



Short Communication

**Microwave Induced Synthesis of Biologically Active Synthesis of
N-acyloxy phthalimides Compounds**

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ABSTRACT

N-hydroxyphthalimide was dissolved in aqueous Potassium carbonate solution. Then adsorbent was added to this solution and stirred well. Then mixture was evaporated in microwave oven for complete removal of water. To this dry contents, acyl halide was added and irradiated in microwave oven at for 1- 4.5 min. Different, N-acyloxy phthalimide have been successfully prepared using different solid supports with MW irradiation technique.

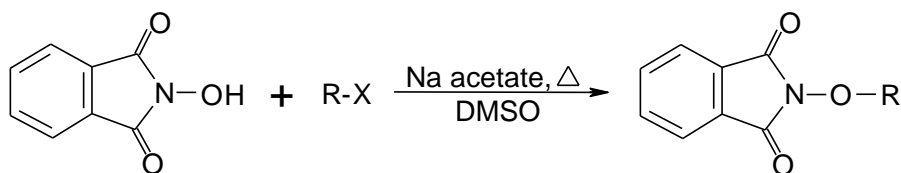
Keywords: N-hydroxyphthalimide, Microwave Irradiation, Alcyl halides, Solid Supports.

INTRODUCTION

Compounds containing a phthalimide moiety are distinguished by their potent fungicidal action [1,2]. N-Hydroxy phthalimides are important intermediates for the preparation of primary amines, O-substituted hydroxylamines, agricultural pesticides and are also used in preservatives, pigments and pharmaceuticals [1-3]. The phthaloyl group is a well-established protective group for primary amines [4] in various types of compounds, particularly peptides [5], aminoglycosides [6] and β -lactam antibiotics [7]. Derivatives of N-hydroxyphthalimide have been reported to possess good antibacterial efficacy and antifungal potency [8,9]. However, a literature survey has revealed that the N-hydroxyphthalimidedimers requires strictly anhydrous conditions with high temperature and long reaction times [10-12]. Furthermore, the purification of compounds is compulsory and tedious.

Several methods have been reported for the synthesis of N- hydroxy phthalimide derivatives:-

For N-acyloxy phthalimides: Diphtalimido oxalate: From N-hydroxy phthalimide, oxalyl chloride and triethyl amine in 1, 2-dimethoxyethane [12] (**Scheme 1.a.**).



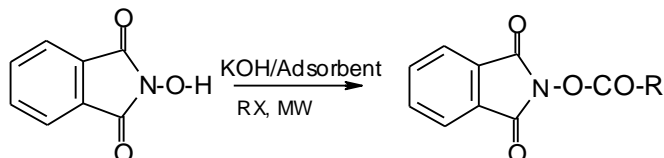
Scheme 1a

The structural modification of N-hydroxy phthalimide through simple, rapid and environmentally friendly approach is a fundamental requirement in the study of bioassay and then structure-activity relationships (SAR). Derivatives of N-hydroxy phthalimide have been reported to possess good antibacterial efficacy and antifungal potency [8-9].

MATERIALS AND METHODS

N-hydroxy phthalimide, Microwave Irradiation, Alkyl halides, Solid Supports such as silica gel, alumina fly ash.

Present work: In continuation of our work on microwave mediated synthesis [8,9,13,14], we report herein a simple, rapid and environmentally friendly method for synthesis of N-hydroxy phthalimide compounds in better yields with higher purity under mild conditions. The present work includes solid state alkylation and acylation and dimerisation of N-hydroxyphthalimide using commercially available silica gel, alumina and fly ash¹³ as a solid support. N-hydroxyphthalimide was adsorbed on silica gel, alumina and fly ash using aqueous potassium hydroxide and irradiated with various alkyl and acid halides, α,ω -dibromoalkanes and acid dichlorides to give the desired products (**Scheme 1b**).



k) R = COCH₃, l) R = COC₆H₅, m) R = COCH₂C₆H₅, n) R = COCH=CHC₆H₅

Scheme 1b

Reagents ratio: N-hydroxyphthalimide – 10 mmol, RX – 10 mmol, XRX = 5 mmol, K₂CO₃ (10 mmol), H₂O = 5 ml, Adsorbent = Silica gel / Alumina / Fly ash (1.63 g).

Experimental: All chemicals were of analytical grade (s.d. fines Chem. Ltd., Mumbai, India) and tetrahydrofuran and methylene dichloride was freshly distilled before use. Microwave oven (model OM9918C, 2450 MHz, 900 W) was used to carry out the reactions. The fly ash was collected from Thermal Power Plant, Deenagar, Bhusawal, Dist. Jalgaon (M.S.), and India and used as such for the reactions. Silica gel (60-120 mesh) and alumina (60-120 mesh) were of synthetic grade. The reactions were monitored by silica gel TLC using Tetrahydrofuran : Ethanol (8:2) mixture. Melting points and boiling points were determined by open capillary method and are uncorrected.

Synthesis of N-acyloxy phthalimides (1k-n): N-hydroxyphthalimide (10 mmol) was dissolved in aqueous Potassium carbonate solution (0.1 N, 5 mL). Then adsorbent (1.63 g) was added to this solution and stirred well. Then mixture was evaporated in microwave oven for complete removal of water. To this dry contents, acyl halide (10 mmol) was added and irradiated in microwave oven at 20 power level at pulse of 5sec. for 1- 4.5 min. After completion of reaction (monitored by TLC), the mixture was cooled and

extracted with dichloromethane (2 x 25 mL). Then this extract was dried with anhydrous calcium chloride, filtered and removal of the solvent afforded the products (1k-n) (Scheme 1b, Table 1)

RESULTS AND DISCUSSION

N-hydroxyphthalimide compounds: Synthesis of N-hydroxy phthalimide compounds and physical properties are presented in table 1 and spectral data in table 2.

Table 1. Synthesis of N-Hydroxy phthalimide Compounds and physical properties

Compd. No.	Irradiation Time (min)	Solid support, Yield (%)			mp(bp ⁺ /mm) (°C)	lit. ²¹⁻²⁵ mp(bp ⁺ /mm) (°C)
		Silica gel	Alumina	Fly-ash		
1k	1	93	92	92	184	184
1l	1.3	91	90	91	171	171
1m	1.7	89	86	87	71	71
1n	1.9	86	85	84	211	212

Solid-supported reagents are easily removed from reaction contents by filtration. Excess reagents can be used to drive reactions to completion without introducing difficulties in purification. Recycling of recovered reagents is economical, environmentally-sound, and efficient. Toxic, explosive and noxious reagents are often more safely handled when contained on solid support

Table 2. Spectral data of N-hydroxy phthalimide compounds

Compd.No	IR (ν, cm ⁻¹)	¹ H NMR (δ, ppm)
1k	1808,1781 and 1740	2.40(s, 3H, CH ₃), 7.95(s,4H,Ar-H).
1l	1800,1775 and1740	8.05-7.5 (m,5H, Ar-H), 8.13 (s,4H,Ar-H),
1m	1816,1784 and 1741	4.0 (s, 2H, CH ₂), 7.43(s,5H,Ar-H), 7.91(s, 4H, Ar-H).
1n	1774,1745,1648,1604 ,1238	6.42 (d, 1H, CH attached to ester gr.)7.89 (s, 4H, Ar-H)

Characterization: The synthesized N-hydroxy phthalimide compounds were characterized by their physical constants, comparative TLC and spectroscopic (1H NMR and IR) techniques. The spectral data of the synthesized compounds were found to be satisfactory with reported data.

APPLICATIONS

Microwave chemistry has opened up several new avenues in organic synthesis. Many reactions that previously were not possible, or resulted in a low yield, can now often be performed quickly, safely and efficiently in a few minutes. In summary, MAOS has changed the world of organic chemistry and drug discovery and it would be wise to embrace this new technology or be left lagging behind with conventional heating methodologies.

CONCLUSIONS

MW methodology leads to clear improvements and simplifications of procedure compared with conventional methods. Microwave assisted solvent less, alkylation, acylation and dimerization of Carbazole. Very faster reaction, higher yields, easy work-up, purity of the products and thus eco-friendly approach. Silica gel, alumina and fly ash are used as a solid support. Importantly, fly ash was found to be new solid support for organic reactions in dry media as efficient as commercial ones such silica gel and alumina.

REFERENCES

- [1] G. S Gruzdyes., V. A. Zinchenko & R. I.Slotsov, in *The Chemical Protection of Plants*, by G. S. Gruzdyes, Mir Publishers, Moscow, **1983**, 272 .
- [2] Sree Ramulu U. S., in *Chemistry of Insecticides & Fungicides*, 2nd Ed., Oxford & IBH Publishing Co. Pvt. Ltd., New Delhi, **1995**, 246,
- [3] *Ullmanns Encyclopedia of Industrial Chemistry*, Editors B. Elvers, S.Hawkins, Schulz G., 5th Ed., **1991**, Vol. A 20, 190-191.
- [4] T. W. Greene and P. G. M. Wuts *Protective Groups In Organic Synthesis*, 2nd Ed., Wiley: New York, **1991**.
- [5] M. Bondanzsky and A. Bondanzsky, *The Practice of Peptide Synthesis*, 2nd Ed., Springer: Heidelberg, **1994**.
- [6] P. J.Kocienski, *Protective Groups*, Thieme: Stuttgart, **1994**.
 - a. T. Kamiya, M. Hashimoto, O.Nakaguchi and T.Oku, *Tetrahedron*, **1979**, 35, 323.
 - b. C. A.Townsend, L. T.Nguyen, *Tetrahedron Lett.*, 25, 4859, (**1982**).
- [7] N.S.Pawar, S.B.Attarde, D.S.Dalal, G.R.Sonar, U.R.Kapadi,
- [8] D.G.Hundiwale, and P.P. Kumbhar (alias Mahulikar), *J. Indian Coun. Chem.*, **2001**, 18 (2), 29.
- [9] N. S.Pawar, U. R.Kapadi, D. G.Hundiwale and P. P. Kumbhar (alias Mahulikar), *J. Sci Ind. Res.*, **2002**, 61, 454, Chem. Abst. **2003**, 137: 196937.
- [10] L.Bauer and K. S.Suresh, *J. Org. Chem.*, **1963**, 28, 1604.
- [11] E.L. Schumann, *J. Med. Chem.*, **1964**, 7, 329.
- [12] L., Bollyky, *J. Org. Chem.*, **1968**33, 4266.
- [13] H. P.Narkhede, U. B.More, D. S.Dalal, N. S. Pawar, D. H. More and P. P.Mahulikar, *Synth. Commun.*, **2007**, 37(4), 575-579.
- [14] D. S.Dalal, N. S. Pawar and P. P.Mahulikar, *Org. Prep. Proced. Int.*, **2005**37, 539.
- [15] A.Roungny & M.Daudon, *Bull. Soc. Chim. Fr.*, **1976**, 5-6, 833.
- [16] E. Grochowski & J. Jupczak, *Synthesis*, **1976**, 683.
- [17] E. Grochowski & J. Jupczak, *Synthesis*, **1977**, 277.
- [18] O.Miitusunobu, *Synthesis*, **1981**, 1.
- [19] L.R.Baue & K. S.Suresh, *J. Org. Chem.*, **1963**, 28, 1604.
- [20] P.P Kumbhar (alias Mahulikar), U.R.Kapadi, D.G.Hundiwale, S.B. Attarde, P.M. Dewang and N.S.Pawar, *Org. Prep. Proc. Int.*, **2000**, 32 (6), 600.
- [21] *Dictionary of Organic Compounds*, 5th and 6th Ed; Chapman and Hall, London, **1982** and **1997**.

- [22] Beilstein Handbook of Organic Chemistry, EII H VI, 526-531.
- [23] D. S .Dalal, N. S. Pawar and P. P. Mahulikar, *Org. Prep. Pro. Int.*, **2007**, 39, 81-85.
- [24] H P Narkhede, *Journal of Applicable Chemistry*, **2014, 3 (2): 678-682.**
- [25] H P Narkhede, *International Journal of Recent Scientific Research*, **2013**, Vol. 4, Issue, 6, pp. 855 -857.