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Photochemical synthesis of indazolo[3,2-*b*]quinazolines and their redox-switching properties

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ABSTRACT

Several indazolo[3,2-*b*]quinazolines were synthesized in moderate to good yields by exposing 2-(2-nitrophenyl)-1,2,3,4-tetrahydroquinazolines to UV light (306 nm) in acetonitrile. The scope, limitation, and possible mechanism of this light-mediated reaction as well as the redox-switching properties of the target compounds were explored. Reduction of the colored indazolo[3,2-*b*]quinazoline with sodium borohydride resulted in a distinct change to colorless and a sharp increase in fluorescence intensity. The reduced product can be swiftly reverted to the original form by 2,3-dichloro-5,6-dicyano-1,4-benzoquinone oxidation. The reversible redox-switching between the indazolo[3,2-*b*]quinazoline and its reduced product utilizing chemical reduction and oxidation as two external stimuli with dual output properties; that is, color change and emission variation was reported.

1. Introduction

Indazoloquinazolines refer to a small family of indazole- and quinazoline-fused heterocycles, including indazolo[2,3-*a*]quinazolines [1], indazolo[2,3-*c*]quinazolines [2], and indazolo[3,2-*b*]quinazolines [3–6] (Fig. 1). The molecular scaffolds of indazoloquinazolines are rarely present in the natural products, but indazoloquinazoline-derived compounds have been reported to possess a wide range of biological activities. Some indazolo[2,3-*a*]quinazoline derivatives [7], for instance, were found to exhibit anti-bacterial activity against Gram-negative bacteria and anti-fungal activity against yeast, whereas indazolo[2,3-*c*]quinazoline-11-sulfonamide [2] was claimed to possess therapeutic activity against inflammation. Nevertheless, the biological and physical properties of indazolo[3,2-*b*]quinazoline derivatives have not yet been described. In light of the potential biological activity associated with the indazole/quinazoline-fused molecular structure, we envisage that an efficient preparation of the indazolo[3,2-*b*]quinazoline derivatives may facilitate the exploration of their properties.

Recently we reported [8] an efficient route for the preparation of indazolo[2,3-*a*]quinoline derivatives from 2-(2-nitrophenyl)-1,2,3,4-tetrahydroquinolines via visible light photoredox catalysis, as shown in Fig. 2. The successful formation of an indazole functionality via light-mediated cyclization of an *N*-(2-nitrobenzyl)aniline moiety prompted us to examine the possibility of extending this methodology to the preparation of indazoloquinazolines. Herein, we describe our efforts to the facile synthesis of indazolo[3,2-*b*]quinazoline derivatives by exposing 2-(2-nitrophenyl)-1,2,3,4-tetrahydroquinazolines to UV light in acetonitrile. The scope and limitation of this photochemical reaction as well as the properties of the target compounds were investigated.

2. Experimental

2.1. General

Melting points were determined on a Mel-Temp melting point apparatus in open capillaries and are uncorrected. MS were performed on JEOL JMS-SX/SX 102A spectrometer. Single crystal structures were determined by a Bruker AXS SMART-1000 X-ray single-crystal diffractometer. IR spectra were obtained using a 1725XFT-IR spectrophotometer. Absorption spectra were recorded using an HP8453 spectrophotometer. Fluorescence spectra were measured with a Hitachi F-4500 fluorescence spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded at 300 and 75 MHz on a Varian VXR300 spectrometer as well as 600 and 150 MHz on a Varian Unity Inova 600 spectrometer. Chemical shifts were reported in parts per million on the δ scale relative to an internal

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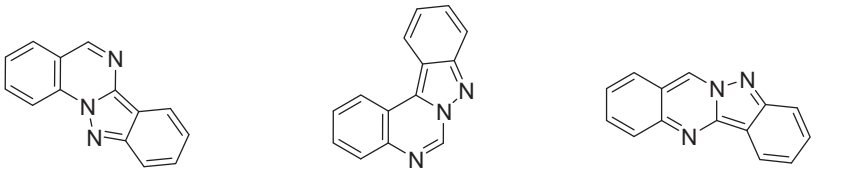

Fig. 1. Structures of indazoloquinazolines.

standard (tetramethylsilane, or appropriate solvent peaks) with coupling constants given in hertz. ^{1}H NMR multiplicity data are denoted by s (singlet), d (doublet), t (triplet), q (quartet), and m (multiplet). Analytical thin-layer chromatography (TLC) was carried out on Merck silica gel 60G-254 plates (25 mm) and developed with the solvents mentioned. Flash chromatography was performed in columns of various diameters with Merck silica gel (230–400 mesh ASTM 9385 kieselgel 60H) by elution with the solvent systems. The visible light irradiation reaction was performed with a 23 W household fluorescence lamp.

2.2. Calculation of fluorescence quantum yield

Quinine hemisulfate salt monohydrate (Φ_f = 0.546, λ_{max} = 455 nm in aqueous H_2SO_4) was used as an external standard for the measurement of fluorescence quantum yields of **1b** and **24**. Fluorescence quantum yields were measured by comparing the integrated area under the fluorescence curve for compounds **1b**, **24**, and quinine sulfate dihydrate at equal absorbance at the same excitation wavelength. The quantum yields were corrected for the refractive index of the solvent.

2.3. General procedure for the preparation of compounds ***4a–e***

To a solution of *o*-aminobenzylamine (**2**, 4.1 mmol) in ethanol (25 mL) was added *o*-nitrobenzaldehydes (**3**, 4.1 mmol) and a catalytic amount of ammonium chloride (0.04 mmol) at room temperature. The resulting mixture was stirred at room temperature for 1–2 h. The precipitate was then filtered and washed with water and hexanes to afford the desired product.

2.3.1. 2-(2-Nitrophenyl)-1,2,3,4-tetrahydroquinazoline (***4a***)

Yellow solid; yield 95%; R_f = 0.4 (20% EtOAc/hexanes); mp 80–81 °C (lit.[9] 80–81 °C); IR ν_{max} (KBr) 3412, 3319, 1605, 1523, 1484, 1359, 1255, 1110, 1043, 748 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.79 (td, J = 8.1, 1.5 Hz, 2H), 7.57 (td, J = 7.8, 1.5 Hz, 1H), 7.45 (td, J = 7.8, 1.5 Hz, 1H), 7.07 (td, J = 7.5, 1.2 Hz, 1H), 6.91 (d, J = 6.9 Hz, 1H), 6.73 (td, J = 7.5, 1.2 Hz, 1H), 6.65 (dd, J = 8.1, 0.9 Hz, 1H), 5.89 (s, 1H), 4.34 (s, 1H), 4.04, 3.73 (ABq, J = 16.5 Hz, 1H each).

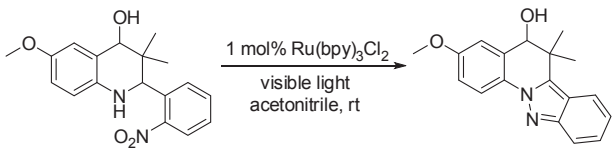

Fig. 2. Visible light-mediated preparation of indazolo[2,3-*a*]quinoline.

2.3.2. N,N-dimethyl-3-nitro-4-(1,2,3,4-tetrahydroquinazolin-2-yl) aniline (***4b***)

Yellow solid; yield 97%; R_f = 0.4 (40% EtOAc/hexanes); mp 115–116 °C; IR ν_{max} (KBr) 3400, 3332, 2871, 1605, 1531, 1483, 1266, 1071, 738 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.57 (d, J = 8.7 Hz, 1H), 7.02–7.11 (m, 2H), 6.91 (d, J = 7.2 Hz, 1H), 6.83 (dd, J = 9.0, 3.0 Hz, 1H), 6.71 (t, J = 7.5 Hz, 1H), 6.61 (d, J = 8.1 Hz, 1H), 5.66 (d, J = 1.8 Hz, 1H), 4.26 (s, 1H), 4.13, 3.85 (ABq, J = 16.5 Hz, 1H each), 3.01 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 150.1, 150.0, 143.3, 129.1, 127.1, 126.1, 121.9, 121.3, 118.1, 115.4, 115.1, 106.9, 64.4, 45.5, 40.1; HRMS (EI) calcd for $C_{16}H_{18}N_4O_2$ [M$^+$] 298.1430, found 298.1435.

2.3.3. 2-(6-Nitrobenzo[d][1,3]dioxol-5-yl)-1,2,3,4-tetrahydroquinazoline (***4c***)

Yellow solid; yield 97%; R_f = 0.6 (40% EtOAc/hexanes); mp 104–105 °C; IR ν_{max} (KBr) 3332, 2779, 1716, 1612, 1501, 1478, 1328, 1251, 1036, 929, 751 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.39 (s, 1H), 7.07 (t, J = 8.1 Hz, 1H), 6.93 (d, J = 7.5 Hz, 1H), 6.74 (td, J = 7.5, 1.2 Hz, 1H), 6.63 (d, J = 8.1 Hz, 1H), 6.12, 6.10 (ABq, J = 1.2 Hz, 1H each), 5.86 (s, 1H), 4.28 (s, 1H), 4.11, 3.82 (ABq, J = 16.5 Hz, 1H each); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 150.4, 146.7, 143.4, 142.7, 133.1, 126.9, 125.8, 120.5, 116.3, 114.2, 108.0, 105.4, 103.2, 63.1, 43.5; HRMS (EI) calcd for $C_{15}H_{13}N_3O_4$ [M$^+$] 299.0906, found 299.0903.

2.3.4. 2-(4-Bromo-2-nitrophenyl)-1,2,3,4-tetrahydroquinazoline (***4d***)

Yellow solid; yield 98%; R_f = 0.4 (20% EtOAc/hexanes); mp 125–126 °C; IR ν_{max} (KBr) 3412, 3331, 1709, 1606, 1530, 1488, 1364, 1258, 1051, 744 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.94 (dd, J = 1.8, 0.9 Hz, 1H), 7.67 (d, J = 1.8 Hz, 2H), 7.08 (t, J = 7.5 Hz, 1H), 6.90 (d, J = 7.2 Hz, 1H), 6.73 (td, J = 7.5, 1.8 Hz, 1H), 6.66 (d, J = 7.8 Hz, 1H), 5.90 (d, J = 3.3 Hz, 1H), 4.32 (s, 1H), 3.96, 3.63 (ABq, J = 16.8 Hz, 1H each); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 149.4, 141.9, 135.3, 135.0, 130.5, 127.5, 127.4, 126.2, 121.9, 121.3, 118.5, 115.2, 63.9, 43.9; HRMS (EI) calcd for $C_{14}H_{12}BrN_3O_2$ [M$^+$] 333.0113, found 333.0117.

2.3.5. 2-(1-Nitronaphthalen-2-yl)-1,2,3,4-tetrahydroquinazoline (***4e***)

Yellow solid; yield 78%; R_f = 0.4 (20% EtOAc/hexanes); mp 121–122 °C; IR ν_{max} (KBr) 3414, 3326, 1710, 1609, 1528, 1489, 1263, 1116, 1066, 748 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.00 (d, J = 9.0 Hz, 1H), 7.92 (dd, J = 7.2, 2.4 Hz, 1H), 7.79–7.75 (m, 2H), 7.68–7.58 (m, 2H), 7.08 (t, J = 8.7 Hz, 1H), 6.93 (d, J = 7.5 Hz, 1H), 6.75 (td, J = 7.5, 1.2 Hz, 1H), 6.65 (d, J = 8.1 Hz, 1H), 5.62 (d, J = 1.8 Hz, 1H), 4.32 (bs, 1H), 4.16, 3.90 (ABq, J = 16.5 Hz, 1H each); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 147.0, 142.6, 133.6, 131.0, 130.5, 128.8, 128.0, 127.6, 127.4, 126.3, 124.4, 124.0, 121.8, 121.3, 118.7, 115.3, 65.5, 45.4; HRMS (EI) calcd for $C_{18}H_{15}N_3O_2$ [M$^+$] 305.1164, found 305.1160.