Displacement of the Acyl Group by Alkyl Radicals. A Novel S_R Reaction of Nitrogen-containing Heteroaromatic Compounds

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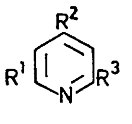
Summary 1-Adamantyl and other alkyl radicals, produced by the Ag^I-catalysed decarboxylation of carboxylic acids by $(NH_4)_2S_2O_8$, react with acyl-heteroaromatic bases effecting the displacement of the acyl group; a mechanism is proposed in which the reacting species is the radical cation of the heteroaromatic compounds.

The recently reported photoinitiated substitution of the cyanogroup by alkyl radicals in protonated cyanopyridines[1] prompted us to report on a closely related reaction of acyl derivatives of heteroaromatic bases with 1-adamantyl and other alkyl radicals resulting in replacement of the acyl group.

The nucleophilic bridgehead radicals, 1-adamantyl (Ad$\cdot$) and bicyclo[2.2.2]octan-1-yl, produced by the Ag^I-catalysed decarboxylation of the corresponding carboxylic acid by $(NH_4)_2S_2O_8$, easily effect substitution at the 2-position of protonated 4-substituted pyridines[2] according to the mechanism proposed by Minisci.[3] In the case of 4-acetylpyridine (**1**), the 4-(1-adamantyl)pyridine (**2**) and 4-(bicyclo[2.2.2]octan-1-yl)pyridine were also obtained in 6 and 4% yields, respectively;† under neutral initial conditions, the product (**2**) was obtained in 20% yield, and the 2,6-di-(1-adamantyl) compound (**3**) was also isolated. This new S_R reaction of nitrogen-containing heteroaromatic compounds seems to be peculiar to those containing a 4-acyl group; with the other substituents investigated: CN, CO_2Me, Cl, Me, and OMe, only substitution at the 2-position was observed.



	R¹	R²	R³		R¹	R²	R³
(**1**)	H	Ac	H	(**8**)	Ac	Me	H
(**2**)	H	Ad	H	(**9**)	Ad	Me	H
(**3**)	Ad	Ac	Ad	(**10**)	Ad	Me	Ad
(**4**)	Bu^t	Ac	H	(**11**)	Ac	Cl	H
(**5**)	Bu^t	Ad	H	(**12**)	Ad	Cl	H
(**6**)	Bu^t	Ac	Ad	(**13**)	Ad	Cl	Ad
(**7**)	Bu^t	Ad	Ad	(**14**)	Ac	CN	H

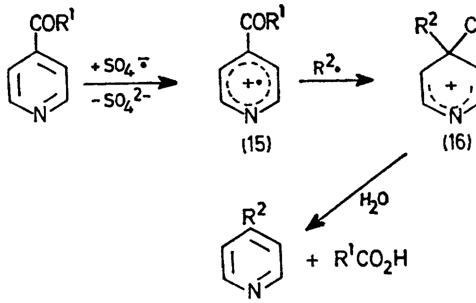
Ad = 1-Adamantyl

2-t-Butyl-4-acetylpyridine (**4**), under both acidic and neutral initial conditions, at low conversions, afforded a mixture of (**5**) and (**6**) in a 1 : 3 ratio, indicating that nuclear substitution at the 6-position and displacement of the acetyl group occur concurrently; the final reaction mixture consisted of (**5**) (20%) and (**7**) (50%), compound (**6**) having been completely transformed into (**7**). Similar results were obtained with (**4**) and the s-butyl radical, while isopropyl and n-propyl radicals gave only the 2-t-butyl-4-isopropyl- (10%) and the 2-t-butyl-4-n-propyl-pyridine (7%) respectively, most of (**4**) being recovered unchanged. From the reaction of 2-t-butyl-4-benzoylpyridine with 1-adamantyl radicals, besides the substitution product (**7**) (60%), benzoic acid was also isolated, indicating that the leaving acyl group is converted into the corresponding carboxylic acid.

Substitution of the acetyl by the 1-adamantyl group was also observed with 2-acetylpyridines. 2-Acetyl-4-methylpyridine (**8**) gave a mixture of (**9**) (30%) and (**10**) (20%); similarly, 2-acetyl-4-chloropyridine (**11**) afforded (**12**) (30%) and (**13**) (15%). In contrast, 2-acetyl-4-cyanopyridine (**14**) gave rise only to products of substitution at the 6- and 5-positions.

Displacement of the acyl group occurred easily from 2-acetyl- and 2-benzoyl-benzothiazole with 1-adamantyl radicals, better yields of the 2-(1-adamantyl)benzothiazole (65%) being obtained under basic conditions.

Substituent effects on this S_R reaction of acylpyridines have not been fully investigated yet; nevertheless, our results so far suggest that the displacement of the acyl group occurs through a mechanism different from that proposed for the substitution of protonated pyridines by alkyl radicals.[3] Substitution occurs equally well under neutral or even basic conditions; it can therefore be assumed that the initial step is the interaction of the free heteroaromatic base with the $SO_4^{\cdot-}$ radical from the $(NH_4)_2S_2O_8$ to give (either directly or through addition to the nitrogen atom followed by loss of SO_4^{2-}) the corresponding radical cation (**15**); coupling with the alkyl radicals and reaction of the cation (**16**) with water would finally afford the observed substitution products (Scheme). This would also explain the behaviour of compound (**14**) where the presence of two electron-withdrawing groups discourages the formation of the radical cation (**15**).



Scheme

Evidence for the intermediate formation of (**15**) was obtained from spin trapping experiments using the nitrone (**17**). E.s.r. analysis of the reaction of 4-acetylpyridine in the presence of the nitrone (**17a**) showed an intense spectrum consisting of a 1 : 1 : 1 triplet (*a* 13·7 G) of 1 : 2 : 2 : 1 quartets (*a* 2·9 G); this spectrum is identical to that reported by

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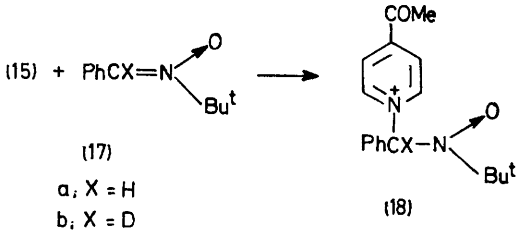
† Reactions were carried out under experimental conditions essentially identical to those described in ref. 2. Products were identified by elemental analysis and spectral data. Reaction mixtures were analysed by g.l.c. Yields are based on the acyl derivatives employed.

Ledwith and Russell[4] in the trapping of the pyridine radical cation by the nitrone (**17a**) and can similarly be attributed to the nitroxide (**18a**). This spectrum was analysed assuming an identical coupling (2·9 G) for the β-hydrogen and the pyridine nitrogen which are responsible for the observed 1 : 2 : 2 : 1 quartets. We have confirmed this analysis using the deuteriated nitrone (**17b**); the resulting spectrum showed two 1 : 1 : 1 triplets due to two non-equivalent nitrogen nuclei, with hyperfine coupling constants of 13·7 and 2·9 G. Owing to the line-width in the experimental spectrum the expected coupling with the β-deuterium atom (a_D *ca.* 0·4 G) was too small to be resolved.


(17)

a; X = H

b; X = D

(18)

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