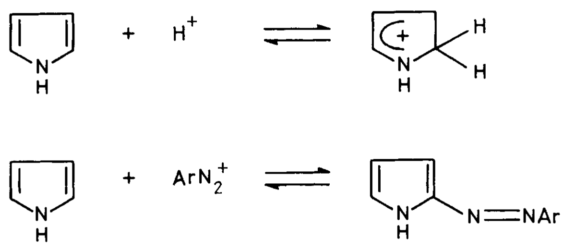
A Mechanistic Study of the Reaction between Aryldiazonium Ions and Imidazoles

Lesley M. Anderson, Anthony R. Butler,* Christopher Glidewell, and Dorothy Hart
Department of Chemistry, The University, St Andrews, Fife, KY16 9ST
Neil Isaacs
Department of Chemistry, The University, Reading, Berkshire

Whereas the neutral form of pyrrole reacts with 4-nitrobenzenediazonium ions, the parallel reaction of imidazole involves the anion. The involvement of the imidazole anion is based on kinetic evidence, pressure studies, and MNDO calculations. *N*-Methylation affects not only the kinetics of reaction but also the products. With the neutral form of imidazole it is suggested that the predominant reaction with an aryldiazonium ion is reversible attack on a ring nitrogen.

Pyrrole and methylated pyrroles react rapidly with benzenediazonium ions. Studies of the products[1] and kinetics of reaction[2] led Butler, Pogorzelec, and Shepherd[2] to propose the mechanism shown in Scheme 1. Pyrroles are known[3] to be protonated on the α-carbon rather than nitrogen and so attack by the electrophilic benzenediazonium ion at the same position to give only one product is as expected. No evidence was found for reaction of protonated pyrrole and benzenediazonium ions, although the reactions were carried out in acid solution. Although imidazole is a much stronger base than pyrrole it seemed likely that the mechanism of reaction would be essentially the same. However, the presence of a second nitrogen in the ring should make imidazole less susceptible to electrophilic attack. Preliminary kinetic studies of the reaction between imidazole, in the form of an imidazole buffer pH = 7.00, confirmed our prediction that the rate would be slower, although still in the stopped-flow range. A more detailed analysis of the rate data, however, did not confirm a mechanism parallel to that shown in Scheme 1. A reason for this had already been proposed by Ridd *et al.*[4] who suggested that reaction of imidazole occurs, not *via* the neutral molecule but *via* the anion, a species present at very low concentrations. We have now been able to confirm this with experimental techniques not available when Ridd *et al.*[4] made their original proposal.



Scheme 1.

Results and Discussion

The products obtained by reaction of benzenediazonium ions with imidazoles were extensively investigated by Pyman and co-workers.[5] They reported that coupling normally occurs at the 2-position to give highly coloured materials. Our work on the position of attack will be described later. Because of the intense colour of the product, its formation is very easy to follow by stopped-flow spectrophotometry. A solution of imidazole in water was partially neutralised with HCl and KCl was added to bring the ionic strength to 0.10 mol dm^{-3}. The pH was measured and aliquots of the solution diluted with 0.10 mol dm^{-3} KCl to give a series of imidazole buffers of constant pH but containing various amounts of unprotonated imidazole. The rate constant for reaction with 4-nitrobenzenediazonium tetrafluoroborate was then measured for each imidazole buffer, with the imidazole in large excess over the benzenediazonium ion. Two other imidazole buffers, of different pH values, were prepared and the process repeated. From a knowledge of the pK_a for imidazole as a base (7.10) it was possible to calculate the concentration of unprotonated imidazole in each buffer. If the reaction mechanism were the same as that for reaction of pyrrole (*i.e.* Scheme 1) a plot of k_{obs} against concentration of unprotonated imidazole should be rectilinear, with all points from the three different buffers falling on a single straight line. As can be seen in Figure 1 this is clearly not the case. If, on the other hand, the concentration of imidazole anion (**1**) in each buffer is calculated from the known pK_a of imidazole acting as an acid (14.5)[6] a plot of k_{obs} against imidazole anion concentration has the required rectilinearity (Figure 2), suggesting that, for imidazole, the reactive species in coupling with benzenediazonium ions is the anion. The proposed mechanism is shown in Scheme 2.

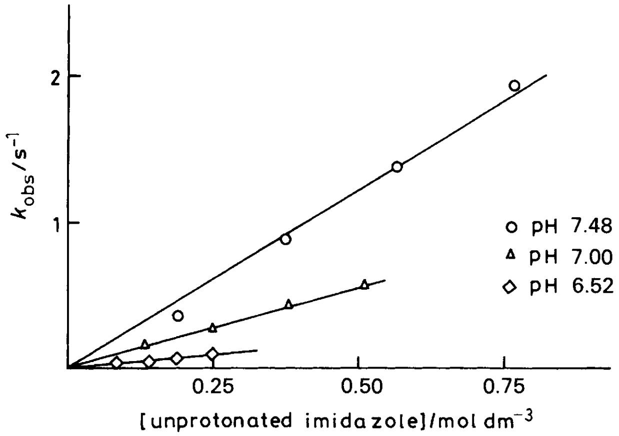


Figure 1. Plot of k_{obs} against concentration of neutral imidazole for reaction with 4-nitrobenzenediazonium ion.

The reaction of benzenediazonium ions with anionic species is characterised[7] by a volume of activation ($\Delta V^{\ddagger}$) in the range +2.2 to −15 cm^3 mol^{-1}, rather different from the value characteristic of reaction with neutral species. Thus the value of $\Delta V^{\ddagger}$ may be used as a criterion in the diagnosis of the reactive

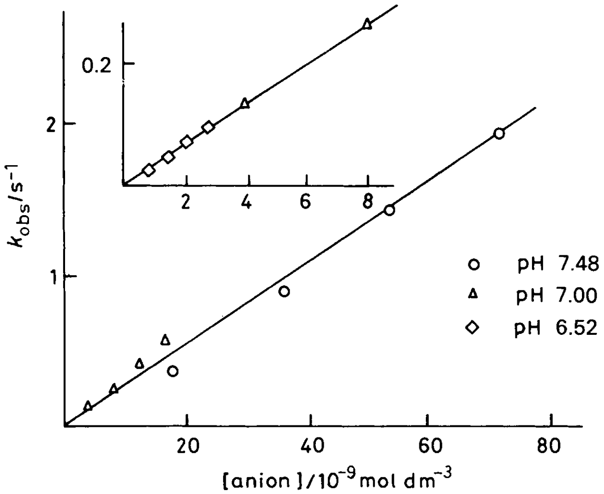


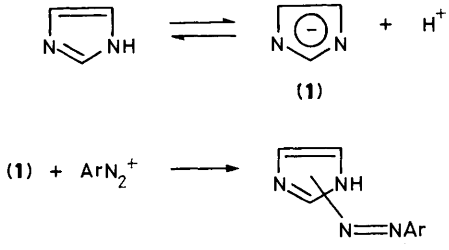
Figure 2. Plot of k_{obs} against concentration of imidazole anion for reaction with 4-nitrobenzenediazonium ion.

species in the coupling of benzenediazonium ions with imidazole. The effect of pressure on the rate constant for reaction of 4-methoxybenzenediazonium ions with imidazole was examined. The use of the 4-methoxy compound was necessary as reaction with 4-nitrobenzenediazonium ions was too fast to measure with the apparatus available.

According to the Eyring equation:

$$\frac{\partial \ln k}{\partial P} = -\frac{\partial \Delta G^{\ddagger}}{\partial P}\cdot\frac{1}{RT} = -\frac{\Delta V^{\ddagger}}{RT}$$

So $\Delta V^{\ddagger}$ (the volume of activation) may be obtained from the slope of a plot of ln*k* against *P*, where *k* is the observed second order rate constant and *P* is the pressure. The results obtained are displayed in Figure 3. There is an excellent linear fit up to 600 bar* with a slope of 1.1934 (correlation coefficient 0.9964) and, taking *R* as 80.98 cm^3 bar K^{-1} and T = 303 K, this gives $\Delta V^{\ddagger}_{obs}$ for the reaction a value of -29 cm^3 mol^{-1}. This is a large negative value, too large for just bond formation with charge conservation. It must indicate additional solvation taking place in the transition state. This would certainly accord with prior dissociation to the anion, with water acting as the base, and subsequent coupling with the benzenediazonium ion (Scheme 2). Dissociation of neutral nitrogen bases has ΔV *ca.* -25 cm^3 mol^{-1} and this would make the largest contribution to $\Delta V^{\ddagger}_{obs}$. For attachment of the diazonium ion we could add another -10 cm^3 mol^{-1} and perhaps lose a little for spreading the charge (solvent relaxation) giving a reduction of 5 cm^3 mol^{-1}. Addition of these estimated figures, derived from the mechanism shown in Scheme 2, gives $\Delta V^{\ddagger}_{obs}$ as -30 cm^3 mol^{-1} which agrees well with the experimentally determined value. Although it would be improper to claim that this analysis proves the proposed mechanism, as the estimates were made after the experimental values were known, a value of $\Delta V^{\ddagger}$ of -29 cm^3 mol^{-1} is certainly consistent with the proposed mechanism.



Scheme 2.

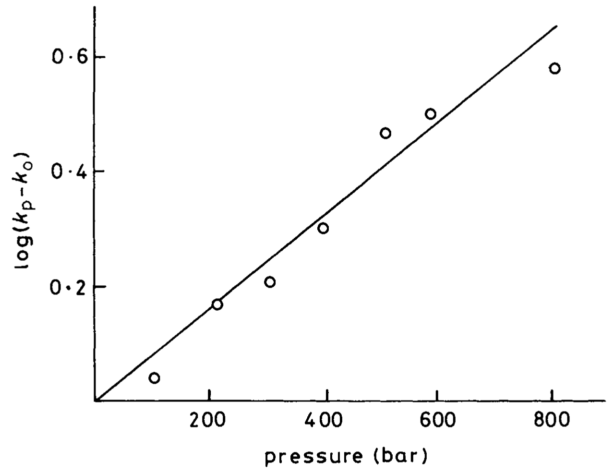


Figure 3. Variation of log (k_p − k_0) with pressure for reaction of imidazole with 4-methoxy benzenediazonium ion.

Previous work [8] has shown that MNDO calculations may be used with success as a probe for reaction mechanism. For this reason we calculated the heats of formation (ΔH_f°/kJ mol^{-1}) of a number of species relevant to this investigation. As far as protonation is concerned the calculations show that, for pyrrole, *C*-protonation is preferred to *N*-protonation but for imidazole the reverse is true [see (**2**)–(**8**)]. These conclusions are borne out by experiment and so deductions from MNDO calculations within these heterocyclic systems are worth considering as indications of mechanism. Although the intermediates formed by reaction of pyrrole with PhN_2^+ have similar heats of formation [see (**9**) and (**10**)] the difference of 15 kJ mol^{-1} is sufficient for (**9**) to be the preferred intermediate as only one isomer occurs in the product, *i.e.* exclusive 2-substitution.

Application of the MNDO method to the intermediates formed by the reaction of benzenediazonium ion with neutral imidazole [(**11**)–(**15**)] gives the values of ΔH_f° shown. The lower value obtained for (**13**) means that reaction should lead to exclusive formation of the 4(5)-product. The difference of 14 kJ mol^{-1} is very similar to the difference between the 2- and 3-positions of pyrrole, where exclusive attack at the 2-position is observed. When the product of the reaction of 4-nitrobenzenediazonium ion and imidazole was examined by n.m.r. spectroscopy it was found that substitution at both the 2- and the 4(5)-position had occurred and this appears to be inconsistent with attack on the neutral species.

The values of ΔH_f° calculated for the intermediates obtained on a reaction of PhN_2^+ with the imidazole anion [(**16**) and (**17**)] portray a rather different picture. The closeness of the values are fully consistent with the formation of two products, as is experimentally observed, and so the MNDO calculations point towards imidazole anion as the reactive species. The low values of ΔH_f° for (**16**) and (**17**) indicate how energetically favoured this pathway is but, of course, imidazole anion is present at very low concentrations in an imidazole buffer of pH 7. It is possible that both the neutral and the anionic forms of imidazole react but that the latter is the greatly favoured species and provides the exclusive pathway, except under rather acid conditions. Other data from Figure 4 will be used later.

A simple test for anion involvement is to examine the reaction of *N*-methylated imidazole. Coloured products are obtained on

---

* 1 bar = 10^5 Pa.

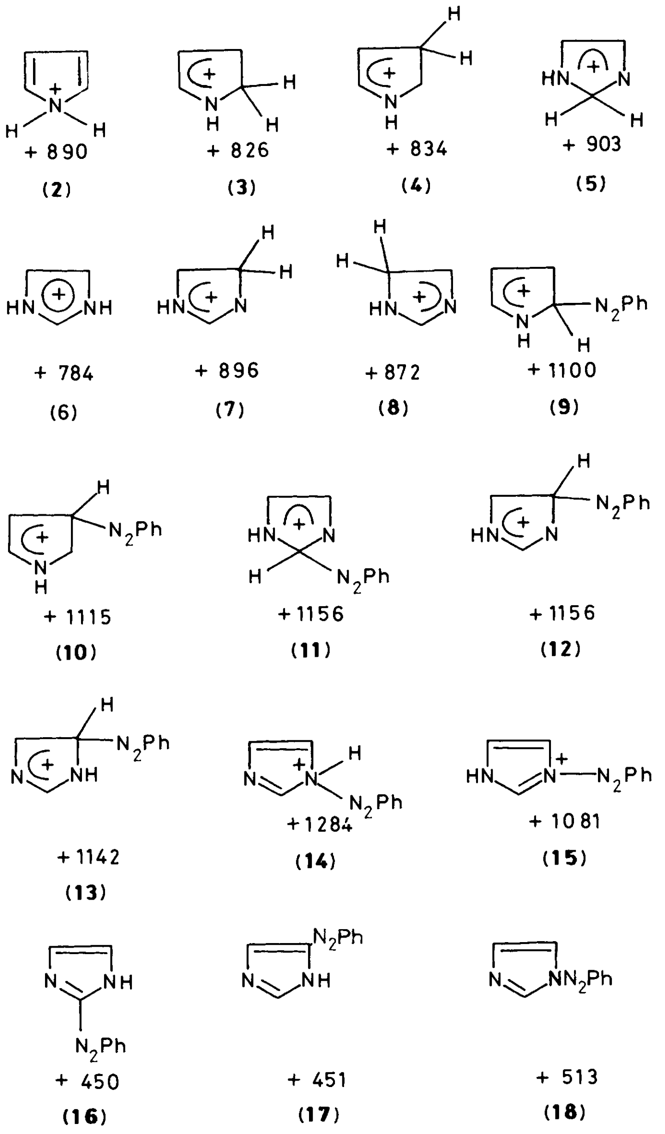


Figure 4. Heats of formation (kJ mol^{-1}) for possible intermediates in the reaction of pyrrole and imidazole with protons and benzenediazonium ions.

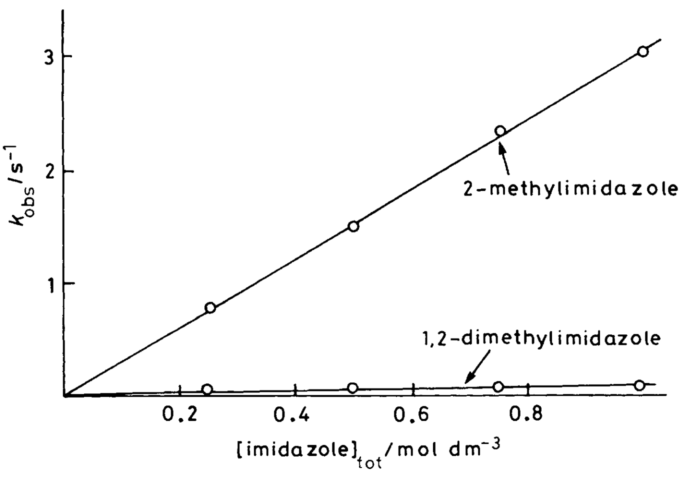
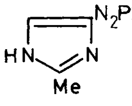


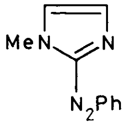
Figure 5. Effect of *N*-methylation on the rate of reaction of 2-methylimidazole with 4-nitrobenzenediazonium ion; both imidazoles were half neutralised with HCl.

reaction of both 2-methylimidazole and 1,2-dimethylimidazole with 4-nitrobenzenediazonium ions. The rate of appearance of coloured products for the latter, and the reaction of 2-methylimidazole, were examined by stopped-flow spectrophotometry and the results are displayed in Figure 5. A direct numerical comparison of the results obtained for each compound is not sensible as all the evidence obtained so far suggests they must react by different mechanisms. However, to indicate the decrease in rate on *N*-methylation, in Figure 5 the stoicheiometric concentration of imidazole or substituted imidazole has been plotted and in both cases the buffer was obtained by half neutralisation with HCl. The marked drop in rate on *N*-methylation is clearly consistent with reaction of 2-methylimidazole occurring *via* the anion. A similar effect was noted in a comparison of the rates of reaction of imidazole and 1-methylimidazole. The fact that 1-methylimidazole and 1,2-dimethylimidazole do react suggest that reaction *via* the neutral species, as well as the anion, is possible. The situation is not quite as simple as has just been suggested, as with 1-methyl- and 1,2-dimethyl-imidazole a more complex mixture of products is obtained (see later).

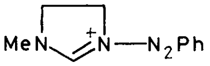
The products obtained by reaction of 4-nitrobenzenediazonium ion with imidazole and methylated imidazole were examined by n.m.r. and mass spectroscopy. The crude product obtained on reaction with imidazole itself had a substantial peak in the mass spectrum at 217, consistent with formation of **(16)** and/or **(17)**. The major signal, in the relevant range of the ^1H n.m.r. spectrum, was a singlet at δ 7.40 which is correct for **(16)**. There are, however, two somewhat smaller signals at δ 7.50 and *ca.* 8.2 consistent with the presence of smaller amounts of **(17)**. The ^{13}C n.m.r. spectrum is too complicated to be diagnostic but is consistent with the presence of both **(16)** and **(17)**. The product from the reaction of 2-methylimidazole should be **(19)**. A molecular ion peak at 231 was observed. In the ^1H n.m.r. spectrum only one singlet at *ca.* δ 8 was observed. The products from both imidazole and 2-methylimidazole gave small signals in their mass spectra corresponding to coupling after elimination of nitrogen *i.e.* phenylation.



(19)



(20)



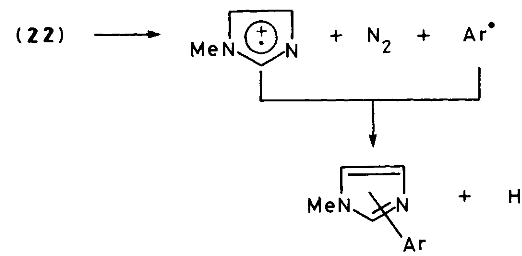
(21)

The n.m.r. spectra of the product obtained from 1-methylimidazole was too complicated for complete assignment. However, the presence of several signals corresponding to methyl groups in different environments suggests formation of a variety of products. In the mass spectrum there were, *inter alia*, signals corresponding to the products of coupling and phenylation. An attempt was made to separate the products by column chromatography. Up to fifteen different highly coloured components were recognised, some present in very small amounts. The task of complete separation and identification seemed not justified by the value of the possible results. Sufficient is the observation that *N*-methylation has a considerable effect on the reaction path.

The essential step in the present reaction is that between the imidazole anion and the cationic benzenediazonium ion, which should be encounter-controlled. Application of the modified Smoluchowski equation[10] to the kinetics of encounter-controlled reactions gives a second order rate constant 7.4×10^9 dm^3 mol^{-1} s^{-1} for reaction in water at 25 °C. The value of this should probably be increased to about 2×10^{10} dm^3 mol^{-1} s^{-1} because of electrostatic interaction. The value obtained from the data in Figure 2 is only 2.7×10^7 dm^3 mol^{-1} s^{-1} suggesting that either the mechanism is incorrect or that, for some reason, the rate constant for an encounter reaction has been reduced. This value can be accommodated in Scheme 2 if one other aspect of the situation is considered.

Although pyrrole is a weaker acid than imidazole the difference is hardly great enough (pK_a 16.5 compared with 14.5 for imidazole) to explain why the anionic route is essentially the only route for imidazole. However, imidazole differs from pyrrole in one other way: there is *N*-protonation rather than *C*-protonation. If the behaviour of the benzenediazonium ion, acting as an electrophile, parallels that of the proton then, on reaction with neutral imidazole, (**15**) should be formed. The data in Figure 4 suggest that this is the case. Because of the high nucleophilicity of the ring nitrogen of imidazole, reflected in the favourable heat of formation of (**15**), encounter between neutral imidazole and a benzenediazonium ion will rarely result in attack on carbon. However, formation of (**15**) is a reversible process and gives rise to no isolable product but reduces the likelihood of irreversible coupling at carbon. We looked for spectral evidence for the formation of (**15**) as the initial product on adding 4-nitrobenzenediazonium ions to an imidazole buffer but, as the benzenediazonium ions are present at such low concentrations and the u.v. spectrum of the buffer is dominated by absorption of protonated imidazole, the changes were deemed to be below the limits of detection.

Encounter between the imidazole anion and benzenediazonium ions is an energetically favourable process and, as the heats of formation of (**16**), (**17**), and (**18**) show, the nitrogen is no longer the preferred site of attack. Meanwhile, attack on carbon results in irreversible formation of product and this is the dominant reaction pathway. One consequence of the formation (**15**) is that the concentration of available benzenediazonium ion is reduced and the rate constant for the encounter-controlled process involving the imidazole anion is apparently reduced. Thus, our calculated low value for the encounter-controlled rate constant can be rationalised while maintaining an encounter-controlled pathway. For reaction of 1-methyl- and 1,2-dimethyl-imidazole there is no anionic pathway and so products like (**20**) must be formed *via C*-attack on the neutral species. Because this process is much slower than reaction with the anion, species such as (**21**) have time to decompose by an alternative pathway. One such pathway (Scheme 3), based on analogy with the reaction of a benzenediazonium ion with aminopyridine,[11] could produce nitrogen, a radical and radical cation. Dimerisation of the latter two, with loss of a proton, would give the phenylated product observed in the reaction mixture. Because of the multiplicity of products the kinetics of reaction between a 4-nitrobenzenediazonium ion and 1-methylimidazole are complex but gave data which could be analysed to give a first-order rate constant. The only deduction we would care to make from Figure 5 is that *N*-methylation produces a substantial decrease in rate; this is fully consistent with the view of both Ridd and ourselves that coupling of imidazole with benzenediazonium ions occurs *via* the anion.



Scheme 3.

Experimental

Materials.—All chemicals were AR grade if available. 4-Nitrobenzenediazonium tetrafluoroborate was prepared by the method of Starky.[12]

Kinetics.—The Hi-Tech stopped-flow spectrophotometer has been described previously.[13] The imidazole buffer, with KCl to maintain the correct ionic strength, was placed in one arm and an aqueous solution of 4-nitrobenzenediazonium tetrafluoroborate in the other. The reaction mixture was monitored at 410 nm. Some of the rates were rather slow for stopped-flow spectrophotometry but an effort was made to use the same equipment throughout. The data was analysed by the method of Kezdy *et al.*[14]

For the high pressure measurements a solution containing all reactants (0.05 mol dm^{-3} imidazole, 0.0025 mol dm^{-3} HCl and 0.005 mol dm^{-3} 4-methoxybenzenediazonium tetrafluoroborate) was poured into a sliding cell of the type described by LeNoble[15] and placed in a Nova Swiss high pressure optical cell used in a Beckman 25 spectrophotometer.

Isolation of Products.—Imidazole, or methylated imidazole, was dissolved in sodium carbonate solution and an equimolar amount of 4-nitrobenzenediazonium tetrafluoroborate added. After 15 min the coloured product was filtered off and washed with water.

Instrumentation.—This has been described previously.[16]

Acknowledgements

L. M. A. thanks the Rollo Trust for the award of a studentship. We thank Drs. D. Reed and I. H. Sadler of the SERC n.m.r. Service at the University of Edinburgh for their continued help and advice.

References

1 A. R. Butler and P. T. Shepherd, *J. Chem. Res.*, (*S*) 1978, 339; (*M*) 1978, 4471.
2 A. R. Butler, P. Pogorzelec, and P. T. Shepherd, *J. Chem. Soc., Perkin Trans. 2*, 1977, 1452.
3 Y. Chiang and E. B. Whipple, *J. Am. Chem. Soc.*, 1963, **85**, 2763.
4 R. D. Brown, H. C. Duffin, J. C. Maynard, and J. H. Ridd, *J. Chem. Soc.*, 1953, 3937.
5 F. L. Pyman and L. B. Timmis, *J. Soc. Dyers Colour.*, 1922, **38**, 269.
6 H. Walba and R. W. Insensee, *J. Org. Chem.*, 1961, **26**, 2789.
7 N. S. Isaacs, T. S. Najen, and R. Van Eldik, *Tetrahedron Lett.*, 1987, **28**, 3043.
8 A. R. Butler and C. Glidewell, *J. Chem. Soc., Perkin Trans. 2*, 1985, 1465.
9 M. J. S. Dewar and W. Thiel, *J. Am. Chem. Soc.*, 1977, **99**, 4899.
10 M. W. Austin and J. H. Ridd, *J. Chem. Soc.*, 1963, 4204.
11 G. Fillipi, G. Vernin, H. J. M. Dou, J. Metzger, and M. J. Perkins, *Bull. Soc. Chim. Fr.*, 1974, 1075.
12 E. B. Starky, 'Organic Synthesis,' Coll. Vol. II, Wiley, New York, 1943, p. 225.
13 A. R. Butler, V. Chaipanich, C. Glidewell, and J. McGinnis, *J. Chem. Soc., Perkin Trans. 2*, 1968, 7.
14 F. J. Kezdy, J. Jaz, and P. Bruylants, *Bull. Soc. Chim. Belg.*, 1958, **67**, 687.
15 W. J. LeNoble and R. Schlott, *Rev. Sci. Insts.*, 1976, **47**, 770.
16 C. J. Broan, A. R. Butler, D. Reed, and I. H. Sadler, *J. Chem. Soc. Perkin Trans. 2*, 1989, 731.

Received 20*th April* 1989; *Paper* 9/01685F