The Boron Trifluoride Catalyzed Aldol Reaction of Methyl 2-(Trimethylsiloxy)acrylate with Aldehydes in the Presence of Alcohols

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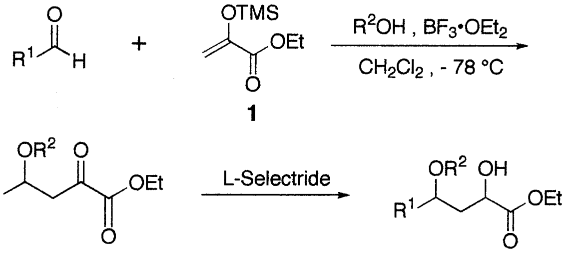
The boron trifluoride etherate catalyzed aldol reaction of methyl 2-(trimethylsiloxy)acrylate with aldehydes proceeded smoothly in the presence of primary, secondary and tertiary alcohol to give corresponding γ-alkoxy-α-ketoesters.

It is well known as the Mukaiyama-aldol reaction that the reactions of carbonyl compounds with silyl enol ethers catalyzed by Lewis acid such as titanium tetrachloride give aldol adducts.[1] However, methyl 2-(trimethylsiloxy)acrylate(**1**)[2] does not react smoothly with aldehyde because **1** is sensitive to the Lewis acid. Sugimura *et al.* have reported that the reaction of **1** with acetals in the presence of boron trifluoride etherate gave corresponding γ-alkoxy-α-ketoesters.[3,4]

We now herein describe the aldol reaction of **1** with aldehyde promoted by boron trifluoride in the presence of various kinds of alcohol. To the mixture of benzaldehyde and two equivalents of methanol, 2-propanol or *t*-butanol in dichloromethane was added boron trifluoride etherlate at -78 °C and stirred for 20 min. **1** was added dropwise to this mixture and stirred for 1 h. The reaction mixture was warmed to -30 °C over a period of 1 h and stirred for additional 2 h at -30 °C. Work-up afforded crude ethyl 4-phenyl-4-alkoxy-2-oxo-butanoate(**2a**-**c**).[5] Without further purification, **2a** was reduced by L-Selectride in THF at -78 °C to give diastereo mixture of *syn* and *anti* ethyl 4-phenyl-4-alkoxy-2-hydroxybutanoate(**3a**-**c**) in good yield.



yield(*syn*:*anti*)

3a: R^1,R^2=Ph, Me; 83%(70:30)
3b: R^1,R^2=Ph, *i*-Pr; 72%(28:72)
3c: R^1,R^2=Ph, *t*-Bu; 73%(32:68)
3d: R^1,R^2=Pr, Me; 73%(58:42)
3e: R^1,R^2=Pr, *i*-Pr; 64%(44:56)
3f : R^1,R^2=Pr, *t*-Bu; 65%(38:62)
3g: R^1,R^2=*i*-Pr, Me; 73%(73:27)
3h: R^1,R^2=*i*-Pr, *i*-Pr; 71%(33:67)
3 i : R^1,R^2=*i*-Pr, *t*-Bu; 71%(28:72)

Scheme 1.

In the similar manner, when butanal and 2-methylpropanal were employed instead of benzaldehyde, corresponding γ-alkoxy-α-ketoesters(**2d**-**i**) were obtained. Further, L-Selectride reduction gave **3d**-**i**.[5] The diastereo ratio of *syn* and *anti* were measured by ^{1}H-NMR of **3a**-**i** and determined by *t*-butydimethylsilylated products which were prepared from **3a**-**i** by *t*-butyldimethylsilyl chloride and imidazole.[6]

References and Notes

1 T. Mukaiyama and M. Murakami, *Synthesis*, **1987**, 1043.
2 M. Sekine, T. Futatsugi, K. Yamada, and T. Hata, *J. Chem. Soc.*, *Perkin Trans. 1*, **1982**, 2509.
3 H. Sugimura , Y. Shigekawa, and M. Uematsu, *Synlett*, **1991**, 153.
4 R. Metternich and W. Lüdi, *Tetrahedron Lett.*, **1988**, 3923.
5 The ^{1}H-NMR(300 MHz, $CDCl_3$) data of **2a**-**i** are as follows. **2a**: 1.40(t, 3H, J=7.2 Hz), 2.98(dd, J=16.8, 4.5 Hz), 3.20(s, 3H), 3.41(dd, 1H, J=16.8, 9.0 Hz), 4.31(q, 2H, J=7.2 Hz), 4.73(dd, 1H, 9.0, 4.5 Hz) 7.45-7.89(m, 5H) **2b**: 1.02(d, 3H, J=6.0 Hz), 1.11(d, 3H, J=6.0 Hz), 1.37(t, 3H, J=7.2 Hz), 2.93(dd, 1H, J=16.2, 4.2 Hz), 3.37(dd, 1H, J=16.2, 9.0 Hz), 3.48(sept, 1H, J=6.0 Hz), 4.31(q, 2H, J=7.2 Hz), 4.96(dd, 1H, J=9.0, 4.2 Hz), 7.24-7.40(m, 5H) **2c**: 1.06(s, 9H), 1.37(t, 3H, J=7.2 Hz), 2.89(dd, 1H, J=16.8, 4.5 Hz), 3.32(dd, 1H, J=16.8, 9.0 Hz), 4.31(q, 2H, J=7.2 Hz), 5.06(dd, 1H, J=9.0, 4.5 Hz), 7.23-7.38(m, 5H), **2d**: 0.93(t, 3H, J=7.2 Hz), 1.34(t, 3H, J=7.2 Hz), 1.38-1.72(m, 4H), 2.88(dd, 1H, 16.8, 4.5 Hz), 3.08(dd, 1H, J=16.8, 7.6 Hz), 3.32(s, 3H), 3.68-3.78(m, 1H), 4.33(q, 2H, J=7.2 Hz), **2e**: 0.92(t, 3H, J=7.2 Hz), 1.08(d, 3H, J=6.0 Hz), 1.11(d, 3H, J=6.0 Hz), 1.37(t, 3H, J=7.2 Hz), 1.42-1.54(m, 4H), 2.89(dd, 1H, J=16.2, 4.8 Hz), 3.05(dd, 1H, J=16.2, 7.2 Hz), 3.65(sept, 1H, J=6.0 Hz), 3.88(m, 1H), 4.31(q, 2H, J=7.2 Hz), **2f**: 0.91(t, 3H, J=6.9 Hz), 1.17(s, 9H), 1.37(t, 3H, J=7.2 Hz), 1.42-1.58(m, 4H), 2.95(dd, 1H, J=15.6, 5.7Hz), 3.01(dd, 1H, J=15.6, 6.3 Hz) 4.03(quint, 1H, J=6.3 Hz), 4.31(q, 2H, J=6.9 Hz), **2g**: 0.87(d, 3H, J=6.6 Hz), 0.89(d, 3H, J=7.2 Hz), 1.36(t, 3H, J=6.9 Hz), 1.93(m, 1H), 2.76(dd, 1H, J=16.2, 3.9 Hz), 3.03(dd, 1H, J=16.2, 8.4 Hz), 3.31(s, 3H), 3.57(ddd, 1H, J=8.7, 8.7, 3.9 Hz), 4,32(q, 2H, J=6.9 Hz), **2h**: 0.89(d, 3H, J=6.9 Hz), 0.91(d, 3H, J=6.6 Hz), 1.06(d, 3H, J=6.3 Hz), 1.10(d, 3H, J=6.3 Hz), 1.37(t, 3H, J=6.9Hz), 1.89(m, 1H), 2.80(dd, 1H, J=15.9, 3.9 Hz), 3.00(dd, J=15.6, 8.1 Hz), 3.60(sept, 1H, J=6.3), 3.76(dt, 1H, J=8.1, 3.9 Hz), 4.32(q, 2H, J=6.9 Hz), **2i**: 0.86(d, 3H, J=7.2 Hz), 0.90(d, 3H, J=6.6 Hz), 1.16(s, 9H), 1.37(t, 3H, J=6.9 Hz), 1.80(m, 1H), 2.90(dd, 1H, J=15.6, 5.7 Hz), 2.96(dd, 1H, J=15.6, 6.0 Hz), 3.93(bq, 1H, J=5.7 Hz), 4.32(q, 2H, J=6.9 Hz)
6 In the silylated product of *anti* **3a**, the coupling constants of Ha, Hb and Hd, Hc were measured as follows. The differences of chemical shift of two methyl groups at silicon for *syn* derivatives were larger than *anti* form.

*J*Ha-Hb=10.2 Hz, *J*Hd-Hc=10.2 Hz
*J*Ha-Hc=2.4 Hz, *J*Hd-Hc=3.0 Hz