

Microwave-Assisted Method for Conversion of Alcohols into *N*-Substituted Amides Using Envirocat EPZG[®] as a Catalyst

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Received 13 August 2003

A rapid conversion of benzyl alcohols into *N*-benzylsubstituted amides has been achieved under microwave irradiation using benzonitriles in the presence of catalytic amount of Envirocatalyst EPZG[®] in solvent-free conditions.

The amidation of alcohols with nitriles is known as the *Ritter* reaction [1]. The method is a very useful procedure as it may be utilized in peptide synthesis or in preparation of amines through the hydrolysis or reduction of initially formed amides. This reaction is carried out by using strong acidic catalyst which limits its use for acid-sensitive compounds. Several modified methods have been described to overcome this problem, but many of these methods have some limitations (toxic, expensive or commercially unavailable reagents and other) [2].

The use of heterogeneous catalysts in production of fine and speciality chemicals is well documented [3]. Recently, the reports on application of silica gel-supported ferric perchlorate and Fe³⁺-Montmorillonite K10 as catalysts in amidation of alcohols was published [4, 5], but these reactions take hours to be completed.

The trends of modern organic synthesis are to develop the processes which would proceed rapidly under simple reaction conditions, with readily available starting materials and the use of an indifferent or no solvent. It is well known that dramatic reduction in reaction time can be achieved when the reactions are carried out under microwave irradiation, especially without using any solvent [6].

The goal of this work was to examine the modified *Ritter* reaction by using commercially accessible acid clays catalyst with exchangeable cations Envirocat EPZG[®] and microwave irradiation to enhance the reaction rate.

At the beginning of this study we examined which type of alcohols can be used as reagent in the microwave *Ritter* reaction. The attempts at amidation of primary (octanol) and some secondary alcohols (pentan-2-ol, cyclopentanol) using EPZG[®] catalyst under microwave irradiation were not successful, probably for a small stability of initially formed carbonium ions. This is in accord with classical *Ritter* reaction,

which functions well only on tertiary alcohols. But the *tert*-butanol provided in our conditions the corresponding amide in very moderate yields (9 %). This fact can be explained by a difficult contact between the active sites of catalyst and the bulky reactant [7].

However, very good results were obtained using different benzyl alcohols both with electron-releasing and electron-withdrawing substituents as the starting materials (Scheme 1).

This is very remarkable because the benzyl alcohol in conditions of the classical *Ritter* reaction does not produce the corresponding amide, but formation of benzimidic acid benzyl ester takes place [8]. All reactions given in Table 1 were very rapid (4–10 min) and the high yields of products were isolated with the exception when *o*-substituted benzonitriles were used as amidation reagents (compounds *IIIId*, *IIIk*). The low yields of the products in these cases are caused by the same steric reasons as it was at *tert*-butanol.

To see if the reaction could be performed without microwave irradiation, some control experiments were carried out by using conventional heating. No product was observed (TLC, ¹H NMR) when just thermal heating (an oil bath) was applied to the reaction mixture. This could be explained by a specific microwave effect which is a consequence of the polar transition state interaction with the electric field [9].

In conclusion, the advantages of the presented method are: high yields, the solvent-free technique, short reaction time, and easy product isolation. The disadvantage is that this method is suitable exclusively for conversion of benzyl alcohols.

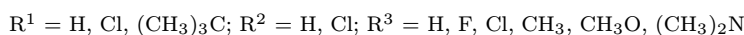
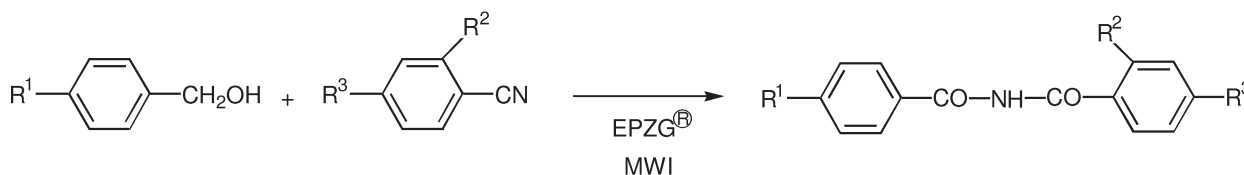
EXPERIMENTAL

Starting materials were commercially available and used without further purification. The Envirocat EPZG[®] is synthesized and supplied by Contract Chemicals, UK. It is a free flowing yellow-green pow-

Table 1. Microwave-Assisted Amidation of Benzyl Alcohols with Benzonitriles Using Envirocat EPZG[®]

Comp.	R ¹	R ²	R ³	$T_{\text{fin}}^c / ^\circ\text{C}$	Time/min	Yield ^a /%	M.p./ $^\circ\text{C}$	M.p.[Ref]/ $^\circ\text{C}$
<i>IIIa</i>	H	H	H	220	6	80 (0 ^b)	104	107 [10]
<i>IIIb</i>	H	H	F	182	6	66	128	129–130 [11]
<i>IIIc</i>	H	H	Cl	101	8	71	167–168	164–166 [12]
<i>III d</i>	H	Cl	H	225	8	5	104–105	104–105 [13]
<i>IIIe</i>	Cl	H	H	197	5	61	130–132	131–132 [2]
<i>III f</i>	H	H	CH ₃	218	5	46	139–140	138–139 [15]
<i>III g</i>	H	H	CH ₃ O	225	6	54 (0 ^b)	129–131	131–132 [2]
<i>III h</i>	H	H	(CH ₃) ₂ N	236	4	62	166	164–166 [16]
<i>III j</i>	Cl	H	Cl	240	6	75	174–176	
<i>III k</i>	Cl	Cl	Cl	230	10	9	181–182	
<i>III l</i>	(CH ₃) ₃ C	H	Cl	250	10	64	142–143	

a) Yields refer to isolated products; b) yield of the reaction performed under thermal heating without microwave irradiation; c) T_{fin} is temperature of the reaction mixture reached at the end of reaction.



Scheme 1

der having a bulk density of 0.76 g cm⁻³ and surface area of ca. 250 m² g⁻¹.

The ¹H NMR and ¹³C NMR spectra were measured on Varian Gemini 2000 instrument at 300 MHz and 75 MHz, CDCl₃ was used as the solvent and tetramethylsilane as an internal standard. Microanalyses were carried out on an Erba Strumenstacione Milano CHN analyzer, model 1106. These results agreed with the calculated values. Melting points were determined on a Kofler apparatus. All microwave experiments were carried out in a SYNTHEWAVE 402[®], PROLABO reactor. The temperature of the reaction mixture was monitored by an IR thermometer.

General Procedure

A mixture of benzyl alcohol (0.01 mol), nitrile (0.01 mol), and Envirocat EPZG[®] (100 mg) was stirred under microwave irradiation in the microwave reactor (240 W input power) for a given time. The reaction mass was, after cooling to room temperature, treated with 50 cm³ of CH₂Cl₂. The catalyst was removed by filtration. The solvent was evaporated and the residue was recrystallized from ethanol–water or purified by column chromatography on silica using isohexane–ethyl acetate ($\varphi_r = 4 : 1$) as the eluent to give pure amides. The reaction time, yields, and melting points are given in Table 1. NMR data of products *IIIa* [17], *IIIe* [14], and *III f* [13] were found to be identical with the data described in literature.

N-Benzyl-4-fluorobenzamide (*IIIb*), ¹H NMR, δ : 4.63 (d, 2H, $J = 5.7$ Hz, CH₂), 6.38 (bs, 1H, NH), 7.11 (d, 2H, $J = 8.7$ Hz, H_{arom}), 7.29–7.36 (m, 5H, H_{arom}), 7.80 (d, 2H, $J = 8.7$ Hz, H_{arom}); ¹³C NMR, δ : 44.4, 115.9, 127.2, 127.9, 128.1, 128.4, 128.8, 129.0, 129.5, 130.7, 138.2, 163.3, 166.6.

N-Benzyl-4-dimethylaminobenzamide (*IIIh*), ¹H NMR, δ : 3.02 (s, 6H, (CH₃)₂N), 4.64 (d, 2H, $J = 5.7$ Hz, CH₂), 6.32 (bs, 1H, NH), 6.66 (d, 2H, $J = 9.0$ Hz, H_{arom}), 7.24–7.36 (m, 5H, H_{arom}), 7.69 (d, 2H, $J = 9.0$ Hz, H_{arom}); ¹³C NMR, δ : 39.1, 42.9, 110.0, 110.1, 120.1, 125.4, 126.4, 126.9, 127.4, 127.6, 127.7, 137.8, 151.5, 166.2.

N-(4-Chlorobenzyl)-4-chlorobenzamide (*IIIj*), ¹H NMR, δ : 4.60 (d, 2H, $J = 5.7$ Hz, CH₂), 6.37 (bs, 1H, NH), 7.29–7.34 (m, 4H, H_{arom}), 7.41 (d, 2H, $J = 6.9$ Hz, H_{arom}), 7.72 (d, 2H, $J = 6.9$ Hz, H_{arom}); ¹³C NMR, δ : 43.5, 128.4, 128.9, 129.0, 129.3, 132.5, 133.6, 136.5, 138.0, 166.3.

N-(4-Chlorobenzyl)-2,4-dichlorobenzamide (*IIIk*), ¹H NMR, δ : 4.62 (d, 2H, $J = 5.4$ Hz, CH₂), 6.53 (bs, 1H, NH), 7.32 (m, 5H, H_{arom}), 7.42 (s, 1H, H_{arom}), 7.67 (d, 1H, $J = 8.4$ Hz, H_{arom}); ¹³C NMR, δ : 43.6, 127.7, 129.0, 129.2, 130.1, 131.5, 132.9, 133.6, 136.1, 137.1.

N-(4-*tert*-Butylbenzyl)-4-chlorobenzamide (*III l*), ¹H NMR, δ : 1.32 (s, 9H, CH₃), 4.61 (d, 2H, $J = 5.7$ Hz, CH₂), 6.29 (bs, NH), 7.29 (d, 2H, $J = 8.4$ Hz, H_{arom}), 7.39 (d, 4H, $J = 8.4$ Hz, H_{arom}), 7.71 (d, 2H, $J = 8.4$ Hz, H_{arom}); ¹³C NMR, δ : 31.3, 34.6, 44.0,

125.8, 127.9, 128.4, 128.9, 132.8, 134.8, 137.8, 150.9, 166.2.

Acknowledgements. Our thanks are due to Contract Chemicals, UK for generous gift of Envirocat EPZG®. The authors thank Dr. E. Solčániová and her staff of the Institute of Chemistry of the Comenius University for ^1H NMR and ^{13}C NMR analyses. The financial support from the Ministry of Education of the Slovak Republic is acknowledged.

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