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Microwave-Assisted Synthesis of Amides from Various Amines and Benzoyl Chloride under Solvent-Free Conditions: A Rapid and Efficient Method for Selective Protection of Diverse Amines*

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Abstract—A number of structurally diverse amides were synthesized by reaction of the corresponding amines with benzoyl chloride under microwave irradiation. The proposed procedure ensures short reaction time, high yields, and excellent selectivity and considerably broadens the series of amines as compared to the microwave-assisted synthesis of amides directly from carboxylic acids. It can also be used for selective protection of various amines, including aromatic, aliphatic, and heterocyclic.

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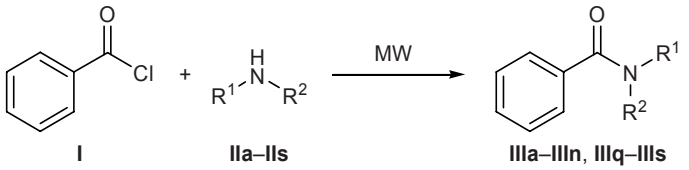
Relatively stable amide bond is not only common in naturally occurring materials (such as peptides and proteins) but is also present in many synthetic substances [1, 2]. This makes the amide function important to synthetic chemists, especially in peptide [1] and lactam [2] syntheses, where the formation of amide bond is crucial. Many methods for the synthesis of carboxamides are known. In general, amides are formed from carboxylic acids and amines in the presence of coupling reagents [3] or via reaction of acyl chlorides with amines in a solvent [4]. Although good results are obtained with both approaches, they are time-consuming and are sometimes associated with difficult separation and poor yields. To improve the efficiency, mild methods for preparation of amides in the absence of coupling reagents and solvent are highly desired.

In the last decade, microwaves (MWs) have been used to simplify and improve reaction conditions for many classical organic reactions. Reactions performed under MW conditions proceed faster, more cleanly, and in much better yields than do similar reactions under conventional conditions [5–9]. In combination with solvent-free conditions, MW methods provide efficient and safe technology conforming to "green chemistry" requirements [5, 10]. Microwave-assisted syntheses of amides have already been reported [11–14]. However, a limited number of amines and carboxylic acids were involved in these studies. Furthermore, because of lower reactivity of carboxylic acids, some reactions between amines and carboxylic acids are characterized by very low conversions despite long reaction times. Therefore, there is still a great demand for methods utilizing acyl chlorides for the synthesis of amides.

Taking into account limitations of the existing methods, we now report on an improved protocol for the synthesis of amides (Scheme 1) from benzoyl chloride (**I**) and various amines **IIa**–**IIs** under microwave irradiation in the absence of a solvent, which considerably broadens the series of available amides. The procedure includes mixing the reactants followed by exposure to microwave irradiation under solvent-free conditions. The reaction course was carefully monitored by TLC to regulate the reactant ratio, irradiation time, and microwave power level to achieve the maximum yield. An equimolar ratio of benzoyl chloride to amine (except for adenine, uracil and cytosine) was the most acceptable in terms of efficiency and safety. All

* The text was submitted by the authors in English.

Scheme 1.



I **IIa–IIs** **IIIa–IIIn, IIIq–IIIs**

For R^1 and R^2, see Table 1.

the products were separated into four groups according to the required power level: amides **IIIa**–**IIId, IIIi**–**IIIk, IIIn**, **IIIr**, and **IIIs** constituted the first group, **IIIe**–**IIIh** and **IIIl**, the second, **IIIm** and **IIIq**, the third, and **IIIo** and **IIIp**, the fourth. A power level of 495 W was the most appropriate for the synthesis of the first group amides. In general, the reaction times were fairly short (3–10 min), and the yields were good to excellent (58–95%). However, the behaviors of amines **IIi**, **IIr**, and **IIs** were slightly different from the other amines. An appreciable amount of the amine remained unchanged, while benzoyl chloride disappeared in 15 min, other conditions being equal. Naturally, the conversions were very low. By raising the amount of benzoyl chloride to a ratio of 2 : 1 we succeeded in strongly increasing the yield of the corresponding amides, even though a small amount of unreacted amine was detected in the reaction mixture. The yield did not increase upon further raising the **I**-to-**II** ratio. It should be noted that the benzoylation of adenine, uracil, and cytosine gave only the corresponding 6-N-, N^1-, and 4-N-benzoyl derivatives, respec-

Table 1. Microwave-assisted synthesis of amides under solvent-free conditions[a]

Amine no.	R^1	R^2	Product	Power, W	Time, min	Yield,[b] %	mp, °C
IIa	H	4-ClC_6H_4	**IIIa**	495	3	93	182–184
IIb	H	4-$O_2NC_6H_4$	**IIIb**	495	4	92	197–198
IIc	H	4-MeC_6H_4	**IIIc**	495	3	95	154–156
IId	Ph	Ph	**IIId**	495	4	85	162–163
IIe	–CH=CHN=CH– (1*H*-imidazole)		**IIIe**	250	1.5	80	Liquid
IIf	H	Pyridin-2-yl	**IIIf**	250	2	92	84–87
IIg	H	Pyridin-4-yl	**IIIg**	250	1	94	207–210
IIh	H	Pyrimidin-2-yl	**IIIh**	250	3	82	140–142
IIi	H	Purin-6-yl	**IIIi**[c]	495	5	81	240–243
IIj	H	9,10-Dioxo-9,10-dihydroanthracen-1-yl	**IIIj**	495	4	89	245–247
IIk	H	4-PhN=NC_6H_4	**IIIk**	495	3	90	202–204
IIl	H	1,3-Thiazol-2-yl	**IIIl**	250	1	91	150–151
IIm	Bu	Bu	**IIIm**	300	5	87	Liquid
IIn	H	PhCO	**IIIn**	495	5	80	149–151
IIo	*o*-$C(O)C_6H_4C(O)$ (phthalimide)		–	495	30	–	–
IIp	H	1,5-Dimethyl-2-phenyl-3-oxo-1,2-dihydro-3*H*-pyrazol-4-yl	–	495	30	–	–
IIq	H	C_7H_{15}	**IIIq**	300	4	93	Liquid
IIr	–C(O)$NHCH_2CH_2C(O)$– (uracil)		**IIIr**	495	8	63	165–168
IIs	H	2-Oxo-1,2-dihydropyrimidin-4-yl	**IIIs**	495	10	58	347–349

[a] All products were reported previously in the literature; they were characterized by melting points and IR and ^{1}H NMR spectra.
[b] Yield of the isolated product.
[c] Reactant ratio **I** : **II** = 2 : 1.

tively, while no N^9-benzoyladenine, N^3-benzoyluracil, or N^1-benzoylcytosine was detected by TLC. These results are consistent with the microwave irradiation power-to-selectivity merit. We also presumed that our procedure can be used as a method for selective protection of amino group.

Next we selected 4-aminopyridine as a model for the preparation of second group amides. When the reaction was performed under the above conditions, the mixture turned black in less than 1 min. Presumably, tarring occurred due to high temperature; therefore, we tried to reduce the power level and found that an irradiation power of 250 W was the most suitable. These conditions were used to synthesize compounds **IIIe**, **IIIf**, **IIIh**, and **IIIl**. In the synthesis of amides **IIIm** and **IIIq**, the reactions were complete in 4–5 min at an MW power of 300 W, and the yields were higher. 4-Amino-1,5-dimethyl-2-phenyl-1,2-dihydro-3*H*-pyrazol-3-one (**IIp**) and phthalimide (**IIo**) failed to react with benzoyl chloride despite variation of the power level and reactant ratio. The results are collected in Table 1.

In order to elucidate chemoselectivity of the process we performed reactions of benzoyl chloride with mixtures of equimolar amounts of two different amines. The reaction mixture was exposed to microwave irradiation for a few minutes, and the product ratio was calculated. As follows from the data in Table 2, significant differences in the reactivities of amines are observed: (1) primary amines are more reactive than secondary amines; (2) aliphatic amines are more reactive than aromatic amines; and (3) aromatic amines bearing electron-donating groups are more reactive than those having electron-withdrawing groups. Thus, the proposed procedure ensures selective protection of amines.

We also examined reactions of *p*-chloroaniline (**IIa**), *p*-nitroaniline (**IIb**), and *p*-methylaniline (**IIc**) with 2 equiv of benzoyl chloride. The products were only the corresponding monobenzoyl derivatives, while no N,N-disubstituted products were detected. Obviously, conjugation between the carbonyl group and lone electron pair on the nitrogen atom in the resulting amide strongly reduces nucleophilicity of the nitrogen atom, thus hampering its subsequent benzoylation; in addition, the second benzoylation is hindered for steric reasons. These factors are responsible for the failure of benzoyl chloride to react with imide **IIo** and heterocyclic amine **IIp**.

Table 2. Competing microwave-assisted solvent-free benzoylation of different amines

Amine no.	Power, W	Time, min	Major product (fraction, mol %)
IIb + **IIc**	495	4	**IIIc** (98)
IIb + **IId**	495	4	**IIIb** (97)
IIm + **IIq**	300	5	**IIIq** (100)
IIb + **IIq**	300	5	**IIIq** (98)
IIc + **IIq**	300	5	**IIIq** (96)

To conclude, the proposed solvent-free procedure for the synthesis of benzamides under microwave irradiation is applicable to structurally diverse amines. It is superior to the existing methods in terms of yield, reaction time, selectivity, and experimental simplicity. The procedure provides a powerful tool for peptide synthesis.

EXPERIMENTAL

The IR spectra were recorded on a FTS-40 spectrophotometer in KBr. The ^{1}H NMR spectra were measured on a Bruker DPX-400M spectrometer using TMS as internal reference. The melting points were not corrected.

***N*-(4-Nitrophenyl)benzamide (*typical procedure*).** 4-Nitroaniline, 276 mg (2 mmol), and benzoyl chloride, 280 mg (2 mmol), were thoroughly mixed in a crucible, and the mixture was exposed to microwave irradiation in a domestic microwave oven at 495 W for 4 min. When the reaction was complete (TLC), the crude product (a powder) was recrystallized from 95% alcohol and dried.

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