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A Practical and Efficient Synthesis of Thalidomide via Na/Liquid NH_3 Methodology[1]

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Abstract:

A facile, efficient, concise, cost-effective, and scalable synthesis of thalidomide in high overall yield (55%) is presented. Treatment of Boc-protected L-glutamic acid diester via Na/liquid (liq.) NH_3 (−33 °C) mediated cyclization methodology produces a corresponding glutarimide ring which was subsequently condensed with phthalic anhydride in the presence of glacial acetic acid to afford thalidomide.

Thalidomide (*N*-α-phthalimido glutarimide) is a glutamic acid derivative that was developed as a nontoxic sedative and safe alternative to barbiturates in the late 1950s.[2] Its notorious human teratogenic effects, i.e., severe congenital abnormalities in babies born to mothers using it for morning sickness and phocomelia, led to its withdrawal in 1963.[3] Interest in thalidomide was initially rekindled in the mid-1960s after approval by the FDA, United States in 1998, because of its effect on erythema nodosum leprosum (ENL).[4] It is now apparent that it has anti-inflammatory properties in other diseases, such as in the treatment of severe aphthous stomatitis, cancer, Behcet's disease, graft-versus-host disease (GVHD), some infestations of HIV infection, and, possibly, malignancies.[5,6] It is a classically quoted example of a drug developed as a racemate in which only one isomer, the S-isomer, carries the negative side effect, teratogenicity.[7a,10] It has been shown that the strongly acidic hydrogen atom at the stereogenic center of thalidomide rapidly epimerizes under physiological conditions at pH 7.4, 37 °C, rendering bioassay of enantiomers difficult due to chiral lability in vitro and in vivo.[9a]

Syntheses of thalidomide have been well documented in literature.[9] Celgene corporation has made significant progress in the synthesis of the drug. Although these synthetic procedures seem to be straightforward transformations, they suffer from several drawbacks on the large scale preparation: (1) involving a high-temperature melt reaction requiring multiple recrystallizations;[8] (2) use of costly starting materials/reagents in the steps involved for the preparation; (3) low overall yields. Usually the above syntheses leave as the final step the formation of the glutarimide ring. The conditions employed include the condensation of liquid and/or gas ammonia with generic cyclic anhydrides,[11] the cyclization of an amide acid with CDI/DMAP,[9a] the reaction of diacid chlorides with lithium nitride,[12] the reaction of a primary and a secondary amide reacted with $AlCl_3$,[13] and the reaction of urea/thiourea with a cyclic anhydride.[9a] These conditions can often cause low yields, byproduct formation, and longer reaction times. Unfortunately, none of these routes is very practical in terms of industrial scale-up operations. To address the above difficulties involved in the preparation of thalidomide, better isolation protocols coupled with replacements of costlier reagents such as L-glutamine which is five times costlier than L-glutamic acid, *N*-phthaloyl DL-glutamic anhydride, CDI (1,1′-carbonyl diimidazole), $Pd(PPh_3)_4/CO$,[9f] etc., became the twin objectives of our approach. Considering the newly discovered activity of the drug in treating infectious diseases and being interested in exploring novel routes for the preparation of the phthalimide and arylalkanoic acid derived drugs and analogues,[14] we wish to report two novel methods of synthesizing thalidomide.

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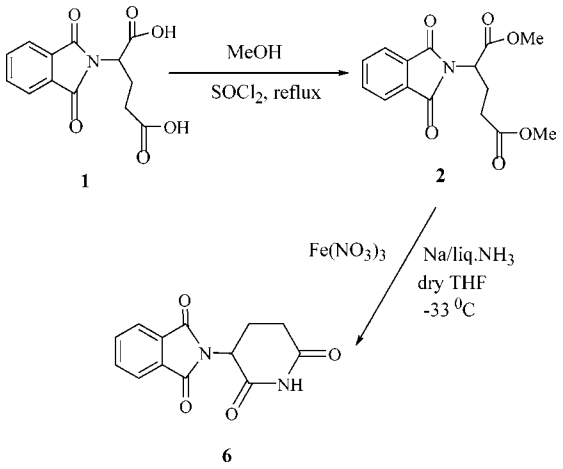
Results and Discussion

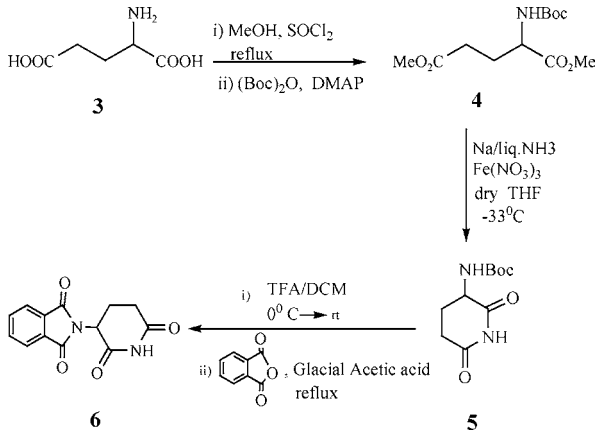
Our initial attempt involved the reaction of L-glutamic acid (L-GA) with a solution of Na_2CO_3 in water and *N*-carbethoxy phthalimide using a standard procedure to furnish *N*-phthaloyl L-glutamic acid **1** in 60% yield (Scheme 1).[15] Treatment of **1** with thionyl chloride in methanol under reflux for 6 h afforded after usual workup *N*-phthaloyl L-glutamic acid dimethyl ester **2** as an oil (71%).[16] The following key step is based on the formation of the glutarimide ring from glutaric acid diesters by using the $NaNH_2$/liq. NH_3/$Fe(NO_3)_3$ methodology, as evidenced in the previous report by Kinoshita.[17] To our satisfaction, the ester **2** was cyclized to give the desired compound **6** in a low yield (1.14 g, 45%).

Scheme 1



Albeit the chemical yield is low, the above two-step synthesis encouraged us to explore the applicability of this methodology in the large scale synthesis of thalidomide using an alternative strategy starting from L-GA. The starting material for this approach is an inexpensive commonly available reagent, and the results from our study are presented herein. The starting material which was converted into dimethyl ester in 95% yield (Scheme 2).[18] The ester was then protected with $(Boc)_2O$ in a mixture of dioxane and water with a catalytic amount of DMAP at room temperature for 12 h to afford *tert*-butoxycarbonyl L-glutamic acid dimethyl ester **4** (88%).[19] The ester was treated with Na/liq. NH_3 at −33 °C in dry THF which was already found to be practically applicable and cyclized to afford the glutarimide **5** in 2 h (68%).[20] This imide was characterized and then deprotected with trifluoroacetic acid in CH_2Cl_2 in 1.5 h to remove the protective group to generate corresponding aminoglutarimide trifluoroacetate in quantitative yield. Without further purification, this compound then was reacted with phthalic anhydride in refluxing glacial acetic acid in the presence of triethylamine to furnish thalidomide (**6**) in 65% yield. Various solvents such as THF, DMF, and toluene were used for the condensation to take place. The reaction was sluggish and took longer reaction times (1−2 days) in THF and DMF which are not practically viable in large scale synthesis, whereas azeotropic removal of water via Dean−Stark is needed in the case of toluene being used as solvent (8 h). We now disclose that glacial acetic acid as solvent is quite efficient in the condensation giving in 2 h complete conversion. Racemization of the product occurs in this step. The overall yield of the synthesis via Scheme 2 is 55%.

Scheme 2



To the best of our knowledge, Na/liq. NH_3 mediated cyclization of glutamic acid diester is for the first time shown to be a good tool and useful in the synthesis of thalidomide. While both routes to the desired compound were ultimately successful, the approach outlined in Scheme 2 proved to be more amenable to multigram scale preparations due to the crystallinity and purity of intermediates in that route.

In summary, the practical short synthesis was developed as an alternative to the previous syntheses of thalidomide, using $NaNH_2$/liq. NH_3 methodology for the first time, which we found to fulfill our initial requirements of economical and readily available starting materials, high overall yield, and ability to be done on a multigram scale. No exceptional purification (such as use of high melt temperatures, acidic purifications) was required for all intermediates and reagents. General applicability of this methodology could be easily extended to other analogues of thalidomide, and efforts are underway.

Experimental Section

General. All reagents were obtained from commercial sources and used without further purification. Solvents for chromatography are of technical grade and were distilled before use. ^1H NMR and ^{13}C NMR spectra were recorded at

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200 and 300 MHz, and chemical shifts are given in δ units relative to the tetramethylsilane (TMS) signal as an internal reference in $CDCl_3$. Coupling constants (J) are reported in hertz (Hz). Mass spectra were recorded in the form of m/z (intensity relative to base 100) on a VG 7070H Micromass mass spectrometer at 200 °C, 70 eV, with a top current of 200 μA and 4 kV acceleration. Melting points have been recorded on an Electro thermal melting point apparatus. IR spectra were recorded on a Perkin-Elmer 1620-F spectrophotometer. Analytical TLC of all reactions was performed on Merck prepared plates (silica gel 60F-254 on glass). Column chromatography was performed using Acme silica gel (100 ± 200 mesh). Reactions were routinely carried out under an atmosphere of nitrogen. Products in organic solvents were dried over anhydrous magnesium sulfate before concentration in vacuo. All of the final compounds synthesized were characterized by ^{1}H NMR, ^{13}C NMR, mass spectrometry, C, H, N elemental analysis, IR, and melting points for solids. Purity of the compounds was checked by HPLC. HPLC conditions: column, Hypersil BDS C_{18}, 5 μm, 250 mm × 4.6 mm; mobile phase of acetonitrile, H_2O in 7:3/6:4 ratio; flow rate, 1.0 mL/min; mobile phase of acetonitrile, H_2O in 7:3/6:4 ratio; detection, 220−250 nm; run time, 20 min. Optical purity was checked by comparing the observed $[\alpha]_D$ values with the reported literature $[\alpha]_D$ values.

L-2-(1,3-Dioxo-2,3-dihydro-1*H*-2-isoindolyl) Pentanedioic Acid (1). L-Glutamic acid (5.0 g, 34.32 mmol) was dissolved in a solution of 10.42 g (98.44 mmol) of sodium carbonate in 50 mL of water. After cooling the mixture to 0 °C, 10.42 g (47.50 mmol) of well-ground *N*-carbethoxyphthalimide was added, and the white suspension was stirred for 5 min at 0 °C and 40 min at room temperature and then filtered. The filtrate was acidified to pH 2.5 with 6 M HCl. The colourless oil that separated slowly crystallized upon cooling. The colorless crystals were collected after 2 days at 5 °C to give **1** (7.9 g, 28.55 mmol, 60% yield) as a solid, mp 160 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.40−2.80 (m, 4H, CH_2−CH_2), 5.05−5.18 (m, 1H, CH), 7.75−7.95 (m, 4H). $[\alpha]^{25}_D = -42.6$ ($c = 1$, EtOH);[15] optical purity, 94.6%.

L-Dimethyl-2-(1,3-dioxo-2,3-dihydro-1*H*-2-isoindolyl) Pentanedioate (2). To a solution of *N*-phthaloyl L-glutamic acid **1** (5.0 g, 18.05 mmol) in methanol (100 mL) was added, dropwise, thionyl chloride (25 mL). The reaction mixture was refluxed for 6 h. The solvent was removed under reduced pressure, dissolved in ethyl acetate (500 mL), and then washed with saturated aqueous Na_2CO_3 solution (2 × 100 mL) and water (2 × 100 mL). The ethyl acetate layer was dried over Na_2SO_4 and then evaporated, leaving oil, which upon purification by silica gel chromatography, using CH_2Cl_2/EtOAc (1:1) as the eluent, gave compound *N*-phthaloyl L-glutamic acid dimethyl ester **2** (3.91 g, 12.82 mmol, 71% yield) as an oil. IR (neat): 1746, 1743, 1714 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.41−2.35 (m, 2H), 2.51−2.44 (m, 1H), 2.67−2.56 (m, 1H), 3.62 (s, 3H), 3.73 (s, 3H), 4.91 (dd, $J = 5$ Hz, $J = 9$ Hz, 1H), 7.75−7.72 (m, 2H), 7.87−7.84 (m, 2H). EIMS: $m/z = 305$ (M^+). $[\alpha]^{25}_D = -168.8$ ($c = 1.4$, $CHCl_3$);[16] optical purity, 97.2%.

2-(2,6-Dioxo-3-piperidyl) Isoindoline-1,3-dione (6) (Scheme 1). To a stirred solution of sodium amide [29.5 mmol; prepared in situ from sodium metal (0.68 g) and ammonia in the presence of a catalytic amount of iron(III) nitrate in liquid ammonia (150 mL)] is added a solution of the *N*-phthaloyl L-glutamic acid dimethyl diester **2** (3 g, 9.83 mmol) in dry THF (100 mL) at −33 °C. After stirring for 1.5 h, ammonium chloride (8.0 g) is added and the ammonia is allowed to evaporate. Water (100 mL) is added to the residue, and the mixture is extracted with chloroform (3 × 20 mL). The extract is dried with Na_2SO_4 and concentrated and column purified on silica gel with chloroform/acetone (9:1) to afford thalidomide **6** (1.14 g, 4.43 mmol, 45% yield) as a white powder, mp 275−276 °C.

L-1,5-Dimethyl-2-aminopentanedioate. To a solution of L-glutamic acid **3** (12 g, 81.6 mmol) in dry methanol (250 mL) was added thionyl chloride (distilled) (40.16 g, 326 mmol) using a dropping funnel at 0 °C over a period of 30 min. Then, the reaction mixture was stirred at room temperature for 12 h under vigorous stirring. Then, the solvent was evaporated under reduced pressure, diluted with aq. $NaHCO_3$, and extracted with dichloromethane (5 × 200 mL). The organic layer was washed with H_2O and brine and dried over anhydrous Na_2SO_4. Evaporation of the solvent gave the diester (12.86 g, 73.47 mmol, 95% yield) as a light yellowish oil. IR (neat): 3255, 1741, 1691 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 4.25−4.32 (q, 1H, CH), 3.3−3.38 (br s, 4H, Ar, 2H), 3.6−3.7 (s, 3H), 3.78−3.90 (s, 3H), 2.37−2.45 (d, 1H, CH_2), 2.25−2.34 (m, 1H, CH_2). $[\alpha]^{25}_D$ for L-glutamic acid dimethyl ester hydrochloride: +22.8 ($c = 2$, MeOH);[18] optical purity, 93.8%. HPLC retention time (t_R) = 5.888 min (purity (area %) 98.98 at 230 nm).

L-1,5-Dimethyl-2-[(*tert*-butoxycarbonyl)amino] Pentanedioate (4). A solution of diester (12 g, 68.6 mmol) and di-*tert*-butyl dicarbonate (17.8 g, 81.6 mmol) in a mixture of dioxane and water (1:1) with a catalytic amount of DMAP was allowed to warm to room temperature and continued stirring for 12 h. Then, solvent was evaporated, and the residue was diluted with aq. $NaHCO_3$ and extracted with DCM (5 × 100 mL). The organic layer was washed with water (3 × 100 mL) and dried over anhydrous Na_2SO_4. Evaporation of the solvent gave NH−Boc protected diester **4** (16.6 g, 60.34 mmol, 88% yield) as an oil. IR (neat): 3367, 1732, 1168 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): δ = 5.17 (br s, 1H, NH), 4.27 (dd, 1H, CH), 3.62−3.78 (s, 3H), 3.80−3.98 (s, 3H), 2.34−2.45 (t, 2H), 2.10−2.25 (m, 1H), 1.85−2.0 (m, 1H), 1.43 (s, 9H). EIMS: $m/z = 275$ (M^+). $[\alpha]^{25}_D = +12.5$ ($c = 2$, $CHCl_3$);[19] optical purity: 96.89%. HPLC retention time (t_R) = 4.683 min (purity (area %) 95.80 at 230 nm).

L-*tert*-Butyl *N*-[2,6-Dioxohexahydro-3-pyridinyl] Carbamate (5). To a stirred solution of sodium amide [65.46 mmol; prepared in situ from sodium metal (1.5 g) and ammonia in the presence of a catalytic amount of iron(III) nitrate in liquid ammonia (250 mL)] is added a solution of the NH−Boc protected glutamic acid diester **4** (6 g, 21.82 mmol) in dry THF (150 mL) at −33 °C. After stirring for 2 h, ammonium chloride (10 g) is added, and the ammonia is

allowed to evaporate. Water (200 mL) is added to the residue, and the mixture is extracted with chloroform (3 × 200 mL). The extract is dried with Na_2SO_4 and concentrated and column purified on silica gel with chloroform/acetone (9:1) to afford **5** (3.38 g, 13.11 mmol, 68% yield) as white crystals, mp 212−214 °C. IR: 3362, 3201, 1731, 1692 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ = 7.92 (br s, 1H, CONHCO), 5.3 (br s, 1H, NHCO), 4.21 (dd, J = 6.2 Hz, J = 11.0 Hz, 1H), 2.75−2.63 (m, 1H), 2.45 (m, 1H), 1.95−1.87 (m, 2H), 1.40 (s, 9H). ^{13}C NMR (DMSO-d_6) δ (ppm): 172.4, 172.0, 155.4, 78.2, 50.6, 31.0, 28.0, 24.4. EIMS: m/z = 228 (M^+). Anal. Calcd for $C_{10}H_{16}N_2O_4$: C, 52.68; H, 7.07; N, 12.28; O, 28.07. Found: C, 52.64; H, 7.12; N, 12.74; O, 27.55. $[\alpha]^{25}_D$ = −58.2 (c = 1.05, MeOH);[20] optical purity, 93.4%. HPLC retention time (t_R) = 6.069 min (purity (area %) 95.05 at 210 nm).

Aminoglutarimide Trifluoroacetate. To compound **5** (2.5 g, 9.69 mmol) in DCM (200 mL) at 0 °C was added TFA (20 mL) slowly, and the solutiong was allowed to stand for vigorous stirring at room temperature for 3.5 h. After the reaction was complete by TLC, the solvent was rotavaped to furnish free amine compound (2.63 g, quant) as a solid. ^1H NMR (300 MHz, DMSO-d_6) δ (ppm): 11.37(s, 1H, NH), 8.68 (br, 2H), 4.32 (dd, J = 5.4 Hz, J = 13 Hz, 1H), 2.86−2.72 (m, 2H), 2.25−2.09 (m, 2H).

(2-(2,6-Dioxo-3-piperidyl) Isoindoline-1,3-dione) (6) (Scheme 2). To aminoglutarimide trifluoroacetate (2 g, 8.26 mmol), phthalic anhydride (1.02 g, 7 mmol) and Et_3N (2.43 mL) were added and kept under reflux conditions for 2 h in glacial acetic acid (75 mL). After monitoring TLC, the reaction mixture was poured into ice. The desired compound was obtained by filtration by a Buchner funnel in vacuo as a powder which was further crystallized from ethyl acetate to give thalidomide **6** (1.15 g, 4.48 mmol, 65%) as a white solid, mp 275−276 °C. IR (KBr): 3194, 1778, 1707 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ = 11.00 (s, 1H, NH), 8.03−7.78 (br s, 4H, Ar, 2H), 5.15 (dd, J = 12.8, 5.4 Hz, 1H, CHCO), 2.89−2.72 (m, 1H, CH_2CO), 2.69−2.47 (m, 2H, CH_2 CH_2), 2.13−2.01 (m, 1H, CH_2). ^{13}C NMR (DMSO-d_6) δ (ppm): 173.2, 170.2, 167.6, 135.3, 131.7, 123.8, 49.5, 31.4, 22.5. FABMS: m/z = 259 (M^+ + 1). Anal. Calcd for $C_{13}H_{10}N_2O_4$: C, 60.47; H, 3.91; N, 10.84; O, 24.78. Found: C, 60.43; H, 3.85; N, 10.83; O, 24.89. HPLC retention time (t_R) = 6.997 min (purity (area %) 96.96 at 230 nm).

^1H and ^{13}C NMR Spectral Pattern for the Compounds 5 and 6. In the ^1H NMR spectrum of thalidomide, the four protons of the aromatic ring resonate as a symmetrical multiplet at δ 7.82. The signal from H-1δ appears as a doublet of doublets (J = 5.4 and 12.8) at δ 5.16. The remaining four protons on the piperidinedione ring appear as three sets of multiplets at δ 2.08, 2.55, and 2.88. The amine proton resonates as a broad singlet at ca. δ 11.00. In the ^{13}C NMR spectrum of thalidomide three signals at δ 173.2, 170.2, and 167.6 attributable to the four carbonyl carbon atoms and three signals at 135.3, 131.7, and 123.8 attributable to the six aromatic carbon atoms are clearly discernible. The three remaining carbon atoms of the piperidinedione ring resonate at 49.5 (C-1), 31.4 (C-5), and 22.5 (C-6), respectively.

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Supporting Information Available

Experimental procedures, complete spectral data for all compounds, and ^1H and ^{13}C NMR spectra for **5** and **6**. This material is available free of charge via the Internet at http://pubs.acs.org.

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