The Reaction of Ketone Enolates with a δ -Oxo Phosphonate: A Carbanion-Based [4+2] Annulation

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Abstract: The reaction of ketone enolates with phosphonate aldehyde **3** followed by acetylation and cyclization represents a useful carbanion-based strategy for the appendage of a functionalized sixmembered ring.

Key words: annulation, cuprate addition, enolate

The soybean cyst nematode (SCN), *Heterodera glycines*, has caused significant crop losses in the soybean industry. A management strategy for the SCN that is cost effective and compatible with sustainable agriculture has not yet been developed.¹ Masamune has shown that glycinoeclepin A (1) is a very effective hatching stimulus, capable of initiating egg hatch at concentrations as low as 10⁻¹² grams per milliliter.² As part of a biorational approach to nematode management, we are using analogs of glycinoeclepin A to effect premature hatching of SCN under conditions where the nematode will not survive. Analog studies by Murai³ and by Kraus⁴ have led to the identification of the functionality necessary for activity. Significantly, Murai has shown that the side chain containing the oxabicyclic ketone is not required for activity. Analog 2 is a key synthetic objective. As part of a direct approach to the synthesis of 2, we developed the annulation described herein.



A direct synthesis of the CD ring system might be accomplished if a suitable C ring precursor could be connected onto a functionalized D ring. One possible reagent for this transformation would be phosphonate **3**. Our plan was that the alkoxide produced by an aldol reaction of a ketone enolate with **3** would intramolecularly abstract the methine proton activated by the ester and the phosphonate, leading to an intramolecular Wadsworth–Emmons reaction and the production of **4**. Although a literature search indicated that aldehyde phosphonates such as **3** had not been prepared, a related ketone had been prepared by the

Michael addition reaction of triethyl phosphonoacetate with 3-pentene-2-one.⁵ Unfortunately, this reaction did not work with acrolein. Alkylation of triethyl phosphonoacetate with 4-bromo-1-butene⁶ and NaH followed by oxidation (NaIO₄ (2.5 equiv), OsO₄) produced **3** in 70% yield.⁷



Although we were concerned that the ketone enolate might abstract the acidic methine proton of the ester phosphonate rather than react with the aldehyde, the reaction of cyclopentanone with LDA followed by aldehyde 3 led to aldol 5 (R = H) in 80% yield. No products derived from the intramolecular Wadsworth-Emmons cyclization were detected. Attempts to force the cyclization by use of an additional equivalent of base or by heating the alkoxide led to the destruction of 5 (R = H). Protection of the alcohol as the THP ether produced some protected alcohol plus significant amounts of dehydration product. Acetylation with acetic anhydride and 4-dimethylaminopyridine and pyridine afforded the acetate in almost quantitative yield. Treatment of 5 (R = Ac) with sodium hydride in THF produced the acetoxy ester 6 in 81% yield as a mixture of stereoisomers.⁸





reaction of the enol silvl ether **10** with boron trifluoride etherate and **3** in methylene chloride at -78 °C followed by acetylation and cyclization afforded a 35% yield of ester **11**.



We next prepared ester **12** from 2-methyl-2-cyclopentenone. Lithium diallylcuprate was generated by the reaction of allyltributylstannane with n-butyllithium followed by addition of cuprous iodide. The resulting cuprate¹⁰ reacted with 2-methyl-2-cyclopentenone and then aldehyde **3** to provide the aldol in 78% yield. The aldol was acetylated using acetic anhydride and DMAP to give acetoxy ketone **13** in 95% yield, as a mixture of isomers. The reaction of **13** with NaH in THF gave a 25% yield of ester **12**. Several bases were examined to improve the yield of this reaction. Although lithium tert-butoxide or LiCl/DBN led to the product in approximately 25% yield, potassium hexamethyldisilazane (KHMDS) in THF at 25 °C afforded a 42% isolated yield of **12**.



The reaction of ketone enolates with phosphonate aldehyde **3** followed by acetylation and cyclization represents a new carbanion-based strategy for the appendage of a functionalized six-membered ring onto a ketone. This annulation will permit the synthesis of analogs of **1** which will be tested in nematode hatch assays.¹¹ This sequence proceeds under mild conditions and will be applicable to other natural product systems.

Acknowledgement

We thank the Iowa Soybean Promotion Board for financial support of the research.

References and Notes

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- (8) Experimental: A 60% dispersion of NaH in mineral oil (2 equiv) was washed with pentane and suspended in dry THF (5 mL/mmole) under an argon atmosphere. A 0.1 M solution of ketone (1 equiv) in THF was added dropwise at r.t. The mixture was stirred at r.t. for 5 h, quenched with saturated NH₄Cl solution, extracted with ethyl acetate, dried over Na₂SO₄, filtered and concentrated in vacuo. The residue was purified by SGC.
- (9) Data for 8 (R = Ac): NMR (CDCl₃) 5.03-4.95 (m, 1 H), 4.19 (q, J = 7.2 Hz, 2 H), 2.52-2.16 (m, 4 H), 2.04 (s, 3 H), 1.99 (s, 3 H), 1.89-1.69 (m, 2 H), 1.29 (t, J = 7.2 Hz, 3 H). ¹³C NMR (CDCl₃) 170.7, 168.3, 142.4, 123.9, 68.8, 60.1, 38.5, 26.8, 23.7, 21.6, 21.4, 14.3. UV 209 nm.
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Article Identifier: 1437-2096,E;2001,0,06,0793,0794,ftx,en;S02201ST.pdf