Efficient Stereoconservative Syntheses of 1-Substituted (S)- and (R)-2-Aminomethylpyrrolidines[#]

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Three-step stereoconservative syntheses of chiral 1-substituted 2-aminomethylpyrrolidines with high optical purities from D- or L-proline are described. The key intermediates, 1-substituted prolinamides, were obtained by N,O-dialkylation of proline followed by ammonolysis or by 1-alkylation of prolinamide. Reduction furnished the optically pure (about 99 % e.e.) pyrrolidine derivatives, which are useful as intermediates in the preparation of antipsychotic substituted benzamides.

During recent years the substituted 2-methoxybenzamides have received much attention as a new class of atypical antipsychotic agents capable of blocking central dopamine-D_2 receptors.[1] The most widely investigated group consists of 1-substituted 2-[(2-methoxybenzamido)methyl]-pyrrolidine derivatives 1.[2] The 1-substituent in the pyrrolidine ring can vary from small alkyl, alkenyl or cyclo-alkyl-methyl groups to more lipophilic benzyl derivatives. In the former cases, the (S)-enantiomers are the more active ones, whereas the stereoselectivity is reversed for the 1-benzylpyrrolidine derivatives.[2–4] In our investigations we required general and efficient routes to the optically pure 1-substituted 2-(aminomethyl)pyrrolidines 2 with the appropriate stereochemistry. Furthermore, the syntheses should be adaptable for large-scale preparations.
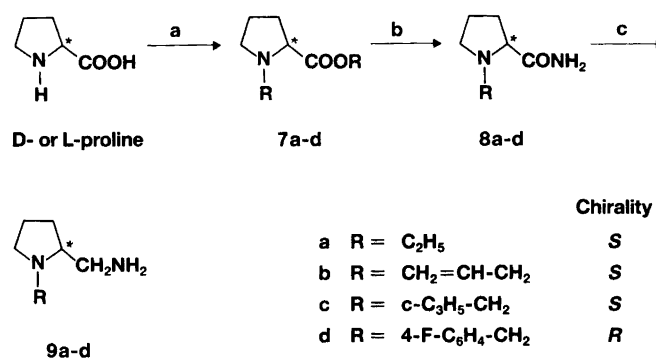

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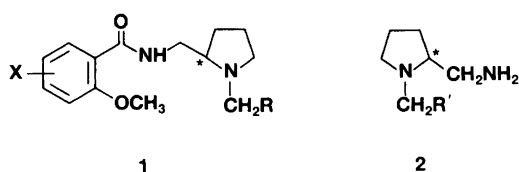
Methods for resolving some of the racemic amines (2) have been described previously.[5] However, a substantial loss of material is inevitable and also expensive resolving agents are often employed. A more direct and attractive methodology has been based on a stereoconservative[6] transformation of chiral starting materials, e.g. D- or L-proline, into the enantiomerically pure amines 2. In one

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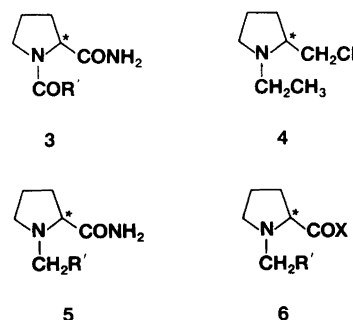
process disclosed in a patent, proline (D or L) is converted into prolinamide which is acylated (3) and subsequently reduced to give the amines 2.[7] This scarcely described method introduces the 1-substituent in a stepwise acylation–reduction sequence. This is also the case in another patent synthesis from L-proline involving N-acetylation, reduction of both carbonyl groups, chlorination (4) and amination.[8] The amine obtained (2, R^1 = CH_3) was not characterized but acylated to give the substituted benzamide (S)-sulpiride and purified as such. The method has the inherent problem of competing ring-expansion of 4 during the amination to give the corresponding 3-aminopiperidine.[9] Our efforts were directed towards a direct introduction of the 1-substituent without the need for a two-step sequence. Thus, the easily reducible chiral 1-substituted prolinamides 5 were identified as key intermediates. Two synthetic routes are obvious, i.e. 1-alkylation of prolinamide or amination of a suitable 1-substituted prolinoyl derivative 6. The present paper describes the application of this strategy into a short and efficient stereoconservative method producing either the (S)- or (R)-enantiomers of pyrrolidines 2 with high optical purities starting from L- or D-proline, respectively.[10]

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Chirality

		R =		
a	R =	C_2H_5		S
b	R =	$CH_2=CH-CH_2$		S
c	R =	$c-C_3H_5-CH_2$		S
d	R =	$4-F-C_6H_4-CH_2$		R

9a-d

Scheme 1. Reagents: (a) R-hal, K_2CO_3, DMF; (b) NH_3, CH_3OH; (c) $LiAlH_4$, THF or $NaAlH_2(OCH_2CH_2OCH_3)_2$, toluene.

Results and discussion

In the synthesis of the chiral prolinamide **5** via the acyl derivative **6**, an O,N-dialkylation of proline would have the added advantage of activating the carboxy group as an ester simultaneously with the direct introduction of the 1-alkyl group (avoiding the acylation–reduction sequence). This principle was explored for four different types of 1-substituents as outlined in Scheme 1. The dialkylation of proline to yield compounds **7 a–d** was performed smoothly in moderate to good yields employing the appropriate halide and one equivalent of potassium carbonate in N,N-dimethylformamide or dimethyl sulfoxide. However, the alkylation of L-proline with chloromethylcyclopropane for the preparation of **7c** was sluggish in spite of an added catalytic amount of potassium iodide. The optical purity of the ethyl ester **7a** was determined by ^{1}H NMR spectroscopy, after the addition of the chiral solvating agent (R)-1-(9-anthryl)-2,2,2-trifluoro-ethanol (Pirkle's alcohol), which induce non-equivalence for several protons. No racemization could be detected. Clearly, chiral N-alkylated proline esters may also be prepared by a stepwise sequence involving esterification followed by N-alkylation in the conventional manner or by reductive alkylation as exemplified in the synthesis of the 1-propyl derivative **9e** (Scheme 2).

In general, the aminolysis of esters is a slow reaction and this was also found to be the case when the ethyl ester **7a** was treated with methanolic ammonia at room temperature. However, complete conversion could be obtained by using a mixture of liquid ammonia and methanol (1:1) at 50 °C in a pressure cylinder. Under these relatively mild reaction conditions no tendency to racemization could be detected when the optical purity to the product **8a** was

analyzed on a chiral GLC column. The obvious limitations of this method urged us to develop a catalyzed conversion of proline esters in to the corresponding amides. We found that, in comparison with a number of commonly used catalysts, cyanide ion was the most efficient catalyst for this transformation.[11] Thus, a marked increase in the reaction rate was found when the ester **7a** was treated with a solution of 10 M ammonia in methanol and 10 mol % sodium cyanide at 50 °C. Also, we found that transesterification with the solvent occurred to a relatively large extent. The pyrrolidine carboxamide **8b** was prepared by this cyanide-catalyzed ammonolysis, which was much faster than the uncatalyzed syntheses of the amides **8c** and **8d**. Surprisingly, the ammonolysis of the 1-propyl substituted ester **7e** required an extended reaction time despite the addition of cyanide catalyst. The (R)-carboxamide **8d** was also prepared in a good yield by N-alkylation of D-prolinamide by the same method as described above for the O,N-dialkylation of proline. The racemic amide **5** (R^1 = H) has been obtained by ammonolysis of the corresponding methyl ester.[12]

A number of reagents are available for the reduction of primary amides to amines, e.g. $LiAlH_4$, $NaBH_4$ complexes with metal salts or carboxylic acids, $NaAlH_2$($OCH_2CH_2OCH_3$)$_2$ and borane. Attempts to reduce **8a** with borane in THF resulted in an incomplete conversion of the starting material. As anticipated, $LiAlH_4$ reduction furnished the target amines in good yields. Thus, the amines **9a** and **9c** were prepared in 65–70 % yield using $LiAlH_4$ in refluxing THF. For comparative purposes the amine **9a** was also synthesized employing the acetic acid complex with $NaBH_4$ in dioxane. However, the work-up procedure was rather lengthy in this case. The hydride

7e   8e   9e
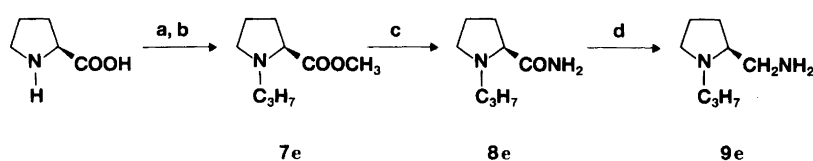
Scheme 2. Reagents: (a) $SOCl_2$, CH_3OH; (b) C_2H_5CHO, H_2/Pd, CH_3OH; (c) NH_3, CH_3OH; (d) $NaAlH_2(OCH_2CH_2OCH_3)_2$, toluene.

complex $NaAlH_2(OCH_2CH_2OCH_3)_2$ in toluene solution proved to be a satisfactory and manageable reagent when applied to the reduction of the amides **8b** and **8e**. The enantiomeric purity of the target amines **9a,b** and **9d,e** was determined by capillary GLC after derivatization with O-methyl mandeloyl chloride or Mosher's acid chloride (2-methoxy-2-trifluoromethylphenylacetyl chloride) and was found to be high, i.e. 99 % e.e., with one exception (97.5 % e.e. in the $LiAlH_4$ reduction of **8a**). The optical purity of the amine **9c** was judged by comparison of the optical rotation with literature values.

In summary, we have described a short, efficient and highly stereoconservative method for the preparation of the enantiomers of 1-substituted 2-aminomethylpyrrolidines (**2**) with high optical purities from D- or L-proline. The new procedure offers the advantage of being suitable for the preparation of these amines on a larger scale.

Experimental

GLC was run on an SE-30 capillary column, and the amounts were determined using a Hewlett-Packard 3390 A integrator, assuming identical response factors. A Chirasil-Val column was used for the determination of the optical purities of the amides **8**. ^1H NMR spectra were recorded on a Varian EM 360 A or a JEOL FX 200 spectrometer. Mass spectra were obtained on an LKB 9000 (EI/70 eV) or an LKB 2091 (EI/70 eV or CI/NH$_3$) instrument. Optical rotations were measured on an Optical Activity AA-100 polarimeter. Melting points were obtained on a Mettler FP 61 apparatus in open capillary tubes and are uncorrected. Elemental analyses were performed by Analytische Laboratorium, Elbach, West Germany, and are to within ±0.4 % of the theoretical values unless otherwise noted.

(−)-*Ethyl (S)-1-ethyl-2-pyrrolidinecarboxylate* (**7a**). Ethyl iodide (80.3 ml, 1.0 mol) was added dropwise to a stirred suspension of L-proline (57.5 g, 0.5 mol) and K_2CO_3 (138 g, 1.0 mol) in 500 ml dry DMF for 3 h at room temperature. Stirring was continued overnight. The reaction mixture was poured onto ice–water and extracted with Et_2O. The combined ether layers were washed with water and brine, and were dried with $MgSO_4$. The solvent was evaporated and distillation of the crude product gave 60.6 g (71 %) of the title ester. B.p. 85–87 °C/2 kPa. $[\alpha]_D^{25}$ −88° (c 0.6, $CHCl_3$). The purity was checked by GLC analysis and was found to be 95 %. Only the (S)-isomer could be detected in the ^1H NMR spectrum after addition of (R)-1-(9-anthryl)-2,2,2-trifluoroethanol. (Both enantiomers were easily observed in the racemate). MS (EI, 70 eV): m/z (% rel.int) 171 (M, 1.1), 98 (100), 70 (11). Anal. $C_9H_{17}NO_2$: C, H, N. The esters **7b–7d** were prepared analogously unless otherwise indicated.

7b: L-Proline (0.18 mol), allyl bromide (0.43 mol) and K_2CO_3 (0.44 mol) in 200 ml DMSO. Chromatography on SiO_2 gave 17.7 g (49 %) **7b** of purity 95 % according to

GLC. MS (EI, 70 eV): m/z (% rel. int.) 195 (M, 1.2), 110 (100).

7c: L-Proline (0.11 mol), chloromethylcyclopropane (0.23 mol), KI (60 mg) and K_2CO_3 (0.24 mol) in 200 ml DMSO were allowed to react for 3 days to give 6.5 g (27 %) of the pure ester **7d** (> 99 % according to GLC). $[\alpha]_D^{22}$ −61° (c 0.12, $CHCl_3$). MS (EI, 70 eV): m/z (% rel. int.) 223 (M, 0.69), 124 (100).

7d: D-Proline (0.08 mol), 4-fluorobenzyl bromide (0.16 mol) and K_2CO_3 (0.17 mol) in 150 ml DMSO gave 22.6 g (87 %) of the crude ester **7d**. MS (EI, 70 eV): m/z (% rel. int.) 331 (M, 0.10), 178 (73), 109 (100).

(−)-*Methyl(S)-1-propyl-2-pyrrolidinecarboxylate* (**7e**). A mixture of methyl (S)-2-pyrrolidinecarboxylate hydrochloride (1.65 g, 0.01 mol), propionaldehyde (2.4 g, 0.04 mol) and 5 % Pd/C (0.3 g) in 30 ml MeOH was shaken in a Parr apparatus at 275 kPa hydrogen pressure for 2 h at room temperature. After filtration and evaporation, the residue was mixed with 10 ml of 2 M HCl and 40 ml ice–water and then extracted twice with Et_2O. Solid NaCl was added to the aqueous phase, which was made alkaline with 20 ml of 2 M NH_3 during the addition of ice. Extraction with Et_2O twice, drying ($MgSO_4$) and evaporation afforded 1.8 g of compound **7e**. $[\alpha]_D^{25}$ −85° (c 1.3, $CHCl_3$); MS (EI, 70 eV): m/z (% rel. int.) 171 (M, 1.9), 112 (100).

(−)-*(S)-1-Ethyl-2-pyrrolidinecarboxamide* (**8a**). The ester **7a**, (3.4 g, 0.02 mol) was added to a cooled solution of 10 ml MeOH and 10 ml liquid NH_3 in a stainless steel reaction bottle containing 3 g of 3 Å molecular sieves. The bottle was heated at 50 °C for 20 h. After being cooled the solvent was allowed to evaporate. The product was dissolved in dry MeOH and filtered. The filtrate was evaporated under reduced pressure to give the title compound as white crystals in quantitative yield (2.8 g). Recrystallization from hexane afforded 2.5 g (88 %) of the amide **8a**. The enantiomeric purity was determined by chromatography on a chiral GLC column (Chirasil-Val, 25 m) and found to be 99.4 % e.e. M.p. 107–108 °C (lit.[11] 110–111 °C); $[\alpha]_D^{20}$ −119° (c 0.5, MeOH) [(lit.[11] $[\alpha]_D^{20}$ −123° (c 0.8, $CHCl_3$)]. Anal. $C_7H_{14}N_2O$: C,H,N.

(−)-*(S)-1-Allyl-2-pyrrolidinecarboxamide* (**8b**). A solution of the ester **7b** (2.5 g, 12.8 mmol) and NaCN (64 mg, 1.3 mmol) in 50 ml 9 M ammonia in MeOH was stirred at 35 °C for 27 h. GLC showed complete conversion. After evaporation, the residue was dissolved in Et_2O and washed with brine. Drying (Na_2SO_4), evaporation and recrystallization from i-Pr$_2$O gave 1.6 g (81 %) of the amide **8b**. M.p. 79–81 °C; $[\alpha]_D^{20}$ −107° (c 0.9, $CHCl_3$); MS (EI, 70 eV): m/z (% rel. int.) 154 (M, 1.7), 110 (100). Found: C 61.36; H 8.65; N 17.71. Calc. for $C_8H_{14}N_2O$: C 62.31; H 9.15; N 18.17.

(−)-*(S)-1-Cyclopropylmethyl-2-pyrrolidinecarboxamide* (**8c**). The ester **7c** (6.30 g, 0.028 mol) was stirred in 400 ml

4 M ammonia in MeOH at room temperature for 21 days. Evaporation, extraction and recrystallization from i-Pr$_2$O gave 4.0 (84 %) of the amide **8c**. M.p. 86–88 °C; $[\alpha]_D^{22}$ −93° (c 0.7, CHCl$_3$). MS (EI, 70 eV): m/z (% rel. int.) 124 (100). Found: C 64.44; H 9.07; N 16.66; O 9.71. Calc. for C$_9$H$_{16}$N$_2$O: C 64.25; H 9.59; N 16.65; O 9.51.

(+)-(R)-*1-(4-Fluorobenzyl)-2-pyrrolidinecarboxamide* (**8d**). *A.* Crude **7d** (2.10 g, 6.3 mmol) was stirred in 25 ml 4 M ammonia in MeOH at room temperature for 4 days. After evaporation the residue was dissolved in Et$_2$O and extracted with 0.5 M HCl. The aqueous phase was made alkaline with ammonia and extracted twice with Et$_2$O. Drying (Na$_2$SO$_4$) and evaporation gave 1.4 g crystalline material. Recrystallization from Et$_2$O/hexane 1:1 gave 0.87 g (62 %) of the pure title amide. M.p. 79–82 °C; $[\alpha]_D^{20}$ +73° (c 0.49, CHCl$_3$); MS (EI, 70 eV): m/z (% rel. int.) 222 (M, 0.27), 178 (46), 109 (100). Anal. C$_{12}$H$_{15}$N$_2$OF: C,H,N.

B. To a mixture of (R)-prolinamide hydrochloride[13] (4.3 g, 23 mmol) and K$_2$CO$_3$ (8.3 g, 60 mmol) in 20 ml dry DMSO was added a solution of p-fluorobenzyl bromide (4.5 g, 23.5 mmol) in 3 ml DMSO at room temperature. The reaction mixture was stirred overnight, poured into 200 ml ice–water and extracted twice with Et$_2$O. The organic layer was washed with water, dried (Na$_2$SO$_4$) and evaporated. The residue was recrystallized from i-Pr$_2$O to give 4.0 g (79 %) pure **8d**. M.p. 82–83 °C; $[\alpha]_D^{22}$ +77° (c 0.8, CHCl$_3$).

(−)-(S)-*1-Propyl-2-pyrrolidinecarboxamide* (**8e**). A mixture of **7e** (1.8 g 0.01 mol) and NaCN (49 mg, 0.001 mol) in 30 ml 9 M ammonia in MeOH was heated at 45 °C for 3 days. After evaporation, the residue was dissolved in CH$_2$Cl$_2$ and washed with brine. The aqueous phase was extracted with CH$_2$Cl$_2$ and the combined organic layers were washed with brine. Drying (MgSO$_4$) and evaporation gave 1.55 g crystalline material, which was recrystallized from hexane to give 1.23 g (79 %) pure **8e**. M.p. 112–113 °C; $[\alpha]_D^{22}$ − 117° (c 1.2, CHCl$_3$). MS (CI, NH$_3$): m/z (% rel. int.) 157 (M +1, 100), 112 (32). Anal. C$_8$H$_{16}$N$_2$O: C,H,N.

(−)-(S)-*2-Aminomethyl-1-ethylpyrrolidine* (**9a**). *A.* A mixture of **8a** (0.50 g, 3.5 mmol) and LiAlH$_4$ (145 mg, 3.9 mmol) was refluxed in 25 ml dry THF overnight. The reaction was quenched by sequential addition of 0.15 ml H$_2$O, 0.15 ml 15 % aqueous NaOH and 0.45 ml H$_2$O. The mixture was filtered, dried (MgSO$_4$) and evaporated. Kugelrohr distillation of the residue afforded 0.31 g (69 %) of the title amine. $[\alpha]_D^{22}$ −92° (c 0.9, CHCl$_3$), $[\alpha]_D^{22}$ − 91° (c 1.0, DMF) [lit.[7] $[\alpha]_D^{25}$ −86° (c 0.6, DMF)]. A sample was derivatized with O-methyl mandelic acid chloride and analyzed by capillary GLC and the enantiomeric purity was determined to be 97.5 % e.e. MS (EI, 70 eV): m/z (% rel. int.) 128 (M, 1.1), 98 (100).

B. Sodium borohydride (5.0 g, 0.13 mol) was suspended in 50 ml dry dioxane. Acetic acid (7.4 mol, 0.13 mol) was added dropwise with stirring at room temperature. After 1 h, **8a** (1.8 g, 13 mmol) in 10 ml dry dioxane was added dropwise with stirring. The mixture was refluxed overnight (16 h). After being cooled the solvent was evaporated *in vacuo* to afford a white precipitate, which was suspended in water. The suspension was made acidic by the dropwise addition of HCl. After the gas evolution had subsided, the solution was made alkaline with NaOH solution and extracted several times with CH$_2$Cl$_2$. The combined extracts were dried (MgSO$_4$) and evaporated to give 2.0 g of the title product. The crude material was distilled to afford 1.1 g (65 %) **9a**. B.p. 50–52 °C/1.3 kPa. The optical purity was 99.0 % e.e., determined after derivatization with 2-methoxy-2-trifluoromethylphenylacetyl chloride.

(−)-(S)-*1-Allyl-2-aminomethylpyrrolidine* (**9b**). A solution of **8b** (1.0 g, 6.5 mmol) in 5 ml THF was added dropwise to a solution of sodium bis (2-methoxyethoxy)aluminium dihydride (3.7 g, 70 % solution in toluene, 13 mmol) and 50 ml toluene at 70 °C. After being heated for 4 h, the reaction mixture was quenched with 2 M aqueous HCl and washed twice with Et$_2$O. The aqueous phase was made alkaline with 45 % NaOH and extracted twice with EtOAc. Kugelrohr distillation of the crude product gave 270 mg (30 %) of the enantiomerically pure ($\geqq$ 99 % e.e.) amine **9b**. MS (EI, 70 eV): m/z (% rel. int.) 140 (M, 0.42), 110 (100).

(−)-(S)-*2-Aminomethyl-1-(cyclopropylmethyl)pyrrolidine* (**9c**). A mixture of **8c** (4.0 g, 24 mmol) and LiAlH$_4$ (0.99 g, 26 mmol) in 50 ml THF was refluxed overnight. After the sequential addition of 1 ml H$_2$O, 1 ml 15 % aqueous NaOH and 3 ml H$_2$O, the mixture was filtered, washed with Et$_2$O and evaporated to give 3.7 g of the crude title product. Kugelrohr distillation gave 2.4 g (65 %) of the amine **9c**. B.p. 105–110 °C/2.4 kPa; $[\alpha]_D^{22}$ −67° (c 0.8, CHCl$_3$) (lit.[7] $[\alpha]_D^{20}$ −69° (c 1.0, DMF)); MS (EI, 70 eV): m/z (% rel. int.) 154 (M, 0.17), 124 (100).

(+)-(R)-*2-Aminomethyl-1-(4-fluorobenzyl)pyrrolidine* (**9d**). Acetic acid (9.5 g, 0.16 mol) in 20 ml dioxane was added to NaBH$_4$ (6.0 g, 0.16 mol) in 50 ml dioxane. After being stirred for 0.5 h at room temperature, the mixture was cooled to 5 °C and **8d** (7.0 g, 0.03 mol) in 50 ml dioxane was added. The mixture was stirred for 0.5 h at 5 °C and then heated at reflux overnight. After evaporation of the solvent, 500 ml ice–water was added and the mixture was extracted twice with CHCl$_3$. Drying (Na$_2$SO$_4$) and evaporation gave 6.7 g of enantiomerically pure ($\geqq$ 99 % e.e.) title amine. $[\alpha]_D^{23}$ +85° (c 0.8, CHCl$_3$), [lit.[7] $[\alpha]_D^{25}$ +82° (c 0.5, DMF]. The L-tartrate salt was recrystallized from aqueous ethanol to give 8.8 g (55 %). M.p. 171–173 °C; MS (EI, 70 eV): m/z (% rel. int.) 208 (M, 20), 178 (48), 109 (100). Anal. C$_{20}$H$_{29}$FN$_2$O$_{12}$ · 0.5 H$_2$O: C,H,N.

(−)-(S)-*2-Aminomethyl-1-propylpyrrolidine* (**9e**) was made analogously to **9b** in a yield of 63 %. B.p. 68 °C/1.3 kPa; $[\alpha]_D^{22}$ −93° (c 0.9, $CHCl_3$); optical purity 99 % e.e.; MS (EI, 70 eV): *m/z* (% rel. int.) 142 (*M*, 0.2), 112 (100).

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