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New fluorescent isoquinoline derivatives

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ABSTRACT

Various structural modifications of 3-amino and 3-hydroxyisoquinolines have been carried out to provide new fluorescent derivatives. The transformations involved nucleophilic substitution of a bromine atom or a triflate moiety at positions 1 and 3, respectively, as well as the condensation reaction of a 3-amino group with triethyl orthoformate and subsequent transformation with amines to give amidines. The new compounds have been studied by fluorescence spectroscopy.

During the course of our recent research in the area of substituted isoquinoline-3-amine derivatives[1,2] we observed visible fluorescence in some cases. These findings prompted us to explore fluorescence of this kind in isoquinoline derivatives in detail by carrying out structural changes and studying the fluorescence properties of the resulting compounds. As the preliminary visual observations occurred mostly with amino compounds, we decided to synthesize various isoquinoline derivatives containing free and substituted amino groups at different positions. For this purpose, transformations of isoquinoline-3-triflate as well as 1-bromoisoquinoline-3-amine and its 4-alkyl derivatives—both compound types have been described previously in the literature[2,3]—seemed of interest.

For comparison of the behavior of primary and tertiary amines, 3-morpholinoisoquinoline (**2**) was synthesized first. Although **2** has already been described,[4] we found that this compound could be prepared more conveniently from **1** with morpholine. Thus, heating triflate[3] **1** in morpholine under reflux conditions (at 130 °C) afforded the desired compound in acceptable yield (75%)[5] (Scheme 1).

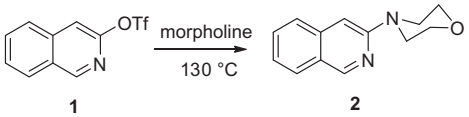
A further set of differently substituted isoquinoline-amines and the applied reaction pathways are shown in Scheme 2.

(a) The bromine atom at position 1 of isoquinolines **3a–c** was substituted by hydrogen (catalytic hydrogenation over Pd/C according to literature procedures[5]) to give derivatives **3d–f**. Furthermore, the same bromine atom was also substituted by a morpholine moiety to yield 1-morpholino compounds **6a–c**.[6]

(b) Primary amines (**3a–f** and **6a–c**) were, then transformed into amidines **5** and **8**. Thus, the primary amines were treated with triethyl orthoformate to give the water-sensitive formimidates **4** and **7**.[7] These compounds when reacted with morpholine in boiling toluene gave rise to the new amidines **5a–f** and **8a–c**.[8]

Of the possible 28 structures involved in Schemes 1 and 2, nine derivatives (**2**, **3d**, **5b**, **5c**, **5f**, **6a**, **6b**, **6c** and **8b**) were selected for detailed photophysical studies. The structures of these selected compounds are separately shown in Figure 1.

Table 1 summarizes the photophysical properties of the selected compounds. The location of the maximum of the first absorption [λ_{max}(abs)] and the fluorescence [λ_{max}(fl)] bands shifts moderately to higher wavelength upon modification of the molecular structure. The largest displacement was observed for compounds **6c** and **6b**. The fluorescence quantum yield (Φ_f) and fluorescence lifetime (τ_f) decreased substantially upon introduction of the bromine atom at position 1 mainly due to acceleration of the triplet formation by the presence of the heavy atom.[9] Comparison of the properties of **5c** and **5f** confirmed that the bromine atom brings about considerable fluorescence quenching. The rate constant of fluorescence emission (k_f) and radiationless deactivation (k_{nr}) from the singlet excited state were calculated using $k_f = \Phi_f/\tau_f$ and $k_{nr} = (1 - \Phi_f)/\tau_f$ relationships, respectively. As shown in Table 1, k_f is insensitive to variation of the molecular structure. Changing the 3-amino substituent to a



1 2

Scheme 1. Synthesis of 3-morpholinoisoquinoline (**2**).

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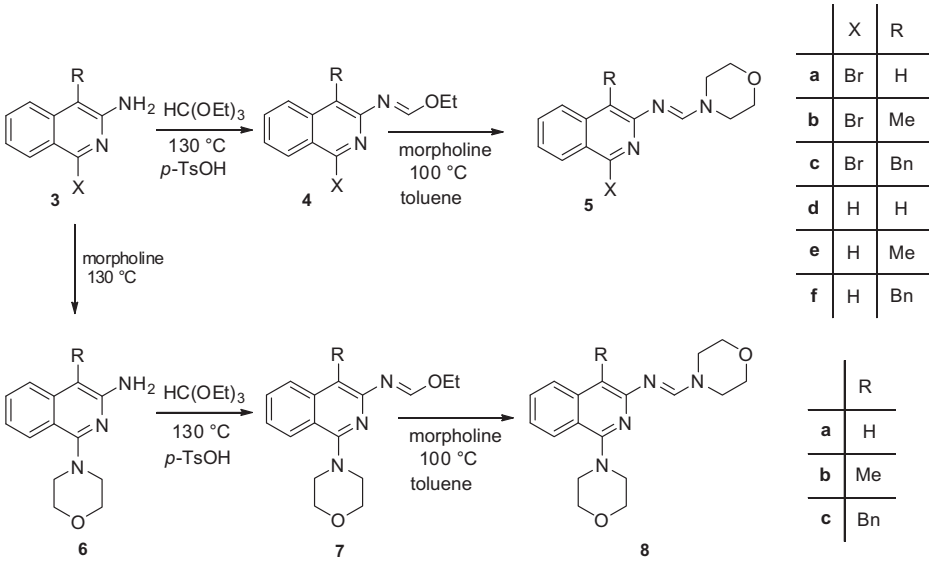

	X	R
a	Br	H
b	Br	Me
c	Br	Bn
d	H	H
e	H	Me
f	H	Bn

	R
a	H
b	Me
c	Bn

Scheme 2. Various transformations of 4-substituted 1-bromoisoquinoline-3-amines (**3a**–**c**).

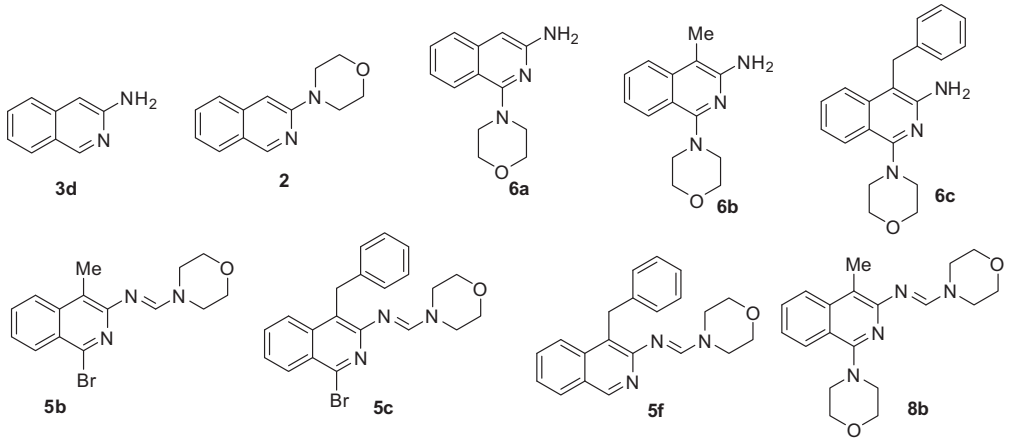

Figure 1. Structures of the isoquinoline-amines selected for photophysical studies.

Table 1
Photophysical properties of the isoquinoline-amines in acetonitrile

	3d	2	6a	6b	6c	5b	5c	5f	8b
λ_{max}(abs)[a] (nm)	363	366	371	377	377	372	370	363	370
λ_{max}(fl) (nm)	431	457	457	468	461	451	451	434	456
Φ_f	0.28	0.22	0.25	0.16	0.19	0.0064	0.0082	0.068	0.11
τ_f (ns)	12.4	14.4	7.7	4.9	4.6	~0.1	~0.1	2.2	3.1
k_f (10^7 s^{-1})	2.3	1.5	3.2	3.3	4.1	[b]	[b]	3.1	3.5
k_{nr}/(10^7 s^{-1})	5.8	5.4	9.7	17	18	>400	>400	42	29

[a] The locations of all absorption maxima are given in Ref. 13.
[b] Fluorescence lifetime is too small to determine precisely.

3-morpholino moiety barely affected k_{nr}, but the introduction of the morpholine moiety at C-1 accelerated energy dissipation from the singlet excited state. Replacement of the H4 atom in **6a** with methyl or benzyl groups (i.e. **6b** and **6c**) led to further increase in k_{nr}. The faster nonradiative deactivation in the case of **8b** compared to **6b** probably implies that the amidine moiety also promotes the transition from the singlet excited to the ground state.

Very little information is available on the fluorescence characteristics of isoquinoline-3-amines. Utilization of the 4-phenyl derivative as a colorimetric Hg^{2+} sensor has been reported.[12] As representative examples, Figure 2 presents the absorption and fluorescence spectra of compounds **3d** and **6a**. These spectra reveal that introduction of the morpholine moiety at position 1 of the isoquinoline causes a significant bathochromic shift (26 nm) in the fluorescence spectrum, whereas a somewhat smaller displacement occurs for the absorption bands.

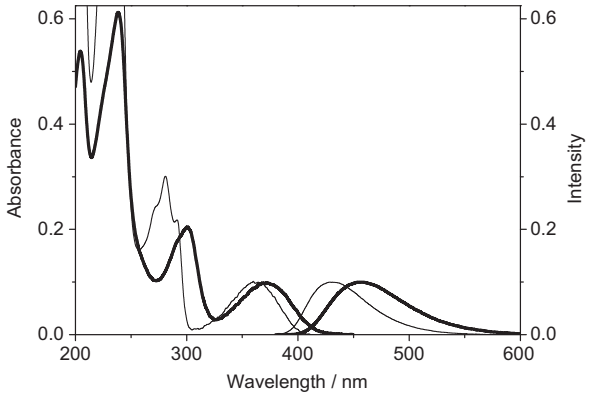

Figure 2. Absorption and fluorescence spectra of isoquinoline-3-amine (**3d**) (thin line) and 1-morpholinoisoquinoline-3-amine (**6a**) (thick line).

These results indicate that the prepared compounds represent a new valuable group of fluorescent isoquinoline derivatives. Comparison of the fluorescence spectra of the variously substituted derivatives shows some significant changes as a consequence of structural variations.

Acknowledgments

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Supplementary data

Supplementary data (analytical data including ^{1}H and ^{13}C NMR spectral assignments, UV and fluorescence spectra for the most important compounds as well as absorption and fluorescence spectra of selected compounds) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.07.143.

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5. (a) Isoquinoline 3-triflate (**1**) (150 mg, 0.54 mmol) was dissolved in morpholine (1 ml) and the solution was heated at 130 °C for 6 h with stirring. After cooling, CH_2Cl_2 (10 ml) was added and the mixture was washed with H_2O (2 × 10 ml). The organic layer was dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by flash column chromatography on silica gel to give bright yellow crystals of **2**, 86 mg (75%), mp 124–126 °C (Lit mp 126–127.5 °C[4]); (b) A similar procedure was applied for the transformation of **3a**–**c** into **6a**–**c**. Thus, a solution of 1-bromoisoquinoline-3-amine **3a** (0.22 g, 1 mmol) in morpholine (2 ml) was refluxed for 24 h. The reaction mixture was evaporated, H_2O (10 ml) was added and the precipitated solid was filtered. Recrystallization from EtOH yielded 0.1 g (45%) of product **6a**, mp 151–154 °C.
6. Analytical and spectral data of **6a**–**c**: 1-morpholinoisoquinoline-3-amine (**6a**): Yield: 45%; brownish yellow crystals; mp 151–154 °C; ν_{max} (KBr, cm^{-1}): 3348, 2847, 1638, 1557, 1109, 858; δ_H (300 MHz, $CDCl_3$): 3.38 (4H, tt, J = 9.2 Hz, H-2′, H-6′), 3.94 (4H, tt, J = 9.2 Hz, H-3′, H-5′), 4.26 (2H, NH_2), 6.36 (1H, s, H-4), 7.15 (1H,dd, J = 7.5, 6.9 Hz, H-7), 7.48–7.38 (2H, m, H-8, H-6), 7.89 (1H, d, J = 8.5 Hz, H-5); δ_C (75 MHz, $CDCl_3$): 52.0 (C-2′,C-6′), 67.3 (C-3′, C-5′), 94.5 (C-4), 116.4 (C-8a), 122.1 (C-5), 125.6 (C-7), 125.7 (C-8), 129.9 (C-6), 141.5 (C-4a), 152.8 (C-3), 161.2 (C-1). m/z (EI): 230.3 (M+H); Anal. calcd for $C_{13}H_{15}N_3O$ (229.27): C, 68.10; H, 6.59; N, 18.33. Found: C, 68.01; H, 6.70; N, 18.25. 4-methyl-1-morpholinoisoquinoline-3-amine (**6b**): Yield: 55%; yellow crystals; mp: 143–145 °C; ν_{max} (KBr, cm^{-1}) 3365, 2957, 1633, 1564, 1114, 755; δ_H (300 MHz, $CDCl_3$): 2.30 (3H, s, H-4-CH_3), 3.33 (4H, t, J = 9.1 Hz, H-2′,H-6′), 3.95 (4H, t, J = 9.2 Hz, H-3′, H-5′), 4.26 (2H, s, NH_2), 7.19 (1H, dd, J = 7.5, 7.8 Hz, H-7), 7.51 (1H, dd, J = 7.8, 7.5 Hz, H-6), 7.72 (1H, d, J = 8.5 Hz, H-8), 7.99 (1H, d, J = 8.4 Hz, H-5); δ_C (75 MHz, $CDCl_3$): 11.5 (Cα), 52.2 (C-2′,C-6′), 67.4 (C-3′,C-5′), 99.5 (C-4), 117.0 (C-8a), 121.6 (C-5), 122.3 (C-7), 126.1 (C-8), 129.8 (C-6), 139.8 (C-4a), 150.2 (C-3), 159.3 (C-1). m/z (EI): 244.3 (M+H); Anal. calcd for $C_{14}H_{17}N_3O$ (243.30): C, 69.11; H, 7.04; N, 17.27. Found: C, 69.01; H, 7.15; N, 17.32. 4-benzyl-1-morpholinoisoquinoline-3-amine (**6c**): Yield: 60%; pale brown crystals; mp 82–84 °C; ν_{max} (KBr, cm^{-1}): 3353, 2844, 1614, 1561, 1112, 762; δ_H (300 MHz, $CDCl_3$): 3.39 (4H, s, H-2′,H-6′), 3.97 (4H, s, H-3′,H-5′), 4.18 (4H, s, H-4-CH_2, NH_2), 7.16-7.26 (6H, m, H-2,H-3″,H-4″,H-5″,H-6″, H-7), 7.48 (1H, dd, J = 7.5, 7.2 Hz, H-6), 7.72 (1H, d, J = 8.5 Hz, H-8), 8.02 (1H, d, J = 8.3 Hz, H-5); δ_C (75 MHz, $CDCl_3$+DMSO-d_6): 31.7 (Cα), 52.1 (C-2′,C-6′), 67.3 (C-3′,C-5′), 102.2 (C-4), 116.9 (C-8a), 121.7 (C-5), 122.3 (C-7), 126.2 (C-4″), 126.5 (C-8), 128.3 (C-3″,C-5″), 128.9 (C-2″,C-6″), 130.2 (C-6), 139.5 (C-1″), 140.1 (C-4a), 150.9 (C-3), 160.0 (C-1). m/z (EI): 320.4 (M+H); Anal. calcd for $C_{20}H_{21}N_3O$ (319.40): C, 75.21; H, 6.63; N, 13.16. Found: C, 75.15; H, 6.42; N, 12.85.
7. A mixture of the appropriate isoquinoline-amine derivative (**3** or **6**, 1 mmol), *p*-TsOH (0.1 mol) and triethyl orthoformate (5 ml) was heated under reflux for 16 h with stirring. Excess triethyl orthoformate was removed by vacuum distillation, 8% aqueous $NaHCO_3$ solution (20 ml) was added and the product was extracted with CH_2Cl_2 (2 × 20 ml). The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated to yield the crude product as a yellow solid (75–90%) which was recrystallized from *i*-PrOH.
8. To a solution of formimidate derivative (**4** or **7**, 1 mmol) in dry toluene (5 ml) was added morpholine (2 mmol). The solution was heated at 100 °C for 1 h with stirring. After evaporation of the solvent the residue was dissolved in CH_2Cl_2 (20 ml) and the solution washed with H_2O (20 ml). The aqueous phase was extracted with CH_2Cl_2 (2 × 20 ml) and the collected organic phase dried over anhydrous Na_2SO_4. The solution was filtered, evaporated, and the crude product (80–90%) recrystallized from *i*-PrOH.
9. The fluorescence quantum yield was determined relative to that of quinine sulfate in 1 N H_2SO_4, for which a reference yield of Φ_f = 0.546 was taken.[10] Fluorescence lifetimes were measured using time-correlated single-photon counting as described previously.[11]
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13. Locations of all absorption maxima in nm for the compounds listed in Table 1: **3d**: 207, 234, 281, 291, 363; **2**: 209, 243, 290, 366; **6a**: 205, 239, 301, 371; **6c**: 204, 240, 305, 377; **6b**: 207, 239, 305, 377; **5b**: 217, 264, 273, 318, 372; **5c**: 214, 264, 273, 320, 370; **5f**: 213, 262, 270, 314, 363; **8b**: 212, 264, 272, 327, 370.