Crystalline, Enantiomerically Pure Aldols from a (-)-Ephedrine-DerivedN-Acylimidazolidin-2-one

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Crystalline, Enantiomerically Pure Aldols from a (−)-Ephedrine-Derived *N*-Acylimidazolidin-2-one

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Reaction of (4*R*,5*S*)-1,5-dimethyl-4-phenyl-3-propanoylimidazolidin-2-one with aromatic aldehydes leads to aldol products which, after one recrystallisation have d.e.s > 99%. Removal of the chiral auxiliary affords optically pure β-hydroxy esters.

New methodology surrounding asymmetric aldol reactions continues to attract widespread interest. In a recent paper Oppolzer[1] comments that such reactions in synthesis would derive benefit from the prospect of purifying the initially formed aldol products by crystallisation. He also stresses the importance of using a chiral auxiliary which is readily accessible and versatile. In this communication we wish to report our results on asymmetric aldolisations with a chiral auxiliary which meets some of the above criteria.

The chiral auxiliary **1** [(4*R*,5*S*)-1,5-dimethyl-4-phenylimidazolidin-2-one] is easily prepared in one step by the method originally described in 1950 by Close[2] using the readily available (−)-ephedrine hydrochloride and urea. Imidazolidin-2-one **1** was smoothly acylated with propanoyl chloride/*n*BuLi to afford (4*R*,5*S*)-1,5-dimethyl-4-phenyl-3-propanoylimidazolidin-2-one (**2**). Recently, Helmchen[3] has found application for **1** in enantioselective homoaldol additions, and Cardillo[4,5] has utilized it in diastereoselective alkylations and in the synthesis of chiral 2-benzyloxy alcohols.

Our approach to the diastereoselective synthesis of aldol intermediates, followed by their conversion to enantiomerically pure α-branched methoxycarbonyl aldols is outlined in Scheme 1. Initially, generation of the enolate was effected with LDA, but a dramatic increase in the diastereoselectivity occurred by changing to di-*n*-butylboron triflate/triethylamine. Boron enolate methodology has been applied with considerable success by Evans[6], Oppolzer[1,7] and Helquist[8].

For a representative selection of aromatic aldehydes we have found diastereoselectivities of 92% and better, rising to >99% *after one recrystallisation* (Table 1). In Scheme 1 the intermediate is shown as the (*Z*)-enolate[6,9], in accordance with the finding that the major isomer **3** has the *syn* configuration from coupling constants[1]. The *syn* configuration was further confirmed by the optical rotation of the previously reported[6] value for **4a**.

Our procedure for determination of the d.e. involved the use of three independent methods. These were

i) Separation of the product mixture (4 possible diastereomers) by GC/MS analysis of the silyl ether derivative of **3a**;

ii) ^{19}F-NMR analysis of the trifluoroacetate derivative of the isomeric mixture of **3**, and

(iii) ^{1}H-NMR analysis of the downfield signals which arise by treating the diastereomeric mixture with trichloroacetyl isocyanate[10,11].

Scheme 1. Details of the aldolisation reaction

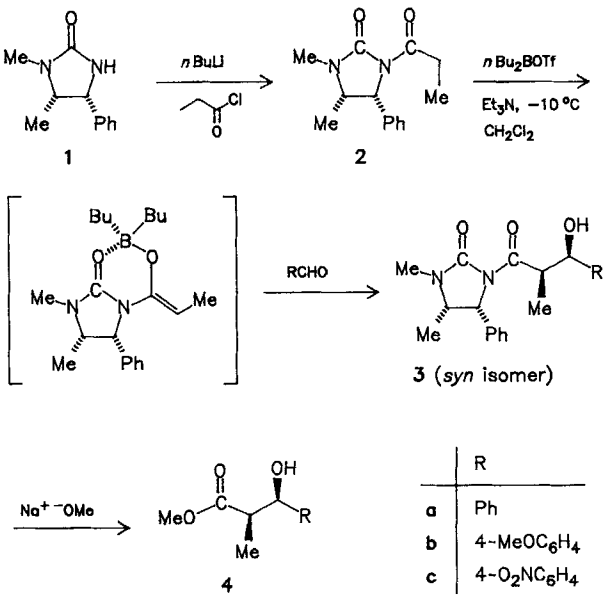

Table 1. Details of the yields of aldol products and esters derived from them

Aldol compound	Ratio of major isomer:others	% d.e. after recrystallisation	M.p. [°C]	Yield (%)[a]	Ester[b]	$[\alpha]_D^{30}$
3a	98:2	>99	135–136	88	**4a**	+23.3[c]
3b	96:4	>99	181–182	92	**4b**	+16.9[d]
3c	96:4	>99	156–157	85	**4c**	+14.3[e]

[a] Yield after recrystallisation. — [b] All new compounds gave satisfactory analyses (C,H,N; ^{1}H and ^{13}C NMR). — [c] c = 1.0 in $CHCl_3$. — [d] c = 0.13 in $CHCl_3$. — [e] c = 1.3 in $CHCl_3$.

Results from the last procedure proved to be in good agreement with the results from the other two, and, since it is more convenient and rapid, it became the method of choice in later reactions.

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Removal of the chiral auxiliary[6] led to its quantitative recovery, and, at the same time afforded in good yield the essentially homochiral β-hydroxy esters **4**. Hydroxy esters of this nature have been used by Evans[12] in the synthesis of ionomycin and by Ku[13] for the preparation of leukotriene antagonists.

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Experimental

Melting points (uncorrected): Kofler hot-stage. – Specific rotations: Perkin-Elmer Model 241 polarimeter.– IR: Shimadzu FTIR-4300. – UV: Pye-Unicam SP8-400. – ^{1}H and ^{13}C NMR: Varian Gemini (200 MHz); TMS and $CDCl_3$ as internal standards.– Elemental analyses: Perkin-Elmer 240B Elemental Analyser.– GC/MS: Hewlett-Packard 5890 gas chromatograph and 5988A spectrometer.

Compound **1** was readily prepared as described in the literature[2,3] and converted into **2** by Cardillo's procedure[4].

(4R,5S,2'R,3'R)-1,5-Dimethyl-4-phenyl-3-(3'-hydroxy-2'-methyl-3'-phenylpropanoyl)imidazolidin-2-one (**3a**): This represents a general procedure for preparation of the aldol products **3a**, **3b** and **3c**. To a stirred solution of *N*-propanoylimidazolidin-2-one **2a** (1.0 g, 4.06 mmol) in CH_2Cl_2 (4 ml) at −10°C was added dropwise over 1 min di-*n*-butylboron triflate (4.7 ml, 1 M in CH_2Cl_2, 1.15 equiv.). After 5 min, Et_3N (0.74 ml, 5.28 mmol) was added. The mixture was stirred for 1 h, cooled to −78°C and benzaldehyde (0.41 ml, 4.06 mmol) added. After 30 min at −78°C, the reaction temp. was allowed to rise to 0 C and maintained at this temp. for 1 h. The reaction mixture was then quenched and worked up in the usual way[6] to afford the crude product. Recrystallisation from benzene yielded 1.20 g (84%) of **3a** as white crystals, m.p. 135 to 136°C. – $[\alpha]_D^{30}$ = −35.3 (*c* = 0.6 in $CHCl_3$). – IR ($CHCl_3$): $\tilde{\nu}$ = 1605 cm^{-1} (Ph), 1660 (C=O), 1730 (C=O), 3500 (OH). – UV (ethanol): λ_{max} (lg ε) = 211 nm (4.146). – ^{1}H NMR ($CDCl_3$): δ = 0.76 (d, *J* = 6.6 Hz, 3H, 5-CH_3), 1.07 (d, *J* = 7.05 Hz, 3H, 2'-CH_3), 2.79 (s, 3H, NCH_3), 3.75 (d, 1H, OH), 3.81 (dq, *J* = 6.6, 8.6 Hz, 1H, 5-H), 4.28 (dq, *J* = 3.13, 7.03 Hz, 1H, 2'-H), 5.10 (m, 1H, 3'-H), 5.28 (d, *J* = 8.6 Hz, 1H, 4-H), 7.10–7.43 (m, 10H, 2 × aromatic H). – ^{13}C NMR ($CDCl_3$): δ = 10.39 (q, 2'-CH_3), 14.98 (q, 5-CH_3), 28.24 (q, 1-CH_3), 44.24 (d, C-2'), 53.80 (d, C-5), 59.29 (d, C-4), 73.49 (d, C-3'), 126.51, 127.02, 127.41, 128.38, 128.60 and 129.03 (d, aromatic CH), 136.74, 142.01 (s, aromatic C), 155.57 (s, C-2), 177.44 (s, C-1').

$C_{21}H_{24}N_2O_3$ (352.4) Calcd. C 71.57 H 6.86 N 7.95
Found C 71.63 H 6.76 N 7.86

Methyl (2R,3R)-3-Hydroxy-2-methyl-3-phenylpropanoate (**4a**): The procedure is a general one[6] and is described for the methanolysis of **3a**. To dry MeOH (4.0 ml) at 0°C under N_2 was added freshly prepared NaOMe (153 mg, 28.4 mmol). The reaction mixture was charged with a solution of **3a** (0.5 g, 14.2 mmol) in dry MeOH (2 ml), stirred at 0°C for 1 h and then quenched with satd. aq. NH_4Cl. After removal of MeOH, the aqueous phase was exhaustively extracted with CH_2Cl_2, and the combined extracts dried ($MgSO_4$) and concentrated in vacuo. Flash chromatography [diethyl ether/hexane (1:1)] afforded 300 mg (76%) of **4a** as an oil. – $[\alpha]_D^{30}$ = +23.3 (*c* = 1.0 in $CHCl_3$) {ref.[6] $[\alpha]^{25}$ = +23.2 (*c* = 3.2 in $CHCl_3$). – IR ($CHCl_3$): $\tilde{\nu}$ = 1734 cm^{-1} (C=O), 34.50 (OH). – ^{1}H NMR ($CDCl_3$): δ = 1.24 (d, *J* = 7.19 Hz, 3H, 2-CH_3), 2.78 (dq, *J* = 7.15, 4.30 Hz, 1H, 2-H), 3.11 (br. s, 1H, OH), 3.64 (s, 3H, OCH_3), 5.07 (d, *J* = 4.31 Hz, 1H, 3-H), 7.24–7.35 (m, 5H, aromatic H). – ^{13}C NMR ($CDCl_3$): δ = 10.78 (q, 2-CH_3), 46.45 (d, C-2), 51.87 (q, OCH_3), 73.66 (d, C-3), 125.95, 127.48 and 128.24 (d, aromatic CH), 141.47 (s, aromatic C), 176.14 (s, C-1). – MS (70 eV): *m/z* (%) = 194 (49) [M^+], 107 (98), 88 (100).

$C_{11}H_{14}O_3$ (194.2) Calcd. C 68.01 H 7.26
Found C 68.32 H 7.11

CAS Registry Numbers

2: 112712-55-7 / **3a**: 136630-05-2 / **3b**: 136630-06-3 / **3c**: 136630-07-4 / **4a**: 76549-05-8 / **4b**: 136734-11-7 / **4c**: 136734-12-8 / PhCHO: 100-52-7 / 4-$MeOC_6H_4CHO$: 123-11-5 / 4-$O_2NC_6H_4$-CHO: 555-16-8

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