Tetrahedron Letters Vol. 21, pp 1285 - 1288
© Pergamon Press Ltd. 1980. Printed in Great Britain
0040-4039/80/0401-1285$02.00/0

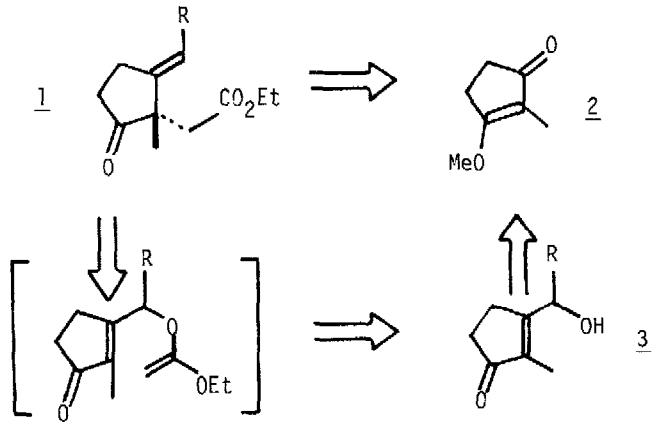
AN EFFICIENT AND VERSATILE SYNTHESIS OF β-ALKYLIDENE-α,α-DISUBSTITUTED CYCLOPENTANONES

Steven D. Burke,* Sandra A. Shearouse,
Daniel J. Burch, and Randy W. Sutton

Department of Chemistry, University of South Carolina
Columbia, South Carolina 29208

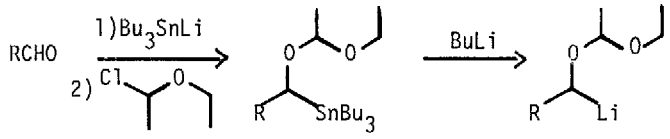
ABSTRACT: A direct, two step synthesis of specifically-substituted cyclopentanones utilizing α-alkoxy organolithium reagents is reported.

The cyclopentanone unit is widespread among structurally and biologically interesting natural products. As a point of departure in a synthetic program directed at a variety of such natural products, we needed to develop a general, reliable, and efficient entry to cyclopentanones with the substitution pattern generalized in 1. For the purpose of subsequent elaboration we had the specific requirements of 1) an E-trisubstituted olefin moiety in the β-position, and 2) an acetic acid ester unit and a methyl group as geminal α-substituents on the cyclopentanone nucleus.



A straightforward two step sequence was envisioned for the conversion of the well-known vinylogous ester 2[1] to 1 via application of the Johnson orthoester Claisen rearrangement[2] to the appropriate allylic alcohol 3. The problem was thus reduced to developing a general synthesis of the requisite allylic alcohols 3 for the deconjugative Claisen rearrangement.

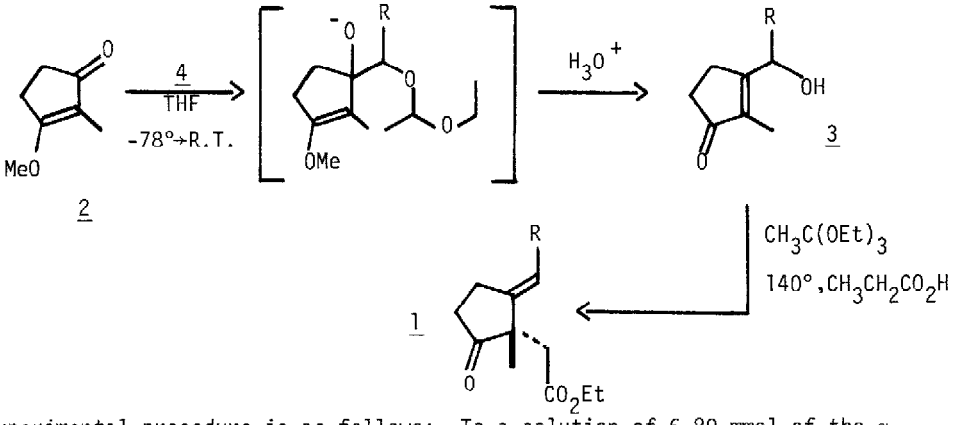
Application of recently developed technology[3] (eq. 1) for generating α-alkoxy organolithium reagents (4) provided the solution. The ready availability of a variety of aldehydes



eq. 1

renders this method particularly versatile for preparing the organometallics 4. In the event, 1,2-addition of the α-alkoxy organolithium reagents 4 to the vinylogous ester 2 (Scheme I) gave, after exhaustive hydrolytic quench, the desired corresponding allylic alcohols 3 in yields of 60 to 98%.[4,5] (See Table I) Straightforward application of the Johnson orthoester Claisen rearrangement provided cleanly the targeted cyclopentanones 1 in yields ranging from 42 to 88%.[5]

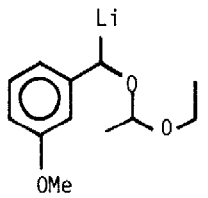
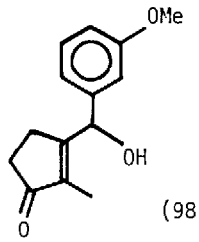
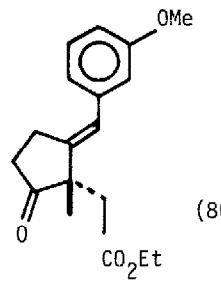
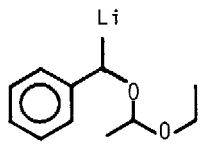
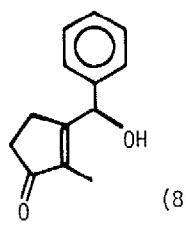
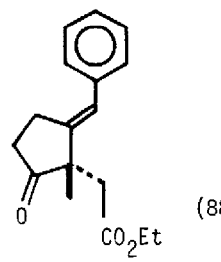
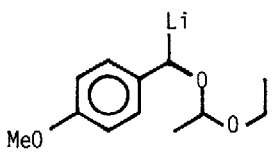
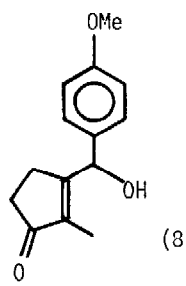
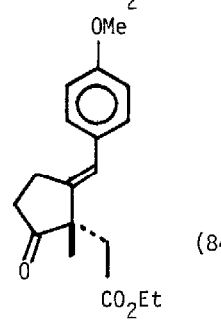
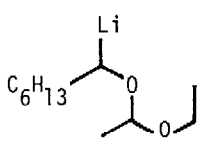
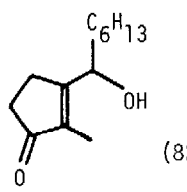
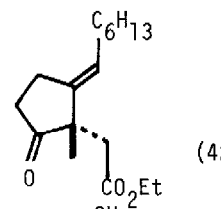
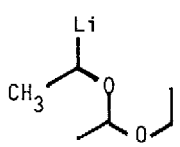
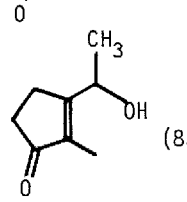
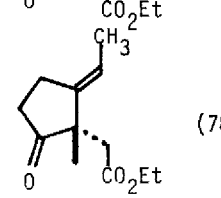
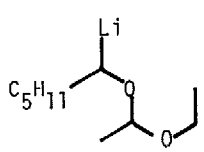
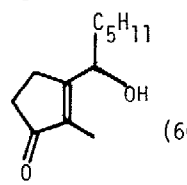
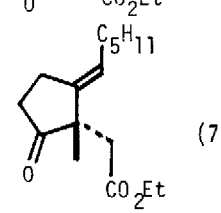
SCHEME I



A general experimental procedure is as follows: To a solution of 6.80 mmol of the α-alkoxy organolithium reagent 4[6] in 40 ml anhydrous tetrahydrofuran (THF) at -78°C was added 5.73 mmol of the vinylogous ester 2 in 11.5 ml THF. The reaction mixture was allowed to warm to ambient temperature over a 2.5 h period, then cooled to 0°C and quenched with 29 ml of 2N HCl. After stirring for 12 h at room temperature the mixture was partitioned between diethyl ether and water. The combined ether extracts were dried (Na_2SO_4) and condensed, and the residue was flash chromatographed on silica gel to provide the allylic alcohol 3. A solution of 0.79 mmol of 3 in 3.75 ml of triethyl orthoacetate containing 2 drops of propionic acid was heated at reflux for 2 h. Direct flash chromatography on a column of silica gel yielded the pure rearrangement product 1.[7,8]

The technology is thus in hand for the preparation of the substituted cyclopentanones 1 via a direct and versatile sequence. Elaborative transformation of these synthetic units is under investigation.

TABLE I

entry	α-alkoxy organolithium 4	alcohol 3 (% yield)	cyclopentanone 1 (% yield)
1		 (98)	 (80)
2		 (80)	 (88)
3		 (81)	 (84)
4		 (82)	 (42)
5		 (83)	 (78)
6		 (60)	 (70)

Acknowledgements. We are deeply indebted to the Petroleum Research Fund, Research Corporation, and NIH Biomedical Studies Grant 5 S07 RR07160 for generous financial support.

References and Footnotes

1. M. L. Quesada, R. H. Schlessinger, and W. H. Parsons, J. Org. Chem. 43, 3968 (1978).

2. W. S. Johnson, L. Werthemann, W. R. Bartlett, T. J. Brockson, T.-T. Li, D. J. Faulkner, and M. R. Peterson, J. Amer. Chem. Soc. 92, 741 (1970).

3. W. C. Still, J. Amer. Chem. Soc. 100, 1481 (1978).

4. It should be noted that the O-ethoxyethyl protected allylic alcohols could be easily obtained by quenching with saturated aqueous ammonium chloride instead of 2N HCl.

5. All compounds exhibited NMR, IR, and MS data in agreement with the assigned structure.

6. Prepared according to the general procedure outlined in ref. 3.

7. All yields reported in Table I refer to isolated, chromatographically pure material.

8. For studies related to the work described herein, see: (a) J.J. Plattner, R.D. Gless, and H. Rapoport, J. Amer. Chem. Soc., 94, 8613 (1972); (b) F.E. Ziegler and J. J. Piwinski, J. Amer. Chem. Soc., 101, 1611 (1979); (c) T.A. Bryson and W. E. Pye, J. Org. Chem., 42, 3214 (1977).

(Received in USA 10 December 1979)