Tetrahedron Letters 51 (2010) 2215–2217

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Comparison of microwave-assisted and conventional preparations of cyclic imides

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ARTICLE INFO

Article history:
Received 13 December 2009
Revised 14 February 2010
Accepted 16 February 2010
Available online 21 February 2010

ABSTRACT

Microwave-assisted preparation of several cyclic imides was performed with four different cyclic anhydrides. All the reactions are significantly faster and the isolated yields are significantly higher compared to conventionally heated reactions. Furthermore, many of these reactions can be performed with a minimal amount of solvent, thereby enabling the synthetic chemist to obtain high quantities of pure cyclic imides in a matter of hours.

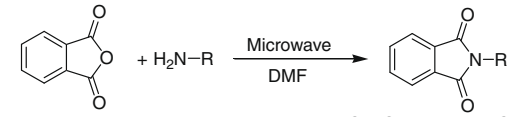
Despite the wide applicability of imides in biology, the availability of high yielding, inexpensive synthetic procedures in the synthetic and polymeric chemistry for the preparation of cyclic imides is limited.[1] The typical synthetic methods of choice are condensation of an anhydride and amine at elevated temperature and cyclization of the amic acid in the presence of dehydration reagents. Because the process of synthesizing an imide consists of the elimination of water, we hypothesized that microwave-assisted heating would be ideal for these reactions (water absorbs most of the microwave power).[2] However, one common problem associated with microwave-assisted chemistry is overheating of the reaction mixture. To circumvent this problem we recently developed a new microwave chemical reactor that uses the same magnetron as traditional household microwaves.[3] This microwave reactor was adapted to resemble a traditional laboratory reactor, in which a reaction mixture can be stirred, the temperature controlled, and the reaction mixture refluxed over long times (~24 h) without the evaporation of solvent from the reaction mixture. Using our newly developed microwave reactor we were able to develop new synthetic procedures that utilize ionic liquid as a reaction media under microwave assistance.[4]

Cyclic imides[5] play an important role in organic syntheses and in medicinal chemistry. For instance, cyclic imides, particularly phthalimides, have been widely used as amino acid protection groups[6] and have attracted considerable attention in medicinal chemistry.[7] Maleimides are important constituents of peptide-conjugate haptens, antibody–antibody conjugates, immune conjugates, and enzyme inhibitors.[8]

Recently, a solvent-free procedure using $TaCl_5$-silica gel as a catalyst was described for the preparation of imides under microwave irradiation.[9] Sandhu and co-workers advocated the use of a more ecofriendly solvent-free system, involving the reaction of equal amounts of anhydride and amines or amino acids in the absence of a solvent in a domestic oven without any catalyst.[11] In the case of the reaction of the anhydride with amino acids, a reaction between two solids was involved, for example between phthalic anhydride and glycine. Unfortunately, no temperature measurements were reported.[11]

To address these limitations we are reporting microwave-assisted preparation of imides in polar solvents such as DMF and pyridine from cyclic anhydrides and corresponding amines. Using conventional reaction methods, time taken for transformation into the corresponding imide ranged from 12 to 16 h (Table 1). However, utilizing the new microwave-assisted method of preparation gave quantitative yields of product in no more than 1 h (Table 1).

Table 1
Preparation of phthalimides[10]



phthalic anhydride

1a: R = 4-$CH_3C_6H_4$, **1b**: R = C_6H_5
1c: R = 3-BrC_6H_4, **1d**: R = 2-C_6H_5-C_6H_4
1e: R = $CH_3(CH_2)_4CH_2$, **1f**: $CH_3(CH_2)_{15}CH_2$

Entry	Imide	Time (min)	Power (W)	Yield (%)	Time[a] (h)	Yield[a] (%)
1	**1a**	60	300	94	16	85[a]
2	**1b**	60	300	95	16	65[a]
3	**1c**	30	300	97	12	65
4	**1d**	60	450	85	16	60
5	**1e**	40	450	95	16	60
6	**1f**	40	450	90	16	63

[a] Conventional heating in toluene as a solvent catalytic amount of TEA.

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0040-4039/$ - see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2010.02.092

In the course of our microwave-assisted reaction studies, we explored the preparation of phthalimides from phthalic anhydride and the corresponding amine in DMF as a solvent. The magnetron power was adjusted for gentle solvent refluxing. The required magnetron power depends on the reaction mixture composition and polarity. After the reaction was completed, the product was isolated by ice-water precipitation from the hot reaction mixture. The reaction time and isolated yields are presented in Table 1.

For conventional preparation of **1** toluene is the superior solvent in comparison to DMF in regards to both the reaction time and isolated yield. For instance, after refluxing the DMF solution for two days the isolated yield of **1a** was only 45%. This is not an unusual finding because the preparation of aromatic and aliphatic phthalimides under conventional heating usually requires prolonged time in solvents such as toluene, acetic acid, .[12] There are also reports of microwave-assisted synthesis without solvent.[13] However, the no-solvent approach can only be successful if one of the reactants absorbs microwave irradiation and has relatively low melting point. On the other hand, our procedure is applicable to broad range of amines regardless of their physical state or microwave radiation absorption because our solvent (DMF) is an excellent microwave reaction media, as it was demonstrated on the examples of aromatic amines (**1a–d**) and aliphatic amines (**1e** and **1f**, Table 1) and microwave-assisted reaction is superior to conventional reaction.

In general, five-membered cyclic anhydrides are more reactive than six-membered cyclic anhydrides. Therefore, it does not come as a surprise that microwave-assisted reaction conditions used for the preparation of cyclic imides with 1,8-naphthalic anhydride are more demanding than those with phthalic anhydride, where the reaction time is more than quadruples. However by replacing DMF as the solvent with pyridine, the isolated yield was higher and the reaction time was shortened (Table 2). The isolation of the product requires quenching the reaction with water or with aqueous hydrochloric acid followed by crystallization of the product. As demonstrated in Table 2, the isolated yields are higher and the reaction times are shortened by 10–20 times in the case of microwave-assisted preparation.

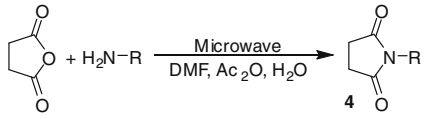
We were not able to prepare succinimide by simple microwave heating in either DMF or pyridine solution of succinic anhydride and the corresponding amine. The major product was the corresponding open amide acid that, upon continued microwave heating, decomposed. Even when the DMF reaction mixture was microwaved for 8 h, only traces of the product were detected with substantial amount of decomposition material. However, if the DMF reaction mixture was first microwaved for a short time and then a water-removing reagent, such as DCC was added followed by short microwave irradiation, then the corresponding succinimide was successfully prepared.

To simplify the isolation and purification of the product, acetic anhydride was used as a dehydration reagent instead of DCC. The reaction was practically completed in 20 min. To eliminate the excess of the acetic anhydride, water was added and the reaction mixture was microwaved for an additional 20 min (Table 3). Considering the nature of the reaction media (DMF + Ac_2O + H_2O), the product can be isolated by ice-water precipitation and purified by simple washing with water or aqueous hydrochloride. If necessary, further purification can be accomplished by column chromatography. The reaction conditions and isolated yields for some of the prepared succinimides are presented in Table 3.

The described procedure that was so successful for the preparation of both aliphatic and aromatic succinimides cannot be accepted as a general procedure for the preparation of maleimides. In many instances, using this preparation approach generated a complex mixture with majority (more than 60%) of the maleimide as a product. Unfortunately, the formed byproducts make the isolation and purification of the maleimide difficult. However this approach is still applicable for the preparation of simple aromatic maleimides such as phenyl and naphthyl maleimides (Table 4). In the case of aliphatic maleimides, the conversion of the amine into maleimide was around 60% therefore a new microwave-assisted preparation strategy was required.

In the conventional synthetic approach, the corresponding maleic acid was prepared from the corresponding amine and

Table 3
Preparation of succinimides[15]

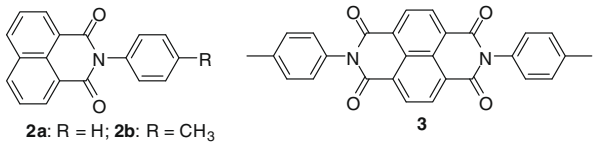


4a R=benzyl; **4b** R=$(CH_2)_6$, **4c** R=4-methylphenyl
4d 4,4'-methanediphenyl; **4e** 1-naphthyl

Entry	Imide	Yield[a] (%)	Time[b] (h)	Yield[b] (%)
1	**4a**	91	24	45
2	**4b**	84	16	35
3	**4c**	85	16	35
4	**4d**	92	24	40
5	**4e**	88	24	35

[a] All microwave-assisted reactions were performed with a power of 300 W and reaction time 30 + 30 + 20 min.
[b] For conventional method only heating with acetic anhydride was reported.

Table 2
Preparation of 1,8-naphthylimides[14]

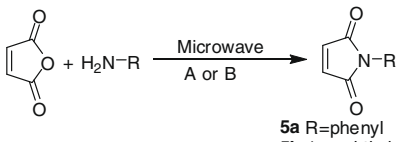


2a: R = H; **2b**: R = CH_3 **3**

Imide	Solvent	Time (h)	Power (W)	Yield (%)	Time[a] (h)	Yield[a] (%)
2a	DMF	4	300	70	48	55
2a	Pyridine	2	450	90	20	70
2b	DMF	4	300	65	48	50
2b	Pyridine	2	450	95	24	75
3	Pyridine	1	450	93	24	50

Note—Different power for DMF and pyridine is required for reflux due to difference in their polarity.
[a] With conventional heating.

Table 4
Preparation of maleimides[17]



Method A: DMF, Ac_2O, H_2O
Method B: a) THF b) Ac_2O-AcONa

5a R=phenyl
5b 1-naphthyl
5c 4-methylphenyl
5d R=bis(4-phenylene)methane

Entry	Method	Imide	Time (min)	Power (W)	Yield (%)
1	A	**5a**	70	450	91
2	A	**5b**	70	450	84
3	B	**5a**	30	450	93
4	B	**5b**	30	450	95
5	B	**5c**	30	450	93
6	B	**5d**	30	450	85

maleic anhydride followed by the ring closure in acetic anhydride with a catalytic amount of acetic acid. Isolated yields of the maleimides range around 50%.[16] In our microwave-assisted preparation approach we also applied the two-step synthesis (Method B Table 4). In the first step, tetrahydrofuran (THF) solutions of the corresponding amine and maleic anhydride were mixed at room temperature. The reaction was completed after a few minutes. The formed precipitate was mixed with acetic anhydride and a catalytic amount of sodium acetate and then microwaved at 450 W. The reaction conditions and isolated yields are presented in Table 4.

In conclusion, we have explored the effects of microwave irradiation on the preparation of cyclic imides. Given the possibility to control the power of microwave radiation, it was possible to use microwave irradiation for the preparation of cyclic imides that require microwave radiation in the range of a few minutes to a few hours. This approach is superior to conventional synthetic approach in both isolated yield of the product and required reaction time (see Tables 1–3 for comparisons).

Acknowledgment

We thank the National Science Foundation for financial support (CHE-0611902) for this work.

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3. The laboratory version of our microwave has a cavity size of 21.6 cm in height, 17.30 cm wide, and 25.4 cm deep with two 2.54 cm hole on the top of the microwave for the condenser and thermometer. The magnetron (700 W) was directly wired to variable electronic autotransformer for the control of the magnetron power. ECM meter (10 A) was wired to the magnetron transformer to control the microwave power. The magnetic stirrer was installed beneath the cavity for stirring the reaction mixture. The reaction temperature was measured directly with a thermometer inserted into the reaction mixture through a condenser and/or by infrared reading.
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10. *General procedure for microwave-assisted synthesis of phthalimides* (**1**): DMF (20 ml) solution of phthalic anhydride (1.5 g; 0.01 mol) and corresponding amine (0.01) were refluxed with magnetic stirring under microwave conditions as outlined in Table 1. The reaction mixture was poured onto crushed ice (~200 g) and the formed white precipitate was separated by filtration, washed with water, and dried under reduced pressure. If necessary further purification was performed by column chromatography. *General procedure for conventional synthesis of phthalimides in conventional method* (**1**): To a suspension of phthalic anhydride (1 g; 6.8 mmol) and corresponding amine (0.85 mmol) in toluene (20 ml) triethylamine (1 ml) was added. The resulting reaction mixture was refluxed. After refluxing for time outlined in Table 1 the reaction mixture was concentrated to ~1/4 cooled and the formed crystalline product was separated by filtration. If necessary column purification was performed.
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14. *General procedure for the synthesis of 1,8-naphthalimides using a microwave* (**2** and **3**): Pyridine or DMF (100 ml) solution of an anhydride (5 mmol) and corresponding amine were refluxed under microwave heating (Table 2). After cooling to room temperature, the reaction mixture was poured over ice. The formed white solid was separated by filtration. If necessary, the product was further purified by dissolving in dichloromethane, washing dichloromethane with water, and 10% hydrochloric acid. *General procedure for conventional synthesis of 1,8-naphthalimides* (**2a**, **2b** and **3**): A suspension of anhydride (5 mmol) and corresponding amine in pyridine (20 ml) or DMF (20 ml) was refluxed for several hours (Table 2). The reaction mixture was concentrated to about 1/4 and poured over ice. The formed crystalline product was separated by filtration.
15. *General method for microwave-assisted synthesis of succinimides* (**4**): DMF (20 ml) solution of succinic anhydride (2 g; 0.02 mol) and corresponding amine (0.015 mol) were refluxed in microwave reactor (magnetron power of 300 W) for 30 min. Into cooled reaction mixtures acetic anhydride (0.06 mol) was added and the reaction mixture was refluxed in microwave reactor for an additional 30 min. This was followed by the addition of water (5 ml) and microwave refluxed for 20 min. The reaction mixture was diluted with dichloromethane (100 ml), washed with saturated water solution of sodium bicarbonate (3 × 50 ml), water (3 × 50 ml), and dried over anhydrous sodium sulfate. After the solvent was evaporated, the crude product was purified by column chromatography with ethyl acetate–hexane (5:1) as an eluent. *General method for conventional synthesis of succinimides* (**4**). DMF (20 ml) solution of succinic anhydride (0.02 mol) and corresponding amine (0.015 mmol) was stirred at 50 °C for 30 min. Into this solution, acetic anhydride (5 ml) was added and the resulting reaction mixtures were refluxed under microwave for a few hours as specified in Table 3. After the refluxing reaction mixture was diluted with ice water (100 ml), it was stirred for 30 min and the product was isolated by dichloromethane extraction followed by column chromatography.
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17. *General procedure for the synthesis of maleimides* **5**: Tetrahydrofuran (20 ml) solution of maleic anhydride (0.01 mol) and tetrahydrofuran solution (20 ml) of corresponding amine (1.1 equiv) were mixed together and stirred at room temperature for 15 min. The solvent was decanted from white precipitate, and acetic anhydride (21 ml) and sodium acetate (1 g) were added to the solid material. The reaction mixture was heated with microwave magnetron power of 450 for 30 min. The reaction mixture was washed with ether (3 × 50 ml). After ether evaporation, the product was purified by column chromatography with 5% ethyl acetate in dichloromethane as an eluent.