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Direct Synthesis of Fluorescent 1,3a,6a-Triazapentalene Derivatives via Click–Cyclization–Aromatization Cascade Reaction

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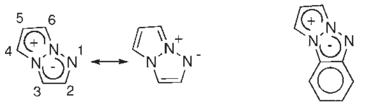
Supporting Information

ABSTRACT: An efficient and versatile method was established for the preparation of 1,3a,6a-triazapentalenes. The 1,3a,6a-triazapentalene skeleton without an additional fused ring system was discovered to be a compact and highly fluorescent chromophore, which exhibited various interesting fluorescent properties such as a noteworthy correlation of luminescent wavelength with the Hammett σ_p value and a strongly positive solvatofluorochromism.

Fluorescent organic molecules constitute an important class of compounds in modern science and technology, and they are widely used as biological imaging probes, sensors, lasers, light-emitting devices, etc.[1] Thus, the development of useful fluorescent organic molecules has been a subject of intensive research due to their significance in the advancement of many industries. However, the commonly used fluorescent molecules have thus far needed to be improved in the following respects. Most highly fluorescent molecules are large and display limited solubility in water. Often the methods used to synthesize them do not allow the facile introduction of functionality and the design of systems whose luminescent properties span a range of wavelength. To develop a new system that will solve the above problems, we focused our attention on 1,3a,6a-triazapentalene (**1a**) possessing a compact 10π-electron system (Figure 1).[2] Although the fluorescent properties of **1a** have not yet been elucidated,[3] it is expected to be an excellent fluorescent chromophore with electric and/or structural effects of various substituents on the triazapentalene ring. Furthermore, the development of an efficient method for the synthesis of **1a** by an intermolecular cycloaddition reaction in a single step enables the connection of two functionalized molecules to generate fluorescent function simultaneously. Thus, we describe herein a facile synthesis of the 1,3a,6a-triazapentalenes and their interesting fluorescent properties.

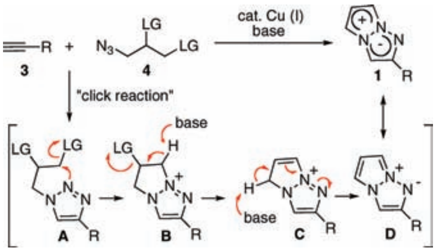
There have been several examples of the synthesis of 1,3a,6a-triazapentalene derivatives with aryl fused and heteroaryl fused systems such as benzotriazapentalene **2**,[4] and they are mainly based on the intramolecular N–N bond-forming reaction of pyrazole derivatives with thermally or photochemically generated nitrenes.[5] In addition, intramolecular alkylation reactions of benzotriazole derivatives have also been reported.[6] In contrast, there have been very few examples of the 1,3a,6a-triazapentalene derivatives without an aryl fused system,[7] and the simple 1,3a,6a-triazapentalene (**1a**) has never been synthesized. Thus far, 2-methyl- and 2-phenyl-1,3a,6a-triazapentalene synthesized by Hirobe are the only examples of monosubstituted triazapentalenes. They were synthesized by different methods using *N*-amination of pyrazoles, and their fluorescent properties were not mentioned.[4b] We have attempted to establish a versatile and common method for the synthesis of various triazapentalenes without aryl fused systems to elucidate the properties of the triazapentalene skeleton as a fluorescent chromophore. To achieve a single-step synthesis of 1,3a,6a-triazapentalenes **1**, we planned to apply the click reaction of various alkynes **3** with azide **4**, which possesses two leaving groups at each of the C2 and C3 positions, as shown in Scheme 1. The Cu(I)-catalyzed click reaction[8] of alkyne **3** with azide **4** under basic conditions would afford a triazole **A**, which should undergo intramolecular cyclization to give a triazolium ion **B**. Under basic conditions, the intermediate **B** would be subsequently converted to **1** by a sequential reaction of E2 elimination and deprotonation.



1,3a,6a-triazapentalene (**1a**) benzotriazapentalene **2**

Figure 1. Structure of 1,3a,6a-triazapentalene (**1a**) and benzotriazapentalene **2**.

Scheme 1. Synthesis of 1 by the click reaction



We began the investigation of the click reaction with 3-azidopropane-1,2-diol bis(trifluoromethanesulfonate) (**4a**) as an azide fragment because of its high reactivity and ready availability. The azide **4a** was easily obtained from 3-chloro-1,2-propanediol by a simple operation in just two steps,[9] and it is stable enough to be purified by column chromatography and stored for several months in the freezer. After the examination of various reaction conditions using 1-pentadecyne (**3b**) as an alkyne fragment, we found that treatment of **3b** with 1.2 equiv of **4a** in the presence of 5 mol % of copper(I) iodide, and 5 mol % of bis[2-(*N*,*N*-dimethylamino)ethyl]ether as a ligand, and 5 equiv of

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Scheme 2. Click reaction of the pentadecyne 3b with the azide 4a

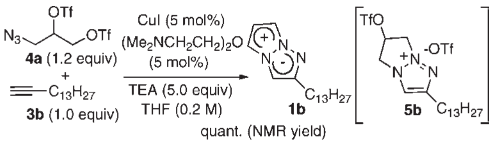
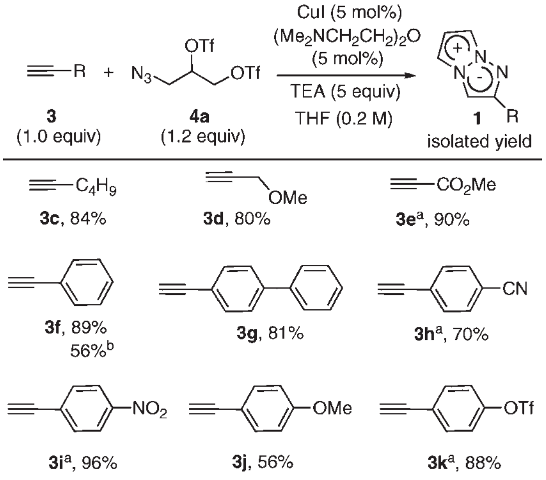


Table 1. Click Reaction of 4a with Various Acetylenes



[a] The reaction was conducted by using 1.2 equiv of alkyne and 1.0 equiv of **4a** in 0.01 M THF. [b] The reaction was conducted in water.

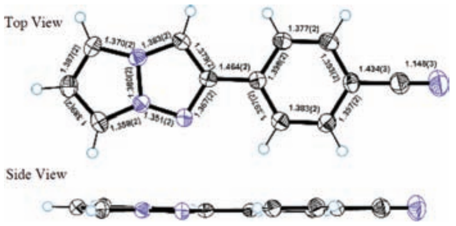
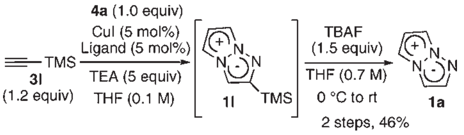


Figure 2. ORTEP of the molecular structure and bond lengths of **1h**.

Scheme 3. Synthesis of 1a



triethylamine as a base in THF (0.2 M) afforded the desired **1b** in quantitative yield by ^{1}H NMR (Scheme 2).[10,11] By comparison, a similar click reaction in the absence of base gave a triazolium ion **5b**[12] in 29% yield, along with a trace amount of **1b**. The formation of **5b** showed that the triazole generated in the click reaction underwent intramolecular substitution to form the bicyclic framework. Very little of the elimination product **1b** was produced. The spontaneous substitution of triazole needs the triflate as a leaving group. A similar click reaction with bis-mesylate and bis-tosylate instead of bis-triflate (**4a**) afforded the corresponding triazoles without the formation of the bicyclic compound.

Having established a preparative method for 1,3a,6a-triazapentalene (**1b**), the click reaction of **4a** with other acetylenes was examined (Table 1). The click reaction of 1-hexyne (**3c**) with **4a** afforded the desired 2-butyl-1,3a,6a-triazapentalene (**1c**) in 84% isolated yield. The acetylenes possessing a functional group such as methyl propargyl ether (**3d**), methyl propioate (**3e**), and phenyl acetylene (**3f**) also gave the corresponding desired triazapentales, **1d**−**1f** in 80%, 90%, and 89% yields, respectively. It is especially noteworthy that the reaction of **3f** with **4a** could proceed even in water to give **1f** in acceptable yield. The reaction of biphenyl acetylene (**3g**) afforded triazapentalene (**1g**) in 81% yield, and the phenyl acetylene derivatives having an electron-withdrawing group such as a cyano group (**3h**) or a nitro group (**3i**) also gave the desired triazapentalenes **1h** and **1i** in 70% and 96% yields, respectively. The reaction of electron-rich derivative **3j** showed a slight decline in yield, and triazapentalene **1j** was obtained in 56% yield. The reaction of triflate derivative **3k**, which has a coupling site for further reactions, also afforded **1k** in 88% yield. Thus, it was confirmed that the established preparation method for the 1,3a,6a-triazapentalenes **1** is applicable to various acetylenes.

The structure of **1h** was unequivocally established by an X-ray diffraction study, which elucidated that **1h** has a 10π-electron resonance structure as an aromatic ring, as shown in Figure 2. The structures of the other 1,3a,6a-triazapentalenes were also confirmed by the correlation of spectral data with **1h**.

Next, the first synthesis of unsubstituted 1,3a,6a-triazapentalene (**1a**) was examined in order to elucidate the properties of the 1,3a,6a-triazapentarene skeleton. A similar click reaction of **4a** with (trimethylsilyl)acetylene (**3l**) afforded **1l** in 71% NMR yield. We found that **1l** decomposed readily during column chromatography. Therefore, the crude **1l** was directly subjected to desilylation with TBAF to give **1a** in 46% overall yield as a volatile oil (Scheme 3).

Having prepared **1a**−**k**, we investigated their fluorescent properties. Except for **1a**, the characteristic absorption bands of synthetic 1,3a,6a-triazapentalenes were observed from 300 to 500 nm in dichloromethane (Supporting Information [SI]), and absorption maxima of selected 1,3a,6a-triazapentalenes are noted in Table 2. We found that **1a**−**k** exhibited fluorescent emissions and studied the emission in several different solvents (see below). In particular, the fluorescent observation of **1a** (excited at 330 nm) is the first direct experimental evidence that the 1,3a,6a-triazapentalene skeleton is a fluorescent chromophore, although the fluorescent quantum yield (Φ_F) is not high, being 0.017 with reference to 9,10-diphenylanthracene. In clear contrast, **2** as an aryl fused system, which was prepared according to the procedure of Bettinetti,[5c] exhibits almost no fluorescence ($\Phi_F = < 0.001$). Also, the various related analogues of **2** have not been reported to have noteworthy fluorescent properties. Thus, we discovered that the absence of an additional fused ring system is an essential factor for fluorescence of the 1,3a,6a-triazapentalenes. Interestingly, the fluorescent intensities and wavelengths of 1,3a,6a-triazapentalenes varied widely with 2-substituents (see Figure 3). For example, the 2-methoxycarbonyl derivative **1e** exhibited highly fluorescent emissions despite its compact molecular size, and the fluorescent quantum yield (Φ_F) of **1e** was dramatically increased to 0.21. Therefore, application of **1e** as the most compact highly fluorescent probe might be interesting. The lithium carboxylate **1o**, which was obtained by hydrolysis of

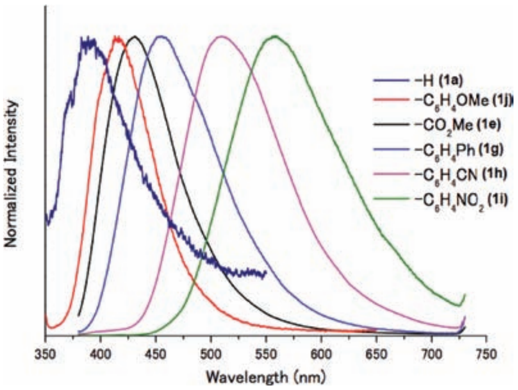


Figure 3. Photonic luminescence of selected 1,3a,6a-triazapentalenes in dichloromethane.

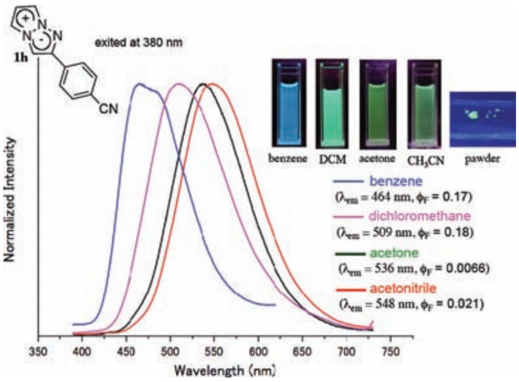
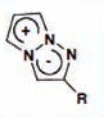
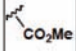
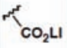
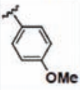
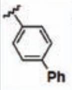
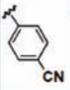
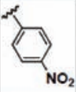


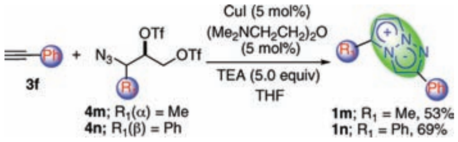
Figure 4. Emissive behaviors and fluorescence spectra of **1h** with various solvents.

Table 2. Fluorescent Properties of Selected 1,3a,6a-Triazapentalenes in Dichloromethane

	1a	1e	1o[a]	1j	1g	1h	1i
	 H	 CO_2Me	 CO_2Li	 OMe	 Ph	 CN	 NO_2
λ_{abs}^{max} (nm)	-	342	317	330	345	381	412
Hammett σ_p	-	-	-	-0.28	0.04	0.71	0.81
λ_{em}^{max} (nm)	389	431	449	413	456	509	556
Φ_F	0.017	0.21	0.034	0.062	0.24	0.18	0.16
color							

[a] Measured in water.

Scheme 4. Click reaction with substituted azidotriflates 4m and 4n



1e,[13] also showed fluorescent emission even in water. Thus, the 1,3a,6a-triazapentalene was found to serve as a compact fluorescent probe having a large Stokes shift (132 nm) in the aqueous system (Table 2). Furthermore, an amide derivative **1p** also exhibits fluorescence, although Φ_F was decreased to 0.039.[13] The simple 1,3a,6a-triazapentalenes **1a**, **1e**, and **1o** are gradually decomposed by UV irradiation, and 2-methoxyphenyl-1,3a,6a-triazapentalene (**1j**) was partly decomposed after sequential irradiation for 5 min. However, 2-phenyl analogues with an electron-withdrawing group such as **1g**, **1h**, and **1i** are still stable after 5 min, and **1h** and **1i** are unbreakable even after 1 h (see SI). More interestingly, the emission maxima of 2-phenyl-1,3a,6a-triazapenthalene derivatives exhibit a noteworthy correlation with the Hammett σ_p value of substituents on the benzene ring such as methoxy group **1j** (σ_p −0.28, λ_{max} = 413 nm), phenyl group **1g** (σ_p 0.04, λ_{max} = 456 nm), cyano group **1h** (σ_p 0.71, λ_{max} = 509 nm), and nitro group **1i** (σ_p 0.81, λ_{max} = 556 nm). Therefore, the 1,3a,6a-triazapentalene system easily provides access to potentially useful fluorescent probes whose emissions span a range of wavelengths. Furthermore, the Hammett σ_p value can be of use in fashioning new systems designed to access additional wavelengths. Another standout fluorescent feature of the 1,3a,6a-triazapentalenes is the large Stokes shifts (83−144 nm), which is a very useful factor to suppress the action of background fluorescence in the various fluorescent analyses.

Furthermore, the synthesized triazapentalenes exhibit strong positive solvatofluorochromism.[14] For example, the fluorescent emissions and spectra of 2-(4-cyanophenyl)-1,3a,6a-triazapentalene **1h** in different solvents are shown in Figure 4. The fluorescence emissions of **1h** shifted to longer wavelengths with increasing solvent polarity. The solvatofluorochromic behavior of the compact molecule with reasonable fluorescence efficiency might be very useful as fluorescent probes.

Finally, we demonstrated that the substituted azidoditriflates **4m** and **4n** could also be used in a similar click reaction to give 2,4-disubstituted-1,3a,6a-triazapentalenes **1m** and **1n**, regardless of the relative stereochemistry of azidoditriflate (Scheme 4). The fluorescent emissions of **1m** and **1n** were confirmed, although the fluorescent quantum yield (Φ_F) is not high (see SI). Therefore, the click reaction described herein is expected to develop as a "luminous click reaction", which connects two functional materials, simultaneously generating fluorescent function.

In this study, an efficient and versatile method was established for the preparation of nonaryl fused 1,3a,6a-triazapentalenes, and the 1,3a,6a-triazapentalene skeleton was proven to be a compact and highly fluorescent chromophore. The limited synthesis of 1,3a,6a-triazapentalenes without an aryl fused system might be the main reason that they have been previously unrecognized as an excellent fluorescent chromophore. The 1,3a,6a-triazapentalenes systems described herein enabled us to design the luminescent wavelength based on the Hammett σ_p value of 2-substituents, and they exhibited a strong positive solvatofluorochromism. The 1,3a,6a-triazapentalenes appear to be ideal fluorescent molecules that have many advantages such as compact molecular size, water solubility, a simple construction method, facile introduction to various functional materials even in water, high functional group selectivity, and an easy design system for luminescent wavelengths. Additional properties of the

1,3a,6a-triazapentalene system such as the fluorescence lifetime, stabilities, and photodecomposition mechanism are currently being investigated in our laboratory, as are various applications as functionalized fluorescent probes.

ASSOCIATED CONTENT

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

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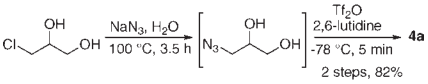
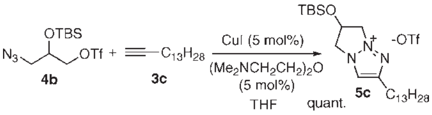
(9) Treatment of 3-chloro-1,2-propanediol with sodium azide in water afforded the corresponding azidodiol, which was directly converted to **4a** in 82% yield. The multigram-scale preparation of **4a** was actually conducted several times without incident. The microscopic observation of thermolytic behavior of **4a** (neat) by melting point apparatus revealed that **4a** decomposes and partially volatilizes at 92 °C. Although we found that a solution of **4a** in 1,4-dioxane is stable enough to be heated to 100 °C for 2 h, manipulating **4a** at high temperature is not recommended. Further investigation about safety is currently underway.



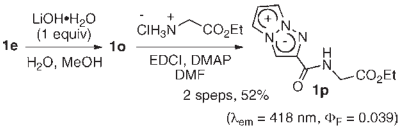
(10) The use of 2,6-lutidine and DBU as bases did not give **1b** because they reacted with **4a** faster than the click reaction. The yield of **1b** was reduced to 66% when diisopropylethylamine was used. The amount of triethylamine could be reduced to 2.0 equiv without a significant loss of yield.

(11) The isolated yield of **1b** was reduced to 71% because a part of **1b** was decomposed to blue product, which strongly adsorbed on silica gel, during column chromatography.

(12) Attempts for isolating the triazolium ion **5b** were unsuccessful. Therefore, the structure of **5b** was determined on the basis of the correlation with triazoium ion **5c**, which was easily obtained by a similar click reaction of **4b** with **3c**.



(13) Treatment of **1e** with 1.0 equiv of lithium hydroxide afforded lithium carboxylate **1o** in quantitative yield. The amide **1p** was prepared by the coupling of **1o** with glycine ethyl ester hydrochloride by the combined action of EDCI and DMAP in DMF.



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