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1,3-Dipolar addition of diethyl diazomethylphosphonate onto a C=N double bond. Synthesis of triazolinyl and aziridinyl phosphonates

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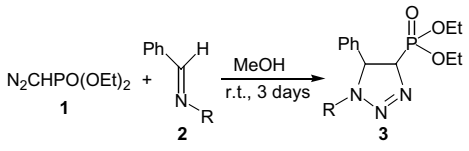
Abstract—Cycloaddition of diethyl 1-diazomethylphosphonate onto a C=N double bond is described. It was found that the reaction of this phosphorus diazomethane with benzylidene-alkyl-amines resulted in the formation of (1-alkyl-5-phenyl-4,5-dihydro-1*H*-[1,2,3]triazol-4-yl)-phosphonic acid diethyl esters, whereas its reaction with methylene-aryl-amines, generated from the corresponding hexahydro-1,3,5-triazines, led to diethyl esters of (aziridin-2-yl)-phosphonic acid.

Aziridine-2-carboxylates are important building blocks for the synthesis of α- or β-amino acids as they can undergo highly regiocontrolled and stereoselective ring-opening reactions.[1] Aziridine-2-phosphonates are expected to play a similar role in the synthesis of α- or β-amino phosphonates.[1] Although methods for the synthesis of aziridine-2-carboxylate esters are well established,[2] there are only a few reports on the synthesis of their P-counterparts. The first was obtained in moderate yield from diethylvinylphosphonate.[3] Racemic aziridine 2-phosphonates have been prepared by the copper catalysed aziridination of vinylphosphonates with [*N*-(*p*-toluenesulfonyl)imino]-phenyliodonane[4] or *N*-[(4-nitrobenzene)sulfonyl]oxy-carbamate[5] and the Darzens-type addition of lithiated chloromethylphosphonate anions to an imine[6] or a sulfinimine.[7] Moreover, 1-vinyl-2-phosphono-aziridines were obtained by the reaction of diazomethane with 1-phosphono-2-aza-1,3-dienes.[8]

Phosphorus diazomethanes have been the most frequently used phosphorus reagents for efficient one-carbon homologation of aldehydes/ketones to terminal/internal alkynes but, to the best of our knowledge, the reaction of these reagents with a C=N double bond has never been applied in the synthesis of three- or five-membered rings.

In this letter we describe our preliminary results on the synthesis of Δ^2-1,2,3-triazolinyl-4- and aziridinyl-2-phosphonates by the cycloaddition of diethyl diazomethyl-phosphonate[9] on to a C=N double bond.

Our initial work focused on the reaction of diethyl diazomethylphosphonate **1** with benzylidene-*N*-alkyl-amines **2a–d**. The reaction with **2a** was carried out in various solvents at room temperature over several days and monitored by ^{1}H NMR spectroscopy. The best result was obtained in methanol for three days in darkness (Scheme 1), giving (1-methyl-5-phenyl-4,5-dihydro-1*H*-[1,2,3]triazol-4-yl)-phosphonic acid diethyl ester **3a** in 77% yield[10] as a single isomer. Similarly, products **3b–d** were obtained in 70–80% yields (Table 1). The configuration of the ring substituents was not studied in detail but the high value of coupling constants *J* (11.7 Hz) between protons at C-4 and C-5 suggests their *trans* arrangement.[11]



Scheme 1.

Keywords: Triazolines; Aziridines; Phosphonic diethyl esters; Cycloaddition.
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Table 1. Preparation of the 4,5-dihydro-1*H*-[1,2,3]triazol-4-yl)-phosphonic acid diethyl esters **3a–d** from imines **2a–d**

Entry	Imine	R	Product (yield, %)[a]
1	**2a**	Me	**3a** (78)
2	**2b**	Et	**3b** (71)
3	**2c**	*i*-Pr	**3c** (82)
4	**2d**	*t*-Bu	**3d** (83)

[a] All the yields refer to isolated products.

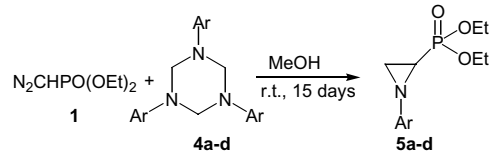
Products **3a–d** were purified chromatographically and characterised by spectroscopic methods. It should be noted that only one method of the synthesis of 1,2,3-triazoline systems containing a diethyl or dimethyl phosphonate had previously been described by reactions of aryl azides with vinylphosphonates.[11] On the other hand our method permits preparation of 1-alkyl- but not 1-aryl-triazolines. All attempts of reactions in question using *N*-aryl imines were unsuccessful.

Although a thermal ring contraction of 1,2,3-triazolines to aziridines is a well-established process,[12] all attempts of N_2-elimination from triazines **3a–d** by thermolysis or photolysis failed. Thus, thermolyses performed under FVT conditions or in high boiling solvents afforded only imines **2** as retro-addition products. In all cases, UV-irradiation of **3** gave complicated mixtures of many components, however, the formation of desired aziridines was not observed.

In parallel investigations, we also studied the cycloaddition reactions of **1** with hexahydro-1,3,5-triazines as precursors of reactive *N*-methylenamines. When mixtures of **1** and 0.33 equiv of 1,3,5-triaryl-hexahydro-1,3,5-triazine: **4a–d** in methanol were left for 15 days in darkness (the progress of reactions was monitored by ^{1}H NMR), the corresponding aziridines **5a–d** were obtained in good yields (Scheme 2, Table 2).

These products were purified by chromatography and identified by spectroscopic methods.[13]

The results show that the cycloaddition of **1** onto a C=N double bond formed in situ, affords the corresponding triazolines, which undergo a spontaneous extrusion of N_2 to aziridines **5**. The fact that these reactions occurred in the absence of a catalyst is remarkable.



Scheme 2.

Table 2. Preparation of the (1-aryl-aziridin-2-yl)-phosphonic acid diethyl esters **5a–d**

Entry	Triazine	Ar	Product (% yield)[a]
1	**4a**	C_6H_5	**5a** (67)
2	**4b**	*p*-$CH_3C_6H_4$	**5b** (70)
3	**4c**	*p*-ClC_6H_4	**3c** (78)
4	**4d**	*o*-$CH_3C_6H_4$	**3d** (74)

[a] All the yields refer to isolated products.

In summary, addition of diethyl 1-diazomethylphosphonate onto C=N double bonds seems to provide a practical alternative to the existing methods to prepare azacycles with a phosphonate group. Further studies directed towards an application of various catalysts in this reaction are in progress.

Acknowledgements

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10. For example **3a**. Purified by chromatography on Al_2O_3 (hexane/AcOEt). Colourless oil. ^{1}H NMR ($CDCl_3$): 1.29 (t, *J* 7 Hz, 3H), 1.34 (t, *J* 7 Hz, 3H), 3.20 (s, 3H), 4.13–4.27 (m, 4H), 4.54 (dd, $^3J_{HH}$ 11.7 Hz, $^3J_{HP}$ 19.6 Hz, 1H), 4.55 (dd, $^3J_{HH}$ 11.7 Hz, $^2J_{HP}$ 30.1 Hz, 1H), 7.24–7.39 (m, 5H). ^{13}C NMR ($CDCl_3$): 16.40 (d, $^3J_{CP}$ 4.6 Hz, CH_2CH_3), 16.48 (d, $^3J_{CP}$ 4.3 Hz, CH_2CH_3), 35.17, (NCH_3), 62.78 (d, $^2J_{CP}$ 6.9 Hz, CH_3CH_2), 63.45 (d, $^2J_{CP}$ 6.9 Hz, CH_3CH_2), 64.95 (C_5), 82.73 (d, $^1J_{CP}$ 161.2 Hz, C_4), 126.90, 128.46, 128.93 ($3\times C_{ar}$), 138.11 (d, $^3J_{CP}$ 10.3 Hz, C_q). ^{31}P NMR ($CDCl_3$): 19.32. [Found: C, 52.74; H, 6.99; N, 14.00. $C_{13}H_{20}N_3O_3P$ (289.37) requires C, 52.52; H, 6.78; N, 14.13%].
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13. For example **5a**. Purified by SiO_2-chromatography (hexane/AcOEt). Colourless oil. ^{1}H NMR ($CDCl_3$): 1.33 (t, *J* 6.9 Hz, 6H), 2.03–2.70 (m, 3H), 4.10–4.43 (m, 4H), 6.85–7.40 (m, 5H). ^{13}C NMR ($CDCl_3$): 16.45 (CH_3CH_2), 16.69 (CH_3CH_2), 31.65 ($^2J_{CP}$ 4.9 Hz, C_3), 32.68 ($^1J_{CP}$ 217.3 Hz, C_2), 62.81 (d, $^2J_{CP}$ 6.1 Hz, CH_3CH_2), 63.12 (d, $^2J_{CP}$ 6.1 Hz, CH_3CH_2), 120.91, 123.56, 129.36 ($3\times C_{ar}$), 153.65 (d, $^3J_{CP}$ 6.1 Hz, C_q). IR (neat): 2984, 1599, 1492, 1453, 1392, 1368, 1358, 1256, 1165, 1097, 1052, 1026, 966, 797, 766, 730, 696. MS (*m/e*, %): 255 (M^+, 87), 226, 198, 182, 168, 147, 146, 132, 119, 118, 117, 109, 105, 104, 92, 91(100), 81, 77, 65, 51. HRMS: calcd for $C_{12}H_{18}NO_3P$ M 255.10192, found $M^{+\cdot}$ 255.10243.