Aldol Reactions of Ethyl *N*-Benzyl-*N*-methylglycinate and of its Borane Adduct: Selective Access to *Syn* or *Anti* α-Amino-β-hydroxyesters

Vincent Ferey,[a] Thierry Le Gall*[a] and Charles Mioskowski[a,b]

[a] *CEA-Saclay, Service des Molécules Marquées, Bât. 547, Département de Biologie Cellulaire et Moléculaire, F-91191 Gif-sur-Yvette Cedex, France*

[b] *Université Louis Pasteur, Laboratoire de Synthèse Bio-organique associé au CNRS, Faculté de Pharmacie, 74 route du Rhin, BP 24, F-67401 Illkirch, France*

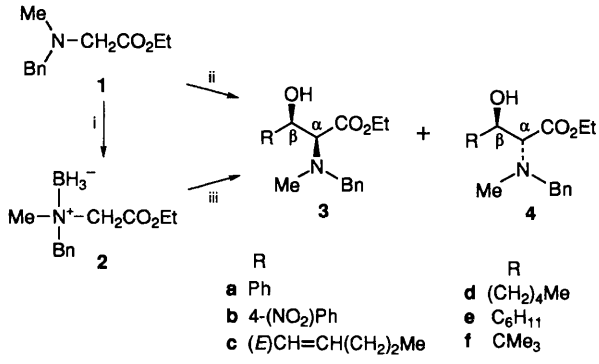
Procedures are developed for the condensation of aldehydes with ethyl *N*-benzyl-*N*-methylglycinate **1** and with its borane adduct **2**, which selectively afford the corresponding *syn* and *anti* aldols, respectively.

Borane–amine complexes have found use in organic chemistry as reducing and hydroborating agents,[1] and as protective groups against oxidation for the amine function.[2] Several borane adducts of α-aminoesters have been prepared[3] and some of them have been used in asymmetric reduction (with low induction) of ketones.[4] However, to the best of our knowledge, no study has been reported on the reactivity of the enolates prepared from such species in aldol reactions. On the other hand, several aldol reactions of *N*,*N*-dialkyl α-aminoesters have been reported.[5,6] This communication deals with the effect of the complexation of the amino group by borane on the stereochemical outcome of such reactions.

While the borane adduct of ethyl *N*,*N*-dibenzylglycinate proved to be unstable in solution, we found that ethyl *N*-benzyl-*N*-methylglycinate **1**[7] reacted with borane–methyl sulfide[8] to yield borane–amine **2**,† purified by column chromatography, as a strong complex, stable in solution. We then compared the aldol reactions of **1** and **2** with various aldehydes according to Scheme 1.

The enolate derived from ester **1** by treatment with LDA (1.2 equiv., 15 min, −78 °C) condensed with benzaldehyde (2 h, −78 °C), to afford the corresponding aldols in good yield, with a 66:34 *syn*:*anti* ratio (Table 1, entry 1).‡ This ratio was not affected when the temperature was allowed to rise to 0 °C over 2 h after addition of the aldehyde. Thus, the former reaction conditions were applied to other aldehydes (see Table 1). The yields were generally good and the *syn* aldol was the major product in each case.‡

The formation of the enolate derived from borane–amine **2** required a longer contact with LDA (2 h, −78 °C). Condensation with benzaldehyde was performed at −78 °C for 2 h. Hydrolysis of the reaction mixture with saturated aq. NH_4Cl also cleaved the boron–nitrogen bonds, hence aldols **3a** and **4a** were obtained, with a low (54:46) *syn*:*anti* ratio. The aldol reaction was then performed in the following manner: benzaldehyde was added to the enolate at −78 °C, stirring at this temperature was continued for 2 h, the reaction mixture was allowed to warm to 0 °C over 2 h, then hydrolysed with saturated aq. NH_4Cl. This procedure afforded aldols **3a** and **4a** with a 6:94 *syn*:*anti* ratio (Table 1, entry 7); it was then applied to other aldehydes (see Table 1). With the exception of pivalaldehyde (entry 12), they all reacted to afford the corresponding aldols, the *anti* aldol always being obtained as the major adduct. In all cases, some esters **1** and **2** were present in the crude product, and byproducts were observed in some examples (entries 7, 8, 12). These facts explain why the yields were lower in the aldol reactions of the borane–amine complex **2**. Not surprisingly, these reactions also appear to be more sensitive to the steric crowding of the aldehyde (entry 12).

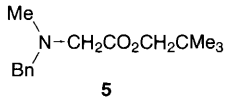


Scheme 1 *Reagents and conditions*: i, $BH_3{\cdot}SMe_2$, THF, 1 h, 65%; ii, LDA, THF, −78 °C, 15 min, then RCHO, −78 °C, 2 h; iii, LDA, THF, −78 °C, 2 h, then RCHO, −78 °C to 0 °C, 2 h

Table 1 Aldol reactions of ethyl *N*-benzyl-*N*-methylglycinate **1** and of its borane adduct **2**

		Substrate : amine **1**			Substrate: borane–amine **2**	
R	Entry	**3**/**4** Ratio[a]	Yield (%)[b]	Entry	**3**/**4** Ratio[a]	Yield (%)[b]
Phenyl	1	66:34	76	7	6:94	63[d]
4-Nitrophenyl	2	57:43	73	8	6:94	52[d]
(*E*)-Pent-1-enyl	3	75:25	82	9	7:93	62
Pentyl	4	84:16	66	10	21:79	67
Cyclohexyl	5	75:25	78	11	17:83	48
tert-Butyl	6	82:18	61	12	[c]	[c]

[a] Ratios were determined by ^1H NMR spectroscopy of the crude product. [b] Yield of chromatographically pure **3** and **4**. [c] No aldol was obtained; compound **5**, derived from 2,2-dimethylpropanol (formed *in situ* by reduction of pivalaldehyde) was isolated. [d] Some alcohol arising from the reduction of the aldehyde was also observed in the crude product.



5

Some comments have to be made on the stereochemical outcomes of these condensations.

A moderate *syn* selectivity was observed in the aldol reactions from aminoester **1**, which proceed through the intermediacy of the corresponding lithium *Z*-enolate; this was demonstrated by its quenching with *tert*-butyldimethylsilyl chloride, which afforded compound **6**§ (Scheme 2). It is well known that the stereoselectivity observed in the aldol reactions from lithium *Z*-enolates is not easily explained by the Zimmerman–Traxler model.[9] In our case, the skewed transition state structures proposed by Dubois and Heathcock[10] better predict the stereochemical outcome of the reactions (Fig. 1). The interaction between R and the benzylmethylamino group should destabilize the transition structure **A**, especially when R is large; thus, the transition structure **B** leading to the *syn* isomer becomes favoured.

The aldol reaction performed at −78 °C starting from borane–amine **2** and benzaldehyde is not diastereoselective, but an *anti* selectivity was observed when the reaction mixture was allowed to warm to 0 °C. These results suggest that, in the latter case, equilibration has occurred.[11] In such a case, the *anti* isomer is expected to be obtained predominantly:[12] in their most stable chair-like conformers (Scheme 3), the *anti* aldolate **8** has more equatorial substituents than the *syn* aldolate **7**. After hydrolysis and concomitant cleavage of the boron–nitrogen bond, the corresponding *anti* aldol is thus obtained as the major isomer.¶[13]

As seen above, the *syn*:*anti* ratio obtained in the aldol reaction of aminoester **1** with benzaldehyde at −78 °C is not modified when the reaction mixture is allowed to warm to 0 °C. It thus seems that no equilibration occurs in that case. The reason for this may be that both aldolates formed are stabilized by an intramolecular chelation of the lithium cation by the nitrogen atom.

In conclusion, the stereochemical outcome of the aldol reactions conducted from borane–aminoester **2** is significantly different from those conducted from aminoester **1**. By using **1** or **2** as the starting ester, it is possible to prepare selectively *syn* or *anti* α-amino-β-hydroxyesters **3** or **4** which are precursors of α-methylamino-β-hydroxyacids, found in nature as constituents of biologically important peptides.[14] Work is currently in progress in our laboratory to take advantage of the chirality present at nitrogen in compounds such as **2** with the goal of performing enantioselective syntheses.

We thank Mrs L. Sergent for realizing the NOE experiments.

Received, 22nd November 1994; Com. 4/07120D

Scheme 2 *Reagents and conditions*: i, LDA, THF, −78 °C; ii, Bu^{t}Me$_2$SiCl, −78 °C to room temp., 84%

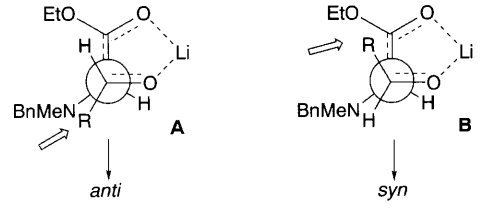
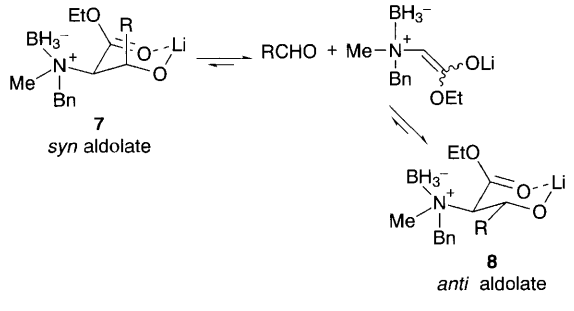


Fig. 1

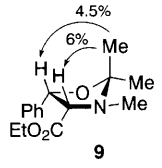


Scheme 3

Footnotes

† *Selected data* for compound **2** (viscous oil): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.31 (t, *J* 6.9 Hz, 3 H), 1.35–2.30 (m, 3 H), 2.82 (s, 3 H), 3.37 (d, *J* 16.4 Hz, 1 H), 3.47 (d, *J* 16.4 Hz, 1 H), 4.27–4.19 (m, 4 H), 7.48–7.25 (m, 5 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.1, 132.4, 131.1, 128.9, 127.9, 63.9, 61.1, 58.5, 49.1, 13.8; ^{11}B NMR (96 MHz, $CDCl_3$) δ −9.0 (q, not well resolved, *J* 81 Hz); IR ν/cm^{-1} 2383, 1742; satisfactory elemental analysis was obtained.

‡ The relative configurations of the aldols obtained in the reaction of benzaldehyde were determined from NOE experiments realized on oxazolidine **9**, prepared in two steps from **4a** (i, HCO_2NH_4, 10% Pd/C, MeOH, reflux, 20 min; ii, $Me_2C(OMe)_2$, TsOH, toluene, reflux, 3 h; overall yield 43%).



Analogies observed in the ^{1}H and ^{13}C NMR spectra of other aldols served to assign their relative configurations (some of these features have been noted for *N*,*N*-dibenzylaminoesters aldolisation adducts by Scolastico *et al.*[5c]): δ(H_α) is always higher for *anti* compounds (the difference varies from 0.04 to 0.14 ppm); Δδ of the two diastereotopic benzylic protons is always larger for *syn* compounds (0.08–0.20 ppm); the coupling constants between H_α and H_β are consistently higher for *syn* adducts (1.0–3.0 Hz); the ^{13}C chemical shift of the carboxylic carbon is always higher in *anti* isomers (2.2–3.1 ppm). Moreover, in all cases, the *anti* adduct was the more polar isomer in thin layer chromatography on silica gel (eluent: hexane–ethyl acetate 80:20).

§ The configuration of *tert*-butyldimethylsilyl ketene acetal **6** was determined by NOE experiments: irradiation of CH_3Si signal gave a NOE of 7% on C*H*=C proton. Previous work has shown that the lithium *Z*-enolate was specifically formed from *tert*-butyl *N*,*N*-dibenzylglycinate under kinetic conditions.[5c]

¶ As for proof of the occurrence of an equilibration process, the following experiment was carried out: an aldol reaction was performed in the usual manner starting from **2** and (*E*)-hex-2-enal; then, after 2 h at 0 °C, benzaldehyde (1 equiv.) was added and the reaction mixture was hydrolysed after 2 h at 0 °C. The crude product contained the benzaldehyde-derived *anti* aldol **4a** as the major compound.

References

1 R. O. Hutchins, K. Learn, B. Nazer, D. Pytlewski and A. Pelter, *Org. Prep. Proced. Int.*, 1984, **16**, 335.
2 A. Picot and X. Lusinchi, *Bull. Soc. Chim. Fr.*, 1977, 1227; C. J. Swain, C. Kneen, R. Herbert and R. Baker, *J. Chem. Soc., Perkin Trans. 1*, 1990, 3183.
3 E. F. Rothgery and L. F. Hohnstedt, *Inorg. Chem.*, 1971, **10**, 181.
4 M. F. Grundon, D. G. McCleery and J. W. Wilson, *J. Chem. Soc., Perkin Trans. 1*, 1981, 231.
5 (*a*) A. M. Touzin, *Tetrahedron Lett.*, 1975, 1477; (*b*) B. D. Gray and P. W. Jeffs, *J. Chem. Soc., Chem. Commun.*, 1987, 1329; (*c*) G. Guanti, L. Banfi, E. Narisano and C. Scolastico, *Tetrahedron*, 1988, **44**, 3671.
6 Recent reviews on the stereoselective synthesis of α-amino acids: R. M. Williams, *Synthesis of Optically Active α-Amino Acids*, Pergamon, 1989; R. O. Duthaler, *Tetrahedron*, 1994, **50**, 1539.
7 U. C. Yoon, Y. C. Kim, J. J. Choi, D. U. Kim, P. S. Mariano, I.-S. Cho and Y. T. Jeon, *J. Org. Chem.*, 1992, **57**, 1422.

8 F. Santiesteban, T. Mancilla, A. Klaébé and R. Contreras, *Tetrahedron Lett.*, 1983, **24**, 759.
9 Y. Li, M. N. Paddon-Row and K. N. Houk, *J. Org. Chem.*, 1990, **55**, 481; S. E. Denmark and B. R. Henke, *J. Am. Chem. Soc.*, 1991, **113**, 2177.
10 J.-E. Dubois and P. Fellmann, *Tetrahedron Lett.*, 1975, 1225; C. H. Heathcock, in *Asymmetric Synthesis*, ed. J. D. Morrison, Pergamon, New York, 1983, vol. 3, ch. 2.
11 J.-E. Dubois and P. Fellmann, *C. R. Hebd. Séances Acad. Sci., Ser. C*, 1972, **274**, 1307; C. H. Heathcock, C. T. Buse, W. A. Kleschick, M. C. Pirrung, J. E. Sohn and J. Lampe, *J. Org. Chem.*, 1980, **45**, 1066.
12 T. Mukaiyama, *Org. React.*, 1982, **28**, 203.
13 An *anti* selectivity has been reported in the thermodynamically controlled aldol reactions of methyl 3,3-dimethylbutanoate, an ester having a sterically crowded group in position α to the carboxylate function: Y. Wei and R. Bakthavatchalam, *Tetrahedron Lett.*, 1991, **32**, 1535.
14 R. M. Wenger, *Angew. Chem., Int. Ed. Engl.*, 1985, **24**, 77; M. F. Mackay, A. Van Donkelaar and C. C. J. Culvenor, *J. Chem. Soc., Chem. Commun.*, 1986, 1219.