Research Article
A Novel Green Synthesis of Thalidomide and Analogs

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Thalidomide and its derivatives are currently under investigation for their antiangiogenic, immunomodulative, and anticancer properties. Current methods used to synthesize these compounds involve multiple steps and extensive workup procedures. Described herein is an efficient microwave irradiation green synthesis method that allows preparation of thalidomide and its analogs in a one-pot multicomponent synthesis system. The multicomponent synthesis system developed involves an array of cyclic anhydrides, glutamic acid, and ammonium chloride in the presence of catalytic amounts of 4-N,N-dimethylaminopyridine (DMAP) to produce thalidomide and structurally related compounds within minutes in good isolated yields.

1. Introduction

Thalidomide has a long and tragic past that stems from its teratogenic effects. However, recent studies prove that it is an effective immunomodulatory, antiangiogenic, and anticancer pharmaceutical [1, 2]. This reemergence of thalidomide has led to a number of FDA approved derivatives including lenalidomide and pomalidomide (multiple myeloma) [3–5]. Currently thalidomide and its derivatives are used in the treatment of numerous diseases including Crohn [6–8], Leprosy [9–11], Graft-Versus-Host (GVHD) [12–14], and multiple forms of cancer [15–17]. They are also known to modulate the expression patterns of several proteins including TNFα [18–22], IL1β [23–27], and COX2 [28–31]. In fact, discovery of lenalidomide and pomalidomide had led scientists to explore the modification of thalidomide (Figure 1) to improve its efficacy and decrease its teratogenic and neurotoxic effects. Although there are several synthetic methods for making thalidomide many of the reported syntheses are often multistep processes which use exotic or expensive reagents, maintain long reaction times, and produce very low yields [32–43].

Our novel microwave assisted synthesis of thalidomide and its derivatives improves over current conventional and microwave assisted syntheses through the high yields of thalidomide and its systematic derivatization within minutes. Microwave application in organic synthesis has seen exponential growth over the last twenty years due to its easy experimental conditions, rapid turnaround, easy workups, and high yields. The speed at which microwave reactions are done matches well with combinational processes to synthesize derivatives for improved biological activity when compared to low-yielding conventional synthesis especially that of thalidomide and its analogs (24%). The power of microwave synthesis is utilized for speeding the reaction and providing an efficient convenient way of obtaining these thalidomide variations or related compounds [44–46].

Thalidomide and a series of its analogs (**2**–**5**) are shown in Figure 2 and synthesized in a one-pot reaction (Scheme 1), using mild conditions and inexpensive reagents, under green (microwave) conditions with relatively high yields. The strategy is based on utilizing the corresponding anhydrides, either commercially available anhydrides or constructed based on our earlier work of microwave assisted Diels Alder reaction of maleic anhydride with the required 1,3-diene. The synthesis of thalidomide (**1**) and derivatives (**2**–**5**) was accomplished in a one-pot reaction of glutamic acid with the corresponding anhydride and ammonium chloride with the use of DMAP as a base catalyst mixture at 150°C in 10 minutes. In this reaction we were able to form both substituted and unsubstituted
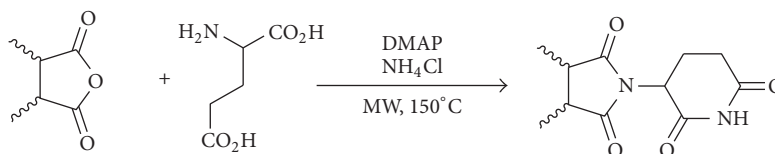
SCHEME 1: The synthesis of thalidomide and its analogs. Microwave conditions: 10 minutes at 150°C.
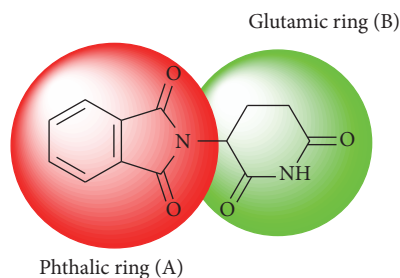

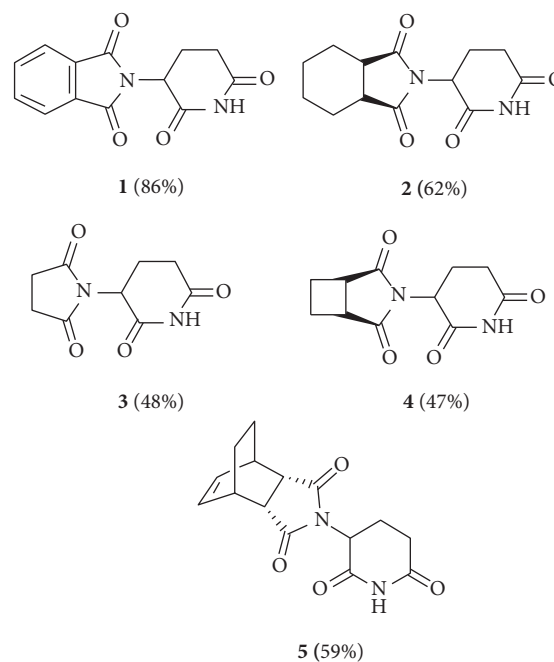FIGURE 1: The structure of thalidomide.

FIGURE 2: Thalidomide and thalidomide analogs synthesized.

cyclic imides through two condensation reactions of the cyclic anhydride and the glutamic acid moieties, respectively. The formation of unsubstituted imide is based on the generation of ammonia through the removal of proton from the ammonium chloride. The thalidomide derivatives produced a glutarimide ring with a diversity of cyclic anhydrides bound.

A primary benefit of our synthetic method over previous thalidomide syntheses methods includes the ability to modify the phthalic ring (Figure 1, moiety (A)). Although extensive work has focused on the modification of glutamic ring (Figure 1, moiety (B)) of thalidomide such as introduction of dithiocarbamate in order to enhance its biological activities, the carbon backbone is modified so that it can allow for variation in structure and functionality. This method focuses on the modification of the phthalic ring moiety of thalidomide (Figure 1), allowing for the addition of multiple carbon skeletons including bicyclic systems. Our synthesis allows for the exploration of the effects of ring size, ring strain, increased polarity, and structural complexity in addition to stereochemistry. These compounds may shed light on structure-activity relationship in thalidomide derivatives thereby improving their efficacy. Another benefit of this method is the ability to easily introduce labeled nitrogen through the use of ammonium-15N chloride in the reaction mixture.

Although this process occurs in one pot, it involves a multistep mechanism in which the amine of glutamic acid has to form an amide acid with the cyclic anhydride. If the cyclic amide-glutamic acid is not formed then reaction seems to proceed towards byproduct formation with the cyclic imide as the major product. A study to determine which catalyst could improve ammonia generation and product formation of thalidomide in the microwave

was done using thiourea, ammonium acetate, and ammonium chloride/DMAP with phthalic anhydride using similar molar ratios. Previous research in our laboratory has found several ways to produce ammonia from ammonium acetate and hydroxylamine (HCl)/DMAP with ammonium acetate being the best [47, 48]. This study used GC-MS for determining the ratio of unsubstituted cyclic imides (phthalimide) to thalidomide. The data shows that ammonium acetate is highly efficient at forming phthalimide (90% yield) but not thalidomide (yield < 7%). On the other hand, the reaction resulted in higher yields of thalidomide when DMAP/NH$_4$Cl (43%) and thiourea (40%) were used, Table 1.

The main byproduct formed when ammonium acetate is used is a cyclic imide and this may be explained by the rapid dissociation of ammonium acetate to give ammonia that initiates quick imide formation. Differences in the reactivity between ammonium acetate and ammonium chloride finds that ammonium chloride is highly stable and does not break down under microwave irradiation. The addition of DMAP as a base catalyst to ammonium chloride causes it to dissociate and generate ammonia at higher temperature, allowing glutamic acid to first react with the anhydrides to
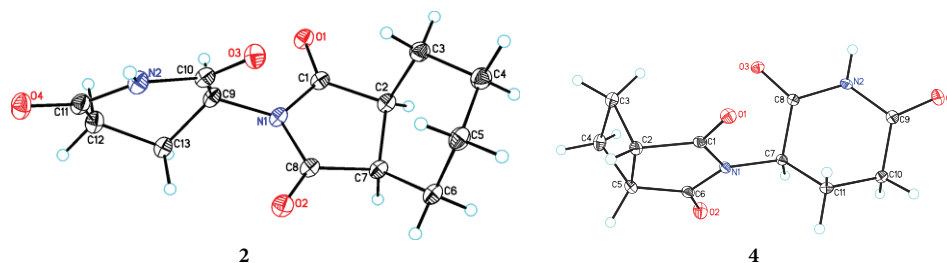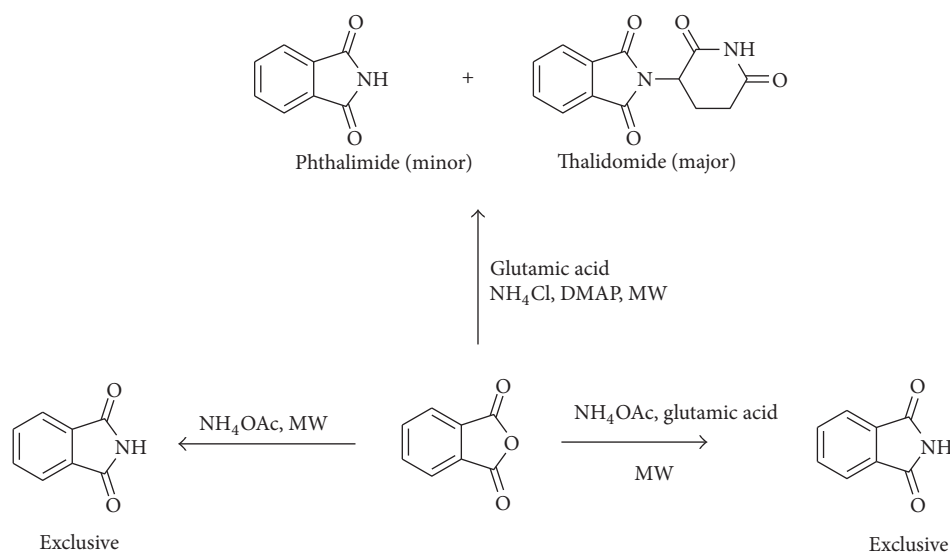
2   **4**

FIGURE 3: ORTEP drawings of compounds (**3**) and (**4**).

SCHEME 2: Synthesis of phthalimide and thalidomide.

TABLE 1: Comparison of thalidomide synthesis using DMAP/NH$_4$Cl, NH$_4$OAc, and thiourea in the monomode microwave at 150°C for 10 minutes.

Reagent	Phthalimide	Thalidomide
Thiourea	59%	40%
DMAP NH$_4$Cl	57%	43%
Ammonium acetate	90%	7%

form the imide (moiety (A)) followed by the generation of ammonia at higher temperature and the formation of the 2,6-dioxopiperidine, NH$_4$Cl ring later (moiety (B)). Long term tests (over 30 minutes) of NH$_4$Cl under microwave irradiation found that it does not readily break down and needs the presence of the DMAP as a base catalyst to initiate ammonia production allowing time for cyclic amide-glutamic acid formation (Scheme 2).

Compounds (**1**–**5**) were generated within minutes, even though the yields are moderate due the competition with ammonia generated in one-pot synthesis system. The yields are acceptable given the ease and simplicity of the reaction system. Compounds (**1**–**5**) were isolated, purified,

and identified by spectroscopic analysis. (Detailed ^{1}H and ^{13}C NMR spectra and mass spectrometry data are presented in the Supplementary Material available online at https://doi.org/10.1155/2017/6436185.) Further structural confirmation was provided by single crystal X-ray structural identifications [49]. Compounds **3** and **4** ORTEP are presented in Figure 3. Compound **3** presents interesting structural features with 4- and 5-membered fused rings with the piperidinedione ring at almost right angle with the pyrrolidine ring containing dihedral angles of 67.6° and 73.9° for the cyclobutane and 2,6-dioxopiperidine rings, respectively. Compound **5** has an intriguing structure that contains a bicyclic system with 4 chiral centers, a double bond that is a handle for further functionalization and a possibility of two more chiral centers.

In conclusion, we have developed a novel green one-pot synthetic technique for the generation of thalidomide and its analogs. Although this article shows only a small subset of compounds, there are a limitless number of derivatives that can be produced/derived using this technique. This technique also has a wide variety of applications as it relates to the production of thalidomide analogs that may be used for the treatment of multiple diseases.

Appendix

Experimental

A CEM Discover monomode microwave was used for microwave enhanced organic synthesis. Isolation procedures use TLC as a basis for the column chromatography of the materials. Gas Chromatography Mass Spectrometry (GC-MS) will be used to quantify and identify the amounts of product and possible byproducts found in the purified materials.

Standardized methods for the identification of products consisted of GC-MS, ^{1}H NMR, ^{13}C NMR, DEPT-C NMR, melting point, and Infrared Spectroscopy (IR). Every new compound synthesized was completely analyzed by all corresponding techniques. Gas Chromatograph Mass Spectrometry was performed using either a Shimadzu GC-17A and GC-MS-QP5050A LabSolutions system or a Varian CP 3800 and Saturn 2200 system.

All IR spectra were performed on a Perkin-Elmer Spectrum RX I IR system. All melting points determinations were performed on a Laboratory Devices Mel-Temp II instrument. ^{1}H, ^{13}C, and DEPT-C NMR were performed on Bruker 400 MHz. All solvents (HPLC grade) were purchased from Fisher Scientific Corporation. All reagents were purchased from Aldrich Chemical Company and were used without purification.

Thalidomide Synthesis

2-(2,6-Dioxopiperidin-3-yl)isoindole-1,3-dione. (**1**): phthalic anhydride (0.10 g, 0.68 mmol), glutamic acid (0.10 g, 0.68 mmol), DMAP (0.02 g, 0.16 mmol), and NH$_4$Cl (0.04 g, 0.75 mmol) were mixed thoroughly in a CEM-sealed vial with a magnetic stirrer. The sample was heated for 10 min at 150°C in a CEM Discover microwave powered at 150 W. It was then cooled rapidly to 50°C. When at room temperature it was dissolved in 15 mL of (1 : 1) ethyl acetate : acetone. The organic layer was washed with 2x (10 mL) distilled water and then dried over sodium sulfate (anhydrous). The organic layer was concentrated under vacuum. The residue was treated with hexanes (30 mL) affording a white solid (0.14 g, 80%). mp 268–270°C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.14 (s, 1 H, NH), 7.94 (m, 4 H, Ar), 5.17 (dd, 1 H, 12.5, 5.5 Hz), 2.92 (m, 1 H), 2.57 (m, 2), 2.09 (m, 1 H); ^{13}C NMR (100 MHz, DMSO-d_6) 172.7, 169.8, 167.1, 134.9, 131.2,123.4, 49.0, 30.9, 22.0; MS *m/z* 258 (M+); 230, 213, 202, 173, 148, 111, 76, 50.

2-(2,6-Dioxopiperidin-3-yl)-hexahydro-isoindole-1,3-dione. (**2**): a white solid (70% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.0 (s, 1 H, NH), 4.9 (dd, 1 H, 12.5, 5.5 Hz), 3.0 (m, 1 H), 2.8 (m, 2 H), 2.5 (m, 1 H), 1.9 (m, 1 H), 1.7 (m, 3 H), 1.6 (m, 1 H), 1.4 (m, 4 H); ^{13}C NMR (100 MHz, DMSO-d_6) 178.8 (C=O), 178.7 (C=O), 172.7 (C=O), 169.4 (C=O), 48.7 (CH), 39.1 (CH), 38.8 (CH), 30.7 (CH$_2$), 23.1 (CH$_2$), 22.9 (CH$_2$), 21.1 (CH$_2$), 21.05 (CH$_2$), 21.00 (CH$_2$); MS *m/z* 264 (M+); 236, 210, 179, 154, 112, 82, 67, 54, 41.

3-(2,5-Dioxopyrrolidin-1-yl)-piperidine-2,6-dione. (**3**): white solid yield (0.10 g, 48%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.0 (s, 1 H, NH), 4.9 (dd, 1 H, 12.5, 5.5 Hz), 3.3 (s, 1 H), 2.8 (m, 3 H), 2.5 (m, 1 H), 2.4 (m, 1 H), 1.9 (m, 1 H); 13C NMR (100 MHz, DMSO-d_6) 176.9, 172.7, 169.3, 49.0, 30.7, 28.0, 22.1; MS *m/z* 210 (M+) 182, 167, 125, 112, 83, 68, 56 41.

3-(2,6-Dioxopiperidin-3-yl)-3-aza-bicyclo[3.2.0]heptane-2,4-dione. (**4**): a white solid (54% yield). 1H NMR (400 MHz, DMSO-d_6) δ 11.06 (s, 1 H, NH), 4.95 (dd, 1 H, 12.5, 5.5 Hz), 2.84 (m, 2 H), 2.52 (m, 4 H), 2.02 (m, 2 H), 1.92 (m, 2 H); ^{13}C NMR (100 MHz, DMSO-d_6) 179.0 (C=O), 172.7 (C=O), 169.4 (C=O), 48.7 (CH), 49.1 (CH), 37.9 (CH), 37.7 (CH$_2$), 30.7 (CH$_2$), 22.1 (CH$_2$), 22.0 (CH$_2$), 21.0 (CH$_2$); MS *m/z* 236 (M+) 208, 151, 106, 112, 96, 83, 55, 41.

(2,6-Dioxopiperidin-3-yl)-3a,4,7,7a-tetrahydro-1H-4,7-etha-noisoindole-1,3(2H)-dione. (**5**): a white solid (62% yield). 1H NMR (400 MHz, DMSO-d6) δ 11.0 (s, 1 H, NH), 6.1 (m, 2 H), 4.8 (dd, 1 H, 12.5, 5.5 Hz), 3.0 (m, 4 H), 2.8 (m, 1 H), 2.5 (m, 1 H), 2.3 (m, 1 H), 1.7 (m, 1 H), 1.6 (d, 2 H, 7.5 Hz), 1.2 (d, 2 H, 7.5 Hz); 13C (100 MHz, DMSO-d_6) δ 177.75 (C=O), 177.71 (C=O), 172.57 (C=O), 168.73 (C=O), 132.09 (CH), 131.82 (CH), 48.75 (CH), 43.37 (CH), 31.39 (CH), 31.22 (CH), 30.48 (CH), 29.79 (CH), 23.17 (CH$_2$), 22.98 (CH$_2$), 22.87 (CH$_2$), 21.29 (CH$_2$); MS *m/z* 288 (M+) 260, 209, 178, 149, 136, 112, 99, 80, 78, 54, 41.

Disclosure

The statements made herein are solely the responsibility of the authors.

Competing Interests

The authors declare that they have no competing interests.

Acknowledgments

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