Nitrile sulfides. Part 13.[1] Synthesis of 5-acyl-1,2,4-thiadiazoles by cycloaddition of nitrile sulfides to acylcyanides

Marion C. McKie and R. Michael Paton*

[a] *Department of Chemistry, The University of Edinburgh, West Mains Road, Edinburgh, EH9 3JJ, UK*
E-mail: R.M.Paton@ed.ac.uk

Dedicated to Professor C. W. Rees on the occasion of his 75th birthday

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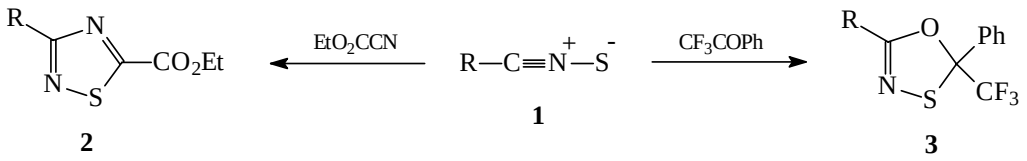
Abstract

The periselectivity of the nitrile sulfide cycloaddition to acyl cyanides has been examined. Benzonitrile sulfide, generated by thermal decarboxylation of 5-phenyl-1,3,4-oxathiazol-2-one, reacted exclusively at the cyano group of benzoyl cyanide to afford 5-benzoyl-3-phenyl-1,2,4-thiadiazole. Similar perispecificity was observed with *p*-toluonitrile sulfide and acetonitrile sulfide, and for cycloaddition of benzonitrile sulfide to 2-furoyl cyanide, acetyl cyanide and 2-oxooctanonitrile. The reactivity of benzoyl cyanide as a dipolarophile was shown to be similar to that of ethyl cyanoformate in a competition experiment which afforded a 51:49 mixture of 5-benzoyl- and 5-ethoxycarbonyl-3-phenyl-1,2,4-thiadiazoles.

Keywords: 1,2,4-Thiadiazole, 1,3-dipolar cycloaddition, nitrile sulfide

Introduction

Nitrile sulfides ($R\text{-}C{\equiv}N^{+}\text{–}S^{-}$)[2] are known to undergo 1,3-dipolar cycloaddition reactions with nitriles and aldehydes/ketones, provided the dipolarophiles are activated by electron-withdrawing substituents. Thus *p*-methoxybenzonitrile sulfide (**1**, R = 4-$MeOC_6H_4$) reacts readily with ethyl cyanoformate[3] and α,α,α-trifluoroacetophenone[4] to afford the 1,2,4-thiadiazole **2** and 1,3,4-oxathiazole **3** (Scheme 1). acyl cyanides **4** are therefore of particular interest as they possess two potential dipolarophiles that are mutually activating. Cycloaddition reactions with nitrile sulfides could therefore yield 5-acyl-1,2,4-thiadiazoles **5** and/or 1,3,4-oxathiazoles **6** (Scheme 2). To test the periselectivity of this process, typical nitrile sulfides (**1**; R = Ph, 4-$MeOC_6H_4$, Me) were reacted with a range of acyl cyanides.

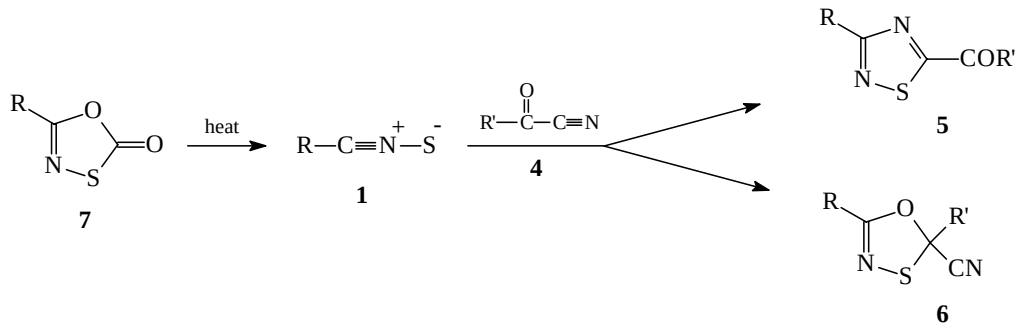


Scheme 1. R = 4-$MeOC_6H_4$.

Results and Discussion

As nitrile sulfides are short-lived species, for preparative purposes they are usually generated *in situ* in the presence of the dipolarophile. For the present work the selected sources were 1,3,4-oxathiazol-2-ones **7**, which are both shelf-stable at ambient temperature and readily accessible from the corresponding carboxamide by treatment with chlorocarbonylsulfenyl chloride.[5] The nitrile sulfides were then generated from the oxathiazolone by thermal decarboxylation at 130-160 °C.[5]

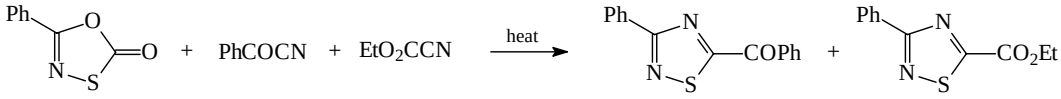
The procedure is illustrated for the reaction of benzonitrile sulfide **1a** with benzoyl cyanide. A solution of phenyloxathiazolone **7a** (10 mmol) and benzoyl cyanide (40 mmol) in dry xylene (25 ml) was heated under reflux until HPLC analysis indicated complete consumption of the oxathiazolone (~20 h). The solvent and excess dipolarophile were removed by distillation under reduced pressure to afford an oil from which 5-benzoyl-3-phenyl-1,2,4-thiadiazole **4ad** (91%) was obtained by crystallisation from ethanol (Table 1, entry 1). There was no evidence (HPLC) for the formation of the isomeric 1,3,4-oxathiazole **6ad**.



Scheme 2. [a]R = Ph, [b]R = 4-MeC_6H_4, [c]R = Me; [d]R' = Ph, [e]R = 2-furoyl, [f]R = Me, [g]R = $CH_3(CH_2)_5$.

p-Tolunitrile sulfide **1b** and benzoyl cyanide reacted similarly affording thiadiazole **5bd** (78%, 88% by HPLC), together with *p*-toluonitrile and sulfur (12%) (Table, entry 2). The formation of sulfur and nitrile by-products is a common feature of nitrile sulfide reactions[2,5] and is attributed to fragmentation of the nitrile sulfide competing with cycloaddition. A lower yield

of adduct **5cd** (27%) was obtained for acetonitrile sulfide. The reaction of benzonitrile sulfide with 2-furoyl cyanide, acetyl cyanide and 2-oxooctanonitrile was also examined and, using a 1:1 reactant ratio, thiadiazoles **5ae** (77%), **5af** (60%) and **5ag** (17%) were isolated (Table, entries 4-6). The yields of cycloadducts (77-91%) obtained from arenenitrile sulfides **1a**/**1b** with aroyl cyanides **4d**/**4e** are much greater than those reported[6] for the corresponding reaction with aryl cyanides, thus demonstrating the activating effect of the acyl substituent on the reactivity of the cyano group towards this class of 1,3-dipoles. Similar yields of adducts have been reported for other activated nitriles including ethyl cyanoformate[3] and trichloroacetonitrile.[7] To establish the relative reactivities of benzoyl cyanide and ethyl cyanoformate a competition experiment was performed using a 9:9:1 mixture of PhCOCN, EtO_2CCN and oxathiazolone **7a** (Scheme 3); HPLC analysis of the product mixture showed that the two dipolarophiles had near identical reactivity with the ratio of thiadiazoles **5ad**:**8** being 51:49.



7a **5ad** **8**

Scheme 3

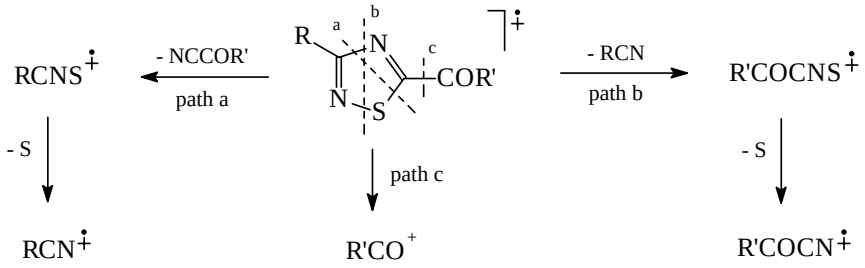
Table 1. Cycloaddition of nitrile sulfides to acyl cyanides

Entry	Oxathiazolone	Acyl cyanide	Reactant ratio	Cycloadduct	Yield / %
1	**7a**	**4d**	4:1	**5ad**	91
2	**7b**	**4d**	4:1	**5bd**	78 (88%)[a]
3	**7c**	**4d**	4:1	**5cd**	27
4	**7a**	**4e**	1:1	**5ae**	77
5	**7a**	**4f**	1:1	**5af**	60
6	**7a**	**4g**	1:1	**5ag**	17

[a] Yield determined by HPLC.

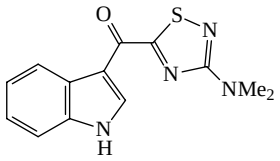
The products are readily identifiable from their spectroscopic properties, which are broadly similar to those of other 1,2,4-thiadiazoles.[8] Their ^{13}C NMR spectra show characteristic peaks for the heterocyclic ring carbons at 174-175 and 185-187 ppm, which were assigned to C-5 and C-3, respectively, with the aid of fully coupled spectra; the signals for the acyl carbon range from 169 to 194 ppm depending on the substituent. The mass spectra show, in addition to the parent ion, peaks attributable to RCNS, RCN and R'COCN, thus suggesting major fragmentation pathways involving cycloreversion to the 1,3-dipole and dipolarophile by cleavage at C(3)-

N(4)/C(5)-S(1) (Scheme 4, path a) and cleavage at S(1)-N(2)/C(3)-N(4) (path b).[8] There are also prominent peaks for the acyl fragment R'CO (path c).



Scheme 4

The only previous example of a nitrile sulfide reacting with an acyl cyanide involved generation of dimethylaminoformonitrile sulfide in the presence of α-oxoindole-3-acetonitrile yielding dendrodoine **9**. [9] The periselectivity of the acyl cyanide reactions observed in this work and in the literature[9] may be attributed to steric and/or electronic effects. Similar selectivity is observed for the reaction of nitrile sulfides with tetracyanoethylene.[10] The major products were 5-alkenyl-1,2,4-thiadiazoles **10** resulting from cycloaddition to one of the nitrile substituents; there was no evidence for reaction at the alkene groups. Likewise the cycloaddition reactions of benzonitrile oxide with acetyl and benzoyl cyanides are also reported to occur exclusively at the nitrile moiety.[11]



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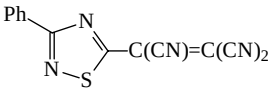

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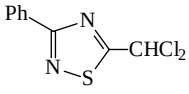

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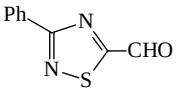

12

We have previously shown[7] that trichloroacetonitrile, in contrast to simple aliphatic nitriles, is a reactive dipolarophile towards nitrile sulfides, and it was therefore of interest to examine the corresponding reaction with dichloroacetonitrile. Heating a 1:1 mixture of oxathiazolone **7a** and Cl_2CHCN in xylene afforded the expected 5-dichloromethylthiadiazole **11** in 41% yield; and using an excess of Cl_2CHCN the yield rose to 54%, *ie* comparable with that observed for trichloroacetonitrile. In contrast, the corresponding reaction with dibromoacetonitrile led only to black tars.

Having established a straightforward and high-yielding route to the 5-dichloromethyl compound **11**, the possibility of converting it into the 5-formyl derivative **12** was examined. However, attempted hydrolysis afforded only traces of carbonyl-containing products, and the major component of the crude product was sulfur (*m/z* 256).

In conclusion, the acyl group activates the C≡N of acyl cyanides for cycloaddition reactions with nitrile sulfides, and 5-acyl-1,2,4-thiadiazoles can therefore be prepared from their readily accessible oxathiazolone precursors.

Experimental Section

General Procedures. The analytical methods for monitoring the reactions and the instruments used for recording IR, ^{1}H and ^{13}C NMR, and mass spectra were as previously described.[12] The 1,3,4-oxathiazol-2-ones **7a-c** were prepared by treatment of the corresponding carboxamide with chlorocarbonylsulfenyl chloride using the established literature procedure.[5]

General procedure for preparation of 5-acyl-1,2,4-thiadiazoles (5)
A solution of the oxathiazolone **7** and the acyl cyanide in dry xylene was heated under reflux until HPLC analysis showed that all of the oxathiazolone had been consumed (*ca* 20 h) (for reactant ratio see Table). After removal of the solvent and unreacted acyl cyanide by distillation under reduced pressure, the products were purified by chromatography (silica; CH_2Cl_2/hexane, gradient elution), sublimation and/or recrystallisation from ethanol.

5-Benzoyl-3-phenyl-1,2,4-thiadiazole (5ad). (91%), mp 91-92 °C (from ethanol) (Found: C, 67.6; H, 3.7; N, 10.4. $C_{15}H_{10}N_2OS$ requires C, 67.7; H, 3.8; N, 10.5%); ν_{max}(Nujol)/cm^{-1} 1635 (C=O), 1590, 1575 (C=N); ^{1}H NMR: δ 8.4-8.2, 7.5-7.3 (10H, m, PhH); ^{13}C NMR: δ 187.0 (C-5), 182.8 (C=O), 174.3 (C-3), 134.0, 132.3 (PhC), 134.5, 131.6, 130.6, 128.7, 128.6, 128.2 (PhCH); *m/z* 266 (M^+), 163 [(*M*-PhCN)$^+$], 135 (PhCNS$^+$), 105 (PhCO$^+$), 103 (PhCN$^+$). Sulfur (4%) was also isolated.

5-Benzoyl-3-(4-methylphenyl)-1,2,4-thiadiazole (5bd). (78% isolated, 88% by HPLC), mp 103-105 °C (from ethanol) (Found: C, 68.7; H, 4.3; N, 10.0. $C_{16}H_{12}N_2OS$ requires C, 68.6; H, 4.3; N, 10.0%); ν_{max}(Nujol)/cm^{-1} 1635 (C=O), 1590, 1575 (C=N); ^{1}H NMR: δ 8.7-8.5, 7.7-7.5 (5H, m, PhH), 8.24 (2H, d, *J* = 8.0 Hz, ArH), 7.27 (2H, d, *J* = 8.0 Hz, ArH), 2.40 (3H, s, CH_3); ^{13}C NMR: δ 186.8 (C-5), 182.7 (C=O), 174.4 (C-3), 140.8, 134.4, 134.0 (ArC), 131.0, 129.6, 129.3, 128.5, 128.1 (PhCH), 21.3 (CH_3); *m/z* 280 (M^+), 149 ($MeC_6H_4CNS^+$), 131 (PhCOCN$^+$), 117 ($MeC_6H_4CN^+$), 105 (PhCO$^+$). Sulfur (12%) was also isolated.

5-Benzoyl-3-methyl-1,2,4-thiadiazole (5cd). (27%), mp 71-72 °C (from ethanol) (Found: *m/z* 204.0357, $C_{10}H_8N_2OS$ requires *M* 204.03573); ν_{max}(Nujol)/cm^{-1} 1638 (C=O), 1590, 1573 (C=N); ^{1}H NMR: δ 8.6-8.4, 7.6-7.4 (5H, m, PhH), 2.79 (3H, s, CH_3); ^{13}C NMR: δ 186.7 (C-5), 182.9 (C=O), 174.6 (C-3), 134.1 (PhC), 134.4, 130.9, 128.5 (PhCH), 19.0 (CH_3); *m/z* 204 (M^+), 131 (PhCOCN$^+$), 105 (PhCO$^+$), 73 (MeCNS$^+$). Sulfur (12%) was also isolated.

5-(2-Furoyl)-3-phenyl-1,2,4-thiadiazole (5ae). (77%), m.p. 147.5-148 °C (from ethanol and sublimation) (Found: C, 60.7; H, 3.0; N, 10.7. $C_{13}H_8N_2OS$ requires C, 60.9; H, 3.1; N, 10.9%); ν_{max}(Nujol)/cm^{-1} 1630 (C=O), 1558 (C=N); ^{1}H NMR: δ 8.4-8.2 (3H, m, PhH), 7.84 (1H, dd, *J* = 1.7, 0.7 Hz, furyl 5-H), 7.6-7.4 (3H, m, PhH & furyl 3-H), 6.70 (1H, dd, *J* = 4.0, 1.7 Hz, 4-H);

^{13}C NMR: δ 185.7 (C-5), 174.3 (C-3), 169.4 (C=O), 149.1 (furan C-1), 149.7, 125.3, 113.0 (furan CH), 132.1 (PhC), 130.7, 128.7, 128.1 (PhCH); *m/z* 256 (M^+), 135 ($PhCNS^+$), 121 ($furylCOCN^+$), 103 ($PhCN^+$), 95 ($furylCO^+$). Sulfur (19%) was also isolated.

5-Acetyl-3-phenyl-1,2,4-thiadiazole (5af). (60%), mp 92-93 °C (from ethanol and sublimation) (Found: *m/z* 204.0357, $C_{10}H_8N_2OS$ requires *M* 204.03573); ν_{max}(Nujol)/cm^{-1} 1690 (C=O), 1600 (C=N); ^{1}H NMR: δ 8.4-8.2, 7.6-7.4 (5H, m, PhH), 2.81 (3H, s, CH_3); ^{13}C NMR: δ 190.7 (C=O), 185.9 (C-5), 174.4 (C-3), 132.0 (PhC), 130.7, 128.6, 128.1 (PhCH), 26.8 (CH_3); *m/z* 204 (M^+), 135 ($PhCNS^+$), 103 ($PhCN^+$), 69 ($MeCOCN^+$), 43 ($MeCO^+$). Sulfur (9%) and benzonitrile (10%, HPLC) were also formed.

5-Heptanoyl-3-phenyl-1,2,4-thiadiazole (5ag). (18%), m.p. 29-30 °C (from ethanol) (Found: *m/z* 274.1141, $C_{15}H_{18}N_2OS$ requires *M* 274.11398); ν_{max}(Nujol)/cm^{-1} 1690 (C=O); ^{1}H NMR: δ 8.4-8.2, 7.6-7.4 (5H, m, PhH), 3.22 (2H, t, *J* = 7.2 Hz, $COCH_2$), 1.81 (2H, m, CH_2), 1.7-1.2 (6H, m, CH_2), 0.90 (3H, t, *J* = 6 Hz); ^{13}C NMR: δ 193.3 (C=O), 186.1 (C-5), 174.4 (C-3), 132.2 (PhC), 130.6, 128.7, 128.2 (PhCH), 39.4, 31.4, 28.7, 28.4, 22.3 (CH_2), 13.9 (CH_3); *m/z* 274 (M^+), 135 ($PhCNS^+$), 113 ($C_6H_{13}CO^+$), 103 ($PhCN^+$). Sulfur (24%) was also isolated.

Thermolysis of oxathiazolone 4a in the presence of benzoyl cyanide and ethyl cyanoformate A mixture of 5-phenyl-1,3,4-oxathiazol-2-one **7a** (0.178 g, 0.99 mmol), benzoyl cyanide (1.19 g, 9.1 mmol) and ethyl cyanoformate (0.90 g, 9.1 mmol) was heated at 140 °C for 12 h. HPLC analysis of the reaction mixture gave the product ratio of 5-benzoyl-3-phenyl-1,2,4-thiadiazole **5ad** to ethyl 3-phenyl-1,2,4-thiadiazole-5-carboxylate **8** as 51:49.

Preparation of 5-dichloromethyl-3-phenyl-1,2,4-thiadiazole (11). A solution of oxathiazolone **7a** (1.79 g, 10.0 mmol) and dichloroacetonitrile (1.1 g, 10.0 mmol) in dry xylene (20 ml) was heated under reflux for 21 hours. Removal of the solvent *in vacuo* afforded yellow oil, which solidified on standing. The solid was washed with chloroform and the residual sulfur (112 mg, 35%) removed by filtration. The filtrate was evaporated to dryness and the residue sublimed to afford 5-dichloromethyl-3-phenyl-1,2,4-thiadiazole **11** as white needles (978 mg, 41%), m.p. 63-64 °C (from ethanol) (Found: *m/z* 247.9566, $C_9H_6{}^{37}Cl_2N_2S$ requires *M* 247.95697; *m/z* 245.9595, $C_9H_6{}^{37}Cl^{35}Cl\ N_2S$ requires *M* 245.95992; *m/z* 243.9628, $C_9H_6{}^{35}Cl_2N_2S$ requires *M* 243.96287); ^{1}H NMR: δ 8.3-8.1, 7.8-7.6 (5H, m, PhH), 7.02 (1H, s, $CHCl_2$); ^{13}C NMR: δ 185.9 (C-5), 173.6 (C-3), 132.0 (PhC), 130.7, 128.7, 128.2 (PhCH), 63.9 ($CHCl_2$); *m/z* 248, 246, 244 (M^+), 135 ($PhCNS^+$), 103 ($PhCN^+$). The experiment was repeated using excess dichloroacetonitrile (10:1) to afford **11** in 54% yield.

Attempted conversion of thiadiazole 9 to 5-formyl-3-phenyl-1,2,4-thiadiazole (12). A mixture of 5-dichloromethyl-3-phenyl-1,2,4-thiadiazole **11** (247 mg, 1.0 mmol), conc. aq. NaOH (10 mL) and ethanol (10 mL) was heated under reflux for 1 hour. The ethanol was removed *in vacuo*, the mixture neutralised with H_2SO_4, and extracted with Et_2O. Evaporation of the solvent afforded a yellow solid (103 mg), ν_{max}(Nujol)/cm^{-1} 1700 (C=O); ^{1}H NMR: δ 10.2 (CH=O); *m/z* 256 (S_8), 64 (S_2); negative Brady's test. Little or no reaction was observed on treatment of

thiadiazole **11** with 5% aq. $NaHCO_3$, or KOH/EtOH, or NaOH/EtOH at ambient temperature. In each case the starting material was recovered unchanged.

Acknowledgements

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