

0040-4039(95)01485-3

Addition of Functionalized Zinc Copper Reagents to Acetylenic Esters: Synthesis of 2-Carboalkoxy Cyclohexenones

Michael T. Crimmins,* Sujuan Huang, Lisa E. Guise, and D. Borden Lacy Venable and Kenan Laboratories of Chemistry University of North Carolina at Chapel Hill Chapel Hill, North Carolina 27599-3290

Key Words: Functionalized zinc reagents, carboalkoxycyclohexenones, homoenolates.

Abstract: Conjugate addition of the zinc-copper reagent derived from ethyl 4-iodobutyrate to acetylenic esters in the presence of TMSCl and HMPA results in cyclization and formation of 3-alkyl-2-carboalkoxycyclohexenones in good yields.

Functionalized zinc reagents have become important reagents in organic synthesis in recent years.^{1,2} These reagents are characterized by the existence of a reactive organometallic species such as an organozinc or organozinc-copper species in the same molecule with an electrophilic functional group such as an ester or a nitrile. The utility of these reagents may eventually surpass that of Grignard reagents and organolithium reagents since the less reactive metals which have been used allow the incorporation of many reactive and sensitive functional groups into the organometallic reagent. Conjugate additions of these reagents to unsaturated aldehydes, ketones and esters have been reported and the use of the zinc homoenolate 1 in the preparation of 3-substituted 2-carbethoxy-cyclopentenones 2 has been developed and exploited in our laboratory.^{3,4} This method allows the rapid and efficient preparation of highly functionalized cyclopentenones, and the possibility of extending this methodology to cyclohexenones seemed a worthwhile synthetic venture. We report here examples utilizing the addition of the zinc-copper bis-homoenolate reagent 3 to unsaturated acetylenic esters. Schemel



While the zinc homoenolate 1 is usually prepared from ethoxytrimethylsilyloxy cyclopropane by the action of anhydrous zinc chloride,⁵ the homologous zinc reagent 3 has been reported and utilized in a number of elegant transformations by Knochel.⁶ It can be prepared directly from ethyl 4-iodobutyrate and zinc dust. When the functionalized zinc reagent 3 was added to CuCN and then treated sequentially with chlorotrimethylsilane, HMPA and acetylenic ester 4, conjugate addition followed by intramolecular acylation occurred to afford cyclohexenone 5 in 68% isolated, purified yield as shown in Scheme 2. This reaction has been carried out on a number of different acetylenic esters a few of which are shown in the table.



In a typical procedure 1.17 g (17.9 mmol) of zinc was activated according to the procedure of Knochel.⁷ To the zinc was added 0.0554 mL (0.63 mmol) of 1,2-dibromoethane and 2 mL THF. The resulting slurry was gently heated with a heat gun until bubbling occurred. After repeating twice, 0.042 mL (0.33 mmol) of TMSCI was added and the solution was stirred for 15 min and warmed to 30°C. The ethyl-4-iodobutyrate 3.94 g (16.3 mmol), chromatographed immediately prior to use, in 6 mL THF was then added dropwise while maintaining the temperature below 45° C. The solution was then stirred at 40° C overnight and then cooled to room temperature.

In a separate flask, 1.31 g (14.7 mmol) of CuCN and 1.45 g (34.2 mmol) of vacuum dried LiCl were dissolved in 15 mL THF at room temperature. The solution was then cooled to -25°C and the solution of zinc reagent was added via cannula. The solution was warmed to 0°C, whereupon 5.2 mL (40.7 mmol) of TMSCI, 5.2 mL (29.3 mmol) of HMPA and 1.95 g (8.11 mmol) of acetylenic ester 4 were added sequentially. The solution was allowed to warm to room temperature and stirred overnight.

The reaction mixture was then treated with saturated NH4Cl and 10% NH4OH. After filtering through a pad of celite, the solution was extracted with ether. The combined organic extract was washed with water, dried over anhydrous sodium sulfate, filtered and concentrated in vacuo. Purification of the residue by flash chromatoraphy provided 1.78 g (71%) of cyclohexenone 5 and 0.65 g (23%) diester of 6. Scheme 3



The course of the reaction likely involves initial syn addition of the organometallic to the acetylenic ester to provide a vinyl organometallic or allene enolate which is silylated on oxygen to give the allene silyl ketene acetal. This species then undergoes cyclization with the aid of zinc salts which act as a Lewis acid catalyst to provide the cyclohexenone product. An alternative pathway is simple protonation of the silyl ketene acetal to produce the alkene 6 which is always isolated as a minor byproduct.

TABLE			
entry	substrate	product	yield
1 R = MOM	CO_2Et RO C_5H_{11}	CO_2Et C_3H_{11} CR	68%
2 R = MOM	RO	O CO ₂ Et OR	63%
3 R = MOM	CO ₂ Et	O CO ₂ Et CH(CH ₃) ₂ OR	35%
4 R = MOM	RO ^{CO2Et}	$\bigcup_{OR}^{O} CO_2 Et$	60%
5 R = TBS; X = CH R = MOM; X = C R = MOM; X = H	H_3	OR OR	46% X 68% 71%

Acknowledgement: We thank the National Science Foundation (CHE 9014641) and the Petroleum Research Fund sponsored by the American Chemical Society for generous financial support. Thanks are also due to the Department of Education for a fellowship to L.E.G.

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- 8. All new compounds gave consistent ¹H, ¹³C, and IR spectra as well as satisfactory C, H combustion analyses or HRMS. All yields are for homogeneous, chromatographically pure products unless otherwise indicated.

(Received in USA 24 July 1995; accepted 8 August 1995)