A Photo-Sensitive Protecting Group for Amines Based on Coumarin Chemistry

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There is a continuing need for the development of new protecting groups for amines which can be cleaved under conditions that are mild and fundamentally different from what are already available. In this paper, we report our studies in using *o*-hydroxy-*trans*-cinnamic acid as a photo-sensitive protecting group for amines. The design takes advantage of the *trans–cis* photo-isomerization and the ensuing facile lactonization of *o*-hydroxy-*cis*-cinnamic acid and derivatives. We have found that both the protection and deprotection can be carried out in high yields for a variety of amines with different structural features. The deprotection reaction uses low intensity UV light (365 nm), which is fundamentally different from the conditions used for the deprotection of other commonly used amino-protecting groups. Therefore, the method complements other available methods in allowing for selective manipulation of different functional groups in a complex organic molecule.

Key words protecting group; coumarinic acid; cinnamic acid; photoisomerization; photo-deprotection

Selective protection and deprotection of organic functional groups are essential components of modern organic synthesis. To achieve selective manipulation of organic functional groups, it is desirable to have protective groups that can be cleaved under different conditions.[2] There is a continuing interest in developing protecting groups for the selective manipulation of different functional groups.[3-7] Earlier, we reported a redox-sensitive protective group for amines that can be cleaved under mild reductive conditions.[8] In this paper, we report our work on the development of a photo-sensitive protecting group for amines using coumarin chemistry. Photo-sensitive protective groups have special appeals because the unique conditions needed for the cleavage are orthogonal to other commonly used methods, such as acid, base, hydrogenation, and fluoridolysis.[3a] There have been earlier reports in using photo-sensitive protecting group for carboxylic acids.[9]

o-Hydroxy-*trans*-cinnamic acid (**1**, X=OH) and derivatives are known to undergo a *trans–cis* photo-isomerization followed by a facile lactonization reaction to give coumarin (**3**) (Chart 1). Such a reaction has been used for the development of photo-sensitive molecular switches of different hydrolytic enzymes.[10-13] We have also recently reported our work in using this facile lactonization system for the development of esterase-sensitive prodrugs of amine-containing drugs.[14] However, such a photo-induced *trans–cis* isomerization followed by lactonization can also be potentially used for the development of a photo-sensitive protective group for amines, in which the amino functional group can be protected as an amide and released photochemically when needed. Here we report our studies demonstrating the generally applicability of this photo-sensitive protecting group for the protection of different amines.

Results and Discussion

For *o*-hydroxy-*trans*-cinnamic acid to be developed into a generally applicable practical amine protecting group, there are two basic requirements. First, coupling of *o*-hydroxy-*trans*-cinnamic acid with a variety of different amines should give reasonably high yields of the corresponding amides. Second, the deprotection should be carried out under mild reaction conditions in high yields within a reasonably short period of time. We have synthesized a series of nine amides (**1a—i**) of amines with a variety of structural features. After searching several conditions, we have found that the deprotection reaction can be accomplished quantitatively using a low-intensity 4 W UV lamp (365 nm) in methanol solutions in the presence of acetic acid.

Coupling of *o*-Hydroxy-*trans*-cinnamic Acid with Amines

To study the general applicability of this *N*-protecting strategy, we studied the coupling of *o*-hydroxy-*trans*-cinnamic acid (**1**, X=OH) with 1) primary amines, in which the nitrogen is attached to a primary carbon (**1a**, **c**, **e**), 2) a primary amine, in which the nitrogen is attached to a secondary carbon (**1f**), 3) secondary amines (**1g**, **h**), 4) an aromatic amine (**1i**), and 5) amines in the presence of a hydroxyl group (**1b**, **d**). The results are listed in Table 1. We chose to use dicyclohexylcarbodiimide (DCC) as the activating reagent in the presence of hydroxybenzotriazole (HOBt), although a variety of other commonly used amide bond formation methods may work just as well.[15] Couplings of the cinnamic acid (**1**, X=OH) with primary amines with the nitrogen attached to a primary carbon (**1a**, **c**, **e**) generally gave about 90% yields. The yields for the coupling of the cinnamic acid (**1**, X=OH) with a primary amine in which the nitrogen is

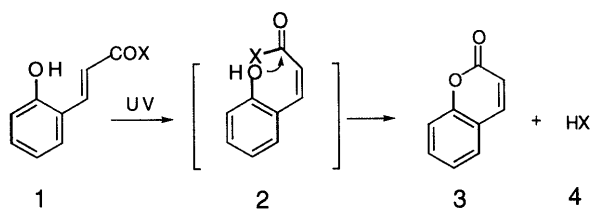

Chart 1

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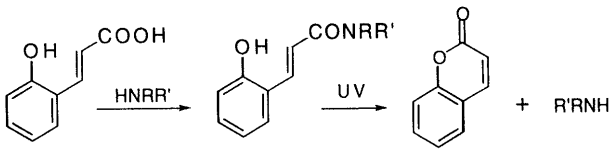
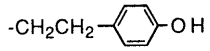
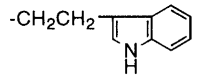
Table 1. Protection of Amines (HNRR') with *o*-Hydroxy-*trans*-cinnamic Acid



No.	R	R'	Formation yield (%)	Release time (h)	Release yield (%)[c]
1a	–H	$-CH_2CH_2CH_3$	89	1.5	100
1b	–H	$-CH_2CH_2OH$	32[a] 71[b]	1.0	100
1c	–H	$-CH_2Ph$	99	1.5	100
1d	–H		86	2.0	100[d]
1e	–H		98	9	100[d]
1f	–H	$-C_6H_{11}$	93	1.0	100
1g	$-CH_2CH_3$	$-CH_2CH_3$	91	2.5	100
1h	$-CH_3$	$-CH_2Ph$	86	2.0	100
1i	–H	$-C_6H_5$	67	18	100

a) 0 °C. *b*) −5 to −10 °C. *c*) Analyzed with HPLC. *d*) Isolated yields for **1d** and **1e** were 95% and 85%, respectively.

attached to a secondary carbon also gave a high yield (**1f**) (93%). So we did the coupling of the cinnamic acid with secondary amines (**1g, h**).

The coupling of ethanolamine with the acid **1** (X=OH) gave a somewhat lower yield under identical reaction conditions (**1b**) (32%) (0 °C, Table 1). This was thought to be due to the interference of the free hydroxyl group competing for reaction with the activated carboxyl group. When the reaction was run at a lower temperature (−5 to −10 °C), presumably affording more selectivity for the amino functional group for the coupling reaction, a higher yield was obtained (71%, Table 1). This, combined with tyramine (**1d**), shows that an amino group can be selectively protected in the presence of a hydroxyl group. As we expected, coupling with aniline, an aromatic amine, afforded a much lower yield (**1i**),[16] indicating the limited utility of this method for the protection of aromatic amines.

Photo-deprotection For the photo-deprotection reaction, we chose to use 365 nm wavelength because earlier photo-isomerization studies have shown that a long UV wavelength favors the *trans* to *cis* isomerization and a shorter wavelength favors the *cis* to *trans* isomerization.[10-13,17,18] In selecting the power level of the UV lamp, we deliberately chose a low power (4 W) lamp because of the potential photochemical side reactions associated with a higher powered, *e.g.*, 500 W, UV lamp. A major consideration in our study was the choice of solvents. Earlier mechanistic studies of photo-isomerization of *o*-hydroxy-*trans*-cinnamic acid (**1**) (X=OH) and derivatives were mostly done in aqueous environments,[10-13] which would not be suitable for large scale organic synthesis purposes. For this protective strategy to be practical, we should be able to achieve photo-deprotection in large scale with fairly high concentration of the compound to avoid using a very large volume of solvent. The concentration certainly should be much higher than what can be achieved in an aqueous environment for most organic amides. With this in mind, we initially studied the photo-deprotection in CH_2Cl_2, dioxane, and methanol and found that the photo-isomerization to give *cis*-cinnamic acid derivatives **2** (Chart 1) indeed occurred, but the lactonization to give coumarin (**3**) (Chart 1) was very slow. Earlier mechanistic studies have demonstrated that coumarinic acid (**2**, X=OH) lactonizes very fast in an aqueous medium with the collapse of the tetrahedral intermediate as the rate limiting step.[19,20] The reaction showed buffer catalysis indicating a general acid catalysis, which by definition involves proton transfer in the rate limiting step leading to the collapse of the tetrahedral intermediate.[19-23] Because the lactonization requires general acid catalysis, it is easy to understand that slow lactonization in pure organic solvents such as CH_2Cl_2, dioxane, and methanol must be due to the lack of acid catalysis. To take advantage of the general acid catalysis of the lactonization reaction, we decided to add a small amount of acetic acid to methanol as the reaction medium, which indeed significantly facilitated the lactonization. Under such conditions, all amines were deprotected within 9 h with the exception of aniline which took 18 h (Table 1). It does seem that the reaction time is longer for the deprotection of secondary amines compared with primary amines. It should be noted that we deliberately chose several amines with different chromophores (benzylamine **1c**, tyramine **1d**, tryptamine **1e**, *N*-benzylmethylamine **1h**, and aniline **1i**) to study the effect of chromophores on the photo-isomerization. The results showed some effect of the chromophores on the photo-isomerization. For example, the deprotection of tryptamine **1e** and aniline **1i** took much longer time than did other deprotection reactions. However, such deprotection reactions still took a reasonably short period of time to allow for their practical applications.

In all cases, the photo-deprotection reactions were

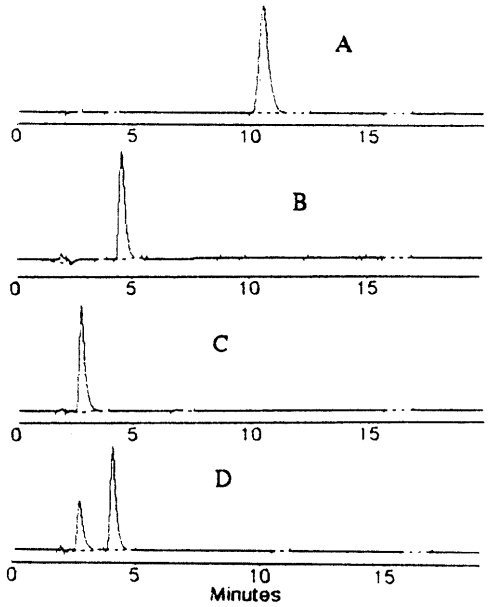


Fig. 1. HPLC Studies of the Deprotection of **1e**

Panel A, **1e** standard; panel B, coumarin standard; panel C, tryptamine standard; panel D, **1e** after irradiation with UV lamp (365 nm) for 9 h in methanol–acetic acid solution. Detailed experimental conditions are described in the experimental section.

completed within the time frame indicated in Table 1 without any side products. The progress of the reaction was monitored with both TLC and HPLC. HPLC analyses of the reactions showed 100% conversion (Fig. 1). Two amines, tyramine (from **1d**) and tryptamine (from **1e**), were isolated in 95% and 85% yields respectively, while coumarin (**3**) was recovered in over 90% yields in both cases.

One drawback if this method is that with the protection at an amino group, a phenol hydroxyl group is introduced. This in certain instance may limit the application of this protective strategy.

Conclusions

In conclusion, *o*-hydroxy-*trans*-cinnamic acid (**1**) (X = OH) can be used as a stable, and yet readily cleavable, photo-sensitive protecting group for amines. This strategy uses a readily available starting material and the protection and deprotection can be carried out in high yields for a variety of amines. The deprotection uses low intensity UV light, which is not expected to cause problems for most functional groups commonly seen in organic compounds or peptides. The photo-deprotection method is fundamentally different from the acid/base and redox chemistry commonly used for amine deprotection and therefore would provide a useful amine protecting method in the selective manipulation of different amino functional groups.

Experimental

General Melting points were determined on a Thomas Hoover capillary melting point apparatus and are uncorrected. ^{1}H-NMR spectra were obtained on a Varian XL-300 spectrometer. All ^{1}H chemical shifts were reported in ppm relative to the internal standard tetramethylsilane (TMS). Mass spectral analyses were conducted by the University of Oklahoma Mass Spectral laboratory, and element analyses were determined by the Midwest Microlab, Indianapolis, Indiana. Column chromatography was performed with 230—400 mesh silica gel (Aldrich Chemical Co.). Thin-layer chromatography was accomplished with TLC plates consisting of polyester sheets precoated with Silica gel 60 F_{254} from Kodak Co. All starting materials and chemical regents were obtained commercially from Aldrich Chemical Co. A spectroline UV lamp (Fisher Scientific Co.), model ENF-240C with 4-W UV tubes and 3 length × 2″ wide (7.6 × 5 cm) longlife filter, was used for photolysis studies. The HPLC study of the deprotection reaction was carried out using a Shimadzu HPLC system consisting of a SCL-10A system controller, two LC-10AS pumps, a SPD-10AV UV-VIS detector, and a SIL-10A auto injector (detection wavelength: 285 and 260 nm). The column was a C_{18} reversed phase analytical column from YMC (length = 15 cm, i.d. = 4.6 cm, particle size = 5 μm). The solvent system was 1.0 M ammonium acetate buffer : methanol = 1 : 1 (v/v).

General Method for Preparation of Amides *o*-Hydroxy-*trans*-cinnamic acid (1—2 eq) was dissolved in anhydrous tetrahydrofuran (THF). After the solution was cooled to 0 °C in an ice bath, DCC (1—2 eq) was added. Ten min later, HOBt (1—2 eq) was added followed by the amines (1.0 eq) and 4-dimethylaminopyridine (DMAP, 0.2 eq). Unless otherwise noted, the reaction solution was stirred under N_2 for 2 h at 0 °C and 7 h at room temperatue (rt). Then the reaction solution was cooled in an ice bath, filtered and concentrated under reduced pressure. The residue was dissolved in EtOAc and washed with saturated $NaHCO_3$ (three times) and 10% citric acid solution (three times) followed by saturated NaCl (two times). The organic phase was dried over $MgSO_4$. After filtration and evaporation, the crude products were purified through silica gel chromatography (CH_2Cl_2 : CH_3OH = 20 : 1, v/v).

***N*-Propyl-3-(2-hydroxyphenyl)-*trans*-2-propenamide (1a)** *o*-Hydroxy-*trans*-cinnamic acid (**1**) (197 mg, 1.20 mmol), propylamine (59 mg, 1.00 mmol), DCC (247 mg, 1.20 mmol), HOBt (162 mg, 1.20 mmol), DMAP (24 mg, 0.2 mmol) and THF (10 ml) were stirred for 7 h at 0 °C and 12 h at rt. It was treated according to general procedure and **1a** (184 mg, 89%) was obtained as a white crystalline solid. mp 173—174 °C. ^{1}H-NMR (acetone-d_6) δ: 8.93 (s, 1H, OH), 7.87 (d, 1H, J = 15.9 Hz, –HC = CHCO–), 7.48 (dd, 1H, J = 7.8, 1.5 Hz), 7.21—6.83 (m, 4H), 6.73 (d, 1H, J = 15.6 Hz, –HC = CHCO–), 3.31—3.24 (m, 2H, –NHCH_2–), 1.59—1.52 (m, 2H, –CH_2CH_3), 0.93 (t, 3H, J = 7.5 Hz, CH_3). EIMS *m/z*: 205 (M^+, 17), 147 (80), 118 (80), 91 (100). *Anal.* Calcd for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37; N, 6.82. Found: C, 70.12; H, 7.16; N, 6.95.

***N*-(2-Hydroxy)ethyl-3-(2-hydroxyphenyl)-*trans*-2-propenamide (1b)** Method 1: Compound **1** (200 mg, 1.22 mmol), ethanolamine (74 mg, 1.22 mmol), DCC (251 mg, 1.22 mmol), HOBt (165 mg, 1.22 mmol) and THF (10 ml) were stirred for 7 h at −5 to −10 °C and 12 h at rt. The reaction mixture was treated according to the general procedure to give **1b** (180 mg, 71%) as a white crystalline solid. mp 176—177 °C. ^{1}H-NMR (acetone-d_6) δ: 8.91 (s, 1H, OH), 7.88 (d, 1H, J = 15.9 Hz, –HC = CHCO–), 7.50 (dd, 1H, J = 7.5, 1.5 Hz), 7.40—6.88 (m, 4H), 6.78 (d, 1H, J = 15.9 Hz, –HC = CHCO–), 3.63 (q, 2H, J = 6.0 Hz, CH_2–), 3.42 (q, 2H, J = 6.0 Hz, –CH_2–). EIMS *m/z*: 207 (M^+, 9), 147 (83), 118 (51), 91 (100). *Anal.* Calcd for $C_{11}H_{13}NO$: C, 63.76; H, 6.32; N, 6.57. Found: C, 63.50; H, 6.19; N, 6.57.

Method 2: Compound **1** (500 mg, 3.0 mmol), ethanolamine (183 mg, 3.0 mmol), DCC (618 mg, 3.0 mmol), HOBt (405 mg, 3.0 mmol) and THF (20 ml) were stirred for 2 h at 0 °C and 18 h at rt. The reaction mixture was treated according to the general procedure to give a white crystalline solid (200 mg, 32%).

***N*-Benzyl-3-(2-hydroxyphenyl)-*trans*-2-propenamide (1c)** Compound **1** (1000 mg, 6.09 mmol), benzylamine (642 mg, 6.00 mmol), DCC (1236 mg, 6.00 mmol), and HOBt (810 mg, 6.00 mmol) were treated according to the general procedure to give **1c** (1510 mg, 99%) as a white powder. mp 172—173 ° C. ^{1}H-NMR (acetone-d_6) δ: 8.94 (s, 1H, OH), 7.93 (d, 1H, J = 15.6 Hz, –HC = CHCO–), 7.71—6.83 (m, 10H), 6.81 (d, 1H, J = 15.6 Hz, –HC = CHCO–), 4.52 (d, 2H, J = 6.0 Hz, CH_2Ar). EIMS *m/z*: 254 (M^+, 0.5), 147 (54), 91 (100). *Anal.* Calcd for $C_{16}H_{15}NO_2$: C, 75.87; H, 5.97; N, 5.53. Found: C, 76.06 ; H, 6.12; N, 5.88.

***N*-[2-(4-Hydroxy)phenyl]ethyl-3-(2-hydroxyphenyl)-*trans*-2-propenamide (1d)** Compound **1** (485 mg, 2.96 mmol), tyramine (406 mg, 2.96 mmol), DCC (618 mg, 3.00 mmol), HOBt (405 mg, 3.00 mmol) and THF (20 ml) were stirred overnight at rt. After working up the reaction mixture according to the general procedure, the compound **1d** (723 mg, 86%) was obtained as a white solid. mp 205—206 °C. ^{1}H-NMR (acetone-d_6) δ: 8.93 (s, 1H, OH), 8.15 (s, 1H, OH), 7.88 (d, 1H, J = 15.9 Hz, –HC = CHCO–), 7.48 (dd, 1H, J = 7.8, 1.8 Hz), 7.30—6.75 (m, 8H), 6.73 (d, 1H, J = 15.9 Hz, –HC = CHCO–), 3.51 (m, 2H, –NHCH_2–), 2.76 (t, 2H, J = 7.8 Hz, CH_2Ar). EIMS *m/z*: 283 (M^+, 9),

147 (100), 91 (35). *Anal.* Calcd for $C_{17}H_{17}NO_3$: C, 72.07; H, 6.05; N, 4.94. Found: C, 71.87; H, 5.97; N, 5.04.

***N*-[2-(3-Indolly)]ethyl-3-(2-hydroxyphenyl)-*trans*-2-propenamide (1e)** Compound **1** (500 mg, 3.05 mmol), tryptamine (480 mg, 3.00 mmol), DCC (618 mg, 3.00 mmol), HOBt (405 mg, 3.00 mmol) and THF (40 ml) were stirred overnight at rt. After working up the reaction mixture according to the general procedure, the product **1e** (900 mg, 98%) was obtained as a white solid. mp 177—178 °C. ^{1}H-NMR (acetone-d_6) δ: 10.0 (br, 1H, –NH–), 8.90 (s, 1H, OH), 7.95 (d, 1H, J=15.6 Hz, –HC=CHCO–), 7.64 (dd, 1H, J=7.8, 1.2 Hz), 7.48—6.82 (m, 9H), 6.74 (d, 1H, J=15.0 Hz, –HC=CHCO–), 3.65 (m, 2H, –NHCH$_2$–), 3.01 (q, 2H, J=7.5 Hz, –NHCH$_2$CH$_2$–). EIMS *m/z*: 306 (M^+, 4), 143 (100). *Anal.* Calcd for $C_{19}H_{18}NO_2$: C, 74.49; H, 5.92; N, 9.14. Found: C, 74.49; H, 5.90; N, 9.15.

***N*-Cyclohexyl-3-(2-hydroxyphenyl)-*trans*-2-propenamide (1f)** Compound **1** (328 mg, 2.00 mmol), cyclohexylamine (99 mg, 1.00 mmol), DCC (412 mg, 2.00 mmol), HOBt (270 mg, 2.00 mmol) and DMAP (24 mg, 0.2 mmol) were treated according to the general procedure to afford **1f** (230 mg, 93%) as a white solid. mp 226—228 °C. ^{1}H-NMR (acetone-d_6) δ: 8.91 (s, 1H, OH), 7.85 (d, 1H, J=15.9 Hz, –HC=CHCO–), 7.47 (dd, 1H, J=7.8, 1.8 Hz), 7.21—6.82 (m, 4H), 6.71 (d, 1H, J=15.9 Hz, –HC=CHCO–), 3.80 (m, 1H), 1.89—1.20 (m, 10H). EIMS *m/z*: 245 (M^+, 26), 147 (100). 91 (86). *Anal.* Calcd for $C_{15}H_{19}NO_2$: C, 73.44; H, 7.81; N, 5.71. Found: C, 73.27; H, 7.84; N, 5.80.

***N*,*N*-Diethyl-3-(2-hydroxyphenyl)-*trans*-2-propenamide (1g)** Compound **1** (200 mg, 1.22 mmol), diethylamine (73 mg, 1.00 mmol), DCC (251 mg, 1.22 mmol), HOBt (165 mg, 1.22 mmol), DMAP (24 mg, 0.2 mmol) and THF (15 ml) were stirred for 10 h in an ice bath and 12 h at rt. It was treated according to the general procedure to afford **1g** (200 mg, 91%) as a white solid. mp 175—177 °C. ^{1}H-NMR (acetone-d_6) δ: 8.98 (s, 1H, OH), 7.95 (d, 1H, J=15.6 Hz, –HC=CHCO–), 7.60 (dd, 1H, J=7.8, 1.8 Hz), 7.17 (d, 1H, J=15.3 Hz, –HC=CHCO), 7.16—6.84 (m, 3H), 3.52 [m, 4 H, –N(CH$_2$CH$_3$)$_2$], 1.21 [m, 6H, –N(CH$_2$CH$_3$)$_2$]. EIMS *m/z*: 219 (M^+, 10), 147 (100), 91 (78). *Anal.* Calcd for $C_{13}H_{17}NO_2$: C, 71.21; H, 7.81; N, 6.39. Found: C, 71.39; H, 7.89; N, 6.48.

***N*-Benzyl-*N*-methyl-3-(2-hydroxyphenyl)-*trans*-2-propenamide (1h)** Compound **1** (200 mg, 1.22 mmol), *N*-benzylmethylamine (148 mg, 1.22 mmol), DCC (251 mg, 1.22 mmol), HOBt (165 mg, 1.22 mmol) were treated according to the general procedure to afford **1h** (279 mg, 86%) as a white solid. mp 172—173 °C. ^{1}H-NMR (acetone-d_6) δ: 9.01 (s, 1H, OH), 8.03 (d, H, J=15.6 Hz, –HC=CHCO–), 7.65—6.79 (m, 10H), 4.79 (s, 1H, NCH$_2$Ar), 4.72 (s, 1H, NCH$_2$Ar), 3.07 (ds, 3H, NCH$_3$). EIMS *m/z*: 267 (M^+, 7), 147 (36), 120 (82), 91 (100). *Anal.* Calcd for $C_{17}H_{17}NO_2$: C, 76.38; H, 6.41; N, 5.24. Found: C, 76.12; H, 6.53; N, 5.94.

***N*-Phenyl-3-(2-hydroxyphenyl)-*trans*-2-propenamide (1i)[16]** Compound **1** (500 mg, 3.05 mmol), aniline (280 mg, 3.01 mmol), DCC (618 mg, 3.00 mmol), HOBt (405 mg, 3.00 mmol) and THF (20 ml) were stirred overnight at rt. It was treated according to the general procedure to afford **1i** (482 mg, 67%) as a pale yellow solid. mp 181—183 °C. ^{1}H-NMR (acetone-d_6) δ: 9.36 (br, 1H, –CONHAr), 9.03 (s, 1H, OH), 7.99 (d, 1H, J=15.6 Hz, –HC=CHCO–), 7.79—6.86 (m, 10H). EIMS *m/z*: 239 (M^+, 11), 147 (100), 118 (48), 9 (71).

General Procedure of Photolysis A 10^{-2}—10^{-3} M solution of *o*-hydroxy-*trans*-cinnamic amides (**1a**—**1i**) in methanol and glacial acetic acid (70 : 1, v/v) was irradiated in a glass vessel with a UV lamp with stirring at room temperature. The process of photolytic reaction was monitored by TLC (ethyl acetate : hexanes = 2 : 1) and HPLC.

Photolytic Deprotection of Compound 1d The solution of amide **1d** (240 mg, 0.85 mmol) in 70 ml methanol and 1 ml glacial acetic acid was irradiated from above the glass vessel. After irradiation with stirring for 2 h at rt, TLC and HPLC indicated that the reaction was complete. The reaction solution was concentrated under reduced pressure and methylene chloride (20 ml) was added. The precipitate was filtered and washed with methylene chloride to give a pale brown solid product (158 mg, 95%) which was consistent to tyramine acetate salt as judged by ^{1}H-NMR. The methylene chloride solution was concentrated to give a white solid (130 mg, 100%), which was identical to standard coumarin as judged by ^{1}H-NMR.

Photolytic Deprotection of Compound 1e Amide **1e** (250 mg, 0.817 mmol) was dissolved in 70 ml methanol and 1 ml glacial acetic acid. After irradiation with stirring for 9 h at rt, TLC indicated that the reaction was complete. The solvent was evaporated. The residue was dissolved in ethyl acetate (30 ml) and washed with 1 N HCl (10 ml × 4) then water (10 ml × 2). The organic phase was dried over $MgSO_4$ overnight. Solvent evaporation gave 110 mg of a white solid (92%) which was identical to coumarin judged by ^{1}H-NMR. The aqueous solution was combined and its pH adjusted with 2 N NaOH to 10. Then the solution was extracted with ethyl acetate (4 × 15 ml) and the combined ethyl acetate was dried over $MgSO_4$ for 3 h. Solvent evaporation gave a light brown solid (110 mg, 85%), which was identical to standard tryptamine judged by ^{1}H-NMR.

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