The Imidate–Amide Rearrangement: an Explanation for the Ambident Nucleophilic Properties of Neutral Amides

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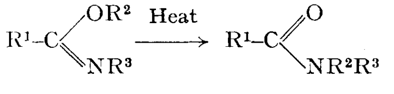
Summary Rearrangement of *N*-methylbenzimidates to tertiary amides (in nitrobenzene at 138°) is readily catalysed by alkyl halides and other electrophilic species, suggesting that alkylation of neutral amides usually proceeds at the O-atom, with *N*-substitution arising from a subsequent rearrangement.

DESPITE its early discovery,[1] the rearrangement of imidates to substituted amides [equation (1)] has never been thoroughly examined. Temperatures of >100° are usually required and there is isolated evidence that addition of alkyl halides,[2] BF_3,[3] and even H_2SO_4[4] is efficacious in some instances. The thermal reaction (Chapman rearrangement) for arylimidates is intramolecular[5] but this is probably atypical[6] as ammonium ion intermediates have been isolated for an alkyl halide-catalysed pathway with other compounds.[7] Because of its relevance to the ambident nucleophilic properties of amides, we have examined the rearrangement of several *N*-methyl-benzimidates kinetically, with special reference to the influence of various electrophilic catalysts.



$$R^1\text{–}C(OR^2)\text{=}NR^3 \xrightarrow{\text{Heat}} R^1\text{–}C(\text{=}O)NR^2R^3 \qquad (1)$$

The catalysed rearrangement of these compounds proceeds readily and cleanly in nitrobenzene at 100—160°, but there is no purely thermal rearrangement below 160°. The reaction can be followed conveniently by n.m.r. spectrometry. Data for isopropyl *N*-methylbenzimidate in the presence of isopropyl iodide at 138° (Table 1) show that the kinetics follow equation (2), implying an S_N2 mechanism. Values of k_2 for several other *N*-methylbenzimidates and catalysts are listed in Table 2. Catalysis by alkyl halides[2b] decreases sharply in the order $\mathrm{Pr^iI} > \mathrm{Pr^iBr} > \mathrm{Pr^iCl}$ for the rearrangement of isopropyl *N*-methylbenzimidate, which is consistent with an S_N2 mechanism (Scheme) in which either the formation (step a) or decomposition (step b) of the intermediate ion (I) is rate-limiting. The observation, however, that catalysis decreases with increased branching of the alkyl halide (*i.e.* MeI > $\mathrm{Pr^iI}$) irrespective of the *O*-alkyl substituent of the *N*-methylbenzimidate clearly fixes step (a) as the slow step for these particular reactions.

TABLE 1. *Effect of isopropyl iodide on the rate of rearrangement of isopropyl* N-*methylbenzimidate in nitrobenzene at* 138°. *Initial* $[\mathrm{PhC(OPr^i)}\text{=}\mathrm{NMe}] = 0{\cdot}9$M.

$[\mathrm{Pr^iI}]$/M	$10^3 \times k_1/(\mathrm{min}^{-1})$[a]	$10^3 \times k_2/(\mathrm{min}^{-1}\ \mathrm{mol}^{-1}\ \mathrm{l}$
0·483	3·30	6·81
0·722	4·87	6·75
0·783	5·16	6·60
1·04	6·19	6·41

[a] Rate = $k_1[\mathrm{PhC(OPr^i)}\text{=}\mathrm{NMe}]$.

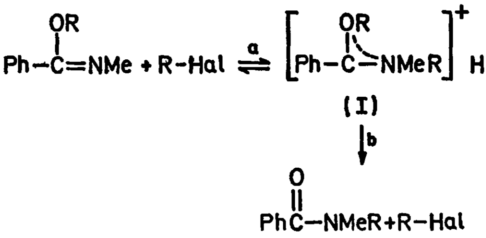
TABLE 2. *k_2 values for the rearrangement of alkyl* N-*methylbenzimidates in nitrobenzene at* 138°.

Alkyl substituent	Catalyst	$10^8 k_2$/(min^{-1} mol^{-1} l)
Pr^i	Pr^{i}I	6·64
»	Pr^{i}Br	0·66
»	Pr^{i}Cl	0·0039
»	MeI	2210
»	I$_2$	38·6
»	MeCOBr	3·05
»	BF$_3$	33·7 min^{-1} [a]
»	HBr (0·22 mol equiv.)	0·67
»	HBr (1 mol equiv.)	No rearr.
»	H$_2$SO$_4$	» »
Pr^n	Pr^{n}I	30·1
Et	EtI	92·2
Me	MeI	777

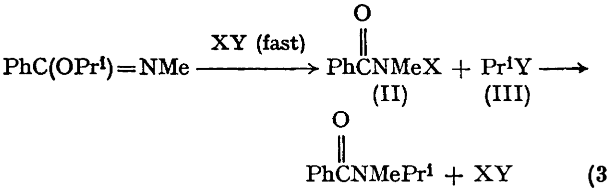
[a] First order coeff. at 101·5° (*i.e.* $v = k_1$[PhC(OPr^i)=NMe]).

$$\text{Rate} = k_2[\text{PhC(OPr}^i)\text{=NMe}][\text{Pr}^i\text{I}] \qquad (2)$$

An earlier report has intimated that the rearrangement might be catalysed by iodine.[8] Our results show that for isopropyl N-methylbenzimidates it is more effective than isopropyl halide and that various other electrophilic species also increase the rearrangement rate. The mechanism of these reactions is under investigation, but the n.m.r. spectra show there is rapid dealkylation [equation (3)] to give the substituted amide (II) and the isopropyl species (III). Formation of the tertiary benzamide then proceeds at the rate recorded in Table 2. With catalytic quantities of HBr (< 1 mol. equiv.), the rate of rearrangement is that expected for isopropyl bromide catalysis. With an equimolar quantity of HBr, no rearrangement ensues, showing that direct alkylation of N-methylbenzamide does not occur under our conditions. No rearrangement is observed for catalytic quantities of H$_2$SO$_4$, consistent with the poor alkylating ability of Pr^{i}HSO$_4$ or the low nucleophilicity of HSO$_4^-$.



SCHEME *Alkyl halide-catalysed rearrangement of alkyl* N-*methyl benzimidates.*



$$\text{PhC(OPr}^i)\text{=NMe} \xrightarrow{\text{XY (fast)}} \underset{\text{(II)}}{\text{Ph}\overset{\text{O}}{\overset{\|}{\text{C}}}\text{NMeX}} + \underset{\text{(III)}}{\text{Pr}^i\text{Y}} \longrightarrow \text{Ph}\overset{\text{O}}{\overset{\|}{\text{C}}}\text{NMePr}^i + \text{XY} \qquad (3)$$

These results seem to have an important bearing on the ambident nucleophilic properties of the amide fragment. N-Substitution is favoured under strongly acidic or basic conditions, where reaction may occur *via* the conjugate acid and base, respectively, whereas mixed O- and N-substitution often occurs under neutral conditions.[9] The presence of Ag$^+$ promotes O-substitution and this agrees nicely with Kornblum's[10] predictions founded on the molecularity of the reaction. In many other respects, however, this kind of explanation is unsatisfactory: *e.g.*, the reaction of alkyl halides with formamides shows that N-substitution predominates with tertiary alkyl halides,[11] which is contrary to Kornblum's hypothesis. Moreover, it is also evident that reaction temperature has an important influence on products under neutral conditions. This suggests that substitution at oxygen is the kinetically favourable pathway *-methyl-* bsequent rearrangement providing the thermody [illegible] ly stable substituted amide.[9] The relatively ready [illegible] sis of this rearrangement by electrophilic reagents, including the alkylating agent itself, supports this alternate explanation. It suggests, too, that at least one function of the Ag$^+$ in promoting O-substitution is to remove nucleophilic anions (such as I$^-$) from the reaction solution.

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