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Facile Synthesis of Pyrazino[2,3-*e*][1,4]diazepine Derivatives *via* The Intramolecular Aza-Wittig Reaction

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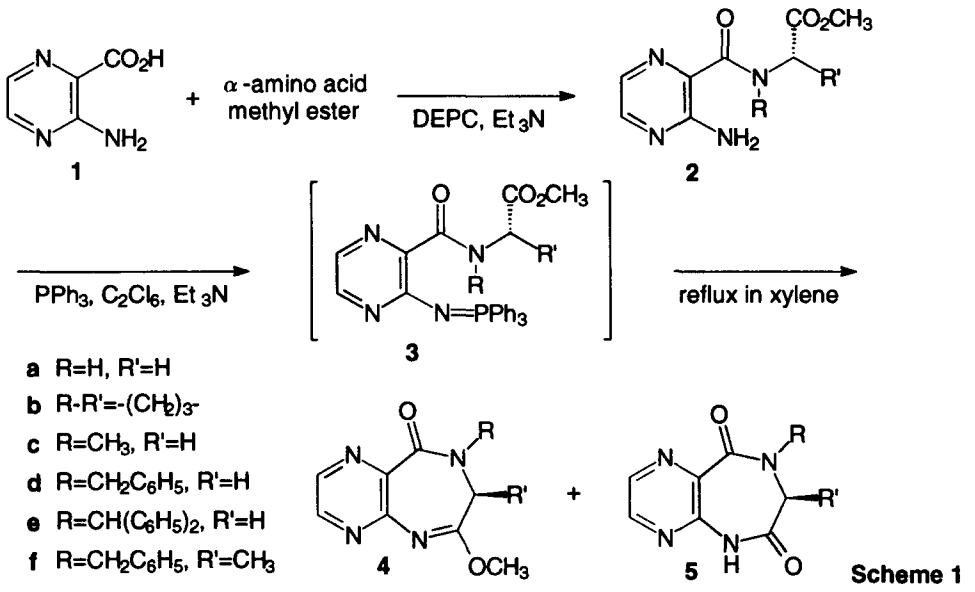
Abstract: Pyrazino[2,3-*e*][1,4]diazepine derivatives were synthesized from 3-aminopyrazine-2-carboxylic acid **1** and α-amino acid esters *via* the intramolecular aza-Wittig reaction.

Over the past decade, the aza-Wittig methodology has received increased attention for its utility in synthesis of C=N (imine) bond-containing compounds, in particular, nitrogen heterocyclic compounds.[1] It is generally known that iminophosphoranes react with carbonyl compounds to form the corresponding imines including heterocumulenes. However, the reactivity of iminophosphoranes is variable in a wide range depending on the substituents of both N and P atoms as well as the carbonyl function.

We have demonstrated recently that the intramolecular aza-Wittig reaction is a powerful tool for synthesis of 5- to 7- membered nitrogen heterocycles such as oxazoles,[2a] imidazolinones,[2b] iminolactams,[2c] 4(3*H*)-quinazolinones,[2b,2d-2g] and 1,4-benzodiazepine-5-ones.[3] On the other hand, the intermolecular aza-Wittig reaction followed by electrocyclization, intramolecular cycloaddition or heterocyclization, *i.e.*, the tandem aza-Wittig and cyclization sequence, has been utilized for synthesis of pyridines, pyrimidines and many other important nitrogen heterocycles by Molina,[1b] Wamhoff,[4] and Motoki *et al.*.[5] Also, *N*-vinyliminophosphoranes are utilized for synthesis of certain heterocycles by Nitta *et al.*.[6] We became interested in preparation of *N*-heteroaryliminophosphoranes because, although these species seem to have been less studied, they are promising building blocks for synthesis of nitrogen heterocycles such as 4(3*H*)-pteridinone derivatives *via* the intermolecular aza-Wittig reaction and heterocyclization.[7] Some fused heterocycles have been prepared *via* such type of iminophosphorane intermediates.

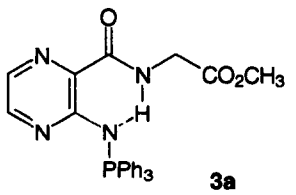
In extension of our study on the intramolecular aza-Wittig reaction with use of *N*-heteroaryliminophosphoranes, we wish to report here a facile synthesis of novel pyrazino[2,3-*e*][1,4]diazepine derivatives by utilizing the corresponding *N*-heteroaryliminophosphoranes. Compounds related to the 1,4-benzodiazepine ring system are known to elicit a wide range of biological activity, for example, anti-tumor antibiotics and psychotropics, *etc.*.[8] Hence, intensive studies of 1,4-benzodiazepines and related compounds have been made to discover a new synthetic route and modified ring systems with new activities. Thus, we examined synthesis of pyrazino[2,3-*e*][1,4]diazepines, 6,9-diaza-analogues of 1,4-benzodiazepines, which are of interest for their potential new activities. The foregoing was based on the relation between methotrexate and its deaza-analogues. In this case, the activity of the former was stronger than that of the latter.[9] At first, we examined synthesis of 3-azidopyrazine-2-carboxylic acid referring to reported synthesis of 1,4-benzodiazepine derivatives; however, we found that it was quite difficult to



Scheme 1

synthesize and/or isolate the corresponding azide derivatives by the standard method using sodium nitrite and sodium azide in aqueous acid. Thus, we planned an alternative synthetic route of 1,4-diazepine derivatives as follows.

3-Aminopyrazine-2-carboxylic acid **1** and α-amino acid ester were condensed to form amides **2**, and then the primary amino function was converted to an iminophosphorane by the Kirsanov type reaction. At first, DCC (*N*, *N'*-dicyclohexylcarbodiimide), as one of the most promising condensation reagents, was used to form amide **2a** from **1** and glycine methyl ester; however, no reaction occurred at all. When DEPC (diethyl phosphorocyanidate)[10] instead of DCC was used (0°C, 1 h ; r.t., 40 min in DME (1,2-dimethoxyethane)), the desired amide **2a** was formed in high yield (76%). In addition, DMC (2-chloro-1,3-dimethylimidazolinium chloride)[11] was useful as a condensation reagent, yielding **2a** in 74% (0°C, 1 h ; r.t., 40 min in DME). In these condensations, DEPC as a liquid reagent was more convenient to deal with than DMC as a solid reagent. Amide derivatives **2b–f** were similarly obtained from **1** and α-amino acid esters in good yields (Table 1). The primary amino function of these amide derivatives was converted into the corresponding iminophosphorane by the modified Kirsanov reaction (Scheme 1). The aza-Wittig reaction was first carried out sequentially by heating the reaction mixture to reflux without isolation of iminophosphorane **3** to avoid hydrolysis during workup by chromatography.[12] Thus, amide **2a** was converted to the corresponding iminophosphorane **3a** with PPh_3, C_2Cl_6 and Et_3N in xylene at 80°C for 3 h (TLC monitored), and then the mixture was heated to reflux for 72 h; however, no cyclization took place at all in this case. Very strong intramolecular hydrogen bonding between the iminophosphorane and the amide proton may inhibit the aza-Wittig reaction (Figure 1).[3b] However, when **2b** prepared from L-proline methyl ester was treated similarly, the



3a

Intramolecular hydrogen bond

Figure 1

Table 1 Synthesis of amides **2**

Entry	α - Amino acid esters	Method [a]	Amides	Yield (%)
1	glycine methyl ester	A	**2a**	76
2	glycine methyl ester	B	**2a**	74
3	L-proline methyl ester	A	**2b**	76
4	sarcosine methyl ester	A	**2c**	72
5	*N*-benzyl glycine methyl ester	A	**2d**	95
6	*N*-(1,1-diphenylmethyl) glycine methyl ester	A	**2e**	69
7	*N*-benzyl L-alanine methyl ester	A	**2f**	95

[a] In method A, DEPC was used and in method B, DMC was used. [b] Isolated yield.

Table 2 Synthesis of pyrazino[2,3-*e*][1,4]diazepines

Entry	Amides	Reaction condition temp., (℃) time, (h)	Pyrazino[2,3-*e*] [1,4]diazepines	Yield (%)[c]
1	**2a**	140, 72 [a]	**4a** + (**5a**)	N.D.[d]
2	**2b**	140, 24 [a]	**4b** + (**5b**)	77 + (18)
3	**2b**	140, 168 [b]	**4b** + (**5b**)	N.D. + (77)
4	**2c**	140, 135 [a]	**4c** + (**5c**)	50 + (34)
5	**2d**	140, 72 [a]	**4d** + (**5d**)	76 + (22)
6	**2e**	140, 480 [a]	**4e** + (**5e**)	26 + (N.D.)
7	**2f**	140, 72 [a]	**4f** + (**5f**)	61 + (N.D.)

[a] *Via* iminophosphorane **3**. [b] From amide **2b**. [c] Isolated yield. [d] Not detected.

cyclization to a 7-membered ring compound, pyrazino[2,3-*e*][1,4]diazepine derivative proceeded smoothly. This compound was proved to be **5b**,[13] a hydrolyzed product of **4b** at the imidate group (Scheme 1). The cyclization to **5b** without the iminophosphorane proceeded very sluggishly only under more severe conditions (140°C, 168h, 77%, see entry 3 in Table 2). In addition, removal of triethylamine hydrochloride generated in the Kirsanov reaction by filtration prior to the aza-Wittig reaction afforded the desired product, **4b**[14] in 77% yield accompanied with **5b**[15] (18%) as a by-product (entry 2 in Table 2). A series of 1,4-diazepine derivatives was prepared in the same way by using *N*-monoalkylated α-amino acid esters[16] (Table 2).

In summary, we have demonstrated that pyrazino[2,3-*e*][1,4]diazepine-5-one derivatives as novel hetareno-annulated[1,4]diazepine derivatives can be synthesized from amide derivatives of 3-aminopyrazine-2-carboxylic acid **1** and α-amino acid esters by the intramolecular aza-Wittig cyclization. Further studies on synthetic potential of these *N*-heteroaryliminophosphoranes in heterocyclic chemistry are

in progress .

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11. We thank Shiratori Pharmaceutical Co., Ltd. for a gift of DMC.
12. Iminophosphorane **3** was isolable after flash chromatography on silica gel column; however, it was hygroscopic and hydrolyzed gradually to the starting amide **2**.
13. These new compounds had satisfactory spectral and analytical data for the given structures. The assigned stereochemistry was based on the fact that no racemization was found to occur during the condensation with use of DEPC (ref. 11) and the intramolecular aza-Wittig reaction (ref. 5).
14. Compound **4b** had a characteristic ^{1}H-NMR ($CDCl_3$, 200MHz) signal at δ 4.05 (3H, $OC\underline{H}_3$, s).
15. Compound **5b** had a characteristic ^{1}H-NMR ($CDCl_3$, 200MHz) signal at δ 9.73 (1H, $N\underline{H}CO$, br).
16. *N*-Benzyl α-amino acid esters for entries 5 and 7 were prepared as follows. Glycine and L-alanine methyl ester hydrochlorides were treated with benzyl bromide and triethylamine to afford *N*, *N*-dibenzyl derivatives, which were converted to *N*-monobenzyl derivatives by Pd-C/H_2, respectively.

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