Cross-Coupling

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Synthesis of Water-Soluble Blue-Emissive Tricyclic 2-Aminopyridinium Salts by Three-Component Coupling-(3+3)-Anellation

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Dedicated to Professor Hans-Ulrich Reißig on the occasion of his 70th birthday

Abstract: *The (3+3) anellation of alkynones and cyclic amidines is a novel and unexpected approach to generate intensively blue luminescent tricyclic 2-aminopyridinium salts with quantum yields Φ_f up to 63 % in water. By implementation into a consecutive three-component reaction, these title compounds are obtained rapidly and efficiently in a diversity-oriented fashion. Most interestingly, these bi- and tricyclic 2-aminopyridinium salts emit in dichloromethane and water solutions, thus making them interesting novel luminophore probes for bioanalytics, as well as in the solid state, thus making them blue emitters with tunable efficiency.*

Organic luminophores are particularly important synthetic targets because of the numerous important applications, such as in organic light-emitting devices,[1] food safety,[2] analytics,[3] and medicine.[4] Fluorescent imaging agents possess extremely high sensitivity, spatial-temporal resolution and tunability, and thus are widely employed, for example, with STED (stimulated emission depletion) microscopy to monitor various biological processes with high accuracy.[5] As water is the naturally most abundant environmental medium, water-soluble luminophores play an important role in biological,[6] medicinal,[7] and environmental analyses.[8] Great efforts have been made to develop synthetic approaches to fluorophores for use in various fields, such as material science,[9] DNA detection,[10] targeted imaging,[11] and theranostics.[12] However, the inherent hydrophobicity of most organic luminophores hampers their practical application in aqueous media, for example, in cytosol. Although hydrophilization might be achieved by introducing charged or other highly polar substituents at the luminescent core, the design of intrinsically hydrophilic luminophores almost ideally solves the quest for water solubility without the need for additional decoration of the functional fluorescent core structure.

The unabated quest for novel functional chromophores in a diversity-oriented fashion for establishing reliable structure–property relationships calls for efficient and efficacious synthetic approaches. Multicomponent reactions (MCRs) in chromophore synthesis[13] appear to be a highly practical method for diversity-oriented synthesis. This enables beneficial properties to be explored[14] and provides access to a maximum of the resulting chemical space with minimal effort. The catalytic synthesis of alkynones, as extremely versatile three-carbon building blocks, has opened straightforward avenues to consecutive multicomponent syntheses of many five-, six-, and seven-membered heterocyclic core structures through the very easy introduction of three points of diversity.[15] In particular, bifunctional nucleophiles, such as acyclic amidines,[16] 2-aminopyridines (as a variation of the Bohlmann–Rahtz synthesis),[17] or 3-amino-3-iminopropanoic acid esters are employed as substrates[18] to give pyrimidines.

Herein, we report an unexpected novel anellation principle of alkynones and cyclic amidines that leads directly to the formation of fluorescent cationic heterocyclic systems. This key reaction is uneventfully embedded into a novel consecutive three-component syntheses starting from acyl chlorides, terminal alkynes, and cyclic amidines to provide a large and highly diverse library of water-soluble 2-aminopyridinium luminophores.

Upon employing 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as a base in consecutive transformations of alkynones, we serendipitously discovered an interesting product, which showed green emission upon excitation with a hand-held UV lamp. This prompted us to investigate this product and the reaction in detail. An equimolar mixture of alkynone **1a** and DBU (**2a**) in dichloromethane at room temperature afforded, after workup with aqueous hydrochloric acid, product **3a** in 13 % yield (Scheme 1). The reaction sequence was optimized by variation of the stoichiometry and Lewis acid catalysts to give compound **3a** in 86 % yield by using 35 mol % $AlCl_3$. (Scheme 1; for details on the optimization, see Table SI-1 in the Supporting Information).

To our delight, the addition-cyclocondensation sequence was found to be compatible with the Sonogashira coupling, which allowed us to develop a consecutive three-component synthesis of anellated 2-aminopyridinium salts **3** (Scheme 2)

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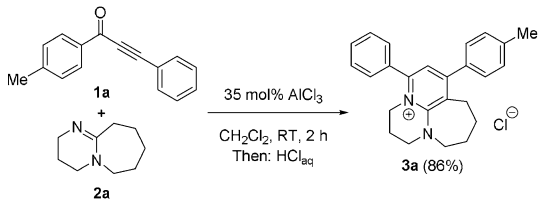
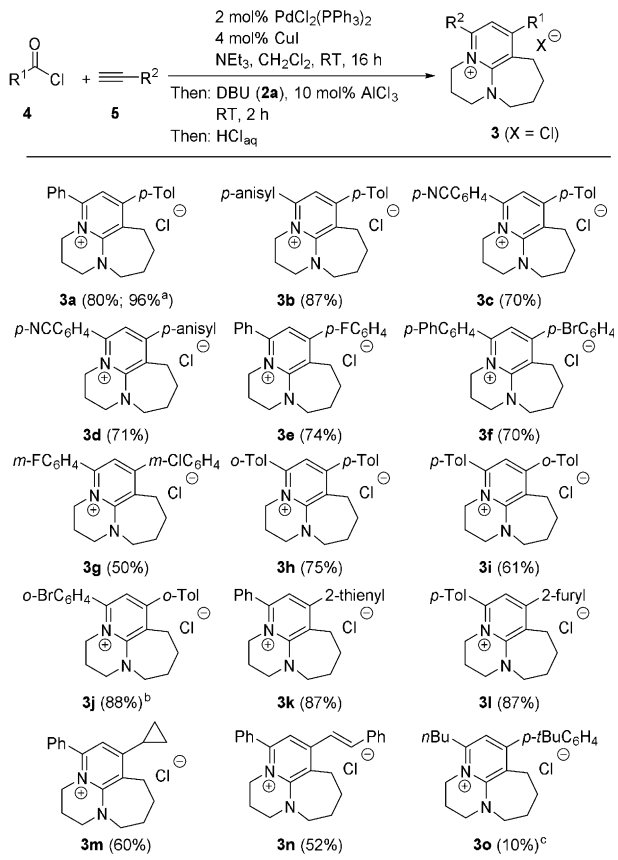


Scheme 1. Synthesis of the anellated 2-aminopyridinium salt **3a** by addition-cyclocondensation of alkynone **1a** with DBU (**2a**).



Scheme 2. One-pot procedure for the preparation of compounds **3**. Reaction conditions: Acid chloride **4** (1 mmol), alkyne **5** (1 mmol), $PdCl_2(PPh_3)_2$ (0.02 mmol), CuI (0.04 mmol), triethylamine (1.1 mmol), CH_2Cl_2 (3 mL), RT, 16 h; then: DBU (**2a**; 3 mmol), $AlCl_3$ (10 mol%), RT, 2 h; yield of isolated product for the one-pot procedure. [a] Reaction was performed on a 7 mmol scale. [b] A 1:1.8 mixture of rotamers was isolated. [c] The yield of compound **3o** by the two-step process starting from the purified alkynone was 21%.

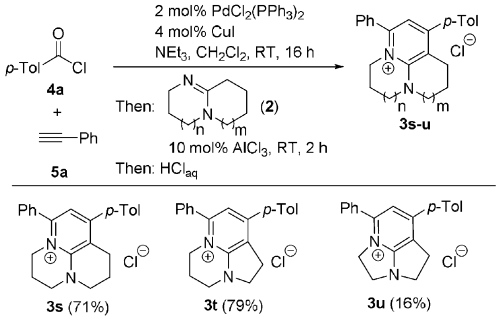
after a simple isolation and purification procedure based upon extraction (for details, see the Supporting Information). The coupling of acyl chlorides **4** with acetylenes **5** in the presence of catalytic amounts of $PdCl_2(PPh_3)_2$ (2 mol%), CuI (4 mol%), and triethylamine furnishes alkynones **1**.[19] The subsequent addition of DBU and $AlCl_3$ to the reaction mixture gives tricyclic 2-aminopyridinium salts **3** (15 examples) in mostly good yields. It is noteworthy that a decrease in the amount of $AlCl_3$ to 10 mol% does not affect the yield of the one-pot procedure. However, the amount of DBU has to be increased to three equivalents to compensate for the deprotonation of triethylamine hydrochloride.

The substitution pattern of R^1 is the same as in other three-component syntheses,[15,16] namely (hetero)aryl and cyclopropyl substituents without any α-acidic hydrogen atoms that could lead to the formation of ketenes. Favorable R^2 substituents are (hetero)aryl moieties, while alkyl alkynes give only poor yields (compound **3o**). The one-pot synthesis of compound **3a** can also be readily scaled up, with the product obtained in 96% yield without any chromatography.

The structures of the products **3** were unambiguously established by NMR spectroscopy, in particular by NOESY, HMBC, and HSQC spectroscopy of **3a**, **3h**, **3i**, and **3l**, which indicated that only a single regioisomer was formed. The chemoselectivity of the Michael addition step with DBU is nicely illustrated by the cinnamoyl substrate, where only the triple bond reacts to give the addition-cyclocondensation product (compound **3n**). According to ^{1}H NMR spectroscopy and HPLC-MS analysis, a 1:1.8 isomeric mixture of the bis(*ortho*-aryl)-substituted product **3j** was obtained. Additional HSQC, HMBC, and NOESY experiments unambiguously supported the identical connectivity of the two isomers. The inequivalence of the methylene protons in the ^{1}H NMR spectrum suggested the presence of rotamers arising from hindered rotation of the *ortho*-substituted aryl moieties. The double signal set in the ^{1}H NMR spectrum of the mixture remained unchanged upon heating to 110 °C, thus indicating a high rotation barrier.

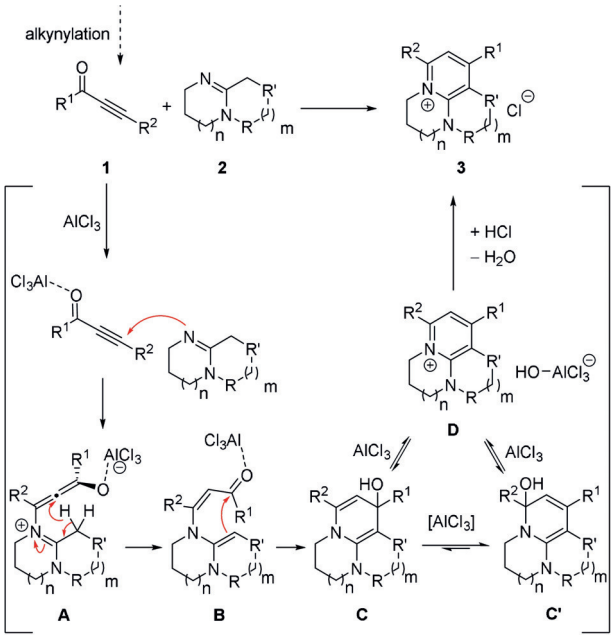
Phenyl propargylic aldehyde and further aliphatic alkynes were separately tested as substrates in the addition-cyclocondensation step with DBU, but furnished only low yields of the predicted heterocyclic structures[20] (see Scheme S1 in the Supporting Information). The method can also be applied to the synthesis of bicyclic 2-aminopyridinium salts by employing monocyclic amidines as substrates (see Schemes S2 and S3 in the Supporting Information).

The structure of the bicyclic amidines **2** was also varied in the sequence starting from model substrates **4a** and **5a** (Scheme 3). Hexahydro-2*H*-pyrido[1,2-*a*]pyrimidine (**2b**) ($n = m = 1$) and 1,5-diazabicyclo[4.3.0]non-5-ene (DBN, **2c**; $n = 1$, $m = 0$) were successfully employed in the sequence and furnished the tricyclic aminopyridinium products **3s** and **3t** in high yields. Strained tetrahydro-3*H*-pyrrolo[1,2-*a*]imidazole (**2d**; $n = m = 0$) delivered product **3u** with two anellated five-membered rings in 16% yield.



Scheme 3. Variation of the bicyclic amidines **2** in the three-component coupling-addition-cyclocondensation synthesis of tricyclic 2-aminopyridinium salts **3p–r**.

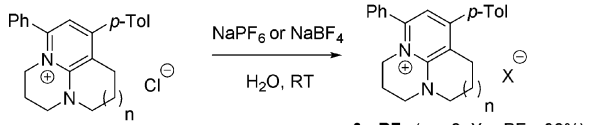
The mechanism of the addition-cyclocondensation step of the sequence can be rationalized as shown in Scheme 4. Alkynones **1** and amidines **2** react in two consecutive nucleophilic additions. First the nucleophilic nitrogen atom of the imine attacks the alkynone to form adduct **A**, which is



Scheme 4. Mechanistic rationale for the Michael addition-cyclocondensation step.

stabilized by tautomerization to *N*,*N*-ketene acetal **B**. This nucleophile now intramolecularly attacks the activated carbonyl group (compounds **1** and **2** are quickly consumed according to TLC) to give a complex mixture of alcohols **C** and **C′** (the alcohols could be verified by HRMS experiments on the reaction mixture) as well as cation **D** (identified by ^{1}H and ^{13}C NMR spectroscopy). Workup with aqueous hydrochloric acid led to the exclusive isolation of tricyclic 2-aminopyridinium chlorides **3**.

All products **3** (with the exception of **3f**) were found to be hygroscopic and highly soluble in both water (at least 0.5 g mL^{-1} for compound **3a**) and organic solvents, such as dichloromethane, ethyl acetate, and acetonitrile (at least 1 g mL^{-1} in dichloromethane for compound **3a**). The solubility of the salts can be additionally tuned by anion metathesis (Scheme 5). Elemental analyses were obtained for the non-hygroscopic salts **3a**-BF_4, **3a**-PF_6, and **3t**-PF_6, which are readily soluble in organic solvents and insoluble in water. Anion exchange also allowed single crystals of compound **3t**-



Scheme 5. Anion metathesis for compounds **3a** and **3t**.

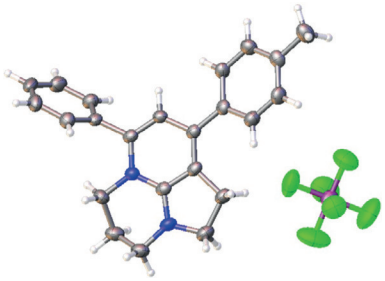


Figure 1. Crystal structure of compound **3t**-PF_6.

PF_6 to be obtained (Figure 1, see also the Supporting Information). X-ray analysis on these crystals unequivocally corroborated the structure.[21]

All the tricyclic 2-aminopyridinium salts **3** show intensely blue to turquoise luminescence in solution and some of them also in the solid state upon excitation by UV light. Particularly interesting is the solubility of 2-aminopyridinium dyes with chloride as the counterion in almost every solvent, even in water. This valuable feature makes them potent candidates as luminophores for application under physiological conditions. All the compounds show a relatively similar absorption pattern In the UV region. In general, two to three distinct broad structureless maxima can be found and the longest wavelength bands $\lambda_{max,abs}$ appear between 327 and 370 nm in dichloromethane. In water, the $\lambda_{max,abs}$ bands are located over a smaller range between 346 and 370 nm. The emission maxima of the investigated compounds appear between 442 and 509 nm, with substantial Stokes shifts $\Delta\tilde{\nu}$ between 5700 and 10500 cm^{-1} and pronounced fluorescence quantum yields Φ_f ranging from 4 to 81 % in dichloromethane. In water, the emission maxima lie between 440 and 516 nm, with Stokes shifts $\Delta\tilde{\nu}$ ranging from 5800 to 9500 cm^{-1} and comparable quantum yields Φ_f from 3 to 63 % (for details see Table S7 in the Supporting Information).[22]

Some structure–property relationships can be corroborated from the photophysical data of the 2-aminopyridinium dyes. First, the counterion of salt **3a** has no significant effect on the photophysical behavior in dichloromethane (see Table S7, entries 1–3 in the Supporting Information). The electronic effect of the R^2 substituent of the 2-aminopyridinium salts **3** on the absorption and emission maxima as well as on quantum yields is only minor in the related series **3a–c** with R^1 = *p*-tolyl (Figure 2).

In the related series with different ring anellation, **3a**, and **3s–u**, the longest wavelength absorption maxima lie between 347 and 363 nm and the emission maxima appear between 442 and 509 nm (see Figure S1 in the Supporting Information).

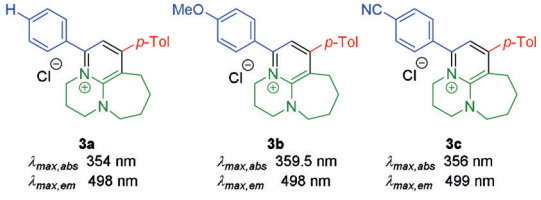


Figure 2. Comparison of the absorption and emission maxima for a related series of 2-aminopyridinium salts **3a–c**.

Increasing rigidification and planarization of the tricyclic system results in the fluorescence quantum yields increasing notably in both dichloromethane and in water. While the six-five-anellated 2-aminopyridinium salt **3t** displays a higher Φ_f value in water than in dichloromethane, the reverse is the case for the five-five-anellated 2-aminopyridinium salt **3u** (Figure 3). Similar trends of tuning the photoluminescence quantum yields by chromophore rigidification have been reported in metal-organic frameworks.[23]

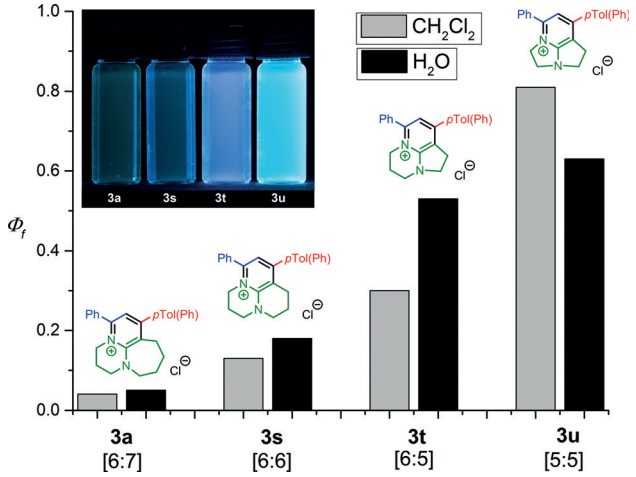


Figure 3. Effect of rigidification in **3a,s–u** on the quantum yields Φ_f in CH_2Cl_2 and water (inset: emission of aqueous solutions of **3a,s–u** under a hand-held UV lamp (c(**3**) = 10^{-7} M, λ_{exc} = 365 nm)).

UV excitation leads to a pronounced solid-state luminescence that can be seen with the naked eye (Figure 4). Consequently, the solid-state emission maxima of selected 2-aminopyridinium salts were recorded (see Table S8 in the Supporting Information). Additionally, the solid-state quantum yields of two selected compounds (**3a-PF$_6$** and **3t-PF$_6$**) were determined using an integrating Ulbricht sphere setup. Interestingly, 2-aminopyridinium salts with PF_6^- and BF_4^- as counterions display solid-state emission maxima at 447 to 477 nm, which are blue-shifted compared to the chloride salts (485 to 509 nm). This indicates that the packing in the crystal, affected by the counterions, exerts a significant effect on the solid-state emission. Extension of the conjugation by implementation of a styryl substituent causes a red-shift. Most interestingly, the 2-aminopyridinium derivatives **3a** and **3t-PF$_6$** with PF_6^- as a counterion are similarly highly fluorescent in the solid state (**3a-PF$_6$**: Φ_f = 56%; **3t-PF$_6$**: Φ_f = 42%).

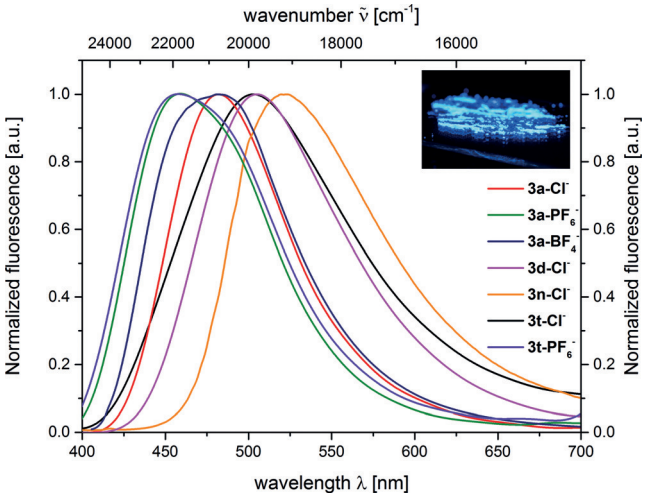


Figure 4. Normalized solid-state emission spectra of 2-aminopyridinium salts **3a-Cl**, **3a-PF$_6$**, **3a-BF$_4$**, **3d-Cl**, **3n-Cl**, **3t-Cl**, and **3t-PF$_6$** (recorded at T = 293 K, λ_{exc} = 365 nm. Inset: solid-state emission of **3a-PF$_6$** under a hand-held UV lamp (λ_{exc} = 365 nm)).

A novel (3+3) cyclocondensation of alkynones and cyclic amidines that furnishes tricyclic 2-aminopyridinium salts has been discovered. This anellation principle was readily embedded into a consecutive three-component synthesis starting from acyl chlorides, terminal alkynes, and cyclic amidines. Most interestingly, this novel class of 2-aminopyridinium salts exhibit remarkable emission in dichloromethane, water, as well as in the solid state. The intensely blue to turquoise luminophores display high fluorescent quantum yields Φ_f through the rigidification (five-five anellation), and the quantum yields Φ_f in dichloromethane and water can be even increased further (up to 63%). This concise and rapid diversity-oriented one-pot approach to water-soluble fine-tunable 2-aminopyridinium fluorophores is particularly suited for developing tailored fluorescence probes for labeling biomolecules in vitro and in vivo as well as on surfaces. This will be the focus of future studies as well as carrying out a deeper investigation of the underlying electronic structure by theoretical and photophysical methods.

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Conflict of interest

The authors declare no conflict of interest.

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