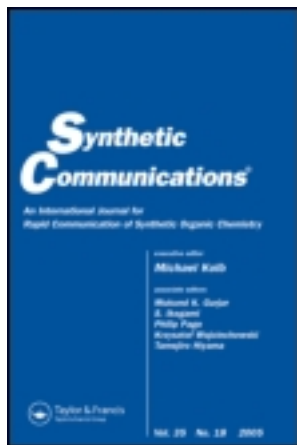


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Rapid and Convenient Microwave-Assisted Synthesis of Aromatic Imides and N-Hydroxymethylimides

Karol Kacprzak^a

^a Department of Chemistry, Adam Mickiewicz University, Poznań, Poland

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Rapid and Convenient Microwave-Assisted Synthesis of Aromatic Imides and *N*-Hydroxymethylimides

Karol Kacprzak*

Department of Chemistry, Adam Mickiewicz
University, Poznań, Poland

ABSTRACT

Extremely simple high-yielding and rapid microwave-assisted synthesis of wide array of aromatic mono and diimides and mono- and *bis-N*-hydroxymethylimides is reported.

Key Words: Imides; *N*-hydroxymethylimides; Microwaves.

*Correspondence: Karol Kacprzak, Department of Chemistry, Adam Mickiewicz University, Ul. Grunwaldzka 6 60-780 Poznań, Poland; Fax: +48 61 8658008; E-mail: k.michal@mailcity.com.



In the course of our studies on various systems containing aromatic imides as the chromophores,^[1,2] we needed a reliable method for the preparation of imides and their various derivatives, e.g., *N*-hydroxymethylimides. In particular we were interested in convenient synthesis of bifunctional imides and *N*-hydroxymethylimides derived from 1,2,4,5-benzenetetracarboxylic anhydride (pyromellitic anhydride) and 1,4,5,8-naphthalenetetracarboxylic anhydride. These imides found numerous applications in polymer^[3] and supramolecular^[4–7] chemistry. Aromatic mono^[8] and diimides^[6,7,9] were used also as nucleophiles in the Mitsunobu reaction as well as in the synthesis of *N*-carboethoxyimides^[10,11] and *N*-alkylphthalimides.^[12] Various *N*-hydroxymethylimides were reported to have potentially interesting pharmacological properties.^[13,14]

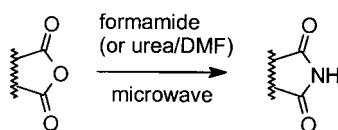
Surprisingly, only a few general methods are available for preparation of unsubstituted imides. These include the reaction of anhydrides with either urea,^[15] aqueous ammonia^[3,7,14,16] or formamide.^[17,18] Although simple, these procedures have some disadvantages as tedious work-up (e.g., long high-vacuum heating^[3,7,17]) or difficult to reproduce.^[17]

Well-known procedure for the synthesis of *N*-hydroxymethylimides based on aqueous formaldehyde solution, requires prolonged heating,^[14,19] the yields are variable and isolation of the products can be difficult. Newer method of the preparation of *N*-hydroxymethylphthalimides involves the use of ultrasounds.^[20]

Since all of these reactions are thermal processes, we expected that they could be significantly accelerated by microwave heating. This well-recognized technique was used successfully in organic synthesis, also in the area of aromatic imides chemistry, e.g., in the synthesis of *N*-alkylphthalimides^[12] and *N*-phthaloyl^[21] or tetrachlorophthaloyl^[22] amino acids.

We now report a very simple and rapid route to a wide array of aromatic mono and bifunctional imides and *N*-hydroxymethylimides, based on microwave acceleration of the imidation reaction.

Synthesis of Imides

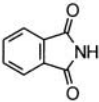
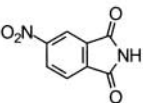
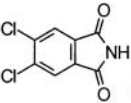
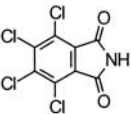
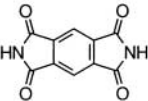
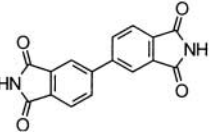
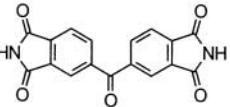
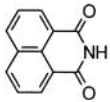
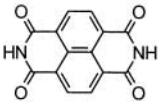


The results are shown in Table 1.

Aromatic Imides and *N*-Hydroxymethylimides

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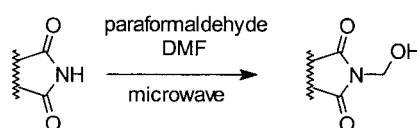
Table 1. Microwave-assisted synthesis of aromatic imides.

Product		Nucleophile/ solvent	Power, time	Yield (%)
	1.1	Formamide	650 W, 3 min	90
		Urea/DMF	650 W, 3 min	80
	1.2	Formamide	650 W, 3 min	64
	1.3	Formamide	650 W, 4 min	96
	1.4	Formamide	650 W, 3 min	79
	1.5	Formamide	650 W, 4 min	90
		Urea/DMF		99
	1.6	Formamide	650 W, 4 min	85
	1.7	Formamide	600 W, 2.5 min	84
	1.8	Formamide	700 W, 5 min	85
	1.9	Formamide	700 W, 5 min	96



It was found that formamide is most universal, serving both as a reagent and as a solvent and can be used in small quantities. In a few cases urea in DMF or DMF/H₂O was also successfully used (see Table I).

Synthesis of N-hydroxymethylimides:



The results are shown in Table 2.

Hydroxymethylation was carried out with either aqueous formaldehyde or with paraformaldehyde, the latter giving the products with higher yields. These reactions were carried out in DMF solution but with more soluble phthalimides water can also be used as a solvent.

Attempts to synthesize *N,N'*-bis-hydroxymethyl-1,4,5,8-naphthalene-tetracarboxylic diimide by this method failed, probably due to the extremely low solubility of the parent diimide.

EXPERIMENTAL

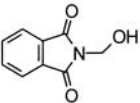
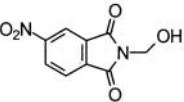
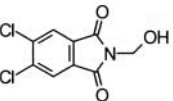
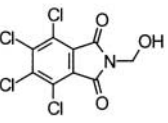
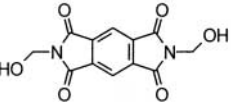
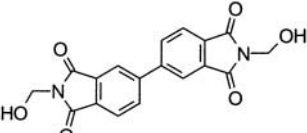
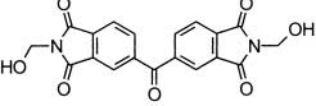
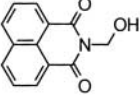
All reactions were performed in commercial microwave oven (Phillips/Whirlpool Model M600). Commercially available phthalic, pyromellitic, 1,8-naphthalenedicarboxylic, 1,4,5,8-naphthalenetetracarboxylic, 3,3',4,4'-biphenyltetracarboxylic and 3,3',4,4'-benzophenone-tetracarboxylic anhydrides (Aldrich) were used as received.

Other anhydrides were obtained from the corresponding diacids by refluxing with acetic anhydride and crystallization. ¹H NMR spectra (all in DMSO) were registered on a Varian or Bruker 300 MHz spectrometer, with TMS as an internal reference. FT-IR spectra were taken in KBr pellets on Bruker IFS 113 v spectrometer. Melting points were determined on a Büchi melting point instrument B-545 and were uncorrected. Note that melting points of *N*-hydroxymethylimides are almost identical with the melting points of the corresponding imides, due to thermal loss of formaldehyde, which can be determined by DSC.^[3]

Aromatic Imides and *N*-Hydroxymethylimides

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Table 2. Microwave-assisted synthesis of *N*-hydroxymethylimides.

Product		Method ^a , power, time (min)	Yield (%)
	2.1	A, 650 W, 7 min, H ₂ O A, 650 W, 5 min B, 650 W, 4 min	97 97 80
	2.2	A, 600 W, 2 min, DMF-H ₂ O (3:1) B, 600 W, 2 min	69 43
	2.3	A, 650 W, 5 min	88
	2.4	A, 650 W, 4 min	92
	2.5	A, 750 W, 4 min B, 750 W, 4 min, aqueous Formaldehyde-DMF (1:1)	92–98 80
	2.6	A, 650 W, 4 min	83
	2.7	A, 700 W, 4 min	98
	2.8	A, 600 W, 6 min, DMF-H ₂ O (1:1)	92–98

^aMethod A: paraformaldehyde/DMF, Method B: aqueous formaldehyde.



General Procedure for the Synthesis of Aromatic Imides

Well-powdered mixture of anhydride (1 mmol) with formamide (3–4 mL) or with urea (2 mmol of urea for monoanhydrides or 3 mmol of urea for dianhydrides) in DMF (3–4 mL), (see Table 1), was placed in 250 mL Erlenmeyer flask covered with watch glass. The mixture was irradiated in two intervals for total time and power as indicated in Table 1. Usually the imides spontaneously crystallize at room temperature (if not, water is added slowly for the precipitation). The products were filtered, washed with water and dried. The purity of the imides is high but if necessary they could be crystallized from dioxane, DMF or DMSO-H₂O.

This procedure was used also for the preparation of gram quantities of imides **1.5** and **1.9** (10 mL formamide for 4 g of pyromellitic anhydride). In this case the use of fume hood is recommended due to intensive formation of gases.

General Procedure for the Synthesis of Aromatic *N*-Hydroxymethylimides

Well-powdered mixture of imide (0.4 mmol) and paraformaldehyde (1 equiv. for monoimides and 3 equiv. for diimides) in DMF (3–4 mL) was placed in 250 mL Erlenmeyer flask covered with watch glass. The mixture was irradiated in two intervals for total time and power as indicated in Table 2 (an additional 2 mL of DMF can be added if the solvent evaporates). Usually the product spontaneously crystallize at room temperature (if not, water is added slowly for the precipitation). The product was filtered, washed with water and dried. In some cases the crude products contained small amount ($\leq 4\%$) of the substrate. If necessary pure *N*-hydroxymethylimides can be obtained by crystallization from dioxane, DMF or DMSO-H₂O.

Paraformaldehyde can be replaced by 2 mL of formaldehyde solution for 1 mmol scale preparation of imides.

Phthalimide (1.1): ¹H NMR δ 11.4 (bs, 1H), 7.84 (s, 4H); IR ν 3202, 3062, 1774, 1751, 1605, 1388, 1308, 1053, 715 cm⁻¹, m.p. 230–233°C (lit. 234°C); yield 80–90%.

3-Nitrophthalimide (1.2): ¹H NMR δ 11.8 (bs, 1H), 8.28 (m, 1H), 8.14 (m, 1H), 8.11 (m, 1H); IR ν 3173, 3075, 1771, 1708, 1615, 1538, 1357, 1313, 1072, 846, 802 cm⁻¹; m.p. 217–219°C (lit. 215°C); yield 64%.



3,4-Dichlorophthalimide (1.3): $^1\text{H NMR}$ δ 11.64 (bs, 1H), 8.13 (s, 2H); IR ν 3257, 3094, 1781, 1724, 1674, 1386, 1342, 1170, 1060, 903, 746 cm^{-1} ; m.p. 218–220°C (lit. 221°C); yield 96%.

2,3,4,5-Tetrachlorophthalimide (1.4): $^1\text{H NMR}$ δ 11.9 (bs, 1H); IR ν 3212, 3078, 1788, 1772, 1708, 1381, 1367, 1087, 754, 714 cm^{-1} ; m.p. 341–343°C (lit. 340°C); yield 79%.

Pyromellitic diimide (1.5): $^1\text{H NMR}$ δ 11.8 (bs, 2H), 8.10 (s, 2H); IR ν 3198, 3068, 1772, 1698, 1378, 1357, 1156, 1061, 860, 727 cm^{-1} ; does not melt below 410°C (lit. 450°C); yield 99%.

3,3',4,4'-Biphenyltetracarboxylic diimide (1.6): $^1\text{H NMR}$ δ 11.5 (bs, 2H), 8.3 (m, 4H), 8.0 (m, 2H); IR ν 3208, 1768, 1736, 1716, 1616, 1425, 1348, 1308, 1112, 1054, 853 cm^{-1} ; does not melt below 400°C; yield 85%.

3,3',4,4'-Benzophenonetetracarboxylic diimide (1.7): $^1\text{H NMR}$ δ 11.7 (bs, 2H), 8.18 (dd, $J=1.6$ Hz, $J=7.7$ Hz, 2H); 8.05 (m, 4H); IR ν 3228, 3070, 1782, 1728, 1703, 1667, 1362, 1247, 1102, 1045, 749, 721 cm^{-1} ; m.p. 380–385°C; yield 84%.

1,8-Naphthalenedicarboxylic imide (1.8): $^1\text{H NMR}$ δ 11.7 (bs, 1H), 8.47 (m, 4H), 7.89 (m, 2H); IR ν 3176, 3061, 2827, 1701, 1683, 1348, 844, 778 cm^{-1} ; m.p. 300–302°C (lit. 299–300°C); yield 85%.

1,4,5,8-Naphthalenetetracarboxylic diimide (1.9): $^1\text{H NMR}$ δ 12.1 (bs, 2H), 8.63 (s, 4H); IR ν 3170, 3069, 2854, 1701, 1678, 1374, 1338, 864, 764 cm^{-1} ; does not melt below 410°C; yield 96%.

***N*-Hydroxymethylphthalimide (2.1):** $^1\text{H NMR}$ δ 7.95–7.87 (m, 4H), 6.44 (t, $J=7.1$ Hz, 1H), 4.99 (d, $J=7.1$ Hz, 2H); IR ν 3445, 1774, 1726, 1468, 1053, 978, 713 cm^{-1} ; m.p. 137–139°C (lit. 138–140°C); yield 97%.

***N*-Hydroxymethyl-3-nitrophthalimide (2.2):** $^1\text{H NMR}$ δ 8.68 (dd, 1H, $J=2.2$ Hz, $J=8.2$ Hz), 8.55 (d, $J=0.5$ Hz, 1H), 8.20 (m, 1H), 6.60 (t, 1H, $J=7.1$ Hz), 5.02 (d, 2H, $J=6.8$ Hz); IR ν 3542, 1776, 1712, 1537, 1460, 1064, 987 cm^{-1} ; m.p. 159–161°C (lit. 162–163°C); yield 43–69%.

***N*-Hydroxymethyl-3,4-dichlorophthalimide (2.3):** $^1\text{H NMR}$ δ 8.25 (s, 2H), 6.53 (t, $J=7.1$ Hz, 1H), 4.97 (d, $J=7.1$ Hz, 2H); IR ν 3468, 1780, 1707, 1456, 1409, 1388, 1357, 1191, 1143, 1047, 1104, 996, 915 cm^{-1} ; m.p. 217–220°C; yield 88%.

***N*-Hydroxymethyl-2,3,4,5-tetrachlorophthalimide (2.4):** $^1\text{H NMR}$ δ 6.62 (t, $J=7.1$ Hz, 1H), 4.98 (d, $J=7.4$ Hz, 2H); IR ν 3520, 1786, 1713, 1460, 1080, 1004, 759, 737 cm^{-1} ; m.p. 340°C; yield 92%.

***N,N'*-bis-Hydroxymethylpyromellitic diimide (2.5):** $^1\text{H NMR}$ δ 8.31 (s, 2H), 6.59 (t, $J=7.1$ Hz, 2H), 5.03 (d, $J=7.1$ Hz, 4H); IR ν 3477, 1770, 1712, 1455, 1054, 977, 800, 744 cm^{-1} ; does not melt below 410°C (lit. 146°C, DSC); yield 92–98%.



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***N,N'*-bis-Hydroxymethyl-3,3',4,4'-biphenyltetracarboxylic diimide (2.6):** ^1H NMR δ 8.4 (m, 4H), 8.0 (m, 2H); 6.49 (t, $J=7.1$ Hz, 2H), 5.02 (d, $J=7.1$ Hz, 4H); IR ν 3481, 3215, 1768, 1716, 1617, 1450, 1425, 1346, 1067, 980 cm^{-1} ; does not melt below 350°C; yield 83%.

***N,N'*-bis-Hydroxymethyl-3,3',4,4'-benzophenonetetracarboxylic diimide (2.7):** ^1H NMR δ 8.24–8.21 (m, 2H), 8.15 (m, 4H), 6.53 (t, $J=7.1$ Hz, 2H), 5.03 (d, $J=7.1$ Hz, 4H); IR ν 3517, 1776, 1715, 1457, 1416, 1247, 1061, 990, 730 cm^{-1} ; m.p. 195°C (lit. 146°C, DSC); yield 98%.

***N*-Hydroxymethyl-1,8-naphthalenedicarboxylic imide (2.8):** ^1H NMR δ 8.53 (m, 4H), 7.91 (t, $J=7.1$, 2H), 6.37 (t, $J=7.1$ Hz, 1H), 5.49 (d, $J=7.1$ Hz, 2H); IR ν 3403, 1698, 1660, 1460, 1060, 990, 781 cm^{-1} ; m.p. 300–302°C (lit. 304–306°C); yield 92–98%.

ACKNOWLEDGMENTS

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