

PHOTOREACTIONS OF 4- AND 3-AZIDOCOUMARINS IN THE PRESENCE OF NUCLEOPHILES

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Abstract— The photoreactions of 4-azidocoumarins (1) and 3-azidocoumarin (2) in the presence of nucleophiles such as alcohols, thiol or amines generally gave 4-substituted 3-amino- and/or 3-substituted 4-aminocoumarins, while pyrone ring fission with incorporation of two moles of nucleophile was observed in the reaction of 1 in the presence of primary or secondary aliphatic amine as a nucleophile. Plausible mechanisms for these reactions are suggested.

Photolysis of aryl and heteroaryl azides is well documented¹ to give rise to a varied group of products, whose identity is influenced by many factors such as reaction medium, substituents, etc. Several azides, including substituted phenyl azides or azidoadenosines, have seen extensive use as photoaffinity probes of biological macromolecular systems.² In connection with our search³ for new type of fluorescent labelling reagents, we report here some novel results of the azide photoreaction using 4- and 3-azidocoumarins in the medium containing a nucleophile.

Photoreactions of 4-azidocoumarins (1a-b) and 3-azidocoumarin (2), both stable enough on exposure to air or even on heating in an ordinary solvent, were conducted in benzene or acetonitrile containing 0.5-15% nucleophile. In the presence of alcohol or phenol as the nucleophile, either 1 or 2 gave the same type of 4-substituted 3-aminocoumarin (3) as the photolysis product. 2-Propanol, the representative secondary alcohol, was less reactive as the nucleophile, and 2-methyl-2-propanol as the tertiary alcohol was almost inactive. In the presence of propanethiol, however, both 3 and its isomeric 3-substituted 4-aminocoumarins (4) were obtained in the photoreactions of 1 and 2. Much lower photoreactivity of 2 was observed in these reactions. Also, the thiol reagent in the photoreaction of 2 appears to behave as a hydrogen donor, rather than a nucleophile, to give 65% of the reduction product, 3-aminocoumarin (6), which was obtained only in 17% yield in the photoreaction without thiol. The photoreactions in acetonitrile containing amine nucleophiles led to somewhat complicated results. The photoreaction of 1b with aniline gave 3, the same type of the compound produced by the reaction in the presence of alcohol. On the contrary, only the isomeric 4 was obtained by the photolysis of 2 in the presence of aliphatic or aromatic amine nucleophiles. All these results are summarized in Table 1.

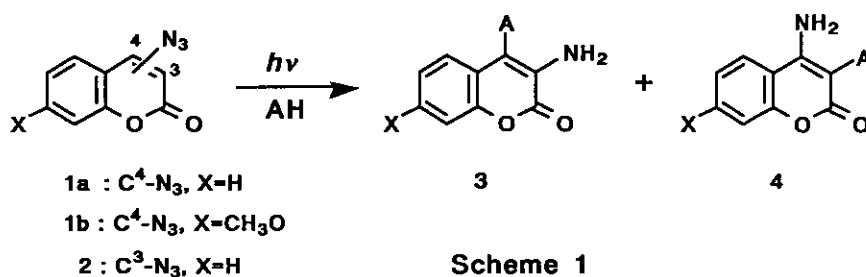
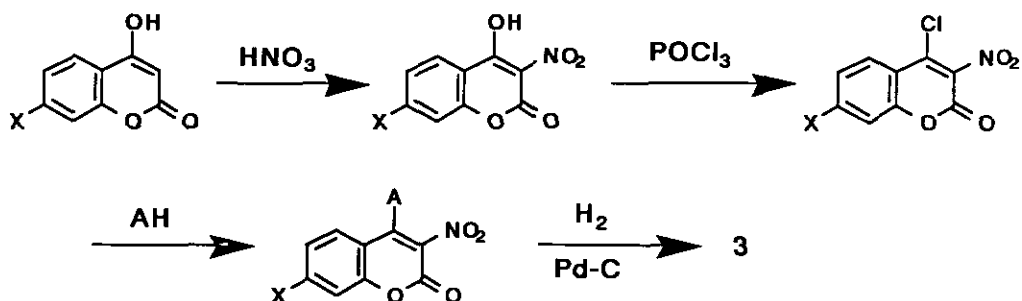


Table 1. Photoreactions in the Presence of Nucleophiles

Run No.	Substrate	AH	Reaction Time (min)	Yield(%) of Product		
				3	4	Others
1	1a	methanol	20	40	---	---
2	1a	methanol ^{a)}	30	45	---	55 ^{e)}
3	1b	methanol ^{b)}	10	79	---	---
4	1b	propanol ^{b)}	25	33	---	6 ^{f)}
5	1b	2-propanol ^{b)}	40	21	---	---
6	1b	2-methyl-2-propanol ^{b)}	10	---	---	---
7	2	methanol	15	4	---	19 ^{g)}
8	2	2-propanol	10	---	---	13 ^{h)}
9	1b	phenol ^{c)}	10	54	---	---
10	1b	propanethiol ^{c)}	10	41	31	---
11	2	propanethiol ^{d)}	15	13	4	65 ^{h)}
12	1b	aniline ^{c)}	30	47	---	---
13	2	aniline ^{d)}	10	---	43	---
14	2	pyrrolidine ^{d)}	10	---	53	---
15	2	morpholine ^{d)}	10	---	2	75 ⁱ⁾
16	2	cyclohexylamine ^{d)}	10	---	53	---

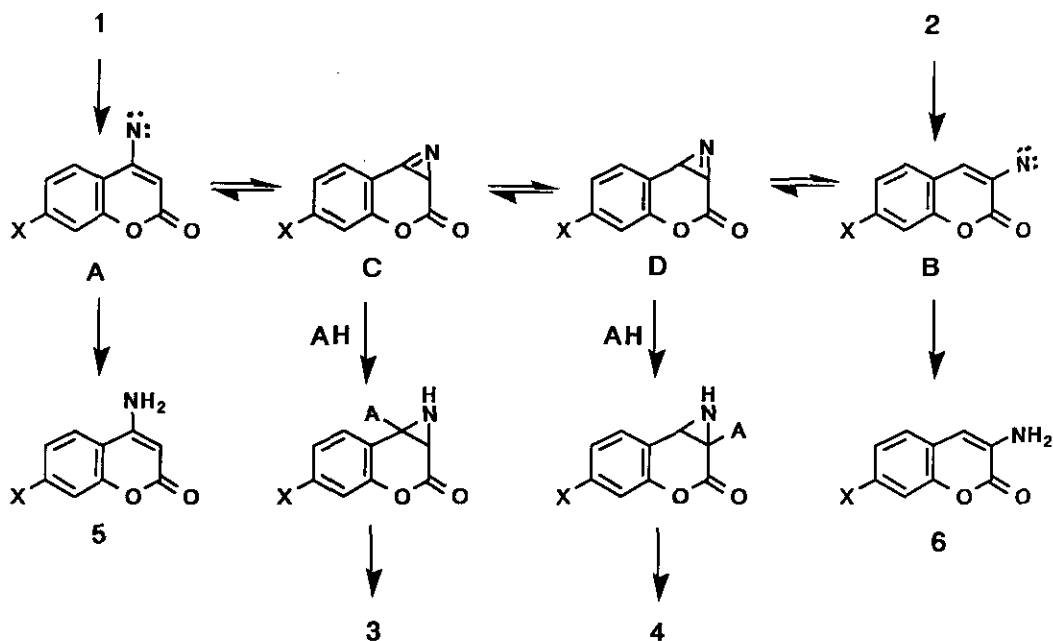
a) Containing 10% CH₃ONa. b) 15% in benzene. c) 15% in acetonitrile. d) 0.5% in acetonitrile
 e) 4-Methoxycoumarin f) % of 1b in weight, unidentified. g) 4-Hydroxy-3-methoxycoumarin
 h) 3-Aminocoumarin i) 4-Amino-3-hydroxycoumarin

Regiochemical differentiation between 3 and 4 was made by the comparison of melting point, nmr spectrum and tlc pattern of the product with those of the pertinent isomer (3), which was independently prepared unambiguously starting from the corresponding 4-hydroxycoumarin, referring to the reported procedure,⁴ as shown in Scheme 2.



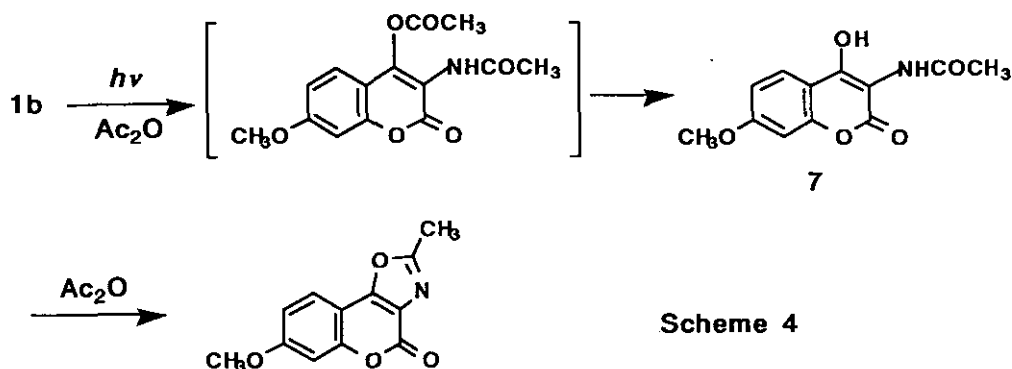
Scheme 2

The formation of 3 or 4, presumably by nitrene reaction, has ample analogy in azide photochemistry.¹ Addition of nucleophile to photochemically derived nitrene (A) or (B) proceeds via azirine intermediate (C) or (D), providing corresponding ortho-substituted amines (Scheme 3). Ineffective azirine cyclization from B, rather unfavorable intermediate (D) relative to C in equilibrium, and lower nucleophilicity of alcohol or thiol may be combined to cause low yields of 3 or 3+4 from 2 with methanol or thiol, respectively. Rapid addition of the strong nucleophiles such as amines into D can result in the sole formation of 4 from 2.

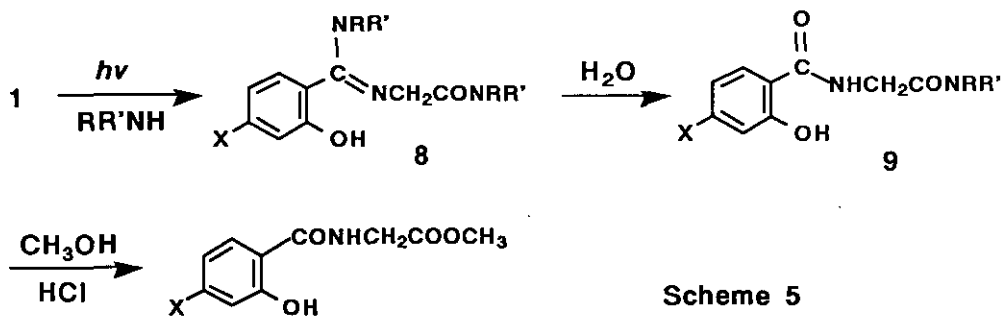


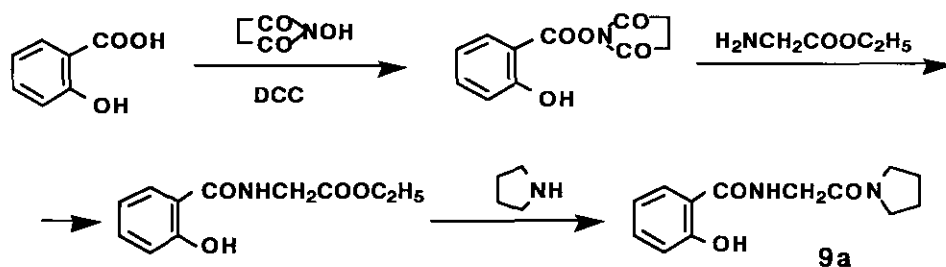
Scheme 3

Generation of 4-hydroxy-3-methoxycoumarin (19%) in methanol (run 7 in Table 1) and 4-amino-3-hydroxycoumarin (75%) in acetonitrile containing morpholine (run 15 in Table 1), both from 2, seems to suggest an unpredictable role of water in these photoreactions. Also, water plays an important role in the photoreaction of 1b in the presence of acetic anhydride resulting in high yield (92%) formation of 7, identified by cyclization into the known⁵ benzopyrano[3,4-d]oxazolone derivative (Scheme 4).



The photoreactions of 1 with aliphatic amines brought about completely different results. For instance, the photolysis of 1b in acetonitrile containing 0.5% pyrrolidine gave, after chromatographic separation, an oily product (8b: X=CH₃O, NRR'=pyrrolidino), along with small amounts of 3 and 5. ¹H-Nmr and ms spectral data of 8b are indicative of the presence of two pyrrolidino groups with the absence of coumarin nucleus. Hydrolysis of 8b afforded needles (9b: X=CH₃O, NRR'=pyrrolidino), which indicates removal of one pyrrolidino function from 8b. Heating 9b in methanolic hydrochloric acid brought about further removal of the other pyrrolidino group, incorporating methyl ester group instead. Using 2D nmr (C-H COSY) technique, 9b was finally confirmed as salicyloylaminoacetamide structure. Thus, N²-carbamoylmethylsalicylamidine structure was assigned to 8b as the primary photolysis product of 1b in the presence of pyrrolidine (Scheme 5). The structure of 9a (X=H, NRR'= pyrrolidino) was further confirmed by its independent preparation from salicylic acid, as shown in Scheme 6. Table 2 shows the photoreactions of 1 in the presence of some primary and secondary aliphatic amines.



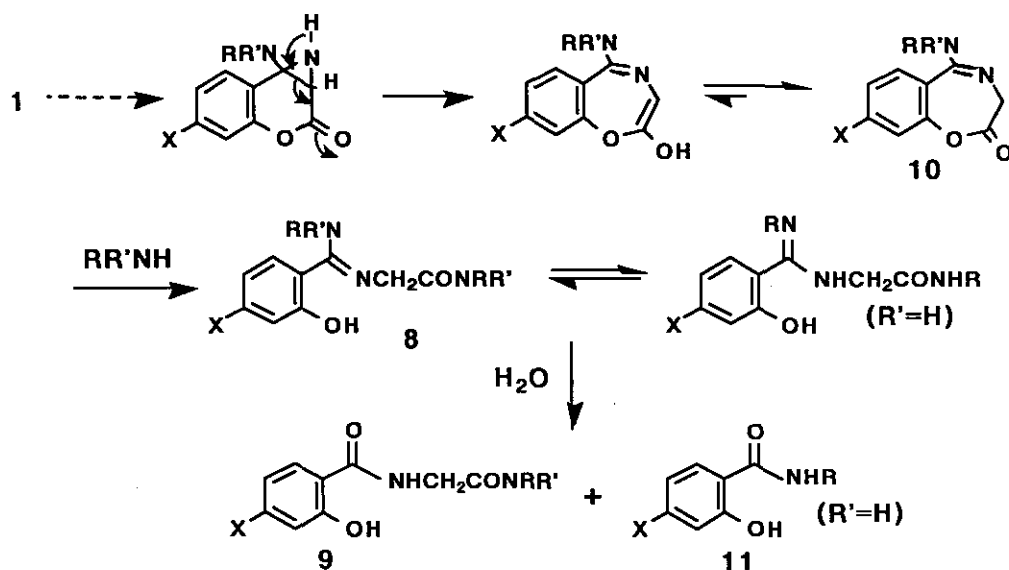


Scheme 6

Table 2. Photoreactions of 1 in the Presence of Aliphatic Amines

Substrate	RR'NH	Yield(%) of Product		
		8	3	5
1a	pyrrolidine	62 (8a)	0.4	20
1b	pyrrolidine	91 (8b)	2	3
1b	morpholine	86 (8c)	2	---
1b	diethylamine	59 (8d)	---	6
1b	propylamine	68 (8e)	---	---
1b	cyclohexylamine	57 (8f)	---	---

We assume that the unusual product (8) arises *via* the intermediate 5-aminobenzoxazepin-2-one (10), heterocyclic ring of which can be cleaved by aminolysis (Scheme 7). Susceptibility of benzoxazepinones toward amine was already reported.⁶ The second hydrolysis product (11) was obtained, together with 9 only in the case of 8f, suggesting the tautomeric structure of 8 when bears primary amine (R'=H). Ring-expanded type of the product such as 10, or the compound derived therefrom, could not be isolated in the photolysis of 2 and also in the photoreactions of 1 in the presence of nucleophiles other than aliphatic amines. In the photolysis of 1b in the presence of propanol, however, there seems a possibility that a small amount of an unstable oily by-product is the same benzoxazepinone type of compound. In these photoreactions described above, we could not use an alkoxide ion, well known¹ strong base preferably to lead to ring expansion of aryl azides, since rapid thermal substitution of azide with alkoxide was observed even at room temperature⁷ (see run 2 in Table 1).



Scheme 7

EXPERIMENTAL

All melting points were determined with a Yanaco micro melting point apparatus and are uncorrected. Ir spectra [$\nu_{\max}$ (KBr), cm^{-1}] were determined using a Hitachi 215 grating spectrophotometer. Ms spectra (m/z , direct inlet at 70 eV) were taken on a Hitachi M-2000 spectrometer. ^1H -Nmr spectra (δ , ppm) were recorded with a JEOL JNM GX-270 spectrometer, using tetramethylsilane as an internal standard. Flash column chromatography was performed on Merck Kieselgel 60 (230-400 mesh).

The photoreactions were carried out in a Pyrex immersion apparatus equipped with 300W high-pressure mercury lamp (Eikosha) at room temperature.

4-Azidocoumarin (1a), mp 164-165°C, and 4-azido-7-methoxycoumarin (1b), mp 177-179°C, were prepared from the corresponding 4-chlorocoumarin and sodium azide in ethanol on reflux, as reported previously.⁸

3-Azidocoumarin (2). Into a suspension of 3-aminocoumarin (500 mg, 3.1 mmol), prepared according to the reported procedure,⁹ in 3% HCl (30 ml) was added, in portion, sodium nitrite (321 mg, 4.6 mmol) at -10-0°C with stirring. After 30 min's stirring, sodium azide (302 mg, 4.6 mmol) was added, and the whole was stirred at 0°C for an hour, then at room temperature for 3.5 h. The resulting precipitates in the suspension were collected and purified by silica gel column chromatography [benzene-ethyl acetate (4:1)]. Yield, 515 mg (88%). Orange prisms from 50% EtOH, mp 117-118°C; ms: 187 (M^+); ir: 2140 (N_3); ^1H -nmr (DMSO- d_6): 7.34-7.68 (4H, m, aromatic-H), 7.68 (1H, s, C^4 -H). *Anal.* Calcd for $\text{C}_9\text{H}_5\text{N}_3\text{O}_2$: C, 57.76; H, 2.69; N, 22.45. Found: C, 57.75; H, 2.61; N, 22.35.

General Procedure for the Photoreaction. The substrate (1 or 2) (200 mg; 50 mg for runs 3 and 12) was dissolved in benzene or acetonitrile (450 ml) containing a nucleophile, and the solution was photolyzed under nitrogen atmosphere at room temperature. The reaction mixture was concentrated *in vacuo*, and the residue was directly submitted to silica gel column chromatography. In run 9, however, the residue was treated with 1N NaOH (500 ml), extracted with CHCl_3 , and then separated. The solvent, nucleophile, reaction time, and yield of the product(s) for each run are shown in Table 1.

3-Amino-4-methoxycoumarin. Pale yellow prisms from petr. ether, mp 80-82°C; ms: 191 (M^+); ir: 3410, 3326, 1694; $^1\text{H-nmr}$ (CDCl_3): 3.93 (3H, s, CH_3O), 4.10 (2H, s, NH_2), 7.31-7.32 (3H, m, aromatic-H), 7.55 (1H, d, $J=7.6$ Hz, $\text{C}^5\text{-H}$). *Anal.* Calcd for $\text{C}_{10}\text{H}_9\text{NO}_3$; C, 62.82; H, 4.75; N, 7.33. Found: C, 62.86; H, 4.62; N, 7.32.

3-Amino-4,7-dimethoxycoumarin. Pale yellow needles from hexane, mp 110-110.5°C; ms: 221 (M^+); ir: 3440, 3320, 1705; $^1\text{H-nmr}$ (CDCl_3): 3.85 (3H, s, CH_3O), 3.89 (2H, br s, NH_2), 3.93 (3H, s, CH_3O), 6.85 (1H, d, $J=2.3$ Hz, $\text{C}^8\text{-H}$), 6.89 (1H, dd, $J=8.6$, 2.3 Hz, $\text{C}^6\text{-H}$), 7.48 (1H, d, $J=8.6$ Hz, $\text{C}^5\text{-H}$). *Anal.* Calcd for $\text{C}_{11}\text{H}_{11}\text{NO}_4$; C, 59.81; H, 4.94; N, 6.33. Found: C, 59.72; H, 5.01; N, 6.33.

3-Amino-7-methoxy-4-propyloxycoumarin. Yellow prisms from hexane, mp 48-50.5°C; ms: 249 (M^+); ir: 3430, 3140, 1700; $^1\text{H-nmr}$ (CDCl_3): 1.10 (3H, t, $J=7$ Hz, CH_3), 1.88 (2H, m, CH_2), 3.85 (3H, s, CH_3O), 3.85 (2H, br s, NH_2), 4.04 (2H, t, $J=7$ Hz, OCH_2), 6.84 (1H, d, $J=2.3$ Hz, $\text{C}^8\text{-H}$), 6.87 (1H, dd, $J=2.3$, 8.6 Hz, $\text{C}^6\text{-H}$), 7.84 (1H, d, $J=8.6$ Hz, $\text{C}^5\text{-H}$). *Anal.* Calcd for $\text{C}_{13}\text{H}_{15}\text{NO}_4$; C, 62.64; H, 6.07; N, 5.62. Found: C, 62.54; H, 6.12; N, 5.60.

3-Amino-4-isopropoxy-7-methoxycoumarin. Yellow needles from hexane, mp 78.5-79.5°C; ms: 249 (M^+); ir: 3460, 3330, 1728; $^1\text{H-nmr}$ (CDCl_3): 1.39 (3H, s, CH_3), 1.41 (3H, s, CH_3), 3.85 (3H, s, CH_3O), 4.65 (1H, m, OCH), 4.65 (2H, br s, NH_2), 6.84 (1H, d, $J=2.3$ Hz, $\text{C}^8\text{-H}$), 6.86 (1H, dd, $J=2.3$, 8.6 Hz, $\text{C}^6\text{-H}$), 7.48 (1H, d, $J=8.6$ Hz, $\text{C}^5\text{-H}$). *Anal.* Calcd for $\text{C}_{13}\text{H}_{15}\text{NO}_4$; C, 62.64; H, 6.07; N, 5.62. Found: C, 62.78; H, 6.12; N, 5.50.

3-Amino-7-methoxy-4-phenoxy coumarin. Yellow needles from hexane, mp 132-133°C; ms: 283 (M^+); ir: 3490, 3370, 1715; $^1\text{H-nmr}$ (CDCl_3): 3.84 (3H, s, CH_3O), 3.92 (2H, br s, NH_2), 6.75-7.40 (8H, m, aromatic-H). *Anal.* Calcd for $\text{C}_{16}\text{H}_{13}\text{NO}_4$; C, 67.84; H, 4.63; N, 4.94. Found: C, 67.88; H, 4.61; N, 4.86.

3-Amino-7-methoxy-4-propylthiocoumarin. Yellow plates from hexane, mp 77-78.5°C; ms: 265 (M^+); ir: 3460, 3340, 1725; $^1\text{H-nmr}$ (CDCl_3): 0.99 (3H, t, $J=7.3$ Hz, CH_3), 1.60 (2H, m, CH_2), 2.75 (2H, t, $J=7.3$ Hz, SCH_2), 3.85 (3H, s, CH_3O), 4.88 (2H, br s, NH_2), 6.82 (1H, d, $J=2.6$ Hz, $\text{C}^8\text{-H}$), 6.89 (1H, dd, $J=2.6$, 8.6 Hz, $\text{C}^6\text{-H}$), 7.79 (1H, d, $J=8.6$ Hz, $\text{C}^5\text{-H}$). *Anal.* Calcd for $\text{C}_{13}\text{H}_{15}\text{NO}_3\text{S}$; C, 58.85; H, 5.70; N, 5.28; S, 12.08. Found: C, 58.87; H, 5.66; N, 5.23; S, 12.02.

4-Amino-7-methoxy-3-propylthiocoumarin. Prisms from CHCl_3 -hexane, mp 149.5-150.5°C; ms: 265 (M^+); ir: 3480, 3420, 3300, 3200, 1610, 1635, 1660; $^1\text{H-nmr}$ (CDCl_3): 0.99 (3H, t, $J=7.3$ Hz, CH_3), 1.60 (2H, m, CH_2), 2.76 (2H, t, $J=7.3$ Hz, SCH_2), 3.87 (3H, s, CH_3O), 5.89 (2H, br s, NH_2), 6.81 (1H, d, $J=2.6$ Hz, $\text{C}^8\text{-H}$), 6.86 (1H, dd, $J=2.6$, 8.9 Hz, $\text{C}^6\text{-H}$), 7.35 (1H, d, $J=8.9$ Hz, $\text{C}^5\text{-H}$). *Anal.* Calcd for $\text{C}_{13}\text{H}_{15}\text{NO}_3\text{S}$; C, 58.85; H, 5.70; N, 5.28; S, 12.08. Found: C, 59.12; H, 5.66; N, 5.27; S, 11.96.

3-Amino-4-propylthiocoumarin. Orange prisms from hexane, mp 88-89°C; ms: 235 (M^+); ir: 3468, 3350, 1712; $^1\text{H-nmr}$ (CDCl_3): 1.00 (3H, t, $J=7.26$ Hz, CH_3), 1.57-1.68 (2H, m, CH_2), 2.76 (2H, t, $J=7.26$

Hz, SCH₂), 5.01 (2H, br s, NH₂), 7.29-7.32 (3H, m, aromatic-H), 7.88-7.92 (1H, m, aromatic-H). *Anal.* Calcd for C₁₂H₁₃NO₂S: C, 61.25; H, 5.57; N, 5.95; S, 13.63. Found: C, 61.24; H, 5.61; N, 5.90; S, 13.62.

4-Amino-3-propylthiocoumarin. Orange prisms from hexane, mp 58-59°C; ms: 235 (M⁺); ir: 3470, 3350, 1710; ¹H-nmr (CDCl₃): 1.00 (3H, t, J=7.43 Hz, CH₃), 1.62-1.70 (2H, m, CH₂), 2.68 (2H, t, J=7.43 Hz, SCH₂), 5.70 (2H, br s, NH₂), 7.28-7.64 (4H, m, aromatic-H).

3-Amino-4-anilino-7-methoxycoumarin. Brown prisms from AcOEt, mp 187-188°C; ms: 282 (M⁺); ir: 3480, 3375, 3330, 1695; ¹H-nmr (CDCl₃): 3.84 (3H, s, CH₃O), 3.84 (2H, br s, NH₂), 5.60 (1H, br s, NH), 6.70-7.35 (8H, m, aromatic-H). *Anal.* Calcd for C₁₆H₁₄N₂O₃: C, 68.08; H, 5.00; N, 9.92. Found: C, 68.14; H, 4.90; N, 9.84.

4-Amino-3-anilino-coumarin. Prisms from benzene, mp 211-212°C; ms: 252 (M⁺); ir: 3490, 3350, 1700; ¹H-nmr (CDCl₃): 5.28 (2H, br s, NH₂), 6.63-7.57 (9H, m, aromatic-H). *Anal.* Calcd for C₁₅H₁₂N₂O₂: C, 71.42; H, 4.79; N, 11.10. Found: C, 71.48; H, 4.87; N, 10.92.

4-Amino-3-pyrrolidinocoumarin. Yellow plates from EtOH-H₂O, mp 159-160°C; ms: 230 (M⁺); ir: 2140, 1730; ¹H-nmr (CDCl₃): 1.93-1.98 (4H, m, 2 x CH₂), 3.02-3.14 (4H, m, 2 x NCH₂), 5.54 (2H, br s, NH₂), 7.30-7.65 (4H, m aromatic-H). *Anal.* Calcd for C₁₃H₁₄N₂O₂: C, 67.81; H, 6.13; N, 12.17.

Found: C, 67.89; H, 6.10; N, 12.35.

4-Amino-3-morpholinocoumarin. Orange prisms from EtOH-H₂O, mp 252-253°C; ms: 246 (M⁺); ir: 3460, 3370, 1670; ¹H-nmr (CDCl₃): 2.52 (4H, m, 2 x CH₂), 3.69 (4H, m, 2 x CH₂), 5.63 (2H, br s, NH₂), 7.28-7.34 (2H, m, aromatic-H), 7.44-7.55 (2H, m, aromatic-H). *Anal.* Calcd for C₁₃H₁₄N₂O₃: C, 63.40; H, 5.73; N, 11.38. Found: C, 63.27; H, 5.78; N, 11.26.

4-Amino-3-cyclohexylaminocoumarin. Prisms from benzene, mp 141-142°C; ms: 258 (M⁺); ir: 3460, 3330, 1680; ¹H-nmr (CDCl₃): 1.18-1.90 (10H, m, 5 x CH₂), 2.87-2.88 (1H, m, CH), 5.09 (2H, br s, NH₂), 7.28-7.51 (4H, m, aromatic-H), 8.30 (1H, br s, NH). *Anal.* Calcd for C₁₅H₁₈N₂O₂: C, 69.75; H, 7.02; N, 10.84. Found: C, 69.82; H, 7.16; N, 10.73.

4-Methoxycoumarin. Needles from ether, mp 121-122°C (lit.,¹⁰ mp 125°C); ms: 176 (M⁺); ir: 1715; ¹H-nmr (CDCl₃): 4.00 (3H, s, CH₃O), 5.70 (1H, s, C³-H), 7.20-7.56 (3H, m, aromatic-H), 7.81 (1H, d, J=8.1 Hz, C⁵-H).

4-Hydroxy-3-methoxycoumarin. Needles from hexane, mp 168-169°C (lit.,¹⁰ mp 161°C); ms: 192 (M⁺); ir: 3340, 1700; ¹H-nmr (CDCl₃): 4.35 (3H, s, CH₃O), 7.27-7.48 (3H, m, aromatic-H), 7.79 (1H, d, J=7.9 Hz, C⁵-H). *Anal.* Calcd for C₁₀H₈O₄: C, 62.40; H, 4.19. Found: C, 62.46; H, 4.16.

4-Amino-3-hydroxycoumarin. Orange prisms from EtOH, mp 230-231°C; ms: 177 (M⁺); ir: 3460, 3340, 1634; ¹H-nmr (DMSO-d₆): 6.78 (2H, br s, NH₂), 7.28-7.48 (3H, m, aromatic-H), 7.31 (1H, d, J=8.9 Hz, C⁵-H), 8.47 (1H, s, OH). *Anal.* Calcd for C₉H₇NO₃: C, 61.01; H, 3.98; N, 7.90. Found: C, 60.97; H, 3.96; N, 7.90.

3-Acetamido-4-hydroxy-7-methoxycoumarin. Needles from AcOH, mp 259-261°C; ms: 249 (M⁺); ir: 3300, 1690, 1620, 1610; ¹H-nmr (DMSO-d₆): 2.09 (3H, s, COCH₃), 3.86 (3H, s, CH₃O), 6.97 (1H, dd, J=2.3, 8.6 Hz, C⁶-H), 6.99 (1H, d, J=2.3 Hz, C⁸-H), 7.77 (1H, d, J=8.6 Hz, C⁵-H), 9.36 (1H, s, OH),

12.2 (1H, br s, NH). *Anal.* Calcd for $C_{12}H_{11}NO_5$: C, 57.83; H, 4.45; N, 5.62. Found: C, 57.69; H, 4.36; N, 5.61.

Refluxing with Ac_2O for an hour followed by concentration, addition of MeOH, and filtration of the resulting precipitates gave 70% yield of 7-methoxy-2-methyl-4*H*-benzopyrano[3,4-*d*]oxazol-4-one, pale yellow plates from MeOH, mp 214-215°C (lit.,⁵ mp 214-215°C); ms: 231 (M^+); ir: 1740; 1H -nmr (DMSO- d_6): 2.65 (3H, s, CH_3), 3.89 (3H, s, CH_3O), 7.08 (1H, dd, $J=2.3, 8.6$ Hz, C^8-H), 7.20 (1H, d, $J=2.3$ Hz, C^6-H), 7.83 (1H, d, $J=8.6$ Hz, C^9-H). *Anal.* Calcd for $C_{12}H_9NO_4$: C, 62.34; H, 3.92; N, 6.06. Found: C, 62.46; H, 3.86; N, 6.00.

General Procedure for the Photoreactions of 1 in the Presence of Aliphatic Amines. The substrate (1) (200 mg) was dissolved in acetonitrile (450 ml) containing an aliphatic primary amine (2 ml), and the solution was photolyzed for 10-20 min under nitrogen atmosphere at room temperature. The solution was concentrated *in vacuo*, and the residue was directly submitted to silica gel chromatography ($CHCl_3$ -AcOEt or $CHCl_3$ -MeOH as eluent) to give N^2 -carbamoylmethylsalicylamidine (8) as an oily product, together with 3 and/or 5. The primary amine and yields of the product(s) for each run are shown in Table 2. Heating 8 (200 mg) at 80°C in acetonitrile (15 ml) containing H_2O (1 ml), followed by silica gel chromatographic separation [$CHCl_3$ -AcOEt (2:1) as eluent] of the concentration residue gave salicyloylaminoacetamide (9).

8a. Ms: 301(M^+); 1H -nmr ($CDCl_3$): 1.70-2.00 (8H, m, pyrrolidino-H), 3.20-3.55 (8H, m, pyrrolidino-H), 3.47 (1H, s, OH), 3.92 and 4.08 (2 x 1H, ABq, $J=15.2$ Hz, NCH_2CO), 6.65-7.22 (4H, m, aromatic-H).

Hydrolysis for 10 h gave **9a**, 82%, plates from EtOH, mp 181-182°C; ms: 248 (M^+); ir: 3350, 1630; 1H -nmr ($CDCl_3$): 1.93 (2H, m, pyrrolidino-H), 2.04 (2H, m, pyrrolidino-H), 3.45 (2H, t, $J=6.6$ Hz, pyrrolidino-H), 3.56 (2H, t, $J=6.6$ Hz, pyrrolidino-H), 4.14 (2H, d, $J=4.0$ Hz, NCH_2CO), 6.87-7.52 (4H, m, aromatic-H), 7.54 (1H, br s, NH), 12.21 (1H, s, OH). *Anal.* Calcd for $C_{13}H_{16}N_2O_3$: C, 62.89; H, 6.50; N, 11.28.

Found: C, 62.80; H, 6.56; N, 11.35.

8b. Ms: 331 (M^+); 1H -nmr ($CDCl_3$): 1.72-2.11 (8H, m, pyrrolidino-H), 3.23-3.71 (9H, m, pyrrolidino-H, OH), 3.77 (3H, s, CH_3O), 3.94 and 4.39 (2 x 1H, ABq, $J=15.2$ Hz, NCH_2CO), 6.06 (1H, d, $J=8.6$ Hz, C^5-H), 6.36 (1H, d, $J=2.6$ Hz, C^3-H), 6.77 (1H, d, $J=8.6$ Hz, C^6-H). Hydrolysis for 1.5 h gave **9b**, 88%, needles from EtOH, mp 169-170°C; ms: 278 (M^+); ir: 3350, 3320, 3300-2700 (br), 1655, 1600; 1H -nmr ($CDCl_3$): 1.92 (2H, m, pyrrolidino-H), 2.04 (2H, m, pyrrolidino-H), 3.44 (2H, t, $J=6.0$ Hz, pyrrolidino-H), 3.55 (2H, t, $J=6.0$ Hz, pyrrolidino-H), 3.81 (3H, s, CH_3O), 4.12 (2H, d, $J=3.6$ Hz, NCH_2CO), 6.40-6.53 (2H, m, $C^3,5-H$), 7.35 (1H, br s, NH), 7.43 (1H, d, $J=8.9$ Hz, C^6-H), 12.55 (s, 1H, OH). *Anal.* Calcd for $C_{14}H_{18}N_2O_4$: C, 60.37; H, 6.51; N, 10.06. Found: C, 60.28; H, 6.48; N, 9.92. Heating **9b** (22.3 mg) in a mixture of MeOH (4 ml) and 10% HCl (4 ml) at 70°C for 4.5 h, followed by silica gel chromatographic separation [$CHCl_3$ -AcOEt (2:1) as eluent] of AcOEt extracts from the reaction mixture, gave 13.3 mg (73%) of **methyl *N*-4-methoxysalicyloylaminoacetate**, prisms from $CHCl_3$ -hexane, mp 134-135°C; ms: 239 (M^+); ir: 3320, 1745, 1605; 1H -nmr ($CDCl_3$): 3.82 (6H, s, CH_3O and $COOCH_3$), 4.21 (2H, d, $J=5.0$ Hz, NCH_2CO), 6.40-6.45 (2H, m, $C^3,5-H$), 6.69 (1H, br s, NH), 7.34 (1H, d, $J=8.6$ Hz, C^6-H), 12.34 (1H, s, OH). *Anal.* Calcd for $C_{11}H_{13}NO_5$: C 55.23; H, 5.48; N, 5.85. Found: C, 55.01; H, 5.35; N, 5.73.

8c. Ms: 363 (M^+); 1H -nmr ($CDCl_3$): 3.20-3.50 (8H, m, morpholino-H), 3.60-3.75 (9H, m, morpholino-H, OH), 3.78 (3H, s, CH_3O), 4.05 (2H, br s, NCH_2CO), 6.41 (1H, dd, $J=2.3, 8.6$ Hz, C^5-H), 6.52 (1H, d, $J=2.3$ Hz, C^3-H), 6.82 (1H, d, $J=8.6$ Hz, C^6-H). Hydrolysis for 1 h gave **9c**, 84%, needles from EtOH, mp 147.5-149°C; ms: 294 (M^+); ir: 3390, 1650, 1605; 1H -nmr ($CDCl_3$): 3.47-3.75 (8H, m, morpholino-H), 3.82 (3H, s, CH_3O), 4.20 (2H, d, $J=3.6$ Hz, NCH_2CO), 6.44 (1H, dd, $J=2.0, 8.0$ Hz, C^5-H), 6.46 (1H, d, $J=2.0$ Hz, C^3-H), 7.33 (1H, br s, NH), 7.42 (1H, d, $J=8.0$ Hz, C^6-H), 12.47 (1H, s, OH). *Anal.* Calcd for $C_{14}H_{18}N_2O_5$: C, 57.13; H, 6.16; N, 9.52. Found: C, 57.23; H, 6.10; N, 9.49.

8d. Ms: 335 (M^+); 1H -nmr ($CDCl_3$): 1.088 (3H, t, $J=7.3$ Hz, CH_3), 1.094 (3H, t, $J=7.3$ Hz, CH_3), 1.15-1.30 (6H, m, 2 x CH_3), 3.19 (2H, q, $J=7.3$ Hz, NCH_2), 3.30-3.45 (6H, m, 3 x NCH_2), 3.77 (3H, s, CH_3O), 4.12 (2H, br s, NCH_2CO), 6.16 (1H, br d, C^5-H), 6.41 (1H, s, C^3-H), 6.73 (1H, d, $J=8.3$ Hz, C^6-H). Hydrolysis for 10.5 h gave **9d**, 90%, pale yellow prisms from benzene-hexane, mp 115-116°C; ms: 280 (M^+); ir: 3290, 1635, 1595; 1H -nmr ($CDCl_3$): 1.18 (3H, t, $J=7.3$ Hz, CH_3), 1.24 (3H, t, $J=7.3$ Hz, CH_3), 3.33 (2H, q, $J=7.3$ Hz, NCH_2), 3.46 (2H, q, $J=7.3$ Hz, NCH_2), 3.82 (3H, s, CH_3O), 4.19 (2H, d, $J=3.6$ Hz, NCH_2CO), 6.40-6.46 (2H, m, $C^3,5-H$), 7.43 (1H, d, $J=8.6$ Hz, C^6-H), 7.43 (1H, br s, NH), 12.55 (1H, s, OH). *Anal.* Calcd for $C_{14}H_{20}N_2O_4$: C, 59.99; H, 7.19; N, 9.99. Found: C, 59.98; H, 7.26; N, 9.97.

8e. Ms: 307 (M^+); 1H -nmr ($CDCl_3$): 0.92 (3H, t, $J=7.3$ Hz, CH_3), 0.99 (3H, t, $J=7.3$ Hz, CH_3), 1.55 (2H, m, CH_2), 1.68 (2H, m, CH_2), 3.24 (2H, br m, NCH_2), 3.40 (2H, br m, NCH_2), 3.76 (3H, s, CH_3O), 4.06 (2H, br s, NCH_2CO), 6.18 (1H, d, $J=8.0$ Hz, C^5-H), 6.32 (1H, s, C^3-H), 7.21 (1H, d, $J=8.0$ Hz, C^6-H).

8f. Ms: 387 (M^+); 1H -nmr ($CDCl_3$): 1.13-1.50 (10H, m, 5 x CH_2), 1.58-2.10 (10H, m, 5 x CH_2), 3.51-3.76 (2H, m, 2 x NCH), 3.77 (3H, s, CH_3O), 4.01 (2H, br s, NCH_2CO), 6.19 (1H, d, $J=9.2$ Hz, C^5-H), 6.36 (1H, s, C^3-H), 7.18 (1H, d, $J=9.2$ Hz, C^6-H). Hydrolysis of **8f** for 7.5 h followed by chromatographic separation on silica gel gave N-cyclohexyl-2-hydroxy-4-methoxybenzamide (**11f**) and **9f**. **11f** (9%): yellow plates from hexane, mp 113-115°C; ms: 249 (M^+); ir: 3380, 1624, 1590; 1H -nmr ($CDCl_3$): 1.15-2.10 (10H, m, 5 x CH_2), 3.81 (3H, s, CH_3O), 3.85-4.00 (1H, m, NCH), 5.91 (1H, br s, NH), 6.39 (1H, dd, $J=8.9, 2.6$ Hz, C^5-H), 6.46 (1H, d, $J=2.6$ Hz, C^3-H), 7.22 (1H, d, $J=8.9$ Hz, C^6-H), 12.80 (1H, s, OH). **9f** (77%): needles from $CHCl_3$ -hexane, mp 175.0-176.5°C; ms: 306 (M^+); ir: 3390, 3300, 3260, 1670, 1625; 1H -nmr ($CDCl_3$): 1.10-2.00 (10H, m, 5 x CH_2), 3.72-3.86 (1H, m, NCH), 3.81 (3H, s, CH_3O), 4.03 (2H, d, $J=4.9$ Hz, NCH_2CO), 5.81 (1H, br m, NH), 6.40-6.45 (2H, m, $C^3,5-H$), 7.17 (1H, br s, NH), 7.39 (1H, d, $J=8.6$ Hz, C^6-H), 12.41 (1H, s, OH). *Anal.* Calcd for $C_{16}H_{22}N_2O_4$: C, 62.73; H, 7.24; N, 9.14. Found: C, 62.06; H, 7.21; N, 8.98.

Preparation of 9a. Into a mixture of salicylic acid (2.0 g, 14.5 mmol) and N-hydroxysuccinimide (1.67 g, 14.5 mmol) dissolved in dry dioxane (23 ml), a solution of DCC (2.99 g, 14.5 mmol) in dry dioxane (7 ml) was dropwise added on ice-cooling. The resulting white precipitates were removed by filtration, washed well with dry dioxane, and the filtrate was concentrated to dryness to give 3.4 g (quantitative) of N-salicyloyloxy-succinimide, prisms from benzene, mp 193-195°C; ms: 235 (M^+); ir: 1740; 1H -nmr ($CDCl_3$): 2.93 (4H, s, $COCH_2CH_2CO$), 6.98-8.01 (4H, m, aromatic-H), 9.52 (1H, s, OH).

The resulting N-salicyloyloxysuccinimide (600 mg, 2.6 mmol), together with ethyl glycinate HCl (356 mg, 2.6 mmol), was dissolved in dry DMF (10 ml). Into the solution was added triethylamine (283 mg, 2.8 mmol) in dry DMF (5 ml) on ice-cooling, and the whole was stirred for 1.5 h on cool. The reaction solution was added with 5% NaHCO₃ (20 ml) and extracted twice with AcOEt. From the AcOEt extracts, 474 mg (83%) of ethyl N-salicyloylaminoacetate was obtained, needles from hexane, mp 89-90°C; ms: 223 (M⁺); ir: 3400, 1720, 1640; ¹H-nmr (CDCl₃): 1.33 (3H, t, J=7.3 Hz, CH₃), 4.22 (2H, d, J=5.0 Hz, NCH₂CO), 4.29 (2H, q, J=7.3 Hz, OCH₂), 6.80 (1H, br s, NH), 6.88-7.46 (4H, m, aromatic-H), 12.01 (1H, br s, OH).

To the above-obtained ethyl ester (250 mg, 1.1 mmol) was added pyrrolidine (5 ml), and the whole was stirred at room temperature for 2 h. After evaporation of the reaction solvent, 278 mg (99%) of 9a was obtained, mp 181-182°C (EtOH), which was identical in all respects with the sample obtained from 8a as described before.

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