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Convenient synthesis of acetaminophen analogues containing α-amino acids and fatty acids via their mixed carbonic carboxylic anhydrides in aqueous organic solvent

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ABSTRACT

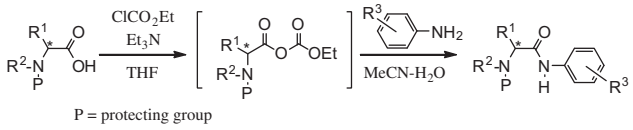
Acetaminophen analogues containing α-amino acid and fatty acids were easily synthesized in 77–99% yields from the corresponding mixed carbonic carboxylic anhydrides of α-amino acid and fatty acids using aniline derivatives in aqueous MeCN.

We have recently reported convenient syntheses of dipeptides and primary amides via mixed carbonic carboxylic anhydrides.[1] In these reports, we have showed that primary amines and ammonia work as an active nucleophile on the reaction of mixed carbonic carboxylic anhydrides in aqueous organic solvent. Aniline derivatives are less active than ammonia as a nucleophile, so it is very exciting to examine the reactivity of aniline derivatives on the reaction of mixed carbonic carboxylic anhydrides in aqueous organic solvent.[2] Acetaminophen, the active species of phenacetin, is a commercially available medicine used as an antipyretic and analgesic and it has been reported that acetaminophen is partly hydrolyzed in the blood and that the produced 4-aminophenol is reacted with arachidonic acid in the brain.[3] Namely, it is suggested that the real active species is N-(4-hydroxy)phenylarachidonamide. Then, it is also well known that the liver-toxicity of acetaminophen is derived from the oxidation of acetaminophen by cytochrome P-450, followed by addition of macromolecules.[4] It is interesting to design acetaminophen analogues which are stable on oxidation by cytochrome P-450.

Herein, we describe synthesis of acetaminophen analogues containing α-amino acids and fatty acids by the reactions of carbonic carboxylic anhydrides of α-amino acids and fatty acids with aniline derivatives in aqueous organic solvent (Scheme 1).

In a preliminary investigation, the reaction of 3-phenylpropionic acid (**1**) with 1.1 equiv of 4-chloroaniline (**2a**) in the presence of 1.4 equiv of $ClCO_2Et$ and 1.1 equiv of Et_3N in aqueous tetrahydrofuran (THF) afforded N-(4-chlorophenyl)-3-phenylpropanamide (**3a**) in 57% yield along with the by-product **4a** in 34% yield based on **2a** as indicated in entry 1 of Table 1. Effect of the quantity of **2a**, ethyl chloroformate and triethylamine on the amidation of **1** in aqueous THF at 0 °C for 1.5 h was examined, and the results are collected in Table 1. The best result (88% yield, entry 3) among them was obtained using 1.1 equiv of **2a**, 1.1 equiv of $ClCO_2Et$ and 1.1 equiv of Et_3N.

Next, effect of solvent on the amidation of **1** at 0 °C for 24 h was checked, and the results are summarized in Table 2. The reactions of **1** in aqueous THF, 1,4-dioxane, acetone, MeCN, EtOH or MeOH afforded the corresponding primary amide **3a** in 92%, 19%, 89%, 96%, 50% and 13% yields, respectively. The best yield (96%) was obtained when the reaction was carried out in aqueous MeCN.



Scheme 1.

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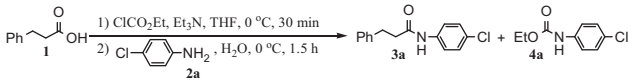
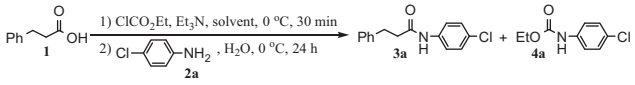
Table 1
Effect of the quantity of 4-chloroaniline (**2a**), ethyl chloroformate and triethylamine on the amidation of 3-phenylpropanoic acid (**1**)[a]



Entry	$ClCO_2Et$ (equiv)	Aniline (equiv)	Et_3N (equiv)	Yield of **3a**[b] (%)	Yield of **4a**[b] (%)
1	1.4	1.1	1.1	57	34
2	1.1	1.1	1.5	83	2
3	1.1	1.1	1.1	88	13
4	1.05	1.1	1.1	77	9
5	1.05	1.05	1.1	74	11
6	1.0	1.05	1.1	79	5
7	1.0	1.0	1.1	83	4

[a] All reactions were carried out with 1.0 mmol of **1** in 20 mL of THF. After stirring for 30 min at 0 °C, 1.5 mL of water and **2a** were added at 0 °C to the reaction mixture.
[b] Isolated yield.

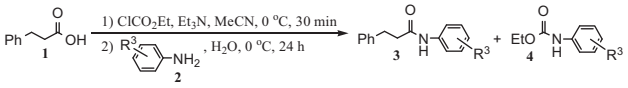
Table 2
Effect of solvent on the amidation of 3-phenylpropanoic acid (**1**)[a]



Entry	Solvent	Yield of **3a**[b] (%)	Yield of **4a**[b] (%)
1	THF	92	4
2	1,4-Dioxane	19	8
3	Acetone	89	3
4	MeCN	96	Trace
5	EtOH	50	35
6	MeOH	13	70

[a] All reactions were carried out with 1.0 mmol of **1**, 1.1 mmol of Et_3N and 1.1 mmol of $ClCO_2Et$ in 20 mL of solvent. After stirring for 30 min at 0 °C, 1.5 mL of water and 1.1 mmol of **2a** were added at 0 °C to the reaction mixture.
[b] Isolated yield.

Table 3
Reaction of 3-phenylpropanoic acid (**1**) with aniline derivatives **2**[a]



Entry	R^3	**2**	Yield of **3**[b] (%)	Yield of **4**[b] (%)
1	4-Cl	**2a**	96	Trace
2	4-F	**2b**	97	0
3	2,3,4,5,6-F5	**2c**	67	34
4	4-EtO_2C	**2d**	70	0
5	4-O_2N	**2e**	65	0
6	3,5-$(O_2N)_2$	**2f**	30	0
7	2,4-$(O_2N)_2$	**2g**	0	0
8	H	**2h**	94	Trace
9	4-Me	**2i**	95	1
10	4-HO	**2j**	92	3
11	2-EtO	**2k**	89	Trace
12	4-EtO	**2l**	98	2

[a] All reactions were carried out with 1.0 mmol of **1**, 1.1 mmol of Et_3N and 1.1 mmol of $ClCO_2Et$ in 20 mL of MeCN. After stirring for 30 min at 0 °C, 1.5 mL of water and 1.1 mmol of **2** were added at 0 °C to the reaction mixture.
[b] Isolated yield.

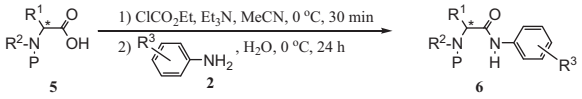
Then, the amidations of **1** with several kinds of aniline derivatives **2a**–**2l** via the corresponding mixed carbonic carboxylic anhydride were carried out in aqueous MeCN, and the results are showed in Table 3. 3-Phenylpropanoic acid (**1**) was reacted with 4-fluoroaniline (**2b**) containing an electron-withdrawing group to afford the corresponding amide **3b** in 97% yield (entry 2). The reactions of **1** with pentafluoroaniline (**2c**), ethyl 4-aminobenzoate (**2d**), 4-nitroaniline (**2e**), and 3,5-dinitroaniline (**2f**) containing an even stronger electron-withdrawing group afforded the corresponding amides **3c**, **3d**, **3e** and **3f** in 67%, 70%, 65% and 30% yields, respectively (entries 3–6). In the case of 2,4-dinitroaniline (**2g**), the reaction did not proceed as indicated in entry 7. The reaction of **1** with aniline (**2h**) easily proceeded to afford N-phenyl-3-phenylpropanamide (**3h**) in 94% yield, which was similar to the case of **2a**. 4-Methylaniline (**2i**), 4-aminophenol (**2j**), 2-ethoxyaniline (**2k**) and 4-ethoxyaniline (**2l**) containing an electron-donating group reacted to afford the corresponding amides **3i**–**3l** in excellent yields (entries 9–12).

Furthermore, the amidations of N-protected α-amino acids **5aL**–**5gL** and **5aD**–**5gD** with 4-ethoxyaniline (**2l**), 2-ethoxyaniline (**2k**) and 4-aminophenol (**2j**) were carried out in aqueous MeCN, and the results are collected in Table 4. The reactions of Cbz-L-Phe-OH (**5aL**) with **2l**, **2k** and **2j** using $ClCO_2Et$ and Et_3N afforded Cbz-L-Phe-NHC_6H_4-4-OEt, Cbz-L-Phe-NHC_6H_4-2-OEt and Cbz-L-Phe-NHC_6H_4-4-OH in good to excellent yields (79–91%, entries 1, 3 and 5) as single enantiomers, respectively, by high-pressure liquid chromatography (HPLC) analysis using Chiralcel OD in all cases.[5] Cbz-D-Phe-OH (**5aD**) reacted with **2l**, **2k** and **2j** in the similar conditions to afford Cbz-D-Phe-NHC_6H_4-4-OEt, Cbz-D-Phe-NHC_6H_4-2-OEt and Cbz-D-Phe-NHC_6H_4-4-OH in good to excellent yields (77–91%, entries 2, 4 and 7) as D-form enantiomers, respectively. Various N-protected α-amino acids were conveniently converted to their corresponding acetaminophen analogues of α-amino acids in 82–99% yields without racemization as indicated in entries 8–19.

Finally, the reactions of fatty acids **7a**–**7f** with 4-ethoxyaniline (**2l**) were carried out, and the results are summarized in Table 5. In all cases, the reactions were easily proceeded in aqueous MeCN to afford the corresponding acetaminophen analogues **8a**–**8f** of fatty acids in excellent yields.

In conclusion, we have found that acetaminophen analogues **3**, **6** and **8** were prepared in 65–99% yields from the corresponding

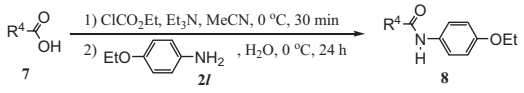
Table 4
Synthesis of acetaminophen analogues **6** containing α-amino acids **5**[a]



Entry	P	R^1	R^2	5	R^3	Yield[b] (%)	% ee[c]	Retention time (min)
1	Cbz	$PhCH_2$ (L)	H	**5aL**	4-EtO	79	>99	14.6
2	Cbz	$PhCH_2$ (D)	H	**5aD**	4-EtO	77	>99	15.9
3	Cbz	$PhCH_2$ (L)	H	**5aL**	2-EtO	91	>99	28.1
4	Cbz	$PhCH_2$ (D)	H	**5aD**	2-EtO	91	>99	51.3
5	Cbz	$PhCH_2$ (L)	H	**5aL**	4-HO	83	>99	35.9
6[d]	Cbz	$PhCH_2$ (L)	H	**5aL**	4-HO	83	>99	35.9
7	Cbz	$PhCH_2$ (D)	H	**5aD**	4-HO	83	>99	39.7
8	Cbz	Me_2CH (L)	H	**5bL**	4-EtO	94	>99	7.9
9	Cbz	Me_2CH (D)	H	**5bD**	4-EtO	96	>99	9.2
10	Cbz	Me (L)	H	**5cL**	4-EtO	82	>99	12.3
11	Cbz	Me (D)	H	**5cD**	4-EtO	87	>99	14.6
12	Cbz	$MeS(CH_2)_2$ (L)	H	**5dL**	4-EtO	85	>99	14.5
13	Cbz	$MeS(CH_2)_2$ (D)	H	**5dD**	4-EtO	87	>99	18.8
14	Cbz	$(CH_2)_3$ (L)		**5eL**	4-EtO	99	>99[e]	40.4
15	Cbz	$(CH_2)_3$ (D)		**5eD**	4-EtO	98	>99[e]	22.9
16	Boc	$PhCH_2$ (L)	H	**5fL**	4-EtO	88	>99	11.3
17	Boc	$PhCH_2$ (D)	H	**5fD**	4-EtO	93	>99	5.7
18	Fmoc	$PhCH_2$ (L)	H	**5gL**	4-EtO	82	>99[e]	36.1
19	Fmoc	$PhCH_2$ (D)	H	**5gD**	4-EtO	91	>99[e]	75.3

[a] All reactions were carried out with 0.50 mmol of N-protected α-amino acid **5**, 0.55 mmol of Et_3N and 0.55 mmol of $ClCO_2Et$ in 10 mL of MeCN. After stirring for 30 min at 0 °C, 0.75 mL of water and 0.55 mmol of aniline derivative **2** were added at 0 °C to the reaction mixture.
[b] Isolated yield.
[c] Determined by HPLC analysis with a 90:10 mixture of hexane and isopropanol as an eluent using Chiralcel OD (1.0 mL/min).
[d] 1.20 g (4.0 mmol) of Cbz-L-Phe-OH (**5aL**) was used.
[e] Chiralcel AD was used.

Table 5
Synthesis of acetaminophen analogues **8** containing fatty acids **7**[a]



Entry	R^4-CO_2H	7	Yield[b] (%)
1	Lauric acid (C_{12})	**7a**	97
2	Palmitic acid (C_{16})	**7b**	98
3	Oleic acid (C_{18-1})	**7c**	89
4	Linoleic acid (C_{18-2})	**7d**	93
5	Linolenic acid (C_{18-3})	**7e**	79
6	Arachidonic acid (C_{20-4})	**7f**	93

[a] All reactions were carried out with 1 equiv of fatty acid **7**, 1.1 equiv of Et_3N and 1.1 equiv of $ClCO_2Et$ in MeCN. After stirring for 30 min at 0 °C, water and 1.1 equiv of **2l** were added at 0 °C to the reaction mixture.
[b] Isolated yield.

carboxylic acids **1**, **5** and **7** using aniline derivatives **2** in aqueous MeCN and racemization does not proceed in our developed method. It is also noted that aniline derivatives **2** are more reactive with the mixed carbonic carboxylic anhydrides than water at 0 °C. Further investigations about this type of condensation for the preparation of various medicines are under way in our group.

References and notes

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4. Ohe, T. *Folia Pharmacol. Jpn.* **2009**, *134*, 338–341.
5. A typical procedure of the amidation of Cbz-L-Phe-OH (**5aL**) with 4-ethoxyaniline (**2l**) using $ClCO_2Et$ is as follows. To a solution of 150 mg (0.50 mmol) of **5aL** in 10 mL of MeCN, 53 μL (0.55 mmol, 1.1 equiv) of $ClCO_2Et$ and 77 μL (0.55 mmol, 1.1 equiv) of Et_3N were added at 0 °C. After stirring for 30 min at 0 °C, 0.55 mmol of **2l** and 0.75 mL of water were added at 0 °C to the colorless suspension. The mixture was stirred for 24 h at 0 °C, and 10 mL of 1.0 M aqueous solution of HCl was added at 0 °C to the mixure. The resulted colorless clear solution was extracted with 50 mL of EtOAc, washed with 5 mL of brine, 10 mL of 1.0 M aqueous solution of $NaHCO_3$, 5 mL of brine and dried over anhydrous $MgSO_4$. The crude product was chromatographed on silica gel with a 1:1 mixture of hexane and EtOAc to afford 155 mg (79% yield) of **6aL**. Compound **6aL**: colorless powder; ^1H NMR ($CDCl_3$): δ 1.39 (3H, t, J = 7.0 Hz, OCH_2CH_3), 3.09 (1H, dd, J = 7.8, 13.7 Hz, $CHCH_APh$), 3.21 (1H, dd, J = 5.6, 13.7 Hz, $CHCH_BPh$), 3.99 (2H, q, J = 7.0 Hz, OCH_2CH_3), 4.40–4.50 (1H, m, $CHCH_2Ph$), 5.11 (2H, s, OCH_2Ph), 5.44 (1H, br s, NH), 6.79, 7.19 (2H, 2H, d, d, J = 8.8, 8.8 Hz, C_6H_4), 7.18–7.34 (11H, m, $C_6H_5 \times 2$, NH).