Tetrahedron: *Asymmetry* 28 (2017) 1690–1699

Contents lists available at ScienceDirect

Tetrahedron: *Asymmetry*

journal homepage: www.elsevier.com/locate/tetasy

Amidation of carboxylic acids via the mixed carbonic carboxylic anhydrides and its application to synthesis of antidepressant (1*S*,2*R*)-tranylcypromine

Tetsuya Ezawa, Yuya Kawashima, Takuya Noguchi, Seunghee Jung, Nobuyuki Imai *

Faculty of Pharmacy, Chiba Institute of Science, 15-8 Shiomi-cho, Choshi, Chiba 288-0025, Japan

ARTICLE INFO

Article history:
Received 15 July 2017
Revised 13 September 2017
Accepted 1 October 2017
Available online 6 November 2017

ABSTRACT

Primary amidations of carboxylic acids **1** or **3** with NH_4Cl in the presence of $ClCO_2Et$ and Et_3N were developed to afford the corresponding primary amides in 22% to quantitative yields. Additionally, we have applied the amidation to the preparation of various amides containing hydroxamic acids and achieved the synthesis of (1*S*,2*R*)-tranylcypromine as an antidepressant medicine via Lossen rearrangement.

1. Introduction

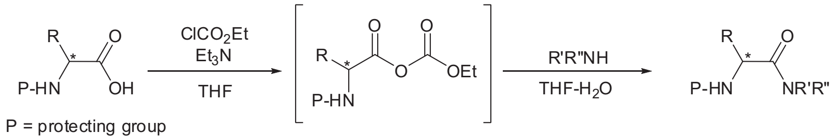
The amide group is one of the most important functional groups in organic chemistry. It is widely found in various compounds such as proteins, bioactive substances, drugs, and agrochemicals.[1] Therefore, development of convenient amidations has been a challenging subject in organic chemistry. Direct amidations of carboxylic acids with amines involving dehydration proceeds at high temperatures, but the conditions are not suitable for most functional molecules.[2] Generally, amides are prepared by reactions of activated carboxylic acids, such as acyl halides, acyl imidazole, mixed anhydrides, and esters with amines or by reductions of acyl azides and hydrazides.[3] The reagents, such as thionyl chloride,[4a] oxalyl chloride,[4b,4c] dicyclohexylcarbodiimide (DCC),[4d,4e] diphenylphosphoryl azide (DPPA),[4f] carbonyldiimidazole (CDI),[4g] alkyl chloroformate,[4h] 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride (DMT-MM),[4i,4j] and *N*-[1-(cyano-2-ethoxy-2-oxoethylidenaminooxy)dimethylamino(morpholino)] uronium hexafluorophosphate (COMU)[4k] have often been used for activation of carboxylic acids. However, it has mainly been reported that secondary and tertiary amides are prepared using these reagents. The synthesis of primary amide is limited due to disadvantages of using ammonia such as low nucleophilicity, toxicity, and gas under ordinary conditions. On the other hand, ammonium chloride is very useful as an ammonia source because it is easy to handle, inexpensive, and safe. Nezhad et al. have reported the efficient primary amidation of carboxylic acids activated by tosyl chloride (TsCl) and 4.0 equiv of silica-supported ammonium chloride.[5] Bhanage et al. achieved the amidation of *tert*-butyl peroxybenzoate (TBPB) with ammonia to afford the corresponding primary amide with a stoichiometric amount of *tert*-butyl hydroperoxide as the by-product.[6] Furthermore, the hydration of nitriles in the presence of acids,[7a–c] bases,[7d,7e] the transition metal[7f–h] and the rearrangement of oximes using transition metal catalysts[8] have been developed as preparations for primary amides. Recently, interesting synthetic methods such as direct transformations of ethylarenes,[9] methyl ketones,[10] carbinols[10] via tandem Lieben-Haller-Bauer reactions, aminocarbonylations of aryl halides with NH_4Cl and $Co_2(CO)_8$ as a carbonyl source,[11] and amidations of ester using magnesium nitride (Mg_3N_2) as an ammonia source[12] have also been reported. Excess amounts of ammonia source, high temperatures, toxic reagents such as transition metals, and/or complicated procedures are required for the synthesis of primary amides.

Recently, we reported the synthesis of primary amides from general carboxylic acids, *N*-protected α-amino acids, and *N*-protected dipeptides via the mixed carbonic carboxylic anhydrides.[13] Herein, we describe in detail the synthesis of various amides from carboxylic acids with ammonium chlorides and amines in the presence of water (Scheme 1). Our method is convenient and green because of inexpensive reagents, mild conditions, and safe byproducts, such as triethylamine hydrochloride, carbon dioxide, and the corresponding alcohols. Furthermore, its application to the synthesis of (1*S*,2*R*)-(+)-*N*-Cbz-tranylcypromine **9** via Lossen rearrangement is also reported.

---

* Corresponding author. Tel.: +81 479 30 4610.
E-mail address: nimai@cis.ac.jp (N. Imai).

https://doi.org/10.1016/j.tetasy.2017.10.015
0957-4166/



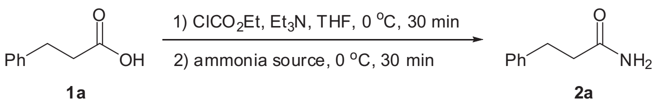
Scheme 1. Amidation via the mixed carbonic carboxylic anhydrides.

2. Results and discussion

In a preliminary investigation, we optimized the conditions of an ammonia source (NH_3, NH_4OH, NH_4Cl, and $MeCO_2NH_4$), and the results are shown in Table 1. Primary amidation with NH_3/MeOH and NH_4OH/H_2O via the mixed carbonic carboxylic anhydride in tetrahydrofuran (THF) afforded 3-phenylpropanamide **2a** in good yields (entries 1 and 2). Excellent yields were obtained by the reactions of **1a** with NH_4Cl and $MeCO_2NH_4$ (entries 3 and 4). On the basis of these results, cost, and safety, we selected NH_4Cl as the optimal ammonia source.

The results of the primary amidation of several types of carboxylic acids **1a**-**1o** with NH_4Cl in the presence of $ClCO_2Et$ and Et_3N are collected in Table 2. The reaction of cinnamic acid **1b** as a conjugated carboxylic acid afforded the corresponding primary amides **2b** in 79% yield (entry 2). 4-Methoxycinnamic acid **1c** containing an electron donating group reacted with NH_4Cl to give the corresponding primary amide **2c** in 33% yield (entry 3). The reaction of pivalic acid **1d** proceeded easily to afford the corresponding primary amide **2d** in excellent yield despite a bulky *tert*-butyl group on **1d** (entry 4). Although benzamide **2e**, 4-nitrobenzamide **2f**, and acetylsalicylamide **2g** were synthesized from benzoic acid **1e**, 4-nitrobenzoic acid **1f**, and acetylsalicylic acid **1g** in 64%, 92%, and 56% yields, respectively (entries 5–7), the yield of 4-methoxybenzamide **2h** was low (entry 8). It is suggested that the carbonyl carbon on the mixed carbonic anhydride of 4-methoxybenzoic acid **1h** is deactivated by the strong electron donating effect of the methoxy group on the aromatic ring. The amidation of **1h** with NH_4Cl via activation by $ClCO_2$*i*-Bu was carried out to afford the corresponding amide **2h** in 22% yield (entry 8). The reactions of heteroaromatic carboxylic acid **1i**-**1o** with NH_4Cl were also examined. Picolinic acid **1i**, nicotinic acid **1j**, and isonicotinic acid **1k** were converted into the corresponding primary amides **2i**-**2k** in 97%, 84%, and 95% yields, respectively. The low electron density of the pyridine ring contributes to these excellent yields (enrties 9–11). The primary amides **2l**-**2o** were prepared from the corresponding carboxylic acids **1l**-**1o** containing electron-rich heteroaromatic rings in moderate yields due to the increasing electron density of the carbonyl carbons. (entries 12–15). Katritzky et al. reported the amidation of carboxylic acid activated by 1-(methanesulfonyl)benzotriazole and Et_3N with ammonium hydroxide, in which the primary amides **2f** and **2i**-**2l** were obtained in quantitative yields.[3b] Moreover, the syntheses of the primary amides **2a**, **2b**, **2d**, **2e**, and **2h** via the activation of carboxylic acids with DMT-MM were achieved in excellent yields by Kunishima et al.[4j] The yields of the primary amides **2a**, **2b**, **2d**, **2f**, and **2i**-**2k** obtained by our method are similar except for the primary amides **2e**, **2h**, and **2l**. It is suggested that the electron density of the expected active carbonyl groups is similar to that of the ethoxycarbonyl group on the corresponding mixed carbonic carboxylic anhydrides in the cases of entries 3, 5, 7, 8, and 12–15.

Table 1
Primary amidation of 3-phenylpropanoic acid **1a**[a]



Entry	Ammonia source	Yield[e]/%
1	NH_3/MeOH[b]	85
2	NH_4OH/H_2O[c]	85
3	NH_4Cl/H_2O[d]	96
4	$MeCO_2NH_4/H_2O$[d]	97

[a] All reactions were carried out with 0.50 mmol of **1a**, 0.70 mmol of $ClCO_2Et$, 1.5 mmol of Et_3N, and 0.75 mmol of ammonia source.
[b] 2.0 mol/L solution in MeOH was used.
[c] 28% aqueous solution was used.
[d] 1.0 M aqueous solution was used.
[e] Isolated yield.

Next, we synthesized the primary amides **4a-4n** from the corresponding *N*-protected α-amino acids **3a-3n** without racemization under the optimized conditions and these results are shown in Table 3. First, we checked the effect of protecting groups such as carboxybenzyl (Cbz), 9-fluorenylmethoxycarbonyl (Fmoc), and *tert*-butoxycarbonyl (Boc). The mixed carbonic carboxylic anhydrides of Cbz-L-Phe-OH **3a**, Fmoc-L-Phe-OH **3b**, and Boc-L-Phe-OH **3c** reacted with NH_4Cl to give the corresponding primary amides **4a**, **4b**, and **4c** in excellent yields, and no racemization was observed (entries 1–3). The primary amide **4d** was prepared from Cbz-L-Val-OH **3d** in 93% (entry 4). The reactions of Fmoc-L-Val-OH **3e** and Boc-L-Val-OH **3f** afforded the corresponding primary amides **4e** and **4f** in 98% and 98% yields with >99% ee under the conditions, respectively (entries 5 and 6). Furthermore, **4g**-**4i** were obtained in excellent yields by the reactions of Cbz-L-Met-OH **3g**, Fmoc-L-Met-OH **3h**, and Boc-L-Met-OH **3i** containing a sulfide group (entries 7–9). Cbz-L-Ala-OH **3j** was converted to the corresponding primary amide **4j** in good yield with >99% (entry 10). The amidation of Cbz-L-Gln-OH **3k** with NH_4Cl under the conditions gave the corresponding primary amide **4k** in 74% yield, but the enantiomeric excess of **4k** was not determined by HPLC analysis because of the low solubility of **4k** in the eluent (entry 11). The low solubility of **3k** possessing the hydrophilic side chain in THF gave a lower yield of **4k** compared to the other primary amides. Cbz-L-Leu-NH_2 **4l** as a branched α-amino acid was synthesized from Cbz-L-Leu-OH **3l** in good yield and with >99% ee (entry 12). The yield of the primary amide **4m** was slightly lower due to the bulky side chain (entry 13). Boc-*O*-Bn-L-Ser-OH **3n** containing a hydrophilic side chain was condensed with NH_4Cl via the mixed carbonic carboxylic anhydride to afford the corresponding primary amide **4n** in 87% yield, and no racemization was observed in the reaction (entry 14). The results of the primary amidation of D-α-amino acids **3a′**-**3n′** with NH_4Cl were similar to those of the corresponding L-forms (see Experimental).

Hydroxamic acid is an important building block for many organic compounds. It is generally used as a starting material for preparation of amines, ureas, and carbamates via Lossen rearrangement. For the preparation of hydroxamic acids, there are a variety of reported reactions of carboxylic acids with toxic hydroxylamines using alkyl chloroformate,[14] with hydroxylamine hydrochlorides in the presence of expensive coupling reagents such as 2,4,6-trichloro[1,3,5]-triazine (cyanuric chloride, TCT)[15] and ethyl 2-cyano-2-(4-nitrophenylsulfonyloxyimino)acetate (4-NBsOXY),[16]