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ASYMMETRIC SYNTHESIS IX[1] : PREPARATION OF CHIRAL α -SUBSTITUTED PHENETHYLAMINES

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ABSTRACT : (S)-N-methyl- α-methyl-phenethylamines 5a-d were obtained in 56-62 % e.e. from the chiral synthon (-)-N-cyanomethyl-4-phenyl-1,3-oxazolidine-1.

Despite their simple structure and important biological activities the asymmetric synthesis of amphetamines has not been the subject of many published work[2]. The recent publication of Takahashi[3] describing the synthesis of chiral 1-alkyl-2-phenylethylamines from 4-phenyl-1,3-oxazolidines prompts us to report the results of our investigations in this area.

In conjunction with our interest in preparation of optically active amines, aminoalcohols and aminoacids we have designed a new N-cyanomethyl-1,3-oxazolidine synthon 1[4]. In recent years, α-aminonitriles have been demonstrated to be useful for alkylation of the α position of the amino group leading to α -substituted amines after decyanation[5]. Our strategy for the

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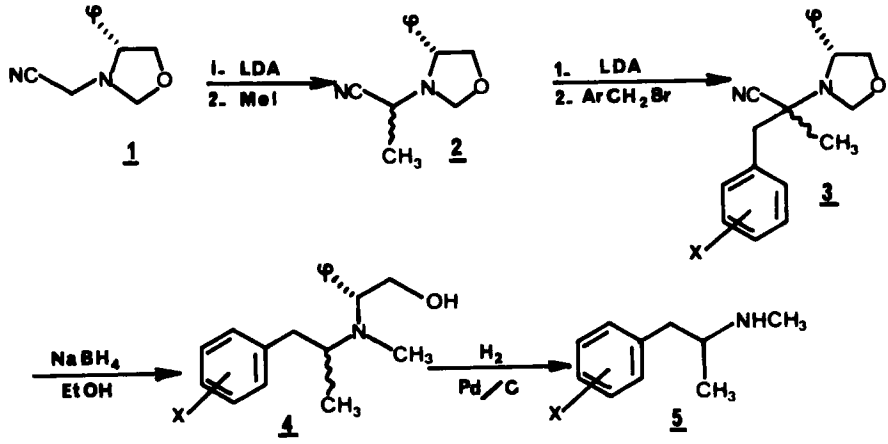
Scheme



a X = H ; b X = 4-OCH$_3$; c X = 3-OCH$_3$; d X = 4-CH$_3$; e X = 4 Cl

Table

Diastereomeric excesses and chemical shifts of the CH_3 and N-CH_3 signals in the ^1H NMR spectra of the diastereomeric mixture of 4 ($CDCl_3$, 200 MHz)

		CH_3		N-CH_3	
Compound	de %	major	minor	major	minor
4a	66	0.86	0.71	2.22	2.40
4b	64	0.83	0.69	2.21	2.37
4c	66	0.85	0.72	2.21	2.37
4d	64	0.83	0.70	2.20	2.35
4e	66	0.84	0.72	2.19	2.34

synthesis of α-substituted phenethylamines 5 is based upon the double alkylation of the aminonitrile 1 followed by a stereoselective decyanation.

Thus, sequential dialkylation of 1 under the conditions previously described[4] afforded 1,3-oxazolidines 3a-e (Scheme) that, without isolation were subjected to reductive decyanation in EtOH using $NaBH_4$ at room temperature. The separation of the diastereomers 3a-e was possible but not helpful since the decyanation reaction which is an elimination-addition process was proved to be non-stereospecific. Compounds 4a-e, isolated as viscous oils, consist of two diastereomers. The d.e.s. were measured by integration of the two methyl signals in the ^1H NMR spectra of the crude mixture (Table). In the course of this work no separation of the diastereomers 4a-e was achieved and the chiral appendage of 4a-e was removed by hydrogenolysis (Pd/C, 10 %, MeOH, rt, 12h) giving (S)-N-methyl-α-methyl-phenethylamines 5a-d[6] in 56-62 % e.e. (Table). The e.e. values for compounds 5 were determined by polarimetry in the case of 5a and 5c and by the ^1H NMR spectra of the Mosher's amides[7] in the case of 5b and 5d. The good agreement of d.e.s. for 4 and e.e. for 5 demonstrated that no racemisation occurred in the hydrogenolysis step.

In conclusion, the procedure described here should be valuable for the synthesis of various α-alkyl phenethylamines since alkylation of synthon 1 can be achieved with a series of alkyl and benzyl halides. Separation of the diastereomers 4 would lead after hydrogenolysis of the chiral auxiliary to optically pure R or S amphetamines 5.

EXPERIMENTAL SECTION

Preparation of 3a

The following procedure is typical of the experimental conditions used for the preparation of compounds 3. Compounds 3 are used without purification for the next step.

To a stirred solution of LDA/HMPA (1/1 ; 5.10^{-3} mol, prepared from 3.12 mL of Buli 1.6 M and 0.75 mL of diisopropylamine at - 10°/- 30° C under a nitrogen atmosphere) in THF (20 mL) was added 2[4] (0.909 g, 45.10^{-4} mol, THF, - 78° C) via syringe over 5 min. After 20 min. the resultant anion solution was added benzyl bromide (2 equiv.) and the mixture was stirred at - 78° C for 1 h, quenched by NH_4Cl then extracted with ether dried and concentrated to dryness. Flash chromatography of the residual oil (SiO_2, hexane-AcOEt, 80-20) yielded compound 3a as a mixture of diastereomers :

MS m/z (relative intensity) 292 ($M^{+\cdot}$, 1), 277 (66), 251 (18), 220 (13), 201 (100), 157 (25), 132 (26), 105 (54), 91 (74), 81 (56).
^1H NMR ($CDCl_3$, 200 MHz) (ppm) :
major compound : 1.08 (s, 3H, CH_3), 2.89 (d, J = 13.5 Hz, 1H, CH_2 Ph), 3.13 (d, J = 13.5 Hz, 1H, CH_2Ph), 4.86 (d, J = 4Hz, 1H, N-CH-O), 5.02 (d, J = 4Hz, 1H, N-CH-O)
minor compound : 1.34 (s, 3H, CH_3), 2.39 (d, J = 13.5 Hz, 1H, CH_2 Ph), 3.03 (d, J = 13.5 Hz, 1H, CH_2Ph), 4.69 (d, J = 3.5 Hz, 1H, N-CH-O), 4.92 (d, J = 3.5 Hz, 1H, N-CH-O)
anal. calcd. for $C_{19}H_{20}N_2O$: C, 77.52 ; H, 6.80 ; N, 9.52.
found : C, 77.64 ; H, 6.70 ; N, 9.55.

Preparation of 4

$NaBH_4$ (1.1 eq.) was added portionwise to a solution of 3 in EtOH (∿ 0.4 M) ; stirring was continued at room temperature overnight.

The solvent was removed and the residue taken in CH_2Cl_2, washed with water then with brine, dried over Na_2SO_4 and evaporated to dryness. The oily residue was purified by flash-chromatography (CH_2Cl_2-MeOH : 95-5)

4a oil (30 % yield from 1)
MS (m/z, relative intensity) : 238 ($M^{+\cdot}$ - 31, 24), 180 (34), 178 (100), 121 (24), 71 (34)
^1H NMR (see table)
anal. calcd. for $C_{18}H_{23}NO$: C, 77.32 ; H, 8.25 ; N, 5.01
found : C, 77.21 ; H, 8.17 : N, 5.27

4b oil (29 % yield from 1)
MS (m/z, relative intensity) : 268 ($M^{+\cdot}$ - 31, 4), 191 (8), 178 (100), 161 (9), 121 (35), 103 (14), 91 (16)
^1H NMR (see table)
anal. calcd. for $C_{19}H_{25}NO_2$: C, 76.15 : H, 8.35 : N, 4.67
found : C, 76.08 ; H, 8.26 ; N, 4.52

4c oil (25 % yield from 1)
MS (m/z, relative intensity) : 268 ($M^{+\cdot}$ - 31, 15), 178 (100), 149 (6), 121 (27), 103 (12), 91 (9)
^1H NMR (see table)
anal. calcd for $C_{19}H_{25}NO_2$: C, 76.15 ; H, 8.35 ; N, 4.67
found : C, 76.09 ; H, 8.12 ; N, 4.57

4d oil (21 % yield from 1)
MS (m/z, relative intensity) : 252 ($M^{+\cdot}$ - 31, 20), 178 (100), 121 (65), 105 (62), 103 (49), 91 (35), 77 (27)
^1H NMR (see table)
anal. calcd. for $C_{19}H_{25}NO$: C, 80.48 ; H, 8.82 ; N, 4.94
found : C, 80.72 ; H, 8.78 ; N, 4.87

4e oil (26 % yield from 1)
MS (m/z, relative intensity) : 272, 274 ($M^{+\cdot}$ - 31, 14, 5), 178 (100), 125 (22), 121 (25), 103 (21), 91 (18), 77 (10), 58 (84)
^1H NMR (see table)
anal. calcd. for $C_{18}H_{28}NOCl$: C, 71.06 ; H, 7.23 ; N, 4.60
found : C, 70.86 ; H, 7.41 ; N, 4.55

Preparation of 5

Compound 4 dissolved in methanol ($\sim$ 0.2 M) was submitted to hydrogenolysis at room temperature and atmospheric pressure in presence of 10 % Pd/C overnight. The reaction mixture was then filtered through a celite bed and the filtrate evaporated in vacuo to yield an oily residue which was purified by flash chromatography on silica (CH_2Cl_2-MeOH).

5a mp. 35-37° (solidified oil) Y : 90 %
^1H NMR ($CDCl_3$, 80 MHz) δ (ppm) : 1.03 (d, J = 7.5 Hz, 3H, CH_3), 1.57 (s, 1H, NH), 2.35 (s, 3H, N-CH_3), 2.42-2.95 (m, 3H), 7.15 (s, 5H, Ar)
MS : m/z (relative intensity), 134 ($M^{+\cdot}$ - 31, 10), 119 (5), 117 (5), 91 (45), 65 (16), 58 (100)
anal. calcd. for $C_{10}H_{15}N$: C, 80.53 ; H, 10.06 ;
found : C, 80.37 ; H, 9.73

5a-HCl mp 170° (EtOH) (lit[2c] 172°)
$[\alpha]_D^{25}$ 12.0° (H_2O, c 1.2), lit[2c] : $[\alpha]_D^{25}$ 19.3° (H_2O, c 1.2) ; e.e. 62 %

5b oil (Y : 55 %), $[\alpha]_D^{25}$ 1.2° ($CHCl_3$, c 1.6) ; e.e. 56 %
^1H NMR ($CDCl_3$, 80 MHz) δ (ppm) : 1.06 (d, J = 7Hz, 3H, CH_3), 2.16 (s, 1H, NH), 2.40 (s, 3H, N-CH_3), 2.47-2.95 (m, 3H), 3.77 (s, 3H, OCH_3), 6.82 (d, J = 8 Hz, 2H, ar.), 7.10 (d, J = 8 Hz, 2H, Ar)
MS : m/z (relative intensity), 179 ($M^{+\cdot}$, 2), 178 (2), 164 (3), 121 (20), 72 (25), 58 (100)

5c oil (Y : 42 %), $[\alpha]_D^{25}$ 5.8° (CH_2Cl_2, c 1.98) lit[2c] $[\alpha]_D^{23}$ 9.7° (CH_2Cl_2, c 2) ; e.e. 60 %
^1H NMR ($CDCl_3$, 80 MHz) δ (ppm) : 1.06 (d, J = 7 Hz, 3H, CH_3), 1.78 (s, 1H, NH), 2.38 (s, 3H, N-CH_3), 2.48-3.16 (m, 3H), 3.77 (s, 3H, OCH_3), 6.58-7.60 (m, 4H, Ar)
MS : m/z (relative intensity), 179 ($M^{+\cdot}$, 5), 164 (6), 148 (13), 121 (17), 91 (12), 96 (7), 72 (11), 58 (100)

5d oil (Y : 45 %) $[\alpha]_D^{25}$ 2.7° ($CHCl_3$, c 0.6) ; e.e. 62 %
^1H NMR ($CDCL_3$, 80 MHz) δ (ppm), 1.05 (d, J = 7.5 Hz, 3H, CH_3), 1.37 (s, 1H, NH), 2.28 (s, 3H, Ar-$C\underline{H}_3$), 2.37 (s, 3H, N-CH_3), 2.5-3.1 (m, 3H), 7.12 (m, 4H, Ar)
MS : m/z (relative intensity) 163 ($M^{+\cdot}$, 2), 148 (3), 105 (6), 91 (4), 77 (4), 58 (100)

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