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A Concise Two-Step Synthesis of Thalidomide

George W. Muller,* William E. Konnecke, Alison M. Smith, and Vikram D. Khetani
Celgene Corporation, 7 Powder Horn Drive, Warren, New Jersey 07059

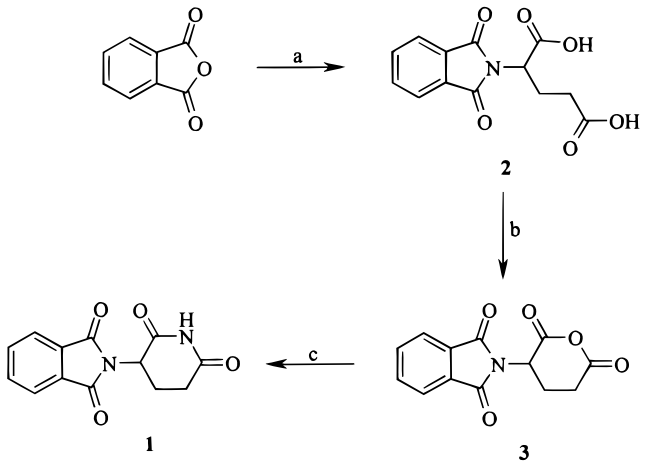
Abstract:

A two-step synthesis of thalidomide is presented. The sequence requires no purifications. Treatment of L-glutamine with *N*-carbethoxyphthalimide produces *N*-phthaloyl-L-glutamine. Cyclization of *N*-phthaloyl-L-glutamine to afford thalidomide is accomplished by treatment with CDI in the presence of a catalytic amount of DMAP.

Thalidomide (2-(2,6-dioxo-3-piperidyl)isoindoline-1,3-dione, **1**) was developed as a safe alternative to barbiturates in the late 1950s in Germany.[1] It was widely used as a sedative and to prevent morning sickness in pregnant women. By 1962, thalidomide's teratogenic effects had become a tragedy. However, even with its teratogenic effects, thalidomide continued to be used clinically. The serendipitous discovery of thalidomide's clinical activity in the treatment of erythema nodosum leprosum (ENL) in leprosy led to the discovery of its immunomodulating and antiinflammatory activities.[2] Since then, thalidomide has been used experimentally with benefit in a number of autoimmune and inflammatory diseases. Although thalidomide was not approved by the FDA in the 1950s, it has been used clinically in the United States on investigational new drug applications for over 20 years. However, thalidomide's immunomodulating properties led to its approval by the FDA for the treatment of ENL in July of 1998 under a strict distribution and monitoring program. In a 1991 publication, the Kaplan group[3] reported that thalidomide was a selective inhibitor of tumor necrosis factor-α (TNF-α). Overproduction of TNF-α is believed to be involved in a variety of inflammatory and autoimmune diseases.[4] Recent clinical trials using TNF-α antibodies have shown efficacy in the treatment of rheumatoid arthritis and Crohn's disease, confirming the role of TNF-α in these diseases.[5]

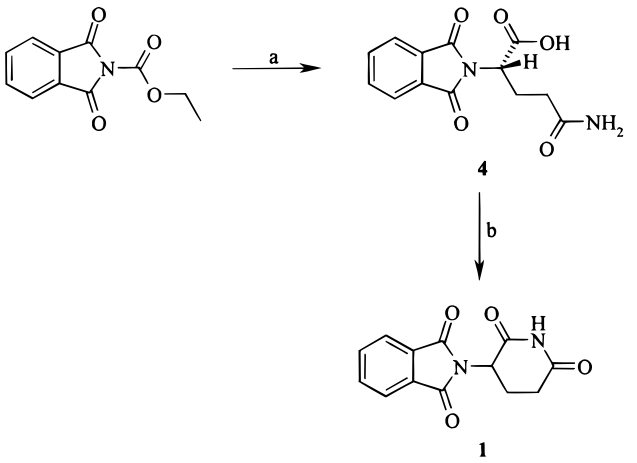
Celgene Corporation is interested in the clinical development of thalidomide for its anti-inflammatory and immunomodulating properties. For this development and for further research into thalidomide's biological properties and mechanism of action, we wanted to develop a concise synthesis of thalidomide which could be used for preparing multigram to multikilogram quantities in standard glassware and pilot plant equipment.

Scheme 1[a]



[a] Conditions: (a) L-glutamic acid/pyridine reflux; (b) Ac_2O; (c) urea, melt.

Scheme 2[a]



[a] Conditions: (a) (1) L-glutamine, Na_2CO_3, (2) 4 N $HCl_{(aq)}$ (67%); (b) CDI, DMAP (91%).

Thalidomide has always been used clinically as a racemate. It is the classically quoted example of a drug developed as a racemate in which only one isomer, the *S*-isomer, carries the negative side effect, teratogenicity. However, recent publications have shown that thalidomide is chirally unstable in vitro and in vivo, thus making the chiral issue moot.[6]

To take advantage of previous preclinical and clinical experience with thalidomide, we were interested in developing a racemic synthesis. Thalidomide has traditionally been

(1) Stirling, D.; Sherman, M.; Strauss, S. *J. Am. Pharm. Assoc.* **1997**, *3*, NS37. (b) Tseng, S.; Pak, G.; Washenik, K.; Pomeranz, M. K.; Shupack, J. L. *J. Am. Acad. Dermatol.* **1996**, *35* (6), 969−979.
(2) Sheskin, J. *Clin. Pharmacol. Ther.* **1965**, *6*, 303−311.
(3) Sampaio, E. P.; Sarno, E. N.; Gallily, R.; Cohn, Z. A.; Kaplan, G. *J. Exp. Med.* **1991**, *173*, 699−703.
(4) (a) Tracey, K. J.; Cerami, A. *Annu. Rev. Med.* **1994**, *45*, 491−503. (b) Sekut, L.; Conolly, K. M. *Drug News Perspect.* **1996**, 261−269. (c) Rink, L.; Kirchner, H. *Int. Arch. Allergy Immunol.* **1996**, *111*, 199−209.
(5) (a)Van Hogezand R. A.; Verspaget, H. W. *Scand. J. Gastroenterol.* **1997**, *32* (Suppl. 223), 105−107. (b) Elliott, M. J.; Feldmann, M.; Maini, R. N. *Int. J. Immunopharmacol.* **1995**, *17* (2), 141−145.
(6) (a) Eriksson, T.; Bjorkman, S.; Roth, B.; Fyge, A.; Hoglund, P. *Chirality* **1995**, *7*, 44−52. (b) Knoche, B.; Blaschke, G. *J. Chromatogr. A* **1994**, *666*, 235−240.
(7) Reepmeyer, J. C.; Cox, D. C. *FDA monograph: Guidelines to Thalidomide Synthesis*; U.S. Food & Drug Administration: Washington, DC, June 1987.
(8) Shealy, Y. F.; Opliger, C. E.; Montgomery, J. A. *Chem. Ind.* **1965**, 1030−1031.

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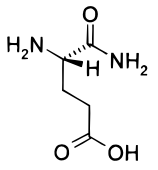
prepared as outlined in Scheme 1.[7] This is a fairly simple three-step sequence. The last step in this synthesis involves a high-temperature melt reaction that affords a crude thalidomide requiring multiple recrystallizations. In our synthesis, we wished to avoid the melt reaction, which is not amenable to standard equipment.

The synthesis in Scheme 1 begins with L-glutamic acid, but a synthesis starting with L-glutamine would allow a more direct two-step synthesis to be developed. In a 1965 paper, the use of 1,1′-carbonyldiimidazole (CDI) for 4 days at room temperature in DMF for the cyclization of *N*-phthaloyl-L-isoglutamine to form (*S*)-thalidomide in low yield (41%) was reported.[8] In the same paper, under similar conditions, *N*-phthaloyl-L-glutamine was cyclized to afford a 31% yield of racemic thalidomide. In an earlier paper, acetic anhydride was used for this cyclization; however, again the cyclization afforded a low yield (33%) of thalidomide.[9]



L-isoglutamine

We felt the approach starting from L-glutamine instead of L-glutamic acid afforded a more direct route (Scheme 2). Glutamine was chosen over isoglutamine because of cost and the desire for racemic material. *N*-Phthaloyl-L-glutamine (**4**) was prepared by a standard technique using *N*-carbethoxyphthalimide. Treatment of L-glutamine with Na_2CO_3 in water followed by the addition of *N*-carbethoxyphthalimide afforded, after workup, a 50−70% yield of **4** as a white powder. During the acidification, the reaction mixture is seeded with solid **4** to ensure solidification of the product. This material requires no purification. Use of *N*-carbethoxyphthalimide produces chirally pure **4**. This is as expected from literature precedent[10] and was confirmed in our laboratories by conversion of the material to (*S*)-thalidomide using the previously published cyclization method of Casini and Ferappi.[11] The cyclization of **4** is accomplished using CDI in THF. Racemization of the product occurs in this step. THF was used since thalidomide has a low solubility in THF and the imidazole byproduct from CDI is soluble in THF. A stirred mixture of **4** and CDI (1.05 equiv) in the presence of a catalytic amount of DMAP in THF is heated to reflux for 15−18 h. Further work demonstrated that DMAP is not required for this cyclization to occur. Thalidomide crystallizes out of the reaction mixture during reflux. The cooled reaction mixture is filtered to produce an 85−93% yield of thalidomide as a white solid.[12] This material is normally of greater than 99% purity.[13] The racemic nature of this material was confirmed by chiral HPLC.[14]

In conclusion, a synthesis was developed which fulfilled our initial requirements of readily available starting materials, no purifications, a good yield, and ability be done in standard glassware and pilot plant equipment. The procedure can easily be used to prepare thalidomide at the 100-g scale in the laboratory, and it was successfully scaled up to the multikilogram scale.

Experimental Section

All reactions were run under a nitrogen atmosphere unless otherwise noted. All of the final compounds synthesized were characterized by ^1H and ^{13}C NMR, C, H, N elemental analysis, and melting point for solids. ^1H and ^{13}C NMR were determined on a Bruker AC250 FT instrument in an appropriate deuterated solvent. Elemental analyses and melting point determinations were done by Quantitative Technologies Inc., Whitehouse, NJ. Reagents and solvents were used as received from commercial suppliers.

***N*-Phthaloyl-L-glutamine (4).** To a stirred solution of L-glutamine (43.8 g, 300 mmol) and Na_2CO_3 (33.4 g, 315 mmol) in 750 mL of water was rapidly added *N*-carbethoxyphthalimide [65.8 g (97% pure, 67.8 g), 300 mmol] as a solid. After 1 h, the reaction mixture was filtered to remove unreacted *N*-carbethoxyphthalimide. The pH of the stirred filtrate was adjusted to 3−4 with 6 N HCl. The mixture was then seeded with *N*-phthaloyl-L-glutamine and the pH adjusted to 1−2 with 6 N HCl. The resulting slurry was stirred for 1 h. The slurry was filtered and the solid washed with copious amounts of water. The solid was air-dried and then dried in vacuo (60 °C, <1 mmHg) overnight to afford 51.8 g (67%) of **4** as a white powder: mp 169−171 °C; ^1H NMR (dmso-d_6) δ 13.22 (br s, 1 H, COOH), 8.05−7.75 (m, 4 H, Ar), 7.22 (s, 1 H, $CONH_2$), 6.74 (s, 1 H, $CONH_2$), 4.76 (dd, 1 H, CH), 2.50−1.95 (m, 4 H, CH_2CH_2), 2.15−2.00 (m, 1 H, CH_2); ^{13}C NMR (dmso-d_6) δ 173.0, 170.4, 167.3, 134.7, 131.2, 123.3, 51.2, 31.3, 23.9. Anal. Calcd for $C_{13}H_{12}N_2O_5$: C, 56.52; H, 4.38; N, 10.14. Found: C, 56.64; H, 4.33; N, 10.10.

Thalidomide (1). A stirred mixture of **4** (125 g, 452 mmol), CDI (76.1 g, 469 mmol), and 4-DMAP (0.20 g, 1.6 mmol) in anhydrous THF (750 mL) was heated to reflux for 16 h. The reaction slurry was filtered and the solid washed with CH_2Cl_2 (200 mL). The solid was air-dried and then dried in vacuo (60 °C, <1 mmHg) to afford 106 g (91%) of the product as a white powder: mp 274−276 °C; ^1H NMR (dmso-d_6) δ 11.16 (s, 1 H, NH), 8.05−7.80 (br s, 4 H, Ar), 5.18 (dd, 1 H, J = 12, 5 Hz, CHCO), 3.05−2.85 (m, 1 H, CH_2CO), 2.70−2.45 (m, 2 H, CH_2CH_2), 2.15−2.00 (m, 1 H, CH_2); ^{13}C NMR (dmso-d_6) δ 172.8, 169.8, 167.1, 134.9, 131.2, 123.4, 49.0, 30.9, 22.0. Anal. Calcd for $C_{13}H_{10}N_2O_4$: C, 60.47; H, 3.90; N, 10.85; O, 24.78. Found: C, 60.42; H, 3.82; N, 10.81; O, 24.98.

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(9) Kig, F. E.; Clark-Lewis, J. W.; Wade, R.; Swindon, W. A. *J. Chem. Soc.* **1957**, 873−880.
(10) Bodanszky, M.; Bodanszky, A. *The Practice of Peptide Synthesis*; Springer-Verlag: New York-Heidelburg-Berlin-Tokyo, 1984; pp 10−11.
(11) Casini, G.; Ferappi, M. *Farmaco, Ed. Sci.* **1964**, 563−56.
(12) Additional material can be obtained from the mother liquor.
(13) The major impurity is **4**.
(14) The racemic nature of the material was determined on a Daicel Chemical Industries Chiralpak OJ column using ethanol as the eluent.