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Stereoselective synthesis of neutral and cationic 2-heterocyclically substituted propanamides

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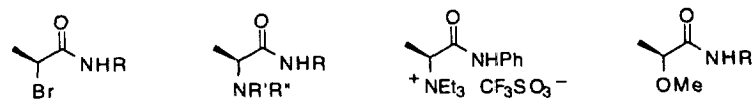
Abstract: Neutral (2*R*)-2-(1′-imidazolyl)-N-[(1′*R*)-phenylethyl]propanamide **5** and the related methylimidazolium and pyridinium salts **6–9** were easily prepared from 2-bromoamide **1a** and imidazole, N-methylimidazole and pyridine at room temperature in toluene. The stereoselectivity was lower than with other nucleophiles, Ag^+ and Ag_2O proving less selective promoters, and Ag_2O allowing racemization of starting material and side reactions to be observed. © 1997 Elsevier Science Ltd

We recently found that (*S*)-2-bromopropanamides and -anilides **1** undergo bromine substitution by a primary, secondary or tertiary amine or methanol, yielding the pertinent 2-amino (or -ammonium) amides or -alkoxamides **2–4** (Scheme 1).[1]



1 **2** **3** **4**

Only (*S*)-configuration is shown. Compound **1**: **a**, R = (*R*)-CH(CH$_3$)Ph

Scheme 1.

Substantial control of stereochemistry was found to operate, according to the use of a reactive nucleophile alone (amine) or the combination of nucleophile (amine or methanol) and a promoter, in toluene. In particular, soluble Ag^+ (triflate) and insoluble Ag_2O promote inversion or, respectively, retention of configuration in some reactions, yielding an excess of either enantiomeric or diastereomeric product, starting from a chiral non-racemic compound. On the other hand, with a nucleophile unreactive in the absence of a promoter, Ag^+ proved to yield either a retention (triethylamine) or an inversion product (methanol). From a synthetic point of view: (i) all expected products could be obtained with the desired configuration at the reaction center (in the case that only one stereoisomer was obtained, the other one was obtainable from the opposite isomer), and (ii) racemisation of the starting material was never observed.

In the present paper, we report on the behaviour of (2*S*)-2-bromo-N-[(1′*R*)-1′-phenylethyl]-propanamide **1a** and three representative heterocyclic nucleophiles, i.e. imidazole, N-methylimidazole, and pyridine, in toluene, either in the absence of a promoter, or in the presence of Ag^+ (triflate) or Ag_2O.[2]

All target products have been obtained. They have important structural features related to the natural aminoacids, from where they actually derive,[3] and were also desired for pharmacological tests.[4] However, an even more selective behaviour in the reactions with the heterocyclic nucleophiles became apparent: (a) instances of racemisation of the reacting enantiomer; (b) failure of Ag_2O to act as reliable promoter for stereochemical control; and (c) intensive decomposition of Ag_2O were,

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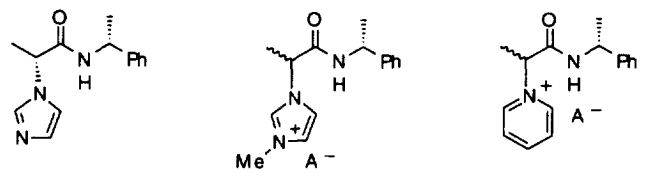
Table 1. Nucleophilic substitution in (2*S*)-2-bromo-N-[(1′*R*)-1′-phenylethyl]-propanamide (**1a**) in toluene

entry	nucleophile[a]	Ag_2O (equiv)	Ag^+ (equiv)	time (h)	substitution products (yield, %)[b]	config[c]	de
1	imidazole			45	**5** (60)	*R*	96
2	imidazole	1		5	**5** (70)	*R*	95.5
3	imidazole		1	45	**5** (71)	*R*	97.8
4	1-methylimidazole			48	**6** (52)	*S*, *R*	42
5	1-methylimidazole		1	5,5	**7** (84)	*S*	88
6	pyridine			96	**8** (32)	*S*, *R*	39
7	pyridine		1	5	**9** (94)	*S*	82

[a] Two equiv were used except in the runs without promoters, where five equiv were used. [b] The balance was given by unreacted **1a**. [c] Prevailing configuration assigned to C-2.

infact observed. Imidazole reacts with **1a** under the usual set of conditions (Table 1), slowly without a promoter or in the presence of Ag^+, faster with Ag_2O. At 60–70% conversion, the recovered **1a** is still enantiomerically pure, and the isolated **5** (Scheme 2) shows an almost quantitative diastereomeric excess of a single diastereoisomer.



5 **6**: A = Br; **7**: A = CF_3SO_3 **8**: A = Br; **9**: A = CF_3SO_3

Scheme 2.

X-Ray analysis demonstrated that it consists of the product having an inverted (*R*) configuration at the reaction center (Figure 1). In forming the neutral aminoamide **5** from protic imidazole, Ag_2O shortens the reaction time, but does not alter the stereochemistry of the unpromoted or Ag^+ promoted reactions, in contrast to previous observations with protic nucleophiles.

In the reacting systems: **1a**/Ag_2O/aprotic nucleophiles (N-methylimidazole or pyridine); hydrolysis of **1a** to the lactamide; and, respectively, decomposition with formation of a Ag mirror were noticed, excluding Ag_2O as a promoter. In the absence of a promoter or with Ag^+, the two aprotic nucleophiles showed divergent behaviour. 2-(N-Methyl-imidazolium)-propanamide bromide **6** and 2-pyridinium-propanamide bromide **8** formed slowly with no promoter, with low diastereomeric excesses, and the unreacted starting material was fully racemized. In the presence of Ag^+, the corresponding triflates **7** and **9**, formed faster with high diastereomeric excess; the starting material **1a** was recovered in a small amount and had almost unaltered diastereomeric purity. No crystals of **7** or **9** suitable for X-ray analysis have so far been obtained. However, by analogy with the stereochemical outcome (retention of configuration) observed in reactions of 2-bromo-N-benzylpropanamide with Et_3N/Ag^+ we propose that the major diastereoisomers **7** and **9** have retained configuration at the reaction center.

Nucleophilic substitution in 2-halocarboxylic acids and 2-halocarbonyls has long been known to occur via competitive mechanisms, leading to opposite stereochemistry, according to different conditions ("anomalies in Walden inversion").[5]

We believe that the combination of: (i) 2-bromocarboxamides carrying a more or less acidic amide moiety adjacent to the chiral halide group; (ii) the capricious effect of Ag^+ or Ag_2O in the presence of nucleophile and non-polar solvent; and (iii) the nucleophilic power of the leaving group (Br^-) are

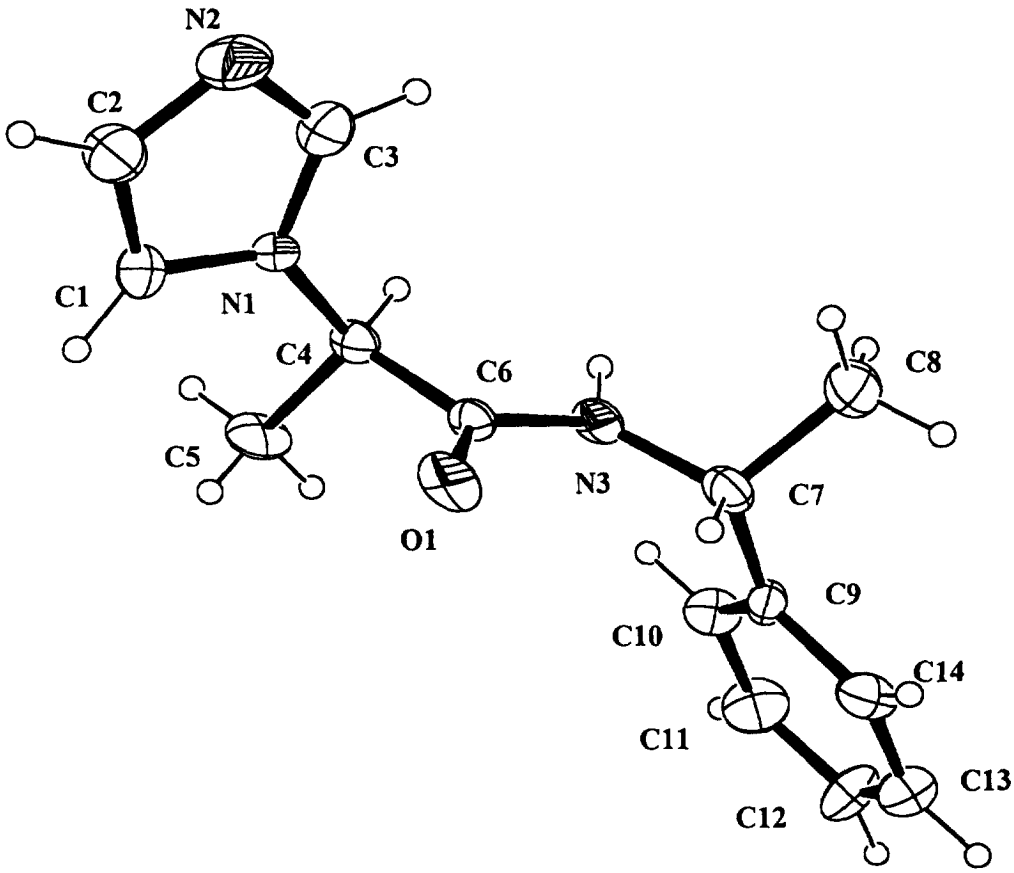


Figure 1. An ORTEP view of the compound [(2*R*)(1′*R*)-5] displaying the thermal ellipsoids at 30% probability.

factors that influence the stereochemical consequences of these reactions, whose explanation requires further studies.

Experimental

All reactions were also carried out with substrates racemic at C-2, to provide diastereomeric mixtures for the necessary comparison. All reaction mixtures were analyzed by HPLC and ^{1}H NMR to check the diastereomeric distribution before and after column chromatography, to avoid wrong conclusions, due to diastereomeric enrichment.

Analytical HPLC analysis was performed on a Waters 600E with a Waters 441 UV detector (visualization at 254 nm). A Saulentechnik silica column, packed with Eurosphere 100 (250×4.6 mm i.d., 5 μm particle size) was used; flow rate: 1.0 mL/min. Isocratic elution with variable mixtures cyclohexane/EtOAc or cyclohexane/CH_2Cl_2/MeOH, as indicated, were used. retention times (t_R) are reported. Thin layer chromatography was done with precoated plates of silica gel (Merck F-254) using the indicated solvent system. A sonicator Microsom XL 2005 with standard microprobe was used for reactions promoted by Ag_2O. All ^{1}H and ^{13}C NMR spectra were recorded on a 200 MHz spectrometer in $CDCl_3$ and/or d_6-DMSO. Chemical shifts are reported as units (ppm) downfield from tetramethylsilane. Signals relevant to the identification of diastereoisomers are italicized. IR spectra were obtained in accordance with the KBr disk technique. Melting points were determined on a Reichert–Kofler apparatus and are uncorrected. Reagents and promoters were purchased from Fluka.

(2R)-2-(1′-Imidazolyl)-N-[(1′R)-phenylethyl]propanamide [(2R)(1′R)-5]

(a) From (2*S*),(1′*R*)-**1a**[6] and imidazole (Table 1, entry 1). To a solution of (2*S*),(1′*R*)-**1a** (256 mg, 1 mmol, de=100%) in toluene (5 mL), imidazole (340 mg, 5 mmol) was added. The reaction mixture was stirred for 45 h and then evaporated to constant weight to give an oil that was analyzed by HPLC.

(b) From (2*S*),(1′*R*)-**1a**, Ag_2O and imidazole (Table 1, entry 2). To a solution of (2*S*),(1′*R*)-**1a** (256 mg, 1 mmol, de=100%) in toluene (5 mL), imidazole (136 mg, 2 mmol) and Ag_2O (232 mg, 1 mmol) were added. The reaction mixture was sonicated for 5 h and then centrifuged three times using EtOAc. The collected supernatants were concentrated to constant weight and the resulting oil analyzed by HPLC.

(c) From (2*S*),(1′*R*)-**1a**, $Ag^+CF_3SO_3^-$ and imidazole (Table 1, entry 3). To a solution of (2*S*),(1′*R*)-**1a** (256 mg, 1 mmol, de=100%) in toluene (5 mL), imidazole (136 mg, 2 mmol) and $Ag^+CF_3SO_3^-$ (257 mg, 1 mmol) were added. The reaction mixture was stirred for 45 h and then centrifuged three times using EtOAc. The collected supernatants were concentrated and the resulting oil analyzed by HPLC. In all cases, HPLC analysis (CH_2Cl_2:*c*.hexane:MeOH=50:45:5) followed by column chromatography (CH_2Cl_2:MeOH:toluene=17:2:1; R_f 0.2) gave a solid consisting *of the same major diastereoisomer*: t_R=11.62; mp 105–107°C; ^{1}H NMR δ 1.38 (d, 3H), 1.72 (d, 3H), 4.73 (q, 1H), 5.07 (m, 1H), 6.18 (br d, 1H), 6.99–7.50 (m, 8H); IR cm^{-1} 3298, 3107, 2982, 1652, 1557, 1284, 1077, 753, 700, 659. Single prisms, suitable for X-ray analysis, were obtained upon recrystallization from THF. The minor diastereoisomer had t_R=10.97, as seen in the run starting with (2*R*,*S*),(1′*R*)-**1a**. Unreacted (2*S*),(1′*R*)-**1a** (35%) recovered from the reaction without promoter had de 97%.

Crystal data of [(2*R*)(1′*R*)-**5**]. $C_{14}H_{17}N_3O$, M_r=243.3, monoclinic, *P*2$_1$, *a*=4.817(2), *b*=9.090(3), *c*=15.246(6) Å, β=96.74(3)°, V=663.0(4) Å^3, Z=2, D_x=1.219 g cm^{-3}, monochromated MoKα (λ=0.71069 Å), μ=0.793 cm^{-1}, F(000)=260, T=295 K, Enraf–Nonius CAD4 diffractometer, 1530 unique reflections measured; 864 reflections observed [I≥3σ(I)]; solutions by direct methods using SIR92;[7] full matrix least-squares refinement using MolEN;[8] non-hydrogen atoms anisotropic, hydrogen atoms included at calculated positions except HN3 which was refined isotropically. An ORTEP[9] view of the molecule is shown in Figure 1. The molecules in the crystal are connected in chains by means of N3–HN3 — O1 hydrogen bonds [N3–HN3=0.94(4) Å, N3 — O1(*x*+1, *y*, *z*)=2.930(4) Å, N3–HN3 — O1=165(3)°]. Atomic coordinates, thermal parameters, bond lengths and angles are available from the Cambridge Crystallographic Data Centre.

(2S,R)-2-(3′-Methyl-1′-imidazolyl)-N-[(1′R)-phenylethyl]-propanamide bromide [(2S,R),(1′R)-6]

To a solution of (2*S*),(1′*R*)-**1a** (256 mg, 1 mmol, de 100%) in toluene (5 mL), 1-methylimidazole (410 mg, 5 mmol) was added. The mixture was stirred for 48 h and then centrifuged. The supernatant was concentrated to constant weight to give an oil that was analyzed by HPLC: sufficient separation was not possible either in normal or reverse phases; however, certain ^{1}H NMR signals allowed us to ascertain that the two diastereoisomers were present. The diastereomeric mixture (71:29) was purified by column chromatography (R_f 0.1, CH_2Cl_2:MeOH:toluene=17:2:1) to give a solid: mp 180–183°C (Table 1, entry 4); de 42%; ^{1}H NMR δ 1.54 (d, 3H), 1.75 (d, 3H), *3.92 (s, 3H)*, 4.93 (m, 1H), 6.25 (q, 1H), 7.15–7.40 (m, 6H), *7.67 (s, 1H), 9.25 (br d, 1H), 9.68 (s, 1H)*; IR cm^{-1} 3400, 3170, 3086, 1650, 1590, 1545, 1440, 1250, 1180, 771. Anal. Calcd. for $C_{15}H_{20}BrN_3O$: C, 53.26; H, 5.96; Br, 23.62; N, 12.43. Found: C, 53.01; H, 6.07; Br, 23.50; N, 12.23. Appropriate fractions from column chromatography gave unreacted (2*S*),(1′*R*)-**1a** (40%): de 24%.

Comparison between ^{1}H NMR data of the above diastereomer and those of the diastereomeric mixture obtained from (2*R*,*S*),(1′*R*)-**1a**, allowed us to assign the following data to the minor diastereoisomer. ^{1}H NMR: δ 1.54 (d, 3H), 1.66 (d, 3H), 3.99 (s, 3H), 4.93 (m, 1H), 6.25 (q, 1H), 7.16–7.40 (m, 6H), 7.79 (s, 1H), 9.16 (br d, 1H), 9.85 (s, 1H).

(2S)-2-(3'-Methyl-1'-imidazolyl)-N-[(1'R)-phenylethyl]propanamide trifluoromethanesulfonate [(2S),(1'R)-7]

To a solution of (2*S*),(1'*R*)-**1a** (256 mg, 1 mmol, de 100%) in toluene (5 mL), 1-methylimidazole (164 mg, 2 mmol) and $Ag^+CF_3SO_3^-$ (257 mg, 1 mmol), were added. The mixture was stirred for 5.5 h and then evaporated to constant weight to give an oil that was analyzed by HPLC: sufficient separation was not possible either in normal or reverse phases; however, certain ^{1}H NMR signals allowed us to ascertain that the two diastereoisomers were present. The diastereomeric mixture (94:6) was extracted with EtOAc (3×5 mL) and the extracts, after concentration, purified by column chromatography (R_f 0.1, CH_2Cl_2:MeOH:toluene=17:2:1) to give a solid: mp 210–213°C (Table 1, entry 5); de 88%; ^{1}H NMR δ 1.47 (d, 3H), 1.73 (d, 3H), *3.84 (s, 3H)*, 4.92 (m, 1H), 5.46 (q, 1H), 7.16–7.48 (m, 6H), *7.50 (s, 1H), 8.51 (br d, 1H), 8.93 (s, 1H)*; IR cm^{-1} 3294, 3140, 1650, 1272, 1254, 1160, 1032, 758, 642.

Comparison between ^{1}H NMR data of the above diastereomer and those of the diastereomeric mixture obtained from (2*R,S*),(1'*R*)-**1a**, allowed us to assign the following data to the minor diastereoisomer. ^{1}H NMR ($CDCl_3$+DMSO-d6): δ 1.48 (d, 3H), 1.77 (d, 3H), *3.93 (s, 3H)*, 4.95 (m, 1H), 5.27 (q, 1H), 7.16–7.40 (m, 6H), *7.61 (s, 1H), 9.71 (br d, 1H), 9.26 (s, 1H).*

(2S,R)-2-(1'-Pyridyl)-N-[(1'R)-phenylethyl]propanamide, bromide [(2S,R),(1'R)-8]

From (2*S*),(1'*R*)-**1a** (de 100%) and pyridine as above for **6**. The reaction mixture was analyzed by HPLC: sufficient separation was not possible either in normal or reverse phases; however, certain ^{1}H NMR signals, allowed us to ascertain that the two diastereoisomers were present. The product was purified by column chromatography (R_f 0.1, CH_2Cl_2:MeOH:toluene=17:2:1) to give a solid: mp 290°C (dec.) (Table 1, entry 6); de 39%; ^{1}H NMR: δ 1.50 (d, 3H), *1.81 (d, 3H)*, 4.88 (m, 1H), 6.87 (q, 1H), 7.09–7.40 (m, 5H), 7.92–8.09 (m, 2H), 8.35–8.50 (m, 1H), *9.52 (d, 2H), 9.60 (br d, 1H)*; IR cm^{-1} 3447, 3019, 1675, 1554, 1483, 1232, 764, 706, 680. Anal. Calcd. for $C_{16}H_{19}BrN_2O$: C, 57.32; H, 5.71; Br, 23.83; N, 8.36. Found: C, 56.98; H, 5.85; Br, 23.75; N, 8.21. Appropriate fractions from column chromatography gave unreacted (2*S*),(1'*R*)-**1a** (67%): de 26%.

Comparison between ^{1}H NMR data of the above diastereomer and those of the diastereomeric mixture obtained from (2*R,S*),(1'*R*)-**1b**, allowed us to assign the following data to the minor diastereoisomer. ^{1}H NMR: δ 1.57 (d, 3H), *1.91 (d, 3H)*, 4.92 (m, 1H), 6.93 (q, 1H), 7.12–7.42 (m, 5H), 7.93–8.11 (m, 2H), 8.37–8.53 (m, 1H), *9.46 (d, 2H), 9.77 (br d, 1H).*

In an identical run but with only 2 equiv of pyridine, we obtained (2*S,R*),(1'*R*)-**8** (134 h, 12%): de 54% and recovery (2*S*),(1'*R*)-**1a** (86%): de 42%.

(2S)-2-(1'-Pyridyl)-N-[(1'R)-phenylethyl]propanamide trifluoromethanesulfonate [(2S),(1'R)-9]

From (2*S*),(1'*R*)-**1a** (de 100%), pyridine and $Ag^+CF_3SO_3^-$, in toluene, as above for **7**. The reaction mixture was analyzed by HPLC: sufficient separation was not possible either in normal or reverse phases; however, certain ^{1}H NMR signals, allowed us to ascertain that the two diastereoisomers were present. The product was purified by column chromatography (CH_2Cl_2:MeOH:toluene=17:2:1, R_f 0.1) to give a solid: mp 160–162°C (Table 1, entry 7); de 82%; ^{1}H NMR: δ 1.49 (d, 3H), 1.90 (d, 3H), 4.91 (m, 1H), 5.92 (q, 1H), 7.18–7.47 (m, 5H), 7.80–7.97 (m, 2H), 8.60 (br d, 1H), 8.69–8.73 (m, 1H), *9.04 (d, 2H)*; IR cm^{-1} 3290, 1653, 1280, 1253, 1170, 1037, 760, 634. Anal. Calcd. for $C_{17}H_{19}F_3N_2O_4S$: C, 50.49; H, 4.74, N, 6.93; S, 7.9. Found: C, 50.28, H, 4.96; N, 6.89; S, 7.79.

Comparison between ^{1}H NMR data of the above diastereomer and those of the diastereomeric mixture obtained from (2*R,S*),(1'*R*)-**1a**, allowed us to assign the following data to the minor diastereoisomer. ^{1}H NMR: δ 1.44 (d, 3H), 1.89 (d, 3H), 4.91 (m, 1H), 5.82 (q, 1H), 7.23–7.36 (m, 5H), 8.06–8.16 (m, 2H), 8.69–8.73 (m, 1H), 8.97 (br d, 1H), *9.14 (d, 2H).*

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