

Microwave Assisted Amine Formylation by a Heterogeneous HCO₂H/SiO₂ System

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A simple, fast and efficient procedure has been developed for the synthesis of formamides by treating a silica gel/formic acid mixture with amines under microwave irradiation.

Keywords: Microwave-assisted reaction; Formylation; Amines; Formic acid; Silica gel.

INTRODUCTION

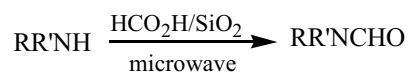
A number of formylating methods have been reported to prepare formylated compounds. Acetic formic anhydride is one of the most widely used formylating agents.^{1,2} However, because of its sensitivity to atmospheric moisture it is decomposed to acetic acid and carbon monoxide. Other useful formylating agents include chloral,³ activated formic acid,^{4,5} activated formic acid esters,⁶⁻⁹ ammonium formate,¹⁰ and formic acid itself.^{11,12} Lipshutz and coworkers have claimed the use of *N*-methoxy-*N*-methylformamide for the first time as a formylating compound.¹³ Bagnò and coworkers in their paper with 32 references have focused on preparation and mechanistic investigations of new formylating agents.¹⁴ Hegedus and coworkers have prepared dibenzylformamide and diallylformamide by refluxing a mixture of the corresponding diamine and ethyl formate (for 72 h and 22 h respectively).¹⁵

RESULTS AND DISCUSSION

Disadvantages of most of the above-cited references are long reaction times and unstable and/or toxic reagents. On the other hand, the use of solid supported reagents accompanying microwave irradiation has become a powerful synthetic tool for the rapid synthesis of a variety of organic compounds, because of altering reactivity, simplicity in operation, mild reaction conditions and improved yields.¹⁶⁻²⁶ In the last reference the authors, after failure in catalytic transfer hydrogenation, have demonstrated the use of Al₂O₃ supported HCOOH or their polymer supported formate for

N-formylation of amines (in both cases, DMSO has been used as solvent).

Keeping in view our general interest in the development of friendlier synthetic procedures, we have succeeded in rapid, high yield preparation of formamides under microwave irradiation by the aid of a silica gel/formic acid heterogeneous system in which the solid silica support may be recycled after product separation.



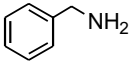
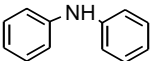
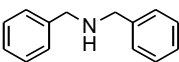
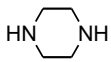
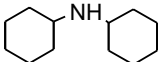


R = H, alky or aryl; R' = alkyl or aryl

Therefore, a good range of primary and secondary amines (aliphatic as well as aromatic) were chosen and subjected to a series of reaction conditions. In this manner, we succeeded in developing a very convenient and efficient procedure for the preparation of formamides (Table 1). As Table 1 shows, the yields are good to excellent (70-99%) and the reaction times range from 35 to 95 seconds, which are much lower than those reported in other works (as an example see ref. 12). It is notable that the reaction times for entries 6 and 10 of Table 1 are somewhat higher than those of others, which may be due to their volatility. However, there is no explanation for entry 5 (reaction time: 90 seconds).

As mentioned above, mono- and disubstituted formamides may be prepared in good to excellent yields and in very short times. A typical example is the preparation of 1,4-piperazinedicarboxaldehyde from piperazine (entry 4), which we have prepared in 35 seconds and in 99% yield. This compound has also been prepared in 1954 by Fujii, K.

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Table 1. Formylation of amines with HCO₂H/SiO₂ under microwave irradiation

Entry	Amine	Reaction Time (sec)	Yield%	Product	
				mp or bp (°C)	
				Found	Reported
1		40	96	Mp 59	54-58 ^b
2		51	82	Mp 70	72 ^c
3		60	92	Mp 50	52 ^d
4		35	99	Mp 128	126-127 ^e
5	H ₂ NCH ₂ CH ₂ NH ₂	90	85	Mp 109-111	110-112 ^f
6	Et ₂ NH	85	80	Bp 176-177	176-178 ^c
7		54	90	Mp 60	62.5-63.5 ^g
8		45	84	Bp 237	236-237 ^h
9		72	91	Bp 222	220-222 ^c
10	EtNH ₂	95	70	Bp 202-204	196-198 ^c

^a Yields refer to the pure isolated products, and the identity of each product was characterized by ¹H and ¹³C NMR data, which are compatible with the authentic samples.

^b Bredereck, H.; Gompper, R.; Rempfer, H.; Klemm, K. *Chem. Ber.* **1959**, *92*, 329-37.

^c Olah, G.; Kuhn, I. *Chem. Ber.* **1956**, *89*, 2211-12.

^d Henbest, H. B.; Thomas, A. *J. Chem. Soc.* **1967**, 3032-39.

^e Horrom, B. W.; Freifelder, M.; Stone, G. R. *J. Am. Chem. Soc.* **1955**, *77*, 753-54.

^f Runti, C.; Sindellari, L.; Ulian, F. *Ann. Chem.* **1960**, *50*, 847-57.

^g Maglio, M. M. *J. Am. Chem. Soc.* **1949**, *71*, 2949-50.

^h Olah, G. A. *J. Org. Chem.* **1984**, *49*, 3856.

(temperature: 40-50 °C; time: 30 min.; yield: 77%; bp₁: 167-70 °C) and then used in 1956 to formylate thiophene.^{27,28} A recent German patent has also described formylation of several primary and secondary amines, including piperazine, in 62-87%.²⁹

In conclusion, the present microwave assisted formylation by a silica gel/formic acid system under microwave irradiation provides an efficient, fast, convenient and easy workup procedure for the synthesis of mono- and disubstituted formamides. It should be noted that the product yields for the heterocyclic amines (Table 1, entries 8 and 9) are much higher than those of Desai and coworkers.²⁶ In addition, the first step of our procedure – irradiation of the amine and HCO₂H/SiO₂ mixture – proceeds without the need of any solvent.

EXPERIMENTAL

Starting materials were obtained from Fluka Company. Melting points were determined by electrothermal melting point apparatus (without further correction). IR and NMR spectra were run using Perkin-Elmer FT-IR and Jeol 90 MHz FT NMR spectrometers, respectively. The solvent for all ¹H NMR spectra was CDCl₃. The source of microwave radiation was the LG domestic microwave oven (model MG-583MC).

Preparation of the HCO₂H/SiO₂

1 mL of formic acid was added to 1 g of silica gel (mesh 70-230) with stirring for 1 minute at room temperature.

Preparation of formamides

Amine (1 mmol, as liquid or fine powder) and the above mixture were mixed thoroughly and then subjected to the 80% power radiation of our domestic microwave oven for a certain period of time. The progress of each reaction was monitored by TLC using n-hexane/acetone (3:1) as the solvent. After completion of the reaction the obtained mixture was allowed to cool, eluted with ethanol, filtered and followed either by crystallization or successive solvent evaporation and vacuum distillation.

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