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단 신

Cinnamic Acid 유래 Phenethyl Carbamate 유도체의 합성 및 DPPH 자유 라디칼 소거능 분석

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Synthesis of Cinnamic Acid-Derived Phenethyl Carbamates and Their Radical Scavenging Ability toward DPPH Free Radicals

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INTRODUCTION

Phenolic acids and their derivatives are widely distributed in plants and are usually found as various simple derivatives including amides, esters,[1a,1c,1f] or in rather more complex dimeric forms such as rosmarinic acid (**1**) or clovamide (**2**)[1b,1d,1e] (*Fig.* 1). These compounds have been reported to possess a broad spectrum of pharmacological properties, including antioxidation, anti-thrombosis, anti-inflammatory, antiviral, anticancer and even inhibition of human immunodeficiency virus (HIV).[2] The recent reports demonstrate that these biological activities would be closely correlated to their antioxidant potential.[2b,3] Due to the interesting biological activities of these natural products, the continuous synthetic efforts have been devoted to the development of novel scaffolds with more improved activities and physiological stability. Their structural modification has been mainly concentrated on the variation of the modular structures of the molecules, i.e. phenolic acids and phenalkyl moieties.

In our extensive survey of the literature relevant to the cinnamic acid-derived compounds, to our surprise, it is fairly rare to find the reports on cinnamic acid carbamate or urea derivatives among the corresponding natural products,[4] while other acid derivatives such as esters and amides occur in common. In particular, the carbamate functionality seems likely to be interesting to us in terms of a useful linker to combine two biologically active modular structures, and its preparation is easy from the viewpoint of organic synthesis. So, we decided to synthesis some cinnamic acid carbamate derivatives in which cinnamic acids of interest were conjugated by phenethyl alcohols. Phenolic acids selected as starting materials included cinnamic acid, coumaric aicd, and caffeic acid in which the number of hydroxyl groups substituted on their aromatic ring is 0, 1, and 2, respectively. Herein, we report simple and efficient synthetic details of cinnamic acid carbamate derivatives (*Scheme* 1) and their antioxidant activities. The antioxidant activity of the compounds was measured by standard free radical scavenging assay (DPPH test) as a primary tool. The activity results were analyzed to determine the quantitative structure-activity relationships.

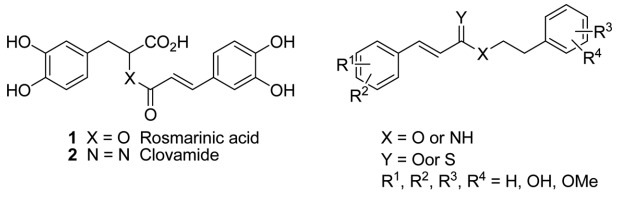


***Fig.* 1.** Phenolic acid-derived natural products.

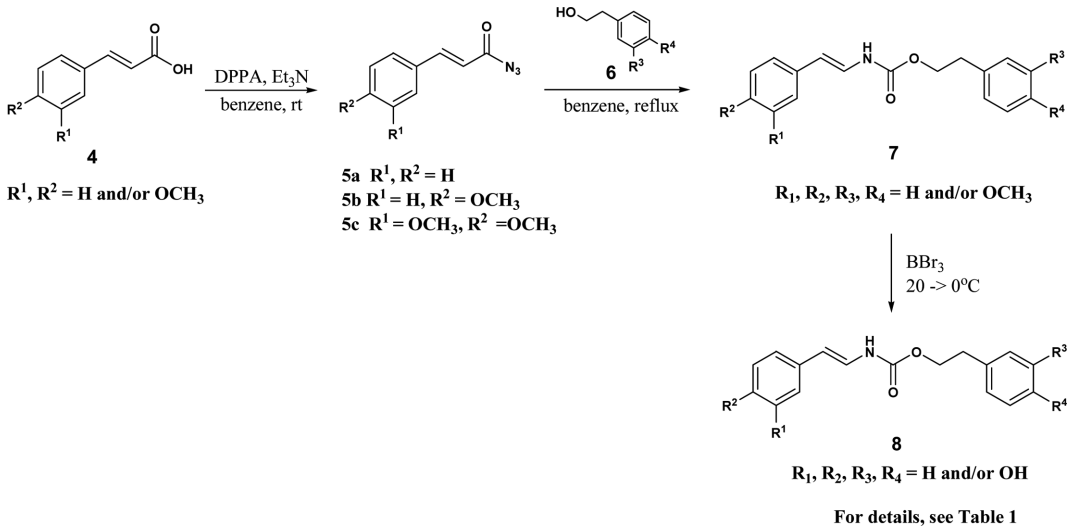
RESULTS AND DISCUSSION

The phenethyl carbamate derivatives derived from cinnamic acid, **7** and **8** were prepared from the reaction of *trans*-cinnamoyl azide analogs **5** and phenethyl alcohols **6** via Curtius rearrangement (*Scheme* 1). Briefly, the cinnamic acid analogs **4** were easily converted to their corresponding azides **5** by treating them with diphenyl phosphoryl azide (DPPA). The resulting isocyanate produced from azide was reacted in situ with phenethyl alcohol to give the carbamate compounds **7**. As a next step, demethylation of carbamates **7** was tried utilizing the several conventional methods (e.g. BBr_3, or 47% HBr etc.), however, provided a rather complicate results. Thus, the demethylation of **7a-e** gave the desired products **8a-e** in fairly low yield (25-40%) along with many unknown side-products (*Table* 1). The same reaction conditions applied to 3,4-dimethoxycinnamic acid-derived phenethyl carbamates (**7g-i**) gave no desired products at all, but only putatively decomposed side-products. With these compounds (**7a-i**, **8a-e**) in hand, the antioxidant activity was measured by DPPH radical scavenging assay as a primary tool to investigate their antioxidant activity, which could analyzed for the study of structure-activity relationship.

***Table* 1.** Structures, yields of synthetic phenolic acid carbamates

Compound	R_1	R_2	R_3	R_4	Yield (%)
7a	H	H	H	H	80
7b	H	H	OCH_3	H	93
7c	H	H	OCH_3	OCH_3	94
7d	OCH_3	H	H	H	89
7e	OCH_3	H	OCH_3	H	80
7f	OCH_3	H	OCH_3	OCH_3	84
7g	OCH_3	OCH_3	H	H	80
7h	OCH_3	OCH_3	OCH_3	H	99
7i	OCH_3	OCH_3	OCH_3	OCH_3	80
8a	H	H	OH	H	27
8b	H	H	OH	OH	37
8c	OH	H	H	H	26
8d	OH	H	OH	H	26
8e	OH	H	OH	OH	25
8f	OH	OH	H	H	-
8g	OH	OH	OH	H	-
8h	OH	OH	OH	OH	-

The statistically analyzed results of scavenging activity of DPPH radicals of each compound are shown in *Fig.* 2. The results revealed that the DPPH radical scavenging activities of the compounds increase in concentration-dependent manner. Except for **8a**, the compounds having more than one substituent, methoxy or hydroxyl group on their benzene rings of the compound generally showed relatively better activities than compound **7a** having no substituent. This observation suggests that the substitution of the benzene ring(s) would afford positive effect on radical scavenging potential. The other notable observation is that the compounds (**7b-c** and **8a-b**) exclusively



***Scheme* 1.** General procedure for the formation of phenolic aicd carbamate derivatives.

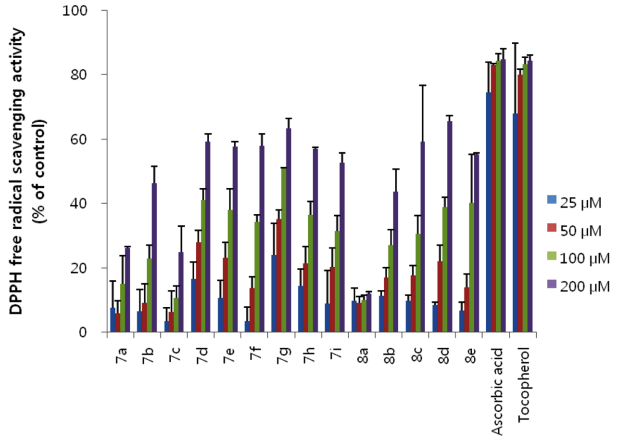


***Fig.* 2.** Rates of scavenging DPPH radicals of phenolic aicd carbamate derivatives **7a-i** and **8a-e**.

having substituent(s) on the benzene ring originated from phenethyl alcohol showed lower radical scavenging activities than the compounds with other substitution pattern. Even though this decrease in activity is not large, but this observed results could indicate that the structural modules coming from phenethyl alcohols does not give significant contribution to activity enhancement. Overall, most of carbamates showed 50 ~ 70% radical scavenging activity of reference materials, ascorbic acid and tocopherol.

In summary, we synthesized cinnamic acid-derived phenethyl carbamates as our program to prepare an additional chemical library of derivatives of cinnamic acid, and investigated the structure-activity relationship. These carbamates would be further utilized for the other important bioactivities such as anticancer and anti-inflammation etc.

EXPERIMENTAL

^{1}H- and ^{13}C-NMR spectra were recorded on Jeol 400 MHz or 600 MHz spectrometer. Chemical shifts are shown in values (ppm) with tetramethylsilane (TMS) as internal standard. All chemicals were purchased from Sigma-Aldrich Co., U.S.A., and all solvents for column chromatography were of reagent grade, and were purchased from commercial sources.

General synthetic procedure for the preparation of azides from phenolic acids (5a-c, *Scheme* 1)

To a solution of *p*-methoxycinnamic acid (200 mg, 1.12 mmol) in benzene (10 mL) was added diphenylphosphoryl azide (DPPA, 0.29 mL, 1.34 mmol) and Et_3N (0.19 mL, 1.34 mmol) under Ar atmosphere at room temperature, and the mixture was stirred at the same temperature for 1 hour. The reaction solvent was evaporated in vacuo, the resulting solid was portioned with sat. aqueous $NaHCO_3$ (60 mL) and ethyl acetate (70 mL). The organic layer was separated and washed with water and brine, dried over anhydrous $MgSO_4$ and evaporated to dryness to yield crude *p*-methoxycinnamoyl azide **5b** which was purified by silica gel column chromatography to give analytically pure compound. **5a**: IR : 2150 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 6.42 (d, 1H, *J*=16 Hz), 7.4 (m, 3H), 7.53 (d, 1H, *J* =5.2 Hz), 7.54 (d, 1H, *J* =6.8 Hz), 7.75 (d, 1H, *J* =16 Hz); ^{13}C-NMR ($CDCl_3$) δ 119.05, 128.53, 129.01, 131.08, 133.80, 146.69, 172.02. **5b**: ^{1}H-NMR ($CDCl_3$) δ 3.85(s, 3H), 6.29 (d, 1H, *J* =16 Hz), 6.92 (d, 2H, *J* =8.4 Hz), 7.49 (d, 2H, *J* =8.9 Hz), 7.71 (d, 1H, *J* =16 Hz); ^{13}C-NMR ($CDCl_3$) δ 55.42, 114.50, 116.48, 126.56, 130.39, 146.47, 162.11, 172.17. **5c**: ^{1}H-NMR ($CDCl_3$) δ 3.91 (s, 3H), 3.92 (s, 3H), 6.29 (d, 1H, *J* =16Hz), 6.88 (d, 1H, *J* = 8.8Hz), 7.05 (s, 1H), 7.13 (dd, 1H, *J* =8.4Hz), 7.69 (d, 1H, *J*=15.6Hz); ^{13}C-NMR ($CDCl_3$) δ 55.90, 55.99, 109.84, 111.06, 116.66, 123.58, 126.79, 146.70, 149.32, 151.90, 172.06.

General synthetic procedure for the preparation of phenolic acid-derived carbamates (4a-i, 5a-e, *Scheme* 1 and *Table* 1)

A solution of phenolic acid azide **5b** (500 mg, 2.46 mmol) in toluene (30 mL) was refluxed for 1 hour, and then phenethyl alcohol **6** (0.32 mL, 2.67 mmol) was added to this solution. The reaction solvent was evaporated in vacuo, the resulting solid was purified by silica gel column chromatography to afford analytically pure compound **7d**. (7**a-h**, *Table* 1). Compound **7d** (100 mg, 0.336 mmol) was dissolved in anhydrous CH_2Cl_2 (10 mL) and stirred at -20 ºC for 10 min. To this solution was added BBr_3 (1M in CH_2Cl_2, 2.0 mL) in dropwise fashion. After checking the completeness of the reaction by TLC, the pH of the reaction mixture was adjusted to pH 6 by adding ice-cooled 5% aqueous K_2HPO_4. The mixture was extracted with EtOAc (50 mL × 2), and the combined organic layer was washed with water and brine, dried over anhydrous Na_2SO_4 and evaporated to dryness to yield crude solid which was purified by silica gel column chromatography to give analytically pure demethylated carbamate **8c**.

7a: ^{1}H-NMR ($CDCl_3$) δ 2.97 (t, 2H, *J*=13.6 Hz), 4.56 (t, 2H, *J*=13.6 Hz), 5.94 (d, 1H, *J*=14.8 Hz), 6.58 (d, 1H, *J* =10.8 Hz), 7.13~7.33 (m, 10H); ^{13}C-NMR ($CDCl_3$) δ 35.32, 65.98, 110.72, 123.93, 125.25, 126.29, 126.61, 128.52,

128.61, 128.85, 136.19, 137.59, 153.52. **7b**: ^{1}H-NMR ($CDCl_3$) δ 2.91 (t, 2H, *J*=13.2 Hz), 3.79 (s, 3H), 4.34 (t, 2H, *J*=12.4 Hz), 5.95 (d, 1H, *J*=14.4 Hz), 6.86 (d, 2H, *J* =8.8 Hz), 7.21 (m, 10H); ^{13}C-NMR ($CDCl_3$) δ 34.47, 55.24, 66.24, 113.97, 123.95, 125.26, 126.31, 128.64, 129.60, 129.89, 136.21, 145.79. **7c**: ^{1}H-NMR ($CDCl_3$) δ 2.92 (t, 2H, *J*=12.8 Hz), 3.86 (s, 3H), 4.36 (t, 2H, *J*=12.8 Hz), 5.95 (d, 1H, *J*=14.8 Hz), 6.59 (d, 1H, *J*=10.8 Hz); ^{13}C-NMR ($CDCl_3$) δ 34.93, 55.85, 55.89, 66.14, 110.74, 111.33, 112,11, 120.82, 123.92, 125.25, 126.32, 128.61, 130.02, 147.80, 148.96, 153.53. **7d**: ^{1}H-NMR ($CDCl_3$) δ 2.91 (t, 2H, *J*= 13.2 Hz), 3.77 (s, 3H), 4.35 (t, 2H, *J*=13.2 Hz), 5.90 (d, 1H, *J*=14 Hz), 6.59 (d, 1H, *J*=10.8 Hz), 6.81 (d, 1H, *J*=8.8 Hz), 7.17 (m, 4H), 7.28 (m, 3H); ^{13}C-NMR ($CDCl_3$) δ 35.33, 55.24, 65.86, 110.44, 114.11, 120.20, 122.31, 126.34, 126.57, 128.49, 128.83, 137.63, 153.56, 158.29. 7**e**: ^{1}H-NMR ($CDCl_3$) δ 2.90 (t, 2H, *J*=13.2 Hz), 3.79 (s, 3H), 4.32 (t, 2H, *J*=13.6 Hz), 5.91 (d, 1H, *J*=14.8 Hz), 6.50 (d, 1H, *J*=10.8 Hz); ^{13}C-NMR ($CDCl_3$) δ 34.47, 55.23, 55.28, 66.14, 110.40, 113.95, 114.12, 122.32, 126.36, 128.83, 129.63, 129.82, 133.46, 158.31, 158.33. **7f**: ^{1}H-NMR ($CDCl_3$) δ 2.91 (t, 2H, *J*=14 Hz), 3.79 (s, 3H), 3.87 (s, 3H), 4.34 (t, 2H, *J*= 13.6 Hz), 5.91 (d, 1H, *J*=14.8 Hz), 6.53 (d, 1H, *J*=10.4 Hz); ^{13}C-NMR ($CDCl_3$) δ 34.96, 55.27, 55.86, 55.90, 66.04, 110.48, 111.34, 112.82, 114.13, 120.82, 122.28, 126.37, 128.80, 130.09, 147.80, 148.96, 153.58, 158.33. **7g**: ^{1}H-NMR ($CDCl_3$) δ 2.96 (t, 2H, *J*=13.6 Hz), 3.85 (s, 3H), 3.87 (s, 3H), 4.37 (t, 2H, *J*=14.0 Hz), 5.90 (d, 1H, *J*=14.4 Hz), 6.58 (s, 1H), 6.78 (s, 1H), 6.78 (s, 1H), 6.83 (s,1H), 7.10 (t, 1H, *J*=7.6 Hz); ^{13}C-NMR ($CDCl_3$) δ 35.32, 55.80, 55.90, 65.92, 107.73, 110.67, 111.34, 118.29, 122.46, 126.60, 128.45, 128.51, 128.84, 129.17, 137.60, 147.88, 149.11. **7h**: ^{1}H-NMR ($CDCl_3$) δ 2.90 (t, 2H, *J*=14 Hz), 3.79 (s, 3H), 3.86 (s, 3H), 3.88 (s, 3H), 4.33 (t, 2H, *J*=13.6Hz), 5.90 (d, 1H, *J*=14.4 Hz), 6.55 (d, 1H, *J*=10.8 Hz); ^{13}C-NMR ($CDCl_3$) δ 34.46, 55.22, 55.83, 55.91, 66.19, 107.72, 110,63, 111.36, 113.94, 118.30, 122.48, 129.20, 129.58, 129.80, 129.93, 147.90, 149.13, 158.33. **7i**: ^{1}H-NMR ($CDCl_3$) δ 2.92 (t, 2H, *J*=7.2 Hz), 3.86 (s, 6H), 3.88 (s, 6H), 4.36 (t,2H, *J*=6.8 Hz), 5.91 (d, 1H, *J*=14.4 Hz), 6.51(d, 1H, *J*=10Hz), 6.75~6.78 (m, 4H), 6.82 (t, 2H, *J*= 8.4 Hz), 7.10 (dd, 1H, *J*=7.6 Hz); ^{13}C-NMR ($CDCl_3$) δ 34.95, 55.85, 55.86, 55.89, 55.92, 66.12,107.72, 110.72, 111.30, 111.36, 112.09, 118.32, 120.82, 122.41, 129.14, 130.02, 147.79, 147.93, 148.73, 148.94, 149.14. **8a**: ^{1}H-NMR (DMSO): δ 2.79 (t, 2H, *J*=6.8 Hz), 4.20 (t, 2H, *J* =7.2 Hz), 6.51 (d, 1H, *J*=14.8 Hz), 6.68 (d, 2H, *J*=8.8 Hz), 7.04 (d, 2H, *J*=8 Hz), 7.10 (d, 2H, *J*=6.4 Hz), 7.223~7.258 (m, 4H), 9.21 (s, 1H), 9.73(d, 1H, *J*=10 Hz). **8b**: ^{1}H-NMR (DMSO) δ 2.73 (t, 2H, *J*=6.8 Hz), 4.18 (t, 2H, *J*=7.6 Hz), 6.02 (d, 1H, *J*=14.4 Hz), 6.49 (d, 1H, *J*=7.2 Hz), 6.80 (t, 2H, *J*=8.4 Hz), 7.11 (d, 1H, *J*=2.8 Hz), 7.167~7.257 (m, 5H), 8.71 (s, 1H), 8.77 (s, 1H), 9.73 (d, 1H, *J*=10 Hz); ^{13}C-NMR (DMSO) δ 34.95, 55.85, 55.86, 55.89, 55.92, 66.12, 107.72, 110.72, 111.30, 111.36, 112.09, 118.32, 120.82, 122.41, 129.14, 130.02, 147.79, 147.93, 148.73, 148.94, 149.14. **8c**: ^{1}H-NMR (DMSO) δ 2.90 (t, 2H, *J*=6.8 Hz), 4.25 (t, 2H, *J*=6.8 Hz), 5.92 (d, 1H, *J*=14.4 Hz), 6.65 (d, 2H, *J*=8.4Hz), 6.89 (dd, 1H, *J*=10.4Hz), 7.06 (d, 1H, *J*=8 Hz), 7.21~7.31 (m, 6H), 9.28 (s, 1H), 9.54 (d, 1H, *J*=10.4 Hz); ^{13}C-NMR (DMSO) δ 34.68, 64,92, 110.05, 115.48, 122.48, 125.98, 126.31, 127.43, 128.33, 128.82, 138.03, 155.72. **8d**: ^{1}H-NMR (DMSO) δ 2.77 (t, 2H, *J*=6.8 Hz), 4.17 (t, 2H, *J*=7.2 Hz), 5.93 (d, 1H, *J*=14.8 Hz), 6.66 (dd, 4H, *J*=6.4 Hz), 6.89 (dd, 1H, *J*=14.4 Hz), 7.06 (dd, 1H, *J*=7.2 Hz), 9.21 (s, 1H), 9.27 (s, 1H), 9.52 (d, 1H, *J*=10.8 Hz); ^{13}C-NMR (DMSO) δ 33.90, 65.31, 109.99, 115.14, 115.50, 122,52, 125.99, 127.48, 127.91, 129.73, 153.82, 155.72, 155.83. **8e**: ^{1}H-NMR (DMSO) δ 2.70 (t, 2H, *J*=6.4 Hz), 4.15 (t, 2H, *J*=6.8 Hz), 5.92 (d, 1H, *J*=14.4 Hz), 6.48 (d, 1H, *J*=8.4 Hz), 6.61~6.70 (m, 6H) 6.89 (t, 1H *J*=10.4, 14 Hz) 7.06 (d, 2H *J*=8 Hz) 9.27 (s, 1H), 9.52 (s, 1H) 9.55 (s, 1H); ^{13}C-NMR (DMSO) δ 34.33, 59.53, 64.31, 115.16, 115.47, 116.16, 119.42, 125.81, 125.98, 126.55, 128.80, 143.62, 145.03, 156.71.

DPPH radical scavenging assay

The DPPH assay was based on the reported methods.[5] Briefly, The ethanolic sample solution of 100 L at several concentrations was added to 100 L of 100 M of 1,1-diphenyl-2picryl-hydrazyl (DPPH) solution in ethanol in 96 well plates. The mixed solution was incubated at room temperature for 30 min. The absorbance of reaction mixture was read at 517 nm using a microplate reader (VERSA max, Molecular device, CA, U.S.A.) and the remaining DPPH was calculated. The free radical scavenging activity was expressed as follow:

$$\text{DPPH scavenging activity (\%)} = \left(\frac{Ac-As}{Ac-Ab}\right) \times 100$$

where Ac was the absorbance of the control, As was the the sample and Ab was the blank (EtOH). Each sample was assayed at five concentrations (10, 20, 50, 100, and 200 μM) and four wells for each concentration. All experiments were carried out in triplicate. The IC_{50} values were defined as the concentration that could scavenge 50% DPPH free radical. Ascorbic acid and -tocopherol were used as positive control.

Statistical analysis

Determination of all samples was carried out in triplicate for DPPA assays. All results were calculated as mean standard deviation (S.D.).

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