Noble Synthesis of Xanthene-based Dyes by Copper-catalyzed Azide–Alkyne Cycloaddition Reaction#

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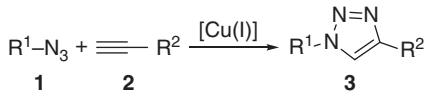
Ever since the concept of "click" chemistry was introduced by Sharpless in 2001, copper-catalyzed azide–alkyne cycloaddition reaction has been drawing much attention in organic synthesis.[1] This 1,3-dipolar cycloaddition reaction, which gives 1,2,3-triazoles (**3**) from azides (**1**) and alkynes (**2**) with high selectivity and wide scope under mild reaction conditions, has been widely utilized in combinatorial, pharmaceutical, and materials chemistry and chemical biology (Scheme 1).[2] Of those various applications, we are interested in the synthesis of new fluorescent dyes based on xanthene by use of "click" chemistry for a new class of fluorophores as a part of our continuous efforts in the preparation of small organic dyes for dye-sensitized solar cell and sensor applications.[3]



Scheme 1. Cu (I)-catalyzed azide–alkyne cycloaddition.

While the 1,3-dipolar cycloaddition has become a reliable methodology as a linking reaction in various applications,[4] there have also been attempts utilizing click chemistry to assemble new fluorophores effectively.[5] For example, the cycloaddition of alkyne-functionalized xanthones or xanthenes with azides[5b] and azidocoumarines with terminal alkynes[5d] provided a variety of fluorescent molecules in a combinatorial manner (Figure 1).

Here we report our preliminary results on the preparation and spectroscopic analysis of new xanthene-type dyes having a triazole ring that was introduced effectively by a copper-catalyzed azide–alkyne cycloaddition reaction.

Our synthetic route for the new class of xanthene-based dyes, shown in Scheme 2, is simple and straightforward, starting from the methoxymethyl (MOM)-protected xanthone **4**. An ethynyl group was introduced to the xanthone by addition reaction with lithium (trimethylsilyl)acetylide in high yield. After the trimethylsilyl (TMS) group on the xanthenol **5** was removed by mixing with tetrabutylammonium fluoride (TBAF), azide–alkyne cycloaddition reaction was performed with both aromatic and aliphatic azides in the presence of 10 mol% of copper(I) iodide in one pot. The "click" reaction proceeded smoothly at ambient temperature to give the desired 1,2,3-triazoles **6** in good yield within 12 h. As expected, acid-catalyzed deprotection of MOM groups on **6** with trifluoroacetic acid provided a new type of xanthene-based dyes **7** having a triazole group. The formation of the fluorescent product **7** was easily detected by irradiation at 365 nm with a hand-held UV lamp to exhibit yellow fluorescence.

From a preliminary evaluation of the absorbance and the fluorescence properties of **7**, it was revealed that wavelengths of maximum absorption (λ_{max}^{Ab}) and maximum emission (λ_{max}^{Em}; excited at 520 nm) were similar to each other regardless of the R substituents in **7**: $\lambda_{max}^{Ab}/\lambda_{max}^{Em}$ (nm/nm) = 520/544 for **7a** (R = Ph); 518/544 for **7b** (R = CH_2Ph); 516/540 for **7c** (R = CH_2CH_2Ph); and 518/540 for **7d** (R = $CH_2(CH)_5Br$). Incidentally, compound **7a** having an aromatic substituent exhibited stronger absorption than the others having benzyl or alkyl substituents, which was confirmed by comparison of the extinction coefficients (see Table S1, Supporting Information). In addition, it was also found that the absorption properties of **7** were pH dependent, which can be attributed to the presence of different protolytic forms depending on the pH.[6] For example, stronger absorption was observed when pH was increased from 6.0 to 10.5, as shown in Figure 2.

In summary, we have synthesized a new type of small organic dyes based on the xanthene skeleton successfully, and evaluated

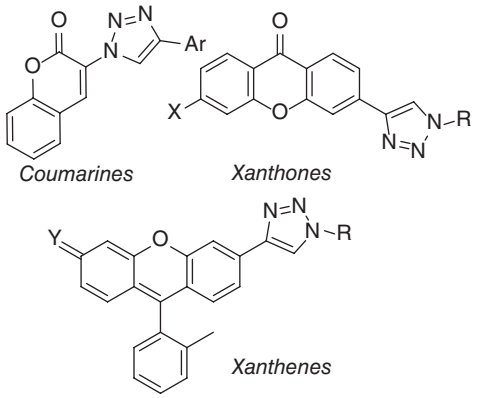
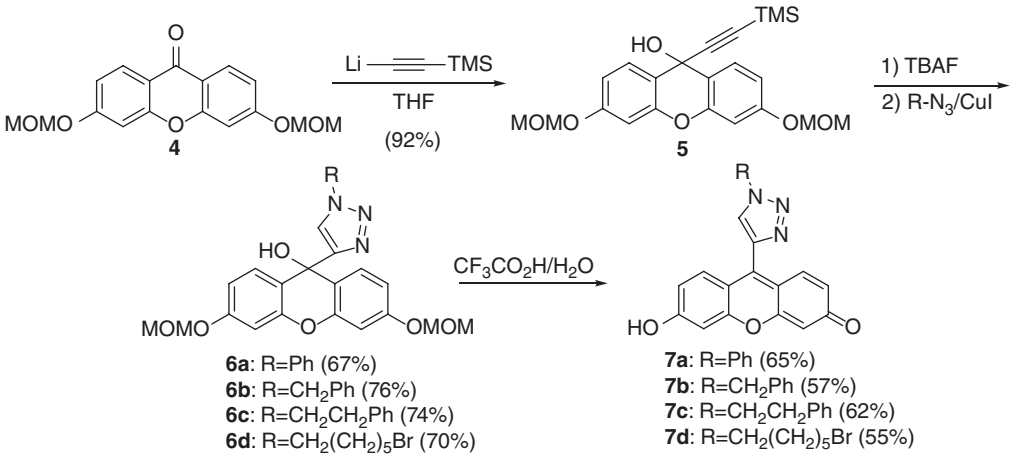


Figure 1. "Click" fluorophores.

This paper is dedicated to Professor Kwan Kim on the occasion of his honorable retirement.



Scheme 2. Synthetic route to xanthene-based dyes (**7**) by use of "click" chemistry.

their absorbance and fluorescence properties. By the use of "click" chemistry, or Cu-catalyzed azide–alkyne cycloaddition reaction, a series of xanthene dyes having 1,2,3-triazole moiety have been prepared effectively and conveniently.

Experimental

General Remarks. ^{1}H and ^{13}C NMR spectra were obtained on a Varian (400 MHz for ^{1}H and 100 MHz for ^{13}C, respectively, USA) spectrometer with Me_4Si as internal reference. Absorption spectra were recorded using an Optizen 2120UV spectrometer (Mecasys, Korea), and fluorescence and excitation spectra were obtained using a FluoroMax spectrometer (Horiba, Japan). The absorbance values of compounds **7** as a function of pH were obtained using the sodium phosphate buffer (0.1 M, Na_2HPO_4 and NaH_2PO_4). The azide compounds were prepared by known procedures.[7]

3,6-Bis(methoxymethoxy)-9*H*-xanthen-9-one (**4**). To a solution of 3,6-dihydroxy-9*H*-xanthen-9-one[8] (7.0 g, 30.7 mmol) in dry THF (tetrahydrofuran, 45 mL) was added DIPEA (*N,N*′-diisopropylethylamine, 7 mL, 92.1 mmol) at 4 °C. After the mixture was stirred for 30 min, chloromethyl methyl ether (MOM-Cl, 16.0 mL, 92.1 mmol) was added to the solution at that temperature. The solution was allowed to warm to 22 °C and stirred for 8 h. Aqueous HCl (5%, 35 mL) was added to the resulting mixture, and the crude product was extracted from ethyl acetate. The organic layer was washed with saturated NaCl and dried over anhydrous $MgSO_4$. After the solvent was removed *in vacuo*, flash column chromatography (hexane/dichloromethane/ethyl acetate = 1:1:0.2) afforded **4** (8.12 g, 84% yield) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 (d, J = 8.8 Hz, 2H), 7.08 (d, J = 2.0 Hz, 2H), 7.01 (dd, J = 2.4, 8.8 Hz, 2H), 5.29 (s, 4H), 3.52 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.6, 162.1, 157.7, 128.1, 116.5, 113.9, 103.0, 94.3, 56.3; HRMS *m/z* calcd for $C_{17}H_{16}NaO_6$ $[M + Na]^+$ 339.0845, found 339.0839.

3,6-Bis(methoxymethoxy)-9-((trimethylsilyl)ethynyl)-9*H*-xanthen-9-ol (**5**). To a solution of **4** (0.24 g, 0.75 mmol) in 5 mL of dry THF was added ((trimethylsilyl)ethynyl)lithium in 5 mL of dry THF at −78 °C for 15 min, and then the mixture was stirred at room temperature for 2 h. The reaction mixture was extracted from dichloromethane and sodium bicarbonate. The organic layer was dried over anhydrous $MgSO_4$ to give **5** (0.29 g, 0.69 mmol, 92%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (d, J = 8.8 Hz, 2H), 6.90 (dd, J = 2.2, 8.4 Hz, 2H), 6.84 (d, J = 2.2 Hz, 2H), 5.19 (s, 4H), 3.48 (s, 6H), 0.21 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.3, 150.7, 129.6, 117.6, 112.6, 106.4, 103.5, 94.4, 91.4, 62.9, 56.0, 25.5; HRMS *m/z* calcd for $C_{22}H_{26}NaO_6Si$ $[M + Na]^+$ 437.1396, found 437.1942.

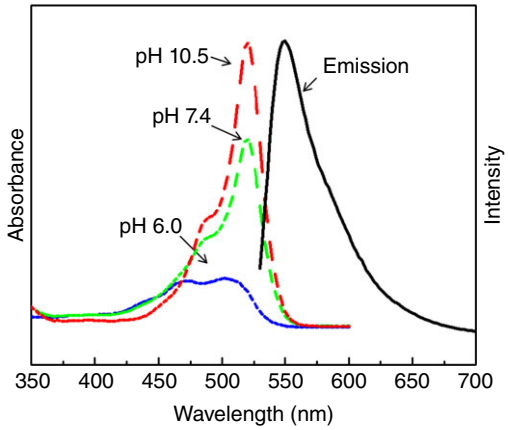


Figure 2. Absorption spectra of **7a** at various pH values and the fluorescence emission spectrum at pH 7.4 (excited at 520 nm).

The representative procedure for compounds 6: 3,6-Bis(methoxymethoxy)-9-(1-phenyl-1*H*-1,2,3-triazol-4-yl)-9*H*-xanthen-9-ol (6a). A solution of **5** (0.86 g, 2.07 mmol) and TBAF (3.1 mL, 3.1 mmol) was stirred in 15 mL of THF for 1 h. To the resulting solution was added azidobenzene (0.49 g, 2.08 mmol) and CuI (0.04 g, 0.20 mmol), and then the mixture was stirred for 12 h. After the reaction, the crude product was extracted from dichloromethane and brine. The product was purified by column chromatography (hexane/ethyl acetate = 2:1) to give **6a** (0.64 g, 2.07 mmol, 67%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (s, 1H), 7.69 (d, J = 7.6 Hz, 2H), 7.49 (m, 5H), 6.87 (d, J = 2.4 Hz, 2H), 6.82 (dd, J = 2.0, 8.8 Hz, 2H), 5.18 (s, 4H), 3.82 (s, 1H), 3.47 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.0, 155.8, 150.7, 137.0, 129.7, 128.7, 120.4, 119.1, 118.8, 112.7, 103.4, 94.3, 66.3, 56.1; HRMS *m/z* calcd for $C_{25}H_{23}N_3NaO_6$ $[M + Na]^+$ 484.1485, found 484.1492.

3,6-Bis(methoxymethoxy)-9-(1-benzyl-1*H*-1,2,3-triazol-4-yl)-9*H*-xanthen-9-ol (6b). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (m, 5H), 7.24 (s, 1H), 7.22 (m, 2H), 6.81 (d, J = 2.8 Hz, 2H), 6.77 (dd, J = 2.4, 8.4 Hz, 2H), 5.44 (s, 2H), 5.15 (s, 4H), 3.81 (s, 1H), 3.45 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.7, 150.5, 134.3, 129.5, 128.9, 128.6, 127.9, 120.8, 118.7, 112.4, 103.2, 94.2, 66.1, 55.9, 54.0; HRMS *m/z* calcd for $C_{26}H_{25}N_3NaO_6$ $[M + Na]^+$ 498.1641, found 498.1635.

3,6-Bis(methoxymethoxy)-9-(1-phenylethyl-1*H*-1,2,3-triazol-4-yl)-9*H*-xanthen-9-ol (6c). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (d, J = 8.8 Hz, 2H), 7.23 (m, 3H), 7.00 (m, 2H), 6.90 (s, 1H), 6.83 (d, J = 2.4 Hz, 2H), 6.79 (dd, J = 2.4, 8.8 Hz, 2H), 5.18 (s, 4H), 4.51 (t, J = 2.8 Hz, 2H), 3.78 (s, 1H), 3.48 (s, 6H), 3.16 (t, J = 2.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.8, 154.5, 150.5, 136.8, 129.6, 128.8, 128.7, 128.6, 126.9, 121.5, 118.8, 112,4, 103.2, 94.3, 77.3, 56.0, 36.6; HRMS *m/z* calcd for $C_{27}H_{27}N_3NaO_6$ $[M + Na]^+$ 512.1798, found 512.1794.

3,6-Bis(methoxymethoxy)-9-(1-(6-bromohexyl)-1*H*-1,2,3-triazol-4-yl)-9*H*-xanthen-9-ol (6d). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (d, J = 8.6 Hz, 2H), 7.23 (s, 1H), 6.85 (d, J = 2.3 Hz, 2H), 6.80 (dd, J = 2.2, 8.6 Hz, 2H), 5.19 (s, 4H), 4.27 (t, J = 7.4 Hz, 2H), 3.83 (br s, 1H), 3.52 (t, J = 6.6 Hz, 2H), 3.48 (s, 6H), 1.26 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.8, 150.5, 129.6, 120.7, 118.9, 112.5, 103.2, 94.3, 60.1, 55.8, 49.9, 44.5, 33.3, 29.7, 27.1, 20.8, 13.9; HRMS *m/z* calcd for $C_{25}H_{30}BrN_3NaO_6$ $[M + Na]^+$ 570.1216, found 570.1215.

The representative procedure for compounds 7: 6-Hydroxy-9-(1-phenyl-1*H*-1,2,3-triazol-4-yl)-3*H*-xanthen-3-one (7a). A solution of **6a** (0.41 g, 0.89 mmol) in 5 mL of CF_3CO_2H/H_2O (9.5/0.5) was stirred at 0 °C for 12 h. After the reaction, the crude reaction mixture was extracted from (*i*-PrOH/dichloromethane = 1:3) and brine. The product was purified by column chromatography (MeOH/dichloromethane = 1:9) to give **7a** (0.21 g, 0.65 mmol, 65%) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.41 (s, 1H), 8.07 (d, J = 8.0 Hz, 2H), 7.72 (m, 4H), 7.75 (t, J = 8.0 Hz, 1H), 6.74 (d, J = 8.8 Hz, 2H), 6.65 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 156.2, 138.7, 136.1, 130.8, 129.7, 129.0, 120.5, 114.2, 103.2; HRMS *m/z* calcd for $C_{21}H_{13}N_3NaO_3$ $[M + Na]^+$ 378.0855, found 378.0849.

6-Hydroxy-9-(1-benzyl-1*H*-1,2,3-triazol-4-yl)-3*H*-xanthen-3-one (7b). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.9 (s, 1H), 7.7 (d, J = 9.2 Hz, 2H), 7.4 (m, 5H), 6.8 (dd, J = 2.0, 9.2 Hz, 2H), 6.7 (s, 2H), 5.8 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 157.8, 138.8, 136.2, 132.2, 129.6, 129.1, 128.8 115.2, 103.9, 54.1; HRMS *m/z* calcd for $C_{22}H_{15}N_3NaO_3$ $[M + Na]^+$ 392.1011, found 392.1003.

6-Hydroxy-9-(1-phenylethyl-1*H*-1,2,3-triazol-4-yl)-3*H*-xanthen-3-one (7c). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.51 (s, 1H), 7.46 (d, J = 8.8 Hz, 2H), 7.26 (m, 5H), 6.80 (d, J = 8.8 Hz, 2H), 6.74 (s, 2H), 4.85 (t, J = 7.2 Hz, 2H), 3.31 (t, J = 7.2 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 157.0, 137.5, 131.3, 128.9, 128.5, 126.7, 114.5, 103.2, 51.0, 35.7; HRMS *m/z* calcd for $C_{23}H_{17}N_3NaO_3$ $[M + Na]^+$ 406.1168, found 406.1162.

6-Hydroxy-9-(1-(6-bromohexyl)-1*H*-1,2,3-triazol-4-yl)-3*H*-xanthen-3-one (7d). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.85 (s, 1H), 7.80 (d, J = 9.6 Hz, 2H), 6.89 (d, J = 9.2 Hz, 2H), 6.82 (s, 2H), 4.57 (t, J = 8.8 Hz, 2H), 3.53 (t, J = 8.8 Hz, 2H), 1.86 (m, 4H), 1.42 (m, 4H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 157.4, 137.8, 131.8, 129.0, 121.2, 114.5, 103.1, 49.9, 35.0, 32.0, 29.3, 26.9, 25.0; HRMS *m/z* calcd for $C_{21}H_{20}BrN_3NaO_3$ $[M + Na]^+$ 464.0586, found 464.0581.

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Supporting Information. Experimental details, characterization of the new compounds, and spectroscopic data are available in the online version of this paper.

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