Reactions of 3-Aryl-5-methyl-1,2,4-oxadiazoles with Benzyl Alcohol and with Benzylamine

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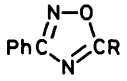
When heated with benzyl alcohol, 3-aryl-5-methyl-1,2,4-oxadiazoles afford mainly the aryl nitrile, benzyl acetate, and benzaldehyde. A number of other products, including 1,3,5-triazines, have been identified. Benzylamine and 5-methyl-1,2,4-oxadiazoles similarly give aryl nitrile and *N*-acetylbenzylamine, but the reaction is slower. However, in mixtures of the alcohol and the amine, the amine reacts the faster. Possible reaction mechanisms are discussed. The methyl group of the oxadiazole was shown to exchange its protons with those of benzyl alcohol more readily than the oxadiazole otherwise reacted with benzyl alcohol.

During an earlier study of the formation of 1,2,4-oxadiazoles from acylamidoximes,[1] it was observed that the product oxadiazoles reacted with benzyl alcohol at the temperatures used for their formation (150—200 °C). Now we report a study of this reaction and an analogous reaction with benzylamine. Although formally a 6π-electron system, 1,2,4-oxadiazoles are better considered as molecules with two double bonds in conjugation.[2] They are normally quite thermally stable,[3] relatively inert to electrophilic reagents, but undergo nucleophilic substitution when a suitable nucleofuge is at C-3 or C-5. Their chemistry has been reviewed.[4]

Since the nature of the ring system was of importance to us in this and subsequent work, INDO SCF molecular orbital calculations[5] were carried out for 3-phenyl-1,2,4-oxadiazole (**1a**) and its 5-methyl analogue (**1b**), taking bond lengths and

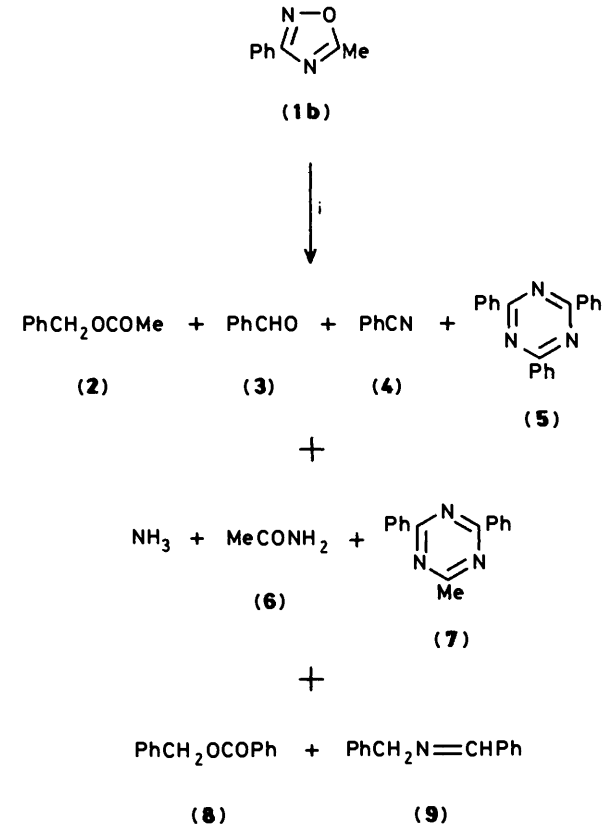


(**1**) **a**; R = H
b; R = Me

angles from the literature,[6] with the results shown in Table 1. Clearly, nucleophilic attack is to be expected at C-3 and C-5; the calculated bond index[7] for C-3 (3.811) is smaller than that for C-5 (3.833). The observed site of such reaction in any particular substituted oxadiazole will also be influenced by steric factors, and then depend on whether subsequent steps are available by which the structure first formed may further react.

Reactions with Benzyl Alcohol.—5-Methyl-3-phenyl-1,2,4-oxadiazole (**1b**), when heated with an excess of benzyl alcohol at 200 °C for 3 h under a slow stream of nitrogen, gave benzyl acetate (**2**), benzaldehyde (**3**), benzonitrile (**4**), and 2,4,6-triphenyl-1,3,5-triazine (**5**) as main products, ammonia (trapped as ammonium chloride), acetamide (**6**), and 2-methyl-4,6-diphenyl-1,3,5-triazine (**7**)[8] as minor products, and traces of benzyl benzoate (**8**) and *N*-benzylbenzylimine (**9**), as shown in Scheme 1. The products were identified by comparison with authentic materials using ^{1}H n.m.r. spectroscopy, g.l.c. and g.c.–mass spectrometry. The triazine products usually precipitated from the cooled reaction mixtures.

The aryl group.† To remove the ambiguity of having the phenyl group in both reactants, the reaction was repeated using



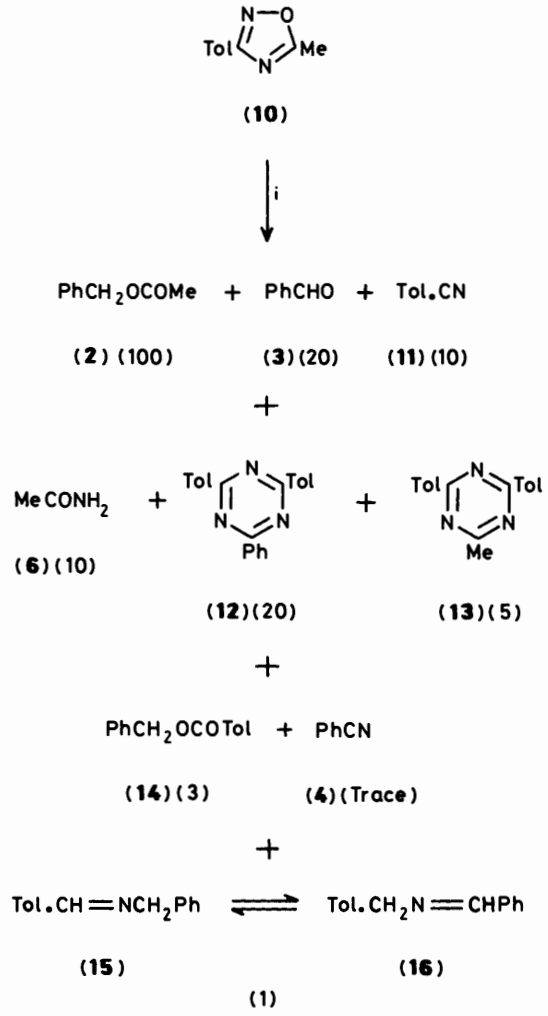
Scheme 1. *Reagents and experimental conditions:* (i) $PhCH_2OH$, 200 °C, 3 h

5-methyl-3-(*p*-tolyl)-1,2,4-oxadiazole (**10**) and benzyl alcohol, with the results shown in Scheme 2, with the amounts of other products relative to benzyl acetate (100%) shown. The more abundant triazine (**12**)[9] is seen to be formed from two aryl groups derived from the oxadiazole and one from the alcohol. The reverse experiment using the 5-methyl-3-phenyloxadiazole (**1b**) and *p*-methylbenzyl alcohol did indeed give 2,6-diphenyl-4-(*p*-tolyl)-1,3,5-triazine (**17**).[10] The trace of benzonitrile must have been formed from benzyl alcohol, as the toluonitrile used in the synthesis of the oxadiazole (**10**) was checked to be quite free of benzonitrile. (Reaction of benzaldehyde with ammonia to give the imine, followed by dehydrogenation, is the possible route to

† Throughout the paper the term tol refers to the *p*-tolyl group.

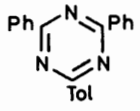
Table 1. Results of INDO SCF MO calculations on 3-phenyl-1,2,4-oxadiazole (**1a**) and 5-methyl-3-phenyl-1,2,4-oxadiazole (**1b**)

	(1a)			(1b)		
Bond	π-Bond order		σ-Bond order	π-Bond order		σ-Bond order
O(1)–N(2)	0.084		0.901	0.079		0.904
N(2)–C(3)	0.672		1.003	0.670		1.005
C(3)–N(4)	0.186		0.937	0.190		0.940
N(4)–C(5)	0.666		1.026	0.624		1.013
C(5)–O(1)	0.241		0.925	0.229		0.909
Ph–C(3)	0.084		0.955	0.083		0.955
H–C(5)	—		0.947	—		—
Me–C(5)	—		—	0.050		0.988
Atom	Charge	π-Density	LUMO coefficient	Charge	π-Density	LUMO coefficient
O(1)	−0.171	1.741	+0.30	−0.185	1.751	+0.29
N(2)	−0.146	1.276	−0.47	−0.155	1.281	−0.46
C(3)	+0.254	0.915	+0.40	+0.253	0.912	+0.40
N(4)	−0.291	1.202	−0.06	−0.312	1.228	−0.07
C(5)	+0.343	0.886	−0.27	+0.350	0.872	−0.26
H	−0.023					



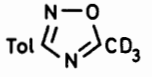
Scheme 2. *Reagents and experimental conditions:* (i) $PhCH_2OH$, 200 °C, 3 h

benzonitrile). Under the reaction conditions the imines (**15**) and (**16**) were shown to equilibrate.



(**17**)

The methyl group. Although the oxadiazole is the only source of the methyl groups in the products, that group is not necessarily transferred intact in that hydrogen exchange may occur at some stage and this may have a bearing on the mechanism. Accordingly, 5-trideuteriomethyl-3-(*p*-tolyl)-1,2,4-oxadiazole (**18**) was heated with benzyl alcohol (4 equiv.) at 200 °C for 3 h to give complete reaction, and for 1 h to give incomplete reaction. The deuterium content of the product benzyl acetate in both experiments and the unconverted starting material in the second experiment was determined by mass spectrometry, with the results shown in Table 2. Benzyl trideuterioacetate (**19**) lost no label under the reaction



(**18**)

$PhCH_2OCOCD_3$

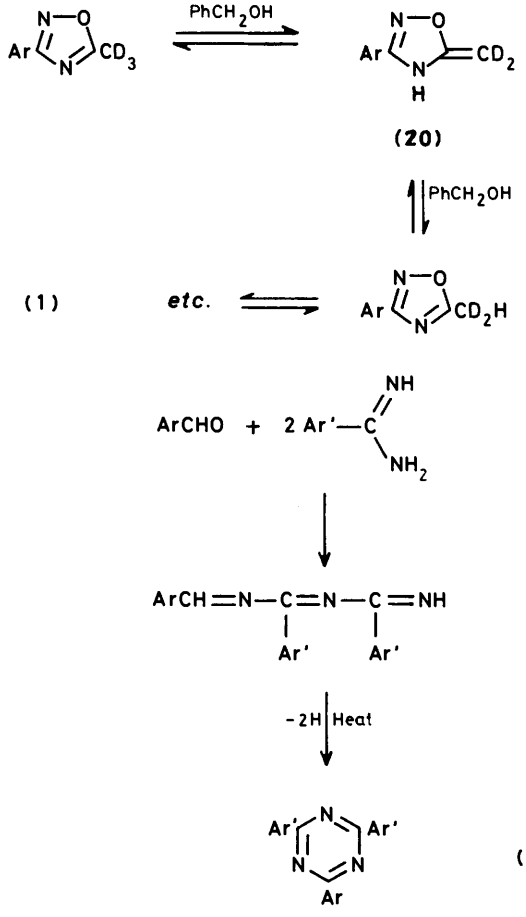
(**19**)

conditions, and a 1:1 mixture of deuteriated and non-deuteriated oxadiazoles (**18**) and (**10**) showed no exchange of label when heated at 200 °C in dibenzyl ether. The labile proton of the benzyl alcohol was thus necessary for the scrambling of label, and that took place at a faster rate than subsequent reaction to give the products seen in Scheme 2. The intermediacy of tautomeric oxadiazoles (**20**) is clearly implied [see equation (1)].

The triazines and acetamide. It is known[9,10] that 1,3,5-triazines with substitution patterns that we observed are formed from aldehydes and amidines [see equation (2)]. Such a route seems probable for products (**5**), (**12**), and (**17**) and amidines will be proposed as unobserved intermediates in these reactions. When 5-methyl-3-phenyl-1,2,4-oxadiazole (**1b**) was heated in benzyl alcohol in the presence of *p*-tolualdehyde, 2,4,6-triphenyl-1,3,5-triazine and 2,6-diphenyl-4-*p*-tolyl-1,3,5-triazine were both formed. The equilibrium [equation (3)], which would have invalidated this result, was not observed at 200 °C, the only product being *p*-tolualdehyde dibenzyl acetal.

Table 2. Isotope distribution (%) after (*a*) 3 h; (*b*) 1 h at 200 °C

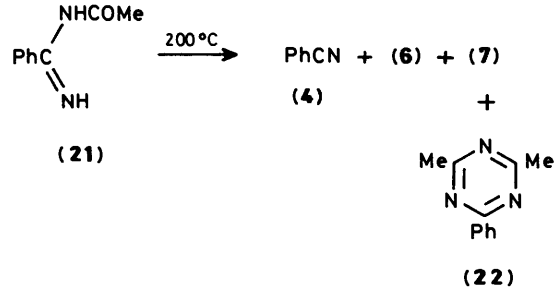
	Me	CH_2D	CHD_2	CD_3
(*a*) Benzyl acetate	2	18	46	34
(*b*) Benzyl acetate	0	16	42	42
Oxadiazole	2	16	42	40



$$\text{Tol·CHO} + \text{PhCH}_2\text{OH} \not\rightleftharpoons \text{Tol·CH}_2\text{OH} + \text{PhCHO} \quad (3)$$

However, this route to triazines cannot account for the methyltriazines (**7**) and (**13**) found in small amounts.

Since, as we shall presently propose, the main reaction mechanism leading to acetylation of benzyl alcohol is nucleophilic attack at C-5 of the oxadiazole, an intermediate amidine could similarly be acetylated and be the source of methyl-substituted triazines. Indeed, *N*-acetylbenzamidine (**21**), when heated at 200 °C, gave benzonitrile (**4**), acetamide (**6**), and the two triazines (**7**) and (**22**),[11] shown in Scheme 3.



Scheme 3.

One source of acetamide is thus indicated, but the probability also exists that ammonia (shown to be a product) might itself be acetylated by the oxadiazole. This was demonstrated as possible when the oxadiazole (**1b**) was heated in benzyl alcohol with a slow stream of ammonia passing through the solution. More acetamide than benzyl acetate was formed. That the ester was not the acetylating agent, with or without benzyl alcohol being present, was shown in separate experiments.

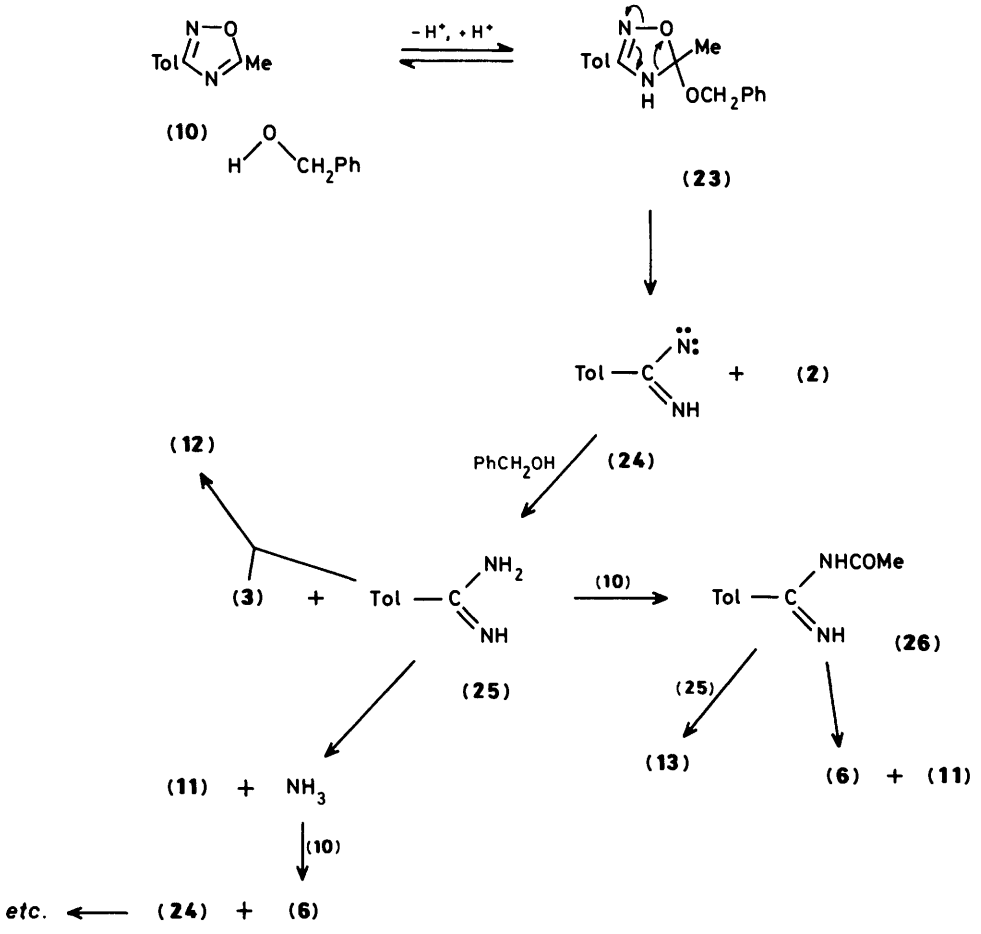
The mechanism. The main and minor products can all be accounted for by nucleophilic attack at C-5 of the oxadiazole ring, the intermediate (**23**) collapsing to give benzyl acetate (**2**) and a second intermediate (**24**). Oxidation of benzyl alcohol to benzaldehyde with reduction of the intermediate (**24**) to an arylamidine (**25**) follows. The intermediate (**24**) is shown as a nitrene in Scheme 4, but we have been unable to provide direct evidence for this by trapping experiments. (An attempt using triphenylphosphine led to an alternative reaction that is the subject of another publication.) E.s.r. spectroscopy failed to provide evidence for an alternative radical species derived from homolysis of the N–O bond, and the products of reaction were essentially unaltered by the addition of 10% dibenzoyl peroxide, di-t-butyl peroxide, or hydroquinone to the initial mixtures. The overall sequence of reactions that we propose is shown in Scheme 4.

We have no satisfactory sequence to account for the small amount of imines (**15**) and (**16**) found, but can account for the benzyl *p*-toluate (**14**) by suggesting that some nucleophilic attack at C-3 of the oxadiazole does take place, and steps analogous to those in Scheme 4 result in the formation of an imidic ester (**27**) that is readily hydrolysed. This is outlined in Scheme 5.

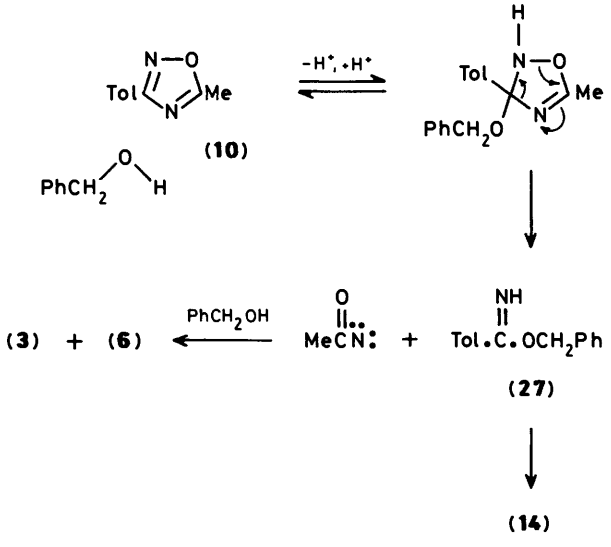
Reactions with Benzylamine.—Although benzylamine is normally a better nucleophile than benzyl alcohol, when the former was heated with oxadiazoles (**1b**) and (**10**). it required a higher temperature (210 °C) and a longer time (11 h) for only 30% reaction, whereas 3 h at 200 °C gave complete reaction with the alcohol. However, reaction with the amine was cleaner, giving the nitrile (**11**), *N*-benzylacetamide (**28**), and a large amount of the imine (**9**), enough for one molecule for each molecule of oxadiazole which reacted. The other product found was *N*-benzyl-*p*-toluamidine (**29**), and no triazine of any kind was formed. It seems that triazines are not formed from amidines and imines in a manner analogous to the reaction between amidines and aldehydes. However, benzylimine (**30**) has an alternative fate in its reaction with benzylamine. The reactions thought to be taking place, by analogy to Scheme 4, are shown in Scheme 6.

Puzzled by the more sluggish reaction of the amine, we heated the oxadiazole (**10**) with an excess of a 1:1 mixture of benzyl alcohol–benzylamine at 200 °C for 3 h. The products were those from the two sets of reactions discussed above (Schemes 4 and 6) but more amine had reacted than alcohol, and from the ratio of the products the amine had reacted at least four times faster than the alcohol. We explain this effect of the alcohol on the reactivity of the amine by hydrogen bonding between N-4 and the solvent/reagent substantially assisting, it not being essential for nucleophilic attack at C-5. as in structure (**31**). In neat alcohol (**31**; X = Y = O), such bonds will be stronger than in neat amine (**31**; X = Y = NH), whereas in the mixture the best combination of hydrogen bonding to the heterocycle and more effective nucleophile is found in array (**31**; X = O, Y = NH).

Attempted Reaction with Phenylmethanethiol.—Reaction between oxadiazole (**10**) and phenylmethanethiol in a sealed tube at 200 °C for 3 h gave only traces of product that might be attributed to the heterocycle. More than 90% of the thiol had reacted, giving hydrogen sulphide, toluene, dibenzyl sulphide,



Scheme 4.

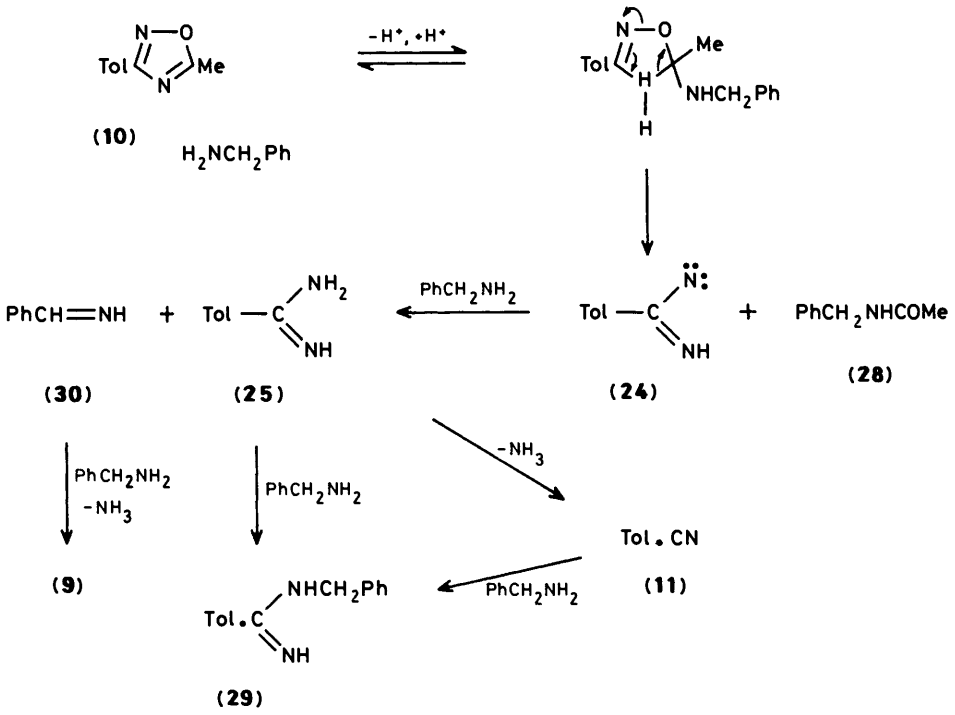


Scheme 5.

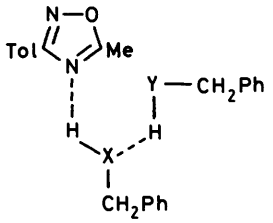
and dibenzyl disulphide. The last two products were determined to be in approximately 2:7 ratio by inverse gated broad-band ^{13}C n.m.r. spectroscopy, a technique necessary because they could not satisfactorily be distinguished by ^{1}H n.m.r. spectroscopy at 360 MHz in $CDCl_3$ or C_6D_6 with or without the addition of $Eu(fod)_3$.

Experimental

Proton n.m.r. spectra were run on Bruker WM-360 and Perkin-Elmer R32 spectrometers in $CDCl_3$ solutions and, when necessary to confirm compounds in mixtures, in C_6D_6 also. G.c.–mass spectrometric analyses were performed on a Finnigan 4500 mass spectrometer fitted wit a 25 m capillary



Scheme 6.



(31)

column coated with CP SIL5, a flow rate of He of 1 ml min^{-1}, and a 10 min period of isothermal operation at 50 °C was followed by a 10 °C min^{-1} temperature increase.

General Procedures.—The oxadiazole (1 g) and freshly distilled reagent (2 ml) were heated under a slow stream of nitrogen, usually at 200 °C for 3 h. Alternatively, sealed Carius tubes were used. After cooling, any solid formed was filtered off and identified (triazines) and the filtrate was subjected to spectroscopic and g.c.–mass spectrometric analysis. In the reactions involving analysis of recovered deuteriated oxadiazole, these were separated from other components in the mixtures by preparative t.l.c. on silica, developing the plates with 1:1 ether–light petroleum (b.p. 40—60 °C).

5-*Trideuteriomethyl*-3-(p-*tolyl*)-1,2,4-*oxadiazole* (**18**).—Tetradeuterioacetic acid (12.8 g, 200 mmol) and dicyclohexylcarbodi-imide (21.8 g, 105 mmol) were mixed in dry dichloromethane and stirred for 3 h at room temperature. The mixture was filtered and the dichloromethane was distilled off. Crude hexadeuterioacetic anhydride (5 g, 46 mmol) was mixed with *p*-toluamidoxime (4.8 g, 32 mmol) and left at room temperature for 3 h. After addition of ice–water, filtration and crystallisation from aqueous ethanol afforded O-*trideuterioacetyl*-p-*toluamidoxime* (2.9 g, 46%), m.p. 130—131 °C; δ($CDCl_3$) 2.32 (3 H, s, ArMe), 5.15 (2 H, br s, NH_2), 7.15 (2 H, d, *J* 8 Hz), and 7.55 (2 H, d) (Found: C, 61.6; H, 5.95; N, 14.9. $C_{10}H_9D_3N_2O_2$ requires C, 61.5; H, 6.2; N, 14.3%).

This material (2.5 g, 13 mmol) was heated at 150 °C for 2 h in an atmosphere of dry nitrogen. The cooled product was crystallised from ethanol to give the 5-*trideuteriomethyl*-3-(p-*tolyl*)-1,2,4-*oxadiazole* (1.8 g, 78%), m.p. 76—77 °C; δ 2.37 (3 H, s, ArMe), 7.25 (2 H, d, *J* 9 Hz), and 7.95 (2 H, d); *m/z* 133 (100%) and 177 (M^+, 81) (Found: C, 67.8; H, 5.6; N, 15.75. $C_{10}H_7D_3N_2O$ requires C, 67.8; H, 5.7; N, 15.8%).

N-*Benzyl*-p-*toluamidine* (**29**).—Ethyl *p*-toluimidate hydrochloride[12] (2.7 g) in ice-cold ethanol (12 ml) was treated with benzylamine (4 ml). After 1 h the crystalline product (1 g) was filtered, m.p. 234—237 °C; δ(D_2O) 2.32 (3 H, s), 4.63 (2 H, s), 7.46 (7 H, m), and 7.69 (2 H, d). This hydrochloride (600 mg) was placed in a separating funnel with ether (30 ml) and shaken with dilute ammonia solution (ammonia, 10 ml; *d* 0.88; water, 20 ml). The ether layer was immediately separated, dried, and evaporated. The residue was sublimed at 60 °C (bath) and 15 mmHg to give N-*benzyl*-p-*toluamidine*, m.p. 82—84 °C, δ($CDCl_3$) 2.32 (3 H, s), 4.50 (2 H, s), 5.1 (1 H, br s, NH), *ca.* 7.3 (9 H, m) (Found: C, 80.2; H, 7.1; N, 12.5. $C_{15}H_{16}N_2$ requires C, 80.3; H, 7.2; N, 12.5%).

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