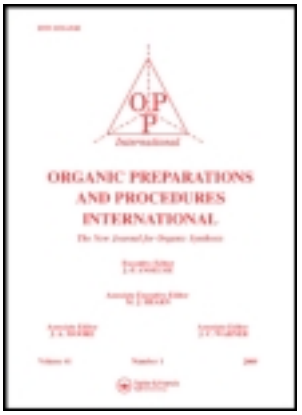

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Synthesis of 2-Amino-1-indanone from DL-Phenylalanine

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2-Amino-1-indanone is a cyclic vicinal amino ketone. Such compounds are of great interest as pharmaceutical agents and as intermediates in natural product synthesis.[1–3] There are four main methods to synthesize this compound. One is an anionic cyclization of *N*-protected *o*-bromophenylalanine ester by lithium-bromine exchange followed by internal trapping of the lithiated intermediate by the carboxylate group under rigorously anhydrous, anaerobic operation at -78°C.[4] The *N*-protected *o*-bromophenylalanine ester requires at least three steps for its preparation. Another method is an intramolecular Friedel-Crafts acylation of the *N*-carboxyanhydride of phenylalanine,[5] in which the anhydride must be prepared by reaction of phenylalanine with phosgene or triphosgene or by reaction of L-*N*-methoxycarbonyl phenylalanine with PBr_3.[5] The third route is a Friedel-Crafts acylation of the *N*-protected (α-aminoacyl)benzotriazole of phenylalanine, obtained from phenylalanine *via* a two-step reaction, with $AlCl_3$ to give *N*-protected 2-amino-1-indanone.[6] The fourth method is an intramolecular Friedel-Crafts cyclization of *N*-phthaloylphenylalanine acid chloride to give *N*-protected 2-amino-1-indanone.[7–12] In this procedure, *N*-methoxycarbonyl or *N*-phthaloyl protected phenylalanine must first be converted to its acid chloride with thionyl chloride. The acid chlorides are moisture sensitive and apt to emit volatile, corrosive hydrogen chloride gas. In continuation of our interest in the synthesis and transformations of amino acids,[13–16] we now describe a new route to 2-amino-1-indanone from DL-phenylalanine (*Scheme 1*).

Polyphosphoric acid (PPA) is known to be an excellent Brönsted acid for cyclodehydration, Friedel-Crafts acylation and alkylation.[17–19] Although PPA is frequently used in Friedel-Crafts acylation, it has not been investigated in the synthesis of 2-amino-1-indanone. There are four advantages for PPA-catalyzed Friedel-Crafts acylation: (1) Transformation from *N*-phthaloylphenylalanine into its acid chloride is avoided; (2) Yield from *N*-protected phenylalanine to *N*-protected 2-amino-1-indanone is much higher (75%); (3) No volatile

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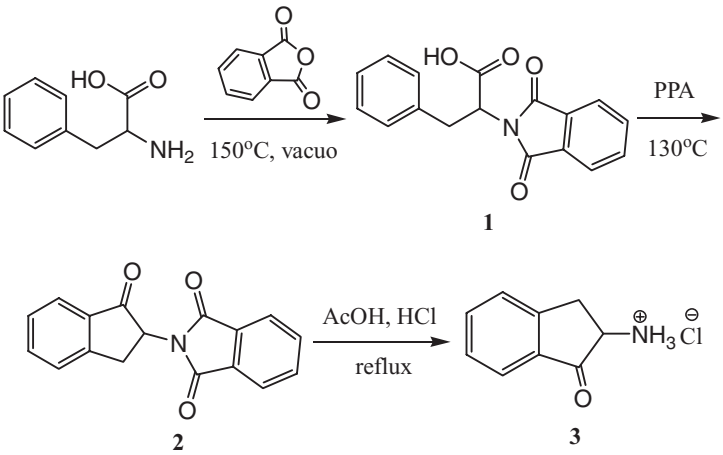

Scheme 1
Synthesis of 2-Amino-1-indanone hydrochloride (**3**)

corrosive gas is produced; and (4) No organic solvents are used in the Friedel-Crafts acylation.

Our synthesis commenced with the preparation of *N*-phthaloylphenylalanine (**1**). Commercially available DL-phenylalanine[20] and phthalic anhydride were heated to melting under low vacuum to speed removal of water generated in the process and thus to accelerate the condensation at a relatively low temperature.[21] When *N*-phthaloylphenylalanine (**1**) was heated at 130°C in PPA, as catalyst and solvent, 2-phthalimido-1-indanone (**2**) was obtained with good yield (75%). Finally, 2-phthalimido-1-indanone (**2**) was hydrolyzed with acetic acid and concentrated hydrochloric acid under reflux for ten hours to give 2-amino-1-indanone hydrochloride (**3**).[8] Attempted cleavage with hydrazine hydrate led to a homogeneous mixture from which it was difficult to remove water. The overall yield from DL-phenylalanine was 40%.

Experimental section

The purity of all the synthesized compounds was checked by thin-layer chromatography (TLC) using various non-aqueous solvents. Melting points were measured on an Electrothermal digital melting point apparatus and are not corrected. The IR spectra were recorded on a Bruker Tensor-27 FT-IR spectrophotometer in KBr discs. ^{1}H NMR spectra were obtained on a Bruker Advance 300 MHz NMR spectrometer at 300 MHz in $CDCl_3$ containing tetramethylsilane (TMS) as an internal standard. The chemicals were purchased from Aldrich, Aladdin, or Kelong Chemical Companies, and used without further purification.

Synthesis of N*-Phthaloylphenylalanine (1).*

DL-Phenylalanine (3.30 g, 20.0 mmol) and phthalic anhydride (3.25 g, 22.0 mmol) were added into a round bottom flask fitted with a magnetic stirring assembly. The flask was connected to a water aspirator (with about 40 mmHg vacuum), and heated in an oil bath

at 150°C. Soon the solid mixture was fused and some water drops were condensed at the top of the flask. After 50 min, the flask was removed from the oil bath and cooled to room temperature. The excess crystalline phthalic anhydride on the wall of the flask was removed by cotton wool dipped in ethyl acetate. The solid crude product at the bottom of the flask was purified by recrystallization from ethanol/water (3/2) to give white needle crystalline solid of *N*-phthaloylphenylalanine **1** (5.156 g, 87% yield), mp. 184–185°C [*lit.*[21] 184–186°C]. IR (neat), ν (cm^{-1}): 3271, 1771, 1749, 1698. ^1H NMR (300MHz, $CDCl_3$): δ 3.60 (d, $J = 9.0$ Hz, 2H), 5.23 (t, $J = 9$ Hz, 1H), 6.4 (br, COOH, 1H), 7.11–7.19 (m, Ar–H, 5H), 7.70 (dd, $J_1 = 5.4$Hz, $J_2 = 3.0$ Hz, 2H), 7.78 (dd, $J_1 = 5.4$ Hz, $J_2 = 3.0$ Hz, 2H). The IR and ^1H NMR spectra are consistent with literature data.[21]

Synthesis of 2-Phthalimido-1-indanone (2)

N-Phthaloylphenylalanine (**1**) (3.01 g, 10.2 mmol), PPA (20 ml) was added to a 250 ml flask fitted with a magnetic stirring assembly and a reflux condenser. The flask was heated in an oil bath at 130°C for 3 h. Then the flask was cooled to room temperature, and water (60 ml) was added to quench the reaction. The resulting solution was transferred to a separatory funnel, and extracted with dichloromethane (3 × 30 ml). The combined organic layer was washed with water (10 ml), saturated sodium bicarbonate (10 ml), saturated sodium chloride (10 ml), and then dried over anhydrous magnesium sulfate. The filtrate was concentrated on a rotary evaporator. The resulting solid was purified by silica gel column chromatography with petroleum and ethyl acetate (4/1) as eluent to give 2-phthalimido-1-indanone (**2**) as a white solid (2.1030 g, 75% yield), mp. 203–205°C [*lit.*[7] mp. 203–204°C]; IR (neat), ν (cm^{-1}): 1780, 1723, 1602; ^1H NMR (300 MHz, $CDCl_3$): δ 3.40 (dd, $J_1 = 16$ Hz, $J_2 = 6$ Hz, 1H), 3.60 (dd, $J_1 = 16$ Hz, $J_2 = 8.4$ Hz, 1H), 5.09 (dd, $J_1 = 8.4$ Hz, $J_2 = 6$ Hz, 1H),7.43 – 7.87(m, 8 H). The ^1H NMR and IR spectra are consistent with the literature data.[8]

Synthesis of 2-Amino-1-indanone Hydrochloride (3)

2-Phthalimido-1-indanone **2** (0.800 g), conc. hydrochloric acid (3 ml) and acetic acid (5 ml) were added into a 100 ml flask fitted with a magnetic stirring assembly and a reflux condenser. The flask was heated on an oil bath at 110°C for ten hours. After cooling to room temperature, water (50 ml) was added to the flask, and white emulsion appeared immediately. The mixture was filtered by gravity to remove the white solid, phthalic acid. The filtrate was extracted twice with ethyl acetate (20 ml) and the ethyl acetate extract was discarded. The aqueous layer was concentrated on a rotary evaporator to remove water. The resulting solid was washed with diethyl ether (5 ml) to give 2-amino-1-indanone hydrochloride **3** as a white crystalline solid (0.3286 g, 62% yield), mp. 167–170°C (*lit.*[8] 168–175°C); IR (neat), ν (cm^{-1}): 2973, 1715, 1591; ^1H NMR (300 MHz, $CDCl_3$), δ (ppm): 3.18 (dd, $J_1 = 17.1$ Hz, $J_2 = 5.1$ Hz, 1H), 3.72 (dd, $J_1 = 17.1$ Hz, $J_2 = 5.1$ Hz, 1H), 4.34 (dd, $J_1 = 8.1$Hz, $J_2 = 5.4$ Hz, 1H), 7.46–7.80 (m, 4H). The ^1H NMR and IR spectra are basically consistent with the literature data.[8]

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