MULTICOMPONENT STRATEGIES FOR THE DIVERSITY-ORIENTED SYNTHESIS OF BLUE EMISSIVE HETEROCYCLIC CHROMOPHORES

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Abstract. *Consecutive multicomponent syntheses of blue-emissive five- and six-membered heterocycles can be efficiently achieved by alkynylation-cyclocondensation, alkynylation-cyclization, and by alkynylation-cycloisomerization sequences starting from simple ar(o)yl halides, alkynes, and bifunctional nucleophiles. The diversity-oriented nature of this approach enables the introduction of numerous substituents and thereby the electronic fine-tuning of the target luminophores.*

Contents

1. Introduction

The advent of organic light-emitting diodes (OLED) has revolutionized illumination technologies and enabled multifaceted applications in display devices ranging from television sets to smartphones.[1] Most interestingly, organic small molecules or polymers can adopt the function of emitters, and if properly selected, multicolor displays can be efficiently and cost-effectively produced. These luminophores are functional π-electron systems[2] emitting light upon exciton formation from hole-electron combination and usually display electroluminescence spectra that are identical to the photoluminescence of these molecules.

As a consequence, tailor-made luminescent molecules with fine-tuned molecular and electronic properties have become highly requested. Besides large Stokes shifts, i. e. the energy difference between longest wavelength absorption and shortest wavelength emission bands, fluorophores emitting at the high energy end of the visible spectrum are indispensable for full color displays and illumination. Therefore, the identification and preparation of efficient molecular blue emitters has remained a challenging goal in organic materials science.[3] Diversity-oriented synthesis, as a conceptual approach to biologically active scaffolds for

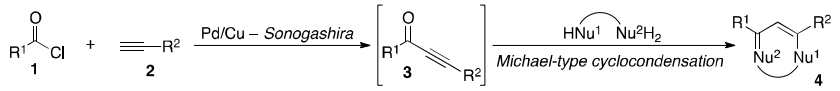
creating vast exploratory spaces in pharmaceutical lead discovery,[4] has turned out to be equally fruitful for designing and exploring functional chromophores.[5] Most interestingly, multicomponent processes[6] employing transition metal catalyzed processes as entries[7] have paved the way many classes of heterocyclic structures.[8] These concept also enables concise and diverse access to functional chromophores[9] and, eventually, functional fluorophores.[10] In this account we summarize our conceptual work on developing multicomponent syntheses of blue-emissive heterocyclic chromophores.

2. Multicomponent Sonogashira alkynylation–cyclization syntheses of blue emitters

The contribution of multicomponent reactions to the convergent synthesis of highly decorated heterocyclic scaffolds in a diversity-oriented fashion is well recognized.[11] An approach becoming increasingly popular for the synthesis of tailor-made functional π-electron systems through a MCR approach, initiates with transition metal-catalyzed cross-coupling reactions, such as Sonogashira and related reactions, which in turn produce functionalized alkynes that are involved in further cyclization.

2.1. Michael-type cyclocondensations of *N*-nucleophiles with the alkynone

If the Sonogashira product is an alkynone (**3**) it can behave as a very efficient Michael acceptor and, using a bifunctional nucleophile, an overall cyclocondensation occurs to afford **4**. The reaction is usually highly regioselective, because the more nucleophilic moiety initiates in the Michael attack, while the less nucleophilic site is responsible for the attack to the electrophilic carbonyl in a cyclocondensation step. In recent years we developed conditions for performing the synthesis of the alkynone and the following Michael-type cyclocondensation as one-pot procedures that can be regarded as consecutive multicomponent processes, as outlined in Scheme 1.



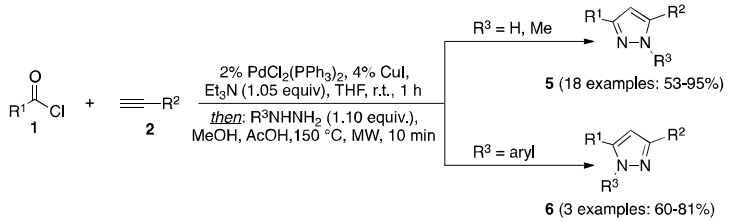
Scheme 1. General strategy for the multicomponent Sonogashira alkynylation–cyclization syntheses.

For instance, we prepared alkynones **3** by a modified Sonogashira coupling between acyl chlorides **1** and terminal alkynes **2** reacting them with hydrazines (Scheme 2) to afford differently 3,5-disubstituted and 1,3,5-trisubstituted pyrazoles.[12]

These five-membered heterocycles are interesting from many points of view: even if the scaffold is rarely present in nature,[13] pyrazoles are very attractive in medicinal chemistry, due to a large variety of biological activities and can be regarded as privileged structures in medicinal chemistry.[14] Furthermore, they find applications in crop protection as herbicides.[15] Pyrazoles usually display remarkable fluorescence and this property has been exploited, for example, to develop sensors for fluoride anion[16] and optical brighteners to be used as additives in detergents.[17] In addition many pyrazoles display an emission at short wavelengths, i. e. blue luminescence, which makes them very attractive in OLED technologies.[1]

The reaction depicted in Scheme 2 occurs under milder conditions with respect to previous reports and can be successfully applied also to very sensitive alkynes. According with the predictable reactivity of monosubstituted hydrazines, where the more nucleophilic nitrogen is the internal one for alkyl hydrazines

and the terminal one in aryl hydrazines, we were able to fully control the regioselectivity (>98% of the prevailing regioisomer). With R^3 = H or Me pyrazoles **5** were almost exclusively obtained while, with R^3 = Ar, pyrazoles **6** were the prevailing products.[18] For the scope of the reaction we varied the other two substituents: R^1 is a *p*-substituted phenyl bearing either electron-withdrawing or electron-donating groups or a 2-thienyl group. On the other hand, a higher degree of diversity is ensured by R^2. This group is usually a differently substituted aryl group but we demonstrated that it can be an alkyl as well. In addition, if trimethylsilyl acetylene is coupled with an acyl chloride, the resulting pyrazole is unsubstituted in position 5 (R^2 = H).



Scheme 2. Regioselective one-pot three-component synthesis of 1,3,5-trisubstituted pyrazoles **5** and **6**.

Finally, as in the major part of the following examples, a beneficial effect both with respect to yield and reaction time was observed when the cyclocondensation was performed under microwave heating. The structures and substitution patterns of these pyrazoles were assigned by spectroscopic methods and, in some cases, by means of single crystal X-ray analysis, which allowed also defining their solid state structures.

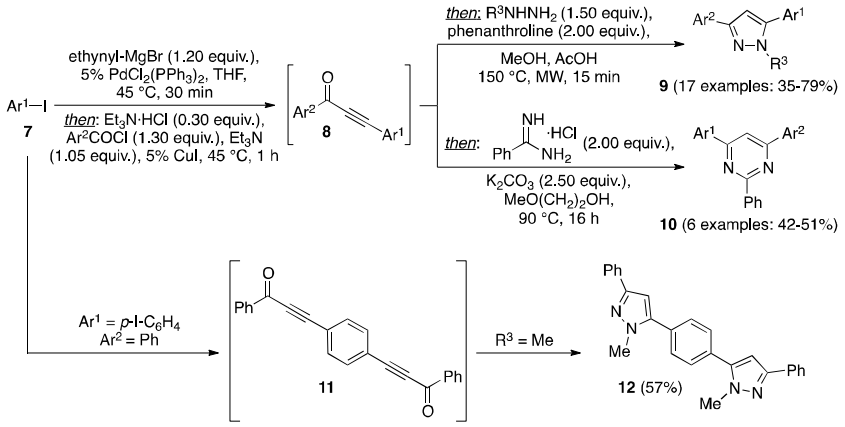
The electronic properties of these pyrazoles were then investigated. All compounds are fluorescent and, expectedly, the absorption and the emission spectra are strongly influenced by substituents and by conformational biases. In solution, the absorption maxima appear between 260 and 385 nm with values of ε ranging from 5300 to 106000 $Lmol^{-1}cm^{-1}$. The emission maxima are found in the 320-460 nm range, which provides these molecules with a considerable blue to blue-green fluorescence. The fluorescence Φ_f yield varies from <0.01 to 0.74. In addition, the large Stokes shifts $\Delta\tilde{\nu}$ from 4200 to 12300 cm^{-1} are responsible for the nearly complete absence of overlap between absorption and emission bands, an effect that is very favorable in potential applications of these molecules as fluorescent dyes.

Very recently we developed a different approach to 1,3,5-trisubstituted pyrazoles and 2,4,6-trisubstitued pyrimidines as well.[19] Again, we employed an alkynone, such as **3** (with both R^1 and R^2 having an aromatic structure) as key intermediate, but we generated it through a different and highly convergent procedure.[20]

The novelty of this approach relies therefore on:

a) the protecting group free sequentially palladium-catalyzed three-component Kumada-Sonogashira synthesis of alkynones **8**, where aryl iodide **7** reacts with ethynyl magnesium bromide and then with an aroyl chloride in a one-pot fashion;
b) the possibility to perform the whole sequence leading to the final heterocycles as a consecutive four-component coupling-coupling-cyclocondensation synthesis after the addition of the appropriate hydrazine (R^1 = H, Me, Ph), to give **9**, or of an amidinium salt, to give **10**.

This approach ensures a very efficient diversity-oriented synthesis of the intermediate alkynone **8**, although a limitation is that this time Ar^1 (R^2 in pyrazoles **5**) can only be aromatic (Scheme 3).



Scheme 3. Consecutive four-component synthesis of substituted pyrazoles **9** and pyrimidines **10**.

The following cyclocondensation reaction required a careful optimization because of the unavoidable presence of magnesium ions, probably responsible for a competing coordination with hydrazine. In the end the problem was solved using a slight excess of the needed hydrazine, adding at the same time phenanthroline, which behaves as a competing and more efficient ligand for magnesium.

With few exceptions, the regioselectivity was complete, affording pyrazole **9** derived from the preferred Michael attack of the more nucleophilic nitrogen (as we observed for pyrazole **5**, Scheme 2). By contrast, using phenyl hydrazine, we obtained a 1:2 mixture of regioisomers where the attack of the terminal hydrazine nitrogen, the most nucleophilic, is prevailing but not exclusive to give the regioisomer of **9** with inverted positions of Ar^1 and Ar^2.

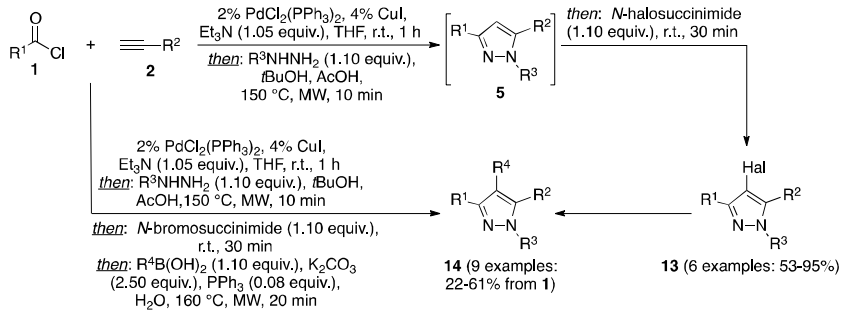
Interestingly, starting from 1,4-diiodobenzene we were able to perform a pseudo-seven-component coupling–coupling–cyclocondensation synthesis. After the formation of symmetric diketone **11**, a double Michael–cyclocondensation involving both alkynone moieties occurred with the simultaneous creation of two pyrazole rings separated by an aromatic spacer (**12**). The whole sequence required of course a double amount of all the involved species, apart from 1,4-diiodobenzene. The same four-component procedure developed to afford **9**, could be successfully applied to the synthesis of 2,4,6-triaryl-substituted pyrimidines **10** in moderate yields, using benzamidinium chloride as a precursor of the bifunctional nucleophile. In the synthesis of pyrimidines microwave heating was not beneficial and the addition of phenanthroline as competing ligand for Mg^{++} did not positively affect the reaction outcome as we experienced for the synthesis of **9**.

For testing the photophysical properties of pyrazoles **9**, we performed a systematic investigation of the effects of two electron-donating groups alternatively placed in the *para* position of Ar^1 (OMe and NMe_2) and two electron-withdrawing groups alternatively placed in the *para* position of Ar^2 (CF_3 and CN). In particular, we compared the absorption/emission spectra of the unsubstituted pyrazole **9** (Ar^1 =Ar^2 = Ph, R^3 = Me) with those compounds bearing just one *para* substituent and those with two *para* substituents (OMe or

NMe_2 in Ar^1 and CF_3 or CN in Ar^2, leading to all four possible combinations). Actually, in the latter case we wanted to explore the influence of a push-pull combination of substituents behaving as an auxochrome or an anti-auxochrome, respectively.

Generally, donors alone as well as acceptors alone showed only modest red-shifts of the longest wavelength absorption bands and of the emission maxima as well. Moreover, this bathochromic shifts were less pronounced in the emission spectra, leading to reduced Stokes shifts in comparison the unsubstituted model. By contrast the push-pull substituted derivatives were all characterized by a strong bathochromic shift of the emission maxima [367-499 nm with respect to 338 nm in the unsubstituted pyrazole (Ar^1 =Ar^2 = Ph)] together with larger Stokes shifts ($\Delta\tilde{\nu}$ in the range 8300-14100 cm^{-1}), the highest being obtained for Ar^1 = *p*-Me_2N-C_6H_4 and Ar^2 = *p*-NC-C_6H_4. Moreover, we studied the solvochromicity of this best performing pyrazole to evaluate the effect of the solvent on the absorption and emission properties, observing an evident positive emission solvatochromism. Thus, the emission is red-shifted with increasing solvent polarity ranging from 363 (cyclohexane) to 595 nm (acetonitrile).

In the previous paragraphs we described two efficient approaches to bi- and, mostly trisubstituted pyrazoles. With the aim to optimize the electronic properties of pyrazoles as fluorophores and to satisfy the increasing quest for tailor-made functional π-systems we developed a one-pot, diversity-oriented, synthesis of persubstituted pyrazoles (Scheme 4). We again planned to apply the strategy summarized in Scheme 2 with the three-component formation of the pyrazole, having in mind to functionalize the unsubstituted carbon 4 of the pyrazole scaffold as the last step: for this purpose we chose a two-step sequence consisting of halogenation followed by Suzuki coupling, one of the most reliable reactions for connecting aromatic and/or (hetero)aromatic fragments. An appropriate choice of the boronic acid would allow an additional increase in diversity at the end of the four step synthesis.[21] Though the separate steps are well documented, the major challenge of the sequence is represented by the possibility to perform the reaction in a one-pot fashion. Furthermore, both Sonogashira and Suzuki couplings are catalyzed by palladium and so we wondered if the starting catalyst would be effective enough to promote the final coupling at a late stage of a sequentially Pd-catalyzed process.



Scheme 4. One-pot four step synthesis of 1,3,4,5-tetrasubstituted pyrazoles **14**.

We first developed the four-component sequence leading to halopyrazoles **13** as a separate step, adding the desired *N*-halosuccinimide (only chlorination and bromination were successful, while we did not succeed with the introduction of the most effective iodine either changing the iodinating agent) to intercept

pyrazole **5**. In order to make the final Suzuki coupling possible we had to overcome the unavoidable oxidation of the Pd-catalyst during the halogenation. The activity of the palladium species was restored by addition of catalytic triphenylphosphane together with the reagents required by the stoichiometry of the cross-coupling. For each step we used an almost equimolar amount of the stoichiometric reagents, which makes this process highly economical. The overall sequence furnished tetrasubstituted pyrazoles **14** with almost complete regioselectivity in moderate to good yields. The scope of the sequence was investigated, demonstrating that electron-rich, electron-poor, (hetero)aromatic and, limited to the alkynes, aliphatic substituents are well tolerated.

Although the comparison between the sequential method, where **14** was directly isolated, and the stepwise procedure with isolation and chromatographic purification of all intermediates (**5**, **13** and **14**), shows a slightly higher yield for the latter route (63% *vs* 54% for pyrazole with R^1 = *p*-anisyl, R^2 = Ph, R^3 = Me, R^4 = *p*-OHC-C_6H_4), in the one-pot procedure the required overall time is reduced by about 60%, and a not negligible saving of solvents, silica etc. needed for work-up and/or column chromatography could be realized as well.

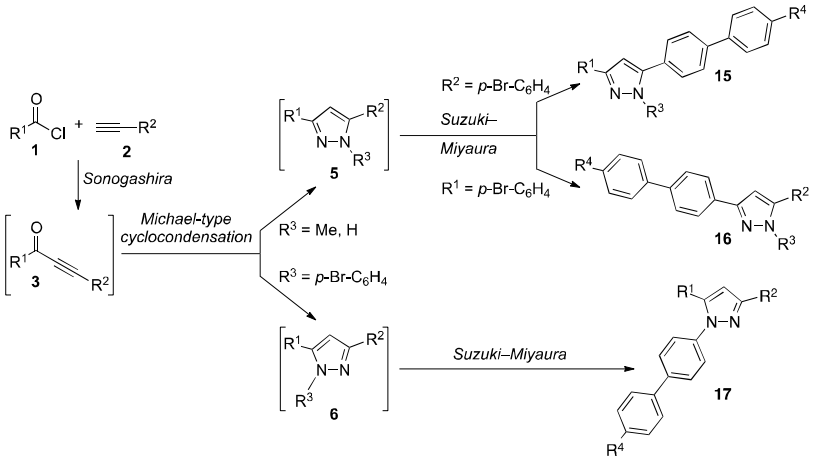
Persubstituted pyrazoles **14** show the longest wavelength absorption maxima between 240 and 311 nm with ε between 14300 and 50800 $Lmol^{-1}cm^{-1}$. These molecules display a strong blue luminescence in solution between 373 and 395 nm. In the solid state emissions are red-shifted, giving a bluish-green luminescence. If compared with the related 1,3,5-trisubstituted pyrazoles **5** (lacking a push-pull system), compounds **14** exhibit larger Stokes shifts ranging from 5300 to 15500 cm^{-1}. Moreover, also the fluorescence quantum yields Φ_f are substantial with values between 0.29 and 0.72. The emission bands are almost insensitive to the substitution pattern and the overlap between absorption and emission bands is essentially absent.

In order to improve the quantum yield we reasoned that the introduction of biphenyl substituents could be a good solution for enhancing the delocalization of the π system. The main reason is that the biphenyl is essentially coplanar in the first excited state S_1, while biphenyls are distorted from coplanarity by about 44° in the electronic ground state S_0.

For this reason, we considered pyrazoles with a biaryl placed in either one of the 1-, 3- or 5-positions with the aim to be able to fine tune the photophysical properties of new scaffolds (Scheme 5). Employing the previously developed strategy, based on the Sonogashira–cyclocondensation one-pot synthesis, a possibility is represented by the employment of biaryl starting materials. However, we envisaged a more efficient and diversity-oriented strategy, based upon sequential catalysis, which was developed for the synthesis of persubstituted pyrazoles **14**.[19] Our idea was to employ the Sonogashira palladium catalyst in a sequential Suzuki-Miyaura coupling to be performed in a one-pot fashion. Therefore, we planned a consecutive four-component sequence where the biaryl moiety is built as the last step, thanks to the presence of a *p*-bromophenyl as one of the substituents of the pyrazole skeleton to be reacted with different boronic acids (Scheme 5).[22]

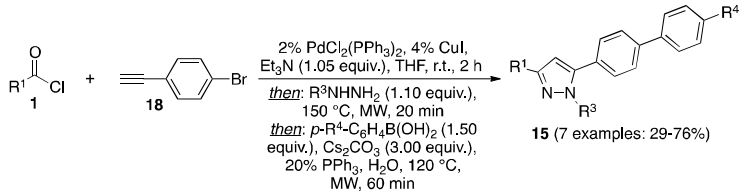
For our sequential Pd-catalyzed coupling–condensation–coupling (C^3) protocol we first placed the *p*-bromophenyl group in the alkynyl component. Coupling of (hetero)aroyl chlorides with *p*-bromophenyl acetylene **18** afforded the expected alkynones that were submitted to the usual cyclocondensation after the addition of hydrazines (R^3 = Me, H). The intermediate cyclocondensation products **5** were directly

transformed into **15** in moderate to good yields after addition of boronic acids and a base, namely cesium carbonate as a concentrated aqueous solution, but without needing additional metal complexes.



Scheme 5. Synthetic plan to biarylsubstituted pyrazoles.

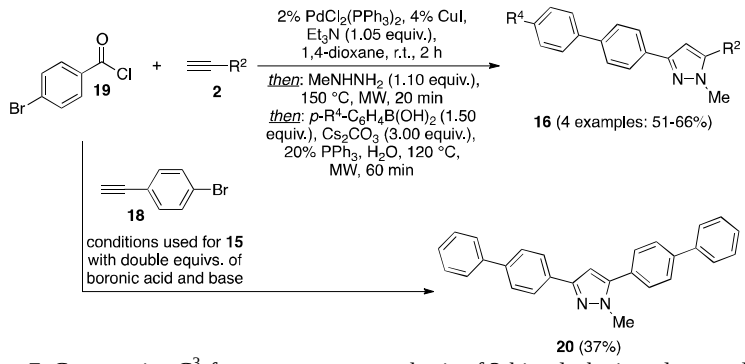
As experienced previously, the addition of 20 mol % of triphenylphosphane was necessary to stabilize the catalytically active Pd(0) species (Scheme 6). The boronic acids were chosen to install biaryls with either electron-donating or electron-withdrawing substituents.



Scheme 6. Consecutive C^3-four-component synthesis of 5-biarylsubstituted pyrazoles **15**.

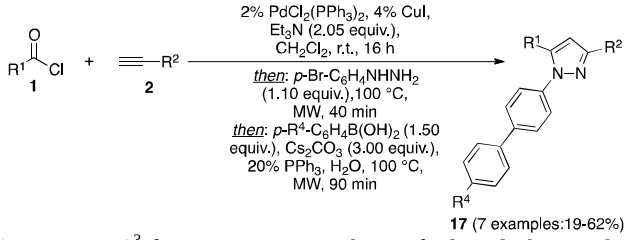
The same protocol was used for the synthesis of 3-biarylsubstituted pyrazoles **16** using *p*-bromobenzoyl chloride **19** and *N*-methyl hydrazine. However, the yields were not as satisfactory and the reaction time resulted significantly longer; eventually, substituting THF with 1,4-dioxane enabled us to obtain the products with a good overall yield in a comparable overall reaction rate, introducing electron-neutral and electron-withdrawing groups (R^4) and also a *t*Bu substituent in the 5-position.

Following the same conditions used for the synthesis of **15**, we were able to combine *p*-bromobenzoyl chloride **19** with *p*-bromophenyl acetylene **18**, methyl hydrazine and phenylboronic acid in a C^3-pseudo-five component synthesis to afford 3,5-bis(biphenyl)-1-methylpyrazole **20** in a good overall yield, taking in account the complexity of this one-pot procedure (Scheme 7).



Scheme 7. Consecutive C^3-four-component synthesis of 3-biarylsubstituted pyrazoles **16**.

Finally, we planned to introduce a biaryl moiety in position 1. However, the conditions used for the synthesis of **15** and **16** turned out to be inappropriate for these compounds and this was due to the troublesome formation of the pyrazole core (Scheme 8). After a careful optimization, we found a beneficial effect in the replacement of the solvent THF with methylene chloride, which required a longer reaction time (16 h) in the Sonogashira coupling, while milder reaction conditions were possible for the following cyclocondensation and Suzuki-Miyaura coupling. Pyrazoles **17** were obtained in satisfactory yield and were fully characterized by spectroscopic methods, as for **15** and **16**, and, in one case, also by X-ray analysis.



Scheme 8. Consecutive C^3-four-component synthesis of 1-biarylsubstituted pyrazoles **17**.

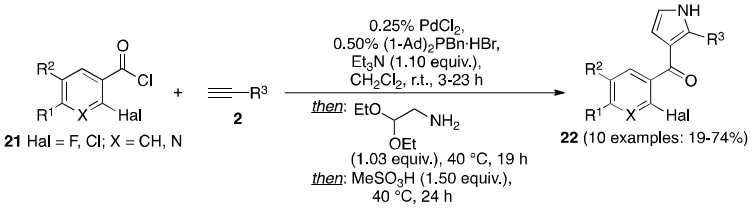
Compounds **15**, **16** and **20** are the result of the Michael attack of the inner nitrogen atom of the hydrazines to the triple bond. On the contrary, using aryl hydrazines, the regioselectivity is reverted, the Michael addition being promoted by the more nucleophilic terminal nitrogen with a ratio in the range 6:1 to 22:1 in favor of compounds **17**.

The solutions of the aforementioned biaryl substituted pyrazoles are visually blue-fluorescent. With respect to 1-methyl-3,5-diphenylpyrazole a bathochromic effect can be evidenced in the absorption maxima which are in a broad range from 256.5 to 311.0 nm, depending on the position of the biaryl moiety on the pyrazole scaffold. A hyperchromic effect is observed as well with considerably high values of ε [33000-44000 Lcm-1mol^{-1} for 3- (**16**) and 5-biarylsubstituted (**15**) pyrazoles and 18900-39900 Lcm^{-1}mol^{-1} for 1-substituted ones (**17**)] in particular for compound **20**, where ε = 66500 Lcm^{-1}mol^{-1}. This behavior can be ascribed to the dominance of π-π* transitions. The emission maxima are in a wider range for 3- (**16**) and 5-biarylsubstituted (**15**) pyrazoles than for 1-substituted ones **17** ($\lambda_{max,em}$ 338.5-394.0 and 382.5-394.0,

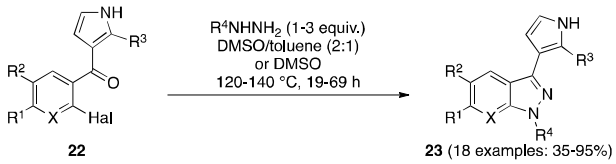
respectively). The relative fluorescence quantum yield of 3- (**16**) and 5-biarylsubstituted (**15**) pyrazoles is usually higher than that of 1-substituted pyrazoles (**17**) (Φ_f up to 0.97 for **15** and **16**, and up to 0.41 for **17**) and dropped to 0.07 in the case of **20**. The Stokes shifts $\Delta\tilde{\nu}$ are remarkably large in the range 6000-11300 cm^{-1} and this result can be rationalized with a change of geometry of the molecule in the excited state, a reorganization of the solvent molecules after excitation or a charge-transfer character of the excited state.

We further applied the strategy based on alkynone chemistry to the synthesis of indazoles, a scaffold usually characterized by a high chemical stability, with the aim to prepare heterocyclic chromophores with additional sites of protonation.[23]

3-Pyrrol-3-yl substituted (aza)indazoles were therefore prepared by a two-step procedure: first we prepared 2-(2'-halo(hetero)aryl)-(1*H*-pyrrol-3-yl)methanones **22** (Scheme 9) by a three-component synthesis, then we transformed them into the corresponding indazoles **23** by treatment with an hydrazine through a cyclizing condensation–S_NAr sequence (Scheme 10).[23]



Scheme 9. Three-component synthesis of 2-(2'-halo(hetero)aryl)-(1*H*-pyrrol-3-yl)methanones **22**.



Scheme 10. Cyclizing condensation–S_NAr synthesis of 2'-substituted 3-(1*H*-pyrrol-3-yl-1*H*-indazoles **23**.

For the synthesis of the intermediate ynone (general formula **3**) we used this time our recently developed copper-free Pd-catalyzed Sonogashira coupling successfully applied to the synthesis of dihydropyrid-2-ones.[24] We coupled *ortho*-halo-substitued (hetero)aroyl chlorides **21** with terminal alkynes **2** in the presence of $PdCl_2$ and di(1-adamantyl)-benzylphosphonium bromide, using triethyl amine as a base. After completion of the cross-coupling we added aminoacetaldehyde diethyl acetal for the following Michael addition leading to the corresponding enaminone. Then we concluded the sequence by a methanesulfonic acid mediated cyclocondensation which allowed obtaining **22** in moderate to good yield after chromatography.

The indazole-forming step, involving a condensation of an hydrazine followed by an S_NAr, was carefully optimized on (2,4-dichlorophenyl)(2-phenyl-1*H*-pyrrol-3-yl)methanone (**22**: R^1 = Hal = Cl; R^2 = H; R^3 = Ph), with respect to several parameters: hydrazine concentration, use of additives, solvents, reaction time, temperature, conductive or dielectric heating. With the best conditions in hand, we prepared a library of 18 indazoles **23** in moderate to excellent overall yields, as summarized in Scheme 10. With the exception

of 5-nitroindazoles (R^2 = NO_2) all indazoles (X = CH) or azaindazoles (X = N) are intensely blue-luminescent in solution upon excitation by UV light. All indazoles and azaindazoles showed two characteristic absorption maxima: for example, for **23** (R^1 = R^2 = H; R^3 = Ph; R^4 = Me; X =CH), these maxima appear at 293.5 and 311.5 nm with ε = 14300 and 11000 $Lcm^{-1}mol^{-1}$, respectively. The presence of a nitro group in position 5 is responsible for a hypsochromic shift of the short wavelength absorption band to 279.0 nm (ε = 21400 $Lcm^{-1}mol^{-1}$) and a bathochromic shift of the longest wavelength absorption to 376.5 nm (ε = 5200 $Lcm^{-1}mol^{-1}$). A similar effect, a blue-shift for the higher and a red-shift the lower energy absorptions, respectively, is caused by the azaindole nitrogen atom exerting a strong electron-withdrawing effect. As a consequence of a less extended π-system, the substitution of the aromatic substituent (R^3) with a cyclopropyl gives a strongly hypsochromically shifted first absorption maximum at 231.0 nm.

In compound **23** (R^1 = R^2 = H; R^3 = Ph; R^4 = Me; X =CH), used as reference, an intense emission band is observed at 390.5 nm with a fluorescence quantum yield Φ_f of 0.46, while in 5-nitroderivatives the emission is completely quenched. On the contrary, for the azaindoles the emission is red-shifted and appears between 430.0 and 454.0 nm with Φ_f between 0.28 and 0.43 respectively.

As expected, the addition of trifluoroacetic acid strongly influences absorption and emission both in indazoles and azaindazoles. In the aforementioned reference compound, the absorption maxima are shifted to 259.0 and 357.0 nm, respectively, after complete protonation, which proves the formation of a new chromophore. We demonstrated that the protonation occurs on the most basic nitrogen atom, i. e. the imine-type N-atom of indazoles and pyridyl nitrogen atom of azaindazoles. Furthermore, after protonation with TFA, we also observed a reversible fluorescence quenching, which makes in principle these molecules suited as biooptical tool for acidity sensing in cells.

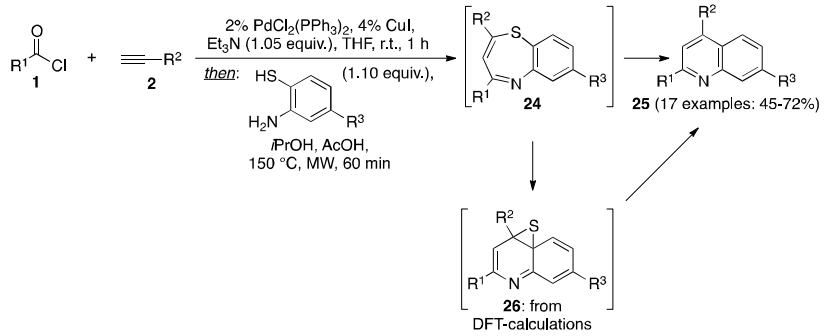
2.2. Michael-type cyclocondensations of *S*-nucleophiles with the alkynone

As described above, the easy access to alkynones **3** under efficient and catalytic protocols allowed us to develop a general diversity-oriented approach to different classes of heterocycles, which is based on multicomponent reactions proceeding in a coupling–addition–cyclocondensation sequence. One of the key steps is the Michael addition to ynones **3** for which, of course, also nucleophiles other than nitrogen are well-suited. In this chapter we describe the employment of *S*-nucleophiles to generate new fluorophores in a multicomponent approach.

Actually, in our first report in this field, the sulfur atom has been exploited as a selective nucleophile in a regiospecific process, but was finally removed in a sulfur extrusion process so that the isolated molecules are 2,4-disubstituted (and 2,4,7-trisusbstituted) quinolines not containing sulfur atoms.[25] The interest in this scaffold is fully justified because quinolines are characterized by an inherent fluorescence and are therefore interesting as emitting chromophores. For the synthesis of these heterocycles we used a consecutive coupling–cyclocondensation–sulfur extrusion sequence (Scheme 11).

The Sonogashira coupling afforded the expected ynone **3**. When treated with 2-aminothiophenols the more nucleophilic sulfur atoms were exclusively involved in the Michael attack to the triple bond, which is followed by the usual cyclocondensation, promoted by the nitrogen atom, to afford benzothiazepine **24**, an intermediate that can indeed be isolated under milder reaction conditions.[26] Sulfur-extrusion is a well-

documented procedure for ring contraction, which is particularly suited for the synthesis of aromatic products, and has been used for example to transform 1,4-thiazepines into substituted isoquinolines.[27]



Scheme 11. Coupling–cyclocondensation–sulfur extrusion synthesis of 2,4-disubstituted (and 2,4,7-trisubstituted) quinolines **25**.

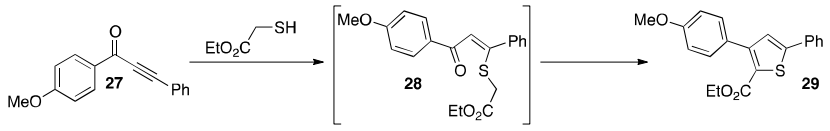
The conditions for the complete and quantitative sulfur extrusion had to be carefully optimized and, after all, we found that microwave heating is essential to achieve good results. We also investigated by DFT-calculations the tentative mechanism of the key sulfur extrusion, demonstrating the conversion of **24** into thiirane **26**, which should be a more stable intermediate at elevated temperatures.

Groups R^1 and R^2 are always aromatic or heteroaromatic (R^1) with or without different electronic properties, while the diversity related to R^3 is limited to H and Cl; unfortunately, the sequence could not be applied to the synthesis of quinolines with R^2 = alkyl.

All 2,4-disubstituted quinolines **25** are blue-florescent and show absorption maxima in the range from 342 to 349 nm with moderate values of ε (up to 13400, but usually < 10000 $Lcm^{-1}mol^{-1}$) and small Stokes shifts ($\Delta\tilde{\nu}$ from 700 to 3000 cm^{-1}). We observed that the absorption maximum is bathochromically shifted by the substituent on C-2 (R^1) with sufficiently strong donor capacity. Both strong donors (*p*-anisyl) and sterically less demanding, but donating, groups on C-2 (2-thienyl or 2-furyl), favor coplanar conformations and thereby generate a push-pull system.

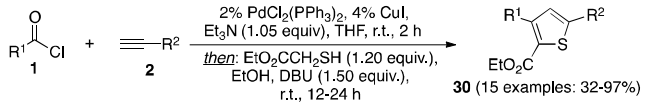
Of course, the sulfur atom can be retained in the final compound and this offers the possibility to access thiophenes and oligothiophenes as well. These compounds are privileged functional π-systems, because they can be used in organic light emitting diodes (OLED),[28] in organic field-effect transistors (OFET),[29] and organic photovoltaics.[30] Likewise 2,5-ligated oligothiophenes and related polymers constitute very important molecular nanoarchitectures.[31] Particularly interesting is the 2,4-connectivity of the thienyl nucleus, because of the linear arrangement and for this purpose we developed a consecutive tree-component one-pot synthesis of 2,4-disubstituted thiophene 5-carboxylates based on a coupling–Fiesselmann cyclocondensation.[32] Again, we exploited the sequential bifunctional electrophilic reactivity of ynones **3**, where the nucleophiles were in turn a sulfur atom and an enolate provided by ethyl 2-mercapto acetate. First, we optimized the Fiesselmann condensation on the isolated ynone **27** (Scheme 12). Several parameters have been considered: temperature, base, amount of nucleophile. After all we realized that the presence of ethanol

as cosolvent is very important for favoring the selective formation of the *Z*-configured Michael product **28**, the only able to undergo the following aldol-type cyclization affording thiophene **29**.



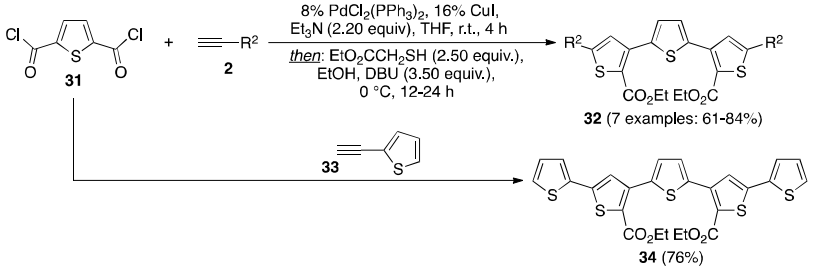
Scheme 12. Optimisation of the Fiesselmann reaction.

Then we switched to the one-pot procedure finding conditions able to sequentially transform (hetero)aroyl chlorides **1** and terminal alkynes **2** into thiophenes **30** (Scheme 13). A huge variety of decorations could be employed. R^1 is an aromatic or heteroaromatic group with electron-deficient or electron-rich and also sterically demanding substituents, while R^2 is usually an aromatic group but can be an organometallic fragment and an alkyl as well.



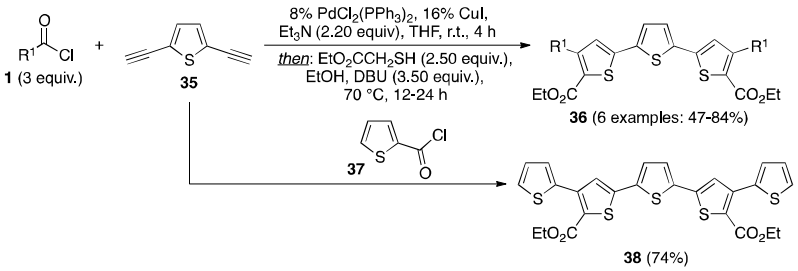
Scheme 13. Synthesis of 2,4-disubstituted thiophene 5-carboxylates **30** through coupling–Fiesselmann cyclocondensation.

Starting from thiophene-2,5-dicarbonyl dichloride **31** (acting as component **1**) we were able to isolate symmetrical terthiophenes **32**[32-33] and even a quinquethiophene **34** (using alkyne **33** as component **2**)[32] in a one-pot sequence which can be regarded as a pseudo-five component reaction (Scheme 14).



Scheme 14. Consecutive pseudo-five-component Sonogashira alkynylation–Fiesselmann cyclocondensation synthesis of symmetrically substituted ter- and quinque-thiophenes **32** and **34** from thiophene-2,5-dicarbonyl dichloride.

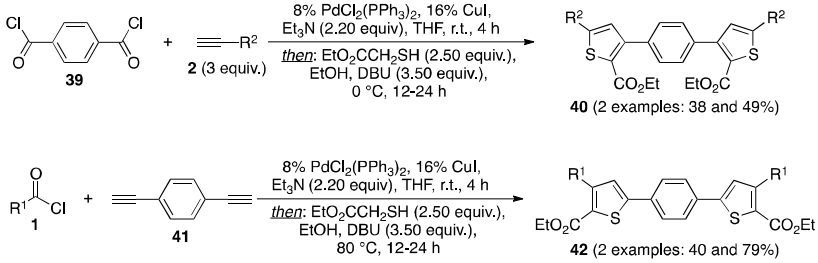
Meanwhile, in order to explore a different connectivity between the thiophenes, we used 2,5-diethynylthiophene **35** (acting as double alkyne component) that was reacted, under Sonogashira conditions, with acyl chlorides **1** (Scheme 15).[33] The expected products **36**, including also this time quinquethiophene **38** (which is a constitutional isomer of **34**) obtained from chloride **37**, were isolated in moderate to excellent yield.



Scheme 15. Consecutive pseudo-five-component Sonogashira alkynylation–Fiesselmann cyclocondensation synthesis of symmetrically substituted ter- and quinque-thiophenes **36** and **38** from 2,5-diethynylthiophene.

It is worth noting that the use of **35** is absolutely not trivial because this compound is unstable and undergoes a relatively easy decomposition already at –25 °C. In order to prevent the decomposition, we had to work under a nitrogen atmosphere, excluding light.

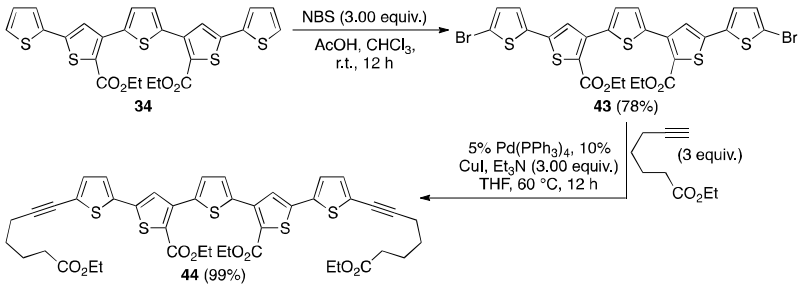
Finally, we built the polythiophene moiety around terephthaloyl dichloride **39** or 1,4-diethynylbenzene **41** through the usual of Sonogashira coupling. In this case two thiophene units act as the terminal part of a dumbbell and compounds **40** and **42** have been obtained in moderate to good yield (Scheme 16).[33]



Scheme 16. Consecutive pseudo-five-component Sonogashira alkynylation–Fiesselmann cyclocondensation synthesis of dithienyl dumbbells **40** and **42**.

The above mentioned strategies clearly highlight the possibility to obtain differently functionalized oligothiophenes by an appropriate combination of simple starting materials not usually requiring functionalized thiophene monomers. A diversity increase can actually be realized as a post-condensation transformation which allows, for example, the α,ω-functionalization of quinquethiophenes with the possibility to prepare higher molecular weight oligomers, thanks to an electrophilic bromination (NBS) (to give **43**) followed by a Sonogashira coupling, able to extend the conjugation (to give **44**) as depicted in Scheme 17.[33]

The electronic properties of oligothiophene derivatives were studied by UV and fluorescence spectroscopy. The absorption maxima of thiophenes **32** are blue-shifted with respect to isomers **36**. In the former case the absorption is in the range of 305-359 nm and depends on the substitution pattern, while for the latter set of compounds the maximum always appears around 395 nm. The values of ε are always considerably high, ranging from 21500 to 63800 $Lcm^{-1}mol^{-1}$.



Scheme 17. Post-condensation transformations of oligothiophene **34**.

Both libraries of compounds reveal a strong luminescence in solution between 440 and 451 nm. The phenylene bridged derivatives **40** possess a single maximum emission similar to that of compounds **32**, while compounds **42** resemble thiophenes **36**, with two emission maxima. The main difference between phenylene-bridged compounds **40** and **42** and the thiophene-bridged compounds **32** and **36** lies in the emission maxima, which are considerably blue-shifted (396-408 vs. 450-460 nm) for the former. All components display strong Stokes shifts ($\Delta\tilde{\nu}$ from 2900 to 10300 cm^{-1}), but only compounds **32** reveal substantial quantum yield (Φ_f in the range 0.07-0.11) while all other systems are only weakly fluorescent with quantum yield below 0.01.

All oligothiophenes display a noticeable red-shifted emission as a film and in the solid state if compared to solution luminescence, in particular compounds of series **32**. This is probably due to the favored planarization occurring during packing, which is responsible for an enhanced π-conjugation.

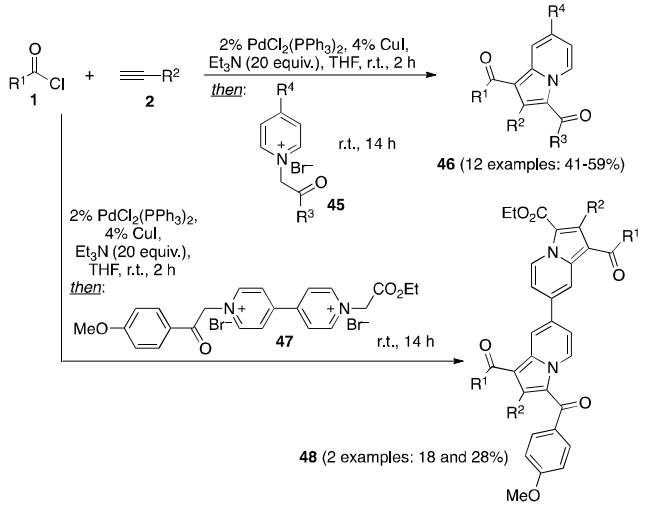
2.3. Miscellaneous alkynylation–cyclization syntheses

For the synthesis of other blue fluorescent molecules, we also envisaged strategies different from the ones described in the previous sections, but having in common the presence of an alkyne (terminal or internal) in at least one of the key reagents used in the multicomponent reaction.

Indolizines are aromatic 10π-electron systems known for their fluorescence properties. Among the known synthetic approaches to indolizines the [3+2]-cycloaddition between a Michael acceptor (equipped with either a double or triple electrophilic C-C bond) and a pyridinium ylide attracted us.[34] We envisaged indeed the possibility to exploit this reactivity in a multicomponent fashion, combining the Sonogashira coupling fully described above with a consecutive cycloaddition.[35]

For our purposes, we submitted a (hetero)arenecarbonyl chloride **1** and a terminal alkyne **2** to the usual Sonogashira coupling (Scheme 18), in the presence of triethylamine, to give alkynones **3**. Then we added a 1-(2-oxoethyl)pyridinium bromide **45** and, after stirring at room temperature for 14 h, we isolated indolizines **46** in moderate to good yield as pale yellow to yellow-green crystalline solids. At the same time, also the bifunctional 4,4'-bipyridinediinium salt **47** participates in the same reaction affording 7,7'-biindolizines **48** as intensively yellow solids albeit with modest yield. Different substituents are tolerated: R^1 is aromatic (with electron-neutral, electron-withdrawing or electron-donating substituents), R^2 can be either aromatic or aliphatic (also with a protected alcoholic function), R^3 can be OR or aryl, R^4 is H or a 4-pyridyl

group. The structures were unambiguously assigned by spectroscopic methods and **46** (R^1 = R^2 = Ph, R^3 = *p*-MeO-C_6H_4, R^4 = 4-pyridyl) was also characterized by X-rays crystallography.



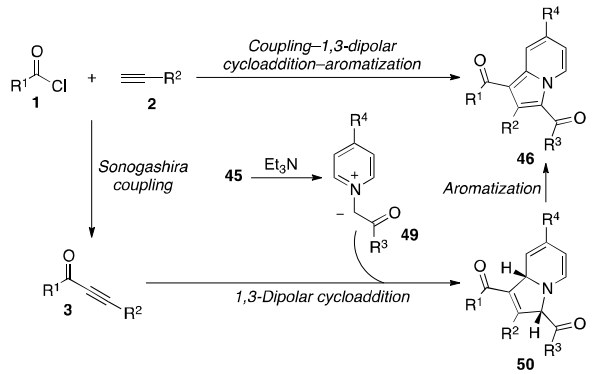
Scheme 18. One-pot three-component coupling–1,3-dipolar cycloaddition synthesis of indolizines **46** and **48**.

A possible rationalization of the reaction mechanism is shown below (Scheme 19):

a) the presence of Et_3N from the previous Sonogashira reaction allows the deprotonation of **45** to give the resonance-stabilized pyridinium ylide **49**, which behaves as an allyl-type 1,3-dipole;

b) **49** undergoes a fast 1,3-cycloaddition with **3** to produce **50**, a highly unstable intermediate;

c) **50** spontaneously undergoes aromatization and we cannot exclude a favorable influence of the Pd and/or Cu species still present on the final oxidative/dehydrogenative step.

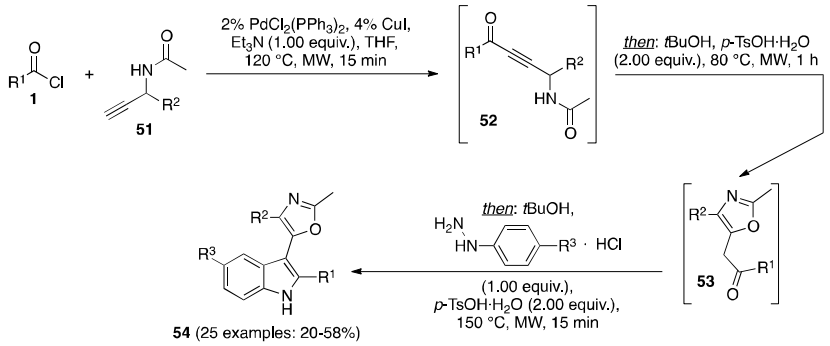


Scheme 19. A possible mechanism for the formation of indolizines **46**.

All compounds **46** absorb in a quite narrow region (356-384 nm) with high values of ε (15900-28800 $Lcm^{-1}mol^{-1}$). The emission maximum is again in a narrow interval (495-512 nm) with high Stokes shifts ($\Delta\tilde{\nu}$ from 6500 to 7900 cm^{-1}). The only compound, which is not at all fluorescent, is the one with R^1 = *p*-O_2N-C_6H_4, R^2 = Ph, R^3 = *p*-MeO-C_6H_4, R^3 = 4-pyridyl. Biindolizines **48** absorb around 432 nm with remarkable values of ε (37500 and 36400 $Lcm^{-1}mol^{-1}$), while the emission lies at 460 nm with considerably lower Stokes shifts ($\Delta\tilde{\nu}$ 1300 and 1400 cm^{-1}). In the 4-pyridyl substituted series we demonstrated that the pronounced fluorescence shifts to a strong day light fluorescence in the protonated form (pyridine nitrogen). Indeed, in **46** (R^1 = R^2 = Ph, R^3 = *p*-MeO-C_6H_4, R^4 = 4-pyridyl) the emission maximum was shifted from 471 to 509 nm after protonation, which was demonstrated to be fully reversible.

If ynones **3** bear an acylated nitrogen atom on the propargylic carbon atom the ketone can undergo a different fate, based upon a cycloisomerization step. This protocol was developed in our group for the synthesis of 2-oxazol-5-ylethanones as a consecutive three-component amidation–coupling–cycloisomerization sequence.[36] More recently we became interested in indolyl oxazoles, compounds were the two heterocyclic scaffolds are conjugated through a C-C bond. This framework is present in some naturally occurring alkaloids[37] and a broad spectrum of activity has been reported, including anticancer properties.[37b] However, our main interest was primarily focused in the determination of photophysical properties of these highly conjugated structures.

For the synthesis of compounds **54** we planned a multicomponent approach having in mind to build first the oxazole moiety through a modification of our previously developed protocol, joining as the last step the nitrogen heterocycle through a Fischer indole synthesis.[38] The structure of the reagents was chosen in order to introduce three diversity factors with the one-pot formation of four new bonds, using starting materials with R^1 = (hetero)aryl and R^2 = aryl (Scheme 20).



Scheme 20. Three-component coupling–cycloisomerization–Fischer indole synthesis of 5-(3-indolyl)oxazoles **54**.

As illustrated in Scheme 20, the key intermediate is represented by the propargylacetamide ynone **52**. This is the product of a Sonogashira coupling performed under our modified conditions,[12] where acyl chloride **1** is reacted with 1-(aryl) *N*-(pro-2-yn-1-yl)acetamides **51**. Ynones **52** were cycloisomerized without being previously isolated, after addition of *p*-toluenesulfonic acid (PTSA), under dielectric heating, to afford **53**. The addition of a supplementary amount of PTSA and an aryl hydrazine in the same reaction vessel

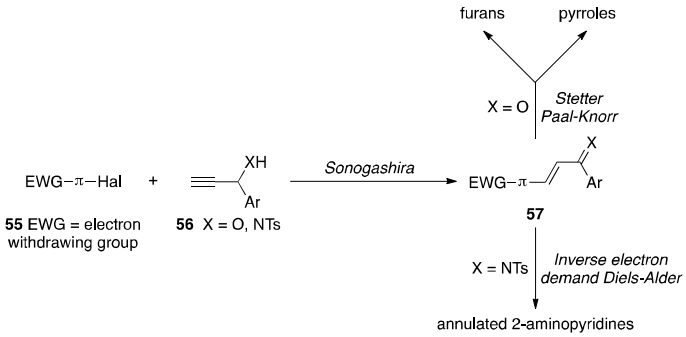
allowed the formation of **54** as colorless to pale yellow crystals in moderate overall yields. The final compounds were intensely blue-luminescent in contrast to the precursors **53**, which permitted an easy monitoring by TLC of the reaction outcome.

The yields are clearly affected by the electronic nature of the substituents. For instance, a *p*-chlorophenyl as R^2 allows higher overall yields if compared to a *p*-tolyl, most likely because of the easier deprotonation of the propargylic position necessary for the cycloisomerization to occur. Also, the combinations of acyl chloride **1** and alkyne **2** are affected by the relative substituents. Electron-neutral and electron-rich **1** react with electron-poor and electron-rich alkynes **2** with comparable yields, while the poorest yields were obtained combining electron-poor **1** and electron-rich **2**.

In the UV/vis spectra the longest wavelength absorption can be found in a narrow range (298-328 nm), which means that the aryl substituents have only a modest electronic influence; however, a heterocyclic substituent in position 2 (indole) is responsible for a slight red-shift.

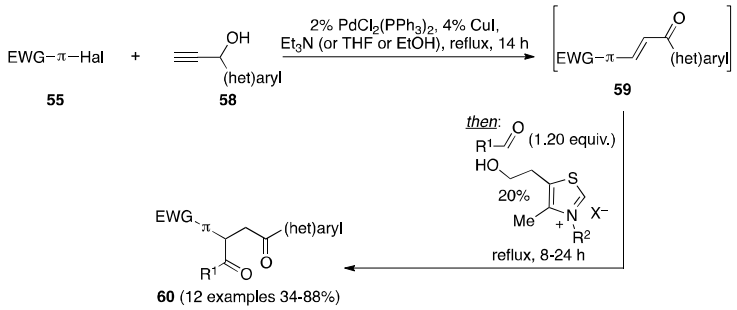
In the emission spectra, all compounds display intense blue luminescence in the range 426-445 nm and very significant Stokes shifts ($\Delta\tilde{\nu}$ from 7700 to 10600 cm^{-1}) and, with the exception of derivatives with R^1 = 2-thienyl, a satisfactory quantum yield is observed (Φ_f in the range 0.10-0.25). The enhancement of Stokes shifts, in comparison to simple 2,5-disubstituted oxazoles, can be attributed to the fact that the nonplanar electronic ground state indicated by the X-ray structure analysis of **54** (R^1 = R^2 = *p*-Cl-C_6H_4, R^3 = Cl) is subject to flattening in the relaxed excited state.

Coupling of terminal propargyl alcohols or amides (**56**) in a Sonogashira reaction is not only limited to the employment of acyl chlorides as electrophiles.



Scheme 21. Coupling–isomerization reaction (CIR).

Actually, we demonstrated that electron-poor halogen-substituted π-systems (**55**) can be used as well, but this time a domino Pd/Cu-catalyzed coupling–isomerization reaction (CIR) occurs. After a rapid alkynylation reaction a slow base-catalyzed isomerization allows the transformation of the expected propargyl coupling product into an enone or an enamine **57**, respectively (Scheme 21), that are excellent building blocks for the diversity oriented synthesis of fluorescent chromophores. For example the former (X = O) can be used as Michael acceptor in a Stetter reaction followed by a Paal-Knorr condensation to afford furans or pyrroles,[39] while the latter (X = NTs) can be behave as an azadiene in a Diels-Alder reaction with inverse electron demand to give differently annulated 2-aminopyridines.[40]



Scheme 22. CIR–Stetter sequence to 1,4-diketones **60**.

The fate of **57** depends on the nature of X. Propargyl alcohols **58** are transformed into 1,3-di(hetero)aryl enones **59** (Scheme 22), also known as chalcones, and these compounds are a good starting material for the umpolung conjugated addition of an aldehyde derived acyl anion, through the Stetter reaction, to install the 1,4-dicarbonyl functionality.

We envisaged 1,4-diketones **60** as ideal substrates for the following conversion into 2,3,5-trisubstituted furans and 1,2,3,5-tetrasubstituted pyrroles, using the old, but still efficient, Paal-Knorr reaction. These heterocycles can be regarded as privileged scaffolds in medicinal chemistry,[14] and moreover they are expected to display interesting fluorescence properties.

For testing the compatibility of the Stetter addition of aldehydes to chalcones we initially studied the consecutive CIR-Stetter reaction isolating diketones **60**.[39] After completion of the Sonogashira reaction, we directly added the aldehyde and the appropriate thiazolium salt in a catalytic amount, working at reflux in the presence of triethylamine as a solvent (sometimes in the presence of a co-solvent).

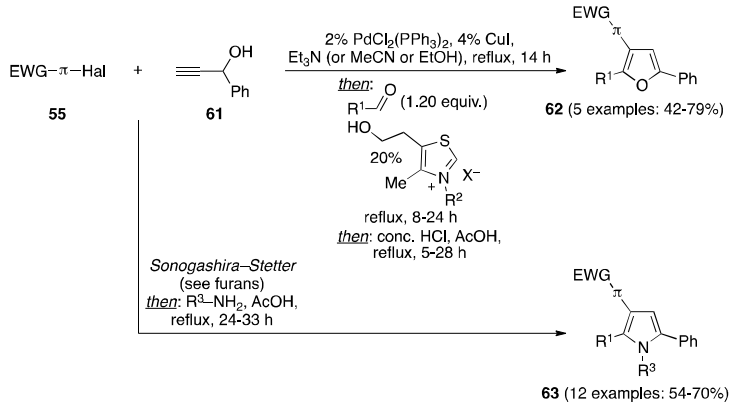
The procedure turned out to be robust and afforded **60** in moderate to excellent yield. The sequence was characterized by an excellent chemoselectivity, since two different catalytic cycles occurred in the same flask without interfering with each other. The Stetter conditions tolerate electron-poor and electron-rich aromatic aldehydes, aliphatic aldehydes and also aldehydes with polar groups. The only limitation is that we had to use two different catalysts: 3,4-dimethyl-5-(2-hydroxyethyl)-1,3-thiazolium iodide (R^2 = Me, X = I) was the catalyst of choice for aromatic aldehydes, while 3-benzyl-4-methyl-(2-hydroxyethyl)-1,3-thiazolium chloride (R^2 = Bn, X = Cl) must be used for aliphatic aldehydes. In addition, aldehydes with a chiral R^1 group, used in the Stetter reaction, showed no facial diastereoselectivity at all.

Encouraged by these results we set out to extend the methodology by adding a further step, i.e. the Paal-Knorr cyclization, for a fast access to highly decorated furans and pyrroles in a one-pot three-component and four-component synthesis, respectively, that occurs under mild conditions (Scheme 23). After the complete conversion of **59** into **60** (only 1-phenylprop-2-yn-1-ol **61** was used this time as propargyl alcohol), we added concentrated hydrochloric acid and acetic acid and refluxed again the mixture until the complete disappearance of **60**, isolating furans **62** in moderate to good yields.

In a similar way **60** was treated with a primary amine or ammonium chloride and acetic acid and, after refluxing again, pyrroles **63** were obtained in moderate to good yield.

All the new heterocycles display an intense blue fluorescence when irradiated with UV light. The longest wavelength absorption maxima are in a narrow range (312-327 nm) with high values of ε (9900-

30700 $Lcm^{-1}mol^{-1}$). A broader range in the emission maximum was observed (407-451 nm) with remarkable Stokes shifts ($\Delta\tilde{\nu}$ from 7100 to 9100 cm^{-1}). Interestingly, furans and pyrroles with the same substitution pattern show very similar fluorescence behavior.



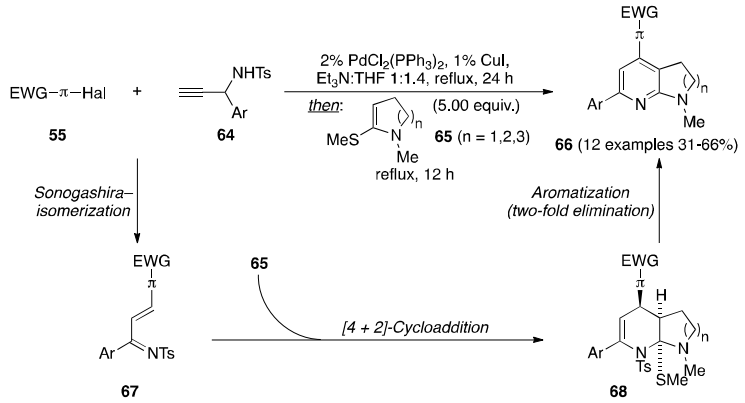
Scheme 23. CIR–Stetter–Paal-Knorr three-step synthesis of furans **62** and pyrroles **63**.

N-Tosyl enimines (**57**, X = NTs) are electron-deficient heterodienes and so we considered them as appropriate partner in a Diels-Alder reaction with inverse electron demand involving an electron-rich dienophile.[40] These highly reactive intermediates, easily accessible by the aforementioned CIR sequence, seemed therefore suited for accessing annulated 2-aminopyridines, compounds where the amino group is included in an annulated saturated ring of different size.

For our purposes, we envisaged cyclic *N*,*S*-ketene acetals **65** as electron-rich dienophiles to be used in a [4 + 2]-cycloaddition, planning to perform a three-component CI–cycloaddition sequence, ending up with an aromatization step.

Our diversity-oriented approach has been designed in order to explore not only the decoration diversity but also the size of the saturated ring in order to access pyrrolo[2,3-*b*]pyridines, [1,8]naphthyridines, and pyrido[2,3-*b*]azepines. The complex sequence we planned worked well. After completion of the Sonogashira–isomerization step we added **65** and, after additional heating at reflux, we isolated heterocycles **66** in moderate to good overall yield (Scheme 24). Their structure was assigned on the basis of spectroscopic data and by X-ray crystallography, which was performed on several members of the library, chosen because of the different size of the saturated ring. The crystallographic analysis revealed that the substituent in the 4-position of central pyridine is twisted out from coplanarity (with the pyridine ring) up to 90 °, the value rising with increasing of the conformational bias of the annulated ring.

A tentative condensed mechanism is reported in Scheme 24. After the Sonogashira coupling between **55** and **64** the isomerization affords enimine **67** that undergoes the [4 + 2]-cycloaddition to give the annulated tetrahydropyridine **68**. Under the same reaction conditions a double elimination of methyl mercaptane and tolylsulfinate occurs with consequent aromatization and the sequence ends up with the formation of **66**.



Scheme 24. CIR–inverse electron demand Diels-Alder reaction to give annulated 2-aminopyridines **66**.

The UV absorption of compounds **66** is in the quite broad range 338-392 nm (longest wavelength) with a wide range of ε (3200-15900 $Lcm^{-1}mol^{-1}$). The highest bathochromic effect is shown by pyrrolo[2,3-*b*]pyridines (**66**, n =1), compounds where the substituent in position 4 (pyridine) is less distorted from coplanarity. Likewise, in annulated 2-aminopyridines **66** the wavelength of emission maximum, upon excitation at the corresponding absorption wavelengths, depends on the size of the saturated ring: 466-469 nm (n = 1), 438-445 nm (n = 2), 478-511 nm (n = 3). The Stokes shifts are rather pronounced ($\Delta\tilde{\nu}$ from 4200 to 9600 cm^{-1}) and significantly higher quantum yields are shown by pyrrolo[2,3-*b*]pyridines (**66**, n = 1; Φ_f = 0.32-0.63) with respect to [1,8]naphthyridines (**66**, n = 2; Φ_f = 0.12-0.25) and pyrido[2,3-*b*]azepines (**66**, n = 3; Φ_f = 0.15-0.34).

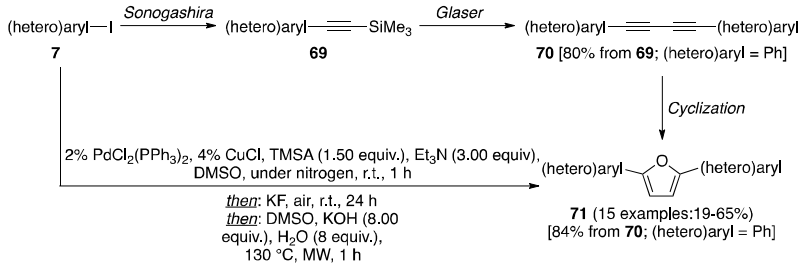
Thanks to the presence of a basic pyridyl nitrogen atom in **66** we also investigated and compared the pH dependence of the absorption and emission properties in two related compounds (EWG–π– = 2-pyrimidyl and n = 1 and 3, respectively). In both cases we observed halochromicity with a bathochromic shift of the longest wavelength absorption maxima by lowering the pH from 9 (384 nm, n = 1; 372 nm, n = 3) to 1 (392 nm, n = 1) or pH 4 (380 nm, n = 3). The protonation affects even more, but not for both compounds, the emission maximum. While for the pyrrolo[2,3-*b*]pyridine (n =1) only a slight shift after protonation occurs (from 478 at pH 9 to 482 nm at pH 1) a significant bathochromic effect is shown by the corresponding pyrido[2,3-*b*]azepine (n =3) from 478 at pH 9 to 512 nm at pH 1.

We recently became interested in finding a new diversity-oriented and multicomponent-based synthetic approach to symmetrically substituted 2,5-di(hetero)arylfurans.

Besides their well-documented biological activity,[41] these compounds have been reported as photonic chromophores,[42] but our interest was boosted by the lack of extended studies on their electronic and photophysical properties.

For our purposes we planned to use a strategy, previously used to prepare the thiophene analogues,[43] based on the one-pot Sonogashira–Glaser–cyclization sequence, a combination between a cross-coupling and an oxidative coupling of two terminal alkynes, followed by a cyclization in the presence of water and a base.

Before optimizing the one-pot sequence we first developed the optimal conditions for performing as separate steps the Sonogashira coupling followed by the Glaser reaction and the final cyclization to the furan ring, choosing 1,4-diphenylbutadiyne as key intermediate [**70**, (hetero)aryl = Ph] (Scheme 25).[44] The cyclization step was initially investigated. The reaction conditions turned out to be crucial, in particular the concentration of the substrate, because, at higher concentration, the formation of oligomers and polymers considerably lowered the yield. This problem was however solved working under more diluted conditions. The amount of base and water and the temperature had to be properly adjusted as well. Under optimized conditions the expected furan **71** was obtained in 84% yield from **70**.



Scheme 25. Sonogashira–Glaser–cyclization synthesis of 2,5-di(hetero)arylfurans **71**.

Then we turned our attention to the Sonogashira–Glaser step in order to find conditions suited for the concatenation of all steps into a one-pot procedure. The usual solvent for this sequence is THF but we had to switch to DMSO, which is suited for the final cyclization, in view of the multicomponent approach. This turned out to be beneficial, because DMSO also brought about an acceptable solubility of potassium fluoride and, after all, the overall yields resulted comparable with those obtained working with THF. The coupling between **7** and trimethylsilyl acetylene (TMSA) to give **69** had to be performed under strictly oxygen-free conditions. But, as soon as fluoride removed the silyl group, we had to introduce air with an efficient stirring for inducing optimal saturation of the solvent and allowing the oxidative coupling to **70**.

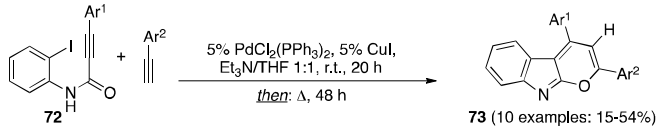
The optimized conditions were finally combined to run the pseudo-five component synthesis of furans **71**, varying the structure of the starting iodide **7**. The overall yields are from moderate to good and the aryl groups can be equipped with either electron-neutral or electron-rich groups.

All furans **71** show strong fluorescence in solution and in the solid state after UV excitation. The absorption maxima are observed in the moderately broad range (321-358 nm) and are characterized by marked values of ε (2100-35000 $Lcm^{-1}mol^{-1}$). In addition, red-shifted shoulders are present between 336 and 377 nm. Likewise, the emission maxima are found between 367 and 439 nm together with blue-shifted shoulders between 351 and 424 nm. The Stokes shifts range from 3500 to 6400 cm^{-1} and the quantum yields are quite large with Φ_f = 0.29-1.00.

These data suggest remarkable geometrical differences between the electronic ground state and the vibrationally relaxed excited state, probably due to the significant distortion of the aryl substituents from coplanarity in the ground state, which is particularly important for *ortho*-aryl substituted derivatives. This fact has been corroborated also by computational analysis.

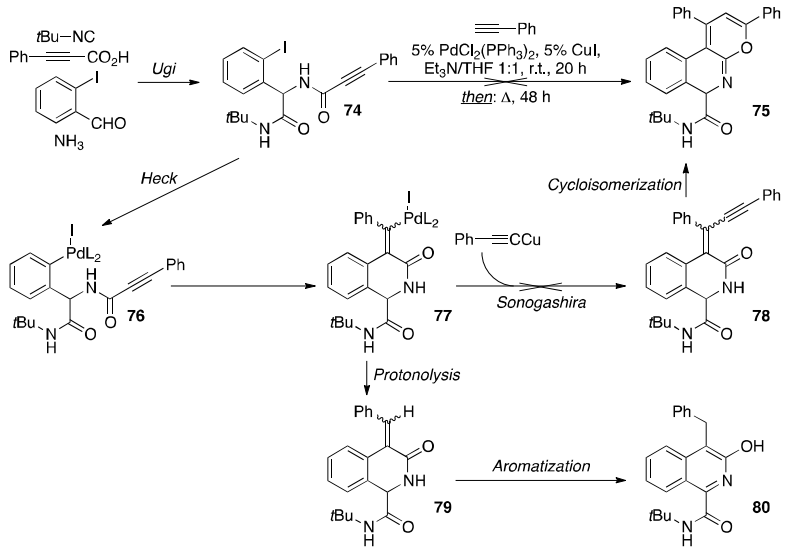
3. Ugi substrates for accessing blue emitters

In recent years we published the synthesis 2,4-diarylpyrano[2,3-*b*]indoles **73**, a previously unknown tricyclic system, obtained through an insertion-coupling–cycloisomerization domino reaction (Scheme 26) combining amide **72** and a terminal alkyne.[45] This protocol involves an intramolecular Heck-type insertion of the internal alkyne to give the indole nucleus, followed by a Sonogashira-type coupling with the terminal alkyne and, finally, by a cyclization of the amide oxygen to give the final pyranoindole. These molecules are nonfluorescent in solution but become intensely green luminescent after protonation, quaternation and complexation with metal ions. In particular, selective halochromic fluorescence in the presence zinc and magnesium over calcium suggests the possibility to use them as metal-selective luminescence sensors.



Scheme 26. Insertion-coupling–cycloisomerization domino synthesis of 2,4-diarylpyrano[2,3-*b*]indoles **73**.

This synthesis is actually not a multicomponent process. However, in order to better understand and possibly improve the photophysical properties of this unusual heterocycle, we planned to synthesize the homologous tricyclic scaffold **75** from precursor **74** (chosen as model compound for testing the strategy), the product of an isocyanide-based Ugi multicomponent reaction where ammonia is used as amine component (Scheme 27).[46] Surprisingly the protocol used for the synthesis of **73** did not afford the expected pyranoisoquinoline **75** and we isolated 3-hydroxyisoquinoline **80** instead (Scheme 27) even if in low overall yield.

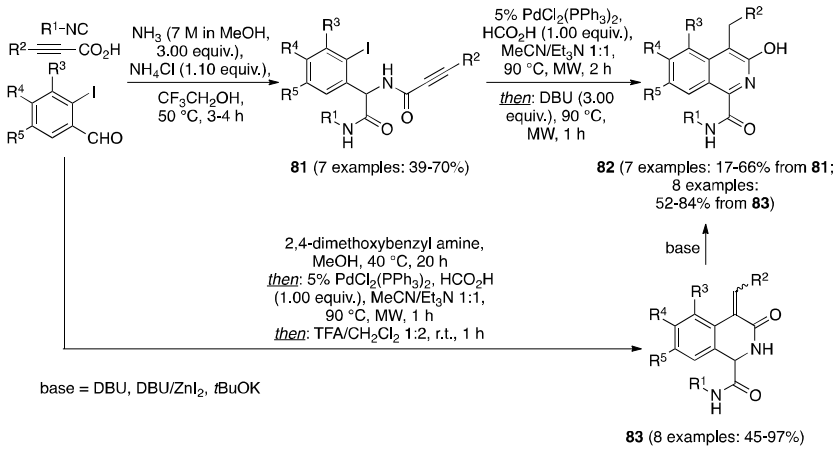


Scheme 27. Attempted Sonogashira–cycloisomerization domino synthesis of **75**.

A possible rationalization is that, after the expected intramolecular Heck reaction involving intermediates **76** and **77**, a protonolysis, followed by the aromatization of **79**, occurs resulting in an overall reductive Heck sequence, and thus not allowing the incorporation of the terminal alkyne.

After many experiments, performed in order to optimize the synthesis of **80**, we found that the addition of formic acid is of paramount importance for an efficient protonolysis and that the addition of DBU, after completion of the Heck reaction, is necessary for achieve a complete aromatization. The latter transformation is indeed the rate determining step. The scope of the reaction, with the synthesis of **81** by Ugi reaction with ammonia (Scheme 28), resulted not fully satisfactorily from the point of view of yields and reproducibility and, in addition, the use of ammonia in the Ugi reaction prevented to explore a one-pot procedure.

On the contrary, using 2,4-dimethoxybenzyl amine as an ammonia surrogate in the Ugi reaction (the 2,4-dimethoxybenzyl group can be easily removed before the aromatization step), we observed that the yields were more reproducible and satisfactory. The transformation of Ugi reagents into **82** can be carried out in one-pot, though for improving the overall yields we obtained more satisfactory results performing the final aromatization from **83** as a separate step. The only drawback is that personalized conditions (choice of the base, temperature, conductive or dielectric heating) for the aromatization have to be found for every substrate.



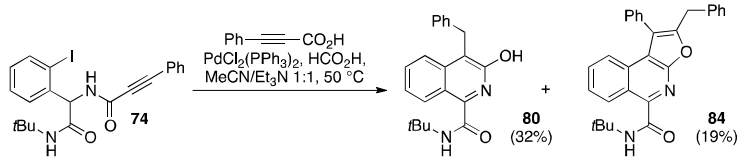
Scheme 28. Synthesis of 3-hydroxyisoquinolines **82** by Ugi-reductive Heck-aromatization.

3-Hydroxyisoquinolines **82** exhibit a remarkable blue florescence even upon eyesight. The longest wavelength maxima are considerably red-shifted with respect to unsubstituted 3-hydroxyisoquinoline (340 nm) and can be found in the range 358-383 nm, with values of ε from 6800 to 10100 $Lcm^{-1}mol^{-1}$. The emission maxima are bathochromically shifted too, compared to the parent system (370 nm), and are found in a range from 394.5 to 446.5 nm. Neither the 4-alkyl nor the 1-amide substituent cause major changes in the emission properties. By contrast, more pronounced effects on the photophysical properties are exerted by the substitution pattern of the benzo core of the isoquinoline.

Moderate Stokes shifts ($\Delta\tilde{\nu}$ from 2600 to 2800 cm^{-1}) characterize the most part of these compounds, with higher values ($\Delta\tilde{\nu}$ up to 3800 cm^{-1}) in those compounds with $R^3 = R^4 = R^5 =$ OMe. All unsubstituted compounds (on the aromatic ring; $R^3 = R^4 = R^5 = H$) show very high quantum yields ($\Phi_f = 0.79$-0.90), with the single exception represented by the isoquinoline with R^1 = 2,6-dimethylphenyl, in which a radiationless deactivation of the excited state occurs. For all other compounds the quantum yield is found in the range from 0.20 to 0.62.

We also examined the solvent effect (dichloromethane, acetonitrile, DMSO) on the photophysical properties of **82** (R^1 = *n*Bu, R^2 = Ph, $R^3 = R^4 = R^5 = H$). The absorption properties are only slightly affected upon variation of the solvent polarity. However, in the emission spectrum a positive solvatochromism is clearly apparent with the maximum red-shift in DMSO ($\Delta\tilde{\nu}$ = 890 cm^{-1} with respect to dichloromethane or acetonitrile). The fluorescence efficiency is controlled by protonation as demonstrated by titration with trifluoroacetic acid, indicating that the protonated species is responsible for a static fluorescence quenching.

During the optimization of the synthesis of **80** from **74** (an Ugi product obtained from ammonia) we came across a strange result, isolating, besides the expected product, furo[2,3-*c*]isoquinoline **84** (Scheme 29).[47] We realized that the additional carbon fragment incorporated in **84** was provided by phenylpropiolic acid, the same acid used in excess in the Ugi reaction and not properly removed during the purification. Its formation can be explained as the result of an intramolecular Heck reaction followed by a copper free decarboxylative Sonogashira and a 5-*exo*-*dig* cyclization. Interestingly **84** is an isomer of **75**, the product initially expected, which is the result of a 6-*endo*-*dig* cyclization instead.

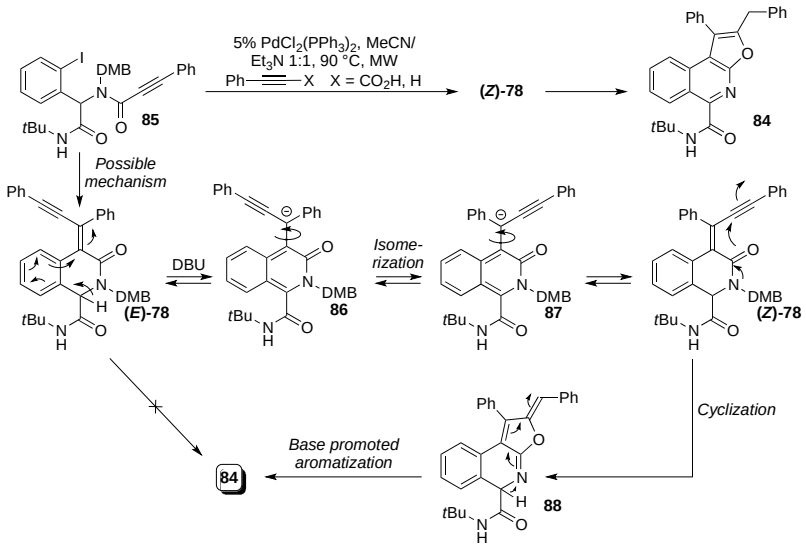


Scheme 29. Serendipity-driven synthesis of **84**.

So, we decided to optimize the reaction conditions for the synthesis of this nearly unknown scaffold, demonstrating that the addition of CuI, the usual co-catalyst in the Sonogashira, does not affect the yields in a significant way. On the other hand, we found that phenylacetylene instead of phenylpropiolic acid works as well in a copper free coupling, improving atom economy of the sequence.

In view of a possible one-pot sequence we switched again to the Ugi reaction using 2,4-dimethoxybenzyl (DMB) amine instead of ammonia (Scheme 30). We submitted the Ugi product **85** to the insertion-coupling sequence, expecting to isolate (*Z*)-**78**. However, surprisingly, the main product was **84**, together with (*E*)-**78** and traces of (*Z*)-**79** (Scheme 27). The formation of (*Z*)-**78** is probably the result of an equilibration following the insertion-coupling, which is expected to lead exclusively to (*E*)-**78**. Thanks to the very easy loss of DMB group, (*Z*)-**78** spontaneously undergoes the following cyclization, while (*E*)-**78** is unable to cyclize. So, we tried to accelerate the *E*/*Z* isomerization and eventually found that the addition of 1 equivalent of DBU, after completion of the first cyclization, was a good solution, allowing the complete transformation of diastereomeric Heck products into **84**.

The role of the base is summarized in Scheme 30. After the Heck reaction occurring as already shown in Scheme 27, DBU is responsible for the *E*/*Z* equilibration of diastereomeric **78**, thanks to the intermediate formation of stabilized carbanions **86** and **87**. Finally, the tertiary amide carbonyl oxygen attacks in a 5-*exo-dig* fashion the triple bond with simultaneous loss of the relatively stable dimethoxybenzyl cation. Then the base promotes the final tautomerism of **88** to give a stable aromatic system (**84**).

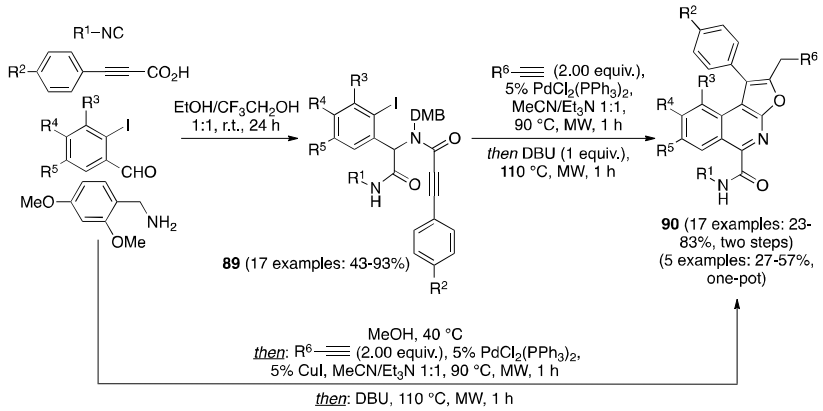


Scheme 30. Direct cycliztion of amide **85** and possible simplified mechanism.

The scope of the reaction was then investigated either as a two-step procedure, requiring the isolation of Ugi product **89**, or as a one-pot procedure, without isolating Ugi products (Scheme 31). In the latter procedure, we observed the addition of CuI to be beneficial. The yields are in most cases from good to excellent with just few exceptions and just two failures to obtain **90** (for $R^2 = NO_2$). The substituents were chosen in order to influence the photophysical properties and, in particular, we prepared compounds with electron-withdrawing and/or electron-releasing groups properly placed on the aldehyde and on the propiolic acid. Actually, we later demonstrated that the influence of electronically different substituents in the *p*-position of the phenyl ring of the furo part on the absorption maximum is only minor.

All dichloromethane solutions of furoisoquinolines **90** display blue fluorescence upon eyesight, but the color and its intensity seem dependent on the substitution pattern. All new molecules display a longest wavelength absorption maximum between 341.0 and 372.0 nm with values of ε between 10300 and 17200 $Lcm^{-1}mol^{-1}$. Moreover, at least one additional absorption band at higher energy was observed. 7-Methoxy-substituted derivatives **90** (R^5 = OMe) possess an additional absorption band in the range of 323.5-336 nm. The emission maxima of the investigated compounds appear between 396.0 and 443.0 nm with substantial Stokes shifts $\Delta\tilde{\nu}$ between 3200 and 5600 cm^{-1} and pronounced fluorescence quantum yields Φ_f ranging from 0.14 to 0.90.

In conclusion, the photophysical characterization by absorption and emission spectroscopy reveals that the emission wavelength, Stokes shift, and fluorescence intensity is largely dependent on the donor substitution pattern on the isoquinoline part of the tricyclic core and also, to a minor extent, by the 4-aryl substituent on the furo moiety.



Scheme 31. Scope of the reaction to give **90**.

4. Conclusions

Consecutive multicomponent syntheses of simple five- and six-membered heterocycles commencing with alkynylation of aroyl and aryl halides followed by cyclocondensation, cyclization or cycloisomerization provide general and versatile accesses to functional fluorophores and, in particular, to blue emissive molecules with tunable electronic properties. While pyrazoles, thiophenes, quinolones, pyrrolyl-(aza)indazoles, oxazolyl indoles and indolizines are founded on initial catalytic alkynone formation, pyrroles, furans, and annulated aminopyridines rely on the coupling-isomerization synthesis of chalcones, and symmetrically substituted 2,5-furans are derived from di(hetero)aryl butadiynes. Most convincingly, various functionalities can be readily introduced by virtue of the diversity-oriented nature of the highly convergent multicomponent approach.

The most recent assets of blue emissive luminophores were obtained by concatenation of Ugi-4CR formation of the substrates that enter Pd-catalyzed transformation to the target structures, namely substituted isoquinolines and furoisoquinolines. With this powerful, multifaceted concept a plethora of blue emitters functionalized with sites for interaction with effectors are conceivable. Ongoing studies to extend this synthetic concept to the preparation of multifunctional fluorophores are currently underway.

Acknowledgements

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