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A Novel, Simple and Cheap Source of Alkyl Radicals from Alcohols, Useful for Heteroaromatic Substitution

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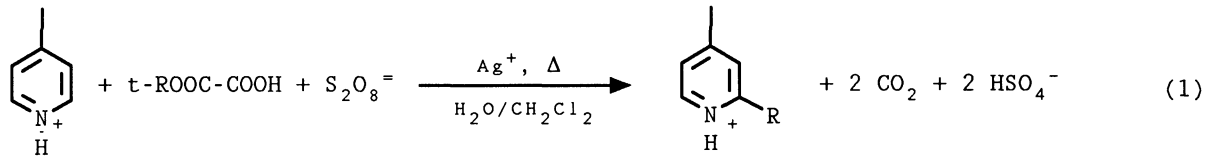
Alkyl radicals were easily produced from secondary or tertiary alcohols in a cheap and simple way by silver-catalyzed decarboxylation of oxalic acid monoesters by $S_2O_8^=$. They were utilized for the alkylation of heteroaromatic bases in a two-phase system, with high yields and selectivity.

Homolytic alkylation and acylation of heteroaromatic bases have been developed as quite general reactions of wide synthetic interest; several of the most important classes of organic compounds have been successfully utilized[1] for this purpose. Recently,[2] secondary alkyl radicals have been generated from the corresponding alcohols through alkyl xantates by a variation of the Barton-McCombie reaction,[3] and successfully utilized for heteroaromatic substitution. However, considering the difficulties implied by the preparation of thiocarbonyl esters from tertiary alcohols, we developed a much simpler and cheaper source of alkyl radicals from alcohols, based on the decarboxylation of oxalic acid monoesters (Eq.1)



(1)

A recent report[4] concerning a similar approach prompts us to report our much more effective, simple and cheap method. Oxalic acid monoesters were easily prepared either from oxalyl dichloride and alcohols or by partial hydrolysis of diesters.

A general experimental procedure is given: a solution of 10 mmol of oxalic acid monoester in 20 ml of CH_2Cl_2 was added to 20 ml of an aqueous

solution containing 5 mmol of heteroaromatic base, 2.5 mmol of H_2SO_4, 10 mmol of $Na_2S_2O_8$, and 0.5 mmol of $AgNO_3$. The mixture was refluxed under stirring for 2 h, then made basic and extracted; the organic layer was analyzed by GC and GC-MS. The reaction products were isolated by flash-chromatography on silica gel and identified by comparison with authentic samples previously prepared by different procedures (i.e., using alkyl iodides[5] or carboxylic acids[6] as sources of alkyl radicals); chlorobenzene was used instead of methylene chloride to reach temperatures higher than 40 °C. The results are shown in Table 1. A two-phase system is much more convenient than operating in homogeneous solution because the extraction of the more lipophilic substitution product by the organic phase allows to minimize the problem of polysubstitution,[8] which arises in the presence of more than one α or γ position on the heteroaromatic ring, e.g. in quinoline, pyridine, pyrazine etc. Alkyl radicals are generated by a catalytic redox chain (Eqs.2-4).

$$S_2O_8^{=} + 2\,Ag^{+} \longrightarrow 2\,SO_4^{=} + 2\,Ag^{2+} \qquad (2)$$

$$ROCO\text{-}COOH + Ag^{2+} \longrightarrow \dot{R}OCO + CO_2 + Ag^{+} + H^{+} \qquad (3)$$

$$\dot{R}OCO \longrightarrow R\cdot + CO_2 \qquad (4)$$

With monoesters of secondary alcohols, alkoxycarbonylation (Eq.5) competes with alkylation in the temperature range 30-100 °C, alkylation increasing with temperature.

$$Het\text{-}H + ROOC\text{-}COOH + S_2O_8^{=} \xrightarrow{Ag^{+}} Het\text{-}COOR + CO_2 + 2\,HSO_4^{-} \qquad (5)$$

With monoesters of methanol or of primary alcohols this latter reaction is by far the prevailing one. Actually, this method represents the simplest and cheapest process for the direct introduction of a carboxylic group in the heterocyclic ring, and, as such, it is suitable for practical applications.[8] Oddly, no carboxylation of the heterocyclic ring was reported in the mentioned Letter,[4] but the formation of oxalic diesters was ascribed to the dimerization of ·COOR radical. This is highly unlikely, because a preliminary evaluation,[9] based on the competition between decarboxylation of known[10] rate (Eq.4) and alkoxycarbonylation (Eq.5), indicates that the rate of addition of ·COOR radical to the heterocyclic ring is in the range 10^5-10^6 $M^{-1}s^{-1}$ at room temperature. Actually, oxalic acid monoesters are easily converted to a mixture of diesters and oxalic acid; this behaviour was observed even under mild conditions.

Table 1. Alkylation of heteroaromatic bases by monooxalates

Heteroaromatic base	Alkyl	Orientation %	Conversion %	Yields[a] %
Quinoline	t-Amyl	2	100	89
Quinoline	t-Butyl	2	81	80
Lepidine[b]	t-Butyl	2	50	93
Quinoline[c]	t-Butyl	2	46	91
Quinoline	1-Methyl-cyclohexyl	2	67	88
Quinoline[d]	i-Propyl	2(21); 4(28); 2,4(11)	86	60
Quinoline[e]	i-Propyl	2(7); 4(9); 2,4(10)	80	26
Quinoline[f]	Ethyl	2(traces); 4(traces)	84	traces
Lepidine	t-Butyl	2	55	98
Lepidine	t-Amyl	2	46	96
Lepidine[g]	i-Propyl	2	100	72
4-CN-Pyridine	t-Butyl	2(70); 2, 6(25)	90	95
4-CN-Pyridine	t-Amyl	2	100	94
4-CN-Pyridine	1-Methyl-cyclohexyl	2	65	93
Qinoxaline	t-Butyl	2	85	97
Benzothiazole	t-Butyl	2	60	94
Pyrazine	t-Butyl	2	100	86

a) yields based on converted heteroaromatic base. b) iodosobenzene diacetate was utilized according to Ref.12. c) The Barton ester was utilized (Tetrahedron Lett., **27**, 1327 (1986)). d) At 100 °C in PhCl. The following derivatives of quinoline were also formed: 2-isopropoxycarbonyl (26%); 4-isopropoxycarbonyl (8%); 2,4-diisopropoxycarbonyl (1.5%); 2-isopropoxycarbonyl-4-isopropyl (3.1%) and 2-isopropyl-4-isopropoxycarbonyl (1.1%). e) At 24 °C in CH_2Cl_2 . The following derivatives of quinoline were also formed: 2-isopropoxycarbonyl (39%); 4-isopropoxycarbonyl (15%); 2-isopropoxycarbonyl-4-isopropyl (3%). f) The following derivatives of quinoline were also formed: 2-ethoxycarbonyl (48%); 4-ethoxycarbonyl (26%); 2,4-diethoxycarbonyl (4%); g) At 100 °C in PhCl. 11% of 2-isopropoxycarbonyllepidine was also formed.

We have also investigated t-alkylation of heteroaromatic bases by decomposition of Barton esters[11] of monooxalates and by decarboxylation of oxalic acid monoesters by iodosobenzene diacetate, according to a recent procedure developed by us;[12] however, both these procedures are less effective and much more expensive than the one presented in this work; moreover, they do not allow to minimize polysubstitution, as they are not suitable for two-phase systems. They can, anyway, prove useful for the manipulation of complex and fragile substrates.

References

1) Recent reviews: F. Minisci, E. Vismara, and F. Fontana, *Heterocycles*, **28**, 489 (1989); F. Minisci, E. Vismara, and F. Fontana, *J.Heterocycl. Chem.*, **27**, 79 (1990).
2) F. Minisci, F. Coppa, F. Fontana, G. Pianese, P. Tortoreto, and L. Zhao, *Tetrahedron Lett.*, **33**, 687 (1992).
3) D. H. R. Barton, and S. W. McCombie, *J.Chem.Soc., Perkin Trans.1*, **1975**, 1574.
4) H. Togo, M. Aoki, and M. Yokoyama, *Chem.Lett.*, **1991**, 1691.
5) F. Minisci, E. Vismara, F. Fontana, G. Morini, and C. Giordano, *J.Org.Chem.*, **51**, 4411 (1986); F. Minisci, E. Vismara, and F. Fontana, *ibid.*, **54**, 5224 (1989).
6) F. Fontana, F. Minisci, M. C. Nogueira Barbosa, and E. Vismara, *Tetrahedron*, **46**, 2525 (1990).
7) F. Fontana, F. Minisci, M. C. Nogueira Barbosa, and E. Vismara, *J.Org.Chem.*, **56**, 2866 (1991).
8) F. Minisci, F. Coppa, F. Fontana, and L. Zhao, Ital.Pat. MIA91002099 (1990).
9) Preliminary results in this laboratory.
10) D. Griller, and B. P. Roberts, *J.Chem.Soc., Perkin Trans.2*, **1972**, 747; K. U. Ingold, R. Maillard, and J. C. Walton, *ibid.*, **1981**, 970.
11) D. H. R.Barton, "Half a Century of Radicals," Lezioni Lincee, Cambridge University Press, in press. We thank prof.Barton for kindly sending us a copy of the manuscript prior to publication.
12) F. Minisci, E. Vismara, F. Fontana, and M. C. Nogueira Barbosa, *Tetrahedron Lett.*, **30**, 4569 (1989).

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