



Direct preparation of primary amides from carboxylic acids and urea using imidazole under microwave irradiation

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Abstract—A very simple and efficient solvent-free procedure for the preparation of primary amides is described from carboxylic acids and urea using imidazole under microwave irradiation. Various aliphatic and aromatic primary amides were prepared in good yields by this direct amidation method.

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The preparation of primary amides from the corresponding carboxylic acids is an important and well-known transformation in organic synthesis.^{1,2} In general, the formation of carboxamides from carboxylic acids requires activation of the carboxyl group. Carboxylic acid activation can be achieved by conversion of the carboxyl group to a more reactive functional group such as acyl halide, mixed anhydride, acyl azide, active ester or in situ activation by coupling reagents, the most common of which is *N,N*-dicyclohexylcarbodiimide (DCC).³ Other coupling reagents that have been used for this purpose include TiCl_4 ,⁴ activated phosphate,⁵ $\text{Sn} [\text{N}(\text{TMS})_2]_2$,⁶ equivalent amounts of triphenylphosphine and *N*-halosuccinimide,⁷ triphenylphosphine and trichloroacetonitrile,⁸ $\text{ArB}(\text{OH})_2$,⁹ Lawesson's reagent,¹⁰ *tert*-butyl-3-(3,4-dihydrobenzotriazin-4-on)yl carbonate (Boc-Odhbt),¹¹ $(\text{R}_2\text{N})_2\text{Mg}$,¹² and 2-mercaptopyridone-1-oxide based uronium salts.¹³

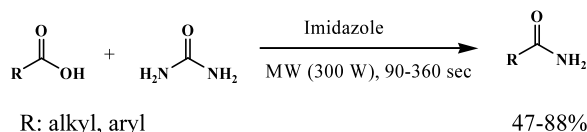
The application of microwave technology in organic chemistry has been explored extensively within the last decade. Microwave irradiation often leads to a remarkable decrease in reaction time, increased yields, easier work up matching with green chemistry protocols, and may enhance the regio- and stereoselectivity of reactions.^{14–16}

More recently, there have been some reports in which are described the preparation of secondary and tertiary

amides under microwave assisted solvent free conditions.^{17–19} However, there have been no reports of the direct synthesis of primary amides from carboxylic acids by this means, although primary amides have been prepared by hydrolysis of the corresponding nitriles under microwave irradiation in the presence or absence of solvents.^{20,21}

Herein, as an extension of our previous studies on the application of microwave irradiation in organic synthesis,²² we describe the first procedure for the synthesis of primary amides by direct reaction of carboxylic acid and urea in the presence of imidazole under microwave irradiation (Scheme 1).

Imidazole was used in this reaction because previously it has been demonstrated that this compound shows useful promotion ability²³ and forms polar carboxylic acid salts for efficient microwave energy absorption.²⁴ The promotion ability of imidazole was attributed to the low melting point of imidazolium carboxylate salts which melt after heating at low microwave power and short irradiation time and homogenize the reaction mixture in dry media.²⁵ Instead of imidazole we used other bases such as 4-dimethylaminopyridine (DMAP),



Keywords: primary amide; microwave irradiation; urea; imidazole.

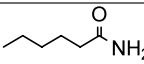
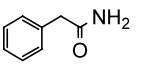
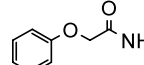
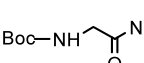
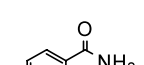
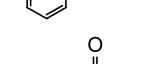
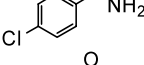
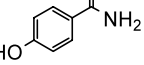
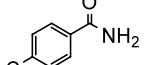
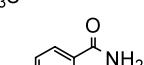
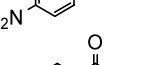
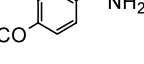
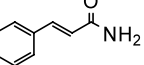
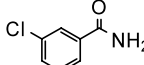
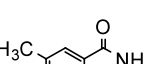
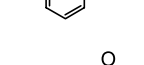
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Scheme 1.

triethylamine and 1,8-diazabicyclo[5,4,0]undec-7-en (DBU), but none of them acted as well as imidazole. The results for amidation of various carboxylic acids are summarized in Table 1.

To investigate the generality and scope of this method, the reaction was examined with various structurally diverse carboxylic acids. As is clear from Table 1 the reactions proceed cleanly, and the desired carboxamides

Table 1. Direct preparation of primary amides from carboxylic acids and urea by using imidazole under microwave irradiation

Entry	Acid	Product ^a	m. p. °C (lit)	Time (sec)	Yield (%) ^b
a	Hexanoic acid		100-102 (101) ²⁶	100	85
b	Phenylacetic acid		154-156 (157) ²⁶	90	85
c	Phenoxyacetic acid		99-101 (101.5) ²⁶	90	85
d	<i>N</i> -Boc-glycine		84-86 (87) ²⁷	80	79
e	Benzoic acid		127-129 (129.1) ²⁶	300	81
f	4-Chlorobenzoic acid		176-178 (179) ²⁶	220	85
g	4-Hydroxybenzoic acid		159-161 (162) ²⁶	250	47
h	4-Methylbenzoic acid		157-159 (160) ²⁶	330	76
i	4-Nitrobenzoic acid		200-202 (201.5) ²⁶	200	85
j	4-Methoxybenzoic acid		165-166 (166.5) ²⁶	360	81
k	<i>trans</i> -Cinnamic acid		147-149(148.5) ²⁶	300	85
l	3-Chlorobenzoic acid		134-136 (135.5) ²⁶	200	86
m	3-Methylbenzoic acid		93-95 (95) ²⁶	320	80
n	3-Nitrobenzoic acid		137-139 (141) ²⁶	180	88
o	Nicotinic acid		127-129 (129) ²⁶	220	82
p	Quinaldic acid		130-132 (133) ²⁶	230	79

^a Products were characterized by their melting points, IR, and ¹H NMR spectra.²⁸

^b Yields refer to isolated pure products.

were obtained in good yields but the presence of a hydroxyl group on the aromatic ring (entry g) lowered the yield. The aromatic carboxylic acids undergo reaction relative slowly than aliphatic ones. In the case of aromatic carboxylic acids, the presence of electron-withdrawing groups on the aromatic ring accelerated the reaction rate and increasing the reaction yields (entries i and n).

To explore the formation of acid anhydrides during reaction progress a mixture of benzoic acid, imidazole and urea was exposed to microwave irradiation. TLC monitoring of this reaction mixture after each 30 s for 6 min showed us that benzoic anhydride was not formed in this conditions. Similarly an experiment with a mixture of benzoic acid and imidazole also confirmed the above result.

In addition, the effect of different ammonia sources on the reaction progress was studied by using several ammonium salts such as ammonium acetate, ammonium chloride, ammonium sulfate, and ammonium carbonate. The results obtained showed that urea is the most suitable source for in situ generation of ammonia.

As previously reported^{17,29} we suggest that this reaction might be proceeding firstly by formation of an imidazolium carboxylate salt. This salt increases the absorption of the microwave energy and this energy absorption increment causes the pyrolysis of urea and liberation of ammonia. In the second step the imidazole is exchanged by ammonia to form the ammonium carboxylate salt, and finally strong heating of the ammonium carboxylate salt gives the corresponding carboxamide.

In summary, the present microwave-assisted procedure provides an efficient and very simple methodology for the preparation of primary amides using urea as a very cheap and safe ammonia source with good yields under solvent free conditions.

General procedure

Our procedure entails the grinding of the mixture of carboxylic acid (1 mmol), urea (2 mmol), imidazole (1 mmol). The mixture was exposed to microwave irradiation in domestic MW oven for appropriate time and power of MW oven (300 W). The resulting crude product extracted was purified by column chromatography using silica gel and EtOAc/*n*-hexane as eluent.

Acknowledgements

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28. Selected ¹H NMR data (DMSO-*d*₆, 250 MHz) for products **c**, **d**, **k**, **o**. **c**: δ 3.72 (s, 2H, CH₂), 6.30 (s, 2H, NH₂), 7.13–7.27 (m, 5H, Ar). **d**: δ 1.61 (s, 9H, 3CH₃), 3.83 (s,

2H, CH₂), 6.02 (s, 2H, NH₂), 8.01 (s, 1H, NH). **k**: δ 5.97 (s, 2H, NH₂), 6.78–6.80 (d, 1H, $J=15.5$ Hz, olefinic), 7.15–7.43 (m, 6H, Ar and olefinic). **o**: δ 7.44–7.49 (dd, 1H, $J=7.7, 4.8$ Hz, Ar), 7.66 (s, 2H, NH₂), 8.20–8.23 (d,

1H, $J=4.5$ Hz, Ar), 8.68–8.69 (d, 1H, $J=4.5$ Hz, Ar), 9.06 (s, 1H, Ar).

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