The Reaction between 3-Aryl-5-methyl-1,2,4-oxadiazoles and Triphenylphosphine: a Fragmentation of the Heterocycle with Deoxygenation

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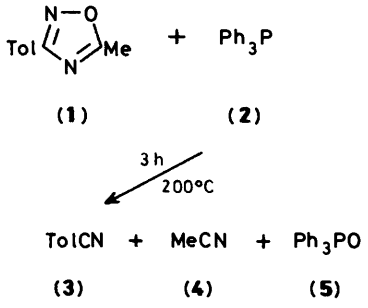
3-Aryl-5-methyl-1,2,4-oxadiazoles react cleanly with triphenylphosphine at *ca.* 200 °C in a bimolecular reaction involving nucleophilic attack at C-3 of the heterocycle to give aryl nitrile, acetonitrile, and triphenylphosphine oxide.

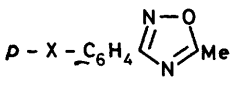
We have previously described[1] reactions between 1,2,4-oxadiazoles and benzyl alcohol and benzylamine that result from nucleophilic attack at C-5 of the heterocycle. We suggested that a nitrene may be an intermediate and attempted to trap such a species by adding triphenylphosphine to the reaction mixtures with benzyl alcohol. However, the phosphine took part in a separate reaction that accompanied reaction with the benzyl derivative. We now describe this reaction.

When 5-methyl-3-(*p*-tolyl)-1,2,4-oxadiazole (**1**) and triphenylphosphine (**2**) are heated together in a sealed glass tube at 200 °C for 3 h, the only products are *p*-toluonitrile (**3**), acetonitrile (**4**), and triphenylphosphine oxide (**5**).

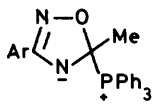


(**1**) (**2**) (**3**) (**4**) (**5**)

Duplicate reactions in diphenyl ether as solvent, using a 20-fold excess of the phosphine (**2**), showed the reaction to be first-order in oxadiazole. Four duplicate reactions, with different starting ratios of phosphine: oxadiazole, showed, from a plot of log(initial rate) against log(initial concentration of phosphine), the reaction to be first-order in triphenylphosphine. Pseudo-first-order reactions over the temperature range 180—220 °C gave values of $E_a = 79.3 \pm 5$ kJ mol^{-1} and $\Delta S^{*} = -177 \pm 10$ J K^{-1} mol^{-1} (at 473 K), consistent with a bimolecular rate-determining step. These kinetic results are summarised in the Table 1. Nucleophilic attack at C-3 of the heterocyclic ring was confirmed by observing the relative reactivities of the four differently *para*-substituted compounds (**1**) and (**6a**—**c**). This was achieved by treating mixtures of equal amounts of two of these oxadiazoles with an excess of triphenylphosphine for times sufficient only for incomplete reaction. The ratio of products was then obtained from ^{1}H n.m.r. spectra at 360 MHz.



(**1**) X = Me
(**6a**) X = Br
(**6b**) X = OMe
(**6c**) X = NMe_2



(**7**)

Table 1. Kinetic results for the reaction of 5-methyl-3-(*p*-tolyl)-1,2,4-oxadiazole (**1**) and triphenylphosphine in diphenyl ether

A Initial [oxadiazole]: 0.38 mol l^{-1}. Bath temp. 200 °C				
(a) Initial [Ph_3P]/mol l^{-1}	0.38	0.76	1.14	1.52
(b) Initial rate/l mol^{-1} s^{-1} (10^6k)	4.5	8.6	16	21
Slope of plot log (a) against log (b) = 1.1				
B Initial [oxadiazole]: 0.076 mol l^{-1}				
Initial [Ph_3P]: 1.53 mol l^{-1}				
Temp./K	457.5	471.5	482.5	494
10^5k^a/l mol^{-1} s^{-1}	1.3	2.45	4.3	5.6

[a] From pseudo-first-order plots.

Table 2. Relative rate constants from incomplete reactions of 5-methyl-3-(*p*-X-phenyl)-1,2,4-oxadiazoles with an excess of triphenylphosphine at 200 °C

Oxadiazole pair (X)	Me/MeO	Me/Br	MeO/NMe_2
Amount reacted (%)	75/50	60/78	72/60
Relative rate constants	Me = 1.0, Br = 2.4, MeO = 0.47, NMe_2 = 0.32		
σ^+	−0.31	0.15	−0.78	−1.7

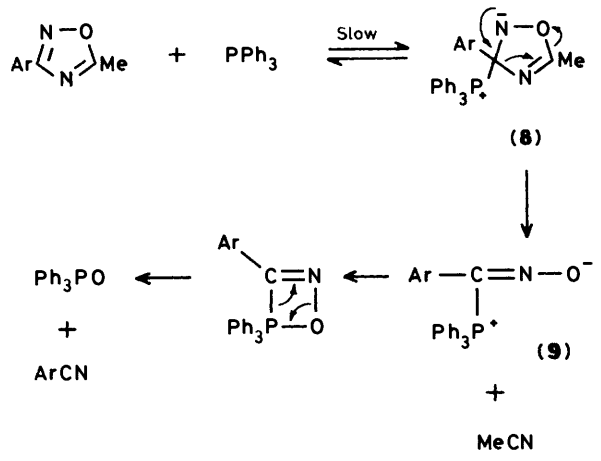
The *p*-dimethylamino compound (**6c**) gave some minor by-products which were assumed to be independant of the reaction being studied. Although this series contains too few compounds for a reliable Hammett correlation to be made, there is nevertheless a reasonable correlation between log(relative rate) and σ^+, with $\rho \sim +0.6$. Table 2 gives these results.

This correlation supports a mechanism in which a nucleophile adds to a C=X bond conjugated with a *para*-substituted phenyl ring in the ground state, the conjugation being lost as reaction proceeds.[2,3]

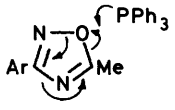
Since the initial conjugation is only with a partial positive charge, the ρ-values for such reactions are not large.[2]

The Mechanism.—Our earlier work[1] would have suggested that nucleophilic attack might have been at C-5 of the oxadiazole ring, but the intermediate (**7**) that would result would have no further reaction path open to it. The alternative nucleophilic attack at C-3 leads to the observed products by a mechanism (Scheme 1) that involves steps that have similarities to the later stages of the Wittig reaction. The correlation with σ^+ supports this mechanism, whilst an alternative (**10**) involving attack directly at oxygen would show little if any change of rate with change of *para* substituent on the C-3 aryl ring, for in that mechanism (**10**) the conjugation present at the beginning between substituent and C=N bond remains throughout reaction.

Under similar reaction conditions, tributylphosphine did not



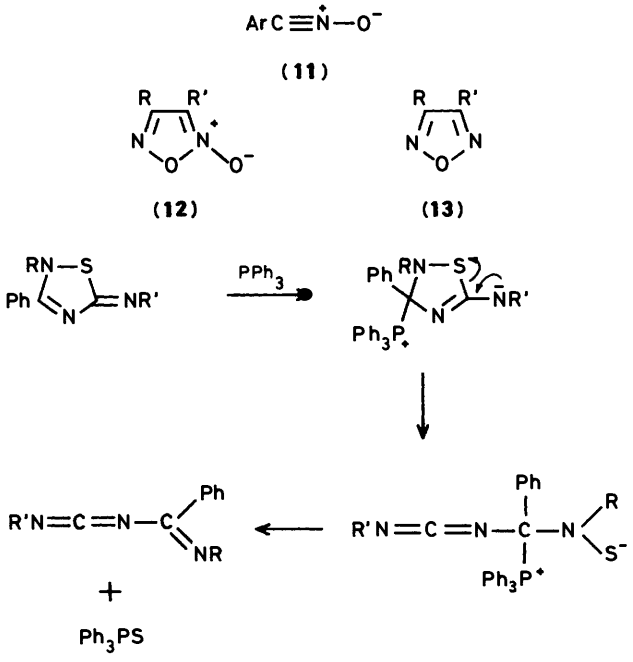
Scheme 1.



(10)

react with 1,2,4-oxadiazoles, whilst trimethyl phosphite gave mainly dimethyl methylphosphonate, the product of a Michaelis–Arbuzov rearrangement,[4] with the oxadiazole being recovered. This was the result of the heterocyclic ring acting as nucleophile towards the phosphite methyl carbons rather than as electrophile towards the nucleophilic phosphorus centre.[5]

Nitrile oxides (**11**) have been reduced to nitriles by trivalent phosphorus compounds[6] and this reaction may also involve the intermediate betaine (**9**). 1,2,5-Oxadiazole 2-oxides (**12**) have similarly been reduced to 1,2,5-oxadiazoles at moderate temperatures,[7] whilst there are two reports[8,9] of the 1,2,5-oxadiazole ring itself (**13**) reacting to give nitrile with triphenyl

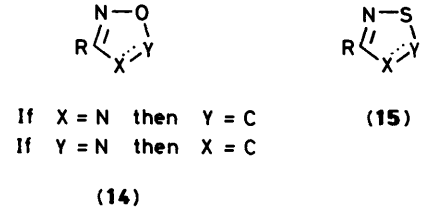


Scheme 2.

or trimethyl phosphite. Mechanisms were not suggested but Scheme 1 provides a ready explanation.

Indeed, a reaction between triphenylphosphine and 5-imino-2,5-dihydro-1,2,4-thiadiazoles[10] can similarly be explained by the sulphur analogue of Scheme 1, shown in Scheme 2, as can the reaction between 5-imino-dihydroisothiazoles and triphenylphosphine.[10]

It seems possible that compounds containing the structures (**14**) or (**15**) may be subject to this fragmentation reaction. This is being investigated.



Experimental

Proton and phosphorus n.m.r. spectra were run on a Bruker WM-360 instrument.

Reaction between 5-Methyl-3-(p-tolyl)-1,2,4-oxadiazole and Triphenylphosphine.—The oxadiazole (400 mg, 2.3 mmol) and the phosphine (1.2 g, 4.6 mmol) were thoroughly ground together, loaded into a glass tube under nitrogen, and heated at 200 °C for 3 h. A sample of the reaction mixture was shown by ^{1}H n.m.r. spectroscopy to contain *p*-toluonitrile, acetonitrile, triphenylphosphine, and triphenylphosphine oxide in approximately equal amounts. No other phosphorus compound was detected by ^{31}P n.m.r. spectroscopy. The acetonitrile was identified by ^{1}H n.m.r. spectral comparison in $CDCl_3$, C_6D_6, and $(CD_3)_2SO$ solvents, and by i.r. spectra, whilst the other products were identified after separation by chromatography on a silica column.

Kinetic Studies.—Solutions of the concentrations given in Table 1 in diphenyl ether were placed in stoppered flasks and suspended in a bath of silicone oil. Samples were taken at timed intervals, quenched by cooling, and analysed by ^{1}H n.m.r. spectroscopy. The course of the reaction was followed by measuring peak areas at δ 2.6 (5-Me of the oxadiazole) and 2.4 (4′-Me of the oxadiazole and Me of the toluonitrile).

For the competitive reactions, two of the oxadiazoles (**1**) and (**6a—c**)[3] (0.085 mmol each) were ground up with triphenylphosphine (1.15 mmol) and heated in sealed tubes at 200 °C for 1 h. In these incomplete reactions, the amount of each oxadiazole reacted was found from the ^{1}H n.m.r. spectra ($CDCl_3$) by integrating the characteristic peaks of the oxadiazoles and the substituted benzonitriles. The results are given in Table 2.

The relative rate constants were obtained, for example with the Me/MeO pair, by substituting initial and calculated mmolar quantities in the equations (1) and (2), and dividing one by the other.

$$k^{Me} = \frac{1}{t(a-b)} \ln \frac{b(a - x^{Me} - x^{MeO})}{a(b - x^{Me})} \quad (1)$$

$$k^{MeO} = \frac{1}{t(a-b)} \ln \frac{b(a - x^{Me} - x^{MeO})}{a(b - x^{MeO})} \quad (2)$$

a = initial triphenylphosphine; b = initial oxadiazole; x^{Me} = *p*-tolyloxadiazole reacted; x^{MeO} = *p*-methoxyphenyloxadiazole reacted.

Acknowledgements

We are grateful to the S.E.R.C. for a grant to J. W. B.

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Received 7th January 1987; *Paper* 7/028