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A Novel and Efficient Synthesis of Thalidomide

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Abstract: A facile, efficient, concise, cost-effective, and scalable synthesis of thalidomide in high overall yield (61%) is presented. The present invention Preparation of Thalidomide which comprises, reacting Phthalicanhydride with L-glutamine to give N-phthaloyl L-glutamine, which is further subjecting to cyclization reaction in the presence of pivaloylchloride to give Thalidomide.
Key words: Synthesis ,Thalidomide.

IINTRODUCTION:

Thalidomide (2-(2, 6-dioxo-3-piperidyl) isoindoline-1, 3-dione, 2) was developed as a safe alternative to barbiturates in the late 1950s in Germany.[1] 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.[2] Interest in thalidomide was initially rekindled in the mid-1960s after approval by the FDA, United States in 1998, because of its effect on (ENL). Interest in the agent was reawakened after thalidomide was found clinically effective in the treatment of erythema nodosum leprosum (ENL) [3] and in the treatment of HIV wasting syndrome and various cancers.[4,5] Mechanistic studies of its ENL activity demonstrated an anti-TNL-α action.[6] Specifically, thalidomide enhances the degradation of tumor necrosis factor-α (TNF-α) RNA and, thereby, lowers its synthesis and secretion.[7,8] It is now apparent that it has anti-inflammatory properties in other diseases, such as in the treatment of severe aphthous stomatitis, cancer, Bechet's disease, graft-versus-host disease (GVHD), some infestations of HIV infection, and,possibly,malignancies.[9,10] 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.[11,12] 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.[13] Syntheses of thalidomide have been well documented in literature.[14]

The mechanisms underlying thalidomide's diverse action, together with identification of the active species, remains an area of intense research. The compound is more active in vivo than would be predicted from its potency in vitro studies.[15, 16]

CHEMISTRY:

L-Glutamine was chosen over isoglutamine because of cost and the desire for racemic material. N-Phthaloyl-L-glutamine (1) was prepared by treatment of L-glutamine and phallicanhydride with Dimethyl formamide was heated for 3 hours, and concentrated dimethylformamide under vacuum, to afforded N-Phthaloyl-L-glutamine a 72 % yield of 1 as a white powder. During the acidification, the reaction mixture is ensuring solidification of the product. This material requires no purification. Use of N-Phthaloyl-L-glutamine produces chirally pure 1 and was confirmed by conversion of the material to (S)-thalidomide using the previously published cyclization method of Casini and Ferappi.[17,18] The cyclization of 1 is accomplished using pivaloylchloride and triethylamine in ethyl acetate. A stirred mixture of 1 and pivaloylchloride (1.2

equiv) in the presence of triethylamine (2.0 equiv) in ethyl acetate is heated to reflux for 2 hours... Thalidomide crystallizes out of the reaction mixture during reflux. The cooled reaction mixture is filtered to produce an 85-90% yield of thalidomide as a white solid. In conclusion, a synthesis was developed which fulfilled our initial requirements of readily available starting materials no purifications and good yield. The basic premise of objective was too tried different a number of bases were studied given table 1. As shown below, but comparison this cyclisation using the reagent was more effective yield and purity.

EXPERIMENTAL SECTION:

All reactions were run under a nitrogen atmosphere unless otherwise noted. All of the final compounds synthesized were characterized by ^{1}H and ^{13}C NMR and melting point for solids.

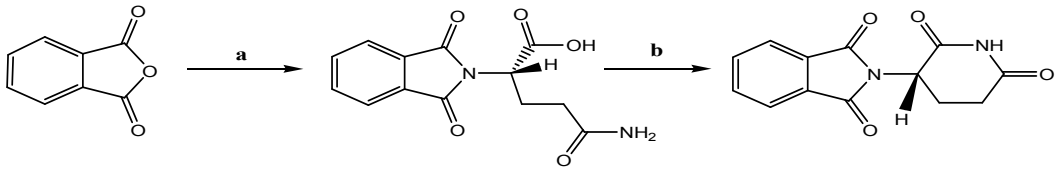
N-Phthaloyl-L-glutamine (1). :To stirred solution of dimethylformamide (15 mL) and L-glutamine (5.0 g, 0.034 mol), slowly heated to 40-45 °C to the resulting solution added phalicanhydride (5.0 g, 0.033 mol) and heated to 90-95 °C.Stirred for 3 hr at this temperature, cooled to 65 °C, and distilled dimethylformamide under vacuum. Add water and adjust the pH 1-2 with 6N HCl, Stirred for 2 hrs at 15 °C. Filtered, washed with chill water. Dried to get N-Phthaloyl-L-glutamine 6.75 g (72%) of 1 as a white powder: mp 169-171 °C.

^{1}H NMR (dmso-d_6) δ: 13.20 (br s, 1 H, COOH), 8.05-7.75 (m, 4H, Ar), 7.22(s, 1H, $CONH_2$), 6.72(s, 1H, $CONH_2$), 4.72 (dd, 1H,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:
IR in KBr(Cm^{-1}):: 3448,3333,3279,2920, 1776, 1708, 1651,1601,1396,1253,1113,1038,718.
Mass *m/z* = 277 (M^+).

Thalidomide (2). A stirred solution of N-Phthaloyl-L-glutamine (1) (5.0 g 0.018 mol) in ethyl acetate (40 mL) and triethylamine (3.6 g, 0.035 mol) at ambient temperature. The solution was cool to 0-5 °C, added pivaloylchloride (2.6 g 0.021 mol). The resulting solution was stirred for 1 hr at 0-5 °C and slowly heated to reflux for 2 hrs, the reaction mixture was cool to room temperature. The reaction slurry was filtered and solid was washed with water (50 ml) and followed by chilled acetone (25 mL). The solid was air-dried and then dried in vacuum (60 °C, <1 mmHg) to afford 3.91 g (85 %) of the product as a white powder: mp 273-275 °C:
^{1}H NMR (dmso-d_6) δ11.13 (s, 1 H, NH), 8.03-7.80 (br s, 4H, Ar), 5.18 (dd, 1 H, CHCO), 2.96-2.85 (m,1H,CH_2CO), 2.63-2.47(m,2H,CH_2CH_2), 2.09-2.05(m, 1H, CH_2):
^{13}C NMR (dmso-d_6): δ 173.2, 170.2, 167.6, 135.3, 131.7, 123.8, 49.5, 31.4, 22.5:
IR in KBr (Cm^{-1}):
3193,3097,2912,1772,1709,1610,1471,1385,1259,1197,728
Mass *m/z* = 259 (M^+).

^{1}H NMR and ^{13}C NMR Spectral Pattern for the Compounds 1 & 2.: In the ^{1}H NMR spectrum of thalidomide, the four protons of the aromatic ring resonate as a symmetrical multiplet at δ 7.82. The signal from H- 1 δ appears as a doublet of doublets (*J* = 5.4 and 12.8) at δ 5.18. 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. δ11.13. 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.

Scheme 1



1 **2**

Reagents: (a) L-glutamine / dimethylformamide (b) pivaloylchloride, Et_3N/Ethyl acetate.

Table 1. Using different bases.

S.No	Base	Solvent	Purity by HPLC
1	Piperidine	Ethyl acetate	98.26
2	DBU	Ethyl acetate	97.05
3	diisopropylethylamine	Ethyl acetate	98.15

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REFERENCES:

1. (a) Stirling, D.; Sherman, M.; Strauss, S. *J. Am. Pharm. Assoc*. 1997, 3, NS37, 306-313. (b) Tseng, S.; Pak, G.; Washenik, K.; Pomeranz, M. K.; Shupack, J. L. *J. Am. Acad. Dermatol* 1996, 35, 969-979. (c) Eger, K.; Jalalian, B.; Verspohl, E. J.; Lupke, N. P. Synthesis, central nervous system activity and teratogenicity of a homothalidomide. *Arzneim. Forsch*. 1990, 40, 1073-1075.
2. (a) Hales, B. F. *Nat. Med*. 1999, 5, 489-49. (b) Hashimoto, Y. *Bioorg. Med. Chem*. 2002, 1, 461-479.
3. (a) Sheskin, J. Thalidomide in the treatment of lepra reaction. *Clin. Pharmocol. Ther*. 1965, 6, 303-306. (b) Hawkins, D. F. *Lancet* 1992, 339, 1057-1060.
4. Kumar, S.; Witzig, T. E.; Rajkumar, S. V. Thalidomide as an anti-cancer agent. *J. Cell Mol. Med*. 2002, 6, 160-174.
5. Richardson, P.; Hideshima, T.; Anderson, K. Thalidomide: emerging role in cancer medicine. *Annu. Rev. Med*. 2002, 53, 628-657.
6. Sampaio, E. P.; Sarno, E. N.; Gallily, R.; Cohn, Z. A.; Kaplan, G. Thalidomide selectivity inhibits tumor necrosis factor a production by stimulated human monocytes. *J. Exp. Med*. 1991, 173, 699-703.
7. Kruys, V.; Marinx, O.; Shaw, G.; Deschamps, J.; Huez, G. Translational blockade imposed by cytokine-derived UA-rich sequences. *Science* 1989, 245 (4920 Aug 25, 1989, 852-855.
8. Moreira, A. L.; Sampaio, E. P.; Zmuidzinas, A.; Frindt, P.; Smith, K. A.; Kaplan, G. Thalidomide exerts its inhibitory action on tumor necrosis factor a by enhancing mRNA degradation. *J. Exp. Med.* 1993, 177, 1675-1680.
9. (a) Ghobrial, I.; Rajkumar, S. V. *J. Support Oncol*. 2003, 1, 194-205. (b) Teo, S. K. *AAPS Journal*. 2005, 7, E14-E19.
10. (a) Richardson, P.; Hideshima, T.; Anderson, K. *Annu. Rev. Med*. 2002, 53, 629-657. (b) Calabrese, L.; Fleisher, A. B. *Am. J. Med*. 2000, 108, 487-495. (c) Mujagic, H.; Chabner, B. A.; Mujagic, Z. Croat. *Med. J*. 2002, 43, 274-285.
11. Eriksson, T.; Bjorkman, S.; Roth, B.; Fyge, A; Hoglund, P. *Chirality* 1995, 7, 44-52.
12. Shealy, Y. E.; Opliger, C. E.; Montgomery, J. A. *Chem. Ind*. 1965,1030-1031
13. Muller, G. W.; Konnecke, W. E.; Smith, A. M.; Khetani, V. D. *Org.Process Res. Dev*. 1999, 3, 139-140.
14. (a) Robin, S.; Zhu, J.; Galons, H.; Chuong, P. H.; Claude, J. R.; Thomas, A.; Viossat, B. *Tetrahedron Asymmetry* 1995, 6, 1249-1252. (b) Flaih, N.; Chuong, P. H.; Galons, H. *Tetrahedron Lett*. 1999, 40, 3697-3698. (c) Seijas, B. A.; Vazquez-Tato, M. P.; Cristobal, G. B.; Martinez, M. M.; Beatriz, P. L. *Synthesis* 2001, 7, 999-1000. (d) Karimi, F.; Kihlberg, T.; Langstrom, B. *J. Chem. Soc., Perkin Trans*. I 2001, 1528-1531. (e) Muller, G. W.; Chen,

R.; Huang, S. Y.; Corral, L. G.; Wong, L. M.; Patterson, R. T.; Chen, Y.; Kalpan, G.; Stirling, D. I. *Bioorg. Med. Chem. Lett*. 1999, 9, 1625-1630. (f) Xiao, Z.; Schaefer, K.; Firestine, S.; Li, P. K. *J. Comb. Chem*. 2002, 4, 149-153. (g) Chang, M. Y.; Chen, S. T.; S. T.; Chang, N. C. *Syn. Commun*. 2003, 33, 1375-1382. (h) Goosen, C.; Laing, T. J.; Jeanetta, D. P.; Goosen, T. C.; Flynn, G. L. *Pharm. Res*. 2002, 19, 13-19.

15. Bauer, K. S.; Dixon, S. C.; Figg, W. D. Inhibition of angiogenesis by thalidomide requires metabolic activation, which is species dependent. *Biochem. Pharmacol*. 1998, 55, 1827-1834.
16. Meierhofer, C.; Wiedermann. C. J. New insights into the pharmacological and toxicological effects of thalidomide. *Curr. Opin. Drug Discovery Dev.* 2003, 6, 92-99.
17. Casini, G.; Ferappi, M. Farmaco, Ed. Sci. 1964, 563-564.
18. George W. Muller, William E. Konnecke, Alison M. Smith, and Vikram D. Khetani *Organic process Research & Development* 1999, 3, 139-140.

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