A Synthesis of Thalidomide

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A synthesis of racemic thalidomide (**1**) was described and the important formal [3+3] cycloaddition strategy was a key step. The total yield of thalidomide (**1**) was 18% in five steps from known **3**.

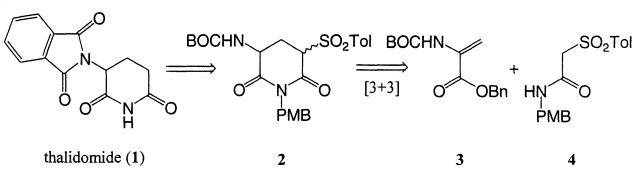
INTRODUCTION

Glutarimides (2,6-piperidinedione) possess various biological activities.[1,2] Therefore, the preparation of these imides has attracted attention in organic chemistry, e.g. cycloheximide,[3] actiketal,[3] thalidomide[4-7] and aminoglutethimide.[4-6,8] The interest in the immuno-suppressor thalidomide has been growing regularly.[9] It is currently used for treatment of AIDS.[10,11] Its activity against angiogenesis has been recently discovered.[12] Thalidomide (**1**) is currently used in therapy as a racemate. The rate of racemization of **1** was determined by its half life to be 556 min at PH = 7.4 (37 ℃).[13] The pure enantiomer was obtained by preparative chiral chromatography.[14] In the report we described the synthesis of racemic thalidomide (**1**) by formal [3+3] cycloaddition reaction.[8]

RESULTS AND DISCUSSION

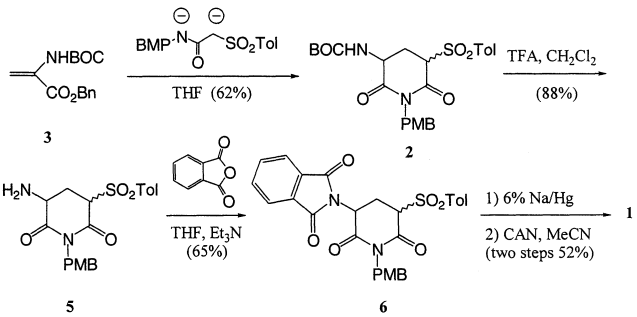
Our strategy for the synthesis of thalidomide (**1**) is illustrated in Scheme I. The key step was formal [3+3] cycloaddition reaction of α,β-unsaturated ester **3** and *N*-*p*-methoxybenzyl-α-sulfonyl acetamide **4**. The given adduct was the 5-substituted α-sulfonyl glutarimide **2** in 62% yield as the mixture. The 2:1 ratio in the mixture **2** was determined by ^{1}H NMR spectra. The α,β-unsaturated ester **3** was prepared from iodide compound[15] and triethylamine in methylene chloride.

Scheme I



The elimination result was afforded in 82% yield. Iodide compound was prepared from serine by known methods.[15] Acetamide **4** was furnished by acetylation of chloroacetyl chloride and *N*-*p*-methoxybenzylamine, followed by nucleophilic substitution of *p*-toluenesulfonic acid sodium salt. Compound **4** was obtained in 90% yield. As shown in Scheme II, the acidolysis of the BOC protective group in **2** with trifluoroacetic acid in methylene chloride gave the amine **5**. The solution of **5** in chloroform appeared an interesting deep-blue color. We made the skeleton of 2-aminoglutarimide by a facile formal [3+3] cycloaddition reaction in two steps from known **3**. Phthaloylation of crude primary amine **5** with phthalic anhydride and triethylamine in reflux temperature provided compound **6** in 65% yield. Treatment of **6** with 6% sodium amalgam (Na-Hg) in methanol afforded PMB-thalidomide.[7] Desulfonylation of compound **6** must control the PH value (7.4) to prevent the ring-opening of glutarimide. Without purification, the crude product **6** was treated with ceric ammonium nitrate to remove the PMB group[16] in **6** and thalidomide (**1**) was afforded. The total yield of thalidomide is 18% in five steps from known **3**. In conclusion, the presented synthesis provided a new strategy for racemic thalidomide by formal [3+3] cycloaddition reaction, and the method could be useful in the search for immunosuppressors. We are

Scheme II



currently studying the scope of this process as well as additional application of the methodology to the synthesis of different heterocyclic atoms at the 2-position of glutarimide.

EXPERIMENTAL SECTION

General

Tetrahydrofuran was distilled prior to use from a deep-blue solution of sodium-benzophenone ketyl. All other reagents and solvents were obtained from commercial sources and used without further purification. Reactions were routinely carried out under an atmosphere of dry nitrogen with magnetic stirring. The organic layer was dried with anhydrous magnesium sulfate before concentration *in vacuo*. Crude products were purified by column chromatography on silica gel. All reported temperatures are uncorrected.

N-*p*-Methoxybenzyl-2-toluenesulfonyl acetamide (4)

To a solution of *p*-methoxybenzylamine (1.37 g, 10.0 mmol) and triethylamine (1.06 g, 10.5 mmol) in tetrahydrofuran (30 mL) was added to chloroacetyl chloride (1.2 g, 10.6 mmol) in tetrahydrofuran (20 mL) in an ice bath for 30 min. After the reaction mixture was stirred at room temperature for 4 h, the mixture was concentrated under reduced pressure. Then the crude product was extracted with ethyl acetate (3 × 50 mL) and the combined organic layers were washed with brine (2 × 20 mL), dried over anhydrous magnesium sulfate, filtered and evaporated. Without purification, the crude product was refluxed with *p*-toluenesulfonic acid sodium salt (3.2 g, 16.5 mmol) in dioxane (70 mL) and water (70 mL) for 10 h. Then the mixture was concentrated under reduced pressure and the residue was extracted with ethyl acetate (3 × 100 mL). The combined organic layers were washed with brine (2 × 20 mL), dried over anhydrous magnesium sulfate, filtered and evaporated. Recrystallization on hexane and ethyl acetate afforded 3.0 g (90%) of acetamide **4**. Electrospray-MS: $C_{17}H_{19}NO_4S$ *m/z* (%) = 334 (M^++1, 100); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (d, *J* = 8.3 Hz, 2H), 7.28 (d, *J* = 8.3 Hz, 2H), 7.21-7.18 (m, 2H), 6.93 (brs, 1H), 6.88-6.85 (m, 2H), 4.36 (d, *J* = 5.8 Hz, 2H), 3.98 (s, 2H), 3.81 (s, 3H), 2.43 (s, 3H).

1-*p*-Methoxybenzyl-3-*tert*-butoxycarbonylamino-5-toluene sulfonyl-piperidine-2,6-dione (2)

A solution of **4** (333 mg, 1.0 mmol) in tetrahydrofuran (10 mL) was added to a rapidly stirred suspension of sodium hydride (60%, 2.2 mmol) in tetrahydrofuran (10 mL). After the reaction mixture was stirred at room temperature for 5 min, a solution of benzyl ester **3** (260 mg, 1.0 mmol) in tetrahydrofuran (10 mL) was added. The resulting mixture was heated at reflux temperature for 20 min, quenched with saturated ammonium chloride solution (1 mL) and the mixture was concentrated under reduced pressure. Then the crude product was extracted with ethyl acetate (3 × 20 mL) and the combined organic layers were washed with brine (2 × 20 mL), dried over anhydrous magnesium sulfate, filtered and evaporated. Purification on silica gel (hexane/ethyl acetate = 4/1) afforded 300 mg (62%) of **2** as a solid: mp 83-84 °C. Electrospray-MS: $C_{25}H_{30}N_2O_7S$ *m/z* (%) = 447 (100), 503 (M^+, 44). IR (film) 1720 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, *J* = 8.3 Hz, 4/5H), 7.55 (d, *J* = 8.3 Hz, 6/5H), 7.33-7.19 (m, 4H), 6.82-6.76 (m, 2H), 5.50-5.20 (brs, 1H), 5.00-4.74 (m, 3H), 4.30-4.10 (m, 1H), 3.77 (s, 9/5H), 3.76 (s, 6/5H), 3.20-2.95 (m, 1H), 2.44 (s, 3H), 2.30-2.17 (m, 1H), 1.45 (s, 9H). Anal. Calcd. for $C_{25}H_{30}N_2O_7S$: C, 59.75; H, 6.02. Found: C, 59.80; H, 6.06.

1-*p*-Methoxybenzyl-3-phthalimido-5-toluenesulfonyl-piperidine-2,6-dione (6)

Compound **2** (486 mg, 1.0 mmol) was dissolved in methylene chloride (10 mL). Trifluoroacetic acid (3 mL) was added into the solution and the mixture was stirred for 30 min at room temperature. Methylene chloride and excess trifluoroacetic acid were removed under reduced pressure to get the crude amine **5** in 88% yield as a viscous oil. Electrospray-MS: $C_{20}H_{22}N_2O_5S$ *m/z* (%) = 403 (M^++1, 100). Triethylamine (600 mg, 5.93 mmol), phthalic anhydride (170 mg, 1.15 mmol) and 4 Å MS were added. After heating for 2 h, the mixture was filtered and the solvent was removed under reduced pressure to get the crude amine **6**. Purification on silica gel (hexane/ethyl acetate = 2/1) afforded 450 mg (65%) of **6** as a solid: mp 110-111 °C. Electrospray-MS: $C_{28}H_{24}N_2O_7S$ *m/z* (%) = 403 (100), 533 (M^++1, 42). IR (film) 1743, 1704 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89-7.74 (m, 4H), 7.53 (d, *J* = 8.2 Hz, 4/3H), 7.33-7.26 (m, 4H), 7.17 (d, *J* = 8.7 Hz, 2/3H), 6.84 (d, *J* = 8.2 Hz, 4/3H), 6.72 (d, *J* = 8.7 Hz, 2/3H), 5.78 (dd, *J* = 6.4, 13.1 Hz, 2/3H), 5.03-4.76 (m, 7/3H), 4.34 (dd, *J* = 8.4, 13.7 Hz, 1/3H), 4.21 (dd, *J* = 1.4, 6.0 Hz, 2/3H), 3.78 (s, 2H), 3.73 (s, 1H), 3.19-3.04 (m, 1H), 2.96-2.92 (m, 2/3H), 2.73-2.70 (m, 1/3H), 2.44 (s, 3H). Anal. Calcd. for $C_{28}H_{24}N_2O_7S$: C, 63.15; H, 4.54. Found: C, 63.19; H, 4.55.

Thalidomide (1)

To a solution of compound **6** (133 mg, 0.25 mmol) and Na_2HPO_4 (142 mg, 1 mmol) in HPLC-grade methanol (5 mL) was added 6% sodium amalgam (360 mg, 0.95 mmol). The mixture was vigorously stirred for 1 h at room temperature. After concentration of the solution, methylene chloride (10

mL) was added to the residue, washed with water (4 × 10 mL), dried over anhydrous magnesium sulfate, and concentrated to get the crude desulfonyl compound. The crude compound was dissolved in acetonitrile (3 mL) and water (1 mL). Excess ceric ammonium nitrate reagent (6 eq, 1.5 mmol) was added (in six portions) into the solution. The reaction was stirred 5 h at room temperature. After concentration of the solution, methylene chloride (3 mL) was added to the residue and was placed in the flash column directly. Purification on silica gel (hexane/ethyl acetate = 1/2) afforded 34 mg (52%) of thalidomide (**1**) as a solid: mp 275-277 °C. Electrospray-MS: $C_{13}H_{10}N_2O_4$ *m/z* (%) = 259 (M^++1, 100). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (brs, 1H), 7.89-7.86 (m, 2H), 7.78-7.75 (m, 2H), 4.98 (dd, *J* = 5.3, 12.4 Hz, 1H), 2.93-2.71 (m, 3H), 2.18-2.12 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.74, 167.89, 167.33, 134.59 (2×), 134.44, 131.82, 123.91 (2×), 123.80, 49.43, 31.49, 22.30.

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Key Words

Glutarimides; Thalidomide; Formal [3+3] cycloaddition reaction; Phthaloylation.

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