Microwave Promoted Synthesis of a Rehabilitated Drug: Thalidomide

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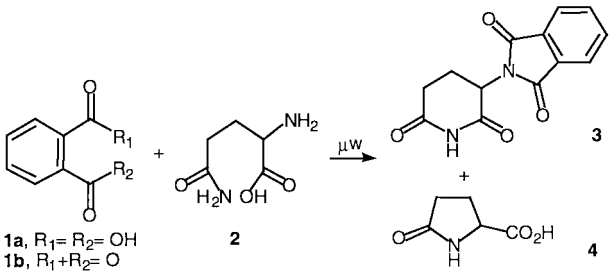
Abstract: A new direct synthesis of thalidomide in high yield by microwave irradiation of *N*-phthaloyl-L-glutamic in the presence of thiourea is described. Thalidomide was also obtained in good yield from L-glutamic acid, phtalic anhydride and thiourea in a one-pot procedure.

Key words: antitumoral agent, antiviral agent, imides, microwave heating, thiourea

Thalidomide is a drug that is achieving great therapeutic importance in the treatment of several diseases: leprosy,[1] rheumatoid arthritis,[2] AIDS,[3] Crohn's disease,[4] cancer related to pathologic angiogenesis,[5] and is still under study for other diseases.[6]

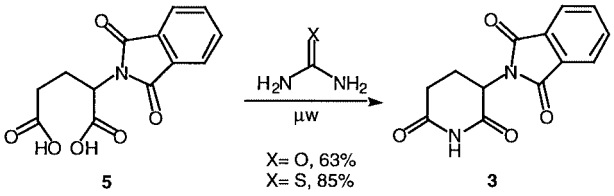
Thalidomide was first prepared in 1956, however due to its catastrophic effects on fetal malformations, it was banned in the early sixties. However, in recent years the interest on this drug has been increasing for the treatment of the above mentioned diseases, attracting interest on the development of new improved synthetic approaches to thalidomide and its derivatives. Several strategies have been employed for its synthesis,[7] the most recent published by Muller et al.[8] Usually these syntheses leave as the final step the formation of the glutarimide ring, thus Reepmeyer et al.[7g] reacted *N*-phthaloylglutamic anhydride with urea at 205–212 °C for 1 hour with a 60% yield after purification. The synthesis of Muller et al. is based on cyclization of *N*-phthaloylglutamine and gave a 91% yield. Lately, the aspect of stereoselectivity in the synthesis of thalidomide has become of minor importance, since it is known that it racemises at physiological pH.

Microwave irradiation has proved to be a useful tool to promote organic reactions.[9] Our last studies on the use of microwaves to enhance some reactions,[10] especially for the formation of amides and imides, led us to consider the possibility of using this type of irradiation to improve the preparation of thalidomide. As a first approach, we tried to close both imide rings in the same step, thus L-glutamine (**2**) was irradiated in the presence of phthalic acid (**1a**), but pyroglutamic acid (**4**) was the only product from the reaction. When a more reactive form of phthalic acid, phthalic anhydride, was irradiated with L-glutamine (**2**) for 19 minutes in the microwave oven, (±)-thalidomide (**3**) was obtained, but mixed with **4**, both in very low yield.



Scheme 1 Synthesis of thalidomide from L-glutamine

It seemed that nucleophilic attack of the α-amino group on the amido group in position 5 of **2** could be avoided by using the anhydride **1b** but only to some extent. These results prompted us to protect the α-amino group by blocking its nucleophilicity with the formation of phthalimide, followed by closure of the six-membered ring. We choose *N*-phthaloyl-L-glutamic acid (**5**)[11] which is a commercially available product derived from L-glutamic acid. So, urea was added as a source of nitrogen instead of the amido group present in **2** and after irradiation for 10 minutes, thalidomide (**3**)[11] was obtained in 63% yield (Scheme 2). This yield is similar to Reepmeyer's but our procedure was carried out in only one step. Further, L-glutamic acid is five times cheaper than L-glutamine – Muller's starting material.



Scheme 2 Synthesis of thalidomide from *N*-phtaloyl-L-glutamic acid

While carrying out studies on the formation of more simple imides, thiourea proved superior to urea for *N*-unsubstituted imide formation. Hence, we carried out the reaction using thiourea instead of urea and the yield of thalidomide increased to 85% after 15 minutes of irradiation (Scheme 2).

Since thiourea proved efficient and improved the latter reaction, the synthesis of thalidomide in a one-pot reaction using thiourea instead of urea was attempted. Thus, when L-glutamic acid, phthalic anhydride and thiourea, all

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mixed together in equal molar amounts, were irradiated for 20 minutes thalidomide was formed in 60% yield without significant formation of pyroglutamic acid.

Since the above reactions employed new sets of reagents for the preparation of thalidomide, the effect of classical heating on the yields was studied. Thus, using a heating mantle, an equimolar mixture of **5** and thiourea was heated at 200 °C for 50 minutes. Thalidomide was obtained in 54% yield compared to 85% yield for the microwave heated reaction. Also, the time required for the consumption of **5** was much longer. The same procedure was followed with the one-pot synthesis of thalidomide by heating L-glutamic acid, phthalic anhydride and thiourea at 160 °C for 40 minutes. After purification, thalidomide was obtained in 44% yield compared to 63% yield for the microwave heated reaction.

In summary, we have presented microwave irradiation as an alternative to the previous syntheses of thalidomide.[7,8] Multimode microwave irradiation seems to be a good and inexpensive tool for the preparation of this drug, thiourea being a better nitrogen donor for the formation of the six-membered imide ring than urea. We believe our procedure could be applied on an industrial scale since microwave irradiation is applicable both in batch, or in continuous processes, and not only for thalidomide itself but for analogues as well, since a great deal of them introduces only minor modifications to thalidomide's original substitution pattern. Actually, we are concerned with this extension of our synthetic method.

(±)-Thalidomide

N-Phthaloyl-L-glutamic acid (**5**) (3.0 g, 10.8 mmol) was mixed with thiourea (0.882 g, 11.6 mmol) and then introduced into a Pyrex test tube. The mixture was irradiated in a domestic microwave oven (1000 W output) with irradiation control set at 70% for 15 min. The crude was dissolved in THF and purified by column chromatography on silica gel (THF-hexane, 1:1) to afford a solid product of (±)-thalidomide (**3**) (2.375 g, 85%).

Mp 269–271 °C (DMF/H_2O) Lit.[7d] mp 269–271 °C.

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