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Asymmetric synthesis of Boc-β^2-homophenylglycine

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Abstract

Enantiomerically pure Boc-β^2-homophenylglycine has been prepared in five steps starting from Oppolzer's sultam. The key step of this route is the acylation of metalated phenylacetonitrile with sultam carbonyl chloride. Subsequent reactions (reduction, N-Boc protection, oxidation of the Boc-amino alcohol) led to Boc-(S)-β^2-HPhg starting from (+)-sultam. © 1998 Elsevier Science Ltd. All rights reserved.

1. Introduction

In the past few years, there has been increasing interest in non-proteinogenic amino acids for mainly two reasons: as secondary-structure inducers (i.e. constrained analogues of α-amino acids) and more recently as starting materials for the syntheses of scaffolds in combinatorial chemistry. β-Amino acids, far less abundant than α-amino acids, are however present in natural products.[1] β-Amino α-hydroxy amino acids have deserved special interest as enzyme inhibitors, since the discovery of bestatin.[2] With the exception of β-alanine, β-amino acids have rarely been incorporated into peptides for structure–activity relationships.[3] Indeed, current strategy for such an analysis is to constrain conformational mobility of peptides[4] and the extra methylene group in β-amino acids should confer an extra flexibility to peptides incorporating β-amino acids. The recent work of two Swiss groups[5] and Gellman[6] show that this *a priori* statement turns out to be incorrect. They have demonstrated that, unexpectedly, β-amino acids induce highly stable helical structures, i.e. 14-helix or 12-helix for penta-, hexa- or heptamers composed of β-amino acids. The stability of the left-handed helical structure made of β^3-substituted amino acids (β^3 that is β to COOH) seemed to be slightly less affected by changing the polarity of the solvent than that of the right-handed helix corresponding to a hexamer made of β^2-substituted amino acids[5c] (β^2 that is α to COOH).

Three recent reports[7] review the various strategies developed for the syntheses of these β-amino acids. Even though diazomethane is the key reagent in the Arndt–Eistert homologation, this procedure is up

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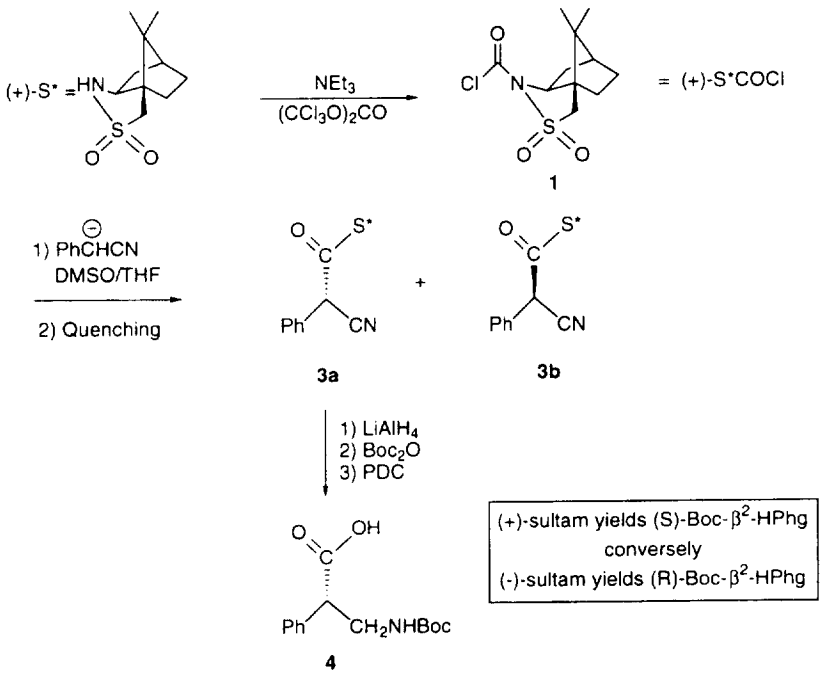
until now the easiest way to prepare enantioselectively β^3-substituted amino acids starting from the corresponding commercially available α-amino acids. The synthesis of β^2-substituted amino acids still remains a challenge,[7–9] usually involving diastereoselective alkylation of an enolate,[8] whose synthesis is the limiting step. Another way of stereoselectively constructing the stereogenic center of a β^2-amino acid may come from an electrophilic carboxylation α to a nitrile function. Herein, we report the one-pot synthesis of an electrophilic sultam derivative **1** and its use in the acylation of phenylacetonitrile which led selectively to one diastereoisomer **3a**. Subsequent reactions (reduction, N-Boc protection and oxidation) of **3a** afforded N-Boc-β^2-homophenylglycine (Boc-β^2-HPhg), in five steps with an excellent enantiomeric excess (99%), Scheme 1.



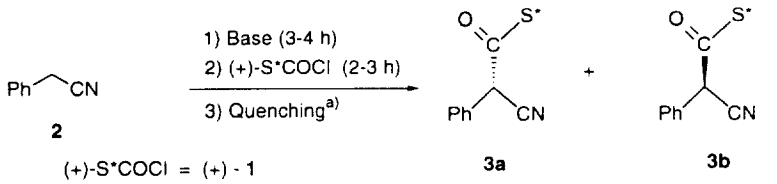
Scheme 1.

2. Results and discussion

Both enantiomers of the electrophilic sultam carbonyl chloride **1** were obtained in 80% yield by reacting one enantiomer of sultam[10] with triphosgene in the presence of triethylamine. The crystallized sultam carbonyl chloride **1** was contaminated with small amounts (<10%, as estimated by ^{1}H-NMR) of unreacted sultam and triethylammonium chloride salt and used without further purification; it may be kept at 0°C for two to three months without further decomposition into free sultam. A pure sample of **1** may be obtained after flash chromatography.

Complex TLC profiles and NMR spectra of the crude extracts were observed when this electrophile was tentatively added to lithiated phenylacetonitrile. These data showed the presence of significant amounts of sultam in the mixture, whatever the conditions (base, solvents, temperature) used for the preparation of lithiated phenylacetonitrile i.e.: BuLi or LDA in THF, THF/HMPT or THF/DMSO at −78°C, 0°C or room temperature. When metallated phenylacetonitrile was prepared at room temperature with sodium hydride in DMSO, acylated species **3a** and **3b** were identified in the crude product by NMR,

Table 1



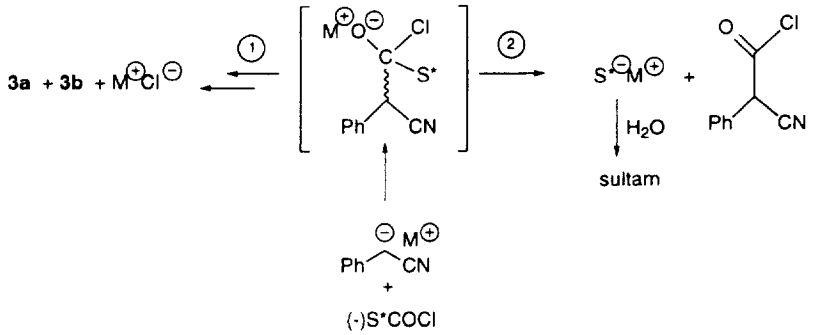
Entry	2[b)] (equiv.)	NaH[b)] (equiv.)	S*COCl	DMSO:THF	T (°C)	S*:**3a**:**3b**[c)] (%)	d.e.[c)] (%)
1	1	1.2	(-)	1:0	r.t.	68:9:23	42
2	2	2.4	(-)	1:0	r.t.	41:4:55	88
3	1	1.2	(-)	1:3	-10°	52:13:35	46
4	2	2.4	(-)	1:3	-10°	20:6:74	84
5	2	4.6	(-)	1:3	-10°	19:14:67	66
6	2	2.4	(+)	1:3	-10°	10:85:5	90(>99)[d)]

a) quenching was performed with either aq.NH_4Cl or CH_3COOH (equiv. amounts to **1**) at the indicated temperature (r.t. or -10°C) ; b) **2** and NaH : equivalent amounts compared to sultam carbonyl chloride S*COCl **1**; c) **3a**, **3b** and S* percentages and diastereoisomeric excess (d.e.) were determined by 400-MHz ^{1}H-NMR with representative signals, either CH3 (sultam moiety) and/or Hα (**3a** and **3b**) and/or CH_2SO_2 chemical shifts ; d) diastereoisomeric exess of **3a** after a single recrystallization with 50 % yield starting from (+) sultam (two steps).

as well as sultam which was still the major product. The diastereoisomeric excess **3a**:**3b** was also poor, entry 1, Table 1. In Table 1 are recorded representative experiments of the attempts performed with (−)- or (+)-sultam carbonyl chloride **1**, to improve both the yield and diastereoselectivity of this acylation reaction.

We found that the amount of sultam in the crude material decreased by increasing the concentration of phenylacetonitrile **2** from one to two equivalents (comparison of entries 1 and 2). Addition of THF in DMSO, which allowed us to conduct the experiment at lower temperature (−10°C), similarly decreased the amount of sultam in the crude product (comparison of entries 1 and 3, and entries 2 and 4). Increasing the concentration of **1** (from 0.08 to 0.25 M) did not significantly modify this ratio. Entry 6 shows that the minimal percentage of sultam expected in the crude product, after extraction, could be reached (10%) considering the purity of sultam carbonyl chloride **1** (90%). Therefore, in the other experiments, free sultam (19 to 68%) must not come from partial hydrolysis of **1** in the reaction medium. We might envisage that sultam might be generated via the pathway in Scheme 2, that is S^{*-} being the leaving group in the tetrahedral intermediate. Sultam derivatives may be readily 'transesterified' by benzyl alcoholate showing that sultam may be a good leaving group.[11] This result might originate from the pyramidalization of the nitrogen atom in cyclic sultam as observed by X-ray.[12]

The diastereoisomeric excess **3a**:**3b** was independent of the solvent, temperature, concentration and also of the equivalent amounts of phenylacetonitrile **2**. The differences in **3a**:**3b** ratios reflected in fact kinetic reprotonation (using independently one or two equivalents of acetic acid or aqueous NH_4Cl)



Scheme 2.

versus thermodynamic equilibrium of the acylated species. If the reaction mixture is not rapidly extracted after quenching and/or the medium buffered with NH_4Cl, the acylated products equilibrated to a 25:75 ratio (thermodynamic products, as established by ^{1}H-NMR with a sample of pure **3a** in $CDCl_3$ with trace amounts of SiO_2). The acidity of the remaining Hα in **3a** precluded purification by flash chromatography on silica gel; **3a** was obtained pure, with no contamination of **3b** as ascertained by ^{1}H-NMR, in acceptable yield after a single crystallization of the crude material obtained after extraction and washings (50% yield for two steps, calculated from starting sultam).

In order to avoid equilibration of **3a** in either acidic or basic conditions required for the reduction of the nitrile function or the deprotection of the sultam, respectively, **3a** was reduced by $LiAlH_4$ into the amino alcohol which was not isolated but N-Boc protected with ditertbutyldicarbonate. This N-Boc-protected β-amino alcohol was oxidized by pyridinium dichromate (3.5 equiv.) in dimethylformamide to N-Boc-3-amino-2-phenylpropionic acid **4**, that is N-Boc-β^2-homophenylglycine (Boc-β^2-HPhg); **4** was obtained with an overall yield for these three steps of 20%. The absolute configuration and the enantiomeric excess of **4** were attributed by comparison of its specific rotation with literature data.[9] Compound (S)-N-Boc-β^2-HPhg was obtained starting from (+)-sultam with excellent enantioselectivity (specific rotation $[\alpha]^{20}_D$ −86 (*c* 1.25, $CHCl_3$) compared to +88 for (R)-Boc-β^2-HPhg, whose enantiomeric excess was ascertained by chiral HPLC[9]). Conversely, (−)-sultam yielded (R)-N-Boc-β^2-HPhg.

These data demonstrated firstly that reduction of **3a** by $LiAlH_4$ into the corresponding amino alcohol did not alter the stereochemical integrity of the initially pure diastereoisomer **3a**, and secondly allowed the orientation of the kinetic reprotonation of the enolate to be determined. Interestingly, identical results have been previously obtained with sultam-derived aldimines,[13] reprotonation (NaH/DMSO, acetic acid, room temperature) of these Schiff bases[14] resulted in the formation of (S)-amino acid starting from (+)-sultam and (R)-amino acid starting from (−)-sultam. This stereochemistry was in contrast to that found for the alkylation of these ketimine[15] or aldimine[13] derivatives which is a kinetically controlled (*si*)-approach of a (Z)-sultam-enolate. With these aldimines the diastereoisomeric ratio of the reprotonation reaction[14] never exceeded 20:80 (in contrast, alkylations were highly diastereoselective). In the present study, the enolate derived from sultam-phenylacetonitrile led to a high diastereoisomeric ratio 95:5, whatever the quenching agent used (NH_4Cl, or equivalent amount of an acid such as acetic acid or 2,5-ditertbutylphenol). This high diastereoselectivity is however restricted to the particular structure of the sultam-phenylacetonitrile enolate, since attempts to use other nitriles such as phenylpropionitrile, propionitrile, 3,3-dimethylpropionitrile were unsuccessful. In all cases, both the diastereoselectivity and the yields of acylated species versus recovered free sultam were rather low (around 65:35 and <30% in the crude material, respectively). The lower acidity of the Hα with these nitriles required the use of lithiated base (BuLi or LDA) and as for phenylacetonitrile (see above) the presence of large amounts of

free sultam (40 to 50%), besides degradation products coming from both nitrile and THF, were detected by NMR and TLC of the crude material.

We must emphasize that this strategy allowed us to prepare Boc-β^2-HPhg. Other β^2-substituted amino acids must be obtained by alkylation of judicious sultam-derived enolate(s). We are currently examining the alkylation of new sultam-derived precursor(s), a strategy which will be inappropriate for obtaining β^2-homophenylglycine.

3. Experimental

Melting points were determined with a Reichert Heizbank (system Kofler) apparatus and are uncorrected. Optical rotations were determined at 20°C on a Perkin–Elmer Model 141 polarimeter equipped with a 10 cm path length cell. TLC was performed on precoated silica gel plates (Merck 60F, 0.25 mm thick). The spots were detected by UV, molybdophosphoric acid oxidation or ninhydrin reagent. Silica gel (0.040–0.063 mm, 60F) supplied by Merck was used for flash chromatography. ^{1}H-NMR spectra were recorded on Brucker ARX-400 or AC-200 instruments. Chemical shifts are reported in δ (ppm) with residual chloroform as an internal reference. Microanalyses and mass spectra were obtained from the University Pierre et Marie Curie.

Tetrahydrofuran (THF) was distilled from sodium benzophenone and kept over 4 Å molecular sieves, dimethylsulfoxide (DMSO) was distilled from CaH_2 and then dried by azeotropic distillation of toluene prior to the experiment. Anhydrous reaction were performed under an argon atmosphere, glassware was flame-dried prior to use under a stream of nitrogen. The course of the reactions was monitored by TLC.

3.1. (−)-10,10-Dimethyl-3,3-dioxo-3-thia-4-aza-tricyclo[5.2.1.0^{1,5}] decane-4-carbonyl chloride **1**

To a solution of (1S)-(−)-2,10-sultam, previously dried by azeotropic distillation of toluene (3.7 g; 17.2 mmoles), in CH_2Cl_2 (70 mL), were added first NEt_3 (2 equiv., 5 mL; 36 mmoles) and after cooling at 4°C, triphosgene, $(CCl_3O)_2CO$, (0.37 equiv., 1.9 g; 6.4 mmoles). After 16 hours stirring at room temperature, the solution was concentrated *in vacuo*. The residual yellow solid was suspended in Et_2O (50 mL), this suspension was stirred vigorously for one hour and then filtered, the solid was washed with Et_2O. The combined filtrates were concentrated to afford **1** as a slightly yellow powder (3.76 g, 79% yield), which is kept under nitrogen at 4°C; m.p. 119–120°C; $[\alpha]_D^{20}$ −133 (*c* 1, $CHCl_3$); MNH_4^+: 295; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 3.96 (q, 1H), 3.55 (q, 2H), 2.4–1.9 (m, 5H), 1.5–1.3 (m, 2H), 1.22 (s, 3H), 1.02 (s, 3H); trace amounts of sultam (7%), characteristic signals, δ 4.0 (NH), 3.08 (AB, 2Hα to SO_2), 1.11 and 0.93 (two s, CH_3); After purification by flash chromatography a pure sample may be obtained. Anal. calcd for $C_{11}H_{16}NO_3SCl$: C, 47.57; H, 5.76; N, 5.04. Found: C, 47.65; H, 5.77; N, 4.97

3.2. Acylation procedure: 3-(10,10-dimethyl-3,3-dioxo-3-thia-4-aza-tricyclo[5.2.1.0^{1,5}] dec-4-yl)-3-oxo-2-phenylpropionitrile ***3a+3b***

A flame-dried 100 mL round-bottomed flask was capped with a septum, purged with argon, charged with DMSO:THF (40 mL, 3:1) containing a crystal of o-phenanthroline and phenyl propionitrile (18 mmoles, 2.1 mL). After addition of sodium hydride (19.8 mmoles, 0.6 g) under an argon stream and four hours stirring at room temperature, the flask was cooled at −10°C and the sultam carbonyl chloride **1** (9 mmoles, 2.47 g) was added under an argon stream. Acetic acid (10 mmoles, 0.6 mL) was added after two hours stirring at −10°C and then ethyl acetate. The organic layer was washed with saturated aqueous

NH_4Cl (3×) and the combined aqueous layers were extracted (2×) with CH_2Cl_2. The combined organic solutions were dried ($MgSO_4$) and concentrated *in vacuo* to yield an orange oil (crude product) which was precipitated by adding Et_2O; filtration led to a slightly yellow solid **3a** (1.6 g, 50% yield); R_f: 0.64 (CH_2Cl_2–MeOH 1%); m.p. 203–204°C; $[\alpha]_D^{20}$ −90 (*c* 1, $CHCl_3$); MNH_4^+: 376; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.57 (m, 2H), 7.40 (m, 3H), 5.46 (s, 1H), 3.97 (m, 1H), 3.54 (s, 2H), 2.01–1.69 (m, 5H), 1.50–1.30 (m, 2H), 0.94 (s, 3H, CH_3), 0.81 (s, 3H, CH_3). Anal. calcd for $C_{19}H_{22}N_2O_3S$: C, 63.69; H, 6.14; N, 7.82. Found: C, 63.57; H, 6.17; N, 7.68.

3.3. Reduction by $LiAlH_4$, N-Boc protection and oxidation: (−)-(S)-(N-tertbutyloxycarbonyl)-3-amino-2-phenylpropanoic acid, (Boc-β ^{2}homophenylglycine, Boc-β^2-HPhg) 4

To a commercial solution of $LiAlH_4$ (8.9 mmoles, 8.9 mL) in THF was added $AlCl_3$ (8.8 mmoles, 1.17 g) and then dropwise at 0°C a solution of **3a** (8 mmoles, 2.86 g) in 2-methyltetrahydrofuran (90 mL). After four hours stirring at room temperature and acidification (1 N HCl), extraction was performed with ethylacetate (3×). The organic layers containing recovered sultam were washed with 1 N HCl, the aqueous layer being reextracted (3×) with ethyl acetate.

The combined aqueous layers (100 mL) were brought to pH 8–9 with 10 N NaOH. After addition of dioxane (50 mL) and cooling at 0°C the resulting amino alcohol was reacted with ditertbutyldicarbonate (16.5 mmoles, 3.6 g) first at 0°C (1 hour) and then for 16 hours at room temperature. The resulting white powder obtained after concentration *in vacuo* was suspended with a saturated solution of Rochelle salt (potassium sodium tartarate tetrahydrate) which was extracted with ethyl acetate (3×). The organic layers were dried ($MgSO_4$) and concentrated *in vacuo*.

The resulting oil dissolved in dimethylformamide (30 mL) was directly reacted, in the dark, with pyridium dichromate (3.5 equiv., 38 mmoles, 14.4 g). After 14 hours stirring, saturated aqueous NH_4Cl (200 mL) was added. The reaction mixture was extracted with diethyl ether (3×). The organic layers were washed with 1 N NaOH (3×) and then the aqueous layers was acidified to pH 2 with 1 N HCl in the presence of CH_2Cl_2. After extraction with CH_2Cl_2 (2×), the combined dichloromethane extractions were washed (NH_4Cl, ×3), dried ($MgSO_4$) and concentrated *in vacuo*, yielding a slightly yellow powder which was purified by flash chromatography (eluant, $CHCl_2$:MeOH:AcOH=95:5:0.2) leading to **4** as a white powder (516 mg, 20% yield); m.p. 135–136°C (lit.[9] 144–146°C); $[\alpha]_D^{20}$ −86 (*c* 1.25, $CHCl_3$), (lit.[9] $[\alpha]_D^{20}$ +88 (*c* 1.25, $CHCl_3$) for (R)-Boc-β^2-HPhg); MH^+: 266; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.38–7.28 (m, 5H), 7.07 (broad s, 0.5H cis–trans isomerism NH), 5.0 (broad s, 0.5H, cis–trans isomerism NH), 3.94–3.8 (m, 1H), 3.6–3.5 (m, 2H), 1.5 and 1.44 (two d, cis–trans isomerism Boc). Anal. calcd for $C_{14}H_{19}O_4N$: C, 63.40; H, 7.17; N, 5.28. Found; C, 63.30; H, 7.08; N, 5.31.

Acknowledgements

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