Monatsh Chem
DOI 10.1007/s00706-014-1387-2

ORIGINAL PAPER

Metallic magnesium: an efficient catalyst toward *N*-aryl and *N*-alkyl substituted amides directly from aliphatic carboxylic acids

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Received: 26 June 2014 / Accepted: 8 December 2014

Abstract An efficient and inexpensive procedure for direct conversion of aliphatic carboxylic acids into amides has been developed using anilines or aliphatic amines and Mg(0) as catalyst in toluene. The amides were obtained by single crystallization in moderate to excellent yields with high purity.

Keywords Direct amidation · Amines · Carboxylic acids · Catalysis · Magnesium

Introduction

Proteins are essential biomolecules that exist in living systems which have amide functional groups in their structures. Because of their biological and chemical significance, amides are important as biologically active compounds [1–6], industrial products [7–9], and precursors for a variety of organic compounds [10–14]. The preparation of amides directly from carboxylic acids is a fairly difficult task. Carboxylic acids and amines can give reaction to form highly stable and unreactive carboxylate salts. Strong heating conditions and long reaction time are necessary to convert these salts directly to the corresponding amides, which leads to oxidative degradation of aromatic amines and long-chained aliphatic carboxylic acids and consequently the amounts of by-products increase. The most commonly used process for synthesizing amides in a laboratory scale is converting the carboxylic acids with special reagents into their more reactive acyl halide or anhydride derivatives and then to make these derivatives interact with amines. However, some reagents such as thionyl chloride ($SOCl_2$) and dicyclohexyl carbodiimide (DCC) are moisture sensitive, toxic, and require special reaction conditions [15–21]. Therefore, alternative methods for the direct synthesis of amides have attracted considerable interest. The solid-supported catalysis was used successively for direct preparation of amides [22–26]. Borate esters are also widely used in the synthesis of amides directly from acids [27, 28]. In the presence of phosphine-based reagents, several amides can be prepared with high yields [29–31]. Georg [32] and Kangani [33] reported that amides can be synthesized from carboxylic acids using the Deoxo-Fluor reagent. On the other hand, many studies have reported catalytic direct conversion routes [34–49]. Each method has its own advantages and a number of major disadvantages. In some of these methods, conversion of carboxylic acids to amides necessitates long reaction times (up to 6–24 h) [37, 39]. Other methods require microwave irradiation or special reagents such as diethyl chlorophosphate [39], ionic liquids such as [BMIM]BF_4 [42], 1,3,5-triazo-2,4,6-triphosphorine-2,2,4,4,6,6-hexachloride (TAPC) [45], prop-2-ene-1-sulfinyl chloride [48], and nano sulfated titania [49]. As stated previously, by conventional amide preparation methods, the carboxylic acid is allowed to react with the amine at elevated temperatures. Especially for the preparation of anilides prolonged heating at 180–200 °C is required and due to these excessive reaction conditions the final product is contaminated with dark colored decomposition products [50]. Also, the by-products complicate isolation of the desired amide from the obtained complex mixture and in most cases considerably reduces its yield. Jursic et al. [51]

Electronic supplementary material The online version of this article (doi:10.1007/s00706-014-1387-2) contains supplementary material, which is available to authorized users.

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Published online: 21 December 2014

Table 1 Optimization of reaction conditions

Entry	Acid	Amine	Reaction conditions[ac]	Yield/%[b]
1	$CH_3(CH_2)_{10}COOH$	$PhNH_2$	No solvent/no catalyst/2 h/160 °C	Trace
2	$CH_3(CH_2)_{10}COOH$	$PhNH_2$	Toluene/no catalyst/2 h/160 °C	Trace
3	$CH_3(CH_2)_{10}COOH$	$PhNH_2$	Toluene/MS-4 Å/Mg/2 h/160 °C	Trace
4	$CH_3(CH_2)_{10}COOH$	$PhNH_2$	Toluene/Mg-I_2/2 h/160 °C	36
5	$CH_3(CH_2)_{10}COOH$	$PhNH_2$	No solvent/Mg/2 h/160 °C	25
6	$CH_3(CH_2)_{10}COOH$	$PhNH_2$	Toluene/Mg/2 h/160 °C	79
7	PhCOOH	$PhNH_2$	Toluene/Mg/2 h/160 °C	Trace
8	PhCOOH	*p*-CH_3PhNH_2	Toluene/Mg/2 h/160 °C	Trace
9	PhCOOH	$CH_3(CH_2)_{11}NH_2$	Toluene/Mg/2 h/160 °C	Trace
10	CH_3COOH	$CH_3(CH_2)_{11}NH_2$	Toluene/Mg (stoichiometric amounts)/2 h/160 °C	–

[a] In all cases: 30 mmol % Mg, 3 cm^3 toluene

[b] Yield after crystallization (MeOH/acetone/H_2O)

[c] Stoichiometric amount of Mg was used (entry 10)

reported a conversion which proceeds at 160–180 °C for 30 min, but the method has some limitations. The method seems to be generally suitable for the aliphatic amines, experimental procedure contains an additional isolation step and most importantly, it requires the thermal stability of the reagents.

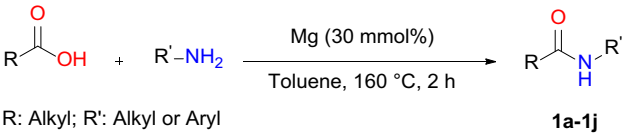
Because of all these disadvantages, an alternative efficient and cheap method for the direct conversion of aliphatic carboxylic acids into *N*-aryl and *N*-alkyl amides was developed. This robust and practically simple method does not require any special coupling reagents.

Results and discussion

Table 1 summarizes the experimental conditions having made to optimize the reaction. Dodecanoic acid was reacted with aniline in the absence of solvent and catalyst. After refluxing for 2 h, traces of the product were obtained (entry 1). When the reaction is carried out by dissolving the starting materials in toluene, trace amounts of the amide were obtained again (entry 2). The reaction was performed by adding Mg powder (30 mmol %) and molecular sieve (MS-4 Å) but still extremely low yield of the amide was obtained (entry 3).

In analogy to the Grignard reaction, molecular iodine is used to activate the Mg surface but only a 36 % yield of the desired amide was isolated (entry 4). At temperatures above 150 °C, aniline is subjected to iodination and oxidative degradation occurs by iodine [52]. Thus, the product yield was quite low. On the other hand, when the reaction was performed in the absence of iodine catalyst, moderate yield was obtained (79 %, entry 6). Furthermore, the reaction strongly depends on the use of toluene as solvent, due to the increase in product yield which is observed in its

Scheme 1



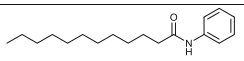
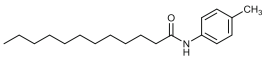
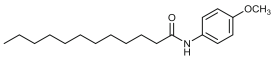
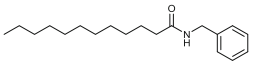
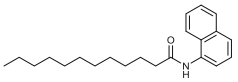
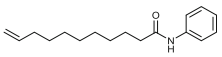
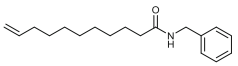
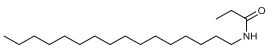
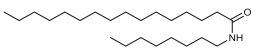
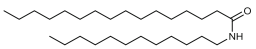
Scheme 1 .

presence (entries 5 and 6). Thus, the optimal reaction conditions were determined for the direct conversion of aliphatic carboxylic acids into amides. Accordingly to achieve maximum conversion both magnesium (as a Lewis acid catalyst) and toluene are needed (Scheme 1).

Furthermore in exploring the reaction, benzoic acid did not react both with aniline or aliphatic amines under the similar reaction conditions (entries 7–9). Specifically with the procedure developed in this study, only the aliphatic carboxylic acids can be converted directly into the amides. The observed results are given in Table 2. As shown in the table, excellent yields were obtained even after crystallization step (entries 6–10). The structures of synthesized amides are given in Table 2.

It can be considered that amidation in the present study occurs by the catalysis of MgO formed in the reaction medium. However, Tamaddonet al. [41] pointed out that in the presence of basic MgO, a carboxylate ion was formed before the attack of the amine and hence the electrophilicity of the carbonyl group was reduced. On account of this, formation of MgO and its catalytic effect is not a reliable mechanism for the amidation performed in this study. Magnesium and acetic acid react rapidly under the reaction conditions (entry 10) with complete consumption of the metal (30 mmol % or in stoichiometric amounts) probably to give magnesium acetate and hydrogen gas. Thus, the other postulate may be that the conversion

Table 2 Direct conversion of aliphatic acids into amides

Entry	Acid	Amine	Amide	Yield /%[b]
1	$CH_3(CH_2)_{10}COOH$	$Ph\text{-}NH_2$	**1a** 	79
2	$CH_3(CH_2)_{10}COOH$	$p\text{-}CH_3\text{-}Ph\text{-}NH_2$	**1b** 	83
3	$CH_3(CH_2)_{10}COOH$	$p\text{-}CH_3O\text{-}Ph\text{-}NH_2$	**1c** 	72
4	$CH_3(CH_2)_{10}COOH$	$Ph\text{-}CH_2\text{-}NH_2$	**1d** 	79
5	$CH_3(CH_2)_{10}COOH$	1-Naphtyl-NH_2	**1e** 	67
6	$CH_2{=}CH(CH)_8COOH$	$Ph\text{-}NH_2$	**1f** 	94
7	$CH_2{=}CH(CH)_8COOH$	$Ph\text{-}CH_2\text{-}NH_2$	**1g** 	96
8	CH_3CH_2COOH	$CH_3(CH_2)_{15}NH_2$	**1h** 	98
9	$CH_3(CH_2)_{14}COOH$	$CH_3(CH_2)_7NH_2$	**1i** 	99
10	$CH_3(CH_2)_{14}COOH$	$CH_3(CH_2)_{11}NH_2$	**1j** 	99

[a]Reaction conditions: Toluene / Mg / 2 h / 160 °C

[b]Yield after crystallization (MeOH / acetone / H_2O)

proceeds via the magnesium carboxylate salt. However, not the product was detected even in trace amounts after the specified time (entry 10).

A most reliable mechanism for the amidation reaction is shown in Fig. 1. According to the proposed mechanism, initially part of Mg atoms forms Mg^{2+} ions by very slow reaction with higher aliphatic carboxylic acids. In this case, the resulted Mg^{2+} ions display electrophilic assistance to nucleophilic attack of amine on the carbonyl group of the carboxylic acid by acting as a Lewis acid to give tetrahedral intermediate. This tetrahedral intermediate then undergoes water elimination and lose proton to yield the desired amide at the specified time (2 h).

In summary, a practical method for direct conversion of aliphatic carboxylic acids into *N*-aryl or *N*-alkyl amides has been developed. The method is fast and requires no special coupling reagents. In addition, the amides were obtained in moderate to excellent yields by simple crystallization (67–99 %).

Experimental

All commercial reagents and solvents were purchased from either Merck or Sigma-Aldrich and used without further purification. Before use, magnesium powder was activated by heating in an oven at 150 °C for 2 h. Thin-layer chromatography was performed using silica gel (60 F_{254}, Merck, Darmstadt, Germany) plates. Melting points were recorded by BÜCHI melting point B-540 apparatus (BUCHI Labortechnik AG in Flawil, Switzerland). The NMR spectra were measured using a Varian mercury plus spectrometer (400 MHz; Varian Inc., California, USA) in $CDCl_3$ using tetramethylsilane (TMS) as an internal standard. Chemical shifts (δ) are reported in ppm and *J* values in Hertz.

Typical amidation procedure

In a 50 cm^3 flat-bottomed one-necked flask, 0.91 g dodecanoic acid (4.54 mmol) was dissolved in 3 cm^3 of toluene. Then, 0.42 g aniline (4.54 mmol) and Mg powder (30 mmol %) was added. The flask was attached to a reflux condenser and heated under atmospheric conditions in an oil bath at 160 °C for 2 h. After the reflux period, the reaction mixture was cooled slightly, 10 cm^3 of acetone was added and the magnesium powder filtered off under vacuum. The clear filtrate was concentrated in vacuo and the residue crystallized from MeOH/acetone/H_2O to give white bright needles (0.98 g).

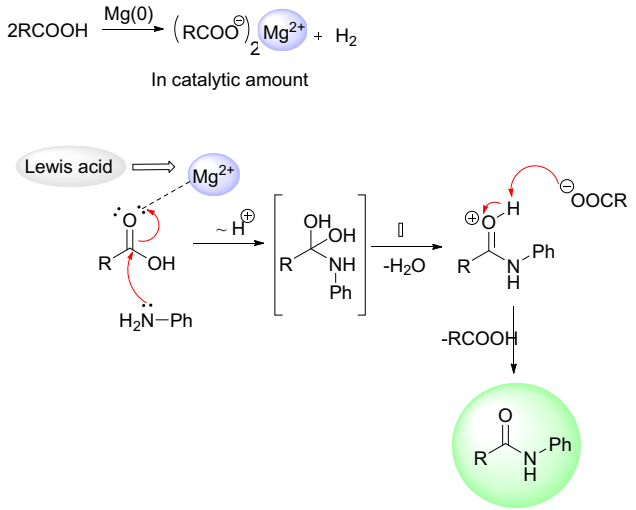


Fig. 1 Proposed reaction mechanism

*N-Phenyldodecanamide (**1a**)*
White bright needles; yield 79 %; *m.p.*: 79–80 °C (Ref. [53, 54] 77–78, 79–80 °C).

*N-(p-Tolyl)dodecanamide (**1b**)*
White bright needles; yield 83 %; *m.p.*: 83–84 °C (Ref. [37, 54] 83–84, 85–86 °C).

*N-(p-Methoxyphenyl)dodecanamide (**1c**)*
Gray bright crystals; yield 72 %; *m.p.*: 105–106 °C (Ref. [54, 55] 104–105, 90–92 °C).

*N-Benzyldodecanamide (**1d**)*
White bright crystals; yield 79 %; *m.p.*: 83.5–84.5 °C (Ref. [56] 82 °C).

*N-(Naphthalen-1-yl)dodecanamide (**1e**, $C_{22}H_{31}NO$)*
Gray solid; yield 67 %; *m.p.*: 106–107 °C; FT-IR (ATR): $\bar{\nu}$ = 3,310, 3,028, 2,917, 2,850, 1,659, 1,595, 1,525, 1,464, 1,405, 1,373, 1,351, 1,329, 1,310, 1,295, 1,270, 1,250, 1,208, 1,181, 1,113, 1,082, 961, 814, 771, 719 cm^{-1}; ^1H NMR (400 MHz, $CHCl_3$): δ = 7.97 (s, 1H), 7.86–7.85 (m, 2H), 7.67 (d, 2H, J = 8.0 Hz), 7.49–7.41 (m, 3H), 2.46 (t, 2H, J = 7.2 Hz), 1.77 (quin, 2H, J = 6.8 Hz), 1.40–1.27 (m, 16H), 0.88 (t, 3H, J = 6.8 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.15, 134.08, 132.30, 128.72, 127.30, 126.20, 125.93, 125.78, 125.71, 121.22, 120.73, 37.65, 31.93, 29.64, 29.55, 29.42, 29.37, 25.91, 22.72, 14.16 ppm.

*N-Phenylundec-10-enamide (**1f**)*
Slightly brown solid; yield 94 %; *m.p.*: 65–66 °C (Ref. [57] 67–68 °C).

*N-Benzylundec-10-enamide (**1 g**)*
White crystals; yield 96 %; *m.p.*: 62–63 °C; the ^1H NMR spectrum agrees with the one given in [58].

*N-Hexadecylpropanamide (**1 h**, $C_{19}H_{39}NO$)*
White solid; yield 98 %; *m.p.*: 68–69 °C; FT-IR (ATR): $\bar{\nu}$ = 3,309, 2,917, 2,849, 1,638, 1,548, 1,472, 1,375, 1,283, 1,268, 1,248, 1,231, 1,209, 1,188, 1,158, 1,119, 1,081, 1,057, 1,016, 992, 955, 921, 892, 719, 698 cm^{-1}; ^1H NMR (400 MHz, $CHCl_3$): δ = 5.55 (br s, 1H), 3.24 (q, 2H, J = 7.2 Hz), 2.20 (q, 2H, J = 7.6 Hz), 1.49 (quin, 2H, J = 6.8 Hz), 1.28–1.25 (m, 26H), 1.16 (t, 3H, J = 7.6 Hz), 0.88 (t, 3H, J = 7.2 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.70, 39.52, 31.92, 29.78, 29.69, 29.65, 29.58, 29.55, 29.36, 29.31, 26.92, 22.70, 14.13, 9.96 ppm.

*N-Octylhexadecanamide (**1i**)*
White solid; yield 99 %; *m.p.*: 77–78 °C (Ref. [59] 78–79 °C).

*N-Dodecylhexadecanamide (**1j**)*
White solid; yield 99 %; *m.p.*: 85–86 °C (Ref. [59] 86–87 °C).

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