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Microwave promoted energy-efficient N-formylation with aqueous formic acid

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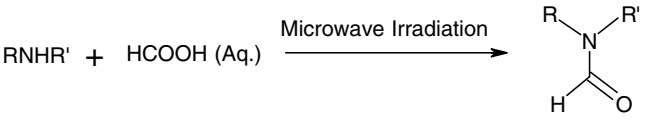
Abstract—Microwave-induced organic reaction enhancement ('MORE') chemistry technique (open vessel; controlled microwave energy to stay below the boiling point of the reaction mixture) was used for the N-formylation of aliphatic and aromatic amines and amino heterocycles with aq formic acid (80%) on a multiple gram scale in a few minutes.

Recently, escalating energy costs have been bringing a new perspective to chemical reactions for desk-top research as well as production development chemistry. It is essential now to design new modes of preparative chemistry that would be highly energy-efficient.

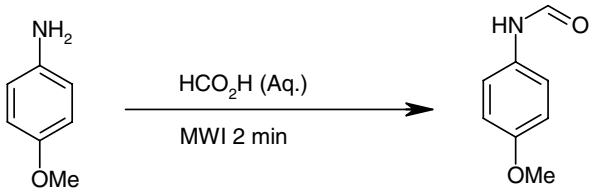
Microwave promoted chemical reactions are energy efficient, since irradiation for only a few minutes is adequate for conducting most endothermic reactions. For exothermic reactions, it is necessary to provide only a short burst of energy to initiate the reaction. After this initiation, the reaction proceeds to completion without the need for any additional energy from an external source.

In our laboratory, a protocol named 'MORE' (microwave-induced organic reaction enhancement) chemistry is used.[1] This procedure is energy efficient and utilizes an open system (thus risk free of explosion). The key point is that microwave energy input is controlled to raise the reaction mixture bulk temperature to about 20 °C lower than the mixture boiling point. This makes it unnecessary to provide the enthalpy of vaporization, which is usually a substantial amount of energy. We were interested in extending 'MORE' chemistry techniques to N-formylation reactions.



A recent publication[2] has shown that N-formylation of amines can be conducted by using aqueous 85% formic acid; a Dean-Stark trap removes the water formed in the reaction over 4–9 h with toluene as the solvent. This method does not formylate *p*-nitroaniline.

We tested our 'MORE' chemistry approach for N-formylation with aq formic acid (80%). Thus, *p*-anisidine (**1**, 2 g) reacted in 2 min under microwave irradiation (350 W) to give the crystalline N-formyl product **2**



1 **2**

Scheme 1.

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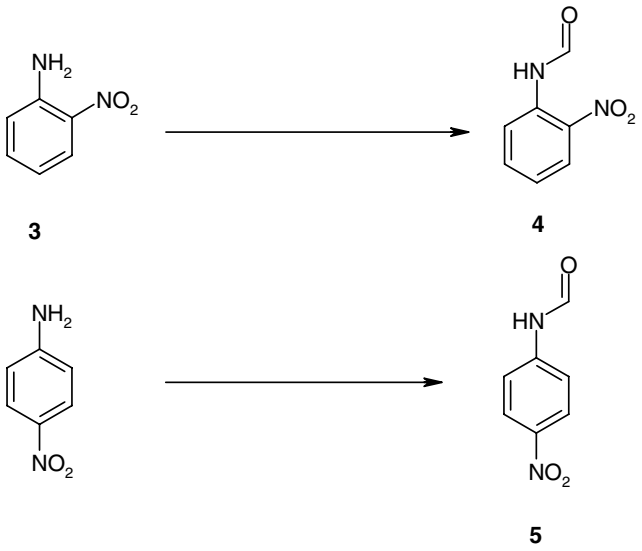
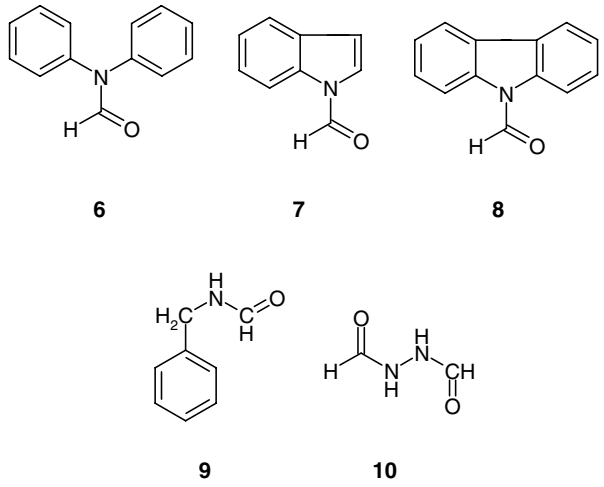


Scheme 2.

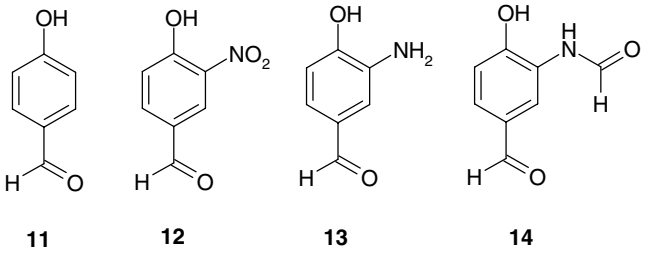
(85% yield) that did not need purification by recrystallization (Scheme 1).

It is well known that the amino group in *o*-nitroanilines (**3a**) and *p*-nitroanilines (**3b**) is of very low basicity and hence not easily acylated. It was interesting therefore to observe that both types of compounds could be N-formylated to **4** and **5** with aq formic acid (80%) under microwave irradiation in high yield in 3 min on a 2–5 g scale[3] (Scheme 2).

A secondary amine—diphenylamine—was allowed to react with aq formic acid (80%) using our 'MORE' chemistry procedure; after a few minutes of microwave irradiation the N-formyl product **6** crystallized out on cooling the reaction mixture. Indole and carbazole also provided the N-formyl derivatives (**7**, **8**) with equal ease. It was also possible to formylate an aliphatic amine (e.g., benzylamine) to **9**; hydrazine was converted to diformamide **10.**



Of special interest to us was the successful formylation of 3-amino-4-hydroxybenzaldehyde (**13**) in high yield because compound **14** could serve as an intermediate for the preparation of the pharmaceutical Foradil and its analogs. This amino compound (**13**) was readily available by the reduction of 3-nitro-4-hydroxybenzaldehyde (**12**) that in turn had been prepared in our laboratory by microwave assisted nitration of commercially available *p*-hydroxybenzaldehyde (**11**).



We used the Milestone Ethos low pressure benchtop microwave reactor for multiple gram scale formylations. Thus, 20 g of *o*-nitroaniline (**3**) was allowed to react with slightly more than an equivalent of aq formic acid (80%) with a computer setting for a maximum temperature of 80 °C and a reaction time of 10 min. After letting the reaction mixture cool, 50 mL of water was added and this mixture was set aside. Yellow crystals that formed were separated by filtration and made acid free by washing with water. After drying, the crystalline product had the correct melting point (without recrystallization) and the yield was about 90%. Much larger scale reactions can be conducted, since this microwave applicator has been modified to allow reactions on a scale of about 3 kg.

We also used the Prolabo 1000 applicator that produces focused microwaves for large scale experiments. In one procedure, 100 g of *o*-nitroaniline and 200 mL of aq formic acid (80%) were allowed to react under microwave irradiation for 7 min; the computer control was set for a maximum reaction temperature of about 90 °C (250–350 W). Product **4** of mp 171 °C (lit. mp 173–175 °C) was obtained without recrystallization in about 90% yield.

It is known that an alkyl(phenyl) formamide group can be converted easily to an isocyanide group (–NC). Many isocyanides are components of marine natural products. The isocyanide group is a pseudo-halogen and can be removed by reaction with tributyltin hydride (or deuteride). The use of ^{13}C-labeled formic acid would lead to rapid, inexpensive and convenient labeling with a stable isotope, providing compounds of value for tracking metabolites and their quantitative analysis by mass spectrometry.

In conclusion, it may be noted that the 'MORE' chemistry procedure allows rapid, eco-friendly access to diverse types of N-formyl compounds with the expenditure of small amounts of microwave energy. A large excess of aq formic acid need not be used. N-formyl products that crystallize out do not need further purification by recrystallization.

Acknowledgments

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References and notes

1. For reviews on 'MORE' Chemistry see: (a) Bose, A. K.; Manhas, M. S.; Ganguly, S. N.; Sharma, A. H.; Banik, B. K. *Synthesis* **2002**, 1578; (b) Bose, A. K.; Banik, B. K.; Lavlinskaia, N.; Jayaraman, M.; Manhas, M. S. *CHEMTECH* **1997**, *27*, 18; (c) Bose, A. K.; Manhas, M. S.; Banik, B. K.; Robb, E. W. *Res. Chem. Intermed.* **1994**, *20*, 1.
2. Jung, S. H.; Ahn, J. H.; Park, S. K.; Choi, J.-K. *Bull. Korean Chem. Soc.* **2002**, *23*, 149.
3. Representative experimental procedure. Formylation of *o*-nitroaniline: *o*-Nitroaniline (2 g) and formic acid (10 mL, 80% strength) in a 100 mL Erlenmeyer flask were irradiated in an unmodified domestic microwave oven (350 W power level) for 3 min. The contents of the flask were cooled to room temperature and mixed with 75 mL of cold water with stirring. A yellow crystalline solid that separated was collected by filtration. This solid was washed with water until the filtrate was acid free. The solid was dried and then recrystallized from ethyl acetate–hexane mixture to provide the N-formyl product (**4**), mp 174–175 °C (lit. mp 173–175 °C), yield 95%.