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CONVENIENT PREPARATION OF *N*-SALICYLOYL-(L)-PHENYLALANINE

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Abstract: *N*-salicyloyl-(L)-phenylalanine was prepared by a simple, two-step process from (L)-phenylalanine benzyl ester and acetylsalicyloyl chloride followed by hydrolysis and catalytic hydrogenation in an overall yield of 85%.

As part of our research in the area of oral drug delivery,[1] we required multigram quantities of *N*-salicyloyl-(L)-phenylalanine (**1**). Although the chemical literature contains numerous reports on the *N*-acylation of α-amino acids[2,3] in general and the preparation of (**1**)[4] in particular, none of these were readily amenable to scale-up.

One of the earliest reported α-amino acid acylation methods is the well-known Schotten-Baumann reaction.[5] This seemingly straight-foward, scaleable process involves reacting an α-amino acid with an acid chloride in aqueous base. Unfortunately, acylated dipeptides also form under these reactions conditions and are not easily separated from the desired acylated amino acid product. The dipeptide-forming process produces significant amounts of this by-product upon scale-up and can account for as much as 10% of the crude reaction product. Chen and Benoiton[6] have reported the use of diisopropylethylamine (DIEA) instead of sodium hydroxide in the Schotten-

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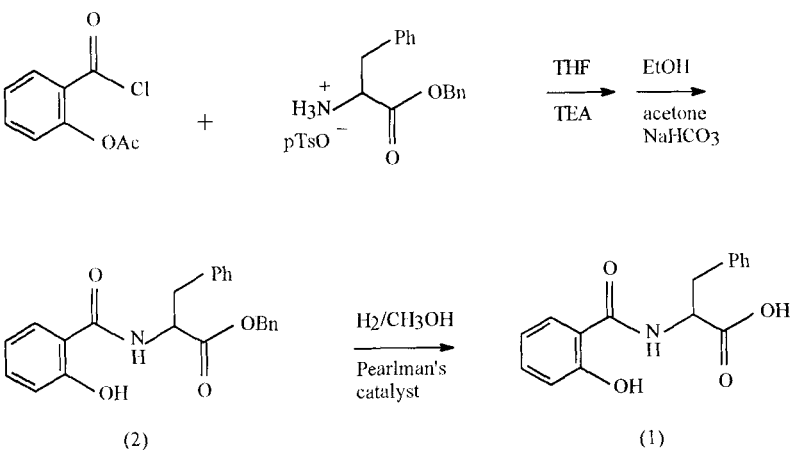
Baumann reaction to limit, but not eliminate, dipeptide formation. amounts of this by-product upon scale-up and can account for as much as 10% of the crude reaction product. Chen and Benoiton[6] have reported the use of diisopropylethylamine (DIEA) instead of sodium hydroxide in the Schotten-Baumann reaction to limit, but not eliminate, dipeptide formation.

The coupling of amino acid esters with carboxylic acids with a coupling agent such as dicyclohexylcarbodiimide, completely supresses dipeptide formation.[7] This process, however, is not amenable to large scale due to difficulties in separating the dicyclohexylurea generated as a by-product of this reaction. Indeed, this method has been used by Amidon[8] to couple (L)-phenylalanine ethyl ester and acetylsalicylic acid followed by chymotrypsin-catalyzed ester hydrolysis to obtain (**1**) in milligram quantities.

Herein, we report a straight-foward, readily scaleable synthesis of (**1**) by reaction of (L)-phenylalanine benzyl ester and acetylsalicoylchloride. The advantages of this reaction procedure include the use of inexpensive, commercially available starting materials, the use of synthetic intermediates without further purification, and an excellent overall yield of the final product after recrystallization.



(2) (1)

Experimental:

Preparation of *N*-salicyloylphenylalanine benzyl ester (**2**). A 2 L, three-neck round bottom flask was equipped with a magnetic stirrer and an addition funnel. The reaction was carried out under nitrogen. Dry THF (600 mL) was added to the flask, followed by phenylalanine benzyl ester p-tosylate (75 g, 0.17 mol). Stirring was initiated and triethylamine (34 mL, 0.26 mol) was added. The reaction mixture was cooled to 0-5°C using an ice/water bath and acetylsalicyloyl chloride (33.8 g, 0.17 mol) in dry THF (50 mL) was added dropwise while the reaction temperature was maintained at 0-5°C. After the addition was complete, the reaction was stirred at 0-5°C for 4 hours, followed by concentration in vacuo. The residue obtained was dissolved in ethyl acetate (400 mL) and washed with 1N aqueous hydrochloric acid (3 x 100 mL). The combined aqueous extracts were back extracted with ethyl acetate (50 mL). The combined organic extracts were dried over magnesium sulfate, filtered and concentrated in vacuo giving N-acetylsalicyloylphenylalanine benzyl ester as a brown oil (164.2 g) which was used without further purification. The oil was dissolved in a mixture of ethanol (150 mL), acetone (150 mL) and saturated aqueous sodium bicarbonate (100 mL) in a 1 L round bottom flask equipped with a magnetic stirrer. The mixture was stirred at room temperature and monitored by TLC (silica gel, 30% ethyl acetate/hexane) until all of the starting material had disappeared (R_f = 0.83) and was replaced by a single product spot (R_f = 0.6). The total reaction time was ~12 hours. The reaction mixture was concentrated in vacuo and the aqueous residue was extracted with ethyl acetate (3 x 100 mL). The combined organic extracts were dried over magnesium sulfate and concentrated in vacuo to give *N*-salicyloylphenylalanine benzyl ester (**2**) as a light brown oil (74 g). This material was used without further purification.[9]

Preparation of *N*-salicyloylphenylalanine (**1**). A 1 L, three-neck round bottom flask was equipped with a magnetic stirrer and an inlet adapter. Crude *N*-salicyloylphenylalanine benzyl ester (**2**, 74 g) was dissolved in absolute methanol (100 mL) and placed in the flask; Pearlman's catalyst (1.1 g) was added to the stirred reaction mixture. The inlet adapter was attached to a balloon containing hydrogen gas and the adapter stopcock was opened. The mixture was stirred at room temperature and monitored by TLC (silica gel, 30% ethyl acetate/hexane) until all of the starting material had disappeared ($R_f = 0.6$) and was replaced by a single product spot at the origin. The total reaction time was ~6 hours. The reaction mixture was filtered through Celite® and the filtrate was concentrated in vacuo to give crude *N*-salicyloylphenylalanine as a brown, viscous oil (52.5 g). Hexane (50 mL) was mixed with the crude product and heated to boiling in a hot water bath. The hexane was decanted and the process repeated three more times. During the final sequence, *N*-salicyloylphenylalanine (**1**, 42.5 g, 88% overall) was obtained as a tan crystalline solid, mp 109-111°C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 13.0 (br, 1H), 12.0 (br, 1H), 9.0 (d, 1H), 7.9 (d, 1H), 7.4 (t, 1H), 7.2 (m, 5H), 6.8 (dd, 2H), 4.7 (m, 1H), 3.2 (m, 2H). Anal. Calcd for $C_{16}H_{15}NO_4$: C, 67.36, H, 5.30, N, 4.90, Found C, 67.16, H, 5.33, N, 4.69.

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9. For structure verification, a sample of crude (**2**) was purified by column chromatography on silica gel using 30% ethyl acetate/hexanes. Compound (**2**) was obtained as a tan solid, mp 68-69°C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 12.0 (s, 1H), 7.4-6.7 (m, 14H), 5.2-5.0 (m, 3H), 3.3-3.2 (m, 2H). Anal. Calcd for $C_{23}H_{21}NO_4$: C, 73.57, H, 5.64, N, 3.73, Found C, 73.36, H, 5.72, N, 3.57.

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