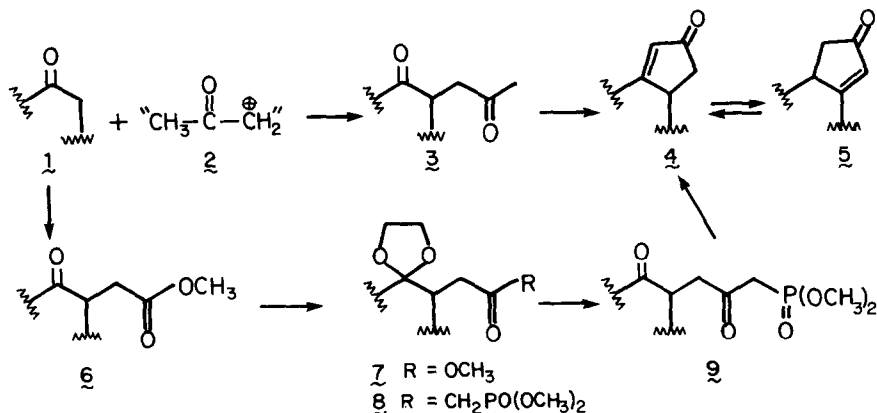


PREPARATION OF, AND ALKYLATION OF ENOLATE ANIONS WITH, DIMETHYL 3-BROMO-2-ETHOXYPROPENYLPHOSPHONATE. AN EFFICIENT, CONVERGENT SYNTHESIS OF 2-CYCLOPENTEN-1-ONES

Edward Piers*, Brian Abeysekera, and John R. Scheffer*
Department of Chemistry, University of British Columbia,
2075 Wesbrook Mall, Vancouver, B.C., Canada V6T 1W5

Abstract. The alkylation of enolate anions with dimethyl 3-bromo-2-ethoxypropylphosphonate, followed by acid hydrolysis of the resultant products, affords diketo phosphonate compounds which can be cyclized efficiently to give the corresponding 2-cyclopenten-1-ones. This overall five-membered ring annelation process can be carried out without affecting acid-labile functional groups (e.g. ketal) in the enolate substrate.

The overall conversion represented in general terms by $1 \rightarrow 4$ is an important method for the formation of five-membered rings. Basically this transformation involves the alkylation of the ketone 1 with an acetonyl cation (2) equivalent to give, after appropriate unmasking of the side chain in the alkylated material, the 1,4-diketone 3 , which is then converted into the cyclic enone 4 via a base-promoted intramolecular aldol condensation. A number of different reagents (e.g. 3-halo-2-methylpropenes¹, 2,3-dihalopropenes², 3-bromo-1-trimethylsilylpropyne³, 3-iodo-2-triethylsilylpropene⁴, 2-nitropropene⁵, 3-bromo-2-methoxypropene⁶, propargyl bromide⁷) have been employed successfully as equivalents of the cation 2 in the alkylation step. However, this type of methodology suffers from two drawbacks. Firstly, the conditions

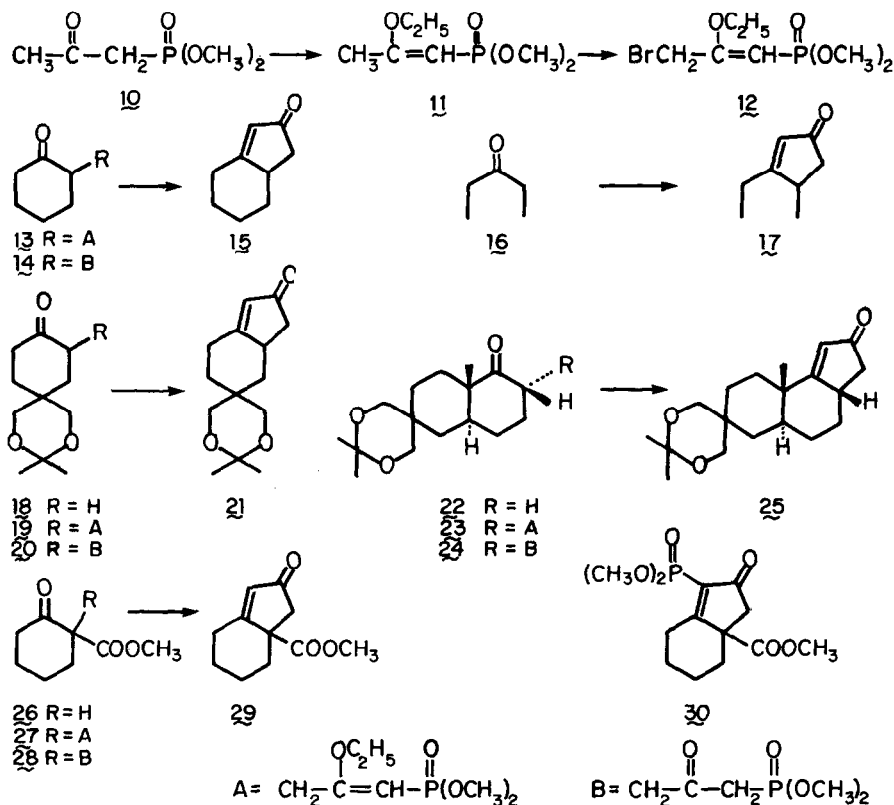


necessary to unmask the various acetonyl equivalents often have deleterious effects on other functional groups which may be present in the molecule, particularly those which are acid-sensitive.⁸ Secondly, the intramolecular aldol condensation process ($3 \rightarrow 4$) can be accompanied

by an undesirable base-catalyzed isomerization of the initially formed product ($4 \rightleftharpoons 5$)⁹.

Recently, Heathcock and coworkers¹⁰ described an elegant method for preparing cyclopentenones which eliminated the second difficulty mentioned above. Essentially, their method involved the following sequence: alkylation of the ketone 1 with haloacetate (1 \rightarrow 6), protection of the ketonic carbonyl (6 \rightarrow 7), conversion of 7 into the keto phosphonate 8, removal of the ketal protecting group (8 \rightarrow 9), and intramolecular Horner-Emmons reaction of 9 to provide 4. Importantly, the last step could be achieved without effecting any isomerization of the initially formed cyclopentenone. However, the first limitation mentioned above was not eliminated by this methodology, since the steps involving formation and removal of the ketal protecting group (preparation of 7 and 9) would clearly affect acid-sensitive functional groups (e.g. ketal) which might be present in the ketonic substrate. We describe herein an efficient, convergent method for effecting the transformation of 1 into 4 via a route which removes this limitation as well.

Treatment of dimethyl 2-oxopropylphosphonate (10) with triethyl orthoformate in the presence of ferric chloride (r.t., 3 days) afforded (94%)¹¹ the enol ether 11^{13,14}. Subjection of this material to allylic bromination (N-bromosuccinimide in carbon tetrachloride, ultraviolet light, reflux, 15 min.) gave the bromo compound 12 (76% after purification by column chromatography), which proved to be an excellent alkylating agent. Thus, when 12 was allowed



to react with the lithium enolate of cyclohexanone in tetrahydrofuran (-78 °C, 30 min.; 0 °C, 30 min.; r.t., 1 h.), the alkylation product 13 was formed in quantitative yield. Hydrolysis (1N hydrochloric acid, acetone, r.t., 30 min.) of the enol ether functionality in 13 proceeded smoothly to give quantitatively the diketo phosphonate 14, which was cyclized (NaH, dimethoxyethane, 60 °C)¹⁰ to the bicyclic enone 15 (74%). In similar fashion, the following conversions were carried out (overall yields indicated in parentheses): 3-pentanone (16) into 17 (82%); 18¹⁵ into 21 (52%); 22¹⁶ into 25¹⁸ (63%); 26 into 29 (50%).

In connection with the conversions summarized above, the following points should be noted.

(a) Although the alkylation of the lithium enolates of cyclohexanone and 3-pentanone with 12 proceeded well in tetrahydrofuran, the corresponding reactions involving the lithium enolates of 18, 22 and 26 gave good yields of the products (19, 23, 27) only when mixtures of tetrahydrofuran and hexamethylphosphoramide were employed as solvent. Furthermore, in the case of the keto ester 26, a longer reaction time (6 h., r.t.) was required. (b) The transformations involving the keto ketals 18 and 22 as substrates are particularly important examples of the present methodology. Thus, it was found that the enol ether functionality of the corresponding alkylated materials 19 and 23 could be hydrolyzed smoothly under conditions (0.5 N hydrochloric acid, acetone, 10-15 °C, 2 h.) which had no effect on the ketal groups. The hydrolysis products 20 and 24 were isolated in high yields (92%, 96%, respectively). (c) It was necessary to control very carefully the conditions employed for the hydrolysis of compound 27. After considerable experimentation, it was found that this reaction could be accomplished efficiently by treating 27 with 0.5 N hydrochloric acid in acetone (r.t., 35 min.). If more concentrated acid or longer reaction times were employed, the initially formed hydrolysis product 28 underwent at least partial intramolecular aldol condensation to afford the bicyclic compound 30. This difficulty was not experienced with any of the other cases studied. (d) The intramolecular Horner-Emmons reactions were accomplished routinely by treatment of the appropriate diketo phosphonate with sodium hydride in dimethoxyethane (0 °C to r.t., 30 min.; 60 °C, 3 h.). In accord with previous observations¹⁰, no isomerization of the initially formed cyclopentenones was observed (products 17, 21, 25).

We are currently engaged in extending this methodology, with the aim of synthesizing more complex cyclopentenone systems.¹⁹

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8. For an example of hydration of the triple bond of the propargyl group with retention of a ketal functionality, see reference 7.
9. Very recently, an intramolecular, base-promoted aldol condensation of this type was achieved without effecting isomerization of the initially formed product: J.E. McMurry, A. Andrus, G.M. Ksander, J.H. Musser and M.A. Johnson, *J. Am. Chem. Soc.*, 101, 1330 (1979). See also E. Brown and M. Ragault, *Tetrahedron Lett.*, 1927 (1973).
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11. The small amount of remaining starting material could be removed conveniently by treating a dichloromethane solution of the crude product with sodium hydride. The insoluble¹² sodium salt of 10 was removed by filtration. Evaporation of the filtrate gave the pure product 11.
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13. All products exhibited spectral data in full accord with assigned structures. New compounds gave satisfactory elemental analyses and/or molecular weight determinations (high resolution mass spectrometry).
14. The stereochemistry of 11 and the corresponding bromo derivative 12 remains unknown.
15. Cf. J.A. Marshall and G.A. Flynn, *Synth. Commun.*, 9, 123 (1979). We are grateful to Mr. M. Burmeister for supplying a sample of this compound.
16. Compound 22 was prepared in an unambiguous fashion from the Wieland-Miescher ketone.¹⁷
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18. Compound 25 has been prepared in our laboratory via a different route (D.J. Herbert, unpublished results), and the stereochemistry of this substance has been established.
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