,2-*b*][1,2,4,6]thiatriazine **36b** both underwent regioselective acylation, alkylation, and sulfonylation; thiatriazoles **5** at N3 (Scheme 7)[26] and thiatriazine **36b** at N5 (Scheme 21).[42] Benzo[*f*][1,2,3,5]oxathiadiazepines **92** were regioselectively acylated at N5 (Scheme 50) whereas benzo[*e*][1,2,4,7]thiatriazepine **97a** underwent regioselective acylation at N1 (Scheme 53).[72]

The chemistry of the pyrazolo[1,5-*b*][1,2,4,6]thiatriazines **40** was particularly rich and interesting.[43,47,50] The unexpectedly high nucleophilicity of C5 and pyrazole ring-expansion reactions, as well as the ability to cleave the thiatriazine ring in controlled ways, allowed the generation of a diverse range of derivatives (Schemes 23 to 36, 55, and 56).

The substitution and other reactions outlined above illustrates the use of these ring systems as novel scaffolds for further elaboration which enables the ready production of screening libraries for a variety of potential medicinal chemistry applications.

Much has been achieved in this area but much still remains to be done. Further studies on the generation of new, related ring systems from dichlorides **1**, with an emphasis on producing products with reactive groups on the newly formed ring system (to introduce a diversity of substituents), are ongoing in our laboratories.

6. Acknowledgements

I am most grateful to a long-time colleague and mentor, Dr Andy Liepa, who first noted the potential of dichlorides **1** in the synthesis of new heterocycles. Many thanks also to Assoc. Prof. Mike Perkins at Flinders University, for enabling the continuation of this work in his laboratories and for his significant intellectual contributions. I warmly thank many hardworking colleagues who have made sizeable contributions to this work, particularly Mrs Teresa Cablewski, Dr Saba Jahangiri, and Dr Peter Duggan at CSIRO for synthetic work, and Dr Rebecca Norman at Flinders University for both synthetic chemistry and X-ray crystallography (with assistance from Dr Chris Sumby at The University of Adelaide). I am grateful to Assoc. Prof. Martin Johnston at Flinders University and Dr Roger Mulder at CSIRO for expert assistance with NMR spectroscopy, Mr Carl Braybrook and Dr Jo Cosgriff at CSIRO and Dr Daniel Jardine at Flinders University for mass spectrometry, and Dr Craig Forsyth at Monash University for much of the X-ray crystallography. Thanks also to DuPont Crop Protection and the Cooperative Research Centre for Cancer Therapeutics for financial support.

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Author's Biography

Dr. Craig Francis obtained his B.Sc. (First Class Honors) in 1987 at The University of Adelaide and qualified for his PhD at the same university in 1991, studying electrophile-initiated cyclization methodology for the synthesis of reduced quinolines related to virantmycin, under the supervision of Dr David Ward. He was a post-doctoral research fellow at The University of

Cambridge with Professor Andrew Holmes from 1991 to 1992, studying asymmetric synthesis of the unsaturated medium ring ether marine natural product obtusenyne. Dr Francis then returned to Australia to join the Commonwealth Scientific and Industrial Research Organization (CSIRO) as a post-doctoral research fellow with Dr Andy Liepa in 1993. Over the following decade he rose up through the ranks and became a Principal Research Scientist in 2004.

Dr Francis' time at CSIRO has been mostly spent applying synthetic organic chemistry, particularly heterocyclic chemistry, to the field of bioactive molecule discovery and development, in a wide variety of discovery, medicinal chemistry, and process development projects. These projects have been in collaboration with several industrial partners in the pharmaceutical, animal health, and crop protection sectors.

His other abiding interest is in the development of synthetic methodology for novel or uncommon heterocyclic ring systems.

