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Synthesis of α,α-Disubstituted α-Amino Acid Amides by Phase-Transfer Catalyzed Alkylation

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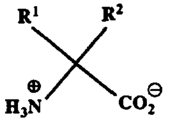
Abstract: α,α-Disubstituted α-amino acid amides were prepared in 17-86% chemical yield by the phase-transfer catalyzed alkylation of N-benzylidene α-H amino acid amides, followed by weak acidic hydrolysis of the Schiff bases.

Optically pure α,α-disubstituted α-amino acids 1, especially α-methyl substituted amino acids, are of increasing interest for the agro chemical and pharmaceutical industry. They may act as enzyme inhibitors and several are antagonists of receptors[1]. The influence of these disubstituted amino acids on peptide structures is of current interest[2].

Recently we described an enzymatic route for the resolution of disubstituted amino acid amides 2 using an amino acid amidase from ***Mycobacterium neoaurum***[3]. By this route optically pure D- and L-disubstituted amino acids are readily available.



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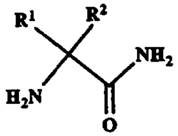

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Asymmetric syntheses of these compounds are labourious and difficult to perform on a large scale[4]. An interesting synthesis of the disubstituted amino acid esters by phase-transfer catalyzed alkylation has been described by O'Donnell[5].

In order to study the substrate specificity of the amino acid amidase reaction[3] with a broader range of substrates, we attempted to convert these disubstituted amino acid esters into the corresponding amides, using aqueous or methanolic ammonia. This procedure failed, however, probably due to steric hindrance. An alternative method of preparation of the desired racemic disubstituted amino acid amides substrates is presented in this paper.

N-Benzylidene α-H α-amino acid amides, readily available from benzaldehyde and α-amino acid amides, can be alkylated at room temperature in 4-18 hours under phase-transfer conditions in CH_2Cl_2 /10 N. NaOH solution using tetrabutylammonium hydrogen sulfate as a phase transfer catalyst (**Scheme 1**). Weak acidic hydrolysis (during the work-up procedure) afforded the α,α-disubstituted α-amino acid amides in 17 - 86% yield. No amide-alkylation was observed. The results are summarized in Table 1.

Scheme 1

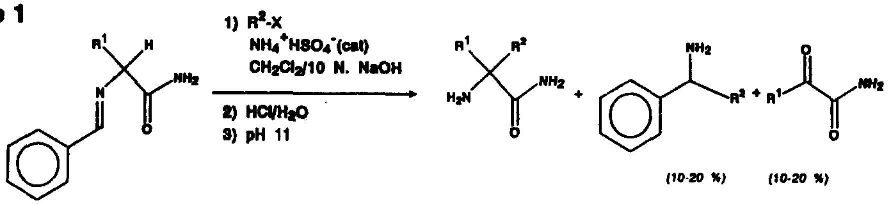
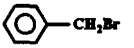
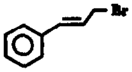
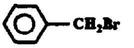
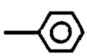
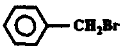
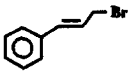
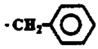


Table 1: Synthesis of disubstituted amino acid amides by phase transfer alkylation.

R^1	R^{2}X	yield^a	m.p. (^{0}C)
-CH_3		72 %^{b}	120 °C/0.5 Torr^c
		55 %	159-161
		73 %	112-114
-$CH(CH_3)_2$		—	—
-$CH_2CH(CH_3)_2$		mixture^d	—
-$CH_2CH_2SCH_3$		45 %	126-128
	CH_3I	45 %	111-112
	n-C_3H_7Br	17 %	109-110
	i-C_3H_7Br	—	—
		60 %	113-114
		79 %	112-113
		86 %	119-121
		53 %	123-124

a) Yields after recrystallization from toluene or ethyl acetate. Crude yield usually were 10-20 % hihger. b) When 1.5 eq. of allyl bromide was used the yield after *chromatography dropped to 40 %, in addition 30 % of* 2-amino-2-methyl-N-(2-propyl)-4-pentanoic acid amide was formed.
c) Bulb to bulb distillation. d) From NMR the conversion was - 50 % after 60hr.

High alkylation yields were obtained from Schiff bases of amino acid amides and 1 equivalent of activated alkyl halides. With sterically hindered amino acid amides yields were lower. In the case of the Schiff base of valinamide no alkylation occurred, even proton exchange in 10 N. NaOH solution was very slow: *Under PTC reaction conditions performed in D_2O only 20% of the α-hydrogen was exchanged* after 20 hrs. In contrast the amide hydrogens and the α-hydrogen in N-benzylidene alanine amide were completely exchanged within 10 minutes under similar conditions. It is also known from the literature that the valine derivatives are 1000 times less acidic[6]. The sluggish reactivity of valine derivatives has also been used in the asymmetric alkylation of bislactim ethers using valine as the chiral auxiliary[4].

Less activated (primary) alkyl halides afforded moderate yields and with secondary alkyl halides only elimination was observed.

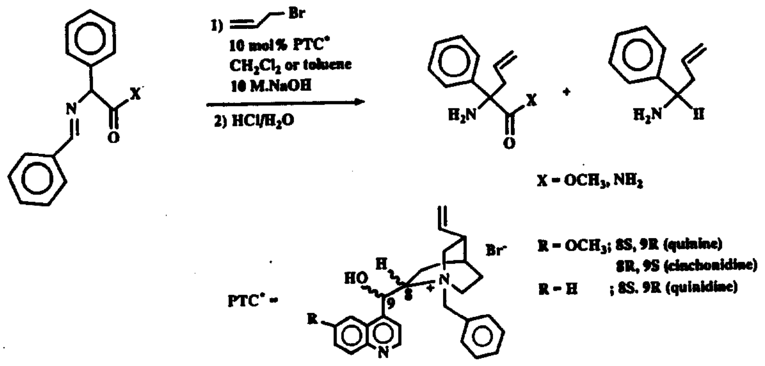
No amide alkylated products are formed during the reaction; this is remarkable especially when the estimated pK_a values of the α-hydrogen and of the amide-hydrogen (19-21[6] and 17[7] respectively) are considered. Probably in apolar organic solvents delocalization[8] of the negative charge is more important, thus hindering the deprotonation of the amide. However, the use of more than 1 equivalent of alkyl halide led to alkylation at the amide nitrogen.

In addition to the desired α-alkylation, some 10 to 20% of alkylation at the imine carbon occurred. After acidic work-up benzaldehyde and α-keto amide were removed by extraction, and α-alkylbenzylamine contaminated disubstituted amino acid amides were obtained. This impurity could be easily removed, however, by washing with ether or by recrystallization from ethyl acetate or toluene.

A unique situation is observed in the benzylation of N-benzylidene methioninamide since facile alkylation at the sulfur atom is expected. This did indeed occur when the compound was benzylated under neutral conditions in dichloromethane. Addition of strong base (i.e. KO^{t}Bu) to this solution, however, caused a shift of the benzyl group from the sulfonium salt to the α-position. Since sulfonium salts are chiral, diastereomeric induction in this alkylation is possible. However, with enantiomerically pure Schiff base a 1:1 ratio of diastereomers is formed according to the NMR spectra.

Recently the asymmetric phase-transfer catalyzed alkylation of glycine derivatives has been described with enantiomeric excesses up to 66%[9]. It therefore appeared attractive to also attempt asymmetric phase-transfer catalyzed alkylation reactions to disubstituted amino acid derivatives. Using benzylated cinchona alkaloids as phase-transfer catalysts in the allylation of N-benzylidene phenylglycine ethyl ester in toluene/10 N. NaOH solution or the corresponding amide in dichloromethane/10 M.. NaOH solution (poor solubility in toluene) gave very low inductions (enantiomeric excesses up to 8 and 5% respectively[10]). Remarkably the byproduct of this reaction, α-allylbenzylamine, was formed with an e.e. of 26%(S)[11] (chemical yield 25%) using benzylquininium bromide as a phase-transfer catalyst. Elucidation of the substrate-catalyst interactions explaining the observed induction would appear difficult, as already noted by O'Donnell[8].

Scheme 2



The work on the enzymatic resolution using the amino acid amidase from ***Mycobacterium neoaurum*** of the synthesized racemic disubstituted amino acid amide is now in progress, and will be published in the near future.

Typical procedure: To a vigorously stirred solution of N-benzylidene amino acid amide (0.50 mol), $Bu_4N^+HSO_4^-$ (30 mmol) in 1 l. of CH_2Cl_2 and 600 ml. of 10 N. NaOH at room temperature, alkyl halide (0.52 mol, 1.05 eq.) was added in one portion. The reaction mixture was stirred for 4 to 18 hrs.[12]. The water layer was discarded and the organic layer washed with water (two times 100ml). To the organic layer 500 ml of 2 N. HCl solution was added and the mixture was stirred vigorously for 15 min.. The water layer was seperated and the organic layer extracted with 100 ml 0.1 M. HCl solution. The combined aqueous layers were washed with CH_2Cl_2 (two times 150 ml), neutralized with 10 M. NaOH solution and extracted with CH_2Cl_2 (three times 200 ml). After washing with water the organic layers were dried over Na_2SO_4 and concentrated in vacuo. The solid residue was recrystallized from ethyl acetate or toluene.
For the liquid α-allylalanine amide a different procedure was followed: The neutralized aqueous layer was first extracted with 100 ml of CH_2Cl_2 to remove the by poduct. The product, which is rather water soluble, was then extracted with CH_2Cl_2 (six times 200 ml) after saturation of the water layer with NaCl. The product was distilled in vacuo (bp. 120°C/0.5 Torr.)

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11. Spec. rot. R-enantiomer $[\alpha]_D$+12.1°(c1,EtOH). Jiang, Y.; Liu, G.; Liu, J.; Zhou, C.; *Synth. Commun.* 1987, *17*, 1545.
12. For convinience the reactions were sometimes left overnight. It is however known that quarternary ammonium salts decompose with a half-life of 5-30 hr. under the reaction conditions (Landini, D.; Maia, A.; Rampoldi, A.; *J. Org. Chem.* 1986, *51*, 3187., '*Catalysis in Novel Media, Volume I*', Catalytic study Nr. 4187 NM, Catalytica ,1989, p 59-161).

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