A Journal of the Gesellschaft Deutscher Chemiker

Angewandte International Edition

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To be cited as: *Angew. Chem. Int. Ed.* 10.1002/anie.201808665
Angew. Chem. 10.1002/ange.201808665

Link to VoR: http://dx.doi.org/10.1002/anie.201808665
http://dx.doi.org/10.1002/ange.201808665

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Water-soluble Blue Emissive Tricyclic 2-Aminopyridinium Salts by Three-component Coupling-(3+3)-Anellation Synthesis

Olga Bakulina,[a,b] Franziska K. Merkt,[a] Tim-Oliver Knedel,[c] Christoph Janiak,[c] and Thomas J. J. Müller*[a]

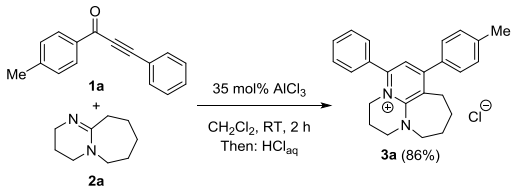
Dedication ((optional))

Abstract: The (3+3) anellation of alkynones and cyclic amidines is a novel and unexpected approach to 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, making them interesting novel luminophore probes for bioanalytics, as well as in the solid state as blue emitters with tunable efficiency.

Organic luminophores are particularly important synthetic targets due to numerous important applications, such as 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, so being widely employed for instance for monitoring of various biological processes with high accuracy by STED (stimulated emission depletion) microscopy.[5] As water is the naturally most abundant environmental medium, water-soluble luminophores play the particular 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, e.g. in the 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 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. Multi-component reactions (MCRs) in chromophore synthesis[13] appear to be a most practical tool for diversity-oriented synthesis for exploring beneficial properties,[14] providing access to a maximum of the resulting chemical space with minimal effort. The catalytic entry to 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 by very easily introducing three points of diversity.[15] In particular, bifunctional nucleophiles, such as acyclic amidines[16] or 2-aminopyridines (as a variation of the Bohlmann–Rahtz synthesis),[17] or 3-amino-3-iminopropanoic acid esters as substrates[18] are employed to give pyrimidines. Herein, we communicate an unexpected novel anellation principle of alkynones and cyclic amidines leading 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, applied 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 UV 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 in the presence of 35 mol% of $AlCl_3$. (Scheme 1, for details on the optimization; see Supp Inf, Table SI-1).



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

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) after a simple isolation and purification procedure based upon extraction (for details, see Supp Inf). The coupling of acyl chlorides **4** with acetylenes **5** in the presence of catalytic amounts of $PdCl_2(PPh_3)_2$ (2 mol%) and CuI (4 mol%) and triethylamine furnishes alkynones **1**,[19] which were reacted by subsequent

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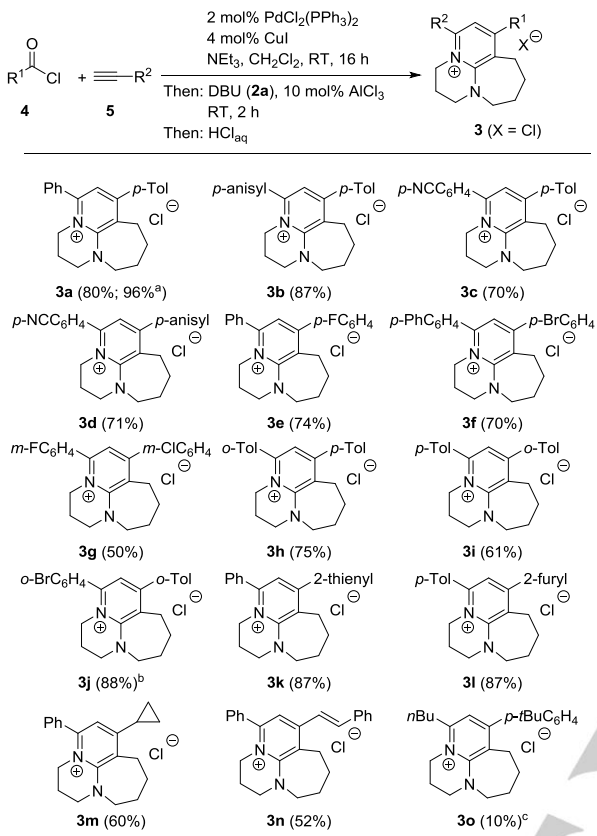
addition of DBU and $AlCl_3$ to the reaction mixture to give 15 tricyclic 2-aminopyridinium salts **3** in mostly good yields.



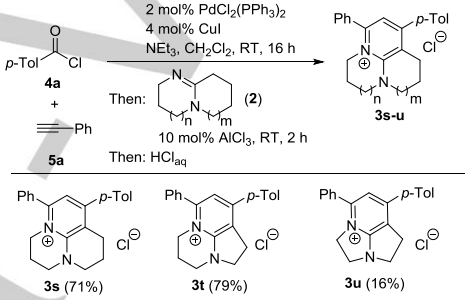
Scheme 2. One-pot protocol for preparation of compounds **3**. (Reaction conditions: Acid chloride **4** (1 mmol), alkyne **5** (1 mmol), $PdCl_2(PPh_3)_2$ (0.02 mmol), CuI (0.04 mmol), triethylamine (1.1 mmol), CH_2Cl_2 (3 mL), RT, 16 h; then: DBU (**2a**) (3 mmol), $AlCl_3$ (10 mol%), RT, 2 h; isolated yield for the one-pot procedure. [a]Reaction was performed on 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% yield.

It is noteworthy to mention that a decrease of $AlCl_3$ to 10 mol% does not affect the yield in the one-pot procedure. However, the amount of DBU has to be increased to three equivalents to compensate the deprotonation of triethylamine hydrochloride. The substitution pattern of R^1 is according to other three-component syntheses,[15,16] i. e. (hetero)aryl and cyclopropyl substituents void of α-acidic hydrogens atoms that could lead to ketene formation. The R^2 substituents are favorably (hetero)aryl moieties, whereas alkyl alkynes give only poor yield (compound **3o**). The one-pot synthesis of compound **3a** is also readily scalable affording the product in 96% yield without any chromatography.

The connectivity of the products **3** was unambiguously established by NMR spectroscopy, in particular by NOESY, HMBC and HSQC spectra for the products **3a**, **3h**, **3i** and **3l**, indicating 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**). For the bis(*ortho*-aryl)-substituted product **3j** a 1:1.8 isomeric mixture was obtained according to ^{1}H NMR and HPLC-MS. While HSQC, HMBC and NOESY unambiguously supported the identical connectivity of both isomers, and 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 ^{1}H NMR spectrum of the mixture remained unchanged upon heating to 110 °C, indicating a high rotation barrier.

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

The structure of the bicyclic amidines **2** was also varied in the sequence starting from model substrates **4a** and **5a** (Scheme 3).



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

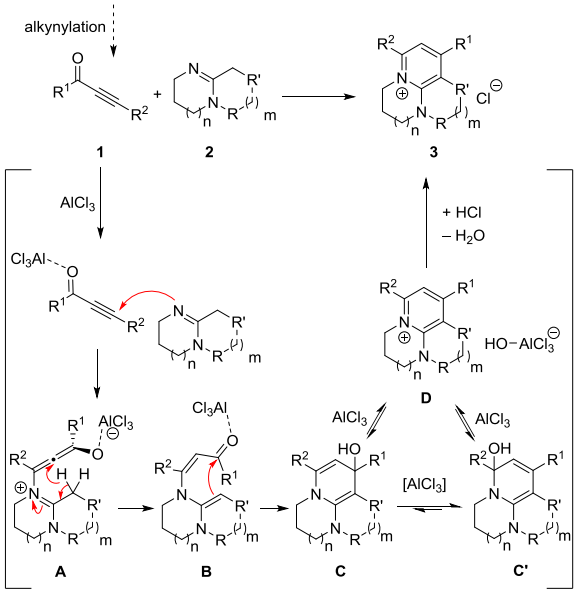
Hexahydro-2*H*-pyrido[1,2-*a*]pyrimidine (**2b**) (n = m = 1) and 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) (**2c**) (n = 1, m = 0) were successfully employed in the sequence, furnishing the tricyclic aminopyridinium products **3s** and **3t** in high yields. Strained tetrahydro-3*H*-pyrrolo[1,2-a]imidazole (**2d**) (n = m = 0) delivered product **3u** with two anellated five-membered rings in 16%.

The mechanism of the addition-cyclocondensation step of the sequence can be rationalized as follows (Scheme 4). Alkynones **1** and amidines **2** react in two consecutive nucleophilic additions. First the nucleophilic imine nitrogen atom attacks the alkynone forming adduct **A**, which stabilizes 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 can be verified by the appearance of the HRMS peak from sample of the reaction mixture) as well as cation **D** (identified by ^{1}H and ^{13}C NMR spectra). Upon workup with aqueous hydrochloric acid exclusively tricyclic 2-aminopyridinium chlorides **3** are isolated.

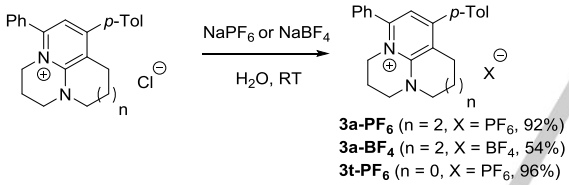
All products **3** (with exception of **3f**) were found to be hygroscopic and highly soluble both in water (at least 0.5 g/mL for compound **3a**) and in organic solvents, such as dichloromethane, ethyl acetate, and acetonitrile (at least 1g/mL in dichloromethane for compound **3a**). The solubility of the salts can be additionally tuned by anion metathesis (Scheme 5).

Elemental analyses were obtained for non-hygroscopic salts **3a**-$\mathbf{BF_4}$, **3a**-$\mathbf{PF_6}$, and **3t**-$\mathbf{PF_6}$, which are readily soluble in organic

solvents and insoluble in water. Anion exchange also allowed to obtain single crystals of compound **3t-PF$_6$** (Figure 1 and ESI) and unequivocally corroborate the structure by X-ray analysis.[21]



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



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

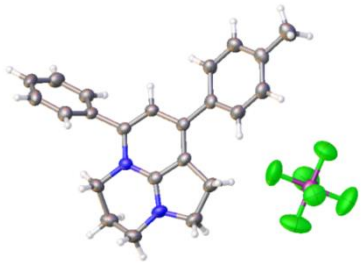


Figure 1 Crystal structure of compound **3t-PF$_6$**.

All tricyclic 2-aminopyridinium salts **3** are intensely blue to turquoise luminescent in solution and some of them also in 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 precious feature makes them to potent candidates as luminophores that can be applied under physiological conditions.

In the UV region all dyes show a relatively similar absorption pattern. 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 $\lambda_{max,abs}$ are located in 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 Supp Inf, Table S7).[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 Supp Inf, Table S7, entry 1-3). The electronic substituent effect of the R^2 substituent of the 2-aminopyridinium salts **3** on 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).

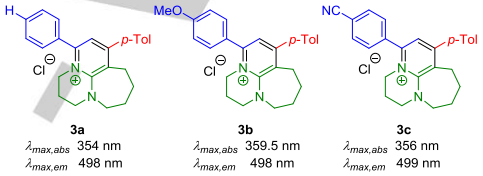


Figure 2: Related series of 2-aminopyridinium salts **3a-c**.

In the related series of different ring anellation **3a**, and **3s-u** the longest wavelength absorption maxima lie between 347 and 363 nm and emission maxima appear between 442 and 509 nm (see Supp Inf, Figure S1).

With increasing rigidification and planarization of the tricyclic system the fluorescence quantum yields notably increase in the same trend in dichloromethane and in water. While the six-five-anellated 2-aminopyridinium salt **3t** displays a higher Φ_f in water than in dichloromethane, the five-five-anellated 2-amino-pyridinium salt **3u** inverts the order (Figure 3). Similar trends of tuning the photoluminescence quantum yields by chromophore rigidification has been reported in metal-organic frameworks.[23]

Upon UV excitation a pronounced solid state luminescence can already be seen upon eyesight (Figure 4). Consequently, solid state emission maxima of selected 2-aminopyridinium salts were recorded (see Supp Inf, Table S8). Additionally, the solid state quantum yields of two selected compounds (**3a-PF$_6$** and **3t-PF$_6$**) were determined using an integrating sphere (Ulbricht setup).

Interestingly, 2-aminopyridinium salts with PF_6^- and BF_4^- as counterions display blueshifted solid state emission maxima at 447 to 477 nm in comparison to the chloride salts (485 to 509 nm). This indicates that 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 redshift. Most interestingly, the 2-aminopyridinium **3a** and **3t-PF$_6$** with PF_6^- as a counterion are equally highly fluorescent in solid state (**3a-PF$_6$**: Φ_f = 56%; **3t-PF$_6$**: Φ_f = 42%).

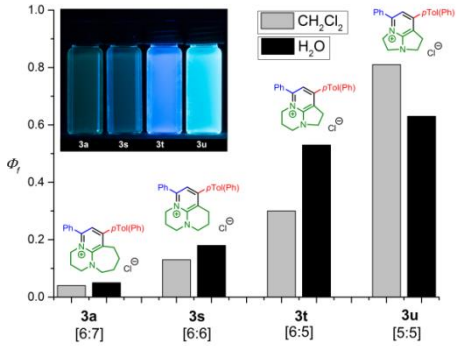


Figure 3. Effect of rigidification in **3a**,**s**-**u** on the quantum yields Φ_f in CH_2Cl_2 and water (inset: emission of aqueous solutions of **3a**,**s-u** under a handheld UV lamp (c(**3**) = 10^{-7} M, λ_{exc} = 365 nm).

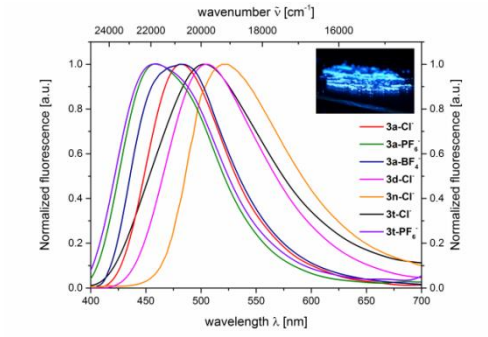


Figure 4. Normalized solid state emission spectra of 2-aminopyridinium salts **3a-Cl**, **3a-PF$_6$**, **3a-BF$_4$**, **3d-Cl**, **3n-Cl**, **3t-Cl** and **3t-PF$_6$** (recorded at T = 293 K, λ_{exc} = 365 nm. Inset: solid state emission of **3a-PF$_6$** under a handheld UV lamp (λ_{exc} = 365 nm)).

A novel (3+3) cyclocondensation of alkynones and cyclic amidines furnishing tricyclic 2-aminopyridinium salts was discovered and 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 by 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 of biomolecules in vitro and in vivo as well as on surfaces, which will be the focus of future studies as well as the deeper investigation of the underlying electronic structure by theoretical and photophysical methods.

Acknowledgements ((optional))

The authors gratefully acknowledge German Academic Exchange Service (DAAD) and “Dmitrij Mendeleev” joint scholarship program of Saint Petersburg State University (O.B.), Deutsche Forschungsgemeinschaft (Mu 1088/9-1), and the Fonds der Chemischen Industrie for financial support. The authors cordially thank M. Sc. Tobias Wilcke (Heinrich-Heine-Universität Düsseldorf) for taking the photographs for this article.

Keywords: alkynylation • catalysis • cross-coupling • fluorescence • multicomponent reaction

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[21] Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-1852295 **3t-PF$_6$**. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (Fax: + 44-1223/336-033; E-mail: deposit@ccdc.cam.ac.uk).

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10.1002/anie.201808665

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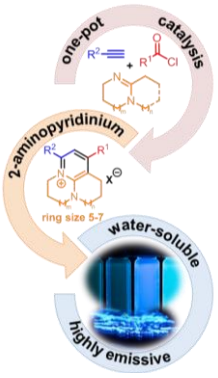
Layout 1:

COMMUNICATION

Consecutive three-component coupling-(3+3)-anellation synthesis of acid chlorides, alkynes and cyclic amidines rapidly furnishes water-soluble blue emissive tricyclic 2-aminopyridinium salts in a diversity-oriented fashion.



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