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α-DIALKYLAMINOALKYLNITRILES: PRACTICAL REAGENTS FOR NUCLEOPHILIC ACYLATION

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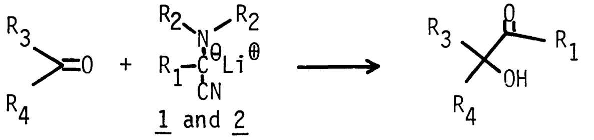
An efficient synthesis of α-hydroxyketones from the reaction of carbonyl compounds and lithio α-dialkylaminoalkylnitriles is described.

The α-hydroxy carbonyl moiety is a very important functional group frequently encountered in many natural products.[1] Methods for the synthesis of this class of compounds have been reported.[2] In most cases the reagents employed are not only expensive but great care must be taken during their preparations. We wish to report a general and convenient method for the synthesis of α-hydroxyketones involving the additions of the carbanions (1 and 2)[3,4] derived from easily accessible N,N-dialkylaminoalkylnitriles[5] to carbonyl compounds. Hydrolyses of the adducts gave the corresponding α-hydroxyketones in high yields (eq.1).



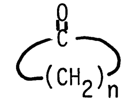
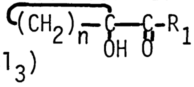
1, R_1 = CH_3-, R_2 = C_2H_5-
2, R_1 = C_2H_5-, R_2 = CH_3- (1)

The following procedure is representative: solutions of the carbanions 1 or 2 were generated by the reaction of lithium diisopropylamide (1 equiv.) with the corresponding α-dialkylaminoalkylnitriles (1 equiv.) in tetrahydrofuran at -78°C for 45 min. After the additions of the carbonyl compounds had been completed, the reaction mixtures were stirred for 5 hr longer at -78°C before being hydrolyzed with hydrochloric acid (2N) for 24 hr at room temperature. The products were extracted with chloroform and further purified by column chromatography on silica gel. The results are summarized in Table I.

Table I

Carbonyl Compounds; $CH_3(CH_2)_nCHO$; n =	α-Hydroxyketones; $CH_3(CH_2)_n\underset{OH}{CH}-\underset{O}{\overset{\|}{C}}-R_1$ R_1	Yields %	NMR($CDCl_3$)
4	CH_3	69	2.2(3H,s); 3.5(OH[a],m); 4.2(1H,m); 0.9-1.4(11H,m)
	C_2H_5	62	1.1(3H,t,J 7Hz); 2.5(2H,q,J 7Hz); 3.6(OH[a],m); 4.2(1H,m); 1.0-1.3(11H,m)
5	CH_3	73	2.2(3H,s); 3.5(OH[a],m); 4.2(1H,m); 0.8-1.3(13H,m)
	C_2H_5	68	1.1(3H,t,J 7Hz); 2.5(2H,q,J 7Hz); 3.4(OH[a],m); 4.2(1H,m); 0.9-1.5(13H,m)
6	CH_3	70	2.2(3H,s); 3.5(OH[a],m); 4.2(1H,m); 0.9-1.3(15H,m)
	C_2H_5	67	1.1(3H,t,J 7Hz); 2.5(2H,q,J 7Hz); 3.6(OH[a],m); 4.2(1H,m); 0.9-1.3(15H,m)
12	CH_3	72	2.2(3H,s); 3.5(OH[a],m); 4.2(1H,m); 0.8-1.3(27H,m)
	C_2H_5	57	1.1(3H,t,J 7Hz); 2.4(2H,q,J 7Hz); 3.9(OH[a],m); 4.2(1H,m); 0.8-1.3(27H,m)

Table I (contd.)

Carbonyl Compounds;  ; n =	R_1	Yields %	α-Hydroxyketones;  NMR($CDCl_3$)
4	CH_3	55	3.6(O$\underline{H}^a$,s); 2.3(3H,s); 1.7(8H,m)
	C_2H_5	60	3.6(O$\underline{H}^a$,s); 2.6(2H,q,J 7Hz); 1.1(3H,t,J 7Hz); 1.9(8H,m)
5	CH_3	68	3.6(O$\underline{H}^a$,s); 2.3(3H,s); 1.7(10H,m)
	C_2H_5	72	3.6(O$\underline{H}^a$,s); 2.6(2H,q,J 7Hz); 1.1(3H,t,J 7Hz); 1.6(10H,m)
6	CH_3	74	3.6(O$\underline{H}^a$,s); 2.2(3H,s); 1.7(12H,m)
	C_2H_5	73	3.8(O$\underline{H}^a$,s); 2.6(2H,q,J 7Hz); 1.1(3H,t,J 7Hz); 1.5(12H,m)
7	CH_3	76	3.4(O$\underline{H}^a$,s); 2.2(3H,s); 1.7(14H,m)
	C_2H_5	78	3.4(O$\underline{H}^a$,s); 2.6(2H,q,J 7Hz); 1.1(3H,t,J 7Hz); 1.7(14H,m)

[a] Signals disappeared upon deuteration with D_2O.

Our results clearly demonstrated the immense potential of the α-dialkylaminoalkylnitriles as the acyl carbanion equivalents. Our preliminary results also indicated that the anions 1 and 2 also reacted smoothly with Michael acceptors and other electrophiles. Further exploratory work is now in progress.

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2. a, G.A. Russell and M. Ballenegger, Synthesis, 104 (1973); b, J.E. Baldwin,G.A. Höfle, and O.W. Lever Jr., J.Am.Chem.Soc., 96, 7125(1974); c, G.M. Rubottom, M.A. Vazquez, and D.R. Pelegrina, Tetrahedron Lett., 4319 (1974); d, S. Hünig and G. Wehner, Synthesis, 391 (1975); e, H. Stetter and G. Dämbkes, Synthesis, 403 (1977); f, L. Colombo, C. Gennari, C. Scolastico, and M.G. Beretta, J.C.S. Perkin I, 1036 (1978); g, E. Vedejs, D.A. Engler, and J.E. Telschow, J.Org.Chem., 43, 188 (1978); h, W. Dumont, D.V. Ende, and A. Krief, Tetrahedron Lett., 485(1979).
3. In the case of $R_1 = CH_3$- and $R_2 = CH_3$-, the reaction of the corresponding carbanion with carbonyl compounds gave low yields of the α-hydroxyketones and the products were very difficult to purify. When $R_1 = C_2H_5$-, we noticed no difference in the yields of the α-hydroxyketones both the cases of $R_2 = CH_3$- and $R_2 = C_2H_5$-.
4. When our investigation was initiated, only one brief report on the reaction of α-alkylaminonitriles was recorded: Z. Welvart, Bull.Soc.Chim.France, 1653 (1961). Very recently two reports on the applications of the α-aminonitriles derived from aliphatic aldehydes have appeared: H. Ahlbrecht, and K. Pfaff, Synthesis, 897 (1978); G. Stork, A.A. Ozorio, and A.Y.W. Leong, Tetrahedron Lett., 5175 (1978). On the other hand, the chemistry of α-aminonitriles derived from aromatic and heterocyclic aldehydes is quite well known: J.D. Albright, F.J. McEvoy, and D.B. Moran, J.Heterocyclic.Chem., 15, 881 (1978); V. Reutrakul, S. Nimgirawath, S. Panichanun, and P. Ratananukul, Chem.Lett., 399 (1979).
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