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Microwave promoted rapid nitration of phenolic compounds with calcium nitrate

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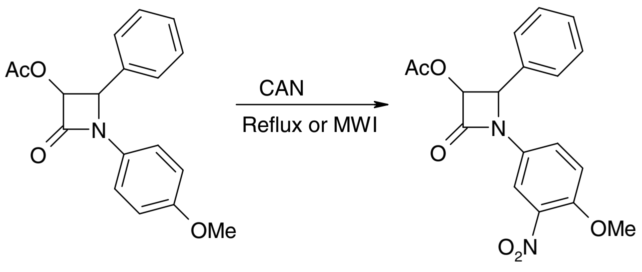
Abstract—Highly accelerated and safe nitration of phenolic compounds has been found to be feasible with a mixture of calcium nitrate and acetic acid as an efficient nitration agent under brief microwave irradiation. This method is compatible with the green chemistry approach because calcium salts—the inorganic byproducts—can be useful agrochemicals rather than waste chemicals. Commercially available ^{15}N-labeled calcium nitrate is convenient for the preparation of ^{15}N-labeled compounds for metabolic studies and mass spectrometry. This safe nitration method can be included in laboratory experiments for high school and college students.

In the course of studies on microwave-induced organic reaction enhancement ('MORE') chemistry techniques,[1,2] we have undertaken a search for eco-friendly nitration reactions that do not require strong acids such as nitric and sulfuric acids. We wish to report here a nitration method for phenolic compounds that is compatible with the requirements of green chemistry.

Our earlier investigations were based on the method of Laszlo and Pennetreau[3] involving the use of metal nitrates deposited on clay (Claycop: copper nitrate on montmorillonite clay; clayfen: ferric nitrate on clay; clayzin: zinc nitrate on clay; etc.) for nitration of electron-rich aromatic compounds. The clay derivatives were prepared by Laszlo et al. by a lengthy procedure. The nitration process required the use of chlorinated solvents for the reaction and solvent extraction of the product from clay and thus led to a substantial amount of chemical waste. We found that the Laszlo method could be conducted under microwave irradiation (MW) in a few minutes instead of a few hours.[4]

While attempting the removal of the *p*-anisyl group from a beta-lactam nitrogen by the oxidative method of Kronenthal[5] we made the serendipitous finding that cerium(IV) ammonium nitrate (CAN) under reflux conditions led to the nitration of the N-aromatic ring of the beta-lactam (Scheme 1). Microwave irradiation instead of heating under reflux shortened the reaction period from hours to minutes.[6] We prepared ^{15}N-labeled clay-zinc from [^{15}N] HNO$_3$, zinc carbonate and montmorillonite clay and utilized this reagent successfully for [^{15}N]NO$_2$ labeling of a beta-lactam under microwave



Scheme 1.

Keywords: Microwave-assisted nitration; Green chemistry approach; Mononitro phenol; Calcium nitrate for nitration; ^{15}N-labeled compounds.

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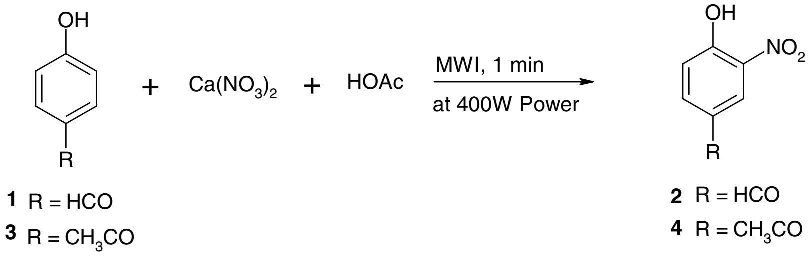


Scheme 2.

irradiation using our simplified variation of the Laszlo protocol.[6]

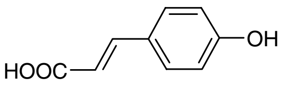
Encouraged by these observations we began a search for a highly suitable metal nitrate for eco-friendly nitration of phenols without nitric acid. After experimenting with several metal nitrates we became interested in easily available calcium nitrate—especially as it is also commercially available with the ^{15}N-label (Scheme 2).

Our experiments were conducted on 2–5 g scale in open flasks placed in unmodified domestic microwave ovens of 700–800 W power. For most of the experiments, the power control was set at 50%; therefore, the on–off cycle of the magnetron averaged about 350–400 W over the period of irradiation. In initial experiments, *p*-hydroxybenzaldehyde (**1**) was used as the substrate for nitration since this phenol can provide only a single mononitro derivative and/or a single dinitro derivative.

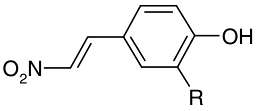
A simplified procedure was tested (Table 1). The reaction of 2 g of **1** mixed with 5 g of calcium nitrate and 10 mL of glacial acetic acid irradiated for 1 min showed the complete disappearance of the starting phenol. The reaction mixture was poured into cold water and stored for some time in a refrigerator. The yellow crystals that separated were washed free of acid with water and then allowed to dry. The mp of the product indicated it to be the mononitro compound **2**; the yield was about 78%. A similar experiment with *p*-hydroxyacetophenone (**3**) led to the mononitro compound **4** in about 83% yield.

4-Hydroxybenzoic acid (**5**) produced the expected mononitrate derivative **6** in 85% yield. Salicylaldehyde (**7**) and salicylic acid (**9**) led selectively to the 5-nitro derivatives (the nitro group *para* to the phenolic hydroxy group) **8** and **10**, respectively (see Table 1 for structures).

The preparation of a dinitro marine natural product (**12**) has been of special interest to us. We[1] have observed that the nitration of *p*-hydroxycinnamic acid (**11**) with dilute nitric acid under microwave irradiation is sensitive to the temperature range of the experiment. Thus, by chilling the reactants to a little below 0 °C, and then irradiating with microwaves to about 10 °C, we obtained the dinitro product **12** in pure form. On the other hand, by starting with the reactants at about −30 °C and raising the bulk temperature to about −10 °C, the mononitro compound **13** along with some starting material was obtained. We tested this '*cold microwave*' technique[2,7] for nitration with calcium nitrate and acetic acid.



11



12 $R = NO_2$
13 R = H

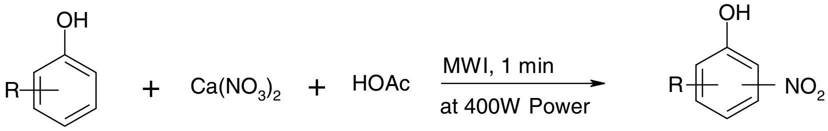
The starting phenol **11** and a mixture of calcium nitrate and acetic acid were pre-cooled separately to about −5 °C and then mixed together and placed in a microwave oven. After irradiation for 1 min, the reaction mixture was worked up in the usual manner; the product was nearly pure **13** in 60% yield. When this material (**13**) was used as the reactant under standard conditions with calcium nitrate and acetic acid, the product was the dinitro compound **12** in 70% yield. The '*cold microwave*' technique is under investigation for the nitration of other phenolic compounds of biological interest.

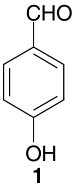
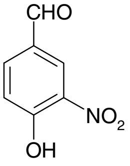
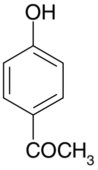
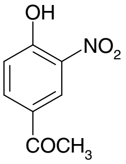
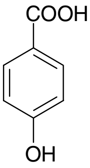
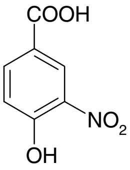
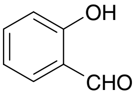
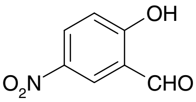
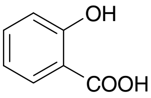
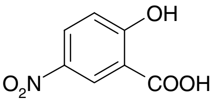
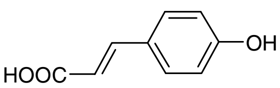
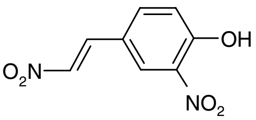
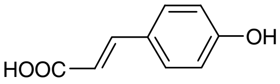
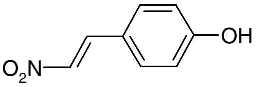
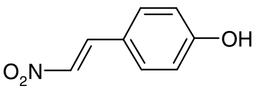
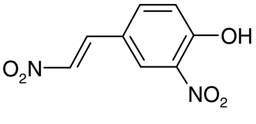
It is reasonable to assume that the microwave-assisted reaction of calcium nitrate with acetic acid produces (in small concentrations) nitric acid that in turn generates nitronium ions. Electrophilic nitration of aromatic compounds is mediated by nitronium ions according to the current theory about the mechanism of nitration. Calcium acetate, the byproduct in this nitration reaction, is environmentally benign as is the unreacted excess calcium nitrate. The total inorganic material at the end of the reaction therefore need not be chemical waste; it could be suitable for use as an agrochemical since calcium nitrate is used as a fertilizer (e.g., in tea gardens).

New protocols for nitration are being reported from various laboratories. For example, bismuth subnitrate in the presence of thionyl chloride has been found to be an efficient nitrating agent[8] (see Ref. 8 and literature citations therein).

In conclusion, we have found that calcium nitrate and acetic acid (glacial or about 80% aqueous) can serve as a fairly efficient nitrating agent for phenolic compounds.

Table 1. Nitrations of phenols



Entry	Substrate	Product	Yield (%)	mp (°C)	Lit. mp (°C)
1	 **1**	 **2**	78	140–141	140–142
2	 **3**	 **4**	83	135	133–135
3	 **5**	 **6**	85	184	184–185
4	 **7**	 **8**	82	129–130	128–130
5	 **9**	 **10**	84	234	233–235
6	 **11**	 **12**	70	146	146
7	 **11**	 **13**	60	210–212	N/A
8	 **13**	 **12**	70	146	146

The reagents and byproducts in this reaction are safe and eco-friendly. It is possible therefore to include this nitration method among laboratory experiments for chemistry students in high schools and colleges. Since $[^{15}N]Ca(NO_3)_2$ is commercially available, this nitration method can be conveniently used for preparing $[^{15}N]$-labeled compounds. Selectivity in the site of nitration has been observed. Studies are in progress for a better understanding of this type of selectivity.

Acknowledgements

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References and notes

1. For a recent review, see Bose, A. K.; Manhas, M. S.; Ganguly, S. N.; Sharma, A. H.; Banik, B. K. *Synthesis* **2002**, *1578*, 1591.
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3. Laszlo, P.; Pennetreau, P. *J. Org. Chem.* **1987**, *52*, 2407.
4. Huarotte, M. P; Masters Thesis, Stevens Institute of Technology, 2001.
5. Kronethal, D. R.; Han, C. Y.; Taylor, M. K. *J. Org. Chem.* **1982**, *47*, 383.
6. Unpublished results from our laboratory.
7. We have previously demonstrated[2] that N-phthaloylation of glycine can be conducted by reaction with phthalic anhydride in *N*,*N*-dimethyl formamide solution under microwave irradiation for a few minutes. We carried out the same reaction in a vial with a septum cap as the reaction vessel. In one experiment, this reaction vial was placed in a beaker of water and the water was frozen to a block of clear ice at −20 °C. When this block of ice was irradiated for 3 min inside a domestic microwave oven, the outer surface of the ice was melted slightly. Analysis of the contents of the encased reaction vial showed the formation of phthalimidoacetic acid in good yield.[2] We have now used initial reaction temperature of 0 °C to −30 °C for other reaction mixtures and raised the temperature by about 20 °C under microwave irradiation; this type of procedure named 'Cold Microwave Chemistry' is currently under study in our laboratory.
8. Muathen, H. A. *Molecules* **2003**, *8*, 593.