

REACTIONS OF LITHIUM ENOLATES WITH MOLECULAR OXYGEN
 α -HYDROXYLATION OF AMIDES AND OTHER CARBOXYLATE DERIVATIVES

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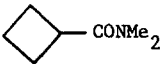
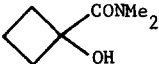
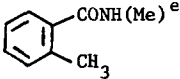
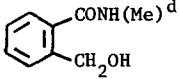
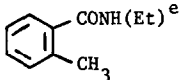
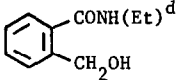
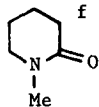
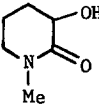
Recently, lithium diisopropylamide (LDA) and related hindered bases have found widespread use in the formation of enolate anions of acids, esters, and other carboxylate derivatives. In suitable solvents such as THF and HMPA at low temperatures, these anions have been employed in a variety of reactions including alkylation,¹ acylation,² halogenation,³ sulfonylation,⁴ selenenylation,⁵ and amination.⁶ The methods have been notable for their mildness, specificity, good yields and absence of side reactions such as self-condensation.

We now report that carbanions generated in the reactions of N,N-dialkyl amides with alkyl-lithium reagents undergo rapid oxidation under mild conditions when treated with molecular oxygen. The α -hydroperoxide intermediates formed in good yields may be cleanly reduced to α -hydroxy derivatives. Dianions formed from monosubstituted amides likewise take part in this reaction. Typical reactions are summarized in Table I.

While base-catalyzed autoxidations are well known⁷ in organic chemistry, the method described below appears to be a significant improvement over oxygenation procedures utilizing potassium t-butoxide. In earlier oxidations, limited to esters and ketones, yields have been lower and reactions often complicated by α -carbon cleavage.⁸

The reaction with oxygen is illustrated in the following α -hydroxylation of N,N-dimethylbutyramide. Addition of the amide (10 mmol) in anhydrous THF under nitrogen, to a THF solution containing lithium diisopropylamide (11 mmol) at 0°⁹ was followed by inverse addition of the lithium enolate to ether contained in the reaction well of an apparatus¹⁰ in which dry oxygen was continuously circulated at 0°. Uptake of oxygen, monitored with a gas buret, was quantitative and practically instantaneous.¹¹ The ether/THF solution was concentrated in vacuo and treated with aqueous sodium sulfite until the starch-iodide test showed the absence of peroxides. Extraction with chloroform or methylene chloride followed by drying (MgSO₄)

TABLE I

Amide	α -Hydroxy Derivative ^a	Yield, %
$\text{CH}_3\text{CH}_2\text{CONMe}_2$	$\text{CH}_3\text{CH}(\text{OH})\text{CONMe}_2$	72 ^b
$\text{CH}_3\text{CH}_2\text{CH}_2\text{CONMe}_2$	$\text{CH}_3\text{CH}_2\text{CH}(\text{OH})\text{CONMe}_2$	85 ^b
$\text{Ph}_2\text{CHCONMe}_2$	$\text{Ph}_2\text{C}(\text{OH})\text{CONMe}_2$	81 ^c
		84 ^b
		70 ^c
		70 ^c
		80 ^b

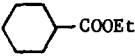
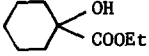
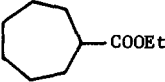
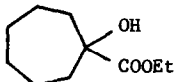
^a Characterized and identified by comparison with authentic samples and/or by comparison of ir and nmr spectra with known spectroscopic data. Conversion was 85-95% in all cases. New compounds showed expected spectroscopic properties and gave satisfactory elemental analyses. ^b After workup and extraction, by glpc. ^c After workup and extraction, by nmr. ^d Characterized by acid hydrolysis to phthalide, identical with an authentic sample. ^e 2.2 Equiv. of n-BuLi. ^f 2.2 Equiv. of LDA used to obtain high conversion.

and removal of solvent yielded α -hydroxy-N,N-dimethylbutylamide (85%). This procedure represents a novel and efficient method for α -hydroxylation of amides, and is of special value because of the lack of carbon-carbon cleavage and the generality, as shown by the variety of systems which take part in the reaction.

Other carboxylate derivatives undergo oxygenation through lithium enolates.¹² Very recently the α -hydroxylation of nitriles has been reported,¹³ and our own studies have included the oxidation of esters. As shown in Table II, the newer methods for generating carbanions permit substantially improved yields of oxygenation products. It should be noted that except for $\text{Ph}_2\text{CHCH}_2\text{CO}_2\text{Et}$, the esters listed below contain a tertiary carbon at the α -position. Systems with secondary α -carbons such as ethyl phenylacetate undergo more complex oxidations with accompanying α -carbon cleavage. The controlled formation of the α -hydroxy derivative from the 3,3-diphenyl

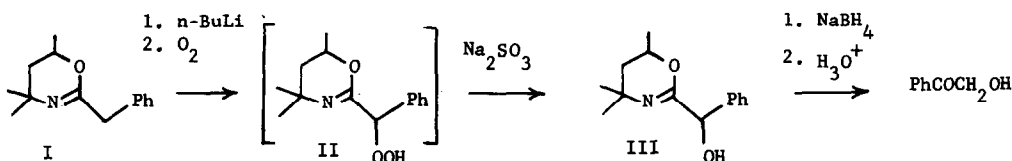
propionic acid ester was exceptional among those esters containing α -methylene groups which we have studied. In our further work we are attempting to determine the factors which control the extent of this oxidation.

TABLE II

Ester	α -Hydroxy Derivative ^a	Yield, % ^b
		76
		76
PhCH(Me)COOEt	PhC(OH)(Me)COOEt	81
PhCH(Et)COOEt	PhC(OH)(Et)COOEt	83
Ph ₂ CHCOOEt	Ph ₂ C(OH)COOEt	85
Ph ₂ CHCH ₂ COOEt	Ph ₂ CHCH(OH)COOEt	90

^a Characterized and identified by comparison with authentic samples and/or by comparison of ir and nmr spectra with data in the literature. New compounds showed expected spectroscopic properties and gave satisfactory elemental analyses. ^b After workup and ether extraction, by glpc.

Along with other carboxylate derivatives, oxazines¹⁴ undergo the oxygenation reaction *via* α -carbanions as illustrated in the sequence below. The oxazine (I) was treated with *n*-butyllithium at -78° and oxygenated as described above. Reduction of the intermediate hydroperoxide with Na₂SO₃ yielded III in essentially quantitative yield.¹⁵ Compound III could be further reduced with NaBH₄ and hydrolyzed to 2-hydroxyacetophenone.



Similarly, it was possible to hydroxylate the α -methyl group of 2-picoline by generating the anion with *n*-butyllithium at -78° followed by oxygenation. Workup with methanolic sodium sulfite followed by removal of solvent and extraction with Et₂O gave 2-pyridylcarbinol (75%), identical with an authentic sample.

REFERENCES AND FOOTNOTES

- (1) a) P.L. Creger, *J. Amer. Chem. Soc.*, **89**, 2500 (1967); b) M.W. Rathke and A. Lindert, *J. Amer. Chem. Soc.*, **93**, 2318 (1971); c) G.H. Posner and G.L. Loomis, *Chem. Comm.*, 892 (1972); d) K. Hiroi and P.A. Grieco, *ibid.*, 1317 (1972); e) J.L. Hermann and R.H. Schlessinger, *ibid.*, 711 (1973); f) R.M. Coates, H.D. Pigott and J. Ollinger, *Tet Lett.*, 4980 (1974); g) B.M. Trost and R.A. Kunz, *J. Org. Chem.*, **39**, 2475 (1974).
- (2) a) M.W. Rathke and J. Deitch, *Tet. Lett.*, 2953 (1971); b) T.J. Brocksom, N. Petragnani and Rui Rodrigues, *J. Org. Chem.*, **39**, 2114 (1974).
- (3) M.W. Rathke and A. Lindert, *J. Amer. Chem. Soc.*, **93**, 2318 (1971).
- (4) a) B.M. Trost and T.N. Salzman, *J. Amer. Chem. Soc.*, **95**, 6840 (1973); b) R.M. Coates, H.D. Pigott and J. Ollinger, *Tet. Lett.*, 4980 (1974).
- (5) a) H.J. Reich, I.L. Reich and J.M. Renga, *J. Amer. Chem. Soc.*, **95**, 5813 (1973); b) K.B. Sharpless, R.F. Lauer and A.Y. Teranishi, *J. Amer. Chem. Soc.*, **95**, 6137 (1973).
- (6) S. Yamada, T. Oguri and T. Shioiri, *Chem. Comm.*, 623 (1972).
- (7) a) R. Hanna and G. Ourisson, *Bull. Soc. Chim. Fr.*, 1945 (1961); 3742 (1967); b) H.R. Gersmann, H.J.W. Nieuwenhuis, and A.F. Bickel, *Proc. Chem. Soc.*, London, 279 (1962); c) E.J. Bailey, D.H.R. Barton, J. Elks, and J.F. Templeton, *J. Chem. Soc.*, 1578 (1962); d) M. Avramoff and Y. Sprinzak, *J. Amer. Chem. Soc.*, **85**, 1655 (1963); e) G. Buchi, P. Kula and R.L. Rosati, *ibid.*, **90**, 2448 (1968); f) H. Muxfeldt, G. Hardtmann, F. Kathawala, E. Vedejs, and J.B. Mooberry, *ibid.*, **90**, 6534 (1968); g) G. Buchi, W. Pickenhagen, and H. Wuest, *J. Org. Chem.*, **37**, 4192 (1972); h) W.E. Doering and R.M. Haines, *J. Amer. Chem. Soc.*, **76**, 482 (1954).
- (8) Recently, however, E. Vedejs, *J. Amer. Chem. Soc.*, **96**, 5944 (1974), has reported a novel method for α -hydroxylation of esters and ketones utilizing the reaction of molybdenum peroxide with enolates generated from LDA in THF-hexane.
- (9) The reactions may be run at -78° as well as 0° .
- (10) C.S. Foote and R.S. Vickers, *Boll. Chim. Farm.*, **109**, 599 (1970).
- (11) While essentially all of the oxygen was consumed in seconds, the reaction was usually allowed to continue for about five minutes before workup.
- (12) Dianions of carboxylic acids prepared by LDA in THF-HMPA have been treated with molecular oxygen to form α -hydroxy acids on workup [P.E. Pfeffer and L.S. Silbert, U.S. Patent 3,652,612 (March 28, 1972); *Chem. Abstr.*, **76**, 1,399,382 (1972)].
- (13) Recently, the reactions of oxygen with secondary nitrile anions generated by LDA have led to cyanohydrins, and subsequently, to ketones in good yields (S.J. Selikson and D.S. Watt., *J. Org. Chem.*, **40**, 267 (1975)).
- (14) A.I. Meyers, *et. al.*, *J. Org. Chem.*, **38**, 36 (1973).
- (15) Identification by spectroscopic properties (nmr, ir, mass spectrum) and elemental analysis.

Acknowledgment

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