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One-pot esterification and amidation of phenolic acids

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ABSTRACT

We developed a new one-pot reaction of phenolic acids to afford the corresponding esters and amides through acyl-protected and activated phenolic acid intermediates. The simultaneous protection/activation of phenolic acids with alkylchloroformates proceeded readily in the presence of DMAP at room temperature; subsequent addition of alcohols or amines afforded the corresponding esters or amides. The use of *iso*-butyloxycarbonyl as the protecting and activating group in the one-pot reactions afforded phenolic esters or amides in 91% average yield. As a practical example of this convenient synthesis, caffeic acid phenethyl ester (CAPE) was readily synthesized from commercially available caffeic acid and phenethyl alcohol in 95% yield, and an isotopomer of CAPE, [3,10-$^{13}C_2$]CAPE, was synthesized in 91% yield from [3-^{13}C]caffeic acid and 2-[1-^{13}C]phenethyl alcohol. This method may be useful for the convenient esterification and amidation of diverse phenolic acids.

1. Introduction

Phenolic acids including hydroxycinnamic acids and hydroxybenzoic acids are ubiquitous in the plant kingdom. Phenolics readily scavenge radical species by forming resonance-stabilized phenoxy radicals, which are responsible for their potent antioxidant[1,2] and radical-scavenging capabilities.[3,4] Recently, phenolic acids and their derivatives are shown to reduce the risk of chronic diseases.[5–9] The esterification and amidation of phenolic acids are practical techniques to improve their solubility and emulsification properties as well as enhance their antioxidant and antidiabetic activities.[10–16] The amidation of selected hydroxycinnamic acids and hydroxybenzoic acids improved their antioxidant activities.[14] The serine esters of phenolic acids exhibited superior antioxidative activity in heterogeneous systems.[15] The amides of ferulic acid with alkyl or cyclic alkyl amines promoted insulin release in *in vitro* experiments.[16] The conversions of phenolic acids to the corresponding esters or amides are generally carried out by three or four synthetic steps: (i) protection of the phenolic hydroxyl group(s), (ii) activation of the carboxylic acid group, (iii) condensation with alcohols or amines, and (iv) deprotection of the phenolic hydroxyl group(s).[15,16] More convenient alternative methods have also been reported. For example, thermally stable phenolic acid esters have been synthesized in one step using an acidic catalyst such as thionyl chloride ($SOCl_2$) under reflux.[17,18] One-step low-temperature (−78 °C) esterification using boron trichloride has been reported.[19] However, these methods suffered from low yields of phenolic acid esters. In a short-step amidation without protecting phenolic hydroxyl groups, the yields were mostly <60%.[17,20] Phenolic acids can also be enzymatically esterified or amidated in one step.[20,21] However, these methods are effective for specific phenolic acids only, particularly when a longtime reaction can be allowed. Thus, a widely applicable, convenient, and high-yield alternative method is still needed for the synthesis of phenolic acid esters and amides. In this paper, we report a new one-pot convenient method for the esterification/amidation of phenolic acids to their esters or amides.

Caffeic acid phenethyl ester (CAPE), which is one of the most effective natural phenolic acid derivatives, exhibits significant anticancer[22] and anti-β-amyloid activities[23] *in vitro* caused by the inhibition of transcription factor NF-κB.[24,25] CAPE was first isolated from propolis, which is a mixture of gathered leaf buds and secretions of honey bees, as a defensive barrier for beehive.[26] The *in vivo* dynamics of CAPE after the oral administration have been studied for practical use.[27] Recently, the accurate mass spectrometric determination of a phenolic compound *in vivo* has been

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reported using the corresponding isotopomer as the internal standard.[28] An isotopomer was also used as the labeled compound for the *in vivo* dynamics analysis.[29] An isotopomer of CAPE is an ideal internal standard and a metabolic tracer. In general, an isotopomer is chemically synthesized and labeled with a stable isotope of ^{13}C. A high-yield method is needed for the synthesis of ^{13}C-labeled compounds because of the expensiveness of the labeled compounds. As a practical example of our convenient developed method, the isotopomers of CAPE were synthesized from ^{13}C-labeled caffeic acid and 2-phenethyl alcohol in excellent yields.

2. Results and discussion

To develop a convenient method to obtain phenolic acid esters and amides, we initially protected the phenolic hydroxyl group by Boc, which has been used extensively as a protecting group in peptide chemistry.[30] Di-*tert*-butyl dicarbonate ($(Boc)_2O$, 1.2 equiv) was reacted with ferulic acid in the presence of 0.1 equiv of DMAP as the catalyst and 1.0 equiv of triethylamine (TEA) as the base. After reacting for 2 h at 0 °C, the Boc-protected ferulate, (*E*)-4-*tert*-butoxycarbonyloxy-3-methoxycinnamic acid (**1**, Fig. 1), was obtained in 60–70% yields in several synthetic experiments. In these reactions, a by-product was formed in 10–20% yields. From the ^1H and ^{13}C NMR analyses, the structure of the by-product was established to be *tert*-butyl (*E*)-4-*tert*-butoxycarbonyloxy-3-methoxy-cinnamate (**2**, Fig. 1). The carboxylic acid group of **1** may have reacted with $(Boc)_2O$ to form a mixed anhydride followed by the reaction of the mixed anhydride with *tert*-butyl alcohol liberated from $(Boc)_2O$ to afford *tert*-butyl ester **2**. Therefore, we synthesized the mixed anhydride of ferulic acid with Boc. Ferulic acid was reacted with 2.2 equiv of $(Boc)_2O$ in the presence of 0.05 equiv of DMAP and 1.0 equiv of TEA at −15 °C for 2 h, and (*E*)-4-*tert*-butoxycarbonyloxy-3-methoxycinnamic mono-*tert*-butyl carbonic anhydride (**3a**) was obtained as a white crystal in 82% yield. The reaction of **3a** with *tert*-butyl alcohol afforded **2**.

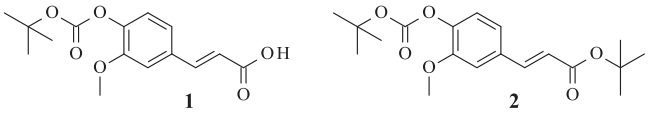
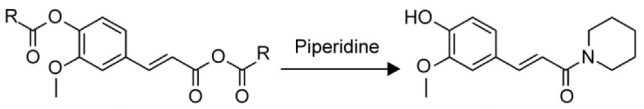


Fig. 1. Structures of compound **1** and **2**.

The simultaneous protection/activation of ferulic acid to form **3a** can be utilized for a high-yield convenient synthesis of phenolic acid derivatives by reducing a synthetic step. Therefore, selected protected ferulic acid mixed anhydrides were prepared to optimize the protection/activation condition. Table 1 shows the results of the preparations of protected ferulic acid monoalkyl carbonate mixed anhydride and their conversions to the corresponding piperidine amides. Compounds **3b**–**h** were synthesized using monoalkyl chloroformates or acid chlorides under the similar conditions as for **3a**. The protected ferulic acid mixed anhydrides were obtained in excellent yields, except unstable **3h**. No by-product such as **2** was formed in the reaction using the monoalkyl chloroformates or acid chlorides. After the reaction, the mixed anhydrides were obtained as almost pure products simply by filtration to remove triethylamine hydrochloride precipitate and evaporation to remove the solvent. All the obtained products except **3c** and **3e** were recrystallized. Usually, the isolation and crystallization of anhydrides are difficult because of the instability at room temperature. The phenolic acid mixed anhydrides are easy to use because of their stable nature.

Table 1
Synthesis of protected-activated ferulic acids[a] and subsequent amide formation with piperidine



3 4

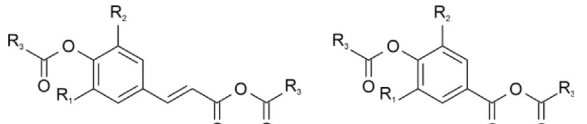
R	Yield %	
	3	**4**[b]
$-OC(CH_3)_3$	82[b] (**3a**)	98
$-OCH_2CH(CH_3)_2$	99[b] (**3b**)	97
$-OCH_2CH_2CH_2CH_3$	99 (**3c**)	94
$-OCH_2CH_2CH_3$	97[b] (**3d**)	90
$-OCH_2CH_3$	96 (**3e**)	73
$-OCH_3$	90[b] (**3f**)	64
$-C(CH_3)_3$	99[b] (**3g**)	0
$-CH_3$	20[b] (**3h**)	0

[a] Reactant **3a**: $(Boc)_2O$, **3b**–**f**: alkyl chloroformates, **3g, h**: acid chlorides.
[b] Crystallized compounds.

Table 1 also shows the yields of (*E*)-*N*-feruloyl piperidine (**4**) obtained from the reaction of **3a**–**h** with piperidine. Urethane-type protecting groups on the phenolic hydroxyl group of **3a**–**f** are cleaved with nucleophilic bases as reported previously.[30] Therefore, the amidation and deprotection could be carried out at once using excessive amounts of piperidine, and **4** was obtained in excellent yields from **3a**–**c**. The yield of **4** from **3d**–**f** improved when the bulkiness of the acyl side chain was increased, even though the reactions of **3g** and **3h** with piperidine did not afford **4**. In the reaction of **3h** with the smallest acyl group, only ferulic acid was obtained. The bulkiness of the acyl group on the protected ferulic acid mixed anhydrides was important to afford **4**. In the reaction of **3g**, the amidation occurred quantitatively; however, the deprotection of the pivaloyl group with piperidine did not proceed. Collectively, $(Boc)_2O$ and *iso*-butyl chloroformate (*i*BocCl) were concluded to be favorable protecting/activating reactants to synthesize the phenolic acid piperidine amides.

Based on the results shown in Table 1, *tert*- and *iso*-butyl carbonate mixed anhydrides were synthesized from selected phenolic acids (Table 2). The protected mixed anhydrides of

Table 2
Synthesis of *O*-protected phenolic mono-*tert* or *iso*-butyl carbonic anhydrides using $(Boc)_2O$ or *i*BocCl[a,b]



5a, 5b, 6a, 6b, 7a, 7b 8 - 11

	R_1	R_2	R_3	Yield (%)
5a[c]	−H	−H	−O-*t*Bu	81
5b[c]	−H	−H	−O-*i*Bu	99
6a[c]	−OMe	−OMe	−O-*t*Bu	70
6b[c]	−OMe	−OMe	−O-*i*Bu	99
7a	−H	−OCOO-*t*Bu	−O-*t*Bu	72
7b	−H	−OCOO-*i*Bu	−O-*i*Bu	96
8	−H	−H	−O-*i*Bu	97
9	−H	−OMe	−O-*i*Bu	97
10[c]	−OMe	−OMe	−O-*i*Bu	96
11	−OCOO-*i*Bu	−OCOO-*i*Bu	−O-*i*Bu	90

[a] Reactants of **5a**, **6a**, **7a**: $(Boc)_2O$, **5b**, **6b**, **7b**, **8**–**11**: *i*BocCl.
[b] Boc: *tert*-butoxycarbonyl, *i*Boc: *iso*-butoxycarbonyl, *t*Bu: *tert*-butyl, *i*Bu: *iso*-butyl.
[c] Crystallized compounds.