

Rapid and Efficient Synthesis of N-alkylbenzamides Under Microwave Irradiation

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Abstract: The microwave-assisted synthesis of N-alkylbenzamides from benzoic acid and primary aliphatic amines has been developed under solvent-free conditions. The different solid catalysts have been investigated. The suggested synthesis is environmentally friendly and excellent yields (97 - 99 %) have been reached.

Keywords: Amino-de-hydroxylation, heterogenous catalyst, microporous materials, microwave assisted synthesis, N-alkylbenzamides, solvent-free reaction.

INTRODUCTION

The development of microwave ovens for the heating of food has more than 60-year old history [1] and since the first application of microwave heating in organic chemistry (Gedye *et al.*, 1986) [2] the number of organic reactions carried out under microwave (MW) irradiation increased exponentially. This increase was related not only with better availability of the commercial microwave equipment. But primarily this rapid development was inflicted by increased reaction yields and shorter reaction times observed in many classical organic reactions [3-5]. During recent years focus shifted to environmentally friendlier methods, especially to the reactions under the solvent-free conditions [6] and the use of solid supported catalyst. These methods in combination with effective microwave heating provide approaches, which fulfill several "green chemistry" principles [7, 8].

The efficient synthesis of amides is important because of their wide range of applications in academia and industry, specially as intermediates in organic synthesis or peptide and protein synthesis. The conventional preparation of amides is well documented [9]. In the first place stands activation of carboxylic acid by attachment of a leaving group to allow the attack by the amino group. Carboxy components can be activated as acyl halides, anhydrides, acyl azides, esters, acylimidazoles etc. This acylating agent can be prepared separately or in situ from the acid in the presence of amine by addition of activation reagents [10]. Although these reactions provide good results, problems can occur with necessary neutralization and cooling or difficult separation.

Heterogeneous catalysts have proven their usefulness in a large variety of organic reactions. Reagents are immobilized

on the porous of the solid support and activated by active reagent sites. Product isolation is simplified, reactions often give higher selectivity and even recovery of catalysts is generally possible, which enables environmentally friendly synthesis [5].

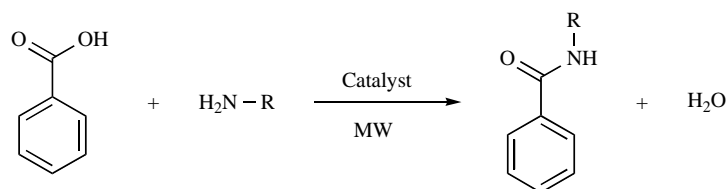
The formation of an amide bond by direct microwave pyrolysis of carboxylic acid and amines under solvent-free conditions reduces waste production, significantly reduces reaction time and simplifies the workflow. Microwave synthesis of amides has already been reported [11-16] and different catalysts like K-10 bentonite [17], imidazole [18], *p*-toluenesulfonic acid [19], TaCl₅-silica gel [20] and zeolite H β [21] were involved. However, some of these reactions were carried out in domestic microwave ovens, without temperature control and reproducible results. In other cases low yields were obtained. Therefore there is still great demand for efficient methods of the synthesis of amides.

We wish to report microwave-enhanced solvent free synthesis of the N-alkylbenzamides carried out in the presence of various heterogenous catalysts (Scheme 1). We optimized reaction conditions and studied various ways of catalytic activation of reactants.

RESULTS

In the first set of experiments, we have tried to evaluate the influence of various catalysts for the acylation reaction of N-hexylamine with benzoic acid (Table 1). A multimodal microwave reactor (RM-DA4, Plazmatronika) allowed us to study the ability of catalysts to absorb microwave energy and convert it into heat. An ammonium salt was formed after mixing N-hexylamine with benzoic acid. This salt interacted strongly with microwave field. For this reason we limited an irradiation MW power to 350 W only. Then we were able to distinguish the catalysts depending on their absorption behavior towards MW radiation. Results (Table 1) indicated

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Scheme 1.

Table 1. Synthesis of N-hexylbenzamide^a, the Influence of Catalysts.

Catalyst	Reaction Temperature after 7 min [°C]	Reaction Temperature after 10 min [°C]	Product Amount ^b [%]
-	217	231	83
SiC	250	250	69
Activated carbon	250	250	68
MgO	195	218	33
SiO ₂ /H ₃ PO ₄	245	250	87
Zeolite ZSM 5	226	242	80
Zeolite X	250	250	76
Clinoptilolite	241	250	77
Montmorillonite K10	229	241	79
Montmorillonite KSF	228	245	88

^a Reaction time 10 minutes, MW power 350 W (multimode).^b Determined by GC.

that montmorillonite KSF was the most efficient catalyst for this reaction.

Further we have investigated the influence of reaction temperature and time on formation of N-hexylbenzamide. Furthermore, we studied the influence of an excess of one reactant (Table 2). The optimized reaction conditions were applied together with catalyst to a number of reactions (Table 3). We have succeeded in improving the yields significantly in comparison with previously published work [11, 22].

DISCUSSION

We have investigated the use of various microporous materials such as catalysts for the acylation reaction of N-hexylamine with benzoic acid (Table 1). Montmorillonite KSF and SiO₂/H₃PO₄ showed good catalytic activity and the reaction leads to very good yields. On the other hand, the reaction was slowed down in basic conditions (excess of amine or addition of MgO). The presence of microwave sensitizer (SiC or activated carbon) increased the reaction temperature dramatically but unfortunately led partly to decomposition of products and to lower yields.

Mixing of the alkaline N-alkylamine with the benzoic acid at room temperature leads to fast acid-base equilibrium

reaction and the ammonium salt is formed. Following pyrolysis of this salt and subsequent nucleophilic attack depend highly on reaction temperature. Experiments with preparation of N-hexylbenzamide in monomode microwave reactor showed exponentially growing yields with temperatures increasing from 150°C to 250°C. Heating at 300°C resulted in very good 89% yield of N-hexylbenzamide (Table 2).

There is a significant difference in yields of N-hexylbenzamide in open vessel multimode microwave oven (RM-DA4, Plazmatonika) and closed vessel monomode reactor (Monowave 300, Anton-Paar). In the first case, conversion to amide was 83% when the reaction temperature reached 231°C after 10 minutes of heating (Table 1). In second case, heating at 225°C for 10 min resulted in 47% yield of amide (Table 2). In the multimode microwave oven temperature was measured only at the surface of the reaction flask unlike the monomode reactor, where core temperatures were measured. Due to volumetric character of microwave heating, surface temperatures are often inferior to core temperatures. This difference may, in specific examples, exceed 30°C [23]. Moreover significant difference may be in easier elimination of water from reactor with open flask system. Both factors may contribute to different conversions in multimode reactor.

Encouraged by the activity of acidic catalysts we further explored the influence of surplus of benzoic acid (Table 2). 1.5 equivalent excess of benzoic acid improved the yield to 96% of N-hexylbenzamide. Under the same conditions (250°C, 10 minutes, monomode reactor) the equimolar amounts of reactants yielded 80% of N-hexylbenzamide. A reaction mechanism was apparently sensitive to acid conditions. We proposed that protonation of carbonyl at Brønsted acid sites is essential for water withdrawal and further reaction with amine. Presence of catalyst (Montmorillonite KSF) in reaction resulted in 88% yield of N-hexylbenzamide. The influence of catalyst was lower, compared to the excess of acid. On the other hand a percentage of carbon incorporated into product, carbon balance, is higher with the use of catalyst and equimolar amounts of reagents.

We compared reactivities of different primary amines with benzoic acid under various conditions. High temperature 250°C necessary to decompose inactive ammonium salt was crucial for good yields. With the montmorillonite KSF and the surplus of benzoic acid we reached excellent yields (Table 3).

EXPERIMENTAL

Equipment: RM-DA4 (Plazmatonika; Poland) a multimode microwave reactor with an installed microwave power

Table 2. Optimization^a of the Reaction Conditions of N-hexylbenzamide Synthesis

Reaction Temperature [°C]	Reaction Time [min]	Relative Amount Ratio [acid/amine]	Yield ^b [%]
150	10	1/1	1
175	10	1/1	3
200	10	1/1	13
225	10	1/1	47
250	10	1/1	80
275	10	1/1	88
300	10	1/1	89
200	30	1/1	90
250	10	1.25/1	86
250	10	1.5/1	96
250	10	1/1.5	38

^a without catalyst.^b of the isolated products.

Table 3. Reaction of Aliphatic Amines with Benzoic Acid (Scheme 1).

R	Reaction Temperature [°C]	Catalyst	Reaction Time [h]	Relative Amount Ratio [acid/amine]	Yield ^a [%]
C ₄ H ₉	110	K ₆₀ silica gel	24	1/1	65 ^b
	250	Montmorillonite KSF	0.167	1.5/1	99
C ₆ H ₁₃	250	Montmorillonite KSF	0.167	1.5/1	98
C ₈ H ₁₇	150	-	0.5	1/1.5	10 ^c
	250	Montmorillonite KSF	0.167	1.5/1	98
C ₁₀ H ₂₁	250	Montmorillonite KSF	0.167	1.5/1	97

^a of the isolated products.^b with conventional heating, determined by Clark and co-workers [22].^c in monomode MW reactor, determined by Loupy and co-workers [11].

700 W, equipped with an infrared temperature detection at the bottom of a reaction chamber, an accurate control of power and a magnetic stirrer was used.

Monowave 300 (Anton-Paar; Austria) a monomode microwave reactor with up to 850 W of microwave power equipped with the Ruby Thermometer and an infrared temperature sensor was used. The temperature monitoring with Ruby Thermometer does not reflect the surface temperature of the reaction vial (like the IR sensor), but mimics the internal reaction temperature with high accuracy. Reactions were performed in closed vessels with pressure control up to 30 bar.

General procedure of synthesis of N-hexylbenzamide in RM-DA4 microwave reactor: In typical reaction procedure, 0.03 mol of benzoic acid, 0.03 mol of N-hexylamine and 0.3 g of catalyst (silicates were activated in an oven at 200 °C for 6 hours) were introduced into a round bottom flask equipped with a reflux condenser. The mixture was homogenized, equilibrated to room temperature and then irradiated in microwave reactor at 350 W for 10 min. Temperature rose during irradiation up to a maximum of 250 °C. Homogeneity

during irradiation was ensured by magnetic stirrer and temperature was measured by built-in IR temperature detector. After irradiation the reaction mixture was allowed to attain room temperature, dissolved in chloroform and the catalyst was filtered off. The conversion was determined by the GC (HP 5890) using N-phenylbenzamide as the internal standard.

General procedure of reactions in Monowave 300 reactor: In typical reaction procedure, 0.01 mol of benzoic acid, 0.01 mol of aliphatic amine were mixed in a pressure resistant tube, sealed and after tempering to room temperature placed into the reactor cavity. Temperature during the irradiation maintained constant as the result of regulation of emitted microwave power. After irradiation the reaction mixture was dissolved in chloroform (25 ml), the catalyst was filtered off when necessary, and washed with 1M NaOH (2 x 25 ml) and 2M HCl (2 x 25 ml). In few cases product was separated by column chromatography. When TLC showed no remaining acid the solvent was evaporated under vacuum and crude product was purified by recrystallization from EtOH/H₂O.

Melting points were taken on a Stuart SMP10 apparatus and were uncorrected. ^1H and ^{13}C spectra were recorded at 400.13 and 100.62 MHz (Bruker AVANCE II 400). Chemical shifts were relative to the signal of solvent, $\delta = 2.55$ (^1H), $\delta = 39.6$ (^{13}C).

N-Butylbenzamide: mp = 40-42°C (Lit. 40-41 [24]); IR (film, cm^{-1}) 3313, 3062, 2954, 2927, 2869, 1636, 1578, 1544, 1488, 1305, 697; ^1H NMR (400 MHz, DMSO- d_6) δ 8.58 (br. s, 1H, NH), δ 7.98 (d, 2H, ArH), δ 7.53 (t, 1H, ArH), δ 7.48 (t, 2H, ArH), δ 3.37 (q, 2H, NCH $_2$), 1.62-1.32 (m, 4H, CH $_2$), δ 0.93 (t, 3H, CH $_3$); ^{13}C NMR (100 MHz, DMSO- d_6) δ 13.8, 19.9, 31.5, 39.1, 127.3, 128.2, 131.0, 135.0, 166.5.

N-Hexylbenzamide: mp = 43-44°C (Lit. 42-44 [25]); IR (film, cm^{-1}) 3318, 3061, 2951, 2923, 2854, 1640, 1576, 1545, 1488, 1307, 695; ^1H NMR (400 MHz, DMSO- d_6) δ 8.51 (br. s, 1H, NH), δ 7.92 (d, 2H, ArH), δ 7.54 (m, 1H, ArH), δ 7.48 (m, 2H, ArH), δ 3.31 (q, 2H, NCH $_2$), 1.61-1.23 (m, 8H, CH $_2$), δ 0.89 (t, 3H, CH $_3$); ^{13}C NMR (100 MHz, DMSO- d_6) δ 13.9, 22.1, 26.3, 29.2, 31.2, 39.3, 127.2, 128.2, 130.9, 134.8, 166.2.

N-Octylbenzamide: mp = 40-41°C (Lit. 39-41 [11]); IR (film, cm^{-1}) 3337, 3063, 2953, 2917, 2845, 1633, 1534, 1466, 714, 691; ^1H NMR (400 MHz, DMSO- d_6) δ 8.49 (br. s, 1H, NH), δ 7.89 (d, 2H, ArH), δ 7.57 - 7.47 (m, 3H, ArH), δ 3.30 (q, 2H, NCH $_2$), 1.61-1.22 (m, 12H, CH $_2$), δ 0.89 (t, 3H, CH $_3$); ^{13}C NMR (100 MHz, DMSO- d_6) δ 14.0, 22.2, 26.6, 28.8, 28.9, 29.2, 31.3, 39.3, 127.2, 128.2, 131.0, 134.8, 166.1.

N-Decylbenzamide: mp = 55°C; (Lit. 56-57 [26]); IR (film, cm^{-1}) 3341, 2953, 2917, 2845, 1629, 1532, 1465, 714, 691; ^1H NMR (400 MHz, DMSO- d_6) δ 8.48 (br. s, 1H, NH), δ 7.89 (d, 2H, ArH), δ 7.54 (t, 1H, ArH), δ 7.48 (t, 2H, ArH), δ 3.29 (q, 2H, NCH $_2$), 1.61-1.20 (m, 16H, CH $_2$), δ 0.88 (t, 3H, CH $_3$); ^{13}C NMR (100 MHz, DMSO- d_6) δ 14.0, 22.2, 26.6, 28.8, 28.9, 29.0, 29.1, 29.2, 31.4, 39.3, 127.2, 128.2, 130.9, 134.8, 166.1.

CONCLUSIONS

In summary, these studies should not only enable an extension of applicability of the microwave heating, but also introduce environmentally friendlier methods in amide bond synthesis. A rapid microwave inducted procedure for the preparation of primary aliphatic amides under solvent-free conditions was introduced. With the use of acidic conditions amides were formed in excellent yields (97 - 99%).

CONFLICT OF INTEREST

The author(s) confirm that this article content has no conflict of interest.

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