

Heterocycles from Ylides. Part III.¹ Reactivity of Allylic Phosphonium Ylides with 1,3-Dipoles

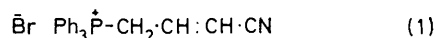
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3-Cyano-, 3-formyl-, and 3-methoxycarbonyl-allylidetriphenylphosphorane react with nitrile imides and nitrile oxides yielding the corresponding substituted pyrazoles and isoxazoles, through elimination of a methyltriphenylphosphonium salt. The differences in reactivity between the foregoing phosphoranes and simple carbonyl-stabilised phosphoranes are discussed.

THE reaction between hydrazone halides and carbonyl-stabilised phosphonium ylides affords pyrazole derivatives.^{2,3} This synthesis is an easy entry to some classes of pyrazoles such as 5-alkoxy- and 5-dialkylamino-substituted compounds.

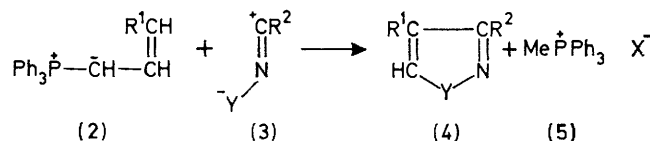
We now report the use of stabilised allylic phosphonium ylides in the preparation of pyrazoles and isoxazole derivatives by reaction with 1,3-dipoles. The ylides employed are vinylogues of carbonyl-stabilised phosphoranes widely used in the synthesis of heterocycles.^{4,5}



3-Cyanoallylbiphenylphosphonium bromide (1) was prepared in 85% yield by treatment of 4-bromocrotononitrile⁶ with triphenylphosphine in acetonitrile at room temperature. The phosphonium salt was converted into the ylide by reaction with aqueous sodium hydroxide as described for 3-methoxycarbonylallylidene-⁷ and 3-formylallylidene-triphenylphosphorane⁸ (2b and c). The ¹H n.m.r. spectrum of the ylide (2a) showed its configuration to be *trans*, as already known for (2b and c).⁹

Treating solutions of the crystalline ylides (2a—c) in chloroform with various 1,3-dipoles (*e.g.* nitrile imides and nitrile oxides) resulted in an extremely clean addition reaction leading, in good yield, to the corresponding pyrazole and isoxazole derivatives (4) (Scheme

1). The structures of the products (4a—f) were consistent with their ¹H n.m.r. spectra and elemental analyses.



	R ¹	R ²	Y	M.p. (°C)	Cryst. solvent	Yield
(4a)	CN	CO ₂ Me	NPh	170—171	MeOH	75
(4b) ^a	CO ₂ Me	CO ₂ Me	NPh	99—100	MeOH	80
(4c)	CO ₂ Me	Ph	NPh	102—103	MeOH	75
(4d) ^b	CHO	Ph	NPh	141—142	EtOH	60
(4e)	CO ₂ Me	C ₆ H ₄ ·NO ₂ -4	O	124—125	EtOH	64
(4f) ^c	CN	C ₆ H ₄ ·NO ₂ -4	O	115—116	EtOH	70

^a L. Balbiano, *Gazzetta*, 1898, **28**, 385. ^b J. D. Kendall and G. Duffin, B.P. 797,144 (*Chem. Abs.*, 1959, **53**, 4984). ^c T. Sasaki and T. Yoshioka, *Bull. Chem. Soc. Japan*, 1968, 2212.

SCHEME 1

The main difference between this reaction and the corresponding one of the carbonyl-stabilised ylides with the same 1,3-dipoles³ is that, in our case, the formation of the five membered heterocycles is accompanied by elimination of a triphenylmethylphosphonium salt.

Our results can be explained in terms of electrophilic attack of the dipole at the γ -carbon atom of the ylide. In this case the positions involved in the formation of the cycloadduct are the β and the γ , without involvement, as in the case of simple carbonyl ylides, of the C=O group.

⁶ W. J. Bailey and J. Bello, *J. Org. Chem.*, 1955, **20**, 525.

⁷ F. Bohlmann and C. Zdero, *Chem. Ber.*, 1973, **106**, 3779.

⁸ M. J. Berenguer, J. Castells, J. Fernandez, and R. M. Galard, *Tetrahedron Letters*, 1971, 493.

⁹ J. R. Neff, R. R. Gruetzmacher, and J. E. Nordlander, *J. Org. Chem.*, 1974, **39**, 3814.

¹ Parts I and II, P. Dalla Croce, *Ann. Chim. (Italy)*, 1973, **63**, 867, 895.

² R. Fusco and P. Dalla Croce, *Chimica e Industria*, 1970, **52**, 45.

³ P. Dalla Croce, *Ann. Chim. (Italy)*, 1973, **63**, 867.

⁴ G. R. Harvey, *J. Org. Chem.*, 1966, **31**, 1587.

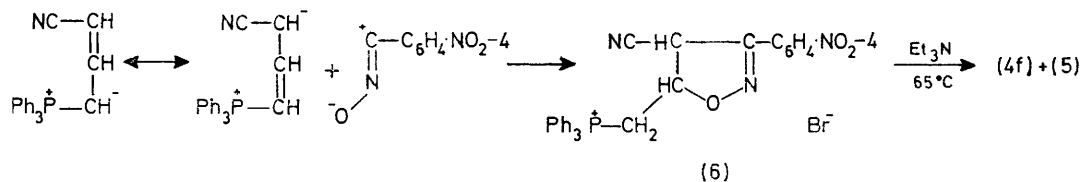
⁵ Y. Hagashi, T. Watanabe, and R. Oda, *Tetrahedron Letters*, 1970, 605.

This fact was experimentally confirmed: the reaction of 3-cyanoallylidetriphenylphosphorane with 4-nitrobenzonitrile oxide in the presence of triethylamine hydrobromide at 0–5 °C afforded [4-cyano-3-(4-nitrophenyl)- Δ^2 -isoxazolin-5-ylmethyl]triphenylphosphonium bromide (6).^{*} On heating with triethylamine in methanol, a nearly quantitative yield of (4f) was obtained (Scheme 2).

The ready elimination of triphenylmethylphosphonium bromide from (6) occurs through a carbanion mechanism, driven by the resulting gain in aromaticity.

EXPERIMENTAL

N.m.r. spectra were measured with a Varian A-60 spectrometer (solvent CDCl_3 ; Me_4Si as internal standard).



SCHEME 2

Elemental analyses for new compounds are available as Supplementary Publication No. SUP 21651 (2 pp.).[†]

3-Cyanoallyltriphenylphosphonium Bromide (1).—Triphenylphosphine (26.2 g) and 4-bromocrotonitrile⁶ (14.6 g) in acetonitrile (70 ml) were left at room temperature overnight. The precipitate was filtered off and recrystallized from ethanol; yield 34.5 g (85%); m.p. 213°.

3-Cyanoallylidetriphenylphosphorane.—The salt (1) (8.16 g) in water (100 ml) was treated with *N*-sodium hydroxide (20 ml) and the product was filtered off; yield 5.9 g (90%); m.p. 164° (from benzene).

^{*} Owing to the lack of solubility of this compound, poor ¹H n.m.r. spectra were obtained from which only qualitative inferences could be drawn.

General Procedure for the Preparation of Heterocyclic Derivatives.—A mixture of the ylide (0.01 mol), the hydrazonyl halide or nitrile oxide (0.01 mol), and triethylamine (0.01 mol) in methanol (50 ml) was kept at room temperature for 2 h and then refluxed for 2 h. The solvent was evaporated off and the residue taken up in benzene (75 ml) and water (25 ml). From the organic solution the heterocyclic compounds (4a–f) were obtained by conventional work-up. Addition of aqueous 60% perchloric acid (2 ml) to the aqueous layer gave triphenylphosphonium perchlorate, m.p. 164° (from methanol).

[4-Cyano-3-(4-nitrophenyl)- Δ^2 -isoxazolin-5-ylmethyl]triphenylphosphonium Bromide (6).—To a stirred solution of 3-cyanoallylidetriphenylphosphorane (3.27 g) in chloroform (50 ml) cooled to 0 °C were added 4-nitrobenzonitrile oxide (1.64 g) and triethylamine hydrobromide (1.81 g). The mixture was set aside for 2 h and evaporated *in vacuo*.

The residue was recrystallized from methanol; yield 2.86 g (50%); m.p. 220°.

4-Cyano-3-(4-nitrophenyl)isoxazole (4f).—A solution of compound (6) (1 g) in methanol (25 ml) was treated with triethylamine (0.5 ml) and refluxed for 2 h. The solvent was evaporated off and the product (4f) (0.32 g, 85%) was obtained from the residue as described above for the preparation of heterocyclic derivatives.

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[†] For details of Supplementary Publications see Notice to Authors No. 7, *J.C.S. Perkin I*, 1975, Index issue.