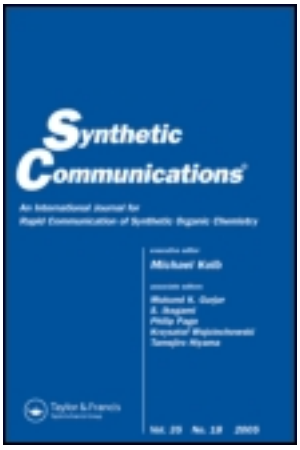

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Microwave-assisted Synthesis of N-Hydroxyphthalimide Derivatives

Kazuhiro Sugamoto [a], Yoh-ichi Matsushita [a], Yu-hei Kameda [a], Masahiko Suzuki [a] & Takanao Matsui [a]

[a] Faculty of Engineering, University of Miyazaki, Gakuen-Kibanadai-Nishi, Miyazaki, 889-2192, Japan

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Microwave-assisted Synthesis of *N*-Hydroxyphthalimide Derivatives

Kazuhiro Sugamoto, Yoh-ichi Matsushita, Yu-hei Kameda, Masahiko Suzuki, and Takanao Matsui
Faculty of Engineering, University of Miyazaki, Miyazaki, Japan

Abstract: *N*-Hydroxyphthalimide derivatives are readily obtained in good yields by the reaction of phthalic anhydrides with hydroxylamine hydrochloride in the presence of pyridine under microwave irradiation.

Keywords: *N*-hydroxyphthalimide, microwave, phthalic anhydride

N-Hydroxyphthalimide and its derivatives are associated with various applicabilities. In synthetic chemistry, *N*-hydroxyphthalimide acts as catalyst for radical oxidation of various organic compounds such as alkylbenzenes,[1–4] alkanes,[1,3,4] alkynes,[3] and sulfide,[3] or mediator for electrochemical oxidation of olefins,[5] amides,[6] lactames,[6] and alcohols.[7] In biochemistry, *N*-hydroxyphthalimide serves as mediator for laccase-assisted oxidation of methylbenzene,[8] allyl alcohols,[8], benzyl alcohols,[9] aryl alkanes,[10] and lignin model.[11] In general, *N*-hydroxyphthalimide derivatives are prepared by condensation between phthalic anhydride derivatives and hydroxylamine hydrochloride in the presence of excess amount of pyridine.[12] Wentzel et al. reported a preparation of *N*-hydroxyphthalimide derivatives from phthalic anhydrides and hydroxylamine hydrochloride in the presence of triethylamine in ethanol under reflux overnight.[13] However, the yield of

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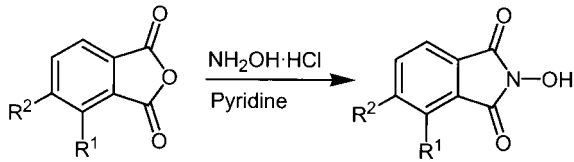
Address correspondence to Kazuhiro Sugamoto, Faculty of Engineering, University of Miyazaki, Gakuen-Kibanadai-Nishi, Miyazaki 889-2192, Japan. Fax: +81-985-58-7323; E-mail: sugamoto@cc.miyazaki-u.ac.jp

N-hydroxy-3-nitorophthalimide was only in 9% yield. Microwave irradiation as an efficient thermal source has been applied to accelerate a variety of organic reactions.[14] Recently, microwave-assisted syntheses of *N*-substituted phthalimides were reported.[15–20] To our knowledge, there are no reports for synthesis of *N*-hydroxyphthalimides by the microwave irradiation method. In this paper, we report the first example of the microwave-assisted synthesis of *N*-hydroxyphthalimide derivatives.

When nitrophthalic anhydrides **1a** and **1b** were allowed to react with 1.2 equiv. of hydroxylamine hydrochloride under the conventional heating conditions, the yields of *N*-hydroxyphthalimides **2a** and **2b** were low (Table 1, entries 1 and 2).[12] On the other hand, under the microwave irradiation method, the reaction of **1a** with 1.2 equiv. of hydroxylamine hydrochloride in the presence of 10 equiv. of pyridine took place smoothly to give **2a** in 50% yield (entry 3). On the reaction, the yield of **2a** was increased in increasing amount of hydroxylamine hydrochloride (entry 4). The microwave irradiation brought about not only a considerable increase in yield but also a remarkable reduction in time. Under similar conditions, the reaction of **1b** gave **2b** in fairly good yield (entry 5). The reactions of phthalic anhydrides bearing both electron-donating groups and electron-withdrawing groups with hydroxylamine hydrochloride gave the corresponding *N*-hydroxyphthalimide derivatives **2c–2h** in high yields (Table 2,

Table 1. The reaction of nitrophthalic anhydrides with hydroxylamine hydrochloride in pyridine under reflux or microwave irradiation



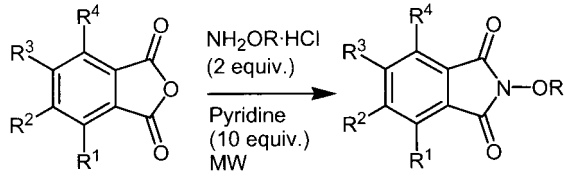
1a-b
a: R^1=H, R^2=NO_2
b: R^1=NO_2, R^2=H

2a-b
a: R^1=H, R^2=NO_2
b: R^1=NO_2, R^2=H

Entry	Substrate	Method	Conditions: NH_2OH/equiv.	Conditions: Pyridine/equiv.	Conditions: Time	Yield of **2**/%
1	**1a**	Δ(reflux)	1.2	40	72 h	18
2	**1b**	Δ(reflux)	1.2	40	72 h	20
3	**1a**	MW[a]	1.2	10	1 min × 7	50
4	**1a**	MW[a]	2.0	10	1 min × 7	70
5	**1b**	MW[a]	2.0	10	0.5 min × 4	58

[a]Microwave was irradiated by domestic microwave oven (2450 MHz, 500 W).

Table 2. Microwave-assisted synthesis of *N*-hydroxyphthalimide derivatives



1c-h

c: $R^2=R^3=R^4=H$, $R^1=OMe$
d: $R^1=R^3=R^4=H$, $R^2=Me$
e: $R^1=R^2=R^3=R^4=H$
f: $R^2=R^3=R^4=H$, $R^1=CO_2Me$
g: $R^1=R^3=R^4=H$, $R^2=CO_2H$
h: $R^1=R^2=R^3=R^4=Cl$

2c-i

c: $R^2=R^3=R^4=H$, $R^1=OMe$, R=H
d: $R^1=R^3=R^4=H$, $R^2=Me$, R=H
e: $R^1=R^2=R^3=R^4=H$, R=H
f: $R^2=R^3=R^4=H$, $R^1=CO_2Me$, R=H
g: $R^1=R^3=R^4=H$, $R^2=CO_2H$, R=H
h: $R^1=R^2=R^3=R^4=Cl$, R=H
i: $R^1=R^3=R^4=H$, $R^2=CO_2H$, R=Bn

			$NH_2OR \cdot HCl$	
Entry	Substract	Time/min	R	Yield of **2**/%
1	**1c**	0.5	H	93
2	**1d**	0.5	H	81
3	**1e**	0.5	H	81
4	**1f**	0.5	H	90
5	**1g**	1.0 × 5	H	70
6	**1h**	0.5	H	99
7	**1g**	0.5 × 14	Bn	90

entries 1–6). Furthermore, the reaction of **1g** using *O*-benzylhydroxylamine hydrochloride instead of hydroxylamine hydrochloride afforded the corresponding *O*-benzyl derivative in 90% yield (entry 7).

The present microwave irradiation reaction proceeds in short time and gives the *N*-hydroxyphthalimides in high yields compared with the conventional heating methods.[12,13] The use of microwave oven to accelerate the reaction rate is becoming an important and useful technique in organic synthesis. We have developed microwave-assisted synthesis of *N*-hydroxyphthalimide derivatives.

TYPICAL PROCEDURE

Typical procedure for the preparation of *N*-hydroxy-4-nitrophthalimide (Table 1, entry 4):

A mixture of 4-nitorophthalic anhydride (386 mg, 2 mmol), hydroxylamine hydrochloride (278 mg, 4 mmol), and pyridine (1.58 g, 20 mmol) in

200 cm^3 round-bottom flask was irradiated in a domestic microwave oven (2450 MHz, 500 W) for 1.0 min. The microwave irradiation was repeated seven times until the *N*-hydroxy-4-nitrophthalimide was completely consumed by monitoring TLC. The pyridine was removed under reduced pressure. The residue was cooled to 0°C, and then 1 mol/dm^3 HCl (10 cm^3) was added. The yellow precipitate was filtered, washed with water (10 cm^3), and dried *in vacuo* to give *N*-hydroxy-4-nitrophthalimide (290 mg, 70%).

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REFERENCES

1. Einhorn, C.; Einhorn, J.; Marcadal, C.; Pierre, J. *Chem. Commun.* **1997**, 447.
2. Arends, I. W.C.E.; Sasidharan, M.; Kühnle, A.; Duda, M.; Jost, C.; Sheldon, R. A. *Tetrahedron* **2002**, *58*, 9055.
3. Ishii, Y.; Sakaguchi, S. *J. Synth. Org. Chem. Jpn.* **2003**, *61*, 16A review.
4. Minisci, F.; Recupero, F.; Gambarotti, C.; Punta, C.; Paganelli, R. *Tetrahedron Lett.* **2003**, *44*, 6919.
5. Masui, M.; Hosomi, K.; Tsuchida, K.; Ozaki, S. *Chem. Pharm. Bull.* **1985**, *33*, 4798.
6. Masui, M.; Hara, S.; Ozaki, S. *Chem. Pharm. Bull.* **1986**, *34*, 975.
7. Gorgy, K.; Lepretre, J.; Saint-Aman, E.; Einhorn, C.; Einhorn, J.; Marcadal, C.; Pierre, J. *Electrochemica Acta* **1998**, *44*, 385.
8. Fritz-Lenghals, E.; Kunath, B. *Tetrahedron Lett.* **1998**, *39*, 5995.
9. Fabbrini, M.; Galli, C.; Gentili, P. *J. Mol. Catal. B: Enzym.* **2002**, *16*, 231.
10. Cantarella, G.; Galli, C.; Gentili, P. *J. Mol. Catal. B: Enzym.* **2003**, *22*, 135.
11. Barreca, A. M.; Fabbrini, M.; Galli, C.; Gentili, P.; Ljunggren, S. *J. Mol. Catal. B: Enzym.* **2003**, *26*, 105.
12. Fieser, L. F.; Fieser, M. *Reagents for Organic Synthesis*; Wiley: New York, 1967; Vol. 1, pp. 485–486.
13. Wentzel, B. B.; Donners, M. P.J.; Alsters, P. L.; Feiters, M. C.; Nolte, R. J. M. *Tetrahedron* **2000**, *56*, 7797.
14. Loupy, A. *Microwaves in Organic Synthesis*; WILLEY-VCH, 2003.
15. Bose, A. K.; Manhas, M. S.; Ghosh, M.; Raju, V. S.; Tabei, K.; Urbanczyk-Lipkowska, Z. *Heterocycles* **1990**, *30*, 741.
16. Khajavi, M. S.; Nikpour, F.; Hajihadi, M. *J. Chem. Research (S)* **1996**, *96*.
17. Chandrasekhar, S.; Takhi, M.; Uma, G. *Tetrahedron Lett.* **1997**, *38*, 10116.
18. Lima, L. M.; Barreiro, E. J.; Fraga, C. A.M. *Syn. Commun.* **2000**, *30*, 3291.
19. Vidal, T.; Petit, A.; Loupy, A.; Gedye, R. N. *Tetrahedron* **2000**, *56*, 5473.
20. Hajipour, A. R.; Mallakpour, S. E.; Imanzadeh, G. *Indian J. Chem.* **2001**, *40B*, 250.