Microwave-promoted synthesis of thalidomide

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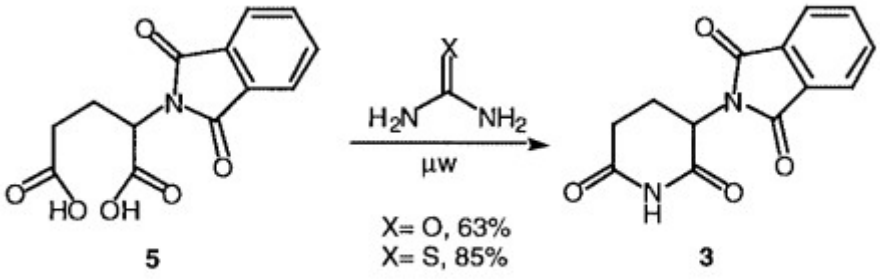
According to a 2001 paper[1], thalidomide can be prepared in a high-yielding solvent-free microwave-assisted synthesis, the only two reactants being N-phthaloylglutamic acid and thiourea (or urea, giving a somewhat lower yield).
The following image is taken directly from the aforementioned paper:



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

A number of other papers[2][3] have reported the microwave-assisted synthesis of thalidomide.
Furthermore, there are innumerable alternative synthetic routes to thalidomide[4][5]
A comprehensive review of the various synthetic routes is referenced below[6]
These experiments were inspired by ScienceMadness member Tsjerk's procedure in karlos's thread[7]

Experiment 1:
1.08g (3.9mmol) N-phthaloylglutamic acid was ground in a mortar and pestle with 0.246g (4,1mmol, a 5% excess) urea, whereupon the mixture was transferred to a ~10mL Pyrex test-tube, which was placed in the microwave oven.
Heating was carried out in ~10 second bursts, however the powder did not absorb any significant amount of microwave radiation, the glass tray in the microwave oven instead absorbing the radiation, the glass becoming very hot while the reaction mixture was still cold.
In order to facilitate the heating of the reaction mixture, a drop of water was added to the test-tube. Even after adding the water, the process was still slow, requiring multiple 10 second bursts before any sign of heating was evident, however, eventually, water vapour began to evolve, with the mixture finally melting into a clear, yellow liquid.
Only water vapour had been evolved by this point; With further heating, the mixture began to bubble and foam, emitting white vapours smelling of ammonia.
A few 10 second bursts were carried out, the mixture foamed up to around three times the height of the molten solids; The liquid inside became gradually yellower and eventually ended up orange.
After it had turned orange, further heating did not seem to cause any obvious further signs of reaction, the foam gradually settled into a small volume of viscous orange liquid, with further heating having no effect, with no further foaming or ammonia evolution.
Once the test-tube had cooled somewhat, ~5mL boiling water was added, this resulted in a suspension of off-white waxy crystals.
Heating the solution to boiling did not dissolve the crystals, this agrees with the low water-solubility of thalidomide.
The suspension of crystals was decanted out of the test-tube into a beaker and cooled in the fridge, whereupon it was suction-filtered and washed three times with ~3mL cold water.
After thorough suction-filtration to remove as much water as possible, 0.54g of damp, off-white/yellowish crystals was obtained, this was placed in a watch-glass on the radiator to dry.
When dry, the material weighed 0.31g.

It was possible that the product contained considerable proportions of impurities such as phthalimide; An alcohol extraction seemed prudent, as phthalimide (and probably many other impurities) are alcohol-soluble, whereas thalidomide is practically insoluble in alcohol.

The product was placed in a beaker to which 10g of isopropanol was added; the beaker was covered with a watch-glass, and heated to boiling in the microwave, whereupon the hot solution was suction-filtered, this removed most of the discolouration from the solids, yielding a fine almost-white powder, weighing 0.11g after drying on the radiator.

A melting-point test was carried out upon the product:
First signs of melting: 256°C
Fully melted: 270°C

The isopropanolic filtrate was yellow, and, upon cooling, crystals began to precipitate out.
These were suspected to be an impurity, as thalidomide itself is not very soluble in alcohols.
Upon cooling to room temperature, the crystals were filtered, yielding around 20mg of fine yellow needle crystals.

A melting-point test was carried out upon the crystals recovered from the isopropanol extraction:
Beginning to discolour: 200°C
First signs of melting: 230°C
Fully melted: 240°C
The results were uncertain, as the material began to blacken from 200°C onwards, becoming completely blackened by 240°C, making an accurate melting-point determination impossible.

Further purification seemed to be necessary to obtain an accurate result in determining the melting-point of this substance (see “Melting-point test carried out upon crystals obtained from isopropanol extractions”).

Experiment 2:
1.02g (3.7mmol) N-phthaloylglutamic acid was ground (with difficulty as it sticks to the sides) a in mortar and pestle with 0.232g (3.9mmol, a 5% excess) urea.
Whereupon it was transferred to a test-tube and heated in the microwave, as before.
Upon completion, ~5mL hot water was added, with stirring and heating, resulting in a suspension of off-white waxy crystals.

These were filtered from suspension, washed twice with 2mL cold water, and dried, yielding 0.25g of off-white powder.
The crude product was extracted with 4g of boiling isopropanol; Once dried, the undissolved product weighed only ~50mg.
A second extraction with boiling isopropanol removed no further soluble impurities, as the undissolved product after the second extraction, upon drying, still weighed ~50mg.

A melting-point test was carried out upon the product:
First signs of melting: 278°C
Fully melted: 280°C (With discolouration)
The substance remained off-white until 278°C, whereupon it began to change visibly, and discolour, by 280°C it was fully melted and black/brown.

The isopropanol filtrate was then evaporated, yielding 140mg of beige crystals.

Experiment 3:
0.95g (3.43mmol) N-phthaloylglutamic acid was mixed with 0.216g (3.60mmol, a 5% excess) of urea, in a test-tube as before, mixed with a pestle and mortar.
This time, the test-tube was placed closer to the wave-guide outlet, in the hope that this would result in a greater degree of microwave absorption.
This didn't seem to make any difference, however, so it was again necessary to add a few drops of water.
As before, this resulted in a solution forming, with further heating boiling off the water and the reaction mixture remaining liquid.
With further heating, the evaporation of water stopped, the mixture turning opaque and foaming, with a white cloudy layer forming on the test-tube walls (perhaps carbamic acid).
With further heating, the mixture turned into a yellow viscous clear liquid, bubbling due to escaping ammonia.
Heating was continued in bursts until the rate of gas production slackened, whereupon the mixture solidified.
Further heating was had no effect upon the product and did not result in re-melting.
The same purification procedure was followed; Water was added, mixed up to separate crystals, suction filtered, washed three times with 2mL cold water, dried, (0.45g) then extracted twice with 4g boiling isopropanol.
The undissolved material, once dried, weighed 0.12g.

Melting-point test carried out upon crystals obtained from isopropanol extractions:
The crystals that precipitated from the isopropanol upon cooling were suction-filtered from the solution, and twice recrystallized from isopropanol, before being dried thoroughly on the hot-plate at 150°C for ~30 minutes.

A melting point determination was then carried out:
Beginning to discolour: 220°C
First signs of melting: 236°C
Fully melted: 238°C (Brown liquid with some black specks)

This agrees nicely with the melting point of phthalimide at 238°C, indicating that the alcohol-soluble impurities are likely to consist of phthalimide.

Conclusions:
The microwave-assisted synthesis of thalidomide seems to be fairly straight-forward, although the yields obtained in these experiments are much lower than the yields published in the literature, this leaves much room for future experimentation for those sufficiently motivated.

The yields of the three experiments are tabulated below:

Experiment	N-phthaloylglutamic acid used (g,**mmol**)	Yield of crude product (g)	Yield of isopropanol-extracted product (g, **mmol**)	Percentage purity of crude product	Percentage yield
1	1.08, **3.9**	0.31	0.11, **0.43**	35.5%	10.9%
2	1.02, **3.7**	0.25	0.05, **0.19**	20.0%	5.3%
3	0.95, **3.4**	0.45	0.12, **0.46**	26.7%	13.6%

Some variation in the published melting points exists, with values of 269-271°C[1][5], 268-270°C[2], and 274-276°C[4] being reported in the literature.
It therefore seems reasonable to assume that the product obtained in these experiments was fairly pure, given the 278-280°C melting-point obtained in Experiment 2.

In order to purify the product satisfactorily, it would probably be necessary to carry out a recrystallization.
There are few good solvents for thalidomide, however DMF, dioxane, and pyridine are possibilities. Furthermore, attempts to find any quantitative solubility data for thalidomide were unsuccessful, so the degree to which it is soluble in various solvents is uncertain.
Since no further decrease in weight of the product was observed with the second isopropanol wash, it seems reasonable to assume that the product is practically insoluble in isopropanol.

References:

[1] “Microwave Promoted Synthesis of a Rehabilitated Drug: Thalidomide” (http://dx.doi.org/10.1055/s-2001-14573) by Seijas, Vazquez-Tato, Gonzalez-Bande, Martinez, Pacios-Lopez (2001)

[2] “A Novel Green Synthesis of Thalidomide and Analogs” (https://doi.org/10.1155/2017/6436185) by Hijji and Benjamin (2017)

[3] “Microwave Assisted Synthesis of Thalidomide on Hectogram Scale” (https://doi.org/10.1080/00304948.2021.2024681) by Nguyen, Vu, Ho Ba, and Phan (2022)

[4] “A Concise Two-Step Synthesis of Thalidomide” (https://doi.org/10.1021/op980201b) by Muller, Konnecke, Smith, & Khetani (1999)

[5] “Facile Synthesis of Thalidomide” (https://doi.org/10.1021/acs.oprd.9b00122) by Vu, Ho Ba, and Phan (2019)

[6] “Synthesis of Thalidomide” (https://doi.org/10.1007/7081_2007_057) by Shibata, Yamamoto, and Toru (2007)

[7] “Preparation of Thalidomide” (https://www.sciencemadness.org/whisper/viewthread.php?tid=154991) by karlos