Recent progress in the synthesis of heterocyclic natural products by the Staudinger/intramolecular aza-Wittig reaction

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Dedicated to Dr. Nitya Anand on the occasion of his 80th birthday

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Abstract

A review of recent progress in the synthesis of heterocyclic natural products by the aza-Wittig method focusing on applications of the tandem Staudinger/intramolecular aza-Wittig reaction.

Keywords: Aza-Wittig reaction, iminophosphorane, quinazolinone annelation, benzodiazepine, tandem intramolecular Staudinger/aza-Wittig reaction, Eguchi aza-Wittig protocol, alkaloids, antibiotics, polymer-supported Eguchi protocol

Contents

Introduction

The synthesis of heterocyclic natural products by the aza-Wittig method has been reviewed for the first time by us in 1997;[1] very recently and timely, Fresneda and Molina have reviewed the application of iminophosphorane-based methodologies for the synthesis of natural products.[2] The utilization of the aza-Wittig method for the synthesis of heterocyclic natural products is spreading out to a variety of nitrogen heterocycles from simple alkaloids to complex functionalized natural products. In this mini review, emphasis will be placed on our results in this area, and in addition on related areas. Topics to be covered include recent examples of heterocyclic natural product syntheses by the aza-Wittig method focusing on the tandem Staudinger/intramolecular aza-Wittig reaction including quinazolinone annelation, benzo-diazepinone synthesis, chemoselectivity in cyclization, synthesis of benzomalvins, and some selected examples of total syntheses of heterocyclic natural products based on the so-called Eguchi aza-Wittig protocol.

1. The aza-Wittig Reaction

1.1 The aza-Wittig reaction

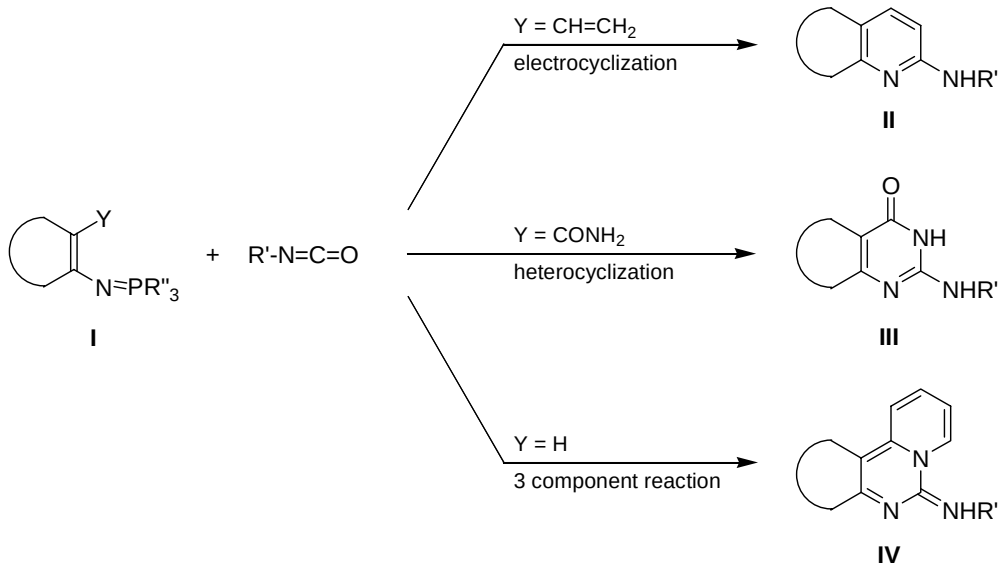
The aza-Wittig reaction[3] is the nitrogen analog of the Wittig olefination process and involves the reaction of an iminophosphorane[4] with a carbonyl group. The reaction is useful in the synthesis of acyclic imines[5] and heterocumulenes,[3] and in the intramolecular formation of carbon-nitrogen double bonds in heterocyclic synthesis.[3] Stability, basicity, and nucleophilicity of imino-phosphoranes are mainly determined by the substituents at the nitrogen atom. General reactivity trends of N- and P-substituted series (R' and R", respectively) are summarized as follows:[1,3a,4]

$$R'N{=}PPh_3 >> ArN{=}PPh_3 >> R'CON{=}PPh_3 \sim R'SO_2N{=}PPh_3$$
$$R'N{=}P(R'')_3 > R'N{=}P(Ar)_3 > R'N{=}P(OR'')_3 > R'N{=}P(OPh)_3$$

Carbonyl groups of aldehydes, ketones, acid halides, and heterocumulenes are generally reactive.[1] In the intramolecular version, amide, imide, and ester carbonyl groups are also reactive giving rise to imino-cyclization (see section 2).[3]

1.2 Heterocyclic synthesis by the aza-Wittig reaction followed by various cyclizations

The intermolecular version has been utilized for various heterocyclic syntheses via initial imine formation followed by electrocyclization, cycloaddition, and nucleophilic cyclization etc. as developed by Molina (tandem aza-Wittig/cyclization strategy),[3d] Saito (aza-Wittig/electrocyclization method),[6] and Wamhoff (three-component reaction)[3a] (Scheme 1). Unique synthetic strategies with *N*-vinyliminophosphoranes by Nitta,[7] Palacios,[8] and benzotriazolyl derivatives by Katrizky[9] have also been developed demonstrating the maturity and excellent prospects of iminophosphorane-mediated syntheses.



Scheme 1

Since applications of the intermolecular aza-Wittig methodology to the synthesis of natural products have been included in previous reviews,[1,2] these examples are not discussed in the present mini review.

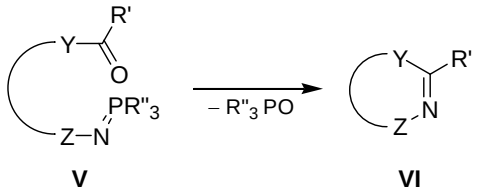
2. Routes to heterocyclic natural products by the intramolecular aza-Wittig reaction

2.1 The intramolecular aza-Wittig reaction

The intramolecular version of the aza-Wittig reaction (Scheme 2) provides a direct route to heterocyclic natural products. The reactivity depends on substituents Y and R' at the carbonyl group, and on Z and R" at the iminophosphorane; thus, a useful application has to consider (1) the ring size (formation of 5–7-membered rings >> 4-membered ring), (2) the carbonyl reactivity (COR, COAr, RCOOR, RCONRCOR >> RNCOR), (3) the substituents on P [$PR"_3$ >

$P(Ar)_3 > P(OR'')_3$], (4) the substituent on N (CH_2, Ar, C=C, CO), (5) the ring strain: OS value ≤20 kcal/mol (the difference of heat of formation between unsaturated and saturated analogs).[3b,c]

The ring closure to a non-cumulated sulfoxide via an intramolecular aza-Wittig type reaction to construct S=N linkage has been recently reported by Hemming.[10]

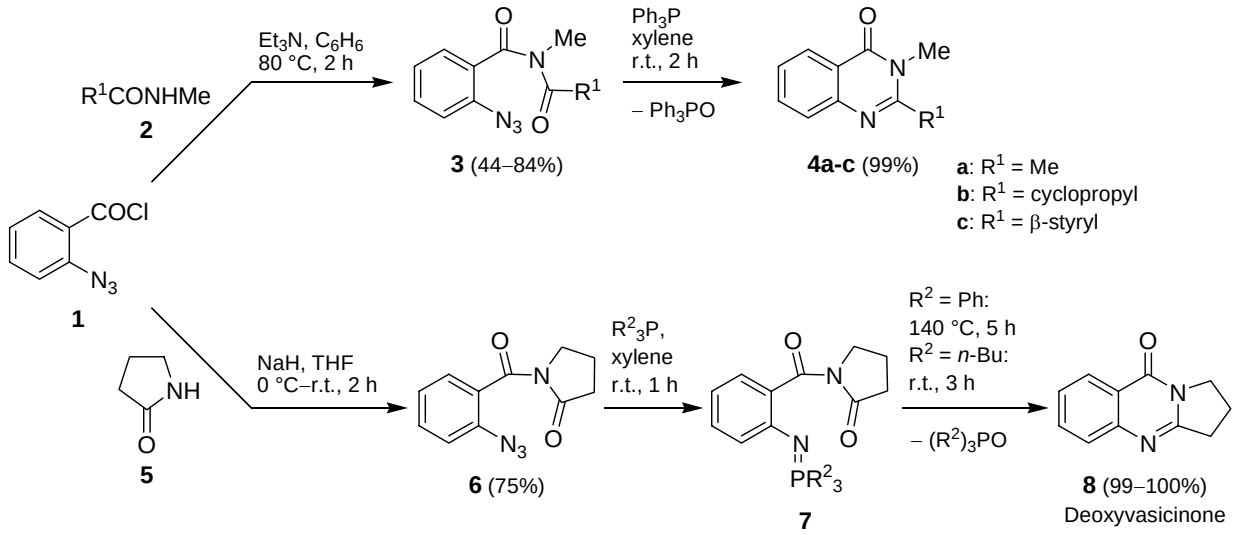


Scheme 2

2.2 Quinazolinone annelation

We had interest in utilizing 2-phosphoranylideneamino-benzoyl derivatives as building blocks, particularly in view of anthranilic acids as important biological precursors of various alkaloids such as glomerine, vascine, and microbial products like tryptanthrin and anthramycine.[11]

Thus, acylation of *N*-methylamides **2** with 2-azidobenzoyl chloride **1** (readily available from 2-azidobenzoic acid[12]) forms imides **3**, which upon treatment with triphenylphosphine (TPP) in the course of consecutive Staudinger reaction/intramolecular aza-Wittig reaction quantitatively give 3-methylquinazolin-4(3*H*)-ones **4a–c** (Scheme 3).[13]

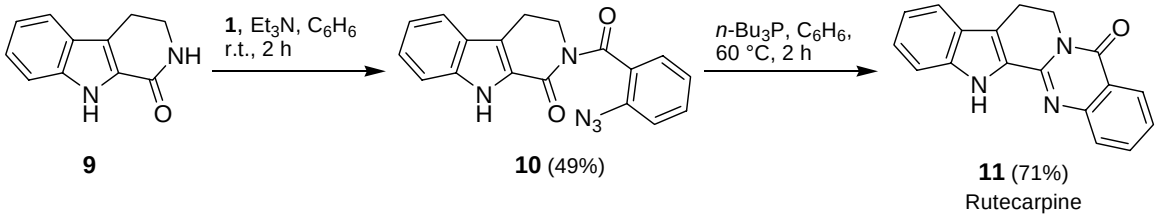


Scheme 3

Application of this method to pyrrolidinone **5** provides a facile synthesis of deoxyvacisinone **8**.[13,14] Cyclization of 2-azidobenzoyl derivative **6** via iminophosphorane **7** to 2,3-

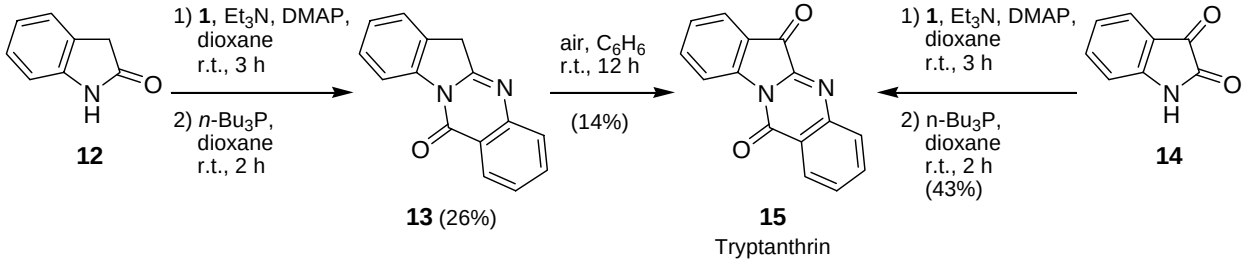
dihydropyrrolo[2,1-*b*]quinazolin-9(1*H*)-one **8** proceeds more rapidly with tributylphosphine (TBP) than with TPP in accordance with the general reactivity trend; however, steric effects should also be considered as an important factor in these aza-Wittig reactions.

This method has been generalized for the quinazolinone annelation of lactams.[15] A successful application is the short synthesis of rutecarpine **11**, an alkaloid of *Evodia rutaecarpa*, from 2,3,4,9-tetrahydro-1*H*-β-carbolin-1-one **9** via 2-azidobenzoyl derivative **10** (Scheme 4); among several known syntheses of **11** this is the most facile one.



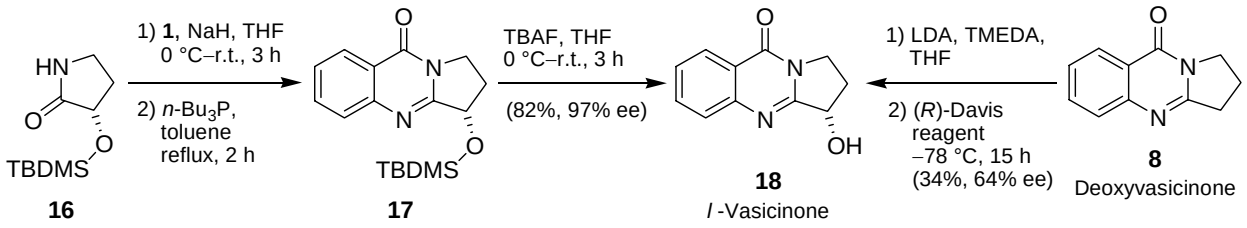
Scheme 4

Similarly, the antimycotic alkaloid tryptanthrin **15** is prepared by quinazolinone annelation of isatin **14** (Scheme 5):[16] Quinazolinone annelation of oxindole **12** affords indolo[2,1-*b*]quinazolin-12(6*H*)-one **13**, which is oxidized by air to form tryptanthrin **15** in low yield (Scheme 5).[16]



Scheme 5

Quinazolinone annelation of the O-protected chiral pyrolidinone **16** (derived from L-aspartic acid) forms pyrrolo[2,1-*b*]quinazolin-9(1*H*)-one **17**; subsequent desilylation affords (*S*)-(–)-vasicinone **18**, which is identical with the natural *l*-product (Scheme 6).[17,18] Asymmetric oxidation of deoxyvasicinone **8** (via the imine enolate) with either (*R*)- or (*S*)-Davis' reagent (10-camphorsulfonyloxaziridine)[19] provides a convenient route to both enantiomers, thus confirming the recently revised stereochemistry of natural vasicinone (Scheme 6).[17,18]

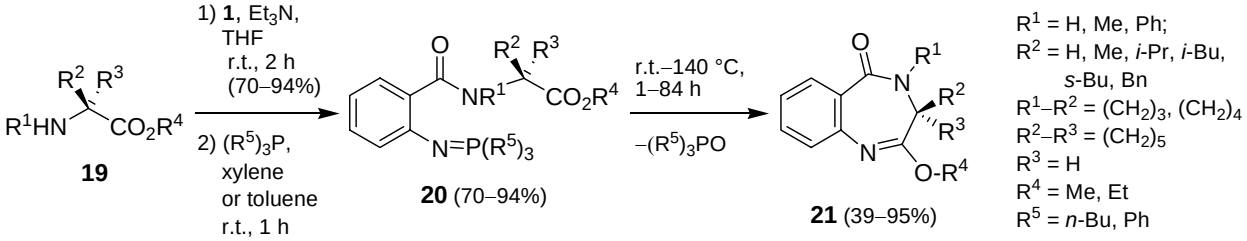


Scheme 6

The quinazolinone annelation procedure described above by acylation of an amide group with 2-azidobenzoylchloride (**1**) followed by the Staudinger/intramolecular aza-Wittig tandem reaction is known as the Eguchi aza-Wittig protocol[2] after its successful application by Snider's group to the synthesis of the pyrazino[2,1-*b*]quinazoline scaffold in the fumiquinazolines,[20,21] and to the preparation of ardeemins by Danishefsky's group[22] (cf. section 2.6).

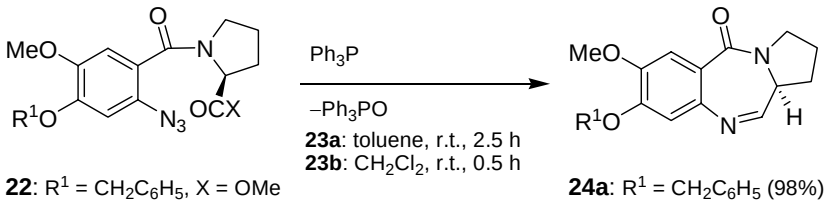
2.3 Synthesis of benzodiazepine derivatives by intramolecular aza-Wittig reactions

Acylation of α-amino esters **19** with 2-azidobenzoylchloride (**1**) gives the corresponding 2-azidobenzoyl derivatives which, on treatment with phosphines, form iminophosphoranes **20** and cyclization products **21** via the tandem Staudinger/intramolecular aza-Wittig reaction, providing a simple route to 1,4-benzodiazepin-5-ones **21** (Scheme 7).[23] The cyclization of N-substituted derivatives ($R^1 \neq H$) with TBP proceeds smoothly under very mild conditions; however, the reaction of N-unsubstituted amino acids **19** ($R^1 = H$) is sluggish at room temperature leaving **20** unreacted and requiring elevated temperatures for completion of conversion.



Scheme 7

The successful application of this procedure to the synthesis of natural antibiotic DC-81 **24b** has been reported by Molina[24] and by Eguchi[23b] (Scheme 8). DIBAL reduction of the readily available methyl 1-(2-azidobenzoyl)prolinate **22** to the aldehyde **23a** and subsequent reaction with TPP at room temperature affords **24a**, the O-benzyl derivative of DC81.[23b] Molina's group achieved an elegant synthesis of DC-81 **24b** from aldehyde **23b** with TPP by consecutive Staudinger/intramolecular aza-Wittig reaction.[24]



22: $R^1 = CH_2C_6H_5$, X = OMe
23a: $R^1 = CH_2C_6H_5$, X = H
23b: R^1 = H, X = H

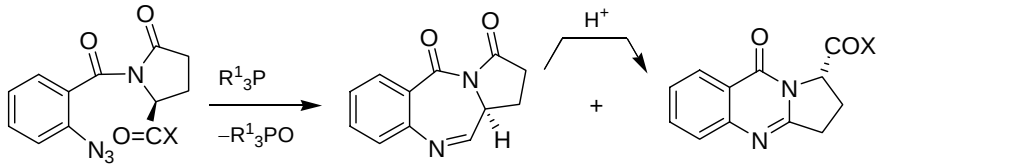
24a: $R^1 = CH_2C_6H_5$ (98%)
24b: DC-81: R^1 = H (79%)

Scheme 8

Some other useful synthetic procedures for the synthesis of functionalized pyrrolo-[2,1-*c*]-[1,4]benzodiazepines (PBDs) have been developed thereafter by O'Neil's group and others,[25] but details of these studies are beyond the scope of this review.

2.4 Chemoselectivity of intramolecular aza-Wittig cyclizations

The chemoselectivity of bifunctional systems is important for the selective ring construction by intramolecular aza-Wittig reactions. The selective cyclization of methyl 1-(2-azidobenzoyl)-5-oxo-L-prolinate **25a** with TBP and TPP involves the ester carbonyl group rather than the imidoyl carbonyl group affording **26a** selectively; but both **26a** and **27a** are formed with triethylphosphite (Scheme 9, Table 1);[26] product ratios **26**/**27** as determined by ^{1}H NMR spectra of the reaction mixture. The isolated **26a** is sensitive to moisture and is converted quantitatively into **27a** by treatment with a catalytic amount of conc. HCl in THF at r.t. for 3 h. The imidocarbonyl group of amide **25b** is more reactive yielding **27b** exclusively. The product ratio of 7-membered rings **26a,b** versus 6-membered rings **27a,b** depends on the carbonyl function and on the steric effect exerted by the substituents of the phosphorane reagents:[13b] The bulkier TBP and TPP form predominantly **26a**; the 6-membered **27a** is formed preferentially with the smaller triethylphosphite. These results may be useful for the synthetic design of related heterocycles.



25a
25b

26a
26b

27a
27b

a: X = OMe
b: X = NEt_2

Scheme 9

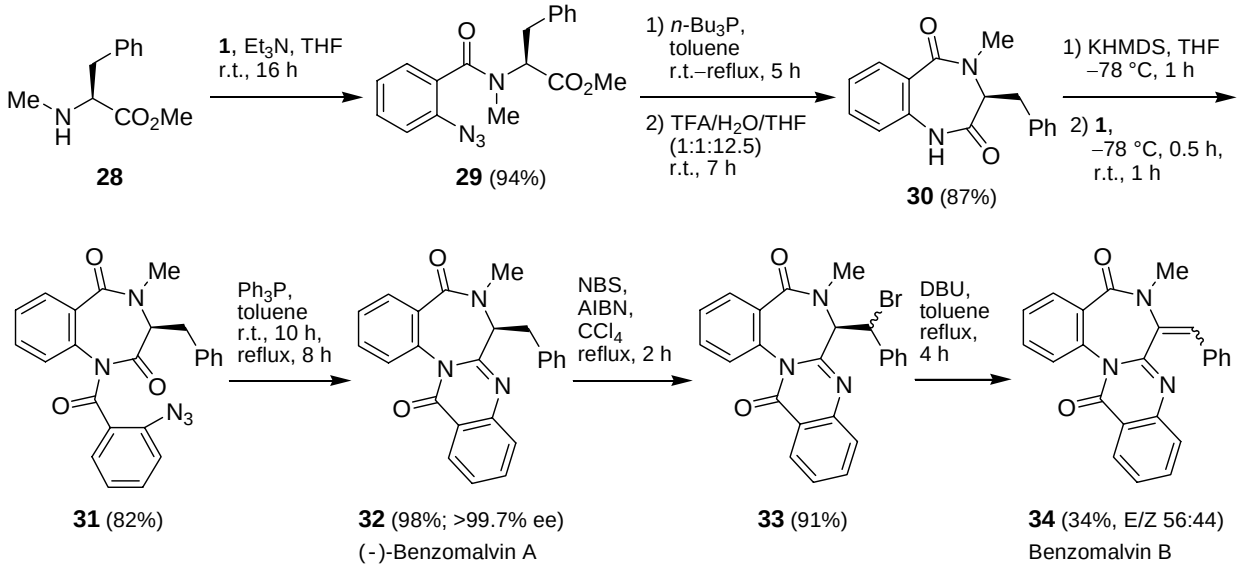
Table 1. Chemoselectivity of the Staudinger/aza-Wittig tandem reaction of **25a,b**[26]

Entry	**25**: X	R^1	Reaction conditions[a]	Yield [%][b]	**26**:**27**[c]
1	OMe	*n*-Bu	r.t., 3 h	79	88:12
2	OMe	Ph	r.t., 4 h	63	97:3
3	OMe	OEt	r.t., 6 h	45	36:64
4	OMe	OEt	r.t., 6 h; 80 °C, 12 h	69	36:64
5	NEt_2	*n*-Bu	r.t., 3 h; 80 °C, 4 h	91	trace:>99
6	NEt_2	Ph	r.t., 4 h; 140 °C 6.5 h	98	trace:>99

[a] In benzene or xylene, 1.1 equivalent of $(R^1)3P$. [b] Yields were determined after conversion into **27**. [c] Determined by ^{1}HNMR.

2.5 Synthesis of (–)-Benzomalvin A

We have successfully applied the intramolecular aza-Wittig method to the synthesis of the neurokinin receptor antagonists (–)-benzomalvin A **32** and B **34**, which contain a 1,4-benzodiazepine ring and a 4-quinazolinone ring, and can be regarded as L-phenylalanine derivatives composed of two anthranilic acid moieties.[27] Our synthesis utilized the 1,4-benzodiazepine synthesis as described above combined with the quinazolinone annelation reaction (Scheme 10). Amino acid ester **28** provided (–)-benzomalvin A **32** with 99.7% ee (based on HPLC analysis).[28]

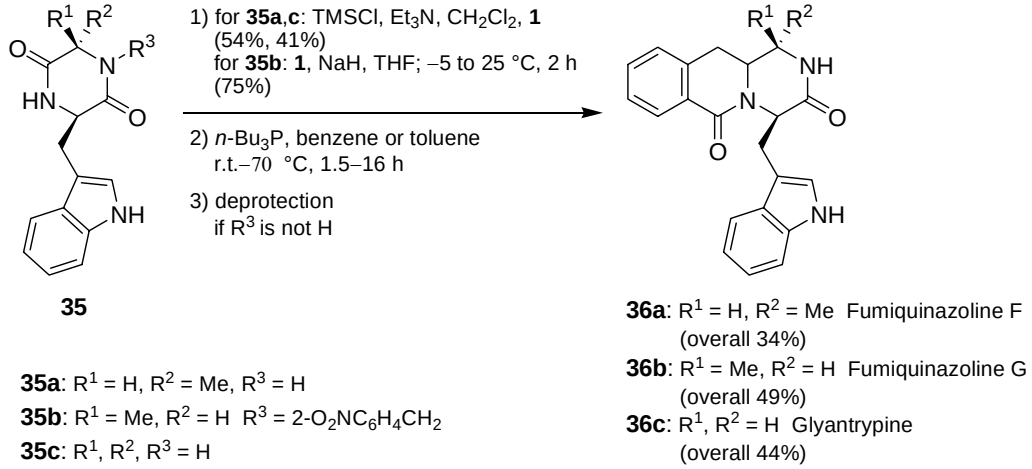


KHMDS: potassium hexamethyldisilazide

Scheme 10

2.6 Examples of natural products synthesis by the quinazolinone annelation method (Eguchi aza-Wittig protocol)

Snider has utilized the quinazolinone annelation method (see section 2.2) for the first synthesis of (+)-fumiquinazoline G **36b** (the natural product is the (–)-enantiomer; a 3:2 equilibrium mixture is obtained with base from either fumiquinazoline F or G[29]). (+)-Fumiquinazoline G **36b** is the simplest member of a quinazolinone fused to a piperazine-2,5-dione ring (Scheme 11).[20] Furthermore, Snider has developed a general procedure for photochemically deprotectable *N*-(2-nitrobenzyl)piperazine-2,5-dione **35b**, which provides a short and efficient synthesis of fumiqunazoline G (**36b**) (Scheme 11).[21]



35

35a: R^1 = H, R^2 = Me, R^3 = H
35b: R^1 = Me, R^2 = H R^3 = 2-$O_2NC_6H_4CH_2$
35c: R^1, R^2, R^3 = H

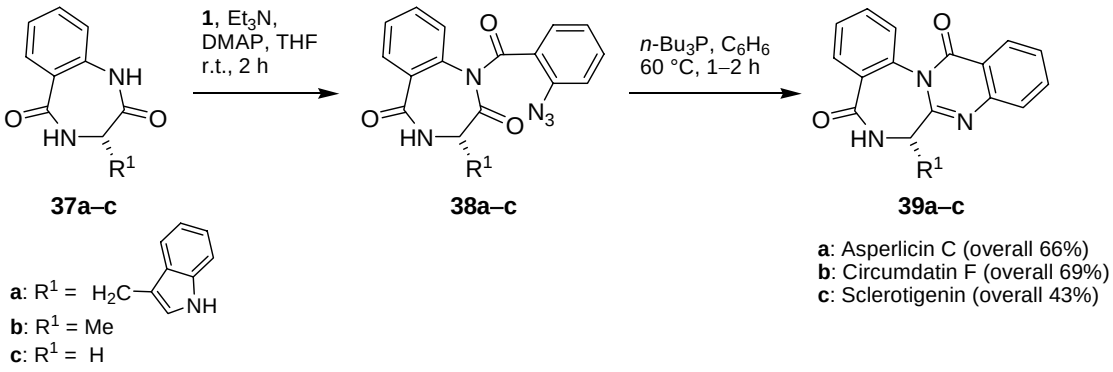
36a: R^1 = H, R^2 = Me Fumiquinazoline F (overall 34%)
36b: R^1 = Me, R^2 = H Fumiquinazoline G (overall 49%)
36c: R^1, R^2 = H Glyantrypine (overall 44%)

Scheme 11

A short synthesis of (–)-fumiquinazoline F (**36a**) and (–)-glyantrypine (**36c**) has been developed by Söllhuber's group: The regioselective acylation of unprotected 3-arylmethyl-piperazine-2,5-diones **35a** and **35c** (derived from methyl tryptophanate) with TMSCl, Et_3N, and 2-azidobenzoylchloride (**1**) is followed by the intramolecular Staudinger/aza-Wittig protocol (Scheme 11).[30] The quinazolinone annelation via acylation with 2-azidobenzoylchloride (**1**) followed by the Staudinger/intramolecular aza-Wittig reaction proceeds cleanly affording **36a–c** in good yields.[21,30] Glyantrypine (**36c**) has been synthesized also by Menéndez via a different route: Condensation of sodium *N*-(2-azidobenzoyl)aminoacylglycinate to the 2,5-piperazinedione derivative is followed by deacetylation and intramolecular aza-Wittig reaction.[31–33]

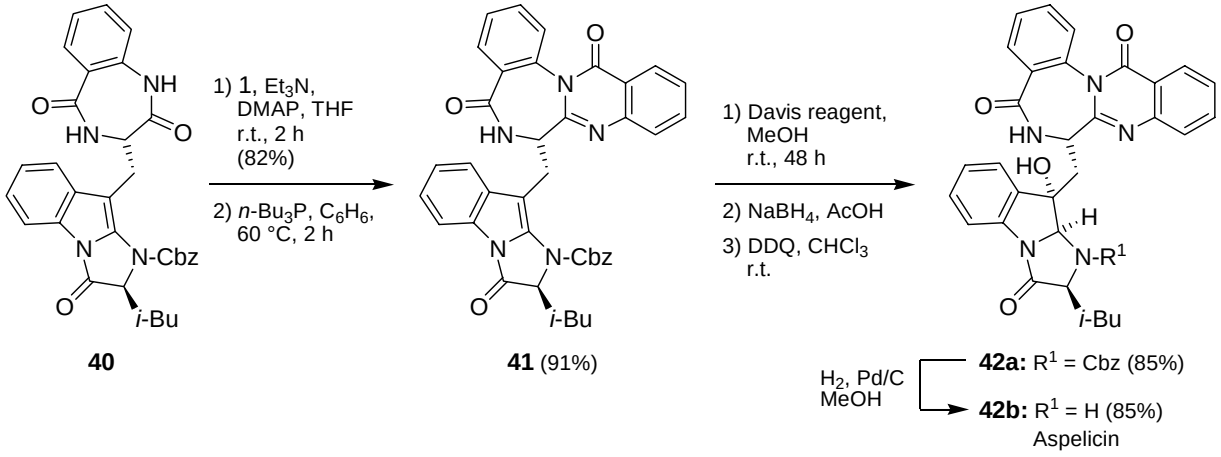
The quinazolinone annelation method has been utilized by Snider's group to provide an efficient entry to quinazolinone alkaloids fused to a benzodiazepinedione ring such as in asperlicin C **39a** Scheme 12.[21] Several successful syntheses of quinazolinone families proved the general applicability of this simple annelation procedure; this method together with intra-molecular aza-Wittig methods is known as the Eguchi aza-Wittig protocol.[2,21,34] For example, this method has been utilized for the synthesis of asperlicin C **39a**, circumdatin F **39b** and

sclerotigenin **39c** by selective acylation of the more acidic anilide nitrogen of benzodiazepinediones **37** without the need for protecting groups, followed by TBP-induced cyclization of the 1-(2-azidobenzoyl)-1,4-benzodiazepine-2,5-dione derivative **38**.[30,35]



Scheme 12

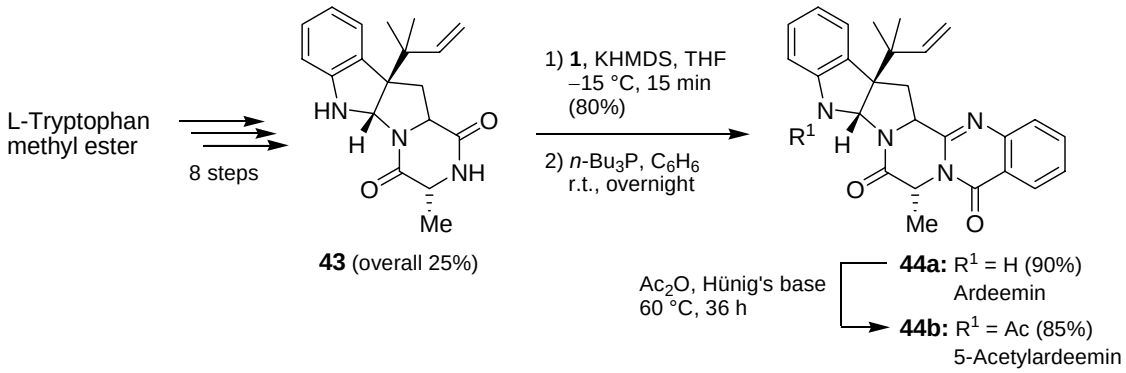
Utilizing the Eguchi aza-Wittig protocol Snider's group achieved the total synthesis of the more complex antibiotic (–)-asperlicin **42b**, known also for its potent cholecystokinin antagonist activity (Scheme 13).[33,37] L-Tryptophan-derived benzodiazepinedione **40** is converted into the fused quinazolinone **41**. Epoxidation of **41** with Davis' oxaziridine reagent,[38] followed by $NaBH_4$ reduction and DDQ oxidation affords **42a**, which upon deprotection by hydrogenolysis gives asperlicin (**42b**) (15 steps from L-tryptophan with 8% overall yield).[33,37]



Scheme 13

The quinazolinone annelation method has been applied to piperazinedione **43** derived from L-tryptophan methyl ester by Danishefsky's group for the synthesis of ardeemin **44a** and 5-*N*-acetylardeemin **44b**, one of the most potent known agents for reversal of multiple drug resistance (MDR)[39] featuring a hexahydropyrrolo[2,3-*b*]indole scaffold substituted at the benzylic ring

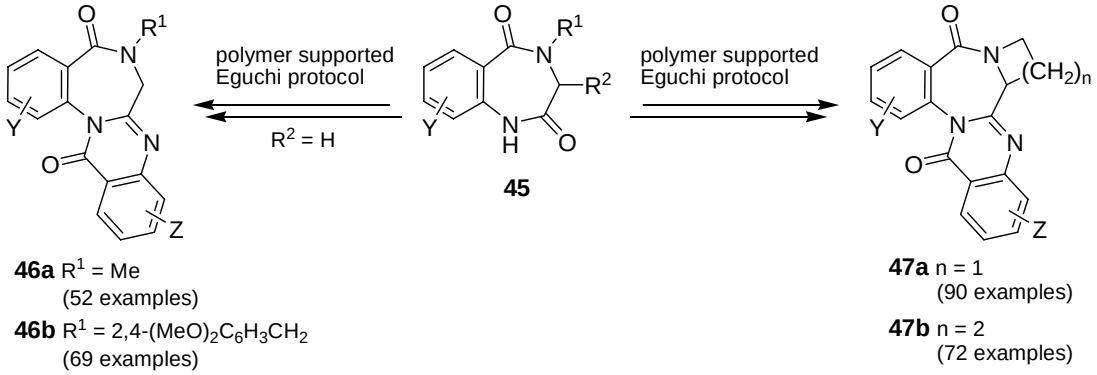
junction with the 1,1-dimethylallyl ("reverse-prenyl") group (Scheme 14).[22] Acylation of **43** with KHMDS and **1** works well to give the corresponding imide in variable yields (50–80%); for technical reasons, on larger scale preparations the use of 2-azidobenzoic anhydride is preferred over the acid chloride **1**.[22b] The Staudinger/intramolecular aza-Wittig reaction of the imide product with TBP gave aredeemin **44a**, which was acetylated to 5-*N*-acetylardeemin **44b** (9 steps with 12.5% overall yield from bis(Boc)tryptophan methyl ester).



Scheme 14

A *seco* analogue of ardeemin has been synthesized by Menéndez' group also using the quinazolinone annelation method.[40]

A diverse library of benzodiazepine-quinazolinone alkaloids (the circumdatin family) has been prepared by Thomas with a polymer supported phosphine-mediated intramolecular aza-Wittig reaction as the key step, a novel modified Eguchi aza-Wittig protocol (Scheme 15).[41] The multi-arrayed library generation strategy starts out from readily accessible benzodiazepinediones **45** and anthranilic acids, and all library members were purified by preparative reversed-phase HPLC, yielding 283 isolated pure products **46a,b** and **47a,b** from 384 individual reactions.



Scheme 15

3. More applications of the intramolecular aza-Wittig method to the synthesis of heterocyclic natural products

3.1 Examples of total synthesis of heterocyclic natural products via cyclic imines by the tandem Staudinger/intramolecular aza-Wittig reaction

The intramolecular Staudinger/aza-Wittig reaction provides a simple and efficient method for the construction of 5–8-membered cyclic imines (cf. section 2.1) and has recently been utilized also for the synthesis of complex natural products as exemplified by **48**–**53** (Figure 1). In these total syntheses, the Staudinger/intramolecular aza-Wittig reaction is applied ingeniously for highly functionalized molecules as explained below.

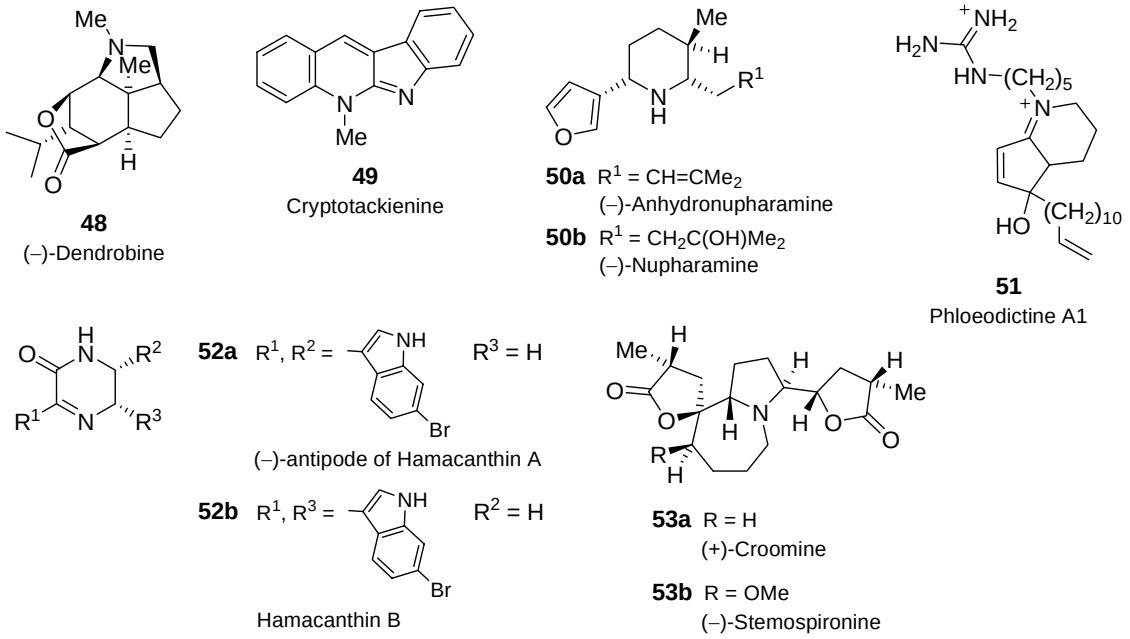
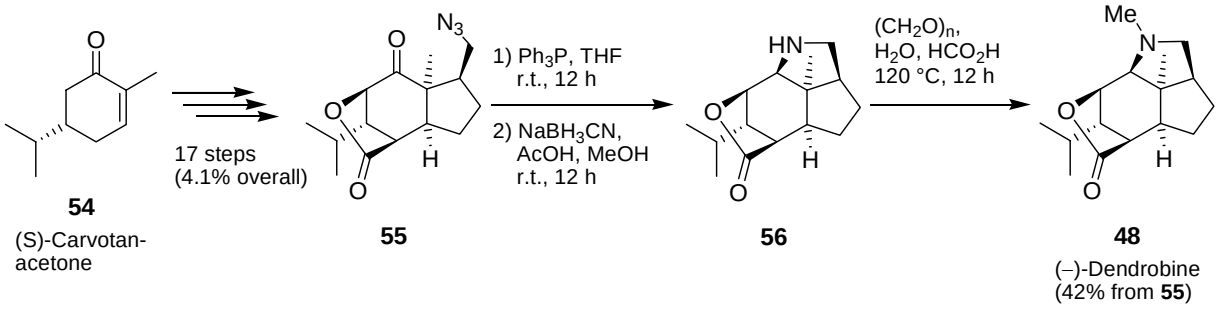


Figure 1

Sha and coworkers used the intramolecular aza-Wittig imine formation reaction followed by $NaBH_4$ reduction to construct the pyrrolidine ring in the total synthesis of (–)-dendrobine **48** from **54** via **55** and **56** (Scheme 16).[42] Direct reduction of the cyclic imine to the more stable pyrrolidine **56** is followed by methylation to afford (–)-dendrobine **48**.

In the first synthesis of indoloquinoline alkaloid cryptotackiene **49**, Fresneda, Molina and Delgado successfully applied the Staudinger/intramolecular aza-Wittig imine formation reaction to 3-(2-azidophenyl)-1-methylquinolin-2(1*H*)-one **57** with a sluggishly reacting carbonyl group (Scheme 17).[43] Treatment of **57** with tri-(*n*-butyl)phosphine in *o*-xylene at room temperature followed by heating at reflux temperature for 24 h gives **49** in only 5% yield; treatment of **57** with trimethylphosphine at room temperature followed by heating in nitrobenzene at reflux for 24 h affords **49** in 24% yield; further improvement up to 40% yield is achieved by microwave irradiation (Scheme 17).[43]



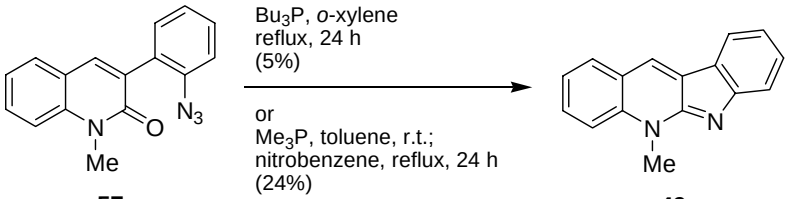
54
(S)-Carvotan-acetone

55

56

48
(–)-Dendrobine
(42% from **55**)

Scheme 16

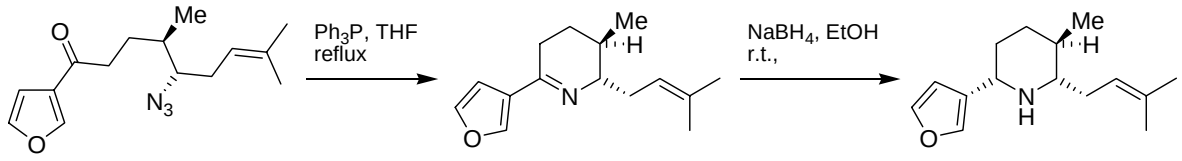


57

49
Cryptotackieine

Scheme 17

Honda's group employed the intramolecular aza-Wittig imination reaction for construction of 6-membered imines in the enantioselective synthesis of the piperidine alkaloids (–)-anhydronupharamine **50a** (Scheme 18).[44] Treatment of the (–)-carvone-derived azide **58** with TPP in THF at room temperature, followed by heating at reflux gives imine **59**, which without isolation upon reduction with $NaBH_4$ yields (–)-anhydronupharamine **50a** as a single stereoisomer in 77% overall yield from **58**. Since **50a** is known to be converted into (–)-nupharamine **50b** (Figure 1) on treatment with hydrochloric acid,[44c] this synthesis constitutes its formal chiral synthesis.



58

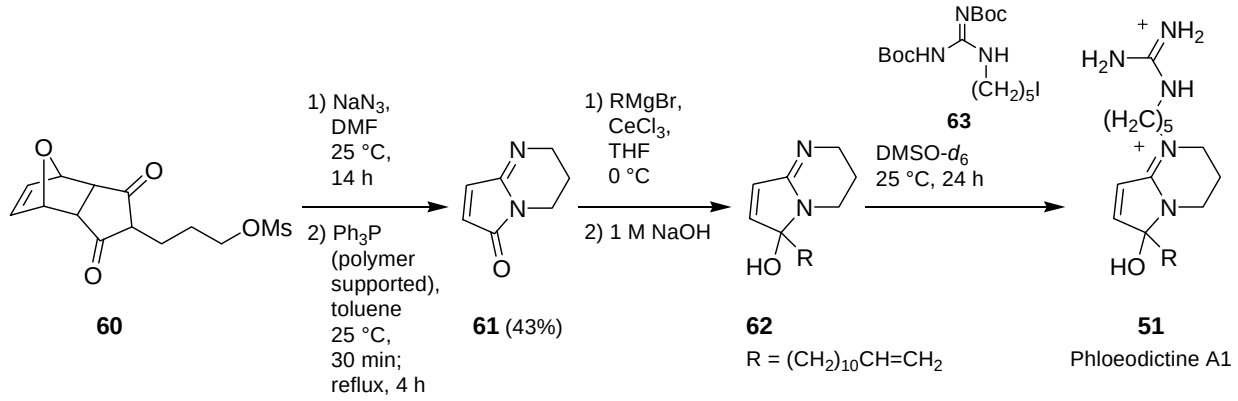
59

50a
(-)-Anhydronupharamine
(77% overall)

Scheme 18

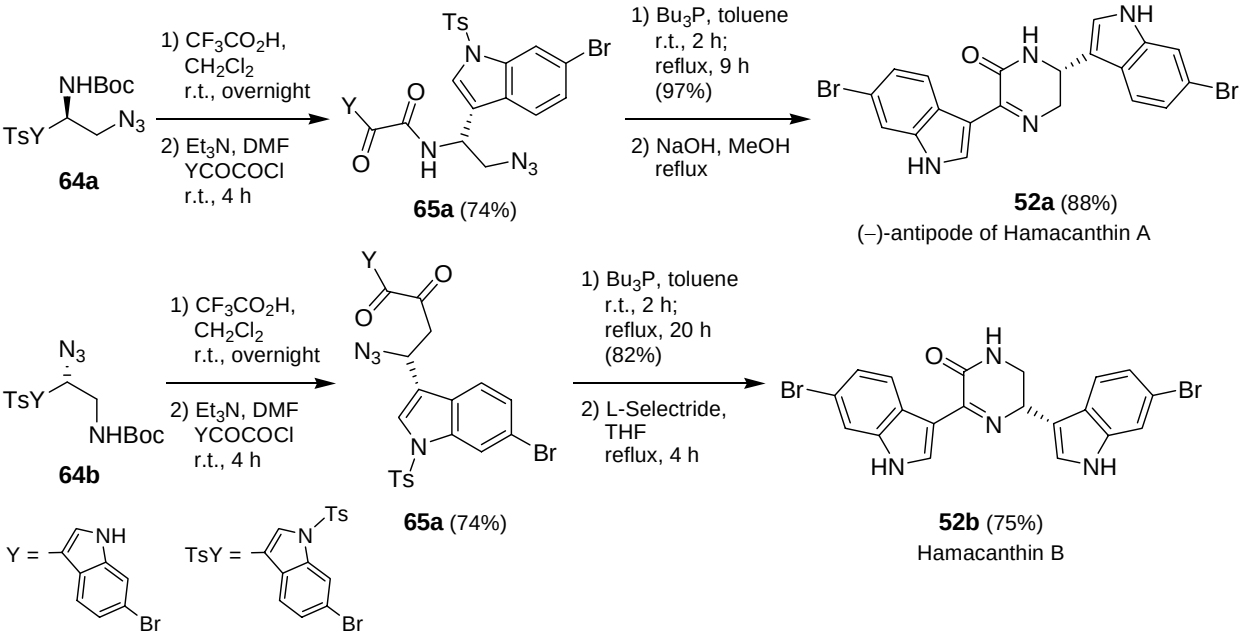
The antitumor antibiotic phloeodictine A1 **51** has been synthesized by Snider's group (Scheme 19).[45] The toluene solution of the unstable azide derived from **60** is subjected to a polymer supported Eguchi aza-Wittig reaction followed by a retro Diels-Alder reaction to prepare intermediate **61**. The use of polystyrene-supported Ph_3P prevents isomerization of **61** and

facilitates purification of the product. Addition of 11-dodecenyl magnesium bromide followed by alkylation with **63** and deprotection completes an efficient synthesis of **51** (Scheme 19).



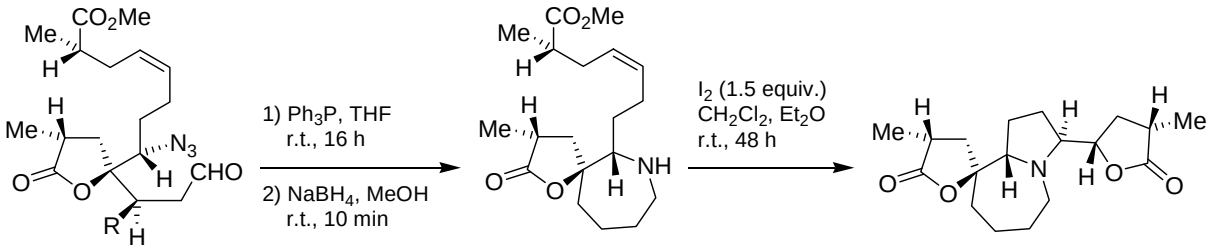
Scheme 19

The intramolecular aza-Wittig imination has been used by Jiang's group to construct the 5,6-dihydropyrazin-2(1*H*)-one ring in the enantioselective syntheses of the (–)-antipode of the marine alkaloids hamacanthin A **52a** and hamacanthin B **52b**[46] (Scheme 20). Coupling of (*S*)-1-azidoethyl-(*N*-Boc)amine **64a** (prepared from 6-bromoindole) with 3-indolyl-α-oxoacetyl chloride affords **65a**. The intramolecular Staudinger/aza-Wittig cyclization constructs the central dihydropyrazinone ring, subsequent deprotection gives **52a** as the (–)-antipode of natural hamacanthin A.[46a] Hamacantin B **52b** is prepared similarly from **64b** via **65b**.[46b]



Scheme 20

The Williams group utilized the tandem Staudinger/aza-Wittig imino-cyclization reaction followed by borohydride reduction to construct a perhydroazepine ring in the total synthesis of polycyclic alkaloids, (+)-croomine **53a**[47a] and (–)-stemospironine **53b**[47b] with the decahydro-5*H*-spiro(furano-2,9'-pyrrolo[1,2-*a*]azepin)-5-one ring system (Scheme 21). Treatment of azido-aldehyde **66a** with TPP in THF affords the corresponding 7-membered imine which is directly reduced to perhydroazepine **67a** with sodium borohydride in methanol. In view of the poly-functional starting material **66a** the high yield of the Staudinger/aza-Wittig iminocyclization protocol is noteworthy. Iodine-induced double cyclization of **67a** directly gives (+)-croomine **53a**; the structure is proven by X-ray crystallographic analysis of the methiodide salt of **53a**.



66a: R = H
66b: R = OMe

67a: R = H (90%)
67b: R = OMe (60%)

53a (25%) (+)-Croomine
53b (25%) (–)-Stemospironine

Scheme 21

The stereocontrolled total synthesis of the polycyclic *Stemona* alkaloid, (–)-stemospironine **53b** has been achieved by Williams' group (Scheme 21). The azidoaldehyde **66b** is subjected to the key transformation, the tandem Staudinger/aza-Wittig iminocyclization; subsequent boro-hydride reduction provides the perhydroazepine ring **67b**. Iodine-induced double cyclization constructs the decahydro-5*H*-spiro[furano-2,9'-pyrrolo[1,2-*a*]azepin]-5-one ring **53b**.

Many more heteroaromatic natural products have been synthesized by Molina and by other groups utilizing the aza-Wittig protocol in tandem reactions followed by electrocyclic ring-closure, heterocumulene-mediated annelation, intramolecular halide displacement methods. These topics are not discussed in this mini review (see references 1 and 2).

3.2 Examples of molecular design of bioactive compounds by the tandem Staudinger/Intramolecular Aza-Wittig reaction

The intramolecular aza-Wittig protocol has been proved useful for the synthesis of (potentially) bioactive heterocyclic molecules (Figure 2). This includes the antitumor agent Batracyclin **68**[48], 1,4-benzodiazepine-fused 4(3*H*)-pteridinone **69,**[49,50] 6,9-diaza-analogs of [1,4]benzodiazepin-5-ones **70a**,**b**,[51] pyrazino[2,3-*e*]pyrido[1,2-*a*]diazepinone (diaza-analog of PBDs) **71**,[51] and benzo-diazocine **72**.[52] Selected examples are discussed from the synthesis point of view.

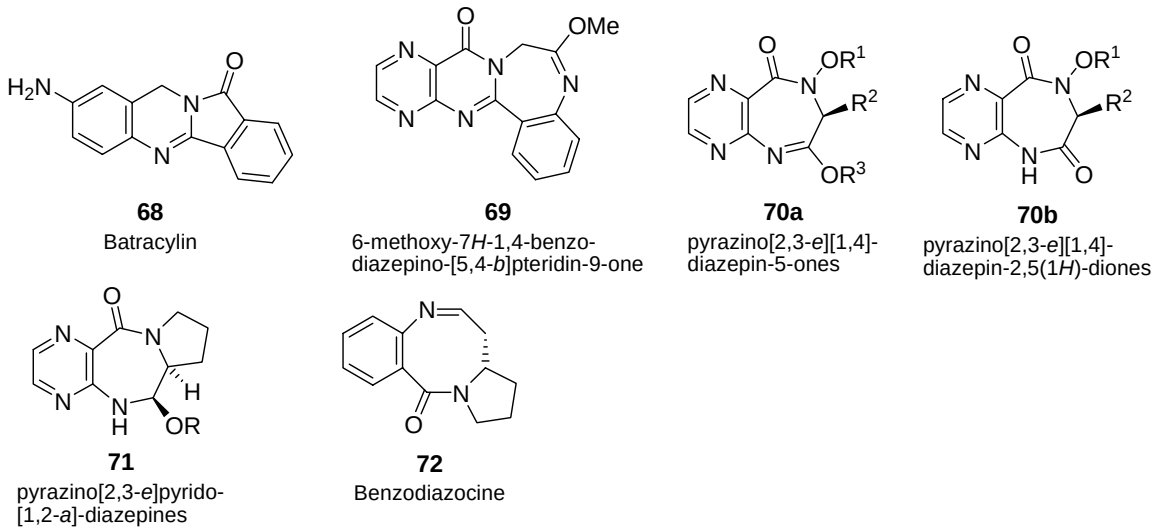
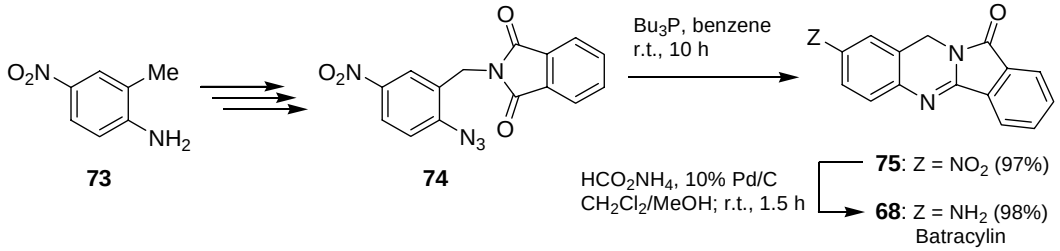


Figure 2

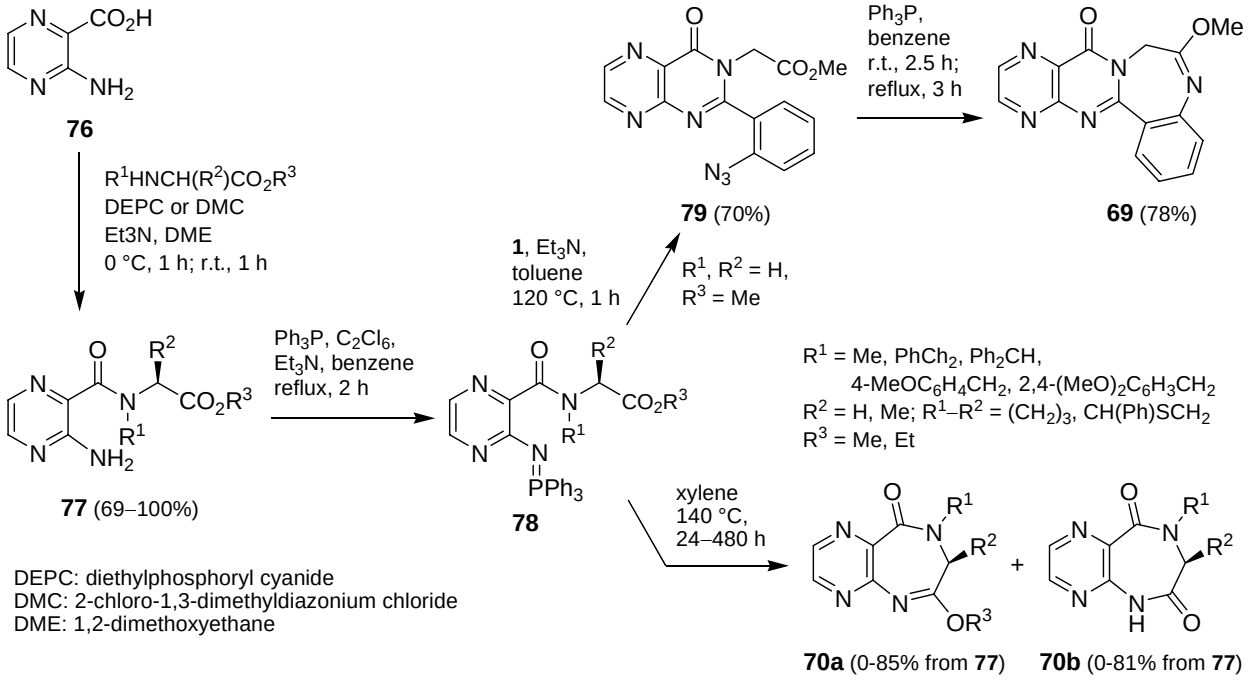
The Staudinger/intramolecular aza-Wittig protocol provided an efficient route to the anti-tumor agent Batracylin **68** (8-aminoisoindolo[1,2-*b*]quinazolin-12(10*H*)-one; BAT; NSC-320846) (Scheme 22).[48a] Conversion of commercially available **73** into azidophenylphthalimide **74** and treatment with TBP gives **75** in high yield. Reduction of the nitro group to amine function provides Batracylin **68**. BAT is known to exhibits antitumor activity in a number of in vivo and in vitro models.[48b]



Scheme 22

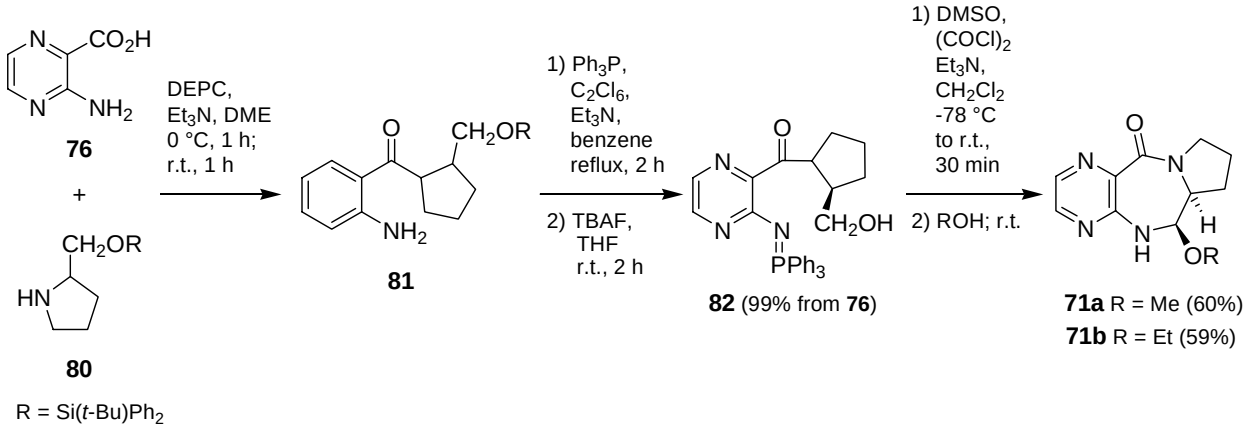
We have synthesized a novel pteridinone derivative **69** by condensation of the commercially available 3-aminopyrazine-2-carboxylic acid **76** with amino acid esters to give amides **77**, which are converted into the corresponding iminophosphoranes **78** by the Appel method,[53] *i.e.*, the modified Kirsanov reaction (Scheme 23).[53] Iminophosphorane **78** (derived from glycine methyl ester, R^1, R^2 = H, R^3 = Me) upon treatment with 2-azidobenzoyl chloride **1** is converted into pteridinone derivative **79**, ultimately affording the novel 1,4-benzodiazepinopteridinone **69** by the Staudinger/intramolecular aza-Wittig cyclization with TPP.[49,50] Other iminophosphoranes **78** upon heating at 140 °C in xylene yield intramolecular aza-Wittig products, the pyrazino[2,3-*e*][1,4]diazepines **70a** and **70b**. Yields and ratios of **70a** and **70b** vary depending on substituents of **78**. For example, **78** [R^1-R^2 = $(CH_2)_3$, R^3 = Me] exclusively affords **70b** in good yields after 24

h, while **78** [R^1 = Ph_2CH, R^2 = H, R^3 = Me] gives only **70a** in modest yields after 480 h of heating[51] (cf. synthesis of 1,4-benzodiazepin-5-ones **21**, Scheme 7).



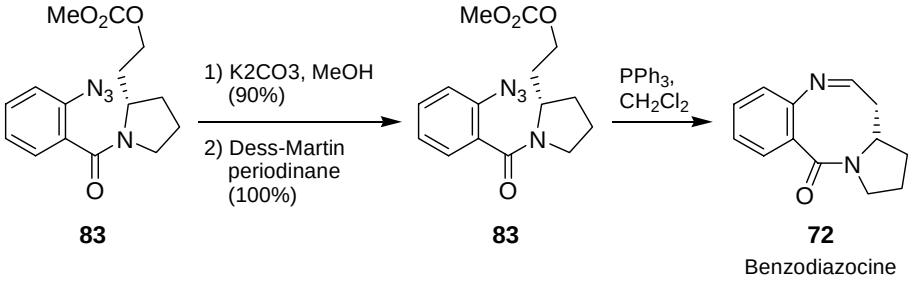
Scheme 23

Pyrazino[2,3-*e*[pyrido[1,2-*a*]diazepines **71** (6,9-diaza analogs of PBDs) have been prepared by us (Scheme 24).[51] Condensation of **76** with *t*-butyldiphenylsilyl-protected (TBDPS) L-prolinol **80** gives **81**, which is converted into iminophosphorane **82** by modified Kirsanov reaction followed by deprotection. Swern oxidation of the hydroxymethyl group of **82** generates the corresponding aldehyde (*in situ*), which by spontaneous intramolecular aza-Wittig cyclization followed by addition of alcohols affords the isolated products **71a**,**b**.[51]



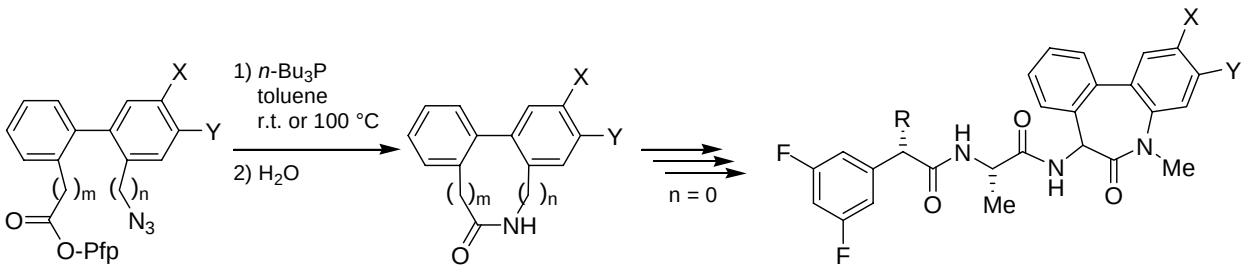
Scheme 24

Utilizing the intramolecular aza-Wittig method many A-ring functionalized derivatives of PBD have been designed by O'Neil's group.[25] These authors have applied this method to synthesize a B-ring modified PBD, benzodiazocine **72** as the first example of an 8-membered cyclic imine (Scheme 25).[52] The requisite amide **83** is obtained from the reaction of 2-azido-benzoyl chloride (**1**) with O-protected homoprolinol. Hydrolysis of the carbonate followed by Dess-Martin oxidation yields the aldehyde **84** which, on treatment with TPP undergoes smooth cyclization to afford the pyrrolobenzodiazocine **72**.



Scheme 25

Recently, Natsugari's group[54] has developed a highly efficient method for the synthesis of medium-sized lactams **86** by the intramolecular Staudinger/aza-Wittig protocol. The intra-molecular aza-Wittig imino-cyclization reaction with the carbonyl group of pentafluorophenyl ω-azido esters **85** followed by hydrolysis proceeds smoothly under high dilution conditions at room temperature affording 7- and 8-membered lactams **86a**–**d**; conversion into 9- and 10-membered lactams **86e,f** requires heating at 100 °C to obtain satisfactory yields (Scheme 24). This procedure has been applied to the synthesis of several analogs **87a** of the potent γ-secretase inhibitor LY411575 **87b** (Scheme 26).[53]



85

Pfp = perfluorophenyl

86a: m = 1, n = 0, X, Y = H (76%)
86b: m = 1, n = 0, X = H, Y = OBn (81%)
86c: m = 1, n = 0, X = OBn, Y = H (99%)
86d: m = n = 1, X, Y = H (93%)
86e: m = 2, n = 1, X, = H (82%)
86f: m = 3, n = 1, X, Y = H (85%)

87a: R, X, Y = H, OMe, $OCH_2C_6H_4$-4-Bz analogs of LY411575

87b: R^1 = OH, X = Y = H LY411575

Scheme 26

Concluding Remarks

Recent progress in the synthesis of heterocyclic natural products by the aza-Wittig methodology has been reviewed focusing on applications of the intramolecular Staudinger/aza-Wittig protocol. The efficient and regioselective construction of nitrogen heterocycles such as quinazolinones, 1,4-benzodiazepinones, and cyclic imines is shown to be the method of choice also for the synthesis of polyfunctional heterocyclic natural products.

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