Tetrahedron. Vol. 27, pp. 3575 to 3579. Pergamon Press 1971. Printed in Great Britain

NUCLEOPHILIC CHARACTER OF ALKYL RADICALS—VI
A NEW CONVENIENT SELECTIVE ALKYLATION OF HETEROAROMATIC BASES

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(*Received in the UK* 22 *March* 1971; *Accepted for publication* 13 *April* 1971)

Abstract—A new method of homolytic alkylation of heteroaromatic bases is described, in which the silver-catalysed oxidative decarboxylation of acids by peroxydisulphate is used as a source of alkyl radicals. The method is particularly noteworthy because of the good yields and the high selectivity obtained, due to the nucleophilic character of the alkyl radicals; for synthetic interest it is comparable to electrophilic alkylation in the homocyclic series.

THE nucleophilic character of alkyl radicals permits the ready and selective alkylation of protonated heteroaromatic bases.[1] Previously we have used a variety of radical sources: oxaziranes,[2] hydroperoxides,[2,5] α-hydroxy-hydroperoxides,[2] acylperoxides,[3] carboxylic acids and lead tetracetate.[3] All of these reagents attack selectively the positions of high nucleophilic reactivity.

In this paper we describe a new homolytic alkylation process, which is particularly useful from a synthetic point of view in that it permits the introduction of a large variety of primary, secondary and tertiary alkyl radicals with good yield and high selectivity under very simple experimental conditions.

RESULTS AND DISCUSSION

The alkyl radicals were generated from the silver catalysed oxidative decarboxylation of acids with peroxydisulphate according to a reaction which was recently well explained by Kochi and co-workers.[4] The catalytic action of the silver salt takes place according to the following redox radical chain:

$$2Ag^{+} + S_2O_8^{--} \rightarrow 2Ag^{++} + 2SO_4^{-\cdot}$$

$$R{-}COOH + Ag^{++} \rightarrow R\cdot + CO_2 + H^{+} + Ag^{+}$$

This radical source offered interesting prospects of synthetic success for the homolytic alkylation of heteroaromatic bases, in that the reaction medium (Ag^{++}, $S_2O_8^{--}$ and $SO_4^{-\cdot}$) has no specific oxidative action towards the alkyl radicals. In fact the main interaction of the alkyl radical R· is not so much its oxidation, but a hydrogen abstraction from the alkanoic acid with the formation of the compound R—H in

high yield.[4] Therefore, in the presence of a protonated heteroaromatic base competition would be between addition of the alkyl radical to the base or hydrogen abstraction. Our previous results[2,3] indicated that the first reaction was considerably favoured and that, therefore. this redox system could be particularly suitable for homolytic alkylation.

In Tables 1–6 are reported the results obtained from a number of alkyl radicals with quinoline, 2-methylquinoline, isoquinoline, pyridine, 4-cyano-pyridine and acridine.

When the heteroaromatic bases have more than one reactive position (α or γ to the heterocyclic nitrogen) it is possible to obtain the monoalkylation products, limiting the conversion because the first alkyl group reduces only slightly the reactivity of the substrate.[5] (Table 4).

TABLE 1. ALKYLATION OF QUINOLINE

R—COOH R =	Base: persulphate Ratio	Converted Base %	Yield on converted Base %	Products (%)
CH_3—	1:3	97	100	2-Me-(23); 4-Me-(25·5); 2,4-diMe-(51·5)-
CH_3—CH_2—	1:2	97·5	100	2-Et-(21·4)[a]; 4-Et-(24·6)[a]; 2,4-diEt-(54)[b]-
CH_3—$(CH_2)_2$—	1:2	87	100	2-Pr-(28)[a]; 4-Pr-(36)[a]; 2,4-diPr-(36)-
CH_3—$(CH_2)_3$—	1:2	99	100	2-Bu(26·8)[c]; 4-Bu-(36·2)[d]; 2,4-diBu-(36)-
$(CH_3)_2CH$—	1:2	99	100	2-isoPr-(12·9)[a]; 4-isoPr-(25·9)[a]; 2,4-diisoPr-(61·2)[e]-
$(CH_2)_5CH$—	1:2	100	100	2-cycloC_6-(24)[f]; 4-cycloC_6-(35·2); 2,4-dicycloC_6-(40·8)-
$(CH_3)_3C$—	1:1	59	96	2-t-Bu-[a]
$(CH_3)_3C$—	1:2	98	95	2-t-Bu[a]-
Ph-OCH_2—	1:2	100	100	2-PhOCH_2-(7·7)[g]; 4-PhOCH_2-(21·6); 2,4-diPhOCH_2-(70·7)-

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TABLE 2. ALKYLATION OF 2-METHYLQUINOLINE

R—COOH R =	Base: persulphate Ratio	converted Base %	Yield on converted Base %	Products
CH_3—	1:2	71·5	90	2,4-diMe-quinoline-
CH_3—CH_2—	1:2	98	100	2Me,4Et-quinoline-[a]
CH_3—$(CH_2)_2$—	1:2	98·5	90·5	2Me,4nPr-quinoline-
$(CH_3)_2CH$—	1:1·5	100	93·2	2Me,4isoPr-quinoline-
$(CH_2)_2CH$—	1:1·5	30	100	2Me,4cycloPr-quinoline-

[a] E. Knovenagel and H. Bähr, *Ber. Dtsch. Chem. Ges.* **55**, 1912 (1922)

TABLE 3. ALKYLATION OF ISOQUINOLINE

R—COOH R =	Base: persulphate Ratio	Converted Base %	Yield on converted Base %	Products
$CH_3—CH_2—$	1:1·5	33	100	1-Et-isoquinoline[a]
$(CH_2)_5CH—$	1:2	99	84	1-cycloC_6-isoquinoline

[a] E. Späth, F. Berger and W. Kuntara, *Ber. Dtsch. Chem. Ges.* **63B**, 134 (1930)

TABLE 4. ALKYLATION OF PYRIDINE

R—COOH R =	Base: persulphate Ratio	Converted Base %	Yield %	Products (%)
$CH_3—CH_2—$	1:3	100	98[a]	2-Et-(1·5); 4-Et-(21·5); 2,6-diEt-(41·5)[c]; 2,4-diEt-(26·5)[d]; 2,4,6-triEt-(9)[e]-
$CH_3—CH_2—$	3:1	—	36[b]	2-Et-(44); 4-Et-(56)-
$(CH_2)_5CH—$	3:1	—	42[b]	2-cycloC_6-(37); 4-cycloC_6-(63)-
$(CH_3)_3C—$	3:1	—	52[b]	2-t-Bu-(32)[d]; 4-t-Bu-(68)[f]-

[a] Yield on converted base
[b] Yield on persulphate used. The yield on converted base is quantitative
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TABLE 5. ALKYLATION OF 4-CYANOPYRIDINE

R—COOH R =	Base: persulphate Ratio	Converted Base %	Yield on Converted Base %	Products (%)
$CH_3—$	1:1	41·4	82	2-Me-(85)[a]; 2,6-diMe-(15)-
$CH_3—CH_2—$	1:1	77	81	2-Et-(78)[a]; 2,6-diEt-(22)-
$(CH_3)_2CH—$	1:1	86	88	2-isoPr-(67)[a]; 2,6-diisoPr-(33)-
$(CH_3)_2C—$	1:1	95	98	2-t-Bu-(87)[a]; 2,6-di-t-Bu-(13)-

[a] D. Liberman, N. Rist, F. Grumbach, S. Cals, M. Moyeux and A. Rouaix, *Bull. Soc. Chim. France* 687 (1958)

TABLE 6. ALKYLATION OF ACRIDINE

R—COOH R =	Base: persulphate Ratio	Converted Base %	Yield on converted %	Products
$CH_3—$	1:2	11	100	9-Me-acridine[a]-
$CH_3—CH_2—$	1:1	24	100	9-Et-acridine[b]-
$CH_3—(CH_2)_3—$	1:2	36·5	100	9-Bu-acridine[a]-
$(CH_3)_2CH—$	1:2	65·5	100	9-isoPr-acridine[c]-

[a] E. Hayashi, S. Ohsumi and T. Maeda, *Yakugaku Zasshi* **79**, 967 (1959)
[b] W. Koenigs, *Ber. Dtsch. Chem. Ges.* **32**, 3599 (1899)
[c] Buu-Hoï and J. Lecocq, *Rec. Trav. Chim.* **64**, 254 (1945)

These results show that the homolytic alkylations of heteroaromatic bases have a synthetic interest comparable to the electrophilic alkylation in the homocyclic series; they indicate a sharp difference between homolytic alkylations and arylations (the protonated quinoline, for example, forms all seven possible isomers in the homolytic phenylation[6]).

Synthetic interest arises from the following characteristics:

(a) The source of alkyl radicals is cheap, readily available and very versatile. A large number of alkyl radicals can be obtained from the corresponding carboxylic acids.

(b) Yields are good and the experimental conditions are particularly simple: the reactions are carried out in aqueous solution at moderate temperatures.

(c) The electrophilic alkylation, which is important in the homocyclic series, is not applicable with the heteroaromatic bases and in any case would cause a completely different orientation. Also nucleophilic alkylations with organo-metal reagents (lithium-alkyls, Grignard reagents) give good results only in a few cases.

(d) The substitution occurs without rearrangement even in the case of the neopentyl[2] and cyclopropyl radicals, and without isomerization of reaction products, which takes place frequently in electrophilic alkylation.

(e) The selectivity of the attack is complete in the positions having high reactivity towards nucleophilic reagents because of the nucleophilic character of the alkyl radicals. This last aspect also allows the introduction of t-alkyl groups, that could not be introduced by homolytic substitution in homocyclic systems.[7] Also, under comparable conditions, higher conversions are obtained with tertiary and secondary than with primary or Me radicals, due to greater nucleophilic character, notwithstanding the fact that the reaction is certainly not favoured for steric reasons. 4-Cyanopyridine is alkylated more readily than pyridine, again because of the nucleophilic character of the alkyl radicals.[5]

This polar influence of the alkyl radicals also fully agrees with the results obtained from the study of the relative reaction rates of the homolytic methylation of 4-substituted-pyridines in which t-Bu-OOH was used as source of Me radical.[5] This behaviour indicates that the strong electron-deficient nature of the protonated heteroaromatic bases causes an enhanced contribution of polar forms in the transition state: and it well emphasizes the intrinsic nucleophilic character of the alkyl radicals, which is difficult to observe to the same extent in other reactions of these radicals.

The very poor reactivity of strong electron-rich substrata, such as 1,3-dimethoxybenzene, towards the alkyl radicals[5] indicates that the reactivity can not be explained on the basis of a dipolar character of the alkyl radicals, which would react as nucleophilic or electrophilic species depending on electron-deficient or electron-rich nature of the substrate.

In the next paper a quantitative study will be published of the influence of the

polar characteristics of the main alkyl and substituted-alkyl radicals formed by the oxidative decarboxylation with peroxydisulphate.

EXPERIMENTAL

All reagents were commercial products, NMR spectra were recorded on a Varian A-60 spectrometer; chemical shifts are in ppm (δ) from TMS as the internal standard. Mass spectra were obtained on a Hitachi–Perkin–Elmer RMU-6D mass spectrometer (70 eV).

General procedure. To a soln of the heterocyclic base (0·01 mole) and $AgNO_3$ (0·1 mole for mole of added peroxydisulphate) in 10% H_2SO_4 (0·01 mole) and the carboxylic acid (0·05 mole), heated at 70°, was added, under stirring in about 10 min, a soln of $(NH_4)_2S_2O_8$ (moles indicated in the tables) in H_2O (0·01 mole of peroxydisulphate were dissolved in 5 ml of H_2O), between 70 and 90 .

For 1 mol of 4-cyano-pyridine 3 moles of H_2SO_4 were used. With the acridine, for 0·01 mole of the base, 0·1 mole of the carboxylic acid and 0·02 mole of H_2SO_4 were used: nevertheless at the end of the addition of the peroxydisulphate two layers were present in the soln.

After emission of CO_2 ceased, stirring and heating were continued for 20 min. The soln was poured into ice and NH_3aq, extracted with $CHCl_3$, the organic layer washed with 5% NaOH and H_2O, dried with $CaCl_2$, solvent removed and the residue analysed by GLC.

Product analysis. Gas chromatographic analyses were carried out under the following conditions: (A) Perkin–Elmer 880, flame ionization detector, with a 50 feet × 0·02 inches i.d. S.C.O.T. column of M Bis (m-phenoxy-phenoxy)Benzene + Ap.L + CO 880 (NBNA). N_2 (7 ml/min.) (B) C. Erba Fractovap GV, flame ionization detector, with a 2 m × 3 mm i.d. pyrex column packed with 2% Silicone gum rubber XE-60 on silanized Gas-Chrom P, 80/100 mesh. N_2 (40 ml/min). (C) Perkin–Elmer 880, ss column, 7% silicone oil DC-550 and 3% Carbowax 20M on Chromosorb P, 60/80 mesh, (+5% KOH). N_2 (25 ml/min). (D) Perkin–Elmer 880, with a 50 feet × 0·02 inches i.d. S.C.O.T. column of Carbowax 20 M. N_2 (7 ml/min). For the alkyl-quinolines (Table 1): conditions A: for Me: 131°, Et: 154°, Pr: 164°, Bu: 165°, t-Bu: 156°; and conditions B, temp; for iso-Pr: 140°, cyclo-hexyl: 183°: For the alkyl-2-Me-quinolines (Table 2): conditions C; temp.; for Me, n-Pr and iso-Pr: 164°; cyclo-Pr: 160°. Conditions B; for Et: 130°. For the alkyl-iso-quinolines (Table 3): B; Et: 120°; cyclo-hexyl: 150°. For the alkyl pyridines (Table 4): Et-: D, 147°; cyclo-hexyl: C, 150°; t-Bu-: A, 147°. For the alkyl-4-cyanopyridines (Table 5): A, Me: 144°; Et, iso-Pr and t-Bu: 153°. For the alkyl acridines (Table 6): B, Me, n-Bu, iso-Pr: 164°; Et: 151°.

Products identification. Some compounds were available by known syntheses and used for the identification by GLC. Most compounds were isolated by column chromatography (Silicagel Merk, 0·05–0·2 mm, hexane: EtOAc 9:1) and identified by their spectroscopic characteristics. Others, of the same series, were assumed to be those expected by analogy and by their behaviour in the gas-chromatographic analysis.

4-*Cyclohexyl-quinoline.* NMR ($CDCl_3$): 1·0–2·0 (m, 10H, CH_2); 2·9–3·4 (m, 1H, CH of the cyclohexyl group); 7·04 (d, 1H, H-3); 8·75 (d, 1H, H-2); 7·30–8·30 (m, 4H, aromatic protons); MS: M^+ at *m/e* 211; major peaks at *m/e* 182, 168, 154, 143, 129, 115, 101.

2-*Cyclohexyl-quinoline* (Table 1).[f] MS: M^+ at *m/e* 211; major peaks at *m/e* 196, 182, 167, 156, 143, 129.

2,4-*Dicyclohexyl-quinoline.* MS: M^+ at *m/e* 293; major peaks at *m/e* 264, 238, 225, 211, 196.

2-*t-Butyl-quinoline.* NMR ($CDCl_3$): 1·47 (s, 9H, CH_3); 7·2–8·2 (m, 6H, aromatic protons).

2,4-*Di-n-Pr-quinoline.* NMR (CCl_4): 0·98 (t, 3H, CH_3 of the propyl group in 2); 1·0 (t, 3H, CH_3 of the propyl in 4); 1·40–2·20 (m, 4H, $—CH_2—\underline{CH_2}—CH_3$); 2·85 (t, 2H, $—\underline{CH_2}—CH_2—CH_3$ in 2); 2·92 (t, 2H, $—\underline{CH_2}—CH_2—CH_3$ in 4); 6·96 (s, 1H; H-3); 7·15–8·15 (m, 4H, aromatic protons). MS: M^+ at *m/e* 213; major peaks at *m/e* 198, 185, 169, 156, 129, 115.

2-*Me*,4-n-*Pr-quinoline.* NMR ($CDCl_3$): 1·0 (t, 3H, $—CH_2—CH_2—\underline{CH_3}$); 1·50–2·0 (m, 2H, $—CH_2—\underline{CH_2}—CH_3$); 2·67 (s, 3H, CH_3 in 2); 2·97 (t, 2H, $—\underline{CH_2}—CH_2—CH_3$); 7·08 (s, 1H, H-3); 7·2–8·2 (m, 4H, aromatic protons). MS: M^+ at *m/e* 185; major peaks at *m/e* 170, 157, 129, 115, 101, 89, 77.

2-*Me*,4-*cyclopropylquinoline.* NMR ($CDCl_3$): 0·50–1·5 (m, 5H, cyclopropyl group); 2·67 (s, 3H, CH_3); 6·9–8·2 (m, 5H, aromatic protons). MS: M^+ at *m/e* 183; major peaks at *m/e* 168, 142, 128, 115, 101, 89, 77.

1-*Cyclohexylisoquinoline.* NMR (CCl_4): 1·0–2·35 (m, 10H, CH_2); 3·60 (m, 1H, CH of the cyclohexyl group); 7·2–8·5 (m, 6H, aromatic protons). MS: M^+ at *m/e* 211; major peaks at *m/e* 182, 156, 143, 129, 115, 91.

2-iso-*Pr*,4-*cyanopyridine.* Table 5).[a] NMR ($CDCl_3$): 1·34 (d, 6H, CH_3); 3·20 (septet, 1H, $CH\langle$); 7·30–7·45 (m, 2H, H-3 and H-5); 8·8 (m, 1H, H-6). MS: M^+ at *m/e* 211; major peaks at *m/e* 145, 131, 118, 104, 77.

2-t-*Bu*,4-*cyanopyridine*. (Table 5)[a] NMR ($CDCl_3$): 1·38 (s, 9H, $-CH_3$); 7·30–7·45 (m, 2H, H-3 and H-5); 8·75 (m, 1H, H-6). MS: M^+ at *m/e* 160; major peaks at *m/e* 145, 129, 118, 104, 77.

2,6-*diiso-Pr*,4-*cyanopyridine*. NMR ($CDCl_3$): 1·34 (d, 12H, CH_3); 3·20 (septet, 2H, $CH<$); 7·30–7·45 (s, 2H, H-3 and H-5). MS: M^+ at *m/e* 188; major peaks at *m/e* 187, 173, 160, 145, 118.

2,6-*Di-Et*,4-*cyanopyridine*. NMR ($CDCl_3$): 1·32 (t, 6H, CH_3); 2·87 (q, 4H, CH_2); 7·22 (s, 2H, H-3 and H-5).

9-iso-*Pr-acridine*. NMR (DMSO D_6): 1·70 (d, 6H, CH_3); 4·50 (q, 1H, $CH<$); 7·30–8·70 (m, 8H, aromatic protons). MS: M^+ at *m/e* 221; major peaks at *m/e* 206, 179, 151, 102.

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