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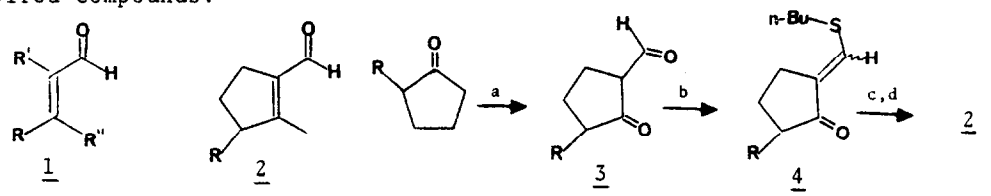
SYNTHESIS OF 1-FORMYL-2-METHYL-3-ALKYLCYCLOPENT-1-ENES; AN APPROACH TO α,β-UNSATURATED ALDEHYDES

Peter R. Bernstein
Chemistry Department, Columbia University, NY NY 10027

Unsaturated aldehydes 1, which may be envisioned as the result of an inverse aldol condensation between an aldehyde and a ketone, are widely used intermediates in organic synthesis. As a result numerous methods have been developed for effecting the homologation of "readily available" ketones into such α,β-unsaturated aldehydes.[1,2] We wished to prepare a series of 1-formyl-2-methyl-3-alkylcyclopent-1-enes.[3] These aldehydes proved to be unavailable by direct application of the literature processes.[1,2,4] One well-known approach[5] which initially appeared pertinent but which failed when applied to the synthesis of the aldehydes we needed involves alkyllithium addition to a β-alkoxyenone and hydrolytic rearrangement of the adduct to the enal. However, modification of this procedure as described herein did yield the desired compounds.



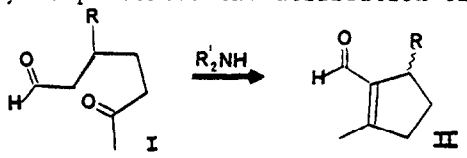
a) NaH, HCO_2Et, ether; b) nBuSH, pTSA, $MgSO_4$, benzene, 25°C, 8 hrs. c) CH_3Li, ether, -78°C→0°C; d) $HgCl_2$-$CdCO_3$, acetone-water, 25°C. R=METHALLYL, ALLYL, PROPYL

This sequence commences with the formylation of a 2-alkylcyclopentanone[6] under standard reaction conditions[7] to afford the α-formyl ketone 3 (R=methallyl, 80%; R=allyl, 83%; R=propyl, 86%).[8] Protection of the formyl ketone as an n-butylthiomethylene ketone was necessitated by the discovery that the alternative more typical β-alkoxyenone derivatives[5] afforded complex mixtures of products[9] on treatment with either methyllithium or methylmagnesium bromide in ethereal solutions. Formation of n-butylthiomethylene ketone 4 was accomplished in quantitative yield by treatment of formyl ketone 3 with n-BuSH-$MgSO_4$.[10] The addition of methyllithium to ketone 4 occurs in a 1,2 manner to afford crude alcohol 5 in yields >95%.[11] This unstable alcohol was directly transformed to enal 2 by treatment with $HgCl_2$-$CdCO_3$[12] (yields of pure 2 after chromatography on silica gel: R=methallyl, 55%; R=allyl, 61%; R=propyl, 66%).

Thus, utilization of the n-butylthiomethylene unit as an aldehyde protecting group allows for the facile synthesis of a series of unsaturated aldehydes.

References and Notes

1. For a discussion of various approaches see; a) E. J. Corey, D. Enders, and M. G. Bock, Tetrahedron Lett., 7 (1976) and ref. 1-8 cited therein. For other recent methods see; b) the oxidative rearrangement of allylic alcohols , W. G. Dauben and D. M. Michno, J. Org. Chem., 42, 682 (1977), and c) the isomerization of α-ethynyl carbinols with tris(triphenylsilyl)vanadate, H. Pauling, Chimia, 27, 383 (1973).
2. For conversion of $RCOCH_2R'$ into $RHC{=}CR'CHO$ see; R. F. Church, R. E. Ireland, and J. A. Marshall, J. Org. Chem., 27, 1118 (1962).
3. These aldehydes were required in conjunction with research directed towards the synthesis of [X.3.0] bicyclic ring systems. See the accompanying communication, P.R. Bernstein and G. Stork, Tetrahedron Lett. submitted.
4. Van Tamelen has shown that treatment of keto-aldehyde I with a secondary amine affords α,β-unsaturated aldehyde II; E. E. Van Tamelen and R. J. Anderson, J. Amer. Chem. Soc., 94, 8225 (1972). The lack of a general route to such keto-aldehydes prevented the utilization of this approach in a synthesis of enal 2.



5. Originally developed for cyclic β-alkoxyenones by Woods; G. F. Woods, P. H. Griswold, Jr., B. H. Armbrecht, D. I. Blumenthal, and R. Plapinger, J. Amer. Chem. Soc., 71, 2028 (1949).
6. Synthesized from methyl-2-oxo-cyclopentanecarboxylate by alkylation and decarboxylation using the conditions of; F. Elsinger, Org. Syn. Coll. Vol., 5, 75 (1976).
7. H. L. Holmes and L. W. Trevoy, Org. Syn. Coll. Vol. 3, 300 (1965).
8. All compounds afforded IR, NMR (60 or 90 MHz), and M.S. in accord with the assigned structures. Purity was further checked by TLC (Brinkmann 0.25 mm plate silica gel 60F-254) and except for alcohol 5 by GLC (5% SE 30, 10'x¼"). Selected intermediates were analyzed by exact mass determination.
9. R. E. Ireland and J. A. Marshall, J. Org. Chem., 27, 1615 (1962).
10. The use of groups other than the n-butylthiomethylene (e.g. enol ether, enol pivalate, and enamine) resulted in predominant 1,4 addition instead of the desired 1,2 adduct. Protection of the formyl group as an acetal followed by the addition of methyllithium afforded a complex mixture of products resulting from partial enolization of the ketone with concurrent elimination of the β-alkoxy group. During the metal hydride reduction of similar systems Ireland (ref. 2) had noted up to 20% 1,4 reduction of enol ether derivatives, whereas the n-butylthiomethylene ketones afforded only 1,2 reduction.
11. The alcohol is contaminated with 5-10% of the enone precursor.
12. M. L. Wolfron, J. Amer. Chem. Soc., 51, 2188 (1929).

13. The author thanks Prof. Gilbert Stork and Columbia University for guidance and financial support.
14. Please address correspondence to: Department of Chemistry, University of Wisconsin, Madison, Wisconsin 53706.