Pergamon

Tetrahedron: Asymmetry, Vol. 7, No. 1, pp. 273-276, 1996

0957-4166/96 $15.00 + 0.00

0957-4166(95)00444-0

Chiral N-Substituted 4,5,6,7-Tetrahydroindoles

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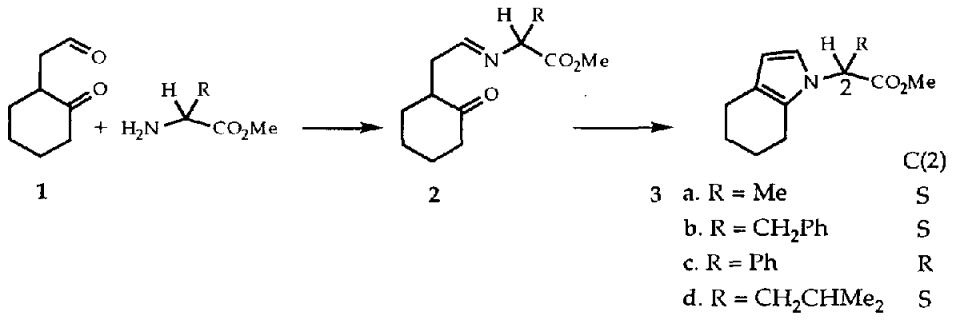
Abstract: 2-Formylmethylcyclohexanone reacts with α-amino esters in dry dichloromethane at room temperature to give homochiral N-substituted 4,5,6,7-tetrahydroindoles in good yield. No Pictet-Spengler products are observed with histidine or tryptophan esters.

There are many methods for the construction of the pyrrole ring system.[1] One of these is the Paal -Knorr synthesis, a long established method, involving reaction of primary amines (including hydroxylamines and hydrazines) with 1,4-dicarbonyl compounds[2] or their masked equivalent.[3]

In connection with other studies we were interested in preparing monoimines **2** of 2-formylmethylcyclohexanone **1** (Scheme). However, when **1** was reacted with chiral α-amino esters at room temperature in methylene chloride for 1h in the presence of 4Å molecular sieves the products, which were obtained in good yield, were the corresponding N-substituted 4,5,6,7-tetrahydroindoles **3a-d** (Table 1).



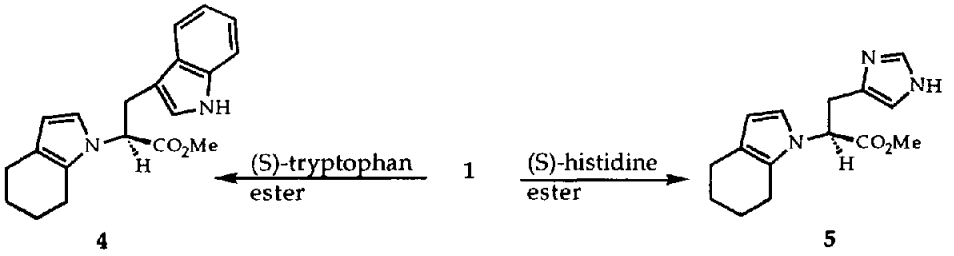


Table 1. Reaction of **1** with α-amino esters to give homochiral 4,5,6,7-tetraydroindoles **3a-d**, **4** and **5**[a]

Amino Ester	Product(%)	%ee[b]	$[\alpha]_D$[d]
alanine	**3a**(70)	92.2	-51.47
phenylalanine	**3b**(69)	99.0	-61.27
phenylglycine	**3c**(68)	100.0	+71.85
leucine	**3d**(66)	99.6	-39.26
tryptophan	**4**(68)	96.8	-49.11
histidine[c]	**5**(56)	96.8	-65.97

a. Reactions carried out at room temperature for 1h in dry dichloromethane containing 4Å molecular sieves.
b. % ee determined by chiral h.p.l.c. using a Chiralcel OJ column except for tryptophan when a Chiralpak AD column was used.
c. Reaction time 16h. Anhy. $MgSO_4$ replacing 4Å molecular sieves.
d. All specific rotations were determined for chloroform solutions.

Analogous reactions could be carried out with tryptophan and histidine methyl esters although in the latter case the reaction conditions were slightly modified. Imines of these latter two amino esters are prone to Pictet-Spengler cyclisation[4] but the mild reaction conditions suppressed this process.

Analysis of the products by chiral h.p.l.c. (Table 1) showed little if any racemisation of the α-amino ester centre occurred except for alanine ester.

Experimental. General experimental conditions were as previously described.[5] Specific rotations were measured at ambient temperature using an Optical Activity Ltd., AA-1000 polarimeter. Chiral h.p.l.c. was performed using Chiralcel OJ or Chiralpak AD columns eluting with 95:5v/v hexane - Pr^iOH at 1ml/min using 254nm detection wavelength.

General procedure for pyrrole preparation. A mixture of aldehyde (1eq), α-amino ester (1.05eq) and 4Å molecular sieves in dry dichloromethane was stirred at room temperature for 1h. After the removal of the molecular sieves the solvent was evaporated and the crude product was purified by flash chromatography eluting with 1:1v/v ether-petroleum ether.

Tetrahydroindole 3a. Aldehyde **1** (2g, 14.29mmol) and (S)-alanine methyl ester (1.55g, 14.99mmol) gave the **product** as a pale yellow oil (2.07g, 70%) (Found: C, 69.55; H, 8.25; N, 6.75. $C_{12}H_{17}O_2N$ requires C, 69.65; H, 8.35; N, 6.8%); δ 1.75(m, 7H, Me and 2xCH_2), 2.48(m, 4H, 2xCH_2), 3.71(s, 1H, OMe), 4.70(q, 1H, J7.2Hz, NCH) and 5.99 and 6.65(2xs, 2x1H, pyrrole H); m/z(%) 207(M^+,57), 179(29), 148(96) and 120(100).

Tetrhydroindole 3b. Aldehyde **1** (1g, 7.14mmol) and (S)-phenylalanine methyl ester (1.34g, 7.49mmol) gave the **product** as a pale yellow oil (1.39g 69%) (Found: C, 76.05; H, 7.6; N, 4.75. $C_{18}H_{21}O_2N$ requires C, 76.3; H, 7.45; N, 4.95%); δ 1.58(m, 4H, 2xCH_2), 2.39(m, 4H, 2xCH_2), 3.17(dd, 1H, J8.6, 13.6Hz, PhCH),

3.38(dd, 1H, J6.5, 13.6Hz, PhCH), 3.68(s, 3H, OMe), 4.67(t, 1H, J6.6Hz, NCH), 6.00(s, 1H, pyrrole H), 6.77(s, 1H, pyrrole H) and 7.09(m, 5H, PhH); m/z(%) 283(M^+,100), 224(62), 192(66), 120(53) and 91(59).

Tetrahydroindole 3c. Aldehyde **1** (1g, 7.14mmol) and (R)-phenylglycine methyl ester (1.24g, 7.49mmol) gave the **product** as a pale yellow oil (1.31g, 68%) (Found: C, .75.55; H, 7.0; N, 5.8. $C_{17}H_{19}O_2N$ requires C, 75.8; H, 7.1; N, 5.2%); δ 1.77(m, 2H, 2xCH_2), 2.48(m, 2H, 2xCH_2), 3.79(s, 3H, OMe), 5.79(s, 1H, NCH), 5.95 and 6.52(2xs, 2x1H, pyrrole H), and 7.30(m, 5H, PhH); m/z(%) 269(M^+,68), 210(100), 149(8), 120(65) and 77(22).

Tetrahydroindole 3d. Aldehyde 1 (1g, 7.14mmol) and (S)-leucine methyl ester (1.09g, 7.49mmol) gave the **product** as a pale yellow oil (1.17g, 66%) (Found: C, 72.2; H, 9.3; N, 5.4. $C_{15}H_{23}O_2N$ requires C, 72.25; H, 9.3; N, 5.6%); δ 0.98(d, 6H, 2xMe), 1.59(m, 1H, C<u>H</u>Me_2), 1.83(m, 6H, 3xCH_2), 2.51(m, 4H, 2xCH_2), 3.70(s, 3H, OMe), 4.62(t, 1H, J6.8Hz, NCH) and 5.99 and 6.66(2xs, 2x1H, pyrrole H); m/z(%) 249(M^+,46), 193(100), 190(33) and 120(21).

Tetrahydroindole 4. Aldehyde **1** (1g, 7.14mmol) and (S)-tryptophan methyl ester(1.64g, 7.49mmol) gave the **product** as a pale yellow gum (1.56g, 68%) (Found: C, 73.9; H, 6.55; N, 8.55. $C_{20}H_{22}O_2N_2$ requires C, 74.5; H, 6.85; N, 8.7%); δ 1.63(m, 4H, 2xCH_2), 2.30(m, 4H, 2xCH_2), 3.30(dd, 1H, J6.4, 14.5Hz, indole-CH), 3.64(m, 4H, OMe and indole-CH), 4.80(t, 1H, J7.4Hz, NCH), 6.03 and 6.53(2xs, 2x1H, pyrrole H), 6.84(s, 1H, indole H), 7.29(m, 4H, indole H) and 7.93(s, 1H, NH); m/z(%) 322(M^+,44), 263(15), 192(6), 130(100) and 120(9).

Tetrhydroindole 5. A mixture of (S)-histidine methyl ester hydrochloride (1.2eq, 4.29mmol, 1.04g), dry triethylamine (1.3eq, 4.64mmol, 0.47g, 0.65ml) and anhydrous magnesium sulphate was stirred in dry dichloromethane for 1h before the addition of aldehyde **1** (1eq, 3.57mmol, 0.5g). After stirring at room temperature for a further 16h, the suspension was filtered and the filtrate evaporated in vacuo. The residual oil was purified by flash chromatography eluting with 9:1v/v ethyl acetate-methanol to afford the product as a pale yellow gum (0.55g, 56%). Accurate mass: 273.1481. $C_{15}H_{19}O_2N_3$ requires 273.1477. δ 1.70(m, 4H, 2xCH_2), 2.33(m, 4H, 2xCH_2), 3.21(dd, 1H, J6.3, 14.7Hz, imidazole-CH), 3.46(dd, 1H, J6.3, 14.7Hz, imidazole-CH), 3.66(s, 3H, OMe), 4.86(t, 1H, J7.7Hz, NCH), 5.97 and 6.58(2xs, 2x1H, pyrrole H) and 6.70 and 7.49(2xs, 1H, imidazole H); m/z(%) 273(M^+,90), 243(8), 214(28), 192(64), 120(100) and 81(24).

We thank Leeds University for support.

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(*Received in UK* 27 *October* 1995)