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Diastereoselective Synthesis of α-Bromoamides leading to Diastereomerically Enriched α-Amino-, α-Hydroxy- and α-Thiocarboxylic Acid Derivatives

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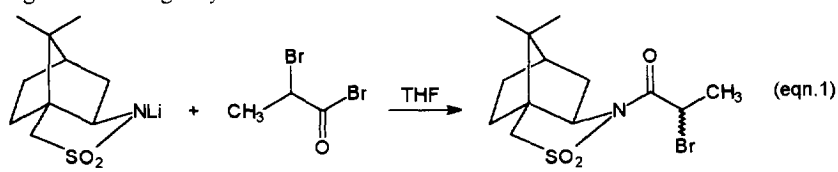
Abstract: α-Bromoamides derived from bornane-10,2-sultam can be prepared diastereoselectively starting from racemic α-bromo acids, and undergo epimerisation under appropriate conditions leading to an enhanced d.e.. By reacting the individual isomers, or in some cases the mixture of diastereoisomers, with a suitable nucleophile it is possible to obtain α-substituted carboxylic acid derivatives in diastereomerically enriched form.

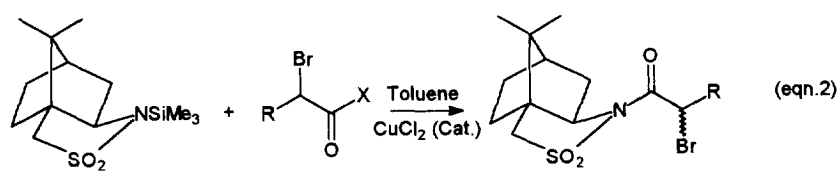
As part of an investigation of the asymmetric synthesis of α-substituted carboxylic acids we have studied the preparation and reactions of a series of N-(2-bromoalkanoyl) derivatives of bornane-10,2-sultam.[1]

Our initial attempts to prepare the α-bromoamides **(1)** using the methods[2-4] usually employed for the preparation of N-alkanoyl sultams were largely unsuccessful. However reaction of the lithium derivative **(2)** of the sultam with racemic 2-bromopropionyl bromide **(3a)** gave a 21% yield of the required α-bromoamide **(1a)**, as a 60/40 mixture of diastereoisomers (eqn.1). The fact that **(1a)** was obtained diastereoselectively was of immediate interest and we decided to find a more efficient method for the preparation of such compounds. We therefore turned our attention to a recently reported method[5] which involves reacting the N-trimethylsilyl derivative **(4)** of the sultam with an acid chloride in the presence of a catalytic amount of copper(II) chloride. This method was applied to the preparation of the α-bromoamide derivatives **(1)** using either the racemic α-bromo acid chloride **(5)** or the α-bromo acid bromide **(3)** as the starting material (eqn.2). The acid bromide was found to give a much higher yield than the acid chloride.



(eqn.1)

2 **(+)-3a** **1a**
21% yield
20% d.e.



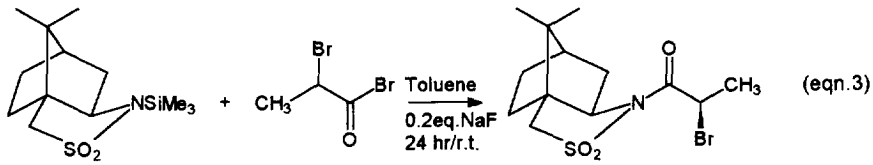
(eqn.2)

4

5 X = Cl
3 X = Br

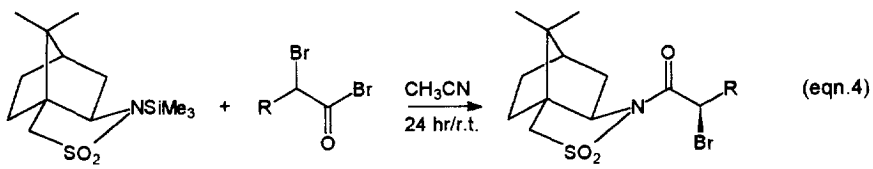
1a R = CH_3 (70% yield from **3a**)
1b R = C_2H_5 (41% from **5b**, 75% from **3b**)
1c R = Ph (0% from **5c**, 33% from **3c**)
1d R = Bn (0% from **3d**)

We therefore investigated the preparation of the 2-bromopropionyl derivative **(1a)** using different solvents and additives. When the reaction was carried out in toluene the d.e. in favour of the *(R)*-isomer was the same no matter which additive was used ($CuCl_2$, $CuBr_2$, NaF, Cu) or with no additive at all. Furthermore the d.e. decreased with time, reaching an equilibrium value of *ca.* 54% after 24 hours. The use of a catalyst did however increase the yield of the reaction, NaF being the best catalyst in this case (eqn.3). Even higher yields and higher d.e. values were obtained in acetonitrile (eqn.4). *Furthermore, in this case the use of a catalyst had no effect on the yield of the reaction.*



(eqn.3)

4 **3a** **(R)-1a**
90% yield
54% d.e.



(eqn.4)

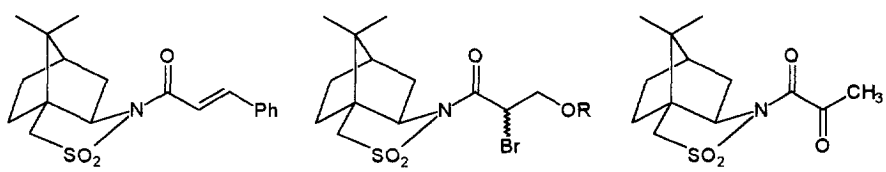
4 **3a** **(R)-1a-d**

We also studied the effect of temperature and found that carrying out the reaction at 60^0C led to the formation of side products which were difficult to separate. *We therefore decided that carrying out the reaction at 40^0C in acetonitrile without a catalyst afforded the optimum conditions in terms of yield, d.e., and ease of purification.* Results obtained under these conditions for a series of α-bromoalkanoyl bromides are shown in Table 1.

Table 1. Preparation of N-(2-bromoalkanoyl)bornane-10,2-sultams

product	R	conversion (%)	d.e. (%)	cryst.yield (%)	corr.yield (%)
1a	CH_3	100	58	75	75
1b	C_2H_5	100	66	72	72
1c	Ph	60	0	45	69
1d	Bn	100	50	48	48

Unfortunately the generality of this procedure is limited by the occurrence of side reactions in some cases. For example the preparation of **(1d)** was accompanied by the formation of *ca.* 30% of the cinnamoyl derivative **(1e)**. Furthermore attempted preparation of the β-oxygenated derivatives **(1f)** and **(1g)** was unsuccessful. The method has however been successfully extended to the preparation of the pyruvyl derivative **1h** in 82% yield.



1e **1f** R = Ac
1g R = Bn **1h**

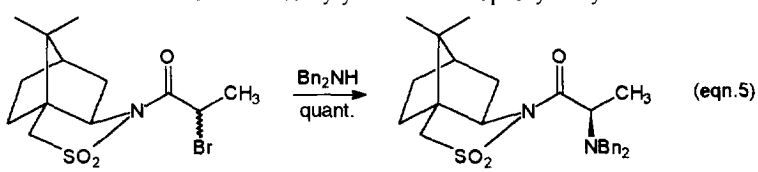
In each of the four cases listed in Table 1 the two diastereomeric α-bromoamides could be clearly resolved on reverse phase HPLC. The two diastereoisomers could also be separated by flash chromatography on silica, and were fully characterised by ^{1}H and ^{13}C NMR spectroscopy, and by X-ray crystallography.

The fact that **1a** and **1b** could be obtained in 70-75% yield and that the d.e. varied depending on the time of reaction prompted us to study the epimerisation of the N-(2-bromoalkanoyl)sultams. The epimerisation of **1a** was studied with various additives in solvents of increasing polarity. Polar aprotic solvents such as acetonitrile and DMSO were found to be the most useful. In refluxing acetonitrile or in DMSO at 60^{0}C addition of KBr increased the d.e. from 0% to 70% in 1 hr, while the increase was much slower in either solvent alone. NaOAc gave the same result as KBr in acetonitrile but gave quantitative displacement of Br in DMSO. KI gave the iodo compound *in situ* leading to a slightly higher d.e. value at equilibrium. However KI also led to extensive cleavage of the sultam. Similar results were obtained with the 2-bromobutyryl and 2-bromo-3-phenylpropionyl derivatives **1b** and **1d**, although in DMSO **1d** readily underwent elimination to give **1e**. In the case of the α-bromophenylacetyl derivative **1c** a 50/50 mixture was obtained at equilibrium whichever additive was used.

Two possible pathways for the epimerisation can be envisaged. The first involves keto-enol tautomerism. The second involves unimolecular or bimolecular displacement of the bromide anion. We have no formal evidence in favour of a specific mechanism although the facile displacement of the bromide by iodide or acetate (in DMSO) would tend to support a displacement. In the case of the 2-bromopropionyl, 2-bromobutyryl and 2-bromo-3-phenylpropionyl derivatives **(1a,b,d)** the *(R)*-isomer with the bromine located on the less hindered face is preferred. In the case of the α-bromophenylacetyl derivative **(1c)** the similar size of Br and Ph would explain the 50/50 mixture obtained.

Starting from either the enantiomerically pure 2-bromoalkanoyl derivative, or the mixture of diastereoisomers, it is possible to obtain enantiomerically enriched α-substituted carboxylic acids. Thus displacement of bromide by a hard, unhindered nucleophile (e.g. azide) occurs without epimerisation and gives the pure *(S)*-product from the pure *(R)*-bromide, and *vice-versa*. On the other hand, displacing the bromide with a soft, quite hindered nucleophile (e.g. Bn_2NH) allows equilibration to occur giving mainly the *(R)*-product which is formed from the more reactive *(S)*-isomer.

Table 2 shows the results obtained by reacting **1a** with dibenzylamine (eqn 5). All of the reactions proceeded in quantitative yield and gave 100% d.e. of the *(R)*-amino acid derivative **6a**. Similar observations involving reactions of α-bromo esters of pantolactone with benzylamine have been previously reported by Durst *et al.*.[6] Unfortunately we have not been able to extend our results to other members of the series since complex mixtures were obtained with the 2-bromobutyryl and α-bromophenylacetyl derivatives **1b** and **1c**.



1a (R)-**6a** (eqn.5)

Table 2. Reactions of 1a with dibenzylamine

conditions	(S)/(R)-bromide	(S)/(R)-amine
toluene/DMSO, reflux	40/60	0/100
DMSO, 60°C	40/60	0/100
acetonitrile, reflux	0/100	0/100
acetonitrile, reflux	45/55	0/100
acetonitrile, reflux	100/0	0/100

Table 3 shows the results obtained with sodium azide. Epimerisation can be prevented in this case by carrying out the reaction at 60°C in DMSO. The yields obtained were 91 - 95%.

Table 3. Reactions of 1a-c with NaN_3

substrate	conditions	(S)/(R)-bromide	(S)/(R)-azide
1a	DMSO, 20°C, 5hr	35/65	41/59
1a	DMSO, 20°C, 5hr	16/84	70/30
1a	DMSO, 60°C, 1hr	0/100	100/0
1a	MeCN, 20°C, 3dy	15/85	72/32
1b	DMSO, 60°C, 1hr	0/100	100/0
1b	DMSO, 60°C, 1hr	100/0	0/100
1c	DMSO, 60°C, 1hr	50/50	50/50

Table 4 summarises the results obtained with O and S nucleophiles. When NaOAc was used some epimerisation was evident. Most alcoholates gave complex mixtures or led to cleavage of the sultam. However using lithium phenolate under carefully controlled conditions minimised this problem and led to direct diplacement with very little epimerisation. Koh and Durst have studied similar reactions using α-bromo esters of pantolactone.[7] Sodium thioacetate displaced bromide, but all diastereoselectivity was lost. However lithium thiophenolate displaced bromide with clean inversion. High yields (81 - 99%) were obtained in all cases.

Table 4. Reactions of 1a with O and S nucleophiles

conditions	(S)/(R)-bromide	(S)/(R)-product
NaOAc, DMSO, 60°C	35/65	40/60
NaOAc, DMSO, 60°C	0/100	94/6
PhOLi, DMSO, 20°C	15/85	76/24
PhOLi, DMSO, 20°C	0/100	95/5
PhOLi, DMSO, 60°C	0/100	100/0
NaSAc, DMSO, 60°C	21/79	50/50
PhSLi, DMSO, 20°C	0/100	100/0

In conclusion we have shown that diastereomerically enriched α-amino-, α-hydroxy- and α-thiocarboxylic acid derivatives can be prepared by reacting diastereoisomeric α-bromoamides with appropriate nucleophiles. Furthermore the α-bromoamides can be prepared diastereoselectively in greater than 50% yield starting from racemic α-bromo acids. These transformations are made possible by interconversion of the diastereoisomeric α-bromoamides under carefully controlled conditions.

Acknowledgement:

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