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A Novel Approach to Phosphonyl–Substituted Heterocyclic System(I)

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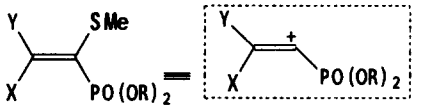
Abstract: The synthesis of α,α-dicyano (α-cyano-α-ethoxycarbonyl) phosphonyl/ S-methyl ketene acetals **2** is reported and the utility of **2** as synthetic equivalent for 1-phosphonyl-2-cyanoethene cation (I) is demonstrated. Phosphonyl–substituted pyrazoles, isoxazoles and pyrimidines have been synthesized through cyclization reaction of **2** with various binucleophilic reagents. © 1997 Elsevier Science Ltd.

The increasing and sustained interest in phosphonyl heterocyclic compounds related to biochemical/biological, pharmacological and pesticidal research had an explosive impact on the development of new synthetic methods for the synthesis of those compounds. Of special value for the preparation of phosphonyl–substituted heterocyclic compounds, substances of paramount interest in pharmaceutical and agrochemical field is the evolution of new building block, such as β-phosphonic enamines[1], isocyanomethyl phosphonate[2], β-functional γ-oxo-alkylphosphonates[3], and acetylenic phosphonate[4]. However, severe limitations are also encountered and only few attempts have been made to develop a general method for various phosphonyl–substituted heterocyclic compounds.



II I

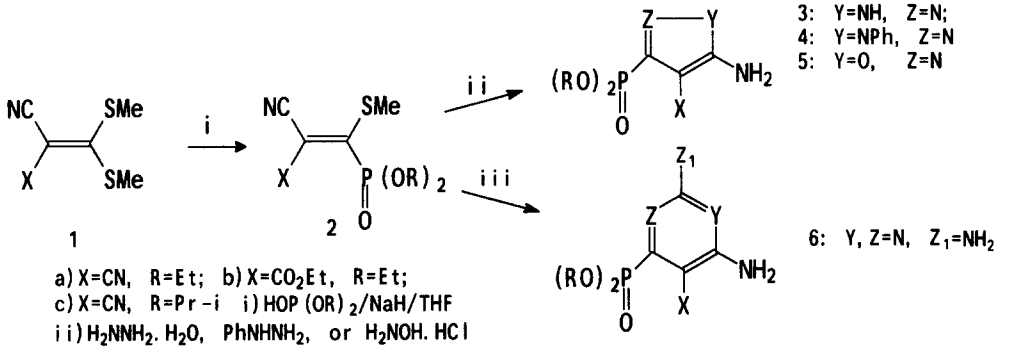
X,Y = CN, C(O)R, C(O)OEt, C=NR, NO_2, etc.

In connection with a project directed towards the design and synthesis of novel ALS(acetolactate synthase) inhibitors with high activities against weeds and acceptable soil half-life(<30 days)[5]. A novel route for various phosphonyl heterocyclic compounds is being pursued. Our effects in this area have centered upon the development of a useful building block **II** derived from α-cyano(oxo, ethoxycarbonyl, nitro, etc.) ketene dithioacetals, which on reaction with various binucleophilic reagents would afford various phosphonyl–substituted heterocyclic compounds.

The basis for this research arose after consideration of ketene dithioacetal chemistry. The chemo- and

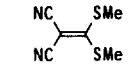
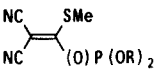
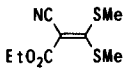
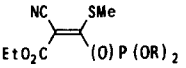
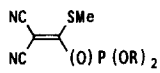
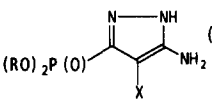
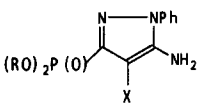
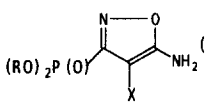
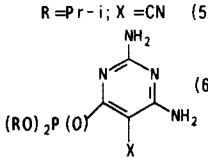
stereo–selective conjugate addition of the amine, organocuprate and Grignard reagent with the ketene dithioacetal is well documented[6], and to the best of our knowledge there is no reported example of the addition of phosphite to the ketene dithioacetal. Therefore, we chose to examine whether the conjugate addition of the phosphite to the ketene dithioacetal occurs to afford the corresponding phosphonyl/S-methyl α-cyano(oxo, ethoxycarbonyl etc.) ketene acetals--novel three carbon fragment (building block) for the synthesis of various phosphonyl heterocyclic compounds.

The α, α-dicyano and α-cyano-α-ethoxycarbonyl ketene dithioacetals were readily prepared from malononitrile and ethyl cyanoacetate respectively. The ketene dithioacetal **1a** underwent smooth conjugate addition with diethyl phosphite in the presence of an excess amount of NaH in anhydrous THF to afford α, α-dicyano phosphonyl/S-methyl ketene acetal **2a** quantitatively. When **1b** was reacted with diethyl phosphite, work up of reaction mixture gave α-cyano-α-ethoxycarbonyl phosphonyl/S-methyl ketene acetal **2b** in 95% with exclusive E-configuration. No trace of the corresponding Z stereoisomer or the product arising by replacement of the second thiomethyl group was detected in the reaction mixture, by HPLC, ^{1}H NMR, and ^{31}P NMR spectroscopy. The stereochemistry of **2b** was supported by the cyclization product (giving cyclization product **3** quantitatively). When R=i-OPr, the reaction was somehow slower, but still completed within about 6h, this might be attributed to the steric effect of isopropyl group.



It has been reported that α-oxo ketene dithioacetals may be cyclized with binucleophilic reagents to give various heterocyclic compounds, such as pyrazole, isoxazole[6]. Our attempts to react the α-cyano phosphonyl/S-methyl ketene acetal **2(a, b, c)** with hydrazine hydrate in ethanol under refluxing failed, but resulted in polymerization. Finally, cyclization reaction of **2(a, b, c)** with hydrazine hydrate to construct 5-amino-4-cyano(ethoxy-carbonyl)-3-phosphonyl pyrazole **3** (see Table 1) was achieved under carefully controlled reaction temperature -5~0 ℃ in essentially quantitative yield. Similarly, reaction of **2(a, b, c)** with hydroxylamine hydrochloride in the presence of sodium ethoxide in ethanol afforded 5-amino-4-cyano(ethoxycarbonyl)-3-phosphonyl isoxazole **5** in good yield at -5-0 ℃.

Table 1. Synthesis of α-Cyano Phosphonyl/S-methyl Ketene Acetals 2 and Phosphonyl–Substituted Heterocyclic Compounds(3, 4, 5, 6)

Entry	Substrate	Reagent/ Conditions	Product (num.) X; R	Yield(%)*	^{31}P NMR ppm
1		3eq $(EtO)_2P(O)H$ 2eq NaH/ THF	 (2a) R=Et	99.0	27.86
2		3eq $(EtO)_2P(O)H$ 2eq NaH/ THF	 (2b) R=Et	94.5	28.67
3		3eq $(i\text{-}PrO)_2P(O)H$ 2eq NaH/ THF	 (2c) R=Pr-i	91.3	25.98
4	2a	$NH_2NH_2 \cdot H_2O$/ EtOH	 (3a) R=Et; X=CN	95.8	5.72
5	2b	$NH_2NH_2 \cdot H_2O$/ EtOH	R=Et; X=COOEt (3b)	94.5	9.28
6	2c	$NH_2NH_2 \cdot H_2O$/ i-PrOH	R=Pr-i; X=CN (3c)	90.2	3.59
7	2a	NH_2NHPh/EtOH	 (4a) R=Et; X=CN	94.2	5.64
8	2b	NH_2NHPh/EtOH	R=Et; X=COOEt (4b)	92.5	8.90
9	2c	NH_2NHPh/i-PrOH	R=Pr-i; X=CN (4c)	88.8	3.41
10	2a	$NH_2OH \cdot HCl$/ 1.5eqEtONa/EtOH	 (5a) R=Et; X=CN	93.0	0.86
11	2b	$NH_2OH \cdot HCl$/ 1.5eqEtONa/EtOH	R=Et; X=COOEt (5b)	90.0	3.49
12	2c	$NH_2OH \cdot HCl$/ 1.5eqi-PrONa/i-PrOH	R=Pr-i; X=CN (5c)	79.1	-2.12
13	2a	$NH_2C(NH)NH_2 \cdot HNO_3$/ 1.5eqEtONa/EtOH	 (6a) R=Et; X=CN	89.8	14.82
14	2b	$NH_2C(NH)NH_2 \cdot HNO_3$/ 1.5eqEtONa/EtOH	R=Et; X=COOEt (6b)	88.5	16.23

*reported yields of isolated, chromatographically purified materials.

In a similar manner as above, reaction of **2** with guanidine nitrate in the presence of sodium ethoxide in ethanol gave 5-cyano(ethoxycarbonyl)-2,6-diamino-4-phosphonyl pyri-midine **6**. The structures of phosphonyl heterocycles **2-6** were confirmed on ^{1}H NMR, ^{31}P NMR, and mass spectroscopy and elemental analysis[7]. The 5-amino-4-cyano-3-phosphonyl pyrazole **3(a, b, c)** exhibited a 1-NH resonance peak at ca:11.5ppm in the ^{1}H NMR Spectra. Each phosphonyl–substituted heterocyclic product showed molecule ion in the mass spectrogram.

In summary, we have developed a new building block **(II)** for the synthesis of various phosphonyl–substituted heterocyclic compounds. The application of this method to other heterocyclic systems and the connectivities with further transformations to complex derivatives are aspects of potential synthetic value some of which are under investigation in our laboratory. The structurally diverse group of phosphonyl heterocyclic compounds that have been prepared using the building block **(II)**, viz. α-cyano (oxo, ethoxycarbonyl, nitro, etc.) phosphonyl/S-methyl ketene acetals clearly, demonstrates the high potential they have in the synthesis of various phosphorus containing heterocyclic compounds, which may show excellent bioactivities. We will report additional finding at a later date[8].

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6. Mehta, B. K.; Ile, H.; Junjappa, H. *Tetrahedron Lett.*, **1995**, 36, 1925. b) Thomas, A.; Singh, G.; Ile, H.; Junjappa, H. *Tetrahedron Lett.*, **1989**, 30, 3093. c) Bhat, L. N.; Thomas, A.; Ila, H.; Junjappa, H. *Tetrahedron*, **1992**, 48, 10377. d) Bhat, L. N.; Ila, H.; Junjappa, H. *Synthesis*, **1993**, 959. e) Junjappa, H.; Ile, H. and Asokan, C. V. *Tetrahedron*, **1990**, 46, 5423.

7. All new compounds have been characterized by spectroscopic means. Selected data: **2b** ^{1}H NMR(200MHz) δ($CDCl_3$): 1.295~1.419(m 9H $OCCH_3$ $POCCH_3$); 2.699(s 3H SCH_3); 4.222~4.303(m 6H OCH_2 $POCH_2$); MS 307(M^+ 12.5); 234(28.7); 205(100) **4b** m.p. 98-99 ℃ 1.312~1.381(m 9H $OCCH_3$ $POCCH_3$); 4.248~4.346(m 6H OCH_2 $POCH_2$); 5.500(b 2H NH_2); 7.480~7.504(d 5H C_6H_5); MS: 367(M^+ 23.85), 265(55.78), 212(100).

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