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Aldol Addition Reaction of Chiral Acetylurea and a Convenient Synthesis of Optically Pure Methyl ß-Alkyl-ß-hydroxypropionate

Keiki KISHIKAWA, Makoto YAMAMOTO, Shigeo KOHMOTO,
and Kazutoshi YAMADA*
Department of Industrial Chemistry,
Chiba University, Chiba 260

The aldol addition reaction of chiral acetylurea with aldehydes diastereoselectively gives ß-alkyl-ß-hydroxypropionylureas (3 and 4) and the methanolysis of the adducts 3 and 4, separated perfectly by conventional column chromatography on silica gel, gives the corresponding optically pure methyl ß-alkyl-ß-hydroxypropionates.

In our previous publications we have reported the application of chiral carbodiimides to diastereoselective reactions[1, 2] exemplifying the following synthetic advantages; a commercial availability of chiral sources (both (R)- and (S)-1-phenylethylamine), a simple separation of the primary formed diastereomeric adducts, and removal of the chiral auxiliary under mild conditions. The synthetic potential of our chiral auxiliary has now been successfully applied to a convenient synthesis of optically pure (>99% ee) methyl ß-alkyl-ß-hydroxypropionates, which are synthetically important intermediates.[3)]

The acetylurea 1 was prepared from acetic acid and N, N-di-((S)-1-phenylethyl)urea 7. In a typical experiment for the aldol addition reaction, deprotonation of 1 (1.0 mmol) was carried out by LDA (1.1 mmol) in THF solution. Aldehyde (1.1 mmol) was then added and the solution was stirred at -50 - -78 °C (Table 1).

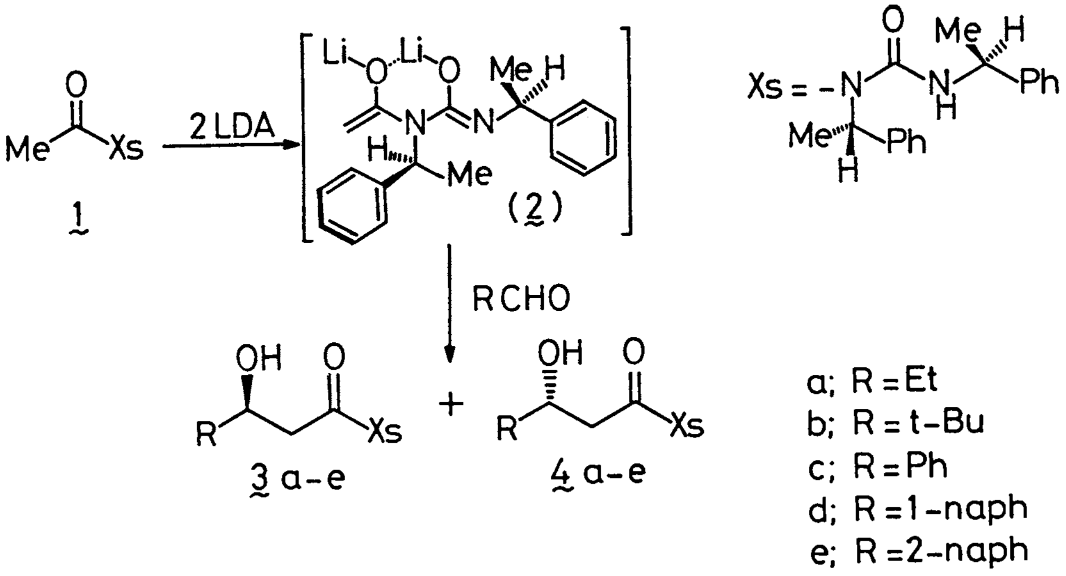


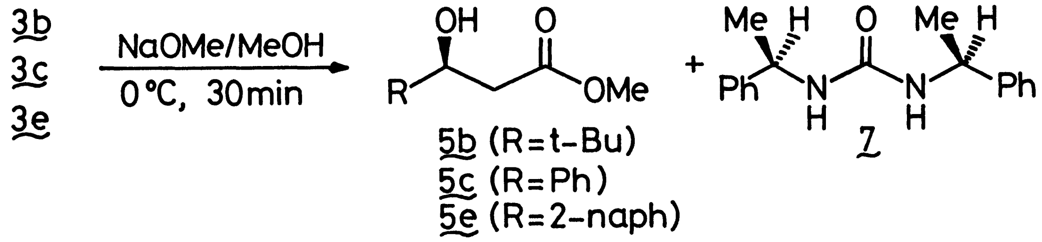
Table 1. Aldol Addition Reaction of Acetylurea 1 with Aldehydes

No.	R	Temp/°C	Time	Yield/%$^{a)}$	3:4$^{b)}$	$\alpha^{b)}$
1	Et	-78	1 h	39	1.86:1	1.21
2	t-Bu	-78	2 h	88	2.70:1	1.57
3	Ph	-78	20 min	87	2.70:1	1.76
4	1-naph	-78	2 h	62	0.96:1	1.85
5	2-naph	-78	2 h	40	3.55:1	1.58
6	2-naph	-50	2 h	87	3.00:1	1.58

a) Isolated yields. b) The ratios and the α value were determined by HPLC (Merk Lichrosorb Si 60, hexane:ethyl acetate=4:1).[4)]

As a result (Table 1), the reaction with bulkier aldehydes (R=t-Bu, Ph, 2-naph) results in higher diastereoselectivity than with propionaldehyde (R=Et). And the reaction at lower temprature improved the ratio 3/4 (Nos. 5 and 6). In HPLC study, all the products 3 ((3S)-form) are more polar than the diastereomers 4 ((3R)-form). There is a tendency that larger alkyl groups (R) gave larger α values (Rf 3/Rf 4). To the best of our knowledge, there is no report which describes such a large α value (α=1.21-1.85) in aldol addition reactions. The difference in Rf is large enough to separate the adducts 3 and 4 by conventional column chromatography on silica gel (benzene-ethyl acetate=4:1).

Treatment of the product 3 and 4 with NaOMe (10 equiv.)/MeOH (0 °C, 30 min) quantitatively gave the corresponding optically pure methyl ester 5 , 6, and the recovered chiral urea 7 which was efficiently recycled. The above methodology can also be extended to the synthesis of optically pure methyl esters starting from N, N'-di((R)-1-phenylethyl)urea.



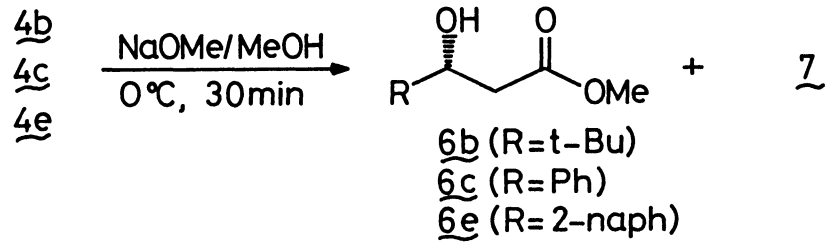


Table 2. Methanolysis of the Diastereomeric Adducts

No.	Starting Material	(de/%) a)	(Rf) b)	Prod.	Yield/% c)	Prod. d) ee/%	$[\alpha]_D^{22}$	(Config.)
1	3b	(>99)	(0.39)	5b e,f)	59	-	-	(S)
2	4b	(>99)	(0.43)	6b e,f)	96	-	-	(R)
3	3c	(>99)	(0.23)	5c	97	>99	-18.3	(S) g)
4	4c	(>99)	(0.33)	6c	96	>99	+18.8	(R) g)
5	3e	(>99)	(0.39)	5e e)	94	>99	-44.3	(S) h)
6	4e	(>99)	(0.48)	6e e)	90	>99	+43.9	(R) h)

a) The ratios were determined by HPLC analysis (Merck Lichrosorb Si 60, hexane: ethyl acetate=4:1). b) The values were determined by TLC (Merck 7731, benzene: ethyl acetate=4:1). c) Isolated Yields. d) The hydroxyesters were converted to (R)-MTPA esters and the ratios were determined by ^{1}H NMR analysis. e) Estimated configurations from polarimetric analysis and ^{1}H NMR study of the acylureas[5)] and the (R)-MTPA esters. f) The product is too volatile to carry out further purification. g) Methyl (R)-3-phenyl-3-hydroxypropionate; $[\alpha]_D^{24}$ +18.3° (c 4.78, EtOH, Ref. 6). h) Chloroform was used as a solvent.

A typical example is as follows; To a solution of lithium diisopropylamide, which was prepared from diisopropylamine (0.88 ml, 635 mg, 6.28 mmol) and n-butyllithium (4.00 ml of a solution of n-butyllithium (1.59 mol dm^{-3}) in hexane) in THF (20 ml) at 0 °C, was added a solution of acetylurea 1 (1.003 g, 3.22 mmol) in THF (5 ml) dropwise at -70 °C within 20 min. The temperature was raised to -40 °C, and the solution was stirred for 20 min. Then, the solution was cooled to -70 °C and stirred for 20 min. Benzaldehyde (0.35 ml, 364 mg, 3.43 mmol) was added dropwise within 15 min. The reaction was quenched by the addition of saturated ammonium chloride solution (20 ml). The organic layer was washed with hydrochloric acid (1 mol dm^{-3}), dried over anhydrous MgSO$_4$, and concentrated in vacuo to give oily product (1.786 g, 3:4=73:27). The crude product was separated by column chromatography on silica gel (Fujigel BW820MH), eluting with benzene: ethylacetate(=4:1), to give 4 (318 mg, 24%) and 3 (846 mg, 63%). From HPLC analysis the both diastereomers have purity of >99% de.

To a solution of 3c (381 mg, 0.915 mmol) in methanol (2.5 ml) was added a solution of sodium methoxide (Na: 211 mg, 0.917 mmol) in methanol (10 ml) at 0 °C. The solution was stirred for 30 min (after 10 min removed urea appeared). To quench the reaction, hydrochloric acid (1 mol dm^{-3}, 10 ml) was added at 0 °C. The solution was extracted with chloroform (20 ml x 5). Methanol in aqueous solution was removed in vacuo, and then the solution was extracted with chloroform (10 ml x 3). The combined organic solution was dried over anhydrous MgSO$_4$ and concentrated to give a mixture (442 mg). The products were separated by column chromatography on silica gel (Fujigel BW820MH) eluting with benzene:ethyl acetate (=4:1) to give 5c (159 mg, 97%) and removed urea (171 mg, 70%). 5c: $[\alpha]_D^{22}$ -18.30° (EtOH), >99%ee (determined from (R)-MTPA ester of 5c).

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References

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5) The configurations were estimated based on the following signals.
^{1}H NMR (δ, J in Hz, $CDCl_3$, 270 MHz):
3b: 2.41 (dd, J=15.3, 2.9, 1H, H-C(2)), 2.49 (dd, J=15.3, 9.5, 1H, H-C(2)), 3.53 (d, J=4.0, 1H, HO-C(3)), 3.59 (ddd, J=9.5, 4.0, 2.9, 1H, H-C(3)).
4b: 2.46 (dd, J=15.1, 10.5, 1H, H-C(2)), 2.61 (dd, J=15.1, 2.4, 1H, H-C(2)), 2.85 (d, J=3.7, 1H, HO-C(3)), 3.84 (ddd, J=10.5, 3.7, 2.4, 1H, H-C(3)).
3c: 2.90 (d, J=5.8, 2H, H-C(2)), 3.67 (d, J=4.0, 1H, HO-C(3)), 5.24 (dd, J=10.3, 5.8, H-C(3)).
4c: 2.68 (dd, J=15.6, 3.1, 1H, H-C(2)), 2.88 (dd, J=15.6, 9.8, 1H, H-C(2)), 4.03 (d, J=3.1, 1H, HO-C(3)), 5.01 (dt, J=9.8, 3.1, 1H, H-C(3)).
3e: 2.77 (dd, J=15.6, 3.3, 1H, H-C(2)), 2.93 (dd, J=15.6, 9.8, 1H, H-C(2)), 4.18 (d, J=3.3, 1H, HO-C(3)), 5.16 (dt, J=9.8, 3.3, 1H, H-C(3)).
4e: 2.98 (d, J=2.4, 1H, H-C(2)), 3.02 (d, J=11.3, 1H, H-C(2)), 3.96 (d, J=4.3, 1H, HO-C(3)), 5.39 (ddd, J=11.3, 4.3, 2.4, 1H, H-C(3)).

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