Direct Preparation of Primary Amides by Reaction of Carboxylic Acids and Ammonia in Alcohols Using DMT-MM

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A simple and mild method for the direct conversion of carboxylic acids to primary amides has been developed by using 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride (DMT-MM). The reaction proceeds by adding DMT-MM to a mixture of carboxylic acids and an ammonia source in methanol, 2-propanol, or THF without any additives. The present method is quite practical in that aqueous ammonia or ammonium chloride/triethylamine can be used as an ammonia source. Methanol or 2-propanol is an ideal polar solvent because it is inexpensive, can be removed by rotary evaporator, and solubilizes many kinds of polar or nonpolar compounds.

A variety of mild one-step dehydrocondensation methods have been developed for synthesizing secondary and tertiary amides from carboxylic acids and amines.[1–3] In contrast, reports of a similar coupling between carboxylic acids and ammonia leading to the formation of primary amides are limited, and therefore, an efficient and convenient method is still being sought. The specific chemical and physical properties of ammonia constitute disadvantages for its use; a weak basicity (the pK_a value of the conjugate acid is 9.2), a low boiling point ($-33\,^{\circ}C$; it is gaseous at ordinary temperatures and pressures), and high water solubility. Since dehydrocondensation is generally conducted in a less polar aprotic solvent under dry conditions, sources of ammonia in the form of a gas, an aqueous solution, or a polar salt would not be suitable here. In traditional thermal methods for direct conversion of carboxylic acids into primary amides, a mixture of the acids and ammonia or its derivatives are heated at high temperature (around $200\,^{\circ}C$) for several hours.[4–7] Activated derivatives of carboxylic acids, such as acid chlorides, acid anhydrides, or activated esters reportedly undergo coupling even with aqueous ammonia.[4,8–13] Unless the activated acid-derivatives are commercially available, a separate step is required for their preparation.

Wang and McMurray reported a simple and more practical method that uses a combination of ammonium chloride (NH_4Cl), DIPEA, HOBt, and typical peptide coupling agents (PyBOP, HBTU, EDCA, and DCC).[14,15] Recently, HOTT or TOTT were reported as being more efficient agents that can be used under similar conditions.[16] Since these reagents enable the activation of carboxylic acid in the presence of ammonia, the reaction procedure is very simple. The former reaction requires expensive HOBt as an additive while the latter does not. The solvent employed in both the reactions is DMF which however is not very easy to use because of its high boiling temperature ($153\,^{\circ}C$). In this letter, we report a simple, inexpensive, and mild method for preparation of primary amides from carboxylic acid that employs 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride (DMT-MM).

We previously showed that a new coupling reagent, DMT-MM, was useful for the preparation of secondary and tertiary amides.[17–19] The coupling reaction between various carboxylic acids and primary or secondary amines occurs readily at room temperature in water, alcohol, and other aqueous solvents as well as in common aprotic organic solvents, such as THF and dichloromethane.[17–20] In early studies, we attempted to prepare primary amides using aqueous ammonia solution, readily available from commercial sources, in water. We were disappointed, however, that, the reaction of 3-phenylpropionic acid (**1a**) gave only a moderate yield (63%) of the desired primary amide **2a**, even though an excess of ammonia (2.5 equiv) was used, as shown in eq 1. We presume this result was due to the weak nucleophilicity of ammonia compared to primary and secondary amines. In addition, strong hydration of ammonia in water may depress the reaction. As a result, hydrolysis of the activated acyl intermediate (acyl triazine) would competitively take place. Thus, DMT-MM seemed to be unsuitable for preparation of primary amides.

After several years, we found that the yield of primary amides using DMT-MM was much improved by using a methanol solution of ammonia. As shown in eq 2, when an amino acid **1b** was treated with ammonia (3.0 equiv) dissolved in methanol and DMT-MM (1.5 equiv) in THF as a solvent, **2b** was obtained in 95% yield. Similarly, **1c** gave **2c** in 97% yields under the same conditions. Because hydrogen bonds formed in methanol are weaker than those in water,[21] ammonia in methanol may have the sufficient nucleophilicity to form primary amides. Encouraged by the result, we again attempted to establish a mild and practical method for the direct preparation of primary amides from carboxylic acids by DMT-MM. Preliminary reactions were performed in methanol with **1a** as a model substrate, and a commercially available methanol solution of ammonia was used. As shown in Table 1, Entry 1, treatment of a mixture of **1a** (1.0 equiv) and ammonia (1.5 equiv) with DMT-MM (1.2 equiv) in methanol for 4 h at room temperature gave **2a** in 90% yield. Since both methanol and ammonia can be readily removed by evaporation, the work-up procedure could be simple. We next

Table 1. Yield of **2a** when prepared in a methanol solvent using different sources of ammonia

Entry	Source of ammonia	Yield/%[a]
1	NH_3 in MeOH	90
2	NH_3 in H_2O	92
3	NH_4Cl/Et_3N	93

[a]Isolated yield.

examined aqueous ammonia, which is less expensive than a methanolic solution, under the same conditions, and found that a small amount of water in methanol did not affect the yield (Entry 2), which was in marked contrast to the earlier results when the reaction was conducted in water (eq 1). The use of ammonia solutions, however, may be inconvenient in a practical sense because of their volatility (uncertainties in ammonia concentration) in addition to their irritating and toxic properties. Thus, we examined in situ generation of ammonia by a combination of NH_4Cl and triethylamine (Et_3N),[22] and obtained the best result (93%) with this system (Entry 3).[23]

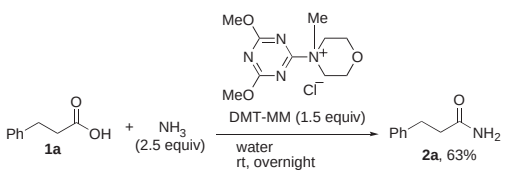
We prepared primary amides from various carboxylic acids by using the system of DMT-MM/NH_4Cl/Et_3N. As shown in Table 2, α,β-unsaturated carboxylic acid and sterically hindered pivalic acid were converted into the corresponding primary amides **2d** and **2e** in good yields. Aromatic carboxylic acids possessing either an electron-donating or an electron-withdrawing group underwent the reaction (Entries 3–5). The conventional thermal reactions would be inapplicable to compounds susceptible to thermal decomposition, such as *t*-butoxycarbonyl group (Boc). Our reaction is applicable to amino acids with a Boc group for N-protection, giving high yields (Entry 6 and eq 2). Dicarboxylic acids, which are soluble in methanol but almost insoluble in common less polar organic solvents when they are mixed with ammonia, can readily undergo the reaction (**2j** was obtained in 74% yield). When reaction of 1,4-benzenedipropanoic acid was conducted in methanol, the desired diamide **2k** was formed in a low yield (47%) along with a half methyl ester (monoamide–monoester). The yield of **2k** was found to increase up to 87% by conducting the reaction in 2-propanol.

Table 2. Preparation of primary amides by a combination of NH_4Cl and Et_3N with DMT-MM in MeOH[a]

Entry	Primary amide	Time/h	Yield/%[b]
1	$PhCH{=}CHCONH_2$ (**2d**)	4	81
2	*t*-$BuCONH_2$ (**2e**)	5	89
3	$PhCONH_2$ (**2f**)	5	84
4	4-NO_2–$C_6H_4CONH_2$ (**2g**)	7	77
5	4-MeO–$C_6H_4CONH_2$ (**2h**)	4	80
6[c]	Boc–Leu–NH_2 (**2i**)	5	93

[a]Reactions were performed with 1.0 equiv of carboxylic acid, 1.5 equiv of NH_4Cl, 1.5 equiv of Et_3N, and 1.5 equiv of DMT-MM. [b]Isolated yield. [c]This reaction was carried out using 1.8 equiv of Et_3N.

In conclusion, we have developed a mild and simple method for the direct preparation of primary amides from carboxylic acids and ammonia by using DMT-MM. The reaction can be conducted by a convenient one-step procedure in which a condensing agent is simply added to a mixture of acids and ammonia. An alcohol such as methanol, ethanol, or 2-propanol solubilizes many kinds of polar or nonpolar compounds and is readily removed by rotary evaporator. Since the reagents, methanol, Et_3N, NH_4Cl, and aqueous ammonia utilized here are cheap, and DMT-MM can be prepared at a low cost, the present reaction is economically favorable.



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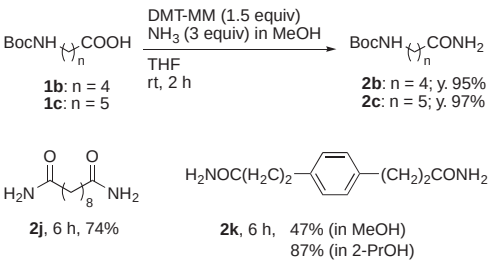

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15 Abbreviations used in this report are as follows: DIPEA: diisopropylethylamine, HOBt: 1-hydroxybenzotriazole, PyBOP: *O*-(benzotriazol-1-yl)tris(pyrrolidino)phosphonium hexafluorophosphate, HBTU: *O*-(benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate, EDCA: 1-ethyl-3-(3′-dimethylaminopropyl)-carbodiimide hydrochloride, DCC: dicyclohexylcarbodiimide, HOTT: *S*-(1-oxide-2-pyridinyl)-1,1,3,3-tetramethyluronium hexafluorophosphate, TOTT: *S*-(1-oxide-2-pyridinyl)-1,1,3,3-tetramethyluronium tetrafluoroborate.

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22 Nájera et al. reported that use of Et_3N instead of DIPEA decreased the yield; see ref. 16.

23 Typical experimental procedure (Table 1, Entry 3): DMT-MM (66.4 mg, 0.24 mmol) was added to a stirred solution of NH_4Cl (16.0 mg, 0.30 mmol), Et_3N (30.4 mg, 0.30 mmol), and 3-phenylpropionic acid (30.1 mg, 0.20 mmol) in methanol (2 mL). The resulting mixture was stirred at room temperature for 4 h. After the solvent was removed by rotary evaporator, the resulting residue was dissolved in CH_2Cl_2, and washed successively with saturated sodium carbonate, water, and brine, and dried over $MgSO_4$. The crude product was purified by preparative TLC (AcOEt) to give the corresponding 3-phenylpropanamide (27.7 mg, 93%) as a colorless crystal.

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