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SYNTHESIS OF 1,3-DIKETONES FROM LITHIUM ENOLATES AND ACYL CYANIDES

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Summary: The title reaction proceeds regiospecifically under mild conditions in high yield; an application in the synthesis of an Elaeocarpus alkaloid is described.

The synthesis of 1,3-diketones by the 1:1 acylation of alkali metal enolates with acyl halides is attended in practice by various problems: regioisomer formation, competing O-acylation, proton exchange between the enolate and the product diketone, diacylation, and generally poor yields.[1] Some of these problems may be surmounted by strict control of the reaction conditions,[2] or by the use of indirect methods, for example, with regiospecifically generated enamines[1a] or dimethylhydrazone α-carbanions[3] rather than enolates. In view of several promising reports in the literature[4-7] of the acylation of various C-nucleophiles with acyl cyanides, we have investigated the reaction of lithium enolates with this neglected class of acylating agents,[8] themselves readily available by a number of procedures.[9,10]

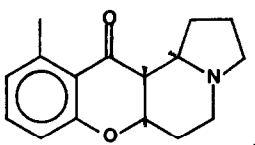
In the present study, ketone enolates (10 mmol) were formed using lithium diisopropylamide (1,1 equivalents) as base. Under the conditions used (0°C, THF solution, 1,1 equivalents of acyl cyanide in THF added in one portion to the enolate solution), acylation of the enolate was rapid, and no complications arose from competing acylation of diisopropylamine. The yields of 1,3-diketones obtained ranged from good to excellent (see Table). Diacylated and O-acylated products were not detected; nor indeed were products which could have arisen from nucleophilic attack by the enolate at the cyanide group, a reaction which is precedented.[4] In addition, the acyl cyanide is sufficiently reactive to acylate at -78°C, thus permitting the regiospecific acylation of a kinetic enolate (entry 3). The overall procedure, combining the advantages of readily available reagents, simple manipulations, and excellent yields, should prove a valuable contribution to the methodology for 1,3-diketones.

We have used the above acylation sequence in studies directed towards the synthesis of Elaeocarpus alkaloids[11] such as elaeocarpine (1). Numerous attempts at C-acylation of (2) and related systems (the syntheses of which will be described elsewhere), using a variety of acylating agents and conditions, failed; the most frequently obtained result was N-acylation followed by cleavage of the bicyclic ring system. However, use of 2-methoxy-6-methylbenzoyl cyanide as the acylating agent gave a 73% yield of the diketone (3), the spectra of which are in accord with those reported for this compound by Tanaka and Iijima in their synthesis of elaeocarpine.[12]

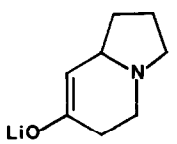
Table: Preparation of 1,3-diketones[a)]

Ketone	Acyl cyanide	Product (B.p.°C/torr and/or m.p.°C; % yield)[b)]
Cyclohexanone	Butyryl cyanide	2-Butyrylcyclohexanone (105-110/2; 94%[c)])
3-Pentanone	Isobutyryl cyanide	2,4-Dimethylheptane-3,5-dione (105-110/10; 72%[c)])
2-Methylcyclohexanone	Butyryl cyanide	2-Butyryl-6-methylcyclohexanone (110-115/0,7; 87%[c)])
Acetophenone	Benzoyl cyanide	Dibenzoylmethane (75-80[d)]; 93%[e)])
Cyclohexanone	Benzoyl cyanide	2-Benzoylcyclohexanone (150-155/0,25; 90-93[d)]; 85%[c)])
Cyclohexanone	4-Methoxybenzoyl cyanide	2-(4-Methoxybenzoyl)cyclohexanone (180-185/0,1; 110-115[d)]; 74%[c)])
Cyclohexanone	4-Nitrobenzoyl cyanide	2-(4-Nitrobenzoyl)cyclohexanone (95-98[f)]; 92%[f)])

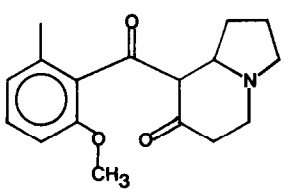
a) Reactions performed at 0°C, except for entry 3, -78°C. b) The products, existing as mixtures of keto and enol forms, gave satisfactory ir, nmr and mass spectra; the data listed agree with reported values.[2, 13, 14)] c) Bulb-to-bulb distillation. d) After recrystallisation. e) Isolated directly from the reaction. f) After column chromatography.



(1)



(2)



(3)

REFERENCES

1. (a) H.O. House, "Modern Synthetic Reactions", 2nd edition, W.A. Benjamin Inc., Menlo Park California, 1972, Chapter 11; (b) F. Korte (ed.), "Methodicum Chimicum", vol. 5, Georg Thieme Verlag, Stuttgart, Academic Press, New York, 1975, p. 372; (c) C.R. Hauser, F.W. Swamer and J.T. Adams, Organic Reactions, 8, 59 (1954).
2. A.K. Beck, M.S. Hoekstra and D. Seebach, Tetrahedron Letters, 1187 (1977).
3. D. Enders and P. Weuster, Tetrahedron Letters, 2853 (1978).
4. R.F. Borch, S.R. Levitan and F.A. Van-Catledge, J. Org. Chem.,37, 726 (1972).
5. G.B. Bachman and T. Hokama, J. Amer. Chem. Soc., 81, 4882 (1959).
6. B. Renger, H. Hügel, W. Wykypiel and D. Seebach, Chem. Ber., 111, 2630 (1978).
7. A. Dornow and H. Grabhöfer, Chem. Ber., 91, 1824 (1958).
8. J. Thesing, D. Witzel and A. Brehm, Angew. Chem., 68, 425 (1956).
9. O. Bayer, in Houben-Weyl· "Methoden der organischen Chemie", vol. 7/2c, Georg Thieme Verlag, Stuttgart, 1977, p. 2487.
10. E.C. Taylor, J.G. Andrade, K.C. John and A. McKillop, J. Org. Chem., 43, 2280 (1978).
11. S.R. Johns and J.A. Lamberton, in "The Alkaloids", vol. XIV, ed. R.H.F. Manske, Academic Press, New York, 1973, p. 325.
12. T. Tanaka and I. Iijima, Tetrahedron, 29, 1285 (1973).
13. B.O. Linn and C.R. Hauser, J. Amer. Chem. Soc., 78, 6066 (1956).
14. S. Hünig and M. Salzwedel, Chem. Ber., 99, 823 (1966).

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