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SYNTHESIS of NOVEL N-(PRIMARY)ALKYLHYDROXAMIC ACIDS

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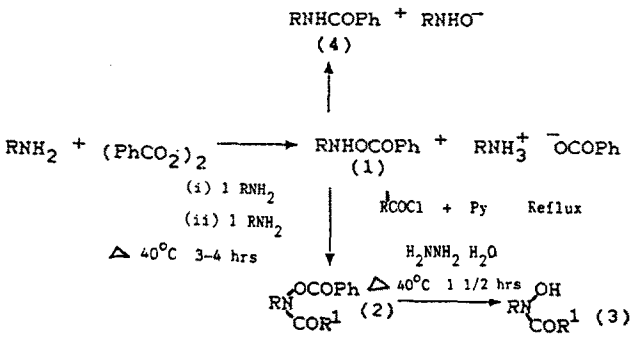
Abstract: Synthesis of N-*primary* alkylhydroxamic acids is described in this paper by benzoyloxylation (benzoyl peroxide) of n-alkylamine and modification of the usual reaction conditions to stabilise the N-alkyl-O-benzoylhydroxylamine as the hydrochloride; this circumvents acyl transfer to amide. N-Acylation of the formed hydroxylamine leads to the formation of N-*primary* alkyl-N-acyl-O-acylhydroxylamine, which is debenzoylated to hydroxamic acid using hydrazine hydrate.

Metabolic transformation of alkyl and aryl amines to hydroxamic acids have been well documented.[1] One-electron oxidation of the formed hydroxamic acids produces acyl nitrones, which are powerful electrophilic acylating agents and are thought to be involved in the metabolic transformation of carcinogenic amines.[2,3] Most of the hydroxamic acids studied in the literature have been on N-*secondary*- and N-*tertiary* alkyl- or N-arylhydroxamic acids.[4] Very little has been published on N-*primary* alkylhydroxamic acids because of difficulties involved in their preparation.

The normal route for the preparation of alkylhydroxamic acids involves the benzoyloxylation of alkylamine with dibenzoyl peroxide at room temperature followed by adding an extra mole equivalent of alkylamine and refluxing for 3-4 hours. N-Acylation of the O-benzoylhydroxylamine **(1)** yields the benzoylhydroxylamine **(2)**, de O-benzoyl of which yields hydroxamic acid **(3)**.[5]



This method can only be used to prepare N-*secondary* and N-*tertiary* alkylhydroxamic acids, since if R = primary alkyl, the N-alkyl-O-benzoylhydroxylamine (1) produced under normal conditions transfer its acyl moiety *in situ* to the precursor alkylamine to form an amide **(4)**.

To date, most primary hydroxamic acids were prepared from methyl- or benzylhydroxylamine and the appropriate acyl chloride, using standard procedures.[6] This is not a general method, as difficulties in the

preparation of precursor alkylhydroxylamine limits its usefulness.

Results presented in this paper, show that slight modification of the reaction conditions of the former method allows the preparation of the (5). The preparation of N-*primary* alkyl-O-benzoylhydroxylamine was done by mixing one mole equivalents of primary alkylamine and dibenzoyl peroxide at room temperature. After 2 - 5 minutes reaction time, the reaction was cooled in an ice bath, and hydrogen chloride gas was bubbled through the reaction mixture, precipitating the hydroxylamine as an hydrochloride salt - this circumvents the acyl transfer to amine to form amide.

$$RNH_2 + (PhCO_2)_2 \longrightarrow \underset{(1)}{RNHOCOPh} \longrightarrow \underset{(5)}{RNHOCOPh \cdot HCL}$$

The salt was filtered and recrystallised from absolute ethanol (yield ca. 10%). One mole equivalent of N-*primary* alkyl-O-benzoylhydroxylamine hydrochloride (5) was reacted with benzoyl or adamantanecarbonyl- chloride and two moles equivalents of distilled pyridine yielding N-*primary* alkyl-N-benzoyl-O-benzoylhydroxylamine (2) (yields 40 - 97%). The removal of O-benzoyl moiety by reaction of (2) with hydrazine hydrate was done under normal conditions, yielding the desired hydroxamic acids (3) (yield 37 -55%).

This method provides the first general method for the preparation of N-*primary* alkylhydroxamic acids and open up a new class of hydroxamic acids to investigation.[8] The described method allowed the synthesis of two novel hydroxamic acids (Table 1). All products and intermediates had elemental analysis, NMR, IR and Mass spectra (EI and FAB) consistent with the assigned structures.

TABLE 1 N-Primary alkylhydroxamic acids.

R	R'	m.p. (°C)
propyl	benzoyl	66-68 (lit.[7] 66-69)
allyl	benzoyl	54-56
allyl	adamantanecarbonyl	103-105
benzyl	benzoyl	98-100 (lit.[5b] 99-101)

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8. Recent work suggests that N-substituted hydroxycarbamates can be prepared by reductive acylation of oximes (for details see Wu, P-L and Sun, C-J, *Tetrahedron Lett.*, 1991, 32, 4137).

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