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Synthesis of Pyrazine-phosphonates and -Phosphine Oxides from 2*H*-Azirines or Oximes

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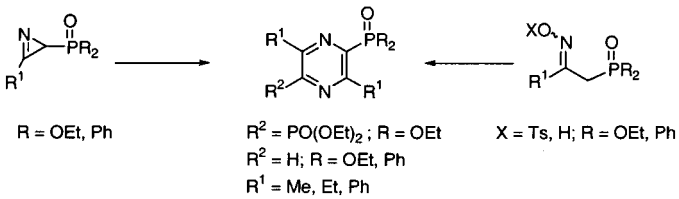
ABSTRACT



Tetrasubstituted pyrazines containing two phosphonate groups 2 in positions 2 and 5 and trisubstituted pyrazines containing a phosphonate 5 or a phosphine oxide group 7 in position 2 are obtained by thermal treatment of 2*H*-azirine-2-phosphonates 1 and -phosphine oxides 6. These pyrazines can also be prepared from *β*-ketoxime tosylates 9 and 10 or from oxime derived from phosphine oxide 11.

Pyrazines are widely used intermediates in medicinal chemistry and for functional transformations.[1,2] Pyrazines and especially 2,5-disubstituted pyrazines, which are biosynthesized from amino acids, are common units in a wide variety of marine natural products with cytostatic and antitumor properties,[3] while pyrazinamide[4] **Ia** (Figure 1, R = NH_2) and more recently pyrazinesters[5] **Ib** (Figure 1, R = OR) have been successfully evaluated in vitro and in vivo for antituberculosis activity. Furthermore, it is known that phosphor substituents regulate important biological functions[6] and that molecular modifications involving the introduction of organophosphorus functionalities could increase their biological activity, in a manner similar to that reported for other pharmaceuticals.[6] For these reasons, pyrazines containing one

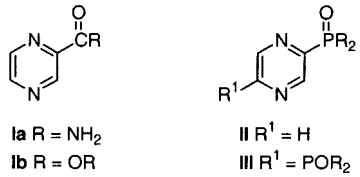


Figure 1.

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(2-position; **II**, Figure 1) or two (2,5-positions; **III**, Figure 1) phosphorus substituents are expected to play a role similar to that observed in their isosteric analogues **I** and could possess biological activity and be used in the preparation of new complex derivatives containing a pyrazine ring and phosphorus substituents. However, as far as we know, no examples of pyrazines containing phosphorus substituents have been described.

Recently, we reported the first asymmetric synthesis of 2*H*-azirines[7] derived from phosphine oxides[8] and the preparation of 3-substituted alkyl and aryl 2*H*-azirine-2-phosphonates[9,10] by alkaloid-mediated Neber reaction of tosyl oximes. A recent publication[11] reporting the preparation and synthetic use of chiral 2-aryl-2*H*-azirine-3-phosphonates prompted us to report our own results concerning the synthesis of the until now unknown pyrazines containing one (2-position; **II**, Figure 2) or two (2,5-positions; **III**, Figure 2) phosphorus

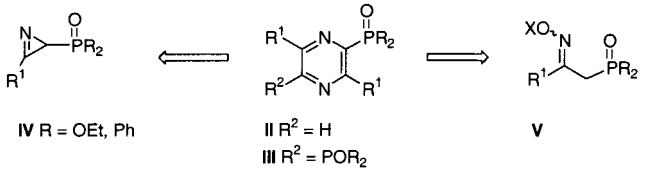
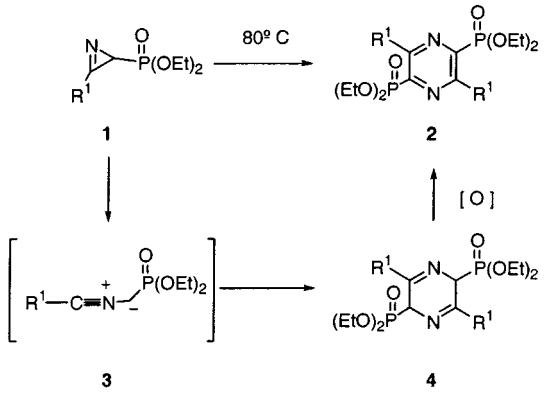


Figure 2.

substituents from easily available azirines derived from phosphonates or phosphine oxides (**IV**, Figure 2) or from their precursors (**V**, Figure 2). The key step is based on the dimerization reaction of azirines.[7a,12]

Ring opening and selective dimerization of 3-alkyl-2*H*-azirine phosphonates **1a** ($R^1 = CH_3$) and **1b** ($R^1 = C_2H_5$)

Scheme 1



took place when these azirines **1a**,**b** were heated (2 h) at 80 °C without solvent to give in almost quantitative yields 3,6-dialkyl pyrazines containing two phosphonate groups in 2,5-positions **2** (Scheme 1, Table 1, entries 1 and 3).[13] Spectro-

Table 1. Synthesis of Phosphorylated Pyrazines **2**, **5** and **7**

entry	compound	R	R^1	yield[a]
1	**2a**	OEt	Me	97[b]
2	**2a**	OEt	Me	61[c]
3	**2b**	OEt	Et	98[b]
4	**2b**	OEt	Et	68[c]
5	**5c**	OEt	Ph	42[d]
6	**5c**	OEt	Ph	90[e]
7	**7a**	Ph	Me	70[e]
8	**7a**	Ph	Me	74[c]
9	**7a**	Ph	Me	53[f]
10	**7b**	Ph	Et	68[e]

[a] Yields refer to isolated compounds. [b] From azirines **1a**,**b**, 80 °C, 2 h. [c] From tosyloximes **9a**,**b**, **10a**, rt, 14 h. [d] From azirine **1c**, 120 °C, 2 h. [e] From azirines **1c**, **6a**,**b**, refluxing toluene, 2 h. [f] One-pot procedure from oxime **12a**.

scopic data were in agreement with the assigned structure of compounds **2**. Mass spectrometry of **2a** showed the molecular ion peak (2%), while in the ^{31}P NMR spectrum the phosphonate group resonated at $\delta_P = 9.7$ ppm. The ^{13}C NMR spectrum showed an absorption at $\delta_C = 146.5$ ppm as a doublet with a coupling constant $^1J_{PC} = 228.4$ Hz for carbon atoms directly bonded to the phosphorus (C-2 and C-5) and a double doublet at $\delta_C = 153.4$ ppm with coupling constants $^2J_{PC} = {}^3J_{PC} = 23.0$ Hz for both C-3 and C-6 of the heterocycle.

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(11) The asymmetric synthesis of dimethyl 2-aryl-2*H*-azirine-3-phosphonates with a small proportion of the isomeric 3-aryl-2*H*-azirine-2-phosphonate by Swern oxidation of chiral *cis*-aziridine phosphonates and the use as a dienophile in cycloaddition reactions of 2*H*-azirine-3-phosphonates have been recently reported. Davis, F. A.; Wu, Y.; Yan, H.; Prasad, K. R.; McCoull, W. *Org. Lett.* **2002**, *4*, 655−658.

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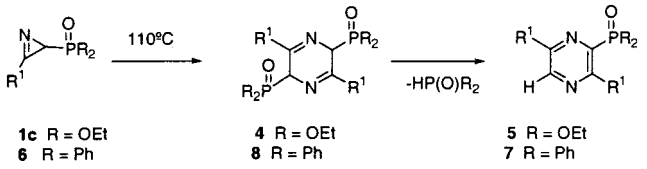
(13) **General Procedure for the Preparation of Pyrazine Phosphonates (2a,b) from Azirines 1.** The corresponding azirine (**1a**,**b**; 1 mmol) was heated at 80 °C for 2 h under a N_2 atmosphere. The crude product was purified by chromatography using silica gel (hexane/ethyl acetate).

The formation of pyrazines **2** could be explained by selective ring opening of azirines **1** involving the C−C single bond and formation of unstable nitrile ylide dipoles **3**, followed by dimerization of the dipole[7a,12f,14] and oxidation of the resulting dihydropyrazines **4**, although an alternative mechanism with formation of vinyl nitrene intermediates by C2−N ring opening of azirines **1**, followed by dimerization[7a,15] and oxidation of resulting dihydropyrazines **4**, cannot be totally excluded (Scheme 1).

However, in the case of 3-phenyl-2*H*-azirine phosphonate **1c** ($R^1 = C_6H_5$, R = OEt), it was necessary to use more drastic reaction conditions. First, azirine **1c** was heated at 120 °C without solvent and (3,6-diphenyl pyrazin-2-yl)-phosphonate **5c** ($R^1 = C_6H_5$, R = OEt) containing only one phosphonate group in the 2-position was obtained in a moderate yield (Scheme 2, Table 1, entry 5). However, the

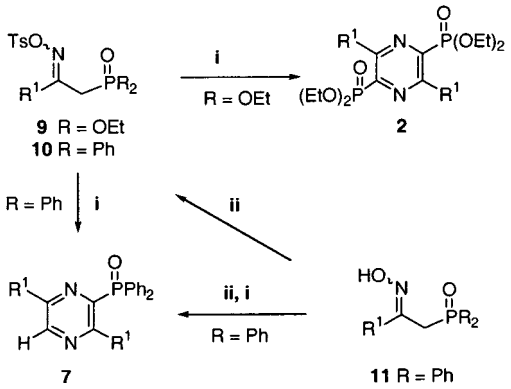
Scheme 2



yield reached 90% when the reaction was performed in refluxing toluene (Scheme 2, Table 1, entry 6). Spectroscopic data were in agreement with pyrazine phosphonate **5c**. Mass spectrometry of **5c** showed the molecular ion peak (27%). In the ^{31}P NMR spectrum, the phosphonate group resonated at $\delta_P = 10.1$ ppm; in the ^1H NMR spectrum, there appears an absorption at $\delta_H = 9.07$ ppm as a doublet with a long-range coupling constant $^5J_{PH} = 4.6$ Hz for H-4, while the ^{13}C NMR spectrum of **5c** showed doublets at $\delta_C = 136.6$ ppm ($^1J_{PC} = 185.3$ Hz) for C-2, 141.7 ppm ($^4J_{PC} = 3.5$ Hz) for C-5, 149.4 ppm ($^2J_{PC} = 17.1$ Hz) for C-3, and 155.6 ppm ($^3J_{PC} = 26.1$ Hz) for C-6. The scope of the reaction was not limited to azirines derived from phosphonate **1c**, given that thermal heating of 3-alkyl azirine phoshine oxides **6a** ($R^1 = CH_3$) and **6b** ($R^1 = C_2H_5$) in refluxing toluene led to the formation of pyrazine phosphine oxides **7a**,**b** (Scheme 2, Table 1, entries 7 and 10).[16] However, 3-phenyl azirine phosphine oxides **6c** ($R^1 = C_6H_5$) seem to be somewhat more stable than the corresponding alkyl-substituted azirines **6a**,**b**, since heating 3-phenyl azirine **6c** in refluxing toluene did not give the pyrazine and the starting product **6c** was recovered instead. The formation of pyrazines **5** (R = OEt) and **7** (R = Ph) could be explained, as before, by selective ring opening of azirines **1c** and **6** involving the C−C single bond, dimerization of the dipole intermediate, and aromatization with the loss of diethyl phosphite ($HPO(OEt)_2$) or diphenyl phosphine oxide ($HPOPh_2$) from resulting dihydropyrazines **4** (R = OEt) or **8** (R = Ph) (Scheme 2).

Taking into account that phosphorylated azirines **1** (R = OEt) and **6** (R = Ph) can be easily prepared from oximes,[8,9] we explored whether *p*-toluenesulfonyl oximes derived from phosphonates **9** (R = OEt) and phosphine oxides **10** (R = Ph) or their oxime precursors **11** (R = Ph) could also be used as synthons for the preparation of phosphorus-substituted pyrazines **2** and **7**. Treatment of *p*-toluenesulfonyl oximes derived from phosphonates **9** (R = OEt) with primary or secondary amines (α-methylbenzylamine, diethylamine, piperidine) at room temperature gave pyrazines **2** (Scheme 3, Table 1, entries 2 and 4).[17] Similarly, pyrazine phosphine

Scheme 3[a]



[a] Reaction conditions: (i) R_2NH, 25 °C; (ii) TsCl, Py.

oxide **7a** can be obtained from *p*-toluenesulfonyl oxime derived from phosphine oxide **10a** (R = Ph) in the presence of piperidine (Scheme 3, Table 1, entry 8). These results suggest that in these cases, vinyl nitrene intermediates or unstable nitrile ylide dipoles **3**, generated from oximes **9** and **10**, followed by dimerization[7a,14] and oxidation of the resulting dihydropyrazines **4**, could explain the formation of pyrazines **2** and **7**. From a synthetic point of view, it is noteworthy that pyrazine **7a** can also be prepared in a one-pot procedure from oxime derived from phosphine oxide **11a** (R = Ph). The preparation of *p*-toluenesulfonyloxime **10a** (R = Ph) was performed in situ by reaction of functionalized *β*-oxime **11a** (R = Ph) with *p*-toluenesulfonyl chloride in pyridine, and after filtration of the pyridinium salt, a secondary amine (piperidine) was added to give substituted pyrazine phosphine oxide **7** (Scheme 3, Table 1, entry 9).

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(16) **General Procedure for Preparation of Pyrazine Phosphonate (5c) and Pyrazine Phosphine Oxides (7a,b) from Azirines 1c, 6a,b.** A solution of the corresponding azirine (1 mmol) in dry toluene (5 mL) was refluxed for 2 h under a N_2 atmosphere. The crude product was purified by chromatography using silica gel (hexane/ethyl acetate).

(17) **General Procedure for Preparation of Pyrazine Phosphonate (2a,b) and Pyrazine Phosphine Oxides (7a,b) from Tosyloximes (9, 10).** To a well-stirred solution of the corresponding tosyloxime (1 mmol) **(9a**,**b**, **10a)** in dry benzene or EtOH was added under a N_2 atmosphere a secondary amine (1.2 mmol) (diethylamine, piperidine). The reaction was allowed to stay at room temperature for 14 h. The resulting mixture was washed three times with distilled water (5 mL), extracted with CH_2Cl_2, dried over anhydrous $MgSO_4$, and evaporated under vacuum. The crude product was purified by chromatography using silica gel (hexane/ethyl acetate).

In conclusion, the first synthesis of phosphorylated analogues of pyrazinamides such as substituted pyrazines containing two phosphonate groups (2,5-positions) **2** and pyrazines containing one phosphonate group (2-position) **5** or a phosphine oxide group (2-position) **7** is described. The process could imply thermal ring opening of 2*H*-azirines derived from phosphonates **1** or phosphine oxides **6** and dimerization of unstable nitrile ylide intermediates. Pyrazines **2** and **7** can also be obtained in a one-pot procedure from tosyloximes **9** and **10** or from oxime **11**. Phosphorylated pyrazines may be important synthons in organic synthesis and for the preparation of biologically active compounds of interest to medicinal chemistry.[3−5]

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Supporting Information Available: General procedures and characterization data of compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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