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SYNTHESIS OF SOME (*S*)-ALANINE DERIVATIVES

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ABSTRACT

In this work, an efficient synthesis for the preparation of *N*-phthaloyl-(*S*)-alanine **(3)** and *N*-phthaloyl-(*S*)-alanyl chloride **(4)** has been presented using economical experimental conditions and the *N*-Phthaloyl-(*S*)-alanine **(3)** has been prepared in excellent enantiomeric excess and with quantitative yield. The acyl chlorination has also been modifide and the reaction time has been reduced by adding an excess of DMF. The compound **(4)** has been obtained in good optically form.

Key words: Phthaloylation, Acyl chlorination, (*S*)-Alanine, *N*-Phthaloyl-(*S*)-alanine, *N*-Phthaloyl-(*S*)-alanyl chloride, NMR spectroscopy.

INTRODUCTION

N-Protected amino acids are important intermediates in organic synthesis, which have been used in various areas such as peptide synthesis [1], medicinal chemistry [2,3], as chiral sources [4-7] and polymer materials [8,9].

A variety of reagents have been reported for the transformation of amino acids into *N*-phthaloyl amino acids, which include thermal conditions [10,11], acid environment [12], basic catalyst [13,14] and microwave irradiation [15,16]. There are other methods, which require multistep reactions to obtain the products, such as the sequence of *N*-protection, esterification and deprotection. Although some of them are widely used, they still have several disadvantages, including tedious workup procedures, safety and waste disposal problems and harsh reaction conditions.

N-phthaloyl-(*S*)-alanine derivatives are very important in organic synthesis. These compounds having bulky substituents at the stereogenic center have been widely used as chiral ligands in asymmetric synthesis. The chiral acyl chloride has been used for the kinetic resolution of heterocyclic amines [17] and for the preparation of optically active

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phosphonic acid [18]. The reactive *N*-protected aldehyde has been used for the synthesis of thiazolidine derivatives [19], the generation of homoallylic alcohols [20] and in the control of the stereoselectivity of the aza-Diels-Alder reaction [21].

The useful synthons *N*-phthaloyl-(*S*)-alanine and *N*-phthaloyl-(*S*)-alanyl chloride were prepared from (*S*)-alanine. The phthaloylation and the acyl chlorination were found to efficiently afford high yields of the target compounds.

Phthalic anhydride has been shown to be a convenient agent for the preparation of N-protected amino acids. This method has been used in the dynamic kinetic resolution of racemic N-phthalyl-amino acids[22]. Some other amino acids have been prepared with high stereoslectivity using chiral auxiliaries[23, 24].

In this paper, we present an efficient synthesis for the preparation of *N*-phthaloyl-(*S*)-alanine **(3)** and *N*-phthaloyl-(*S*)-alanyl chloride **(4)** using economical experimental conditions. In order to ovoid the racemization under high temperature, we have examined the applicability of the method. We have prepared the *N*-Phthaloyl-(*S*)-alanine **(3)** in glacial acetic acid just below its boiling point (t_{bath} = 118°C), with an excellent enantiomeric excess and quantitative yield.

In this communication, we report that DMF is an efficient reagent for acylation of amino acid. We have obtained the compound **(4)** in good optically form.

EXPERIMENTAL

General

Sensitive reaction was carried out under argon with magnetic stirring. R_f values were monitored by TLC on silica gel 60 F_{254} precoated plates (0.25 mm thickness) with UV detection (254 nm) and by heating after dipping in ethanolic solution of phosphomolybdic acid. Melting points were determined on a Büchi B-545 capillary melting point apparatus and are uncorrected.

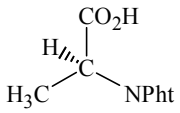
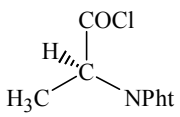
IR spectra were recorded on a Perkin-Elmer Spectrum One FT-IR spectrophotometer. Proton NMR spectra were recorded on a Bruker DRX250 (250 MHz), or Bruker AC360 (360 MHz) spectrometer.

Chemical shifts were recorded in parts per million from the solvent resonance ($CDCl_3$ at 7.27 ppm). Carbon NMR spectra were recorded on a Bruker DRX250 (62.9

MHz), or Bruker AC360 (90.56 MHz) spectrometer. Chemical shifts are reported in parts per million from the solvent resonance ($CDCl_3$ at 77.14 ppm).

Optical rotations were determined at 20 °C on a Perkin-Elmer Model 341 polarimeter. All reagents and chemicals used were obtained from the Aldrich and Acros Chemical Companies. Characterization data of the products are summarized in Table 1.

Table 1. Spectral data of the *N-phthaloyl-(S)-alanyl chloride* (4).

Compound	IR (NaCl, neat) ν (cm^{-1})	^{1}H NMR (360 MHz, $CDCl_3$) δ (ppm)	^{13}C NMR (90.56 MHz, $CDCl_3$) δ (ppm)
 (**3**)	3271.2 (OH), 1780.4, 1714.5 (N-C=O), 1690 (HO-C=O) 1610, 1468 (CH=)	11.14 (br, 1H, CO_2H) 7.74 (dd, J_1 = 5.5 Hz, J_2 = 3.25 Hz, 2H, C_6H_4) 7.87 (dd, J_1 = 5.5 Hz, J_2 = 3.25 Hz, 2H, C_6H_4) 5.05 (q, J = 7.5 Hz, 1H, CH) 1.74 (d, J = 7.5 Hz, 3H, CH_3)	175.68 (1C, Cipso, $\underline{C}O_2H$) 167.4 (2C, Cipso, O$\underline{C}$N$\underline{C}$O) 134.27 (2C, CHar, C_3, C_4, Ph) 131.79 (2C, Cipso, C_1, C_6, Ph) 123.61 (2C, CHar, C_2, C_5, Ph) 47.28 (1C, CH) 15.03 (1C, CH_3)
 (**4**)	1830.9, 1794.4 (Cl-C=O), 1778, 1714 (N-C=O) 1611, 1469 (CH=)	7.80 (dd, J_1 = 5.4 Hz, J_2 = 3.24 Hz, 2H, C_6H_4) 7.92 (dd, J_1 = 5.4 Hz, J_2 = 3.24 Hz, 2H, C_6H_4) 5.18 (q, J = 7.2 Hz, 1H, CH) 1.80 (d, J = 7.2 Hz, 3H, CH_3)	171.73 (1C, Cipso, $\underline{C}$OCl) 166.22 (2C, Cipso, O$\underline{C}$N$\underline{C}$O) 134.34 (2C, CHar, C_3, C_4, Ph) 131.11 (2C, Cipso, C_1, C_6 Ph) 123.44 (2C, CHar, C_2, C_5 Ph) 55.56 (1C, CH) 14.97 (1C, CH_3)

Synthesis of compounds

N-Phthaloyl-(S)-alanine (3)

(*S*)-Alanine **(1)** (6.477 g, 72.86 mmol) and phthalic anhydride **(2)** (10.77 g, 72.86 mmol) were heated under reflux in glacial acetic acid (65 mL) for 3 h (bath temperature = 118 °C). The acetic acid was evaporated under vacuum. Water (14 mL) was added to the residue and the mixture was refluxed for 1 hour. After cooling, the resulting mixture was extracted with ether-water (1 : 4). The precipitated solid was filtered and dried under vacuum to give white crystals of the title compound **(3)** (14.97 g). Yield = 93.6 %. M. p = 146.8°C. R_f (methanol/ petroleum ether : 4/6) = 0.22. $[\alpha]_D^{20}$ = -28.4 (c1, CH_2Cl_2).

N-Phthaloyl-(S)-alanyl chloride (4)

To a stirred solution of *N*-phthaloyl-(*S*)-alanine (3) (2.25 g, 10 mmol) in cyclohexane-benzene (1 : 1) mixture (40 mL), oxalyl chloride (1.75 mL, 20 mmol) was added dropwise and then freshly distilled DMF (0.02 mL). The mixture was stirred at room temperature for 4 hours. The solvents were evaporated to dryness under vacuum. The residue was treated with dry cyclohexane and then evaporated in vacuum to dryness to give acyl chloride **(4)** as yellow pale crystals (2.26 g). Yield = 93 %. M. p = 50.5°C. $[\alpha]_D^{20}$ = -12.4 (c1, CH_2Cl_2).

The proton chemical shift values reported in Table 2 show that the Δ value of the tertiary proton is the big one. This Δ variation is due to H ··· Cl interaction. The estimated δ values were calculated using the CS ChemDraw software.

Table 2. Proton chemical shifts of the *N-phthaloyl-(S)-alanyl chloride* (4).

Proton	^{1}H NMR (360 MHz, $CDCl_3$) δ (ppm)	^{1}H NMR (estimated values) δ (ppm)	Δ (ppm)
C=H(β)	7.92	8.13	-0.21
C=H(α)	7.80	7.69	+0.11
N-CH	5.18	4.63	+0.55
CH_3	1.80	1.41	+0.39

Δ (ppm) = δ(^{1}H, 360 MHz) - δ(^{1}H, estimated value)

For the carbon chemical shifts, it clearly appeared that the *N*-heterocycle induces shielding of the aromatic 2- and 5-carbons (Δ' = -3.96, Table 3). This effect is maximum

with the asymmetric carbon (Δ' = -5.94). The estimated δ values were calculated using the CS ChemDraw software.

Table 3: Carbon chemical shifts of the *N-phthaloyl-(S)-alanyl chloride* (4).

Carbon	^{13}C NMR (90.56 MHz, CDCl3) δ (ppm)	^{13}C NMR (estimated values) δ (ppm)	Δ' (ppm)
Cipso	171.73	173.6	- 1.87
Cipso	166.22	165.9	+ 0.32
C_1, C_6	131.11	132.3	+ 1.19
C_3, C_4	134.34	132.0	+ 2.34
C_2, C_5	123.44	127.4	- 3.96
CH	55.56	61.5	- 5.94
CH_3	14.97	13.9	+ 1.07

Δ' (ppm) = δ(^{13}C, 90.56 MHz) - δ(^{13}C, estimated value)

Magnetic anisotropic effect of carbonyl groups and steric interaction by neighboring proximate atoms affected the chemical shift of the asymmetric H in the acyl chloride **(4)** (Fig. 1).

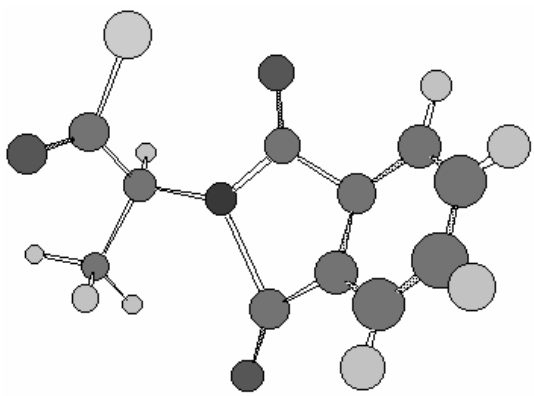


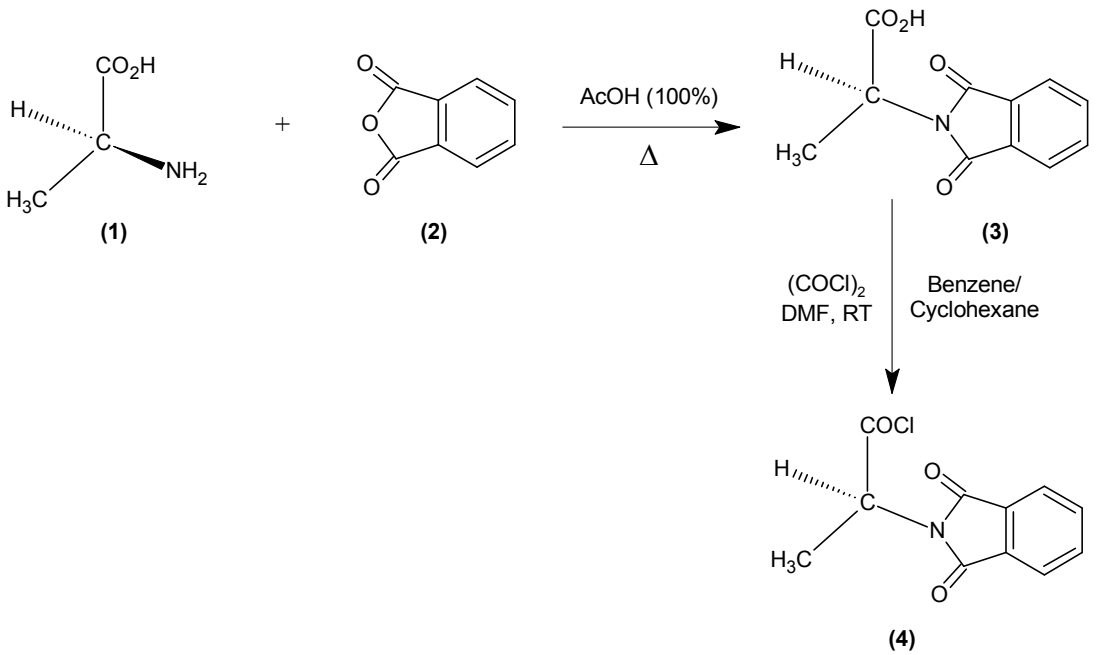
Fig. 1

RESULTS AND DISCUSSION

It has made known that phthaloylation by the fusion of an amino acid with phthalic anhydride can lead compounds to racemize under high temperature (up 150°C) [25]. In order to avoid the phenomenon of racemization, the mixture of amino acid and phthalic

anhydride was refluxed in toluene, in the presence of triethylamine and using a Dean-Stark water trap [25]. Later, the same procedure has been occurred without catalyst [18]. Recently, the fusion process on free amino acid and phthalic anhydride has experimented under low pressure (40 mmHg at 130-135°C) [26].

Here, we have performed the method of phthaloylation. So, we have prepared the *N*-phthaloyl-(*S*)-alanine **(3)** in excellent enantiomeric excess and quantitative yield from (*S*)-alanine **(1)** and phthalic anhydride **(2)** in glacial acetic acid just below its boiling point[27, 28] **(Scheme 1)** ($[\alpha]_D^{20}$ = -28.4, c = 1, CH_2Cl_2; $[\alpha]_D^{24}$ = -24.2, c = 2.6, EtOH [25]; $[\alpha]_D^{20}$ = -23 c = 0.8, EtOH [26]; $[\alpha]_D^{20}$ = -23.9, c = 1.8, EtOH [29]; $[\alpha]_D^{21}$ = -22.5, c = 1, EtOH [30]).



Scheme 1

By analogy with the phthaloylation reaction, the acylation process gives us an important racemization degree when we have heated the reaction (33 % e. e determined by ^{1}H NMR). So, we have modified the acyl chlorination [17].

The action of oxalyl chloride on *N*-phthaloyl-(*S*)-alanine **(3)** in cyclohexane-benzene mixture in the presence of 20 µL of DMF as catalyst at room temperature, allow us to reduce the reaction time. We have obtained the compound **(4)** in good optically form

(determined by ^{1}H NMR) ($[\alpha]_D^{20}$ = -12.4, c = 1, CH_2Cl_2, $[\alpha]_D$ = -33.8, c = 0.8, C_6H_6 [31]).

Compared to the methods mentioned above the use of glacial acetic acid just below its boiling point (for phthaloylation) and an excess of DMF (for acyl chlorination) were more advantageous due to the following features : easy operations, mild reaction conditions, simple workup and excellent yields.

In Table 1, it can be seen that the resonance of the tertiary H initially appears at a lower frequency, then reaches a maximum (5.18 ppm) in the acyl chloride **(4)**, where the electronegative halogen atom produces a high field effect on the asymmetric center, so the chemical shift of tertiary hydrogen increases. The same trend is observed with the hydrogens in the methyl group and also in the aromatic protons.

CONCLUSIONS

In summary, some chiral alanine derivatives have been prepared under mild and simple operating conditions without racemization. We have obtained the *N*-protected amino acid in good yield and with high e. e. using a new and efficient phthaloylation process. The acyl chlorination reaction was accomplished with a lesser amount of catalyst and in a reduced time.

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