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A Conversion of Carboxylic Acids to Amides under Microwave Irradiation

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An efficient and rapid solvent-free method for the direct conversion of carboxylic acids to primary, secondary, tertiary alkyl and aromatic amides in the presence of corresponding ammonium salts, tosyl chloride, K_2CO_3, SiO_2 and tetrabutylammonium bromide under microwave irradiation is described.

Key Words: Carboxylic acid, Amide, Microwave, Solvent-free, Ammonium salt, Tosyl chloride.

INTRODUCTION

Microwave-assisted organic reactions have been applied as a useful technique in organic synthesis[1,2]. Microwave irradiation often leads to shorter reaction times, increased yields, easier workup, matches with the green chemistry protocols and may enhance the regio- and stereoselectivity of reactions[1,2]. Furthermore, its unique capabilities allow its application in reactions which are difficult or impossible to carry out by means of customary conventional methods[1,2].

Amides are one of the most important carboxylic acids derivatives as they have various biological activities, such as antibacterial[3], antimicrobial[4], antifungal[5] and antihistaminic properties[6]. These compounds are usually prepared directly from corresponding carboxylic acids by *in situ* conversion of their carboxyl group to a more reactive group by coupling reagents, including N,N-dicyclohexylcarbodiimide (DCC)[7], activated phosphate[8], trichloroacetonitrile/PPh_3[9], $Sn[N(TMS)_2]_2$[10], N-halosuccinimide/PPh_3[11], $ArB(OH)_2$[12], Lawesson's reagent[13], *tert*-butyl-3-(3,4-dihydrobenzotriazine-4-on)yl carbonate (Boc-Odhbt)[14], 2-mercaptopyridone-1-oxide based uronium salts[15], SO_2ClF[16], $(R_2N)_2Mg$[17] and chlorosulfonyl isocyanate[18].

It is worth noting that the methods have been established for the direct conversion of carboxylic to amides are associated with one or more of the following drawbacks: (i) long reaction times, (ii) unsatisfactory yields, (iii) difficult procedure, (iv) inability to produce all kinds of amides including primary, secondary, tertiary alkyl and aromatic amides and (v) the use of expensive reagents.

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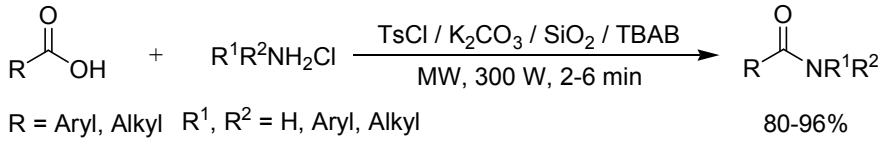
Keeping these aspects in mind and also in continuation of our previous studies on application of microwave technology in organic synthesis[19-26], in present studies, the direct conversion of carboxylic acids to primary, secondary, tertiary alkyl and aromatic amides in the presence of respective ammonium salts, tosyl chloride (TsCl) as a coupling agent, K_2CO_3, SiO_2 and tetrabutylammonium bromide (TBAB) under microwave irradiation have been reported (**Scheme-I**).



Scheme-I

The ammonium salts instead of the amines were employed in the reaction, because; (i) ammonium salts of gaseous or volatile amines such as ammonia, methyl amine and dimethyl amine can be easily used in the reaction, (ii) amines are hazardous compounds and application of their salts decreases the environmental pollution.

EXPERIMENTAL

All chemicals were obtained from Merck or Fluka Chemical Companies. All compounds were identified by comparison of their melting point and ^{1}H NMR data with the authentic samples. The reactions were carried out using domestic microwave oven (MB 245, Butan Industrial Co., Iran). ^{1}H NMR spectra (250 MHz) were recorded with on a Bruker Avance DPX-250, FT-NMR spectrometer. Melting points were determined on a Büchi B-545 apparatus in open capillary tubes.

General procedure for the direct conversion of carboxylic acids to amides: A well-ground mixture of carboxylic acid (1 mmol), respective ammonium salt (2 mmol), TsCl (1 mmol), K_2CO_3 (1 mmol), SiO_2 (0.3 g) and TBAB (1 mmol) in a test tube was irradiated in a microwave oven at 300 W for the times reported in Table-4. Afterward, the reaction mixture was cooled to room temperature and suspended in ethyl acetate (50 mL), filtered and the filtrate was washed with 0.02 N solution of HCl (2 × 50 mL) and water (2 × 50 mL). The organic layer was separated and dried with $MgSO_4$. The solvent was evaporated and the crude product was purified by column chromatography on silica gel eluted with ethyl acetate/*n*-hexane (1/1).

RESULTS AND DISCUSSION

To optimize reaction conditions, the conversion of benzoic acid to benzamide was selected as a model reaction. At first, amidation of benzoic acid was examined in the presence of NH_4Cl, TsCl, K_2CO_3 and TBAB under microwave irradiation (300 W). These conditions afforded the formation of benzamide in 75 % yield within 3 min. The reaction yield improved to 96 % when silica gel was added to the reaction mixture. The effect of different ammonium salts in the presence of TsCl,

K_2CO_3, SiO_2 and TBAB upon the reaction was also studied. The results are summarized in Table-1. As is shown in Table-1, ammonium chloride is the most suitable source for *in situ* generation of ammonia.

TABLE-1
EFFECT OF DIFFERENT AMMONIUM SALTS ON AMIDATION OF BENZOIC ACID UNDER MICROWAVE IRRADIATION (300 W)

Ammonium salt	Time (min)	Yield (%)*
NH_4Cl	2	96
NH_4I	2	85
NH_4NO_3	2	76
NH_4OAc	2	80
$(NH_4)_2SO_4$	3	70
$(NH_4)_2CO_3$	3	73

*Isolated yield.

In order to select the best base for the reaction, the influence of various bases on the model reaction was investigated (Table-2). As Table-2 indicates, the best results were obtained when K_2CO_3 was applied. Thus, K_2CO_3 was the base of choice in all reactions.

TABLE-2
INFLUENCE OF BASES ON THE REACTION OF BENZOIC ACID WITH NH_4Cl IN THE PRESENCE OF TsCl, SiO_2 AND TBAB UNDER MICROWAVE IRRADIATION (300 W)

Base	Time (min)	Yield (%)*
K_2CO_3	2	96
Na_2CO_3	4	82
MgO	6	67
CaO	6	70
NaOH	3	46
DABCO	6	87

*Isolated yield.

In another study, the model reaction in the presence of NH_4Cl, TsCl, SiO_2 and TBAB was examined at different microwave powers (100-600 W). The best result was obtained at 300 W of microwave power.

To study the role of TBAB in the reaction, the reaction of benzoic acid with NH_4Cl in the presence of TsCl, K_2CO_3 and SiO_2 was examined without TBAB at 300 W of microwave power. However, these conditions afforded the product in 23 % yield after 10 min. Increasing the reaction time and the microwave power did not improved the reaction yield. Thus, the presence of TBAB in the reaction media is critically significant. In general, TBAB melts at 100 °C and creates a homogeneous reaction media[20,23,24]. Moreover, this quaternary ammonium salt absorbs the microwave irradiation as well as generates *in situ* heat and increases the temperature higher than its melting point (100-103 °C)[20,23,24].

To compare the efficiency of the solvent-free conditions *vs.* solution conditions, a mixture of benzoic acid (1 mmol), NH_4Cl (2 mmol), TsCl (1 mmol), K_2CO_3 (1 mmol) and SiO_2 (0.3 g) in different (5 mL) was irradiated in a microwave oven (300 W) (Table-3). As Table-3 shows, the solution conditions were not efficient.

TABLE-3
COMPARATIVE AMIDAION OF BENZOIC ACID WITH NH_4Cl IN CONVENTIONAL SOLVENTS *versus* SOLVENT-FREE METHOD UNDER MICROWAVE IRRADIATION (300 W)

Solvent	Time (min)	Yield (%)*
DMSO	10	37
DMF	10	29
HMPTA	15	22
o-Xylene	15	14
**Solvent-free	2	96

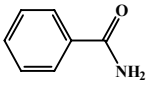
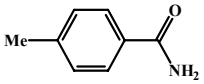
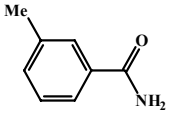
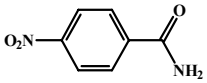
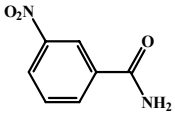
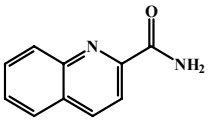
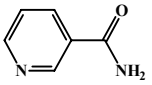
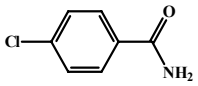
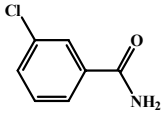
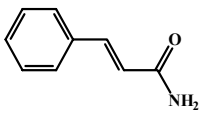
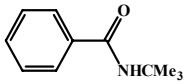
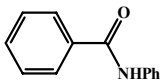
*Isolated yield; **Our Solvent-free method.

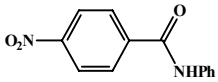
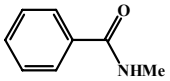
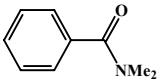
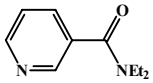
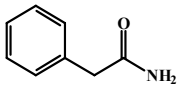
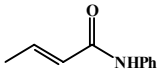
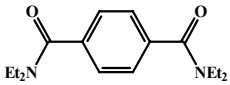
To determine whether microwave irradiation was an essential factor to promote the amidation reaction, the model reaction was tested in thermal conditions in the 70-130 °C temperature range. The results showed that longer reaction times were required using conventional heating than those under microwave irradiation. Furthermore, the yield was lower under thermal conditions. It was clear that microwave irradiation significantly accelerated this reaction.

After optimization of reaction conditions, the amidation reaction was carried out using various structurally diverse carboxylic acids and ammonium salts. The results are displayed in Table-4. As is shown in Table-4, the reactions proceeded efficiently and the respective amides were obtained in good to excellent yields and short reaction times. The effect of electron-releasing and electron-withdrawing substituents on the aromatic ring of carboxylic acids upon the amidation reaction was studied (Table-4). As Table-4 demonstrates, electron-releasing substituents slightly decreased the yields. However, electron-withdrawing substituent (NO_2) had no significant influence on the reaction yields. The presence of halogen atoms (Cl or Br) on the aromatic ring of acids did not affected significantly on the reaction results. Interestingly, no Michael addition side products were observed when cinnamic and crotonic acid were used (Table-4). The method was also efficient when sterically hindered and aromatic ammonium salts were applied.

In conclusion, we have introduced a new method for the direct conversion of carboxylic acids to amides with the following advantages: high yields, short reaction times, ability to produce all sorts of amides including primary, secondary, tertiary alkyl and aromatic amides, low cost and simplicity.

TABLE-4
DIRECT CONVERSION OF CARBOXYLIC ACIDS TO AMIDES IN THE PRESENCE OF CORRESPONDING AMMONIUM SALTS, TsCl, K_2CO_3, SiO_2 AND TBAB UNDER MICROWAVE IRRADIATION (300 W)

Acid	Product	$R^1R^2NH_2Cl$	Time (min)	Yield[a] (%)	m.p., ºC (Lit.)
Benzoic acid		NH_4Cl	2	96	126-128 (129.1)[27]
4-Methylbenzoic acid		NH_4Cl	3	87	158-160 (160)[27]
3-Methylbenzoic acid		NH_4Cl	3	89	94-96 (95)[27]
4-Nitrobenzoic acid		NH_4Cl	2	94	202-203 (201.5)[27]
3-Nitrobenzoic acid		NH_4Cl	2	95	139-141 (141)[27]
Quinaldic acid		NH_4Cl	2	94	130-132 (133)[27]
Nicotinic acid		NH_4Cl	2	96	128-130 (129)[27]
4-Chlorobenzoic acid		NH_4Cl	2	92	177-178 (179)[27]
3-Chlorobenzoic acid		NH_4Cl	2	95	134-136 (135.5)[27]
Cinnamic acid		NH_4Cl	4	86	147-149 (148.5)[27]
Benzoic acid		Me_3CNH_3Cl	5	87	134-136 (135.1)[16]
Benzoic acid		$PhNH_3Cl$	4	91	161-163 (163)[27]

Acid	Product	$R^1R^2NH_2Cl$	Time (min)	Yield[a] (%)	m.p., °C (Lit.)
4-Nitrobenzoic acid		$PhNH_3Cl$	4	93	212-214 (216)[27]
Benzoic acid		$MeNH_3Cl$	4	91	75-77 (75-77)[28]
Benzoic acid		Me_2NH_2Cl	5	85	43-45 (41-45)[28]
Nicotinic acid		Et_2NH_2Cl	5	84	24-26 (24-26)[27]
Phenylacetic acid		NH_4Cl	5	80	154-156 (157)[27]
Crotonic acid		$PhNH_3Cl$	5	83	111-113 (114)[18]
Terephthalic acid[b]		Et_2NH_2Cl	6	80	124-127 (127)[27]

[a]Isolated yield. [b]In this reaction, 4 eq. ammonium salt were used.

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