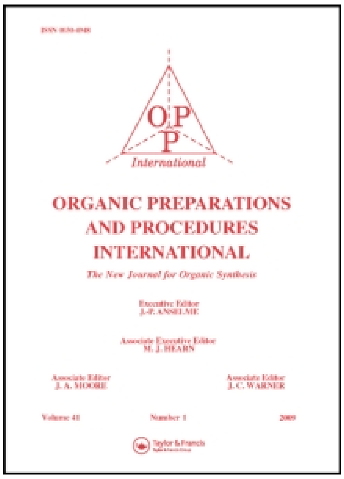

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AMIDES BY MICROWAVE-ASSISTED DEHYDRATION OF AMMONIUM SALTS OF CARBOXYLIC ACIDS

Yanqing Peng[a]; Gonghua Song[a]
[a] Institute of Pesticides and Pharmaceuticals, East China University of Science and Technology, Shanghai, P. R. China

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OPPI BRIEFS

AMIDES BY MICROWAVE-ASSISTED DEHYDRATION OF AMMONIUM SALTS OF CARBOXYLIC ACIDS

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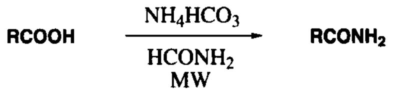
Yanqing Peng and Gonghua Song*

Institute of Pesticides and Pharmaceuticals
East China University of Science and Technology
Shanghai 200237, P. R. CHINA

The preparation of primary amides is an important reactions in organic chemistry. Reported methods for such conversion include a) direct reaction of acids with ammonia; b) ammonolysis of the corresponding anhydrides or esters and c) reaction of acyl chlorides with gaseous or aqueous ammonia.[1] The ammonolysis of esters is generally a sluggish reaction unless the esters have good leaving groups.[2] Litjens and co-workers have developed lipase-catalyzed amidation of carboxylic acids with an ammonium salt as a source of ammonia. Although this procedure is mild and selective, is time-consuming (17 days).[3] Direct amidation of carboxylic acids with ammonia requires drastic conditions (200°,7 bar, and anhydrous ammonia).[4]

Microwave heating and its applications in organic synthesis have received extensive attention and has been reviewed recently.[5] We report herein a direct and rapid procedure for the preparation of primary amides from ammonium salts of carboxylic acids in formamide under microwave irradiation. To the best of our knowledge, this is the first report on rapid synthesis of primary amides where microwave technique is utilized.



$$\mathrm{RCOOH} \xrightarrow[\substack{\mathrm{HCONH_2} \\ \mathrm{MW}}]{\mathrm{NH_4HCO_3}} \mathrm{RCONH_2}$$

The present method is simpler and more convenient than the previous ones described above. The products were identified by their melting points and IR spectra. Different types of carboxylic acids were converted to their corresponding amides by this procedure with satisfactory yields. The results are presented in Table 1.

The ammonium salts of carboxylic acids were formed *in situ* from ammonium bicarbonate and corresponding carboxylic acids. Formamide ($HCONH_2$), a readily available and inexpensive reagent, was suitable for this procedure both as a solvent and a dehydrating agent. As an example, this microwave-assisted procedure produced benzamide in 86% yield in only 9 minutes (Entry 1). In the same way, a series of primary amides were readily prepared using this rapid, one-pot procedure. While an increase in the power level speeds up the reaction rate, lower yields were obtained due to the formation of by-products. Unfortunately, in the case of hydroxybenzoic acids (Entry 10 and 11), none of desired products were obtained because of the formation of phenol by decarboxylation. Cinnamic acid (Entry 16) required longer reaction time (15 min) and only 42% yield of cinnamamide was obtained. We failed to amidate the carboxylic acid in the absence of ammonium bicarbonate with formamide because of extensive sublimation.

In conclusion, this procedure compares favorably to other classical methods. It has the advantages of simple work-up, short reaction time, and the use of inexpensive and readily available reagents.

EXPERIMENTAL SECTION

Melting points (uncorrected) were taken in an open capillary on a WRS-1 digital melting point apparatus manufactured in Shanghai. IR spectra were recorded using KBr pellets on a Model 7650 spectrometer. All reagents were commercially available and used without further purification. Reactions were conducted in a MW-800 II multimode cavity refluxing system made by Microwave Research Center at East China Normal University.

Table 1. Microwave-assisted Dehydration of Ammonium Salt of Carboxylic Acids

Entry	R	Time (min)	Yield (%)[a]	mp. (°C)	mp. (lit.[7]) (°C)	IR (ν_{max} / cm^{-1},KBr)
1	C_6H_5	10	75	130	130	3365, 3080, 1660
2	3-MeC_6H_4	10	76	98	97	3340, 3160, 1665
3	4-ClC_6H_4	9	80	177	179(170)	3370, 3060, 1660
4	2-ClC_6H_4	9	78	140	142(139)	3360, 3080, 1650
5	4-$O_2NC_6H_4$	8	81	200	200	3410, 3150, 1660
6	2-$O_2NC_6H_4$	9	75	174	174-176	3360, 3080, 1660
7	4-MeOC_6H_4	8	70	162	163	3390, 3160, 1650
8	2-MeOC_6H_4	9	69	130	129	3380, 3180, 1660
9	2, 4-$Cl_2C_6H_3$	7	82	195	193-194	3370, 3070, 1650
10	2-HOC_6H_4	—	—	—	—	—
11	4-HOC_6H_4	—	—	—	—	—
12	2-$H_2NC_6H_5$	9	59[b]	111	109-111.5	3410, 3200, 1630
13	Furfural	6	75	142	142-143	3560, 3200, 1680
14	1-Naphthyl	10	77	201	202	3340, 3200, 1660

Table 1. Continued...

Entry	R	Time (min)	Yield (%)[a]	mp. (°C)	mp. (lit.[7]) (°C)	IR (ν_{max} / cm^{-1},KBr)
15	$C_6H_5CH_2$	7	81	159	157-158	3360, 3155, 1630
16	$C_6H_5CH=CH$	15	42	146	147	3370, 3180, 1660
17	$C_{11}H_{23}$	9	79	107	110	3250, 3050, 1650
18	$C_{17}H_{35}$	9	82	109	109	3400, 3190, 1650

a) isolated yields; b) decolored with $Na_2S_2O_4$ and activated carbon, respectively.

General Procedure.- A mixture of carboxyl acid (10 mmol), ammonium bicarbonate (12 mmol), and formamide (4 mL) was transferred into a 100 mL flask and irradiated (300W) for the specified period of time as indicated in Table 1. After completion of the reaction (monitored by TLC), the content of the flask was cooled to room temperature and treated with 20% aqueous ammonium bicarbonate. The precipitate was dissolved in ethanol, decolorized with activated carbon. Removal of ethanol *in vacuo* and recrystallization of the residue from aqueous ethanol gave the purified product.

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