Pergamon

Tetrahedron Letters 41 (2000) 4033–4034

TETRAHEDRON LETTERS

Control of diastereoselectivity in the aldolization of methyl phenylacetate

Sergio Pinheiro,* Marcelo B. Lima, Clara B. S. S. Gonçalves, Sérgio F. Pedraza and Florence M. C. de Farias

Instituto de Química, GQO, Universidade Federal Fluminense, CEG, Niterói, 24210-150, RJ, Brazil

Received 15 February 2000; revised 4 April 2000; accepted 5 April 2000

Abstract

The aldolization of methyl phenylacetate with benzaldehyde in several conditions was studied. While the use of LDA in THF–HMPA gave the *anti*-aldol, the dibutylboron triflate furnished the *syn*-aldol in high diastereoselectivity (*syn*:*anti*=97:3). © 2000 Elsevier Science Ltd. All rights reserved.

Keywords: phenylacetate; aldol; diastereoselection; dibutylboron triflate.

In contrast to the importance of the asymmetric α-alkylation of arylacetic derivatives to prepare biologically active compounds,[1] the aldol reaction from arylacetic esters has been scarcely used in organic synthesis due to the modest diastereoselections observed.[2,3] It can be due, in many cases, to the formation of mixtures of *E* and *Z*-lithium enolates[4,5] upon deprotonation of this class of esters. Some time ago was reported[6] the aldol reaction of benzaldehyde with the *E*-boron enolate produced from ethyl phenylacetate and c-Hex_2BI to give the *anti*-aldol (*anti*:*syn*=97:3) and recently the c-Hex_2BOTf and the widely used Bu_2BOTf were employed[7] for the aldolization of propionate esters with aldehydes.

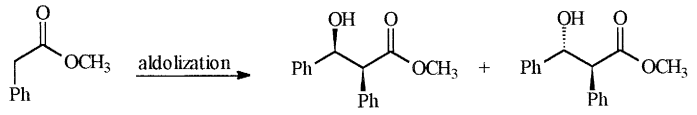
As part of our interest in the aldol reaction of arylacetic esters for the synthesis of isoflavans, we describe herein the aldolization of methyl phenylacetate with benzaldehyde employing different metal enolates and the use of Bu_2BOTf as a highly stereoselective reagent for this purpose (Table 1).

In spite of the *E*-enolate being predominant (*E*:*Z*=81:19),[4a] the aldolization in LDA at −78°C led a mixture of isomers (entry 1),[8] with the product of *anti*-aldol being favored at 0°C (entry 2). The reaction under Mukaiyama's conditions did not show high preference for the *anti*-aldol (entry 3). This selectivity was dramatically increased by the enolization in the presence of THF–HMPA (entry 4),[8] a condition that leads to the *Z*-enolate (*E*:*Z*=9:91).[4a] While the zirconium[9] and titanium[10] enolates were not selectives (entries 5 and 6), the use of Bu_2BOTf in *i*-Pr_2NEt in the deprotonation[11] gave the *syn*-aldol in excellent diastereoselectivity (entry 7) perhaps due to the formation of a *Z*-boron enolate.[6]

* Corresponding author. E-mail: spinuff@hotmail.com (S. Pinheiro)

PII: S0040-4039(00)00582-7

Table 1
Stereoselectivities in the aldolization of methyl phenylacetate



syn-aldol
H3: 5.30 ppm (J = 7.8 Hz)

anti-aldol
H3: 5.18 ppm (J = 9.3 Hz)

Entry	Aldolization	% [a]	*Syn:Anti* [b]
1	LDA, THF, -78°C, 45 min. then PhCHO, 5 min.	95	48 : 52
2	LDA, THF, 0°C, 45 min. then PhCHO, 5 min.	76	27 : 73
3	LDA, THF, -78°C, 45 min. then TBDMSCl, HMPA and PhCHO, $TiCl_4$	82	13 : 87
4	LDA, THF-23 % HMPA, -78°C, 45 min. then PhCHO, 5 min.	90	02 : 98
5	LDA, THF, -78°C, 45 min. then Cp_2ZrCl_2, THF, 2h and PhCHO, 1h	56	30 : 70
6	$TiCl_4$, i-Pr_2NEt, CH_2Cl_2, -23°C then PhCHO, -78°C, $TiCl_4$, 1h	60	54 : 46
7	n-Bu_2BOTf, i-Pr_2NEt, CH_2Cl_2, 0°C then PhCHO, -78°C, 45 min.	85	97 : 03

[a] Both isomers were characterized by comparison of their m.p., IR and ^{1}H NMR spectra with those of the authentic samples.[3, 6]
[b] By relative intensities of the signals of OCH_3 for *anti* (3.73 ppm) and *syn* (3.54 ppm) isomers.

While the formation of *syn*-aldol (entry 7) from a *Z*-boron enolate is attributed to a widespread accepted Zimmerman–Traxler chelate transition state,[8] in the presence of HMPA (entry 4) the *Z*-lithium enolate could lead to the *anti*-aldol by means of a acyclic transition state.[12]

In conclusion, while the use of LDA in THF-23% HMPA is an attractive alternative to reach the isomer *anti*-aldol from methyl phenylacetate, the commercially available Bu_2BOTf was proved to be an excellent and complementary organoboron reagent to the use of c-Hex_2BI to access *syn*-aldols.

References

1. Beaulieu, C.; Spino, C. *Tetrahedron Lett*. **1999**, *40*, 1637–1640 and references cited therein.
2. van Aardt, T. G.; van Rensburg, H.; Ferreira, D. *Tetrahedron* **1999**, *55*, 11773–11786.
3. Canceill, J.; Basselier, J.-J.; Jacques, J. *Bull. Soc. Chim. Fr*. **1967**, 1024–1030.
4. (a) Tanaka, F.; Node, M.; Tanaka, K.; Mizuchi, M.; Hosoi, S.; Nakayama, M.; Taga, T.; Fuji, K. *J. Am. Chem. Soc*. **1995**, *117*, 12159–12171. (b) Solladié-Cavallo, A.; Csaky, A. G.; Gantz, I.; Suffert, J. *J. Org. Chem*. **1994**, *59*, 5343–5346.
5. Corset, J.; Froment, F.; Lautié, M.-F.; Ratovelomanana, N.; Seyden-Penne, J.; Strzalko, T.; Roux-Schmitt, M.-C. *J. Am. Chem. Soc*. **1993**, *115*, 1684–1694 and references cited therein.
6. Ganesan, K.; Brown, H. C. *J. Org. Chem*. **1994**, *59*, 2336–2340.
7. Liu, J.-F.; Abiko, A.; Pei, Z.; Buske, D. C.; Masamune, S. *Tetrahedron Lett.* **1998**, *39*, 1873–1876.
8. Heathcock, C. H.; Pirrung, M. C.; Montgomery, S. H.; Lampe, J. *Tetrahedron* **1981**, *37*, 4087–4095.
9. Katsuki, T.; Yamaguchi, M. *Tetrahedron Lett*. **1985**, *26*, 5807–5810.
10. Ghosh, A. K.; Onishi, M. *J. Am. Chem. Soc*. **1996**, *118*, 2527–2528.
11. Evans, D. A.; Bartroli, J.; Shih, T. L. *J. Am. Chem. Soc*. **1981**, *103*, 2127–2129.
12. Oppolzer, W.; Starkemann, C.; Rodriguez, I.; Bernadinelli, G. *Tetrahedron Lett*. **1991**, *32*, 61.