ChemPubSoc Europe

DOI: 10.1002/chem.201404209

CHEMISTRY
A European Journal
Full Paper

Fluorescent Compounds

Diversity-Oriented Synthesis of Intensively Blue Emissive 3-Hydroxyisoquinolines by Sequential Ugi Four-Component Reaction/Reductive Heck Cyclization

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Abstract: A convergent approach to highly functionalized 3-hydroxyisoquinolines is reported. The key steps are an Ugi multicomponent reaction and a subsequent intramolecular reductive Heck reaction; these can also be performed as a one-pot procedure. The structures display very interesting properties as blue-fluorescence emitters. Photophysical studies on the absorption and static fluorescence indicate that the substitution pattern on the pyridyl part influences the optical properties only to a minor extent, unless the amide substituent becomes sterically demanding and leads to significant nonradiative deactivation. The donor substitution on the benzo core considerably enhances the fluorescence quantum yields and trimethoxy substitution causes a pronounced redshift of the emission bands. Protonation of the isoquinolyl nitrogen atom causes efficient static quenching of the fluorescence.

Introduction

The quest for novel functional π-electron systems,[1] that is, chromophores, fluorophores, and electrophores as functional molecular entities in molecule-based electronics,[2] molecular photonics,[3] and biophysical analytics,[4] is an ongoing task for synthetic chemistry. In particular, the efficient preparation of these π systems in a diversity-oriented fashion[5] by multicomponent processes[6] and domino reactions,[7] concepts with considerable stimulation in pharmaceutical lead discovery, remains a peculiar challenge and the concept of diversity-oriented synthesis (DOS) is still quite novel with respect to functional chromophores.[8]

Transition-metal-catalyzed processes have enabled rapid accesses to π-electron frameworks with extended conjugation. Therefore, novel consecutive multicomponent syntheses of heterocycles based upon transition-metal catalysis with excellent compatibility of numerous polar functionalities and mild reaction conditions turned out to be a conceptual breakthrough in the DOS of fluorophores.[9] Based upon Sonogashira alkynylation, the catalytic generation of alkynones and alkenones allowed a plethora of multicomponent syntheses of many classes of heterocycles[10] and fluorophores.[11] The domino insertion/coupling sequence of alkynoyl *ortho*-iodo anilides and alkynes furnished indolone-based frameworks with conformationally rigidified, highly fluorescent butadiene units in a spirocyclic corset,[12] solid-state luminescent push–pull chromophores with indolone as the acceptor moiety,[13] and pyranoindoles.[14] Conceptionally inspired by the insertion/coupling/cycloisomerization scenario furnishing the latter protochromic pyranoindole luminophores, we became intrigued in expanding this domino process to use Ugi four-component-reaction (4CR) products as substrates for the synthesis of the corresponding isoquinoline systems. Herein, we report the unexpected formation of multiply substituted 3-hydroxyisoquinolines, the elaboration of the synthetic methodology, and photophysical studies of the self-evident intense blue luminescence upon UV excitation.

Results and Discussion

Synthesis

The initial scaffold we intended to synthesize was inspired by structure **2** (Scheme 1), recently assembled through a domino insertion/coupling/cycloisomerization sequence from acyclic derivative **1**, by taking advantage of a double Pd–Cu catalytic system.[14] Indeed, we planned to prepare the homologous tricyclic scaffold **3** from precursor **4**, the product of an isocyanide-based Ugi multicomponent reaction (MCR), as illustrated in the retrosynthetic plan. A similar approach (Ugi reaction, or Ugi type reaction, followed by a domino organometallic proce-

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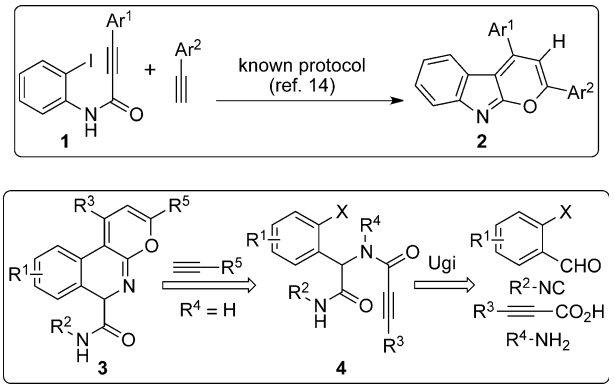
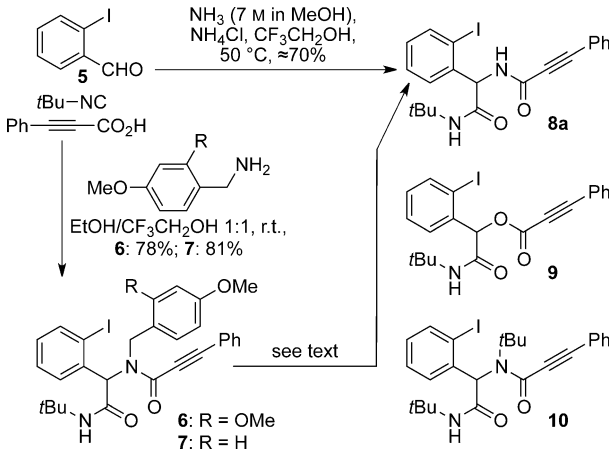
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201404209.



Scheme 1. State of the art and retrosynthetic plan. Ar = aryl.



Scheme 2. Synthesis of the Ugi products.

dure) has been occasionally described for the synthesis of different scaffolds.[15]

An isoquinolinone scaffold was, however, built through a Pd-mediated carbopalladation/Suzuki–Miyaura coupling sequence by starting from an acyclic derivative not obtained through an MCR.[16]

To allow the final cyclization, substituent R^4 in compounds **4** needs to be equal to hydrogen: these intermediates might be synthesized by a classical Ugi 4CR reaction by using a primary amine with a cleavable R^4 group or directly by using ammonia in the MCR. Even though it was less atom and step economical, we initially preferred to explore the first possibility, because it is known that ammonia often behaves poorly as an "amine surrogate" in the Ugi reaction.[17]

Initial aldehyde **5** was obtained in nearly quantitative yield by oxidation of the corresponding alcohol, by using either catalytic tetrapropylammonium perruthenate (2%) or 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO) in the presence of *N*-methylmorpholine-*N*-oxide and [bis(acetoxy)iodo]benzene (BAIB) as stoichiometric oxidants,[18] which thus avoided the use of highly toxic pyridinium chlorochromate.[19] We were pleased to find that both 2,4-dimethoxy- and 2-methoxybenzylamine gave the desired Ugi adducts **6** and **7** in excellent yield, notwithstanding the somewhat unpredictable reactivity of propynoic acids in such reactions (Scheme 2). For example, it is well known that triple bonds may add to isocyanides to give zwitterions, which can react in a different way and lead to side products.[20]

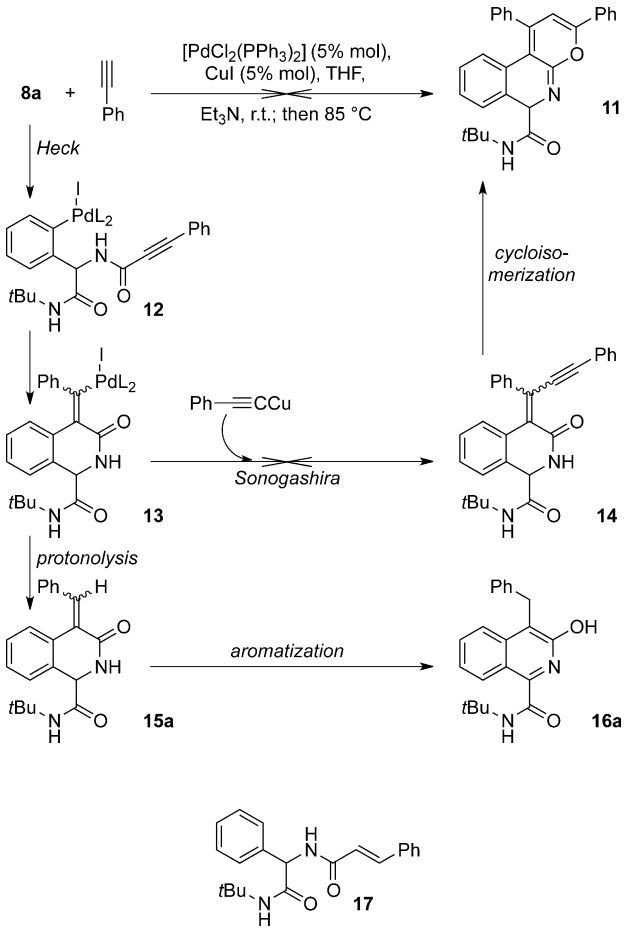
By contrast, removal of the substituted benzyl group was rather troublesome with either acidic (trifluoroacetic acid, TFA) or oxidative conditions (cerium(IV) ammonium nitrate, CAN). Compound **6** was too reactive and underwent extended decomposition, whereas **7** gave **8a** but under unpractical experimental conditions (high excess of CAN, long reaction time, etc.) with moderate and not reproducible yield. We demonstrated that the cause of this unexpected behavior is the presence of the triple bond,[21] even though we are unable to explain the reason.

Therefore, we turned our attention to the Ugi 4CR with ammonia (Scheme 2). As expected, the reaction was problematic and required considerable optimization. In particular, a non-nucleophilic solvent, such as trifluoroethanol,[22] was required, together with the presence of NH_4Cl. The reaction had to be done in a sealed tube at 50 °C in the presence of a slight excess of ammonia (not more than three equivalents), which is necessary to suppress the formation of the Passerini product **9** and to avoid also the formation of **10**, both of which were observed when unoptimized conditions were used. This latter by-product is often the result of the Brønsted acid catalyzed competitive pathway that may occur when stronger carboxylic acids (propynoic acids have $pK_a \approx 2.2$) are used.[23] On the other hand, if an excessive amount of ammonia was used instead, many other by-products were obtained, as during preformation of the imine.[22a,b]

Another crucial aspect is represented by the concentration of the ammonia solution: the commercially available 7 M solution in methanol was most efficient, but only if a freshly opened bottle was used were the yields satisfactory and reproducible. By taking all these precautions, the overall yield was good, with the consideration also that **8a** is obtained in just one step.

We then turned our attention to the domino cyclization, by using the conditions of our previously described protocol.[14] We were quite surprised not to identify expected product **11**, the result of a Heck carbocyclization, followed by a Sonogashira coupling and the final cycloisomerization of **14** (Scheme 3). The only new isolated compound was 3-hydroxyisoquinoline **16a** instead, although in very low yield. Seemingly, on this scaffold, the Sonogashira coupling did not take place and the vinyl palladium species **13** underwent a protonolysis to afford **15a**, whereas the released Pd^{II} species is reduced by an unidentified agent to regenerate the active catalyst. Finally, **15a** isomerizes to the final aromatic product **16a**.

Compound **16a** is, therefore, the result of an Ugi reaction followed by a reductive intramolecular Heck reaction. Some examples of Ugi MCRs followed by simple Heck cyclizations to afford six- or seven-membered heterocycles[24] and other isoquinoline[25] or indole scaffolds,[26] or, with more complex sequences, such as ring-closing metathesis/Heck,[27] Pd-mediated S_N2'/Heck,[28] or Staudinger/aza Wittig/Heck,[29] have been reported so far, but none of them involved a reductive Heck car-



Scheme 3. Attempted domino insertion/coupling/cycloisomerization reaction. L = ligand.

bocyclization as the secondary transformation. Nevertheless, the reductive Heck reaction is a known process, has been used to build the 3-benzazepine core[30] and tricyclic isoquinoline core structures,[31] and is an unwanted side reaction in the palladium-catalyzed alkyne insertion/Suzuki reaction of aryl iodides.[32]

3-Hydroxyisoquinolines are rather unexplored heterocycles, although they have shown interesting biological properties.[33] Moreover, preliminary analyses showed exciting fluorescence properties, which made this scaffold very attractive for us.

We, therefore, worked on the optimization of the reaction, focusing our attention on two main aspects: a) Which species is responsible for the reduction of Pd? b) By which mechanism does the isomerization/aromatization take place?

We first hypothesized Et_3N to be the reducing agent, in accordance with literature data.[34] Actually Et_3N plays a crucial role in the Heck reaction and cannot be substituted; other bases such as cesium carbonate[28] or diazabicycloundecene (DBU; Table 1, entries 8 and 9) were unsuitable. However, the reaction with this base turned out to be erratic anyway, with the yields of isolated **16a** even close to zero in some instances. Also, the choice of solvent was crucial, because acetonitrile afforded **16a**, albeit in low yield, whereas DMF did not allow the formation of **16a**, even in traces.

Table 1. Reductive Heck reaction.[a,b,c]

Entry	Base ([amount])	Reducing agents ([amount])	T [°C]	t [h]	Yield of **16a** [%]	Yield of **17** [%]
1[d]	Et_3N (3 equiv)	PPh_3 (5%)	120[e]	1	–	–
2	Et_3N	HCO_2H (2 equiv)	50	17	15	–
3	Et_3N	HCO_2H (2 equiv)	85	72	58	–
4	Et_3N	HCO_2H (3 equiv)	85	17	53	11
5	Et_3N	HCO_2H (1.2 equiv)	85	24	62	7
6	Et_3N	HCO_2H (1 equiv)	85	8	32[f]	8
7	Et_3N	HCO_2H (1 equiv)	90[e]	2	30	–
8	$CsCO_3$ (4 equiv)	HCO_2H (2 equiv)	85	63	–	–
9	DBU (3 equiv)	HCO_2H (1 equiv)	85	24	2	–
10	Et_3N, then DBU (3 equiv)	HCO_2H (1.2 equiv)	85	7,[g] then 16	64	8
11	Et_3N, then DBU (2 equiv)	HCO_2H (1 equiv)	90[e]	2,[g] then 1	62	1

[a] All reactions were performed in the presence of 5% $[PdCl_2(PPh_3)_2]$. [b] Unless stated otherwise, acetonitrile (0.2 M) was used as the solvent. [c] Unless stated otherwise, all reactions with Et_3N had a 0.2 M concentration of base. [d] The solvent was DMF. [e] Under microwave heating. [f] In addition, 50% of **15a**, as a diastereomeric mixture, was isolated. [g] Only Et_3N was added at the beginning. After heating for the first reported time, DBU was added and the heating was continued as indicated.

Therefore, we decided to investigate the effect of an added reducing agent. Triphenylphosphine was not effective at all (Table 1, entry 1), whereas formic acid, which has been used either as the free acid or as the sodium salt in the reductive Heck cyclization,[30] gave encouraging results with a noticeable increase of both the yield and the reproducibility.[35] The yields are strictly dependent on the temperature, with 85 °C being the best conditions (Table 1, entries 3 and 5).

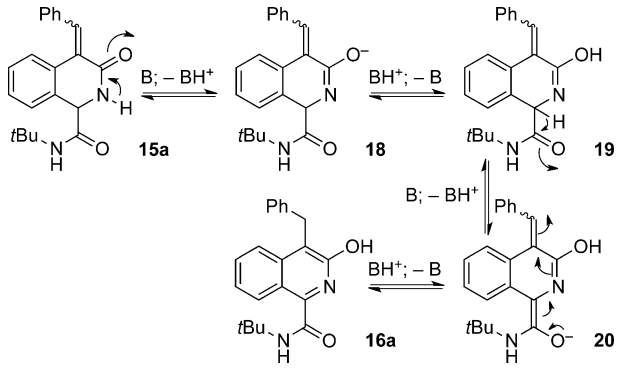
Also, the amount of formic acid is crucial. With three equivalents, the reaction was faster but compound **17**, the result of deiodination and partial reduction of the triple bond of **8a**, was obtained as a by-product (Table 1, entry 4). Between 1 and 1.2 equivalents of formic acid are enough to afford a good yield of **16a** with minimal formation of **17** (Table 1, entry 5).

Another very important feature is the reaction time. If the reaction was stopped after 8 h (Table 1, entry 6), a considerably lower amount of **16a** was obtained, whereas the yield of **17** was not significantly affected. The prevailing product in this case was **15a** (50%, as a 2:1 *Z/E* diastereomeric mixture, with the configuration of the double bonds assigned through an nOe experiment as described in the Supporting Information). This suggests that the final aromatization is the rate-determining step of the whole sequence summarized in Scheme 3. To achieve a faster rate, we tried different conditions (different bases, acids, or buffers) and found a beneficial effect when DBU was used as an ancillary base to be added after completion of the cyclization (Table 1, entry 10). In contrast, the addi-

tion of acids or a buffer system did not affect the reaction outcome.

Finally, to shorten the reaction time, we employed microwave heating and obtained **16a** with a comparable yield, by using also less formic acid and DBU (Table 1, entry 11).

Scheme 4 describes a possible mechanism for the base-promoted aromatization: the base is not only able to accept



Scheme 4. Possible mechanism for the base-promoted aromatization. B = base.

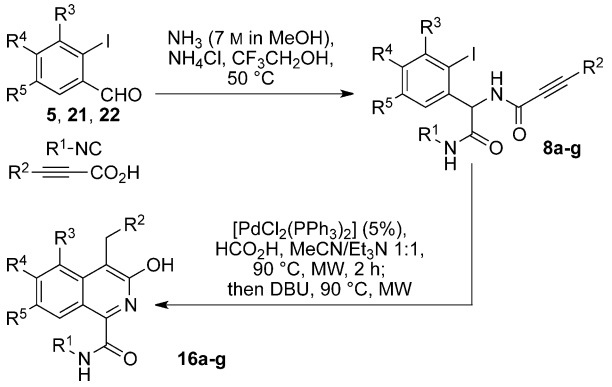
a proton from either **15a** or **19** but acts twice as a proton shuttle on intermediates **18** and **20**. However, an aromatization occurring through a hydride transfer from the C1 atom to the exocyclic benzylic carbon atom cannot be completely ruled out.[36]

With the optimized protocol (Table 1, entry 11) in hand, we started to test the scope of the sequence. To this purpose, we synthesized *o*-iodobenzaldehydes **21**[37] and **22**,[38] by improving the literature procedures, and used them in the Ugi reaction with ammonia as previously described. As shown in Table 2, the Ugi reaction occurred in satisfactory yields in most of the reported examples to afford **8a**–**g**.

By contrast, the following reductive Heck reaction was more problematic. With the exception of compounds **16a** and **16d** (Table 2, entries 1 and 4), all of the other 3-hydroxyisoquinolines were obtained only in moderate or, in some cases, poor yields. We demonstrated that the low yield for **16b** (Table 2, entry 2) was a consequence of incomplete aromatization because, after addition of DBU and heating for 2 h at 90 °C, 34% of **15b** was still present. Similar results were obtained in the synthesis of **16c** and **16f** (Table 2, entries 3 and 6, respectively), in which cases heating up to 110 °C was necessary to complete the aromatization. This behavior seems to be peculiar for compounds in which R^2 is an alkyl group. In addition, during the preparation of isoquinolines with R^2 = Me or *n*Pr, we also isolated the oxidized analogues of **16** with an unsaturation in the side chain, conjugated with the heterocyclic scaffold. Finally, during the preparation of **16f** and **16g**, we also found a series of fluorescent by-products that have not been identified.

To improve the step economy, we explored the possibility to carry out the whole sequence to **16** as a domino reaction or, at least, as a one-pot procedure.

Table 2. Ugi reaction with ammonia followed by the reductive Heck reaction.



Entry	R^1	R^2	R^3	R^4	R^5	**8** (yield [%][a])	**16** (yield [%][a])
1[b]	*t*Bu	Ph	H	H	H	**8a** (70)	**16a** (64)
2[b]	2,6-dimethylphenyl	*n*Pr	H	H	H	**8b** (51)	**16b** (17)
3[b]	cyclohexyl	*n*Pr	H	H	H	**8c** (51)	**16c** (40)
4[c]	*t*Bu	Ph	H	OCH_2CH_2O		**8d** (50)	**16d** (66)
5[c]	*t*Bu	*n*Pr	H	OCH_2CH_2O		**8e** (46)	**16e** (44)
6[c]	Me	Me	H	OCH_2CH_2O		**8f** (39)	**16f** (23)
7[d]	benzyl	Ph	OMe	OMe	OMe	**8g** (49)	**16g** (35)

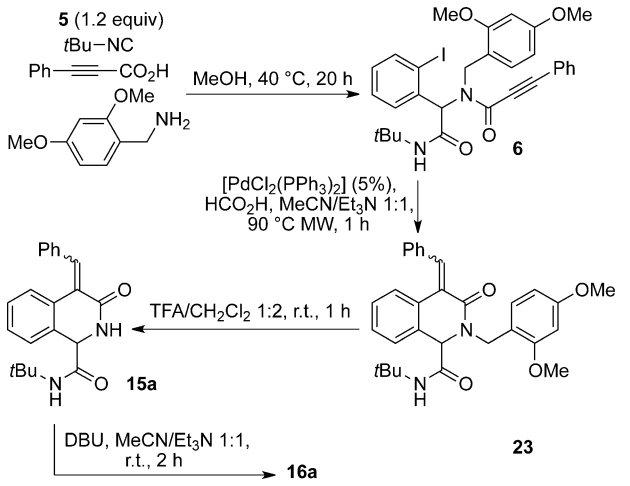
[a] Yield after isolation. [b] Aldehyde **5**. [c] Aldehyde **21**. [d] Aldehyde **22**.

The first attempts, by using the optimized conditions of Scheme 2 and Table 1, were disappointing, with **16a** being formed just in traces. We attributed this to the contemporaneous presence of an excess of ammonia, which was mandatory to avoid the formation of by-products, and the isocyanide itself, because they may both act as ligands for palladium and interfere with the catalytic cycle. Moreover, even when the excess of ammonia was removed after the Ugi reaction, the following cyclization was unsatisfactory.

For these reasons, we returned back to our initial idea and substituted ammonia with 2,4-dimethoxybenzylamine in the Ugi reaction. However, this time, our plan was to remove the 2,4-dimethoxybenzyl (DMB) group only after the reductive Heck reaction to allow for the final aromatization. Once again, we used the synthesis of **16a** as a model.

We found the stoichiometric ratio of the components of the Ugi reaction to be crucial, with the best conditions requiring a slight excess (1.2 equivalents) of aldehyde **5** with respect to the other reagents (Scheme 5). To test the overall sequence, we first transformed **6** into **23** (a 10:1 mixture of diastereomers) and, after intermediate isolation, converted **23** into **16a** by stepwise treatment with TFA, which causes deprotection, and DBU, which promotes isomerization/aromatization. We were pleased to isolate both **23** and **16a** in excellent yield (92 and 84%, respectively) and observed again that the DMB group can be efficiently removed in the absence of the triple bond.

After demonstrating the feasibility of this two-step protocol and knowing that a domino process is not consistent with the different conditions required for the planned reactions, we focused our attention on the development of a one-pot proce-



Scheme 5. One-pot synthesis of compound **16a**.

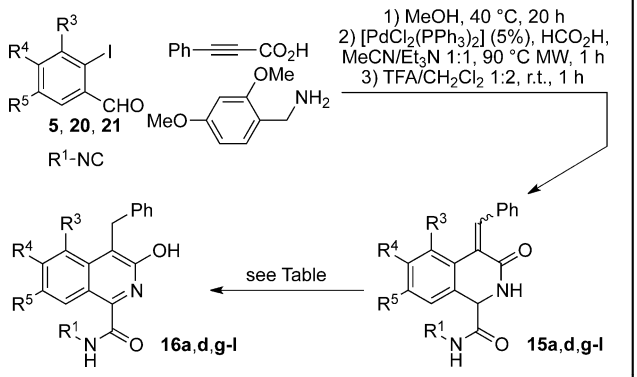
dure. After completion of the Ugi reaction, the Pd catalyst, formic acid, and the MeCN/Et_3N (1:1) solution were directly added and the mixture was heated in a microwave apparatus to afford **23**. After concentration of the mixture, the DMB group was removed by means of TFA to give **15a**, then DBU in MeCN was added to promote the aromatization.

Apart from two very fast work-ups, the four-step sequence was performed without isolating or purifying any intermediate. The overall 77% yield (the same as that of the previously described two-step procedure) is therefore excellent if we consider the high degree of convergence of the protocol. From the point of view of atom economy, this route is clearly less convenient; this drawback is compensated for by step economy, by the operational simplicity, and by the higher overall yields.

Upon extending this protocol, under the same optimized conditions, to the synthesis of other compounds **16**, we found again that the yields depended heavily on the nature of the starting components. After a careful investigation, we realized that the first three steps (Ugi/Heck/DMB removal) worked well in all cases. By contrast, the crucial step is the final aromatization, which requires a fine tuning of conditions for each substrate.

For enabling this tailored optimization, we preferred to isolate and purify intermediates **15** to search for the best conditions for their conversion into **16**, by changing the base, temperature, and reaction times and possibly by adding a Lewis acid. The results are summarized in Table 3 and show that, in all cases, we were able to set up a satisfactory aromatization step. The yields, based on the HPLC analyses of the crude product, ranged from good to excellent. In contrast, the isolated yields after chromatography were usually less satisfactory. A possible explanation may be the poor solubility of these compounds, which crystallized on the silica and prevented complete elution from the stationary phase.

Table 3. Two-step synthesis of compounds **16** (R^2: Ph).



Entry[a]	R^1	R^3	R^4	R^5	**15** (yield [%])[b]	**16** (yield [%])
1	*t*Bu	H	H	H	**15a** (92)	**16a** (84[b])
2	2,6-dimethyl-phenyl	H	H	H	**15h** (56)	**16h** (92,[c] 54[b])
3	cyclohexyl	H	H	H	**15i** (90)	**16i** (60[b])
4	benzyl	H	H	H	**15j** (97)	**16j** (95,[c] 59[b])
5	*n*Bu	H	H	H	**15k** (79)	**16k** (91,[c] 52[b])
6	*t*Bu	H	OCH_2CH_2O		**15d** (88)	**16d** (66[b])
7	*t*Bu	OMe	OMe	OMe	**15l** (45)	**16l** (79,[c] 64[b])
8	benzyl	OMe	OMe	OMe	**15g** (63)	**16g** (88[c])

[a] Conditions for aromatization: Entry 1: DBU, RT, 2 h; entry 2: DBU/ZnI_2, 100 °C, MW, 30 min; entry 3: *t*BuOK, RT, 10 min; entry 4: *t*BuOK, RT, 30 min; entries 5 and 6: *t*BuOK, RT, 40 min; entry 7: DBU, 100 °C, MW, 2 h; entry 8: DBU/ZnI_2, 100 °C, MW, 45 min. [b] Yield after isolation. [c] HPLC yield of the crude residue.

Photophysical properties

Even upon eyesight, the 3-hydroxyisoquinolines **16** exhibit a remarkable deep-blue fluorescence under the handheld UV lamp (excitation at around 350 nm; Figure 1) and the photophysical properties were, therefore, studied by UV/Vis and fluorescence spectroscopy to determine the absorption and emission maxima, molar extinction coefficients (ε), Stokes shifts ($\Delta\tilde{\nu}$), and relative fluorescence quantum yields (Φ_f; Table 4).

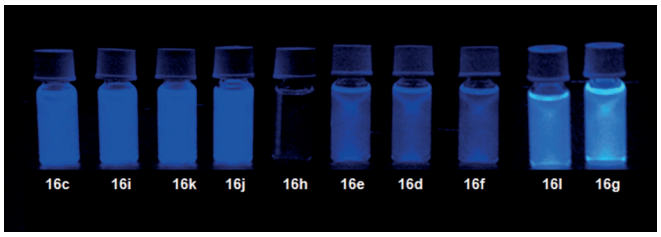


Figure 1. Dichloromethane solutions ($c = 1\times10^{-4}$ mol L^{-1}) of 3-hydroxyisoquinoline derivatives **16c**, **16i**, **16k**, **16j**, **16h**, **16e**, **16d**, **16f**, **16l**, and **16g** under a handheld UV lamp ($\lambda_{excitation} \approx 350$ nm).

In comparison to that of the unsubstituted 3-hydroxyisoquinoline ($\lambda_{max,abs} = 340$ nm),[39] the longest wavelength maxima of all of the derivatives **16** are considerably redshifted and appear between 358 and 383 nm. Also, the emission maxima of derivatives **16** are bathochromically shifted, relative to that of the parent system ($\lambda_{max,em} = 370$ nm) and are found in a range from 394.5 to 446.5 nm.

By considering the substitution pattern on the benzo moiety of the 3-hydroxyisoquinoline core, three classes of moiety can

Table 4. Selected photophysical properties of 3-hydroxyisoquinolines **16**.

Compound	$\lambda_{max,abs}$ [nm][a] (ε [L mol^{-1} cm^{-1}])	$\lambda_{max,em}$ [nm][b] (Φ_f [a.u.])	Stokes shift ($\Delta\tilde{\nu}$) [cm^{-1}][c]
16a	358.5 (9000) 282.5 (3400)	395.5 (0.87)[d]	2600
16c	358.5 (8600) 286.5 (3500)	396.0 (0.79)[d]	2600
16d	359.0 (9400) 314.0 (5600) 249.5 (47300)	396.0 (0.20)[d]	2600
16e	358.5 (8200) 308.0 (4600) 249.5 (44700)	394.5 (0.25)[d]	2600
16f	358.5 (7500) 317.0 (4200) 249.0 (42300)	394.5 (0.38)[d]	2600
16g	382.5 (7600) 260.5 (34900)	446.5 (0.65)[e]	3800
16h	361.5 (10100) 287.0 (3800)	401.0 (<0.01)[d]	2700
16i	359.0 (9600) 282.0 (3700)	399.5 (0.79)[d]	2800
16j	359.5 (8700) 281.0 (3300)	397.0 (0.90)[d]	2600
16k	358.5 (8900) 282.0 (3100)	395.5 (0.84)[d]	2600
16l	380.0 (6800) 258.0 (33500)	443.5 (0.62)[e]	3800

[a] Recorded in CH_2Cl_2 at RT. [b] Recorded in CH_2Cl_2 at RT with $\lambda_{excitation}=350.0$ nm. [c] $\Delta\tilde{\nu}=1/\lambda_{max,abs}-1/\lambda_{max,em}$. [d] Quantum yields were determined with anthracene as a standard in cyclohexane ($\Phi_f=0.36$).[40,41] [e] Quantum yields were determined with 9,10-diphenylanthracene as a standard in cyclohexane ($\Phi_f=1.00$).[40,42]

be distinguished: unsubstituted (**16a**, **16c**, **16i**, **16k**, **16j**, and **16h**), dioxolannelated (**16e**, **16d**, and **16f**), and 5,6,7-trimethoxy-substituted (**16l** and **16g**) derivatives. With the exception of the 5,6,7-trimethoxy-substituted derivatives **16l** and **16g**, the Stokes shifts ($\Delta\tilde{\nu}$; that is, $1/\lambda_{max,abs}-1/\lambda_{max,em}$) lie at around 2600–2800 cm^{-1} for all of the other 3-hydroxyisoquinolines **16**, whereas derivatives **16l** and **16g** display considerably larger Stokes shifts of 3800 cm^{-1}. In comparison to the parent system, 3-hydroxyisoquinoline, derivatives **16** are unlikely to undergo hydrogen-bond-assisted dimerizations. Moreover, the 1-amide functionality offers an intramolecular hydrogen-bond donor for the isoquinoline nitrogen atom to stabilize the monomer structure. Obviously, this intramolecular hydrogen bonding is hampered by the steric demand of the 2,6-dimethylphenyl amide substituent in compound **16h**, which causes a radiationless deactivation of the excited state (see below).

The spectra of the series of unsubstituted derivatives, that is, **16a**, **16c**, **16h**, **16i**, **16j**, and **16k**, display two distinct absorption maxima. The first shorter wavelength band with weaker intensity (ε values ranging from 3100 to 3800 L mol^{-1} cm^{-1}) appears between 281.0 and 287.0 nm and the intense longest wavelength maximum is found at around 360.0 nm (ε values ranging 8600 to 10100 L mol^{-1} cm^{-1}). With exception of **16h**, all of the compounds of this series are strongly luminescent and the quantum yields determined with anthracene as a relative standard ($\Phi_f=0.36$) fall in the range of 0.79 to 0.90. Unless the amide does not bear a sterically demanding substituent (**16h**), neither the amide nor the 4-alkyl substitution influences the electronic structure of the ground state (absorption maxima) or the excited state (fluorescence maxima, quantum yield).

The second series is represented by 3-hydroxy-1,3-dioxol[4,5-*g*]isoquinoline derivatives (**16e**, **16d**, and **16f**), of which all three derivatives are fluorescent. In the absorption spectra, three distinct maxima can be found. The highest and lowest energy transitions are located in the very narrow ranges of 249.0 to 249.5 nm and 358.5 to 359.0 nm, with molar extinction coefficients (ε) of 42300–44700 and 7500–9400 L mol^{-1} cm^{-1}, respectively. However, it is noticeable that the intermediate absorption maxima appearing between 308.0 and 317.0 nm, with molar extinction coefficients between 4200 and 5600 L mol^{-1} cm^{-1}, are clearly affected by the substitution pattern. This is surprising because the structural variation occurs at a position that is not in conjugation with the isoquinoline chromophore. Hence, it can be concluded that this transition is sensitive to minute inductive substituent effects. All of the emission maxima appear at around 395 nm, which indicates that the vibrationally relaxed excited S_1 state is unaffected by the substitution pattern. Also, the quantum yields determined with anthracene as a relative standard ($\Phi_f=0.36$) fall within the range of 0.20 to 0.40, that is, with lower fluorescence efficiencies relative to those of the unsubstituted series (**16a**, **16c**, **16i**, **16k**, **16j**, and **16h**).

The third series consists of the trimethoxy-substituted derivatives **16l** and **16g**, in which methoxy groups as +M and −I substituents exert their effects on the electronic properties. The donor substitution on the benzo core of the isoquinoline shifts both the absorption and emission maxima bathochromically. Two distinct absorption maxima are found. The higher energy transitions appear at around 260.0 nm with molar extinction coefficients (ε) of 33500 and 34900 L mol^{-1} cm^{-1}, respectively, and the longest wavelength maxima are found at around 381.0 nm with molar extinction coefficients of 6800 and 7600 L mol^{-1} cm^{-1}, respectively. The emission maxima appear at 443.5 and 446.5 nm, respectively. In comparison to the second series (see above), the fluorescence quantum yields (Φ_f) are significantly higher (0.62 and 0.65) and the luminescence appears brighter to the eye (Figure 1).

For scrutinizing the solvent effects on the photophysical properties of the 3-hydroxyisoquinolines, derivative **16k** was considered to be an appropriate model and the absorption and emission maxima, molar extinction coefficients (ε), Stokes shift ($\Delta\tilde{\nu}$), and fluorescence quantum yield (Φ_f) were determined in dichloromethane, acetonitrile, and DMSO (Table 5).

The absorption properties are only slightly affected upon variation of the solvent polarity. With increasing polarity, a very modest bathochromic shift of the longest wavelength maximum can be observed (358.5 nm for CH_2Cl_2 and acetonitrile and 361.0 nm for DMSO). It should be noted that, in DMSO, the second maximum at 271.5 nm is shifted hypsochromically (relative to 281.0 nm for acetonitrile) and hyperchromically, that is, the molar extinction coefficient almost doubles in magnitude, relative to the corresponding bands in the other sol-

Table 5. Solvent effects on selected photophysical properties of compound **16k**.

Entry	Solvent	$\lambda_{max,abs}$ [nm][a] (ε [L mol^{-1} cm^{-1}])	$\lambda_{max,em}$ [nm][b] (Φ_f [a.u.])	Stokes shift ($\Delta\tilde{\nu}$) [cm^{-1}][c]
1	dichloromethane	358.5 (8900) 282.0 (3100)	395.5 (0.84)[d]	2600
2	acetonitrile	358.5 (8600) 281.0 (3800) 230.5 (39800)	395.5 (0.60)[d]	2800
3	DMSO	361.0 (7500) 271.5 (6500)	410.0 (0.22)[e]	3300

[a] Recorded in CH_2Cl_2 at RT. [b] Recorded in CH_2Cl_2 at RT with $\lambda_{excitation}$ = 350.0 nm. [c] $\Delta\tilde{\nu} = 1/\lambda_{max,abs} - 1/\lambda_{max,em}$. [d] Quantum yields were determined with anthracene as a standard in cyclohexane (Φ_f = 0.36).[40,41] [e] Quantum yields were determined with 9,10-diphenylanthracene as a standard in cyclohexane (Φ_f = 1.00).[40,42]

vents. However, in the emission spectrum, a positive solvatochromism is clearly apparent (Figure 2). The modest bathochromic shift by 900 cm^{-1} suggests that the nature of the excited state should be slightly more polar and it thereby experiences stabilization by DMSO.

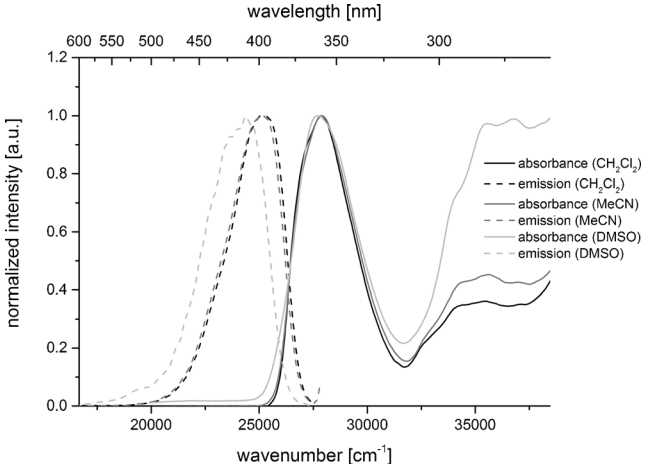


Figure 2. Normalized absorption and emission spectra of **16k** in dichloromethane, acetonitrile, and DMSO (recorded at T = 293 K, $\lambda_{excitation}$ = 350.0 nm).

3-Hydroxyisoquinoline derivatives **16** contain basic pyridyl-type nitrogen atoms that can be protonated. Qualitative tests indicated that the protonation of 3-hydroxyisoquinoline derivatives opens a channel for nonradiative deactivation of the excited state. This behavior was more thoroughly investigated in a titration experiment of compound **16j** with trifluoroacetic acid. The titration was easily quantified with absorption spectroscopy. In the absorption spectra, the appearance of a new redshifted absorption maximum at 390 nm was observed upon titration; this maximum can be attributed to the protochromicity of the underlying isoquinoline chromophore. The pK_a value of **16j** was determined to 2.24 in dichloromethane from the measured data, with the assumption of complete dissociation of TFA as a strong acid ($c(H^+) = c(TFA)$). Most likely, the first protonation occurs at the basic isoquinoline nitrogen atom. This also matches with the pK_a value of protonated 3-hydroxyisoquinoline (2.18).[43] The occurrence of an isosbestic point (Figure 3) upon titration indicates an equilibrium between the protonated and nonprotonated species without the formation of further intermediates (Scheme 6).

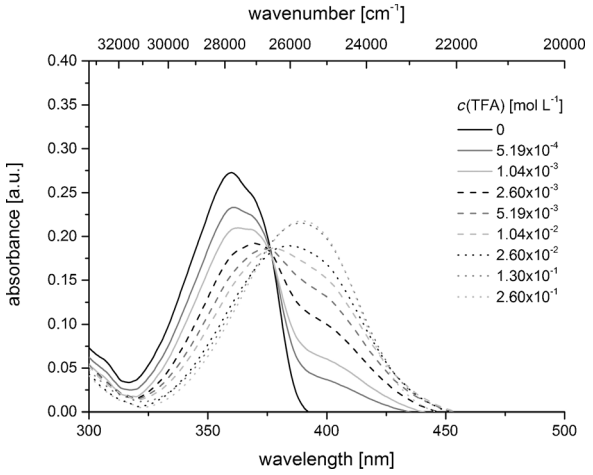
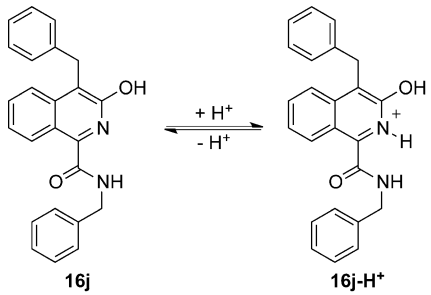


Figure 3. Absorption spectra for the titration of compound **16j** ($c = 3.3 \times 10^{-5}$ mol L^{-1}) with TFA in dichloromethane (recorded at T = 293 K).



Scheme 6. Protonation equilibrium of compounds **16j** and **16j**–H$^+$.

Computations on the DFT and time-dependent (TD) DFT level of the theory, with the B3LYP functional and the 6-31G* basis set by using the SM8 solvent model for dichloromethane, were carried out on the structures of free base **16j** and its conjugated acid **16j**–H$^+$.[44] The calculations qualitatively reproduce the trend of the absorption maxima. Upon protonation, the longest wavelength maximum of **16j** shifts from 339 nm (λ_{exp} = 360 nm) to 373 nm (λ_{exp} = 390 nm) for **16j**–H$^+$. The TD-DFT computations indicate that these longest wavelength bands arise from π–π^* transitions, which are best represented by highest occupied molecular orbital (HOMO)–lowest unoccupied molecular orbital (LUMO) transitions in both cases (Figure 4).

Furthermore, protonation of the isoquinoline nitrogen atom can be also observed in the emission behavior (Figure 5). The emission of the chromophore is quenched with an increased amount of TFA.

Based on the emission data, a Stern–Volmer plot was produced[45] (Figure 6), in which F_0 is the emission intensity of

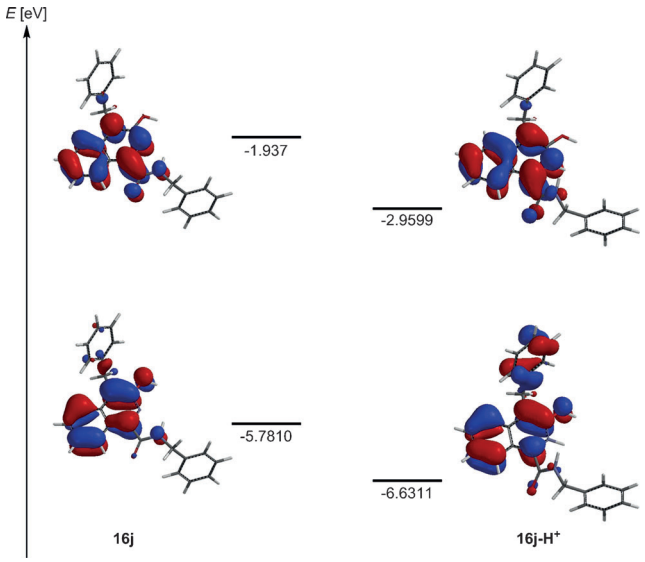


Figure 4. Frontier molecular orbitals of **16j** and **16j**–H^+ (bottom: HOMOs; top: LUMOs) contributing to the longest wavelength π–π^* transitions (computed frontier molecular orbital energies are given in eV).

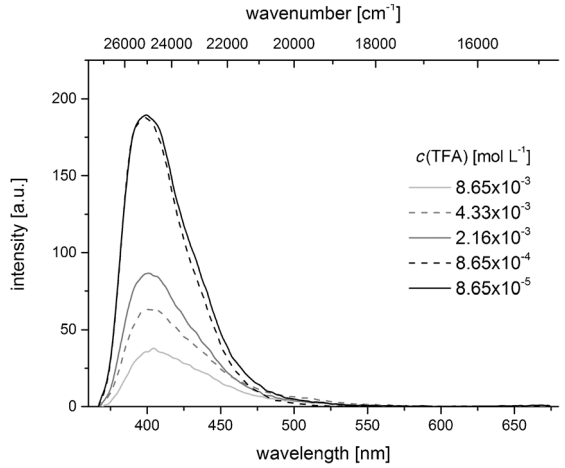


Figure 5. Emission spectra for the titration of compound **16j** ($c = 1.8\times10^{-8}$ mol L^{-1}) with TFA in dichloromethane (recorded at $T = 293$ K; $\lambda_{excitation} = 350.0$ nm).

compound **16j** and F is the emission intensity upon addition of TFA as a quencher. The Stern–Volmer constant (K_{SV}) for compound **16j** was determined to 432.96 L mol^{-1}. The linear plot supports a steady-state quenching with the Stern–Volmer constant (K_{SV}) representing the pK_a value (2.67) of compound **16j** in the electronic ground state. This value matches reasonably well with the pK_a value determined from absorption spectroscopy (2.24).

Conclusions

In summary, a novel approach to the highly functionalized 3-hydroxyisoquinoline scaffold through a convergent strategy involving an MCR followed by a Pd-based cyclization of the Ugi

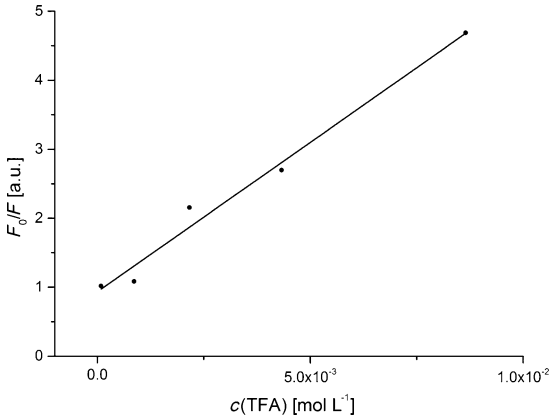


Figure 6. Stern–Volmer plot of compound **16j** (c_0(**16j**) $= 1\times10^{-6}$ M in dichloromethane, $T = 293$ K; $F_0/F = 0.933 + 432.96$ [H^+]; ($r^2 = 0.979$)).

4CR adduct has been discovered and methodologically explored.

The multiply substituted 3-hydroxyisoquinoline derivatives **16** display, in comparison with the parent system, remarkably high fluorescence quantum yields, which renders them excellent blue-light singlet emitters. Furthermore, neither the 4-alkyl nor the 1-amide substituent causes major changes in the emission properties, which opens up additional points of diversity for further functionalizations through the alkynyl and isonitrile substrates. Much more pronounced effects on the electronics of the ground and excited states can be exerted by the substitution pattern of the benzo core of the isoquinoline. The fluorescence efficiency is controlled by protonation, as unambiguously supported by Stern–Volmer quenching, which indicates that the protonated species is responsible for a static fluorescence quenching. As already shown by the trimethoxy-substituted derivatives, the redshift of both the absorption and emission maxima still maintains the intense blue luminescence and makes this class of luminophores particularly interesting for photonic applications. Studies directed toward more complex 3-hydroxyisoquinoline luminophores and their photophysical and electronic characterization are currently underway.

Experimental Section

General conditions

NMR spectra were taken at room temperature in $CDCl_3$ or [D_6]DMSO at 300 MHz (^{1}H) and 75 MHz (^{13}C) by using internal standards: in $CDCl_3$, tetramethylsilane (TMS) for ^{1}H NMR spectroscopy and the central peak of $CDCl_3$ (at $\delta = 77.02$ ppm) for ^{13}C NMR spectroscopy; in [D_6]DMSO, the central peak of DMSO (at $\delta =$ 2.506 ppm) for ^{1}H NMR spectroscopy and the central peak of DMSO (at $\delta = 39.429$ ppm) for ^{13}C NMR spectroscopy. Chemical shifts (δ) are reported in ppm and coupling constants (J) are reported in Hertz. Peak assignments were also made with the aid of gCOSY and gHSQC experiments. In an ABX system, proton A is considered upfield and proton B is considered downfield. IR spectra were recorded as solid, oil, or foamy samples, with the attenuated total reflectance (ATR) technique, or as $CHCl_3$ solutions. TLC analyses were carried out on silica gel plates, viewed with UV light

($\lambda = 254$ or 360 nm), and developed with Hanessian stain (dipping into a solution of $(NH_4)_4MoO_4{\cdot}4H_2O$ (21 g) and $Ce(SO_4)_2{\cdot}4H_2O$ (1 g) in H_2SO_4 (31 mL) and H_2O (469 mL) and warming). R_f values were measured after an elution of 7–9 cm. Absorption spectra were recorded in CH_2Cl_2 or cyclohexane UVASOL at 293 K on a Perkin–Elmer UV/Vis/NIR Lambda 19 spectrometer. Emission spectra were recorded in CH_2Cl_2 or cyclohexane UVASOL at 293 K on a Perkin–Elmer LS55 spectrometer. The molar extinction coefficients and quantum yields were measured in a multipoint setup. The quantum yields were measured relative to the noted standard. HRMS was performed by employing an ESI+ ionization method. GC-MS analyses were performed on an HP-1 column (12 m long, 0.2 mm wide), with electron impact at 70 eV and a mass temperature of about 170 °C. Only $m/z > 33$ were detected. All analyses were performed (unless otherwise stated) with a constant He flow of 1.0 mL min^{-1} with an initial temperature of 100 °C, initial time of 2 min, rate of 20 or 30 °C min^{-1}, final temperature of 290 °C, injection temperature of 250 °C, and detection temperature of 280 °C. HPLC analyses (determination of the purity of compounds **16**, Table 3) were performed on a Gemini 3 μm C6-Phenyl 150×3 mm column, at 26 °C with a flow of 0.3 mL min^{-1} and H_2O/MeOH (from 90:10 to 0:100 in 15 min) as the eluent. Melting points are uncorrected. Column chromatography was done with the "flash" methodology by using 220–400 mesh silica. Petroleum ether (40–60 °C) is abbreviated as PE. All reactions employing dry solvents were carried out under a nitrogen or argon atmosphere.

Representative procedure for the one-step synthesis of compounds 16

4-Benzyl-*N*-(*tert*-butyl)-3-hydroxyisoquinoline-1-carboxamide (16 a): A stirred solution of **5** (100 mg, 0.43 mmol) in dry MeOH (1 mL) was treated with 2,4-dimethoxybenzylamine (54 μL, 0.36 mmol), phenylpropiolic acid (53 mg, 0.36 mmol), and *tert*-butylisocyanide (41 μL, 0.36 mmol). The mixture was stirred at 40 °C until consumption of the amine was complete (22 h). The mixture was then put under an argon atmosphere, treated with MeCN/Et_3N (1:1, 3 mL), $[PdCl_2(PPh_3)_2]$ (12 mg), and formic acid (13 μL), warmed at 90 °C with microwave heating for 1 h, and concentrated. The residue was diluted with CH_2Cl_2 (2 mL) and treated with TFA (1 mL) at room temperature for 1 h. After evaporation of the solvents, the crude residue was diluted with CH_2Cl_2, washed with saturated aqueous $NaHCO_3$, dried (Na_2SO_4), and concentrated. The crude residue was directly dissolved in dry MeCN (3 mL), then DBU (107 μL, 0.72 mmol) was added. The reaction mixture was stirred at room temperature for 2 h, then diluted with CH_2Cl_2, washed with saturated aqueous NH_4Cl, dried (Na_2SO_4), and concentrated. The residue was eluted from a column of silica gel with CH_2Cl_2/AcOEt (from 100:2 to 100:4) to give **16 a** (93 mg, 77%) as a yellow solid. Comparable yields have been obtained by purifying **23** by chromatography with PE/AcOEt (from 5:2 to 2:1) as the eluent (procedure (*b)* in the Supporting Information) and submitting it to the following deprotection and aromatization. The complete spectroscopic characterization is reported in the Supporting Information.

Acknowledgements

The authors acknowledge Loris Allegra and Elisa Martino for experimental support, PRIN 2009 (Synthetic Methodologies for Generation of Biologically Relevant Molecular Diversity), University of Genova, and the Fonds der Chemischen Industrie for financial support, and the International Exchange Erasmus Student Network for a grant to G.V.

Keywords: fluorescence · Heck reaction · isoquinolines · multicomponent reactions · photochromism

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Received: July 2, 2014
Published online on ■■ ■■, 0000

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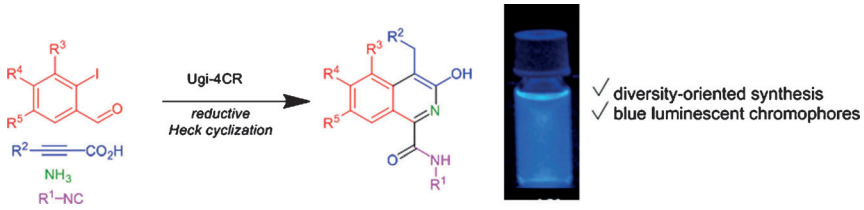

Blue is the color: A library of highly substituted 3-hydroxyisoquinolines was prepared by coupling the isocyanide-based Ugi four-component reaction (Ugi-4CR) with an intramolecular reductive Heck reaction (see scheme). The prepared compounds are intensively blue emitting fluorophores, as supported by high fluorescence quantum yields.

Fluorescent Compounds

L. Moni, M. Denißen, G. Valentini, T. J. J. Müller, R. Riva**

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Diversity-Oriented Synthesis of Intensively Blue Emissive 3-Hydroxyisoquinolines by Sequential Ugi Four-Component Reaction/ Reductive Heck Cyclization