Tetrahedron Letters,Vol.23,No.35,pp 3595-3596,1982 0040-4039/82/353595-02$03.00/0
Printed in Great Britain

# REGIOSPECIFIC α-DIALKOXYMETHYLATION OF PREFORMED ENOLATES

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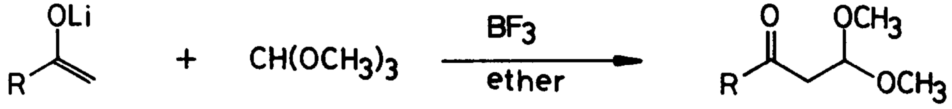
Summary: Reaction of a preformed lithium enolate and trimethyl orthoformate with added boron trifluoride leads to the corresponding α-dimethoxymethyl ketone.

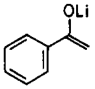
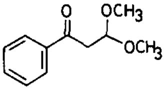
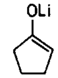
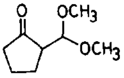
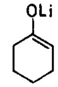
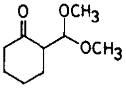
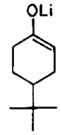
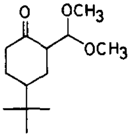
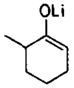
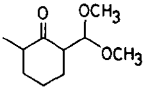
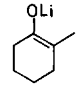
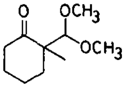
Formylation and related operations triggered by carbonyl functions are subjects perennially interesting to synthetic chemists.[1] One of the widely used methods stems on the in situ generation of enolates by exposure of ketonic substrates to strong bases such as sodium alkoxides or sodium hydride, followed by trapping by alkyl formates. However, this method, based on the high stability of the resulting β-dicarbonyl compound enolates, is applicable only to primary alkyl ketones. Relevantly, reaction of ketones and orthoformamides affords the corresponding aminomethylene ketones.[2] Regiospecific α-dialkoxymethylation is achievable by treatment of a mixture of an enol trimethylsilyl ether and an ortho ester by a stoichiometric amount of titanium tetrachloride[3] or a catalytic amount of trimethylsilyl trifluoromethanesulfonate.[4] We have found a new procedure for the dialkoxymethylation via preformed lithium enolates, which, complementary to such existing methods, provides a useful synthetic tool.

Lithium enolates generated from the enol trimethylsilyl ethers and methyllithium in ether[5] react with an equimolar amount of trimethyl orthoformate at a low temperature in the presence of boron trifluoride to give the corresponding dimethoxymethylated ketones in reasonable yields. Several examples are given in Table I. Here the order and way of mixing of the reagents affects strongly the product yield. Boron trifluoride should be added in one portion to an ethereal solution containing a lithium enolate and the orthoformate; prior mixing of the enolate and boron trifluoride results in a drastic decrease of product yield.[6,7]



Several characteristics have been noted. Only mono-dimethoxymethylation takes place. The reaction preceeds under kinetic control and is regiospecific with respect to lithium enolates (entries 5 and 6). The products do not undergo epimerization under the reaction conditions.[8] Importantly, unlike the conventional ketone formylation reaction using sodium methoxide and methyl formate,[1a] this condensation is applicable even to fully substituted enolates (entry 6).

Table I. Dimethoxymethylation of Lithium Enolates[a]

|  |  | reaction conditions[c] |  |  |  |
|---|---|---|---|---|---|
| entry | lithium enolate[b] | $BF_3$, equiv | temp, °C (time, h) | product | % yield[d] (cis:trans) |
| 1 |  | 1.0 | -78 (1) |  | 84 |
| 2 |  | 1.0 | -78 (1) |  | 80 |
| 3 |  | 1.0 | -78 (1) |  | 87 |
| 4 |  | 1.0 | -78 (1) |  | 72 (50:50) |
| 5 |  | 1.0 | -78 (1) |  | 79[e] (28:72) |
| 6 |  | 1.0 | -78 (1) |  | 68[e] |

[a] All reactions were carried out in ether under argon atmosphere. [b] Prepared by treatment of the corresponding trimethylsilyl ether with 1 equiv of methyllithium in ether at 25 °C for 1—2 h. [c] Boron trifluoride etherate was added at -95 °C. [d] Isolated yield after silica gel column chromatography. [e] No regioisomer was formed. Major byproduct was 2-methylcyclohexanone.

## REFERENCES AND NOTES

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6. When trimethyl orthoformate was added to an equimolar mixture of cyclohexanone lithium enolate and boron trifluoride etherate after 5-min and 1.5-h duration at -95 °C, 2-dimethoxymethylcyclohexanone was obtained in only 59 and 8%, respectively (reaction at -78 °C for 1 h).
7. A typical procedure is illustrated by the formation of 2-dimethoxymethylcyclohexanone (entry 3 of Table I). In a 150-mL ampule was placed a solution of 1-trimethylsiloxycyclohexene (1.024 g, 6.01 mmol) in dry ether (40 mL) under argon atmosphere. To this was added an ethereal solution of methyllithium (6.20 mL, 6.01 mmol) at 25 °C, and the mixture was stirred for 1 h and cooled to -95 °C. After the addition of trimethyl orthoformate at this temperature, boron trifluoride etherate (0.85 g, 6.01 mmol) was added quickly and in one portion under vigorous stirring. The mixture was stirred at -78 °C for 1 h and quenched by addition of saturated ammonium chloride solution (20 mL) with vigorous shaking. The ethereal extracts were dried ($Na_2SO_4$) and evaporated. The residue was chromatographed on silica gel (30 g, 1:3 ether—hexane mixture) to give the desired condensation product (0.903 g, 87% yield) as a colorless oil.
8. Cis/trans isomeric ratios under equilibrium conditions ($NaOH_3$ /$CH_3OH$, 25 °C) are: 4-t-butyl-2-dimethoxymethylcyclohexanone, 75:25; 2-dimethoxymethyl-5-methylcyclohexanone, 71:29.

(Received in Japan 22 May 1982)