ORGANIC LETTERS

2012
Vol. 14, No. 21
5554–5557

One-Pot Synthesis of Highly Fluorescent 2,5-Disubstituted-1,3a,6a-triazapentalene

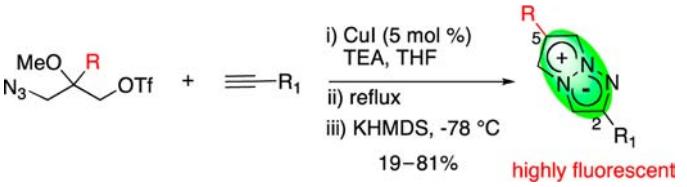
Kosuke Namba,*,† Akane Mera,‡ Ayumi Osawa,‡ Eri Sakuda,† Noboru Kitamura,† and Keiji Tanino*,†

Department of Chemistry, Faculty of Science, Hokkaido University, Kita-ku, Sapporo 060-0810, Japan, and Graduate School of Chemical Sciences and Engineering, Hokkaido University, Sapporo 060-0810, Japan

namba@mail.sci.hokudai.ac.jp; ktanino@sci.hokudai.ac.jp

Received September 27, 2012

ABSTRACT



A one-pot synthetic method was established for the preparation of 2,5-disubstituted-1,3a,6a-triazapentalenes. The fluorescence observation of the synthetic 2,5-disubstituted-1,3a,6a-triazapentalenes revealed that the introduction of a substituent at the C5 position allowed a substantial change in the fluorescence quantum yield with little effect on the fluorescence wavelength.

Fluorescent organic molecules are an important class of compounds in modern science and technology and are widely used for such applications as biological imaging probes, sensors, lasers, and light-emitting devices.[1] Thus, the development of useful fluorescent organic molecules has been a subject of intensive research due to their importance to the advancement of many industries.[2] Recently, we discovered that a 1,3a,6a-triazapentalene skeleton without an additional fused ring system was a compact and highly fluorescent chromophore that exhibited various interesting fluorescence properties, such as a strong positive fluorescence solvatochromism and a noteworthy correlation of the fluorescence wavelength with the inductive effect of the 2-substituents.[3−5] For example, the fluorescence of the 1,3a,6a-triazapentalenes shifted to longer wavelengths along with increases in the Hamett σ_p value of substituents on the benzene ring of 2-phenyl analogs (Figure 1). Therefore, the 1,3a,6a-triazapentalene system provides a breakthrough fluorescent molecule that enables the same fluorescent chromophore to exhibit various fluorescence colors. For expansion of the fluorescent wavelength to the red color region, an introduction of an additional electron-withdrawing substituent was considered to be effective. An alternative potential approach is the introduction of an electron-donating substituent at the C5 position so that the push−pull effect on the 10π-electron system could be enhanced. Thus, we became intrigued with the synthesis of 1,3a,6a-triazapentalenes possessing

† Department of Chemistry.
‡ Graduate School of Chemical Sciences and Engineering.

(1) (a) Shinar, J., Ed. *Organic Light-Emitting Devices*; Springer: New York, 2004. (b) Valeur, B. *Molecular Fluorescence*; WILEY-VCH: Weinheim, 2002. (c) Willardson, R. K.; Weber, E.; Mueller, G.; Sato, Y. *Electroluminescence 1, Semiconductors and Semimetals Series*; Academic Press: New York, 1999.

(2) For selected recent examples of a fluorescent molecule: (a) Shimizu, M.; Takeda, M.; Higashi, M.; Hiyama, T. *Angew. Chem., Int. Ed.* **2009**, *48*, 3653–3656. (b) Lorbach, A.; Molte, M.; Li, H.; Lerner, H.-W.; Holthausen, M. C.; Jäkle, F.; Wagner, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 4584–4588. (c) Mercier, L. G.; Piers, W. E.; Parvez, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 6108–6111. (d) Zhao, Z.; Wang, Z.; Lu, P.; Chan, Y. K.; Liu, D.; Lam, J. W. Y.; Sung, H. H. Y.; Williams, I. D.; Ma, Y.; Tang, B. Z. *Angew. Chem., Int. Ed.* **2009**, *48*, 7608–7611. (e) Caruso, A., Jr.; Siegler, M. A.; Tovar, J. D. *Angew. Chem., Int. Ed.* **2010**, *49*, 4213–4217. (f) Ren, Y.; Baumgartner, T. *J. Am. Chem. Soc.* **2011**, *133*, 1328–1340. (g) Siamaki, A. R.; Sakalauskas., M.; Arndtsen, B. A. *Angew. Chem., Int. Ed.* **2011**, *50*, 6552–6556. (h) Zhang, Z.; Xu, B.; Su, J.; Shen, L.; Xie, Y.; Tian, H. *Angew. Chem., Int. Ed.* **2011**, *50*, 11654–11657. (i) Zhao, D.; Hu, J.; Wu, N.; Huang, X.; Qin, X.; Lan, J.; You, J. *Org. Lett.* **2011**, *13*, 6516–6519. (j) Liu, B.; Wang, Z.; Wu, N.; Li, M.; You, J.; Lan, J. *Chem.—Eur. J.* **2012**, *18*, 1599–1603.

(3) Namba, K.; Osawa, A.; Ishizaka, S.; Kitamura, N.; Tanino, K. *J. Am. Chem. Soc.* **2011**, *133*, 11466–11469.

(4) The 1,3a,6a-triazapentalenes with an aryl fused system exhibit very little fluorescence (Φ_F = 0.0001). See: Albini, A.; Bettinetti, G.; Minoli, G. *J. Am. Chem. Soc.* **1991**, *113*, 6928–6934.

(5) Other examples of the 1,3a,6a-triazapentalene derivatives without an aryl fused system: (a) Koga, H.; Hirobe, M.; Okamoto, T. *Tetrahedron Lett.* **1978**, *19*, 1291–1294. (b) Chen, Y.; Wang, D.; Petersen, J. L.; Akhmedov, N. G.; Shi, X. *Chem. Commun.* **2010**, *46*, 6147–6149.

10.1021/ol302668y
Published on Web 10/16/2012

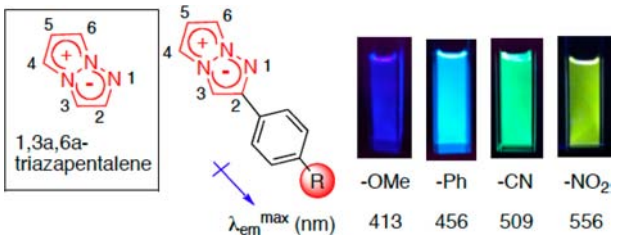
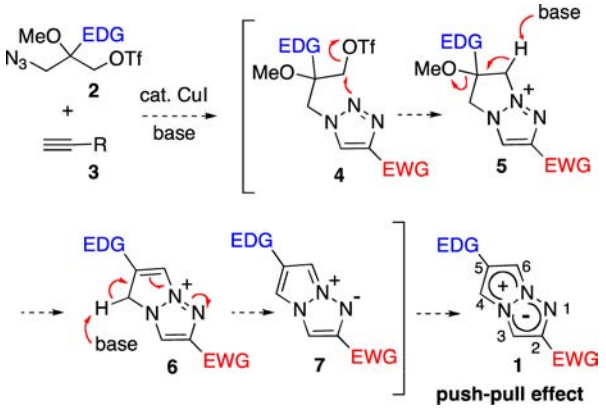


Figure 1. Fluorescence properties of 1,3a,6a-triazapentalene.

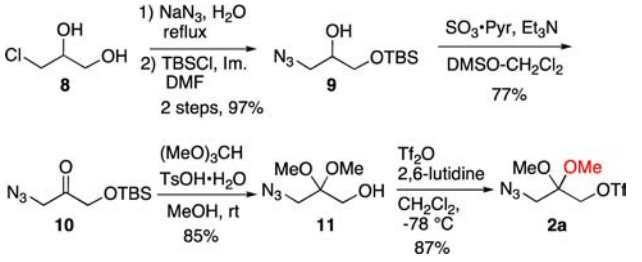
various substituents at the C5 position in order to elucidate the push−pull effect on the fluorescence properties of the 1,3a,6a-triazapentalenes. To this end, we designed an azide **2** having methoxy and triflate groups at the C2 and C3 positions, respectively, which were expected to be more stable than the corresponding azidoditriflates, as the precursor of 5-substituted-1,3a,6a-triazapentalenes **1**. The click reaction[6] of **2** with an alkyne would give the 1,2,3-triazole **4** which may undergo a cyclization reaction to afford the bicyclic triazolium ion **5**. Finally, treatment of the intermediate with a base would give the desired 5-substituted-1,3a,6a-triazapentalene **1** through elimination of the methoxy group followed by aromatization (Scheme 1). Our previous study showed that the basic treatment of the corresponding free alcohol of **5**, which was obtained by the epoxide ring-opening reaction, afforded alkanenitrile unexpectedly. Therefore, the methoxy group was adopted as a leaving group. Herein, we describe the synthesis of 2,5-disustituted-1,3a,6a-triazapentalenes and their interesting fluorescence properties.

Scheme 1. Synthetic Plan of 2,5-Disubstituted-1,3a,6a-triazapentalene



The synthesis of azide fragment **2a** started with easily available 3-chloro-1,2-propanediol **8**. Nucleophilic displacement

Scheme 2. Synthesis of the Azide Fragments **2a**



of the chloride with azide followed by selective protection of the primary alcohol afforded **9**, which was oxidized by SO_3•Pyr-DMSO to give ketone **10**.[7] The acetal formation reaction of **10** simultaneously induced the removal of a TBS group to give alcohol **11**. Subsequent treatment of **11** with Tf_2O at −78 °C afforded the desired **2a** as a precursor of 5-methoxy-1,3a,6a-triazapentalenes (Scheme 2).

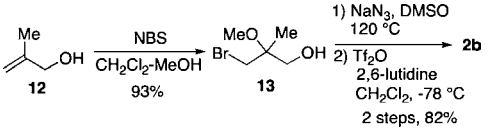
Having prepared the azide fragment **2a**, we next attempted the cascade reaction leading to 1,3a,6a-triazapentalene. Although the click reaction of **2a** with phenylacetylene (**3a**) was stopped at the 1,2,3-triazole **4a**, refluxing after the click reaction induced the cyclization to afford the bicyclic triazolium ion **5a**. However, subsequent direct elimination of the methoxy group by coexisting triethylamine did not proceed. The use of DBU as a stronger base and the use of *p*-TsOH under acidic conditions were also unsuccessful, whereas the use of KHMDS at −78 °C was later found to give the desired 2-phenyl-5-methoxy-1,3a,6a-triazapentalene **1a** in 64% yield from **2a**. This is the first example of the synthesis of 2,5-disubstituted-1,3a,6a-triazapentalenes without an additional fused ring system (Scheme 3). Thus, the one-pot preparative method for the 2,5-disubstituted-1,3a,6a-triazapentalenes was established.

We next examined the introduction of various substituents at the C5 position in order to elucidate the effect of the 5-substituent on the fluorescence properties (Table 1). First, 4-cyanophenyl acetylene (**3b**) was adopted as an alkyne fragment because the cyanophenyl group exhibited a high fluorescence quantum yield and the excellent stability to UV irradiation among the various 2-substituents.[3] The similar sequential reaction of **2a** with **3b** afforded the desired 2-cyanophenyl-5-methoxy-1,3a,6a-triazapentalene **1b** in 60% yield (entry 1). The click reaction of methyl analog **2b**[8] with **3b** afforded the bicyclic triazolium ion without reflux conditions. Subsequent direct treatment with KHMDS at −78 °C resulted in the

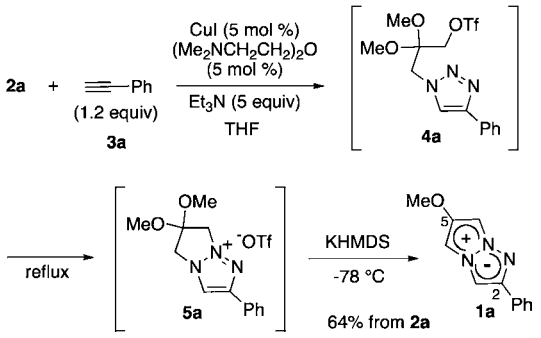
(6) (a) Kolb, H. C.; Finn, M. G.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2001**, *40*, 2004–2021. (b) Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2002**, *41*, 2596–2599. (c) Tornøe, C. W.; Christnesen, C.; Meldal, M. *J. Org. Chem.* **2002**, *67*, 3057–3064. (d) Wu, P.; Fokin, V. V. *Aldrichimica Acta* **2007**, *40*, 7–17.

(7) Parikh, J. R.; Doering, W. E. *J. Am. Chem. Soc.* **1967**, *89*, 5505–5507.

(8) The methyl substituent **2b** was easily obtained from β-methallyl alcohol **12** by a sequential operation of a haloetherification, a substitution with azide, and a triflation.

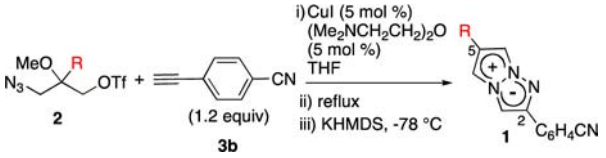


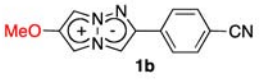
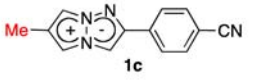
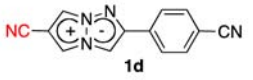
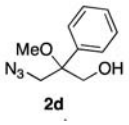
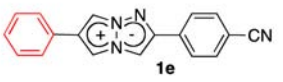
Scheme 3. Synthesis of 2-Phenyl-5-methoxy-1,3a,6a-triazapentalene **1a**



desired 5-methylsubstituted-1,3a,6a-triazapentalene **1c** in 63% yield (entry 2). Next, the reaction of cyano analog **2c**[9] was attempted in order to examine the opposite effect of the electron-withdrawing group, and the desired 5-cyano-1,3a,6a-triazapentalene **1d** was obtained in 57% yield (entry 3). In addition, the effect of the aromatic substituent was also intriguing. Since the corresponding triflate of **2d**[10] easily induced the [1,2]-shift of the phenyl group during column purification, the synthesis was started with a triflation reaction of alcohol **2d** to afford the desired 5-phenyl analog **1e** in 19% yield (entry 4).

Table 1. Synthesis of the Various 5-Substituents of 2-(4-Cyanopheyl)-1,3a,6a-triazapentalenes

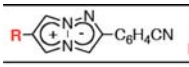
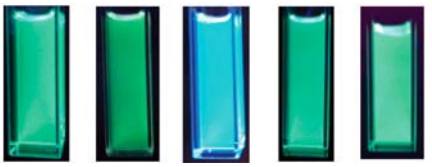


entry	azide	product	yield[a]
1	**2a**: R = OMe	 **1b**	60%
2[b]	**2b**: R = Me	 **1c**	63%
3	**2c**: R = CN	 **1d**	57%
4[b,c]	 **2d**	 **1e**	19%

[a] Isolated yield. [b] Reflux condition was not needed. [c] Corresponding triflate was used without purification.

Having prepared the various 5-substituents of 2-cyanophenyl-1,3a,6a-triazapentalenes, we investigated their fluorescence properties (excited at 370 nm) (Table 2). Although the introduction of an electron-donating group at the C5 position was expected to induce a longer-wavelength shift, the methoxy-substituted analog **1b** exhibited a similar absorption and fluorescence maxima with those of unsubstituted **1f**.[3] The methyl analog **1c** also showed a small longer-wavelength shift of the fluorescence maximum. Neither shift was assigned to the wavelength shift of the phenyl analog **1e** despite the extended π-conjugation system. In contrast, the fluorescence maximum of cyano analog **1d** shifted to a shorter wavelength, indicating that the electron-withdrawing group has an effect on the fluorescence wavelength. Although the expected shifts of the fluorescence wavelength were not observed, it was especially noteworthy that the fluorescence quantum yields (Φ_F) of all 5-substituted-1,3a,6a-triazapentalenes **1b**–**1e** were dramatically increased.[11] This suggested that the introduction of an electron-donating group at the C5 position allowed a substantial increase in Φ_F without any effect on the fluorescence wavelength, and the 5-substituted-1,3a,6a-triazapentalene system easily provides access to potentially useful fluorescent probes exhibiting a high fluorescence quantum yield.

Table 2. Fluorescence Properties of 5-Substituted-1,3a,6a-triazapentalenes **1b**–**e** and Unsubstituted **1f** in Dichloromethane

	**1b** R = OMe	**1c** R = Me	**1d** R = CN	**1e** R = Ph	**1f** R = H
λ_{abs}^{max} (nm)	378	385	360	383	381
λ_{em}^{max} (nm)	505	518	453	506	509
Φ_F	0.57	0.55	0.45	0.48	0.18
color					

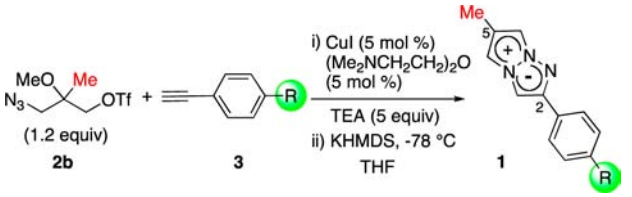
Finally, we examined the effect of the application of a 5-substituent in the variously colored 1,3a,6a-triazapentalenes on the increment of Φ_F without a significant shift of the fluorescence wavelength (Table 3). The methyl analog **2b** was adopted as the azide fragment due to its ready availability and high fluorescence quantum yield of **1c**. The click reaction of **2b** with phenyl acethylene (**3a**) followed by basic treatment afforded a desired 2-phenyl-5-methyl-1,3a,6a-triazapentalene **1g** in 81% yield. As we expected,

(9) The cyano substituent **2c** was converted from ketone **10** via a cyanohydrin forming reaction followed by methylation reactions; see Supporting Information.

(10) The phenyl substituted analog **2d** was prepared from 2-phenyl-2-propene-1-ol in the same manner as **2b**.

(11) Fluorescence quantum yields were estimated by using 9,10-diphenylanthracene (9,10-DPA) in cyclohexane as a standard (Φ_F = 0.91).

Table 3. Click Reaction of **2b** with Various Acetylenes **3** and Fluorescence Properties of Various 5-Methyl-1,3a,6a-triazapentalenes in Dichloromethane



entry	alkyne (Hammett σ_p)	yield[d]	λ_{em}^{max} (nm)	Φ_F	color
-	**3b**: R = CN (0.71)	**1c**: 63%	518 (509)[e]	0.55 (0.18)[f]	
1[a]	**3a**: R = H (0.00)	**1g**: 81%	422 (419)[e]	0.074 (0.030)[f]	
2[b]	**3c**: R = Ph (0.04)	**1h**: 59%	466 (456)[e]	0.27 (0.24)[f]	
3[a]	**3d**: R = OMe (-0.28)	**1i**: 72%	421 (413)[e]	0.025 (0.062)[f]	
4[b,c]	**3e**: R = NO_2 (0.81)	**1j**: 27%	575 (556)[e]	0.022 (0.16)[f]	

[a] Excited at 340 nm. [b] Excited at 370 nm. [c] The reaction was conducted at −78 to 0 °C by using Et_2NLi as a base. [d] Isolated yield. [e] Fluorescence maximum of corresponding 5-unsubstituted analog. [f] Fluorescence quantum yield of corresponding 5-unsubstituted analog.

the Φ_F value of **1g** was substantially increased compared with that of the corresponding 5-unsubstituted-1,3a,6a-triazapentalene, and the fluorescence wavelength showed a small longer-wavelength shift (Table 3, entry 1). The similar one-pot reaction of **2b** with 4-biphenylacetylene **3c** afforded 2-(4-biphenyl)-5-methyl-1,3a,6a-triazapentalene **1h** in 59% yield, and **1h** also exhibited an increase of Φ_F with a small longer-wavelength shift (entry 2). The reactions of (4-methoxyphenyl)acetylene **3d** and (4-nitrophenyl)acetylene **3e** also gave the corresponding 2,5-disubstituted-1,3a,6a-triazapentalenes **1i** and **1j** in 72% and 27% yields, respectively. Surprisingly, however, **1i** and **1j** showed a considerable decline in Φ_F, although the fluorescence spectral shifts exhibited the same tendency toward a slightly longer shift (entries 3 and 4). Therefore, it was found that the introduction of a C-5 substituent did not entirely increase the Φ_F of the 1,3a,6a-triazapentalenes. However, we found that the change in Φ_F in the case of the electron-withdrawing substituents (Hammet σ_p value 0 (H) $\sim$ 0.71 (CN)) at the C-2 position increased Φ_F, whereas an electron-donating ($\sigma_p \leq -0.28$ (OMe)) and the much stronger electron-withdrawing substituent ($\sigma_p \geq 0.81$ (NO_2)) exhibited a substantial decline in Φ_F. Thus, the 1,3a,6a-triazapentalenes provide a useful fluorescent system in which the Φ_F value can be easily modified by introducing 5-substituents based on the Hammet σ_p value of 2-substituents.

In this study, an efficient and versatile method was established for the preparation of 2,5-disubstituted-1,3a,6a-triazapentalene, and the effect of a 5-substituent on the fluorescence properties was elucidated. The introduction of a 5-substituent substantially enhanced the fluorescence quantum yield (Φ_F) of the 1,3a,6a-triazapentalenes with little effect on the fluorescence wavelength, and the tendency for the Φ_F value could be estimated from the Hammet σ_p value of the 2-substituent. Therefore, the 1,3a,6a-triazapentalenes as fluorescent chromophores provide an innovative fluorescent system that can tune both the fluorescence wavelength and quantum yield. That is, the fluorescence wavelength and quantum yield can be controlled by the 2- and 5-substituents, respectively. Applications of the 1,3a,6a-triazapentalene system as functionalized fluorescent probes in the life sciences fields are currently being investigated in our laboratory.

Acknowledgment. This work was partially supported by the Global COE program (Project No. B01: Catalysis as the Basis for Innovation in Material Science), Grant-in-Aid for Scientific Research (Grant No. 24310162), and Grant-in-Aid for Scientific Research on Innovative Areas (Project No. 2105: Organic Synthesis Based on Reaction Integration and No. 2301: Chemical Biology of Natural Products) from the Ministry of Education, Culture, Sports, Science, and Technology, Japan.

Supporting Information Available. Experimental details, absorption and fluorescent spectra, and ^1H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.