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**HIGHLY ACCELERATED MICROWAVE ASSISTED AROMATIC NITRATION WITH
DILUTE NITRIC ACID**

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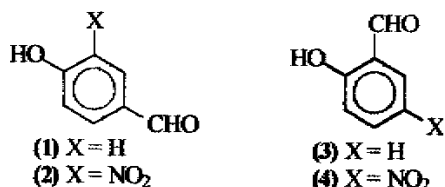
Commercial microwave ovens are now widely accepted as safe and convenient devices for domestic use. These ovens are set at a frequency of 2450 MHz for raising the temperature of water molecules through the efficient absorption of microwave energy. We have found that by using untraditional experimental arrangements it is possible to conduct a wide variety of organic reactions in open vessels inside domestic microwave ovens. These inexpensive ovens have now become essential equipment in our research and teaching laboratories. In the work reported from other laboratories, the reactions under microwave irradiation are conducted under rather unusual conditions, in sealed tubes, for example, or with the reactants absorbed on silica gel or embedded in vermiculite. The theoretical explanation for these remarkable accelerations is not yet clear. It is possible that the effect is purely a thermal one, with the rapid attainment of very high local temperatures due to the efficient absorption of microwave energy. However, a specific effect due to the microwave frequencies used has not been completely ruled out. Whatever the explanation, it is apparent that the microwave induced reaction techniques constitute new methods for carrying out chemical reactions. We wish to describe here our recent findings on microwave assisted reactions for aromatic nitration.

in a very recent review on the nitration of electron-rich aromatics, Dwyer and Holzaptel (*Tetrahedron*, 1998, **54**, 7843) state that "the nitration of aromatic rings has received considerable attention of late, due to unsolved problems pertaining to regioselectivity,

overnitration and competitive oxidation of substrates". We have found a simplified approach to nitration in an eco-friendly reaction which is described below.

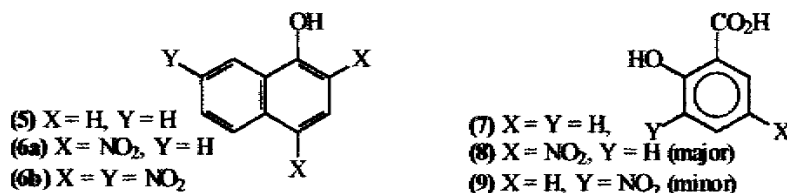
Microwave Assisted Reaction with Dilute Nitric Acid

We have found that dilute HNO₃ (10-20%) can be very effective for nitration of phenolic compounds under microwave irradiation. For example, when finely powdered 4-hydroxybenzaldehyde (**1**) was added to aqueous nitric acid (about 15% HNO₃) and the suspension was irradiated in a domestic microwave oven, the starting material disappeared in 1-2 minutes; in the next 1-2 minutes yellow crystals appeared. The nitration was complete in less than 5 minutes and nearly pure 4-hydroxy-3-nitrobenzaldehyde (**2**) was obtained in 70% yield by simple filtration and washing with water. This reaction was also conducted successfully on a 50 g scale. The bulk temperature of the reaction mixture was about 80°C. A similar reaction with salicylaldehyde (**3**) led to pure 2-hydroxy-5-nitrobenzaldehyde (**4**) in 64% yield after 90s of irradiation.



Naphthols were very reactive towards dilute HNO₃, e.g., 1-naphthol (**5**) gave two nitro compounds: the major product was 2,4-dinitro-naphthol (**6a**) and the minor product 2,4,7-trinitronaphthol (**6b**). Nitration under these conditions of 2-naphthol gave in 3 min a mixture of 1-nitro-2-naphthol and 1,6-dinitro-2-naphthol.

Nitration of salicylic acid (**7**) using 15% nitric acid and irradiation for several minutes in a domestic microwave oven at high power gave rise to several nitro compounds; the major product was a 60:40 mixture of 5-nitro-salicylic acid (**8**) and 3-nitro-salicylic acid (**9**); small amounts of 2,4-dinitrophenol were obtained; a very minor amount of 2,4,6-trinitrophenol was also detected.



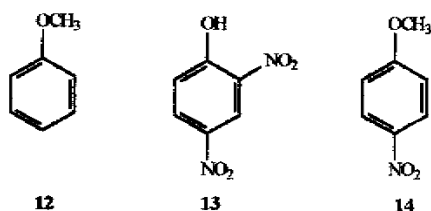
Nitration under Monomodal Microwave Irradiation

For obtaining a close control on the input of microwave energy into nitration reactions, we conducted experiments in a Prolabo Synthewave S402 instrument monitored by a computer. The microwave energy required to raise a volume of water to 90°C was reduced by 80% when a drop of HNO₃ was added to the water showing thereby that the

ions from the acid were very efficient in absorbing microwave energy. The nitration of salicylic acid (**7**) with dilute HNO_3 was then conducted using 15-20 watts of power. A single product was obtained which was identified as 5-nitrosalicylic acid (**8**). It was thus apparent that in the experiment for nitration of salicylic acid using a domestic microwave oven, too much power had been used.

The magnetron in a domestic microwave is controlled by an on-off circuit which provides only a moderate control of the energy input on to the reaction mixture. For obtaining a finer control we find it convenient to use a "heat sink" (a beaker of water) next to the vessel. When a "heat sink" was used and the power level of the domestic microwave oven was reduced, nitration of salicylic acid with dilute aqueous HNO_3 gave only the 5-nitrosalicylic acid in about 70% yield. The material that crystallized out on cooling the reaction mixture showed no detectable amounts of the 3-nitro isomer when examined by ^1H NMR spectroscopy.

Irradiation at high power for 2 minutes 20 sec of anisole (**12**) and aqueous HNO_3 gave about 40% yield of 2,4-dinitrophenol (**13**) with only a trace amount of 4-nitroanisole (**14**). It is remarkable that demethylation was achieved by dilute HNO_3 in such a short time. Conventional methods for the demethylation of the methyl ethers of phenols require such strong reagents such as BBr_3 or HI . Again, using the Prolabo Synthrowave S402 equipment and monomodal microwave irradiation it was found that much lower levels of energy can provide mostly 4-nitroanisole (**14**).



Reaction with HNO_3/HOAc

By the addition of concentrated HNO_3 to glacial HOAc , dilute HNO_3 (about 15% concentration) was prepared and used for the nitration of salicylaldehyde and salicylic acid. The progress of reaction was monitored by TLC. It was observed that the microwave assisted reaction for a nitric acid/acetic acid mixture was very fast. In case of salicylaldehyde the same product (**4**) was obtained that was produced by reaction with aqueous HNO_3 . In the case of salicylic acid, the product obtained - in high yield and good purity - was the 5-nitro isomer. This reaction again was very fast - almost 5-10 times faster than the reaction with aqueous HNO_3 .

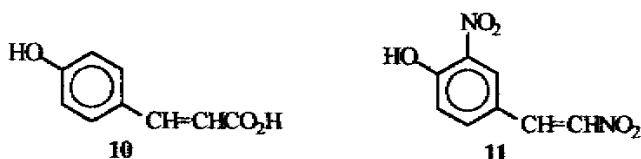
Efficient Synthesis of a Marine Natural Product

In the course of a collaborative Indo-US research project an unusual dinitro compound (**11**) had been isolated from the leaves of an Indian mangrove plant (*Sonneratia acida*).

On biosynthetic grounds it would appear that (**11**) is related to cinnamic acid. Therefore, we attempted the nitration of cinnamic acid and derivatives with dilute HNO_3

under microwave irradiation. However, dilute nitric acid failed to react with cinnamic acid. But, when 4-hydroxycinnamic acid was subjected to the action of dilute aqueous HNO_3 under microwave irradiation, **11** was obtained in 60-70% yield. In some experiments it was possible to isolate 4-hydroxy-3-nitrocinnamic acid as an intermediate. It is remarkable that the carboxy group was replaced so easily by a nitro group.

After some experimentation it has been discovered that a highly efficient and a very rapid microwave assisted conversion of **10** to **11** can be achieved by reaction with 15% HNO_3 in HOAc. Thus, 1g of **10** was transformed in 92% yield to **11** in 15 sec of irradiation in a domestic microwave oven (600-800 watts).



Concluding Remarks

Most of the conventional nitration methods are ecologically unfriendly as they involve such reagents as concentrated sulfuric acid, phosphoric acid, trifluoroacetic anhydride, etc. The microwave assisted nitration reactions reported here are much friendlier to the environment than their conventional counterparts. There is considerable difference of opinion among experts regarding the effect of microwaves on chemical bond and transition states: It will be quite some time before definitive answers are obtained about the nature of microwave assistance to chemical reactions.