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Two-Step Synthesis of Fluorescent 3-Arylated 1,3a,6a-Triazapentalenes via a Three-Component Triazolization Reaction

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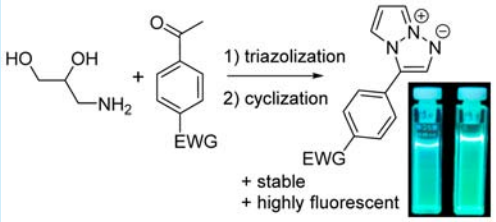
Supporting Information

ABSTRACT: Novel 3-arylated 1,3a,6a-triazapentalenes were synthesized using a metal-free three-component triazolization reaction followed by a triflate based cyclization step. This method starts from simple commercial starting materials and provides an easy functionalization strategy for the 3-position of the triazapentalenes. By introducing electron-withdrawing groups onto this position, stable and highly fluorescent dyes could be synthesized.



Small fluorescent organic molecules are indispensable tools in many applications as biological labels and probes, chemosensors, laser dyes, photoactive materials in light-emitting devices, etc.[1] Recently, 1,3a,6a-triazapentalenes **3** were discovered as compact 10π-electron fluorophores exhibiting various promising properties, such as emission in the UV to the visible light region between 380 and 630 nm, a strong solvatochromism, a large Stokes shift, solubility in water, and a very small size.[2,3] Unfortunately, most triazapentalenes **3** exhibited modest to poor stability. This low stability has been explained as either susceptibility to air oxidation[4] in analogy with 3a,6a-diazapentalenes,[5] to protonation,[2a] or to dimerization[3] in analogy with pentalenes.[6] However, introducing an electron-withdrawing group on the triazapentalene core can improve the stability of the resulting dye.[3] Indeed, the majority of the reported 1,3a,6a-triazapentalenes **3** bear an electron-withdrawing group at their 2- and/or 3-positions.[2,3]

Currently, only two synthetic pathways toward fluorescent triazapentalenes have been reported.[2,3] The first published procedure is based on a copper-catalyzed azide−alkyne cycloaddition between a 3-azidopropane-1,2-diol bis(trifluoromethanesulfonate) **1** and a terminal alkyne **2** (Scheme 1, path A).[2] Under the basic reaction conditions an intramolecular substitution followed by base-induced elimination and aromatization takes place to form the desired 1,3a,6a-triazapentalene **3**. Unfortunately, this method is only useful to synthesize 2-substituted fluorophores. The other positions are much more difficult to functionalize using this strategy,[2b,e] whereas the 3-position cannot be functionalized because this reaction would require an internal alkyne which is unreactive under click reaction conditions.

The second reported pathway toward triazapentalenes starts with an iron-catalyzed alkylation of a 2*H*-1,2,3-triazole **4** with a propargyl alcohol **5** followed by a gold-catalyzed cyclization (Scheme 1, path B).[3] This method allows the introduction of substituents onto the 4- and 6-positions of the fluorophore. However, the starting triazole **4** requires electron-withdrawing substituents to ensure the correct regiochemistry for the alkylation step and to allow the gold-catalyzed cyclization step. Hence, the 2,3-positions are not easy to modify with this strategy; particularly, the scope of the 3-position, which was always substituted with a carbonyl functional group, is limited. An additional disadvantage of both procedures is that their starting materials, 3-azidopropane-1,2-diol bis(trifluoromethanesulfonate) **1** for the first protocol and 2*H*-1,2,3-triazole **4** and propargyl alcohol **5** for the second procedure, are not commercially available.

Recently, our group developed a metal-free three-component reaction between a primary amine, an enolizable carbonyl compound, and *p*-nitrophenyl azide to synthesize 1,4,5-trisubstituted 1,2,3-triazoles.[7] We hypothesized that by using the commercially available 3-aminopropane-1,2-diol **8** as the primary amine, it should be possible to make with this reaction a triazole **10** containing a 2,3-dihydroxypropyl at its 1-position (Scheme 1, path C). Such a triazole could be a precursor for the synthesis of a 3-functionalized 1,3a,6a-triazapentalene **11**, whose accessibility is still very limited using the current procedures, by transforming the hydroxyl groups into leaving groups so that under the influence of base the desired pyrazolium ring can be formed by substitution and elimination (Scheme 1, path C). Hence, we set out to investigate the feasibility of this novel strategy to synthesize new 3-arylated triazapentalenes **11**. Furthermore, the spectroscopic properties of these new dyes were measured in detail.

In order to synthesize the precursor **10**, the three-component reaction developed in our group was used.[7] For the initial test reaction 3-aminopropane-1,2-diol **8** was reacted with acetophenone **9a** and *p*-nitrophenyl azide using 4 Å molecular sieves and a catalytic amount of acetic acid in toluene at 100 °C. Unfortunately, 3-aminopropane-1,2-diol **8** did not dissolve in toluene under the used reaction conditions and only a trace amount of the desired triazole **10a** was formed. However, when the more polar 1,4-dioxane was used as the solvent the amine

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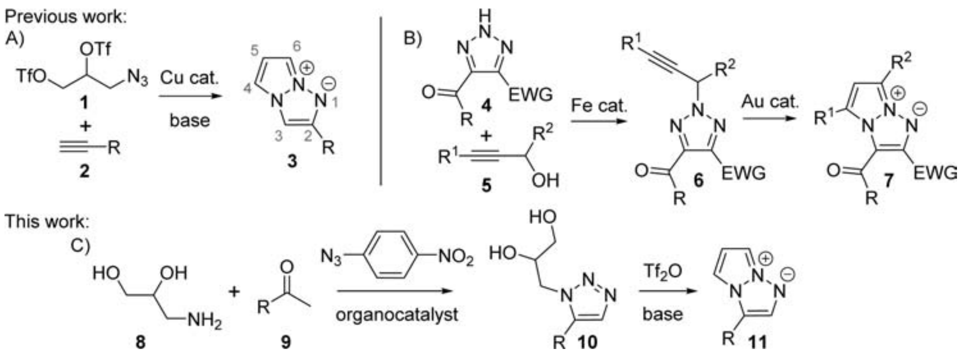
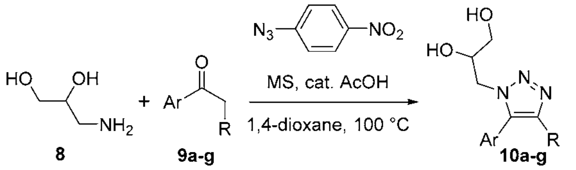
Scheme 1. Summary of the Synthetic Pathways toward Fluorescent Triazapentalenes and the Numbering of the Triazapentalene Core



did dissolve and the reaction occurred, producing the expected 5-phenyl-1,2,3-triazole **10a** in a yield of 60% (Table 1, entry 1).

Table 1. Synthesis of the Triazapentalene Precursor Triazole 10[a]



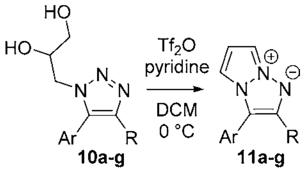
entry	compd	Ar	R	time (h)	yield (%)[b]
1	a	phenyl	H	45	60
2	b	phenyl	Me	44	32
3	c	4-nitrophenyl	H	46	38
4	d	4-cyanophenyl	H	45	44
5	e	4-(methoxycarbonyl)phenyl	H	47	39
6	f	4-chlorophenyl	H	48	59
7	g	pyridin-2-yl	H	24	83

[a]Experimental conditions: 0.5 mmol of aryl ketone **9**, 1.1 equiv of *p*-nitrophenyl azide, 1.2 equiv of 3-aminopropane-1,2-diol **8**, 60 mg of 4 Å molecular sieves (MS), 30 mol % AcOH, 2.5 mL of 1,4-dioxane, stirring for the indicated time at 100 °C. [b]Isolated yield.

Similarly, using propiophenone **9b** as the aryl ketone resulted in a 4-methyl-5-phenyl triazole **10b** (Table 1, entry 2). Moreover, substituted acetophenones **9c–f** under the same reaction conditions gave the corresponding 5-arylated triazoles **10c–f** in modest yields (Table 1, entries 3–6). Reaction with 2-acetylpyridine **9g** was faster than the other reactions and produced a 5-(pyridin-2-yl) triazole **10g** in an excellent yield of 83% (Table 1, entry 7).

To obtain the desired triazapentalene compounds **11** the hydroxyl groups of the triazoles **10** need to be transformed into leaving groups so that in the presence of base the pyrazolium ring of the final products **11** can be formed. The first published procedure to make fluorescent triazapentalenes used triflates as leaving groups for a similar cyclization step.[2a] The cyclization was unsuccessful, however, when a mesylate or a tosylate was used instead of a triflate.[2a] Even though our strategy is different for those in literature, triazole **10** containing triflate substituents might be able to ring close to a 1,3a,6a-triazapentalene. Hence, to test the cyclization step with our triazoles **10**, the hydroxyl groups were converted into triflate leaving groups. To this end, 5-phenyl triazole **10a** was reacted under standard triflate synthesis conditions,[8] using triflic anhydride and pyridine in dichloromethane at 0 °C. This resulted in a quick consumption of the starting material **10a** and the formation of a new product. Unfortunately, attempts to isolate this new product were unsuccessful, as this product decomposed during workup (Table 2, entry 1). Most of this decomposition occurred during evaporation resulting in several unidentifiable colored compounds. However, the NMR of this crude dark green-blue mixture did show that it contained the desired 3-phenyl triazapentalene dye **11a** (Figures S1 and S2). Mass spectroscopy of this crude mixture also confirmed the presence of the desired compound **11a** (Figure S3). Sadly, the instability of this triazapentalene **11a** prevented its isolation and full characterization. When 5-phenyl triazole **10a** was converted to a bistosylate instead of a bistriflate, again no cyclization occurred under the influence of base, not even when the reaction mixture was heated.

Table 2. Synthesis of 1,3a,6a-Triazapentalenes 11 Starting from Substituted Triazoles 10[a]



entry	compd	Ar	R	time (min)	yield (%)[b]
1	a	phenyl	H	30	–[c]
2	b	phenyl	Me	30	–[c]
3	c	4-nitrophenyl	H	40	69
4	d	4-cyanophenyl	H	30	76
5	e	4-(methoxycarbonyl) phenyl	H	30	70
6	f	4-chlorophenyl	H	30	–[c]
7	g	pyridin-2-yl	H	80	–[c]

[a]Experimental conditions: 0.1 mmol of triazole **10**, 10 equiv of pyridine, 3 equiv of Tf_2O, 1 mL of DCM, stirring for the indicated time at 0 °C; afterward the reaction was quenched by addition of 6 equiv of MeOH. [b]Isolated yield. [c]Product decomposes during work up.

In an attempt to limit the decomposition of the final product, the more substituted 4-methyl-5-phenyl triazole **10b** was reacted with triflic anhydride under the same conditions. Unfortunately, the formed product also decomposed during workup and no pure compound could be obtained (Table 2, entry 2). Nonetheless, crude NMR (Figure S4) and mass spectroscopy (Figure S5) showed that the expected 2-methyl-3-phenyl-triazapentalene **11b** was indeed formed during the reaction.

It has been mentioned in the literature that placing an electron-withdrawing group onto the triazapentalene core can improve the stability of the resulting dye.[2a,3] Hence, a series of triazoles **10c**−**g** bearing electron-poor aryl groups were subjected to the cyclization reaction, in order to test if they could form more stable triazapentalene derivatives **11c**−**g** (Table 2, entries 3−7). Reacting triazoles with strongly electron-withdrawing 4-nitrophenyl (in compound **10c**), 4-cyanophenyl (in compound **10d**), or 4-(methoxycarbonyl)-phenyl (in compound **10e**) substituents did indeed produce stable 3-aryl-triazapentalene dyes **11c**−**e** that could be isolated in good yields of around 70% (Table 2, entries 3−5). The less electron-withdrawing 4-chlorophenyl (in triazole **10f**) or pyridin-2-yl (in triazole **10g**) groups were unfortunately not stabilizing enough, and the corresponding triazapentalenes **11f**−**g** decomposed during workup and could not be isolated (Table 2, entries 6 and 7).

The three reactions that gave the stable 1,3a,6a-triazapentalene dyes **11c**−**e** only formed this compound after quenching the reaction with methanol at room temperature. After addition of triflic anhydride at 0 °C and consumption of the starting material **10c**−**e** but before quenching the reaction, the reaction mixture contained a different product, which is assumed to be the bistriflate intermediate. Nonetheless, after quenching and stirring at room temperature a colored compound was formed that could be isolated. Characterization proved that this colored compound is indeed the desired triazapentalene dye **11c**−**e**.

The spectroscopic properties of the newly synthesized 3-aryl-triazapentalene dyes **11c**−**d** (Figure 1) were studied in three solvents (Table 3, Figures S6−S8). As these new compounds seem to be stable under UV irradiation, in contrast to most reported triazapentalenes,[2] their absorption and emission spectra and their fluorescence quantum yield could be fully determined. The results of this investigation are presented in Table 3.

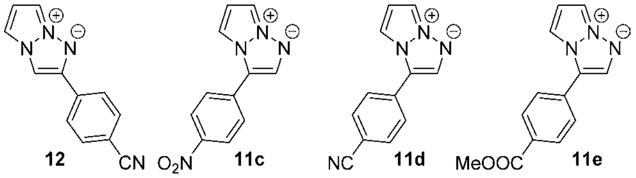


Figure 1. Structures of the new 3-aryl-triazapentalene dyes **11c**−**e** for which the spectroscopic properties were measured together with the structure of the reference compound **12**.[2a]

For comparison, the spectroscopic properties of the related and previously reported[2a] 2-(4-cyanophenyl)-triazapentalene **12** were added to Table 3 as well. This allows us to compare the effect of 2-aryl and 3-aryl substituents on the characteristics of the resulting dyes. The absorption maximum of the dye with a 4-cyanophenyl substituent at the 3-position **11d** is 20 nm red-shifted compared to its 2-substituted derivative **12**. In contrast, the emission maxima show the opposite trend; the 2-arylated dye **12** emits at a longer wavelength than the 3-functionalized derivative **11d**. Hence, the Stokes shift of 2-(4-cyanophenyl)-triazapentalene **12** is larger than the Stokes shift of 3-(4-cyanophenyl)-triazapentalene **11d**.

Comparing the different 3-aryl triazapentalenes shows that the absorption maxima of the ester dye **11e** are located at similar wavelengths as those of the cyano derivative **11d** around 400 nm. Furthermore, the absorption maxima of both compounds are slightly bathochromically shifted when going from polar to apolar solvents. In contrast, a more significant blue shift is observed in the emission maxima of both compounds, located between 442 and 522 nm, with increasing solvent apolarity. Hence, the Stokes shift of the ester **11e** and cyano **11d** dyes are larger in a polar solvent than in an apolar solvent. This blue shift is most pronounced in the ester compound **11e**, when going from acetonitrile to toluene the emission maxima display a hypsochromic shift of 62 nm for the cyano dye **11d** and 79 nm for the ester dye **11e**. Lastly, the emission peaks of both fluorophores in the polar acetonitrile are broader than their absorption peaks, whereas in the apolar toluene they are narrower. The broadness of these peaks for the cyano **11d** and ester **11e** compounds are similar to each other.

The nitrophenyl dye **11c** behaves differently fom the corresponding cyano **11d** and ester **11e** compounds. Most noticeable is that this triazapentalene with a strongly electron-withdrawing nitro group at its 3-position is not fluorescent. In contrast, its 2-substituted derivative, 2-(4-nitrophenyl)-triazapentalene, has been reported before to be fluorescent.[2a]

Table 3. Spectroscopic Data of the New 3-Aryl-triazapentalene Dyes 11c−d and the Reference Compound 12[2a] in Three Solvents

dye	solvent[a]	$\lambda_{\text{abs, max}}$ (nm)	$\lambda_{\text{em, max}}$ (nm)	Stokes shift (cm^{-1})	fwhm$_{\text{abs}}$ (cm^{-1})	fwhm$_{\text{em}}$ (cm^{-1})	Φ_f[b]
12[2a]	MeCN	–[c]	548	–[c]	–[c]	–[c]	0.021
	DCM	381	509	6600	–[c]	–[c]	0.18
	benzene	–[c]	464	–[c]	–[c]	–[c]	0.17
11c	MeCN	471	–[d]	–[d]	4542	–[d]	–[d]
	DCM	475	–[d]	–[d]	4039	–[d]	–[d]
	toluene	470	–[e]	–[e]	3563	–[e]	–[e]
11d	MeCN	397	504	5348	2916	4755	0.17
	DCM	401	464	3386	2686	3495	0.57
	toluene	403	442	2189	2829	2522	0.12
11e	MeCN	395	522	6159	3417	4418	0.04
	DCM	399	476	4054	3267	3675	0.79
	toluene	404	443	2179	2886	2597	0.29

[a] Solvents are listed from top to bottom according to increasing refractive index n. [b] Fluorescence quantum yield determined vs fluorescein in ethanol (Φ_r = 0.79) as a reference. [c] Data were not reported in the literature.[2a] [d] No fluorescence was detected. [e] Fluorescence was too weak to determine this value accurately.

Another difference with the other synthesized triazapentalenes is that the absorption maxima of the 3-(4-nitrophenyl) dye **11c** are red-shifted, by about 70 nm, compared to its cyano **11d** and ester **11e** derivatives. Furthermore, the absorption peak of the nitro compound **11c** is broader than those of the other two 3-aryl triazapentalenes. The nonfluorescence, the red-shifted absorption, and the broader peaks of nitrophenyl dye **11c**, compared to the corresponding cyano **11d** and ester **11e** compounds, might be due to a photoinduced intramolecular charge transfer caused by the strongly electron-withdrawing nitro group.[1a]

The fluorescence quantum yields of the two fluorescent 3-aryl dyes were determined and proven to be higher, particularly in DCM, than the reference 2-(4-cyanophenyl)-triazapentalene **12**. In fact, the synthesized cyano **11d** and ester **11e** fluorophores are both among the most fluorescent triazapentalenes described in the literature.[2,3] To the best of our knowledge, the 3-(4-(methoxycarbonyl)phenyl) dye **11e** possesses the highest fluorescence quantum yield (0.79) of all the 1,3a,6a-triazapentalene compounds reported so far.

In conclusion, using a metal-free three-component triazolization reaction, novel 3-arylated 1,3a,6a-triazapentalenes were synthesized in two steps starting from simple commercial starting materials without needing a toxic heavy metal catalyst. This proved to be a good strategy to functionalize the 3-position of the triazapentalene core. Furthermore, introducing electron-withdrawing groups onto this position was demonstrated to give stable triazapentalene dyes, which allowed their full spectroscopic characterization and is important to develop applications for these dyes. The resulting 3-(4-cyanophenyl) **11d** and 3-(4-(methoxycarbonyl)phenyl) **11e** compounds were found to be highly fluorescent. Moreover, both possess a reactive functional group, a cyano or an ester group, that might be useful as reactive handles for further functionalization.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03309.

> Experimental procedures and characterization data (^{1}H and ^{13}C NMR spectra of all new compounds, NMR spectra and mass spectra of unstable triazapentalenes, and absorption and emission spectra of the triazapentalene dyes) (PDF)

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Notes

The authors declare no competing financial interest.

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