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CONTROL OF ENANTIOSELECTIVITY IN THE FORMATION OF A MODEL ALANINAMIDE FROM A 2-BROMOPROPANAMIDE

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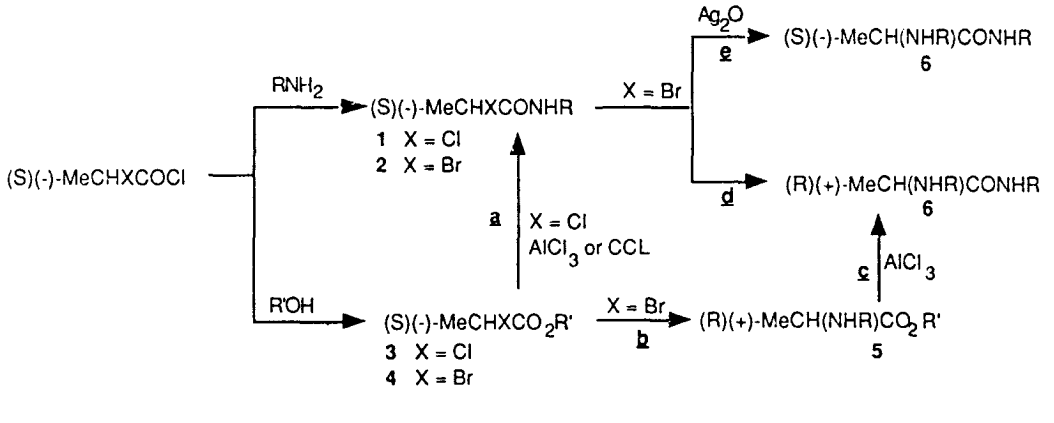
Abstract - Reactions of (R)- or (S)-2-chloro- or -bromopropanamides 1,2 and related compounds with benzylamine in the presence of $AlCl_3$, Ag_2O, or a lipase (CCL) in an organic solvent, are described. N,N'-Dibenzylalaninamide 6 of either optical activity is obtained from optically active 2 by proper use of Ag_2O.

We have been evaluating simple syntheses of α-aminoacid derivatives,[1] in particular, 2-aminoamides. In spite of early achievements in peptide synthesis, obtained through ammonolysis of haloacyl intermediates,[2a] amination of α-substituted acids has been little studied.[2b] 2-Trifluoromethylsulphonyloxypropanoates enantioselectively yield 2-alkylaminopropanoates, whereas 2-halopropanoates may suffer racemization and other side reactions.[3] On the other hand, 2-chloropropanoates undergo regio- and enantio-selective ester aminolysis with secondary aliphatic or aromatic amines in the presence of $AlCl_3$[4] or with benzylamine and other amines in the presence of a yeast lipase (Candida Cylindracea; CCL).[5] We considered it interesting to have a better insight into the regio- and stereochemistry of the reactions of 2-halopropanamides or 2-halopropanoates[6] towards a representative amine in an organic solvent (Scheme).

Scheme



When appropriate, runs were checked starting from the other enantiomer. Paths **a-e** *are with benzylamine (1 mol, room temperature, unless otherwise indicated). The halogen and/or promoter(s) are indicated only when satisfactory results are obtained. R = CH_2Ph throughout the paper. R'= Me unless otherwise indicated.*

(R)- or (S)-2-chloro- or -bromopropanamides **1**, **2** or -propanoates **3** (R'=Et), **4** were obtained from (D)(-)- or (L)(+)-alanine through the respective 2-haloacyl halides.[7a,b] Competitive ester aminolysis

(**path a**) or nucleophilic substitution (**path b**) would transform 2-haloesters **3,4** into a 2-haloamide **1**, **2** or -aminoester **5**, each product being susceptible, in principle, to proceed to a 2-aminopropanamide **6**. Benzylamine was used as the nucleophile in all instances.[8a] It has been proposed previously as an analytical reagent for converting esters into amides, but unsatisfactory results with 2-haloesters were reported.[8b] The (S)- or (R)-2-chloropropanoate **3** was poorly converted by benzylamine into the related (S)- or (R)-2-chloropropanamide **1** (**path a**) and the inverted (R)-or (S)-2-aminoester **5** (**path b**) (product ratio 4:1). With 2 mol of benzylamine, the 2-aminoamide **6** was the major product: the molar ratio of the resulting products **1, 5, 6** averaging 1:1:3 (9 days). Aluminum chloride or CCL markedly accelerated ester aminolysis (**path a**) forming **1** chemo- and enantioselectively,[7c] as reported for **1** itself[5] or related products.[4] On the other hand, 2-bromopropanoate (S)(-)-**4** slowly afforded 2-aminoester (R)(+)-**5** in high yields and ee (**path b**)[9a,b] with benzylamine alone (1 or 2 mol). However, it was reluctant to undergo $AlCl_3$ or CCL promoted ester aminolysis (**path a**): yields of (R)(+)- or (S)(-)-2-bromopropanamide **2**[7d] being ca 10%.[10]

To obtain direct information on **paths c, d** , we contrasted 2-haloamides **1, 2** and aminoester **5** towards benzylamine alone or in the presence of a promoter. (R)(S)-2-chloroamide **1** did not react with benzylamine in the following conditions: i) 2 or 10 mol of amine up to 10 days; ii) 2 mol of amine and 1 mol of Ag_2O, 3 days; iii) with $AlCl_3$, 2 days; iv) 4 h at reflux. Conversely, 2-bromoamide **2** reacted with benzylamine alone yielding 2-aminoamide **6** almost quantitatively (**path d**). Either enantiomer of **2** showed apparent inversion of configuration at C-2.[11a,12]

Whereas $AlCl_3$ had no promoting effect on the reaction of **2** with benzylamine, Ag_2O strongly accelerated the reaction: optically active **2** yielded **6** with high ee and apparent retention of configuration (**path e**).[11a,b] Aminoester **5** was stable towards benzylamine alone, and no catalysis by CCL on the aminolysis of either (R)- or (S)-**5** was observed. The negative results observed with CCL on **4** or **5** point to a less general capability of CCL in the formation of chiral amides from esters, than previously suggested.[5] Finally, and somewhat unexpectedly, $AlCl_3$ favoured the aminolysis of (R)(+)-**5**, yielding (R)(+)**6**, (**path c**) in high yield and ee at the unreacted chiral centre.[11a]

TABLE

Preparation of 6: representative runs in ethyl ether (E) or toluene(T)

Starting material	RNH_2 (mol)	Promoter $AlCl_3$ (mol)	Promoter Ag_2O (mol)	Solvent	Time h / d	Product(6)	%	ee%
(R)(+)2	2			*E*	10	(S)(-)	90	98
(R)(+)2	10			*E*	3	(S)(-)	90	98
(S)(-)2	2		1	*E*	20	(S)(-)	93	98
(R)(+)5	2	1		*T*	1	(R)(+)	70	98

Within the above results, a 2-bromopropanamide **2**, allows enantioselective synthesis of an N-N'-dialkyl-alaninamide. The opposite optical activities of **6** when obtained from **2** (**paths d, e**) in the absence or presence of Ag_2O suggest that different mechanisms operate. Benzylamine alone would react through an S_N2 pathway, under inversion of configuration, whereas the results with Ag_2O would favour a neighbouring group mechanism,[13] yielding a product with apparent retention of configuration. Further studies with other amines, nucleophiles or promoters are being carried out, to establish the scope and limitations of this

reaction in which the proper use of a promoter may afford a chiral amide derivative of the desired stereochemistry.

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7b- (R)(+)- and (S)(-)-**3** were from Aldrich.

7c- (S)(-)- and (R)(+)-**1**: from (S)(-)- or (R)(+)-**3** and $AlCl_3$, 70% in 22 h, $[\alpha]_D$ ±6 (20°, 1, $CHCl_3$). (S)(-)-**1** from (S)(-)-**3** and Candida Cilindracea Lipase [CCL; E.C.3.1.1.3. Sigma], 58% in 24h, as for (S)(-)-**3** (R'=Et).[5]

7d- (R)(+)-**2** $[\alpha]_D$ +1.2; (S)(-)-**2** $[\alpha]_D$ -1.2.[7a,11b] ^1H nmr (Bruker AC 200, $CDCl_3$, δ, tetramethylsilane): methyl doublets of (R,S)-**2** (2.4 mg, 0.01 mmol) in $CDCl_3$ (0.5 ml), shift with tris [3-(trifluoromethylhydroxymethylen)-(+)-camphorato]-europium(III): $Eu(tfc)_3$ (6mg, 0.066 mmol) from 3.32, 3.26 to 3.38, 3.48 δ; ee of (S)(-)- and (R)(+)-**2**: 98%. **2** is under investigation also because of its mutagenic activity: L. Dolzani, M. Tamaro, C. Monti Bragadin, G. Cavicchioni, G. Vecchiati, and F. D'Angeli, Mutat. Res., 1986, 172, 29.

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9b- (R)(+)-**5** (R'=Et) (92%) from (S)(-)-**4** (R'=Et) (1 g, 5.6 mmol) and benzylamine (1.2 g, 11.2 mmol) in ether (10 ml), 3 days at r.t.: workup as for (S)(-)-**6**, Rf 0.6 [tlc: 0.25 mm SiO_2 plates (Merck), ethyl acetate-toluene (1:1), visualisation with iodine vapours]; $[\alpha]_D$ +36, ee 86%: (R)(+)-**5**(R'=Et) (3.1 mg, 0.014 mmol) with $Eu(tfc)_3$ (9.5 mg 0.0106 mmol) in $CDCl_3$ (0.5ml): the triplet shifts from 1.29 to 1.71 δ. The corresponding shift of (S)(-)-**5** (R'=Et) was to 1.56 δ. ^{13}C nmr:14.3, 19.1 (2 Me), 51.9 (C-Ph), 56.0 (CH), 60.7 (C-O), 175.7 (C=O). (S)(-)-**5** (R'=Et) from (R)(+)-**4** (R'=Et).

(R)(+)-**5** was obtained from (S)(-)-**4** and benzylamine (86%; 6 days).[9a]

10 - CCL promoted aminolysis of (S)-2-chloroester **3** was impaired when **3** was admixed with an equimolecular amount of (S)-2-bromoester **4**. On the contrary, CCL catalizes enantioselective esterification of 2-chloro- or -bromopropanoic acid at a similar extent (G. Kirchner, M. P. Scollar, and A. M. Klibanov, J. Am., 107, 7072). For general aspects and optimisation of enantioselective biocatalysis by lipase in organic solvent see: C. S. Chen and C. J. Sih, Angew. Chem. Int. Ed., 1989, 28, 695. Catalysis by a D-alanine aminopeptidase on the aminolysis of D-alanine methyl ester hydrochloride was reported (Y.Asano, A. Nakazawa, Y. Kato, and K. Kondo, Angew. Chem. Int. Ed., 1989, 28, 450).

11a- (S)(-)-**6**: a) ***(path d)*** (R)(+)-**2** (242 mg, 1mmol) in ethyl ether (10 ml) and benzylamine (214 mg, 2 mmol) under stirring; **2** disappears in 10 days (tlc). Filtration, concentration and column chromatography (SiO_2, Merck KG 60) gave an oil (240 mg, 90%); Rf 0.25; $[\alpha]_D$ -4.2; ee 98%. IR [$CHCl_3$, Perkin-Elmer 299 B] 3380, 3010, 1670, 1520, 1500, 1460 cm^{-1}. ^1H nmr ($CDCl_3$), δ: 1.35 (d, 3H, Me), 1.66 (s, 1H, amine NH), 3.31 (q, 1H, CH) 3.72 (s, degen. AB, 2H, amine CH_2), 4.45 (d, 2H, amide CH_2)7.25 (m, 10H, 2Ph), 7.62 (br s,1H, amide NH). Found %: C, 75.31, H, 7.63, N, 10.40. $C_{17}H_{20}N_2O$ requires: C, 76.08, H, 7.51, N, 10.44 %. b)With 10 mol of benzylamine; 3 days. $[\alpha]_D$ -4.2; ee 98%. c) ***(path e)*** From (S)(-)-**2** as under a) but in the presence of Ag_2O (232 mg, 1 mmol), 20 h stirring, and filtration on celite: 248 mg (93%) $[\alpha]_D$-4.O; ee 98%. Using only 1 mol of benzylamine: 60 h, 90%, $[\alpha]_D$ -2.

(+)(-)-**6** according to a), but in toluene at reflux 2 h.

(R)(+)-**6**. a') as under c), from (R)(+)-**2**. b') from (R)(+)-**5** in the presence of $AlCl_3$: $AlCl_3$ (1 mmol, 133 mg) was covered with toluene (ml 10). Benzylamine (214 mg, 2 mmol) was then added dropwise under stirring. After 1h the mixture was treated with (R)(+)-**5** (1 mmol, 213 mg) and stirred for 1 day. Filtration, concentration and column cromatography gave (R)(+)-**6** (188 mg, 70%); $[\alpha]_D$ +4.2.

(S)(-)-**6** Hydrochloride. (S)(-)-**6** (70 mg, 0.26 mmol) in EtOH (2 ml) with 37% HCl (0.02 ml, 0.26 mmol) was taken to dryness and the residue triturated with ether and dryed. Prisms, mp 185-9° C. $[\alpha]_D$ +1.2.

11b-**2** reacts with carboxylates or DMF in the presence of Ag_2O with still uninterpreted enantioselectivity: G. Cavicchioni, F. D'Angeli, A. Casolari and P. Orlandini, Synthesis, 1988, 947; F. D'Angeli, G. Cavicchioni, G. Catelani, P. Marchetti, and F. Maran, Gazz. Chim. It.,1989, 119, 471.

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