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Microwave assisted synthesis of an unusual dinitro phytochemical

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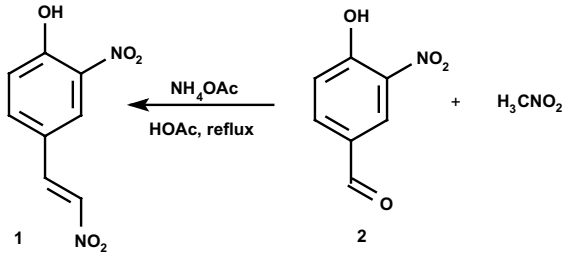
This paper is dedicated to Dr. Nitya Anand

Abstract—A novel dinitro secondary metabolite, 2-nitro-4-(2′-nitroethenyl)phenol from a marine source, has been prepared via highly accelerated, microwave assisted, nitration reactions using mild reagents. *ipso*-Substitution of a carboxy group by a nitro group is discussed.

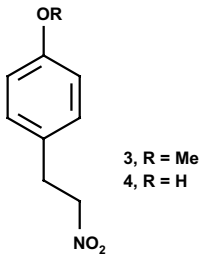
In the course of a joint Indo-US project[1] on 'Bioactive Substances from the Indian Ocean' during 1986–1993, leaves of the mangrove plant, *Sonneratia acida*, collected from the Gangetic delta of Sundarban, West Bengal, India were studied.[2,3] One of the colored compounds—isolated in milligram quantities from these leaves by extensive chromatographic separation—was obtained as a crystalline yellow-red solid, mp 146 °C. The structure of this compound was established to be **1** by detailed spectroscopic investigation and later confirmed by single crystal X-ray diffraction studies.[4] Such nitrostyrenes or dinitrostyrenes had not been reported earlier from natural sources.

A search of the chemical literature at this point revealed that structure **1** and a few related compounds had been prepared by synthesis and reported in 1962 by Japanese scientists[5] who noted that **1** showed antifungal activity. The synthetic method used by these workers involved the condensation reaction between 2-nitro-4-formylphenol (*p*-hydroxy-*m*-nitrobenzaldehyde, **2**), and nitromethane. We repeated this synthesis and verified our structure assignment by a direct comparison of samples. This metabolite **1**, therefore, is one of those rare compounds that was synthesized first in the laboratory (in 1964 in Japan) and isolated later from a natural source (in 1991 in India).



A recent publication has described the formation of **3** and **4** as stress metabolites by the leaves of skunk cabbage (*Lysichitum americanum*) treated with cupric chloride.[6] A glucoside of **4** had been reported in 1986 to be a component of *Thalictrum aquilegifolium*.[7]

In view of the biological activity of compounds related to **1**, we became interested in devising eco-friendly synthetic methods for the preparation of large quantities of **1** for pharmacological evaluation and other studies. For our synthetic work we planned to use Microwave-induced Organic Reaction Enhancement (**MORE**) chemistry techniques developed in our laboratory.[8]



Keywords: *ipso*-Substitution; Mild nitration; Dinitrostyrene; Clay-based reactions; Phytochemicals; Antifungal compounds.
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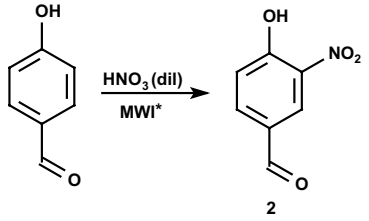
Recently, we have studied microwave assisted, eco-friendly methods of nitration of electron rich aromatic compounds that avoid the conventional reaction with nitric acid and sulfuric acid mixtures.[9] Following the method of Laszlo,[10] 'Claycop' (copper nitrate adsorbed on Montmorillonite clay) was used successfully to prepare nitro-derivatives of several phenolic compounds. It was observed that under microwave irradiation this type of reaction required only a few minutes instead of several hours for completion. Also, chlorinated solvents used by Laszlo et al. could be replaced by acetonitrile. Since copper is not environmentally benign, it was desirable to find alternative methods.

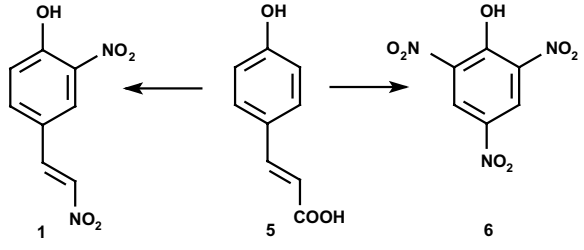
After some experimentation we found that nitric acid diluted with acetic acid or with water can be used for the rapid nitration of phenols under microwave irradiation. Readily available *p*-hydroxybenzaldehyde was converted in good yield by this method to the fairly expensive nitro compound **2**[11] that is, the starting material for the synthesis of **1** by the Japanese method.[5]



MWI* = microwave irradiation

Another synthetic approach to large quantities of **1** was investigated. From the biosynthetic point of view **1** appears to be related to cinnamic acid. Therefore we attempted the nitration of 4-hydroxycinnamic acid (**5**), a commercially available compound, which is a plausible biosynthetic precursor of **1**. After some trials it was observed that **5** could be nitrated with dilute nitric acid under microwave irradiation.

Reaction with nitric acid diluted with acetic acid under brief microwave irradiation led to the desired product **1** along with a small amount of another crystalline compound **6** that could be separated from **1** by column chromatography. Spectroscopic data, melting point and mixture melting point with an authentic sample established **6** to be picric acid (2,4,6-trinitrophenol). **Caution**: *picric acid is toxic and is an explosive in the dry state.*

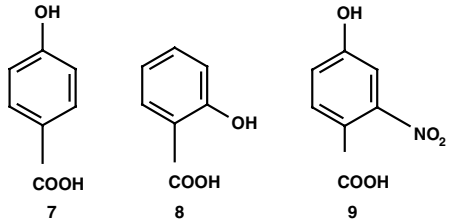


Treatment with a strong alkali (such as, sodium hydroxide solution) can be used for destroying picric acid.

The *ipso*-Substitution of a vinyl carboxyl group with a nitro group to produce **1** from **5** is unusual. It is very likely that **1** and **5** underwent hydrolysis and oxidation to a benzoic acid, which is susceptible to *ipso*-nitration with decarboxylation.

To test this hypothesis **1** was submitted to reaction with a nitric acid/ acetic acid mixture under microwave irradiation when **6** was produced in about 10% yield after a few minutes of irradiation.

For obtaining additional data, reaction of the following compounds with nitric acid/acetic acid was studied: *p*-hydroxybenzoic acid (**7**), *o*-hydroxybenzoic acid (**8**, salicylic acid), *o*-nitro-cinnamic acid (**9**). The reaction of **7** and **8** led to picric acid in good yield; compound **9**, however was unchanged.



When aq HNO_3 was used as the reagent, mononitro compounds were obtained from **7** and **8** without the formation of picric acid.

After further trials it was found that when a suspension of 1–2 g of **5** in aqueous nitric acid of about 10% strength was irradiated at medium power for a few minutes in a domestic microwave oven, the target compound **1** was obtained in about 75% yield without the formation of picric acid as a side product. This method was utilized for preparing several grams of pure **1**.[12]

Nitration of **5** was also conducted under monomodal (focused) microwave irradiation in a Prolabo Synthewave 402 applicator.[13,14] This instrument allows computer controlled input of microwave energy and keeps a record of the bulk temperature of the reaction mixture measured by an infrared sensor. On a 5 g scale the nitration of **5** with dilute (about 15% strength) aqueous nitric acid was complete in 5 min; the bulk temperature rose from room temperature to 80 °C with the microwave power level set at 75 W.

In summary, dilute aqueous nitric has been found to be a convenient reagent for the rapid nitration of electron rich compounds (such as phenols) under irradiation with low to medium levels of microwaves.

A mixture of nitric acid and acetic acid, however, should not be used for the microwave assisted nitration of phenolic compounds since picric acid is one of the products in many cases.

With easy access to **1** assured by microwave assisted reactions that are environmentally more benign than previous methods, pharmacological studies on this novel

natural product and its analogues and derivatives will now be undertaken.

Acknowledgements

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References and notes

1. This project was jointly sponsored by the Department of Science and Technology (DST) of the Government of India and the Oceanic Biology Program of the Office of Naval Research (ONR) of the United States Government. Funding for this project was under the authority of US Public Law 480 that supported in part research of international importance to be conducted in a foreign nation (India) where an excess of US currency existed.
2. Samples were collected from mangrove plants growing in brackish waters subject to rise and fall in salinity with the ebb and flow of the tide. During the monsoon season the salinity of the water was reduced due to the heavy influx of fresh water from rivers and rivulets. This change in salinity may constitute stress on the mangrove plant.
3. In an earlier study leaves of the mangrove plant were found to contain plant-growth regulators, gibberellins, cytokinin, and zeatin: Ray, M.; Ganguly, S. N. *Plant Physiol. Biochem.* **1988**, *15*, 248.
4. Urbanczyk-Lipkowska, Z.; Lee, M. Y. *Polish J. Chem.* **1992**, *66*, 1805.
5. Chibu, M.; Abiko, M.; Kawamura, Y. Japan Patent 3902 6960, 1964.
6. Hanawa, F.; Tahara, S.; Towers, G. H. N. *Phytochemistry* **2000**, *53*, 55–58.
7. Ina, H.; Iida, H. *Chem. Pharm. Bull.* **1986**, *34*, 726.
8. (a) MORE chemistry techniques were devised to avoid possibility of explosion reported by earlier workers in some cases when reactions were conducted in sealed systems under microwave irradiation. The strategy behind MORE chemistry is to use open vessels with reactants in a shallow layer (no stirring needed in most cases), with minimal quantities of a higher boiling solvent (or no solvent if one or more reactants are liquid). The microwave energy input is controlled to reach an appropiate bulk temperature of the reaction mixture with minimal vaporization (by maintaining the reaction mixture about 20 °C below the boiling point of reactants). Reflux condensers and flasks with ground glass joints thus are not needed. For a recent review on 'MORE chemistry for less polution', see Bose, A. K.; Manhas, M. S.; Ganguly, S. N.; Sharma, A. H.; Banik, B. K. *Synthesis* **2002**, 1578–1591; (b) This paper is MORE chemistry Part 21; for part 20, see Pramanik, B. N.; Ing, Y. H.; Bose, A. K.; Zhang, L.-K.; Liu, Y.-H.; Ganguly, S. N.; Bartner, P. *Tetrahedron Lett.* **2003**, *44*, 2565–2568.
9. Bose, Ajay K.; Manhas, M. S.; Ganguly, S. N.; Srirajan, V.; Lavlinskaia, N.; Bari, S. S.; Lavlinski, D. 'Microwave Assisted Aromatic Nitration: Eco-friendly Rapid Processes', Presented at the 215th ACS National Meeting, Dallas, TX, 1998, ORGN 233.
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11. Nitration of 4-hydroxybenzaldehyde: 4-Hydroxybenzaldehyde (2 g) mixed with 15 mL of 10% aqueous nitric acid was irradiated in a domestic microwave oven for 1 min at power level 500 W. The final temperature of the reaction mixture was 85 °C. An examination of the reaction mixture by thin layer chromatography showed the disappearance of the starting material. The reaction mixture was cooled to room temperature and 70 mL of cold water was added to it when a light orange colored solid separated. This solid was filtered, washed with water till free from acid, dried and then recrystallized from a benzene-methanol mixture, mp 141–142 °C. This compound, obtained in 85% yield, was found to be identical with an authentic sample of 3-nitro-4-hydroxy benzaldehyde.
12. Nitration of 4-hydroxycinnamic acid: A mixture of 1 g of 4-hydroxycinnamic acid and 10 mL of 15% aq. nitric acid was placed in a 100 mL conical flask. This flask with a funnel as the top was placed in an unmodified domestic microwave oven. Microwave irradiation was conducted at 400 W level for 1 min. The bulk temperature of the reaction was found to be about 60 °C. An examination of the reaction mixture by thin layer chromatography showed the disappearance of almost all of the starting material. After cooling the reaction mixture to room temperature 60 mL of cold water was added to it. The orange yellow solid that separated was collected by filtration, washed free of acid with cold water, dried and then recrystallized from methanol–benzene, mp 146 °C. The yield of the desired dinitro compound **1** was 80%.
13. Japanese workers had recorded the mp of **1** as 152 °C.[5] We have observed that the mp of different batches of **1** varies from 146–152 °C depending on the solvent and the mode of crystallization. This is not surprising because X-ray diffraction studies have shown that there are two polymorphic forms of **1**, which differ from each other in color, hydrogen bonding pattern, crystal lattice construction, and melting point.[4] The samples prepared in our laboratory were shown to have the correct structure by studying their ^{1}H NMR spectra in $CDCl_3$ solution and their mass spectra.
14. Monomodal microwave applicators are now available from the CEM Corporation.