Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron Letters
Tetrahedron Letters 47 (2006) 3213–3215

Cold microwave chemistry: synthesis using pre-cooled reagents

Ajay K. Bose,* Subhendu N. Ganguly, Maghar S. Manhas, William He and Jeffrey Speck

George Barasch Bioorganic Research Laboratory, Department of Chemistry and Chemical Biology, Stevens Institute of Technology, Hoboken, NJ 07030, USA

Received 8 January 2006; revised 3 March 2006; accepted 9 March 2006
Available online 29 March 2006

Dedicated to Dr. Linda Glazer

Abstract—A novel experimental procedure for chemical reactions has been devised that involves mixing and then freezing the reagents (organic solvent-free) to a sub-zero temperature such as −30 °C. This frozen mixture is exposed to microwave irradiation for a brief period of time. The use of pre-cooled reagents may give a single product not obtained by traditional microwave irradiation at room temperature. Interestingly, such a product may provide information about mechanisms by identifying the first step of a multiple step reaction.

Microwave irradiation is a convenient procedure for conducting reactions in minutes that otherwise would require hours under traditional heating.[1] Publications that discuss microwave promoted chemistry appear frequently; they record acceleration of diverse organic reactions under microwave irradiation—starting *at room temperature* and raising the temperature of the mixture by about 30–100 °C.

Recent studies in our laboratory have led to a new experimental strategy that we have named 'Cold Microwave Chemistry.' Our approach involves cooling a mixture of reagents—free of organic solvents—to a suitable sub-zero temperature (such as −30 °C) with the help of a cooling bath. The frozen mixture is exposed to microwave irradiation (400–800 W) for approximately 2 min in a domestic microwave oven (see Tables 1 and 2 for details); it is our experience that this amount of microwave exposure is adequate. The reaction mixture is removed from the microwave oven and allowed to reach the room temperature; it is then worked up in the usual manner, and the organic product(s) is isolated.

These studies have led to the following observations:

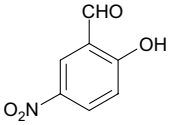
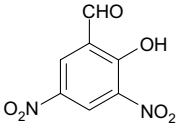
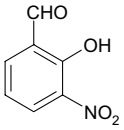
1. Chemical reactions under microwave irradiation may be modified by the temperature range of the irradiation experiment. Identical reaction mixtures exposed to microwaves at room temperature or at sub-zero temperature (such as −30 °C) may give different products (for example, 5- vs 3-nitro aromatic compounds in nitration experiments); for additional information, see Tables 1 and 2.
2. The 'Cold Microwave Chemistry' product (obtained by microwave irradiation of pre-cooled reagents) could provide information about reaction mechanism since it might identify the first step in a reaction that involves two or more steps.

It may be noted that the traditional microwave chemistry experiment involves placing a mixture of reagents inside a microwave oven (in a sealed or open container) and conducting irradiation at a selected power level for a few minutes. Starting at room temp (20–25 °C), the reaction mixture is subjected to a bulk temperature rise of about 20–100 °C in the course of a few minutes to obtain new products. In contrast, the experimental approach for using 'Cold Microwave Chemistry'

Keywords: Selective nitration reactions; Nitration of phenols; Microwave assisted nitration reactions; Microwave irradiation of pre-cooled reagents.
* Corresponding author. Tel.: +1 610 258 8624; fax: +1 610 438 8232; e-mail: abose@stevens.edu

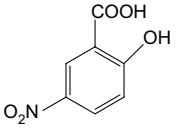
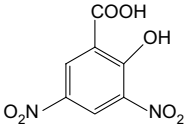
0040-4039/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2006.03.059

Table 1. Nitration products of salicylaldehyde

Starting conditions	Microwave parameters	Melting point of product (yield)	Structure of product[a]
Room temp	12 s, 400 W, max temp 85 °C (in Milestone Microwave Lab-station)	126 °C[b] (62%)	
Room temp	1 min, 400 W, max temp 120 °C (in Milestone Microwave Lab-station)	68–71 °C[c] (67%)	
Cold temp (cooled in liquid nitrogen, −30 °C)	3 min, 500 W (in Milestone Microwave Lab-station)	110 °C[d] (65%)	

[a] Characterized by GC–MS.
[b] Lit. mp 128–130 °C (Aldrich catalog).
[c] Lit. mp 68–70 °C (Aldrich catalog).
[d] Lit. mp 105–109 °C (Aldrich catalog).

Table 2. Nitration products of salicylic acid

Starting conditions	Microwave parameters	Melting point of product (yield)	Structure of product[a]
Room temp	2 min, 200 W, max temp 85 °C (in Milestone Microwave Lab-station)	228–229 °C[b] (72%)	
Room temp	1 min, 400 W, max temp 120 °C (in Milestone Microwave Lab-station)	169–170 °C[c] (76%)	

[a] Characterized by GC–MS.
[b] Lit. mp 233–235 °C (Aldrich catalog).
[c] Lit. mp 169–172 °C (Aldrich catalog).

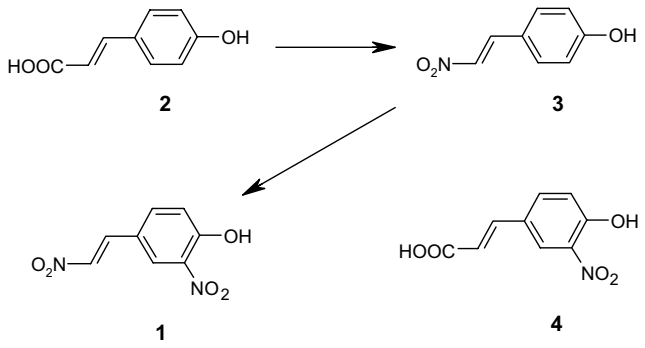
requires prior lowering of the temperature of the reactants to a sub-zero level before microwave irradiation.

Recently we have studied the microwave promoted preparation of an unusual dinitro natural product (**1**), which we had isolated in milligram quantities from a natural source.[2] It was found that when a mixture of 4-hydroxycinnamic acid (**2**) and dilute nitric acid (10%) was exposed to microwave irradiation for a few minutes, the dinitro compound **1** was obtained in 80–90% yield.[2] In an attempt to obtain the mononitro analogues (**3**, **4**), microwave irradiation was conducted at about 0 °C, but only the dinitro product **1** was formed.

The conversion of **2** to the dinitro compound **1** involves two chemical steps: (i) nitration of a phenol, (ii) *ipso* replacement of a carboxy group by a nitro group. It was possible to determine the sequence of these two steps by a 'Cold Microwave Chemistry' experiment.

A mixture of the starting compound **2** and nitric acid (10%) was cooled to about −30 °C with a cooling bath and the frozen mixture was exposed to low power (300 W) microwave irradiation for a brief period of time (about 2 min). The frozen reaction mixture was placed outside the oven and allowed to warm up to the room temperature; it was then worked up in the usual manner and the organic product(s) was isolated. This product was identified as **3**—the result of *ipso* displacement of a carboxy group by a nitro group.[3] The yield was 90%. Microwave promoted nitration of **3** with nitric acid (10%) provided the dinitro compound **1**—in 80% yield.

These reactions clearly indicate the possibility of obtaining different products from identical reaction mixtures when the microwave irradiation is started at different temperatures. As shown above, compound **3** or compound **1** could be obtained selectively from compound **2** depending on whether the reagents were pre-cooled or not. These experiments also show that the favored pathway from **2** to **1** is via **3** and not via **4.**



Scheme 1.

The interrelations shown in Scheme 1 indicate the sequence of steps leading to the dinitro compound. It is interesting to note that the first step is the *ipso* decarboxylation with replacement by a nitro group; nitration of the phenolic ring is therefore the second step.

The 'Cold Microwave Chemistry' approach could thus allow easy determination of the first step in a reaction involving two or more steps. These are novel aspects of microwave enhanced reactions that do not appear to have been reported before.

In summary, chemical reactions under microwave irradiation may be modified by the starting temperature of the irradiation experiment. For example, microwave irradiation of identical reaction mixtures at room temperature or pre-cooled to −30 °C may give different products. The cold microwave chemistry product (obtained by microwave irradiation of a pre-cooled reagent mixture) may identify the first step in a reaction that involves two or more steps; this could provide useful information about reaction mechanisms and thus supplement traditional studies involving reaction kinetics. These microwave chemistry experiments can be conducted in inexpensive domestic microwave (800–1000 W) ovens.

Acknowledgments

We thank Union Mutual Foundation, Merck Company, and The Camille and Henry Dreyfus Special Grant Program in the Chemical Sciences for financial support. For useful discussions and encouragement we are grateful to Dr. F. T. Jones, Dr. Malcolm MacCoss, and Dr. Mark Cardillo. We are indebted to the reviewer for valuable suggestions.

References and notes

1. (a) Loupy, A. *Microwave in Organic Synthesis*; Wiley-VCH: Weinheim, 2002; (b) Kingston, H. M.; Haswell, S. J. *Microwave Enhanced Chemistry*; American Chemical Society Publications: Washington, 1997; (c) Tierney, J. P.; Lidstrom, P. *Microwave Assisted Organic Chemistry*; CRC Press: Boca Raton, 2005; (d) Kappe, C. Oliver; Stadler, A. *Microwaves in Organic and Medicinal Chemistry*; C.H.I.P.S. Books: Weimar, 2005.
2. Bose, A. K.; Ganguly, S. N.; Manhas, M. S.; Srirajan, V.; Bhattacharya, A.; Rumthao, S.; Sharma, A. *Tetrahedron Lett.* **2004**, *45*, 1179.
3. Experimental procedure: Cold microwave chemistry for the nitration of 4-hydroxycinnamic acid: 4-Hydroxycinnamic acid (2 g, 12 mmol) and aqueous nitric acid (20 mL, 10% strength) in a 100 mL Erlenmeyer flask was cooled to −30 °C with a liquid nitrogen bath. This frozen reaction mixture was irradiated in an unmodified domestic microwave oven at 300 W power for 30 s. Immediately after irradiation, 75 mL of ice cold water was added with stirring. An orange yellow solid that separated was collected by filtration. The solid was washed with cold water until the filtrate was acid free and then dried. It was crystallized from methanol–ethyl acetate mixture to provide the mono-nitro product **3** (1.8 g, 11 mmol), mp 204–205 °C, yield 90%. An analytical sample was prepared by repeated crystallization. IR (KBr): 3280, 1518, 1320, 976, and 825 cm^{-1}. ^1H NMR ($CDCl_3$, δ): 7.58 (d, $J = 13.7$ Hz, 1H); 7.96 (d, $J = 13.7$ Hz, 1H); 7.42–8.09 (aromatic protons, 4H); 10.65 (s, chelated, 1H). Anal. Calcd for $C_8H_7NO_3$: C, 58.18; H, 4.24; N, 8.48. Found: C, 58.31; H, 4.22; N, 8.44.