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A NOVEL RADICAL REACTION OF ALKYL XANTATES USEFUL FOR THE SELECTIVE SUBSTITUTION OF HETEROAROMATIC BASES

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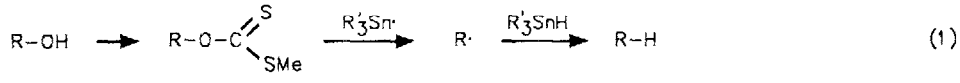
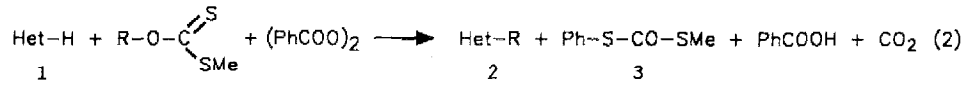
Abstract : Cyclohexyl radical is generated from cyclohexyldithiocarbonate and benzoyl peroxide. The radical source is used for the alkylation of heteroaromatic bases.

The homolytic alkylation and acylation of heteroaromatic bases are among the most important reactions of this class of compounds[1]. Now we report a new source of alkyl radicals from alcohols, useful for this reaction. The Barton-McCombie[2] deoxygenation of alcohols is a particularly ingenious method to generate alkyl radicals from alcohols; there have been spectacular synthetic applications[2] of this free-radical chain reaction (eq.1)



(1)

This source is not suitable for the aromatic substitution, which is an oxidative alkylation; thus, we have developed a new method based on eq.2



Cyclohexanol has been chosen as a typical alcohol simply because the reagents and the reaction products were already available in our laboratory; the results are reported in the Table.

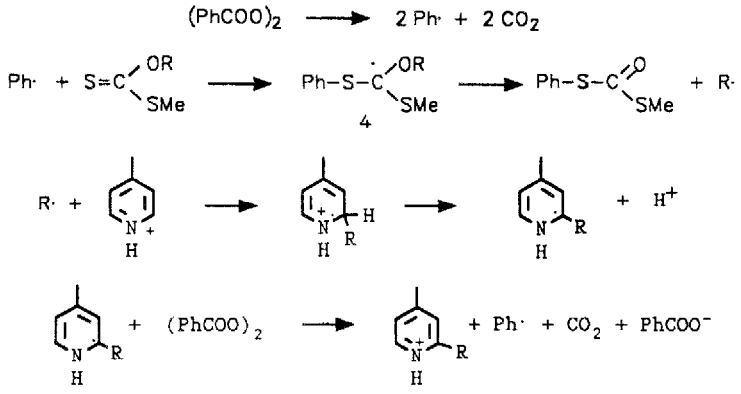
The procedure is very simple: a solution of benzoyl peroxide (6 mmol) in 10 ml of chlorobenzene is dropped within 1 hour into a solution of the heteroaromatic base (2 mmol), trifluoroacetic acid (2 mmol) and dithiocarbonate (6 mmol) in 10 ml of refluxing chlorobenzene. The solution is refluxed for 30′ more and, after cooling, the basic products are extracted with 10% aqueous H_2SO_4 and isolated by alkalinization and extraction with CH_2Cl_2. The heterocyclic bases **1** and the cyclohexylation products **2** reported in the Table are the only basic products observed by g.l.c and t.l.c.; they were isolated by flash-chromatography and identified by comparison (NMR, g.l.c.-MS) with authentic samples previously[1] obtained by different procedures. Benzoic acid and the thiocarbonate **3** were isolated from the non-basic fraction and identified by g.l.c.-MS.

Table . Cyclohexylation of Heteroaromatic Bases .

Het-H (I)	Orientation (%)	Conversion(%)	Yields[a](%)
lepidine	2	68	92
quinoline	2 (42); 4 (44) 2,4 (14)	53	94
benzothiazole	2	40	83
isoquinoline	1 (67) 3 (33)	46	95
4-cyanopyridine	2	41	91

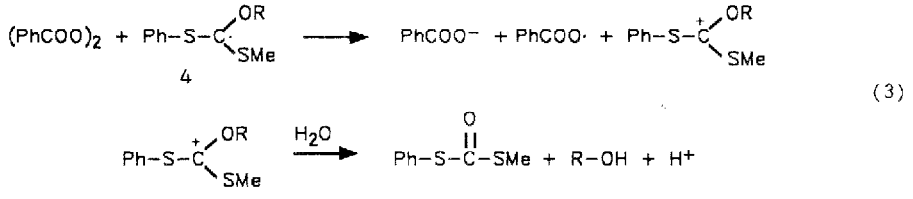
a) yields based on the converted heterocyclic base .

The mechanism of the reaction is shown by the Scheme.



Scheme

The formation of **3**[3] is a good evidence of this mechanism and it brings further support also to the Barton mechanism of reaction (1), which has been subjected to some mechanistic controversy[4]. The kinetic chain length appears to be quite short under these reaction conditions: benzoic acid and the dithiocarbonate **3** are formed in larger amount than expected from the stoichiometry of eq.2 (the amounts of **3** and of benzoic acid are twice and three times, respectively, higher than the amount of the alkylated heterocycle), which could be due to the competitive oxidation of radical **4** by $(PhCOO)_2$ (eq.3)



(3)

The rate constant for the addition of phenyl radical to dithiocarbonate appears to be very high ($>10^8$ $M^{-1}s^{-1}$) since no phenylation

of the heteroaromatic bases has been observed (the rate constants for these reactions[5] are in the range 10^6-10^7 $M^{-1}s^{-1}$).

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1.Minisci,F.; Vismara,E.; Fontana,F. *Heterocycles* **1989** , *28*,489. *J.Heterocyclic Chem.* **1990** , *27* , 79.

2.Barton,D.H.R.; McCombie S.W. *J.Chem.Soc.Perkin Trans.I* , **1975** ,1574. Hartrig,W. *Tetrahedron* **1983** , *39* , 2609.

3.Note added in proof - The formation of **3** according to the mechanism proposed in the Scheme has also been suggested by D.H.R.Barton, whom we thank for kindly sending us a copy of his paper prior to publication.

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