Title

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Journal

The Journal of Organic Chemistry, 83(24)

ISSN

0022-3263

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Publication Date

2018-12-21

DOI

10.1021/acs.joc.8b02356

Peer reviewed

HHS Public Access

Author manuscript

J Org Chem. Author manuscript; available in PMC 2019 December 21.

Published in final edited form as:

J Org Chem. 2018 December 21; 83(24): 15493–15498. doi:10.1021/acs.joc.8b02356.

Photochemical Preparation of 1,2-Dihydro-3*H*-indazol-3-ones in Aqueous Solvent at Room Temperature

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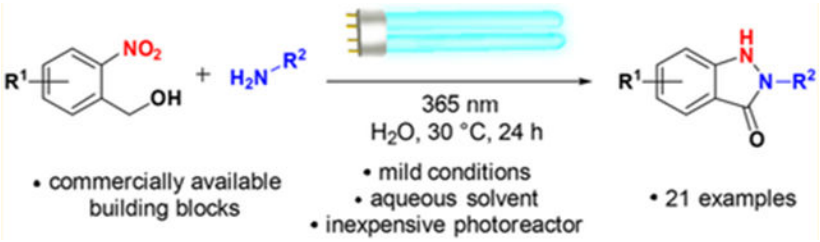
Abstract

o-Nitrosobenzaldehyde is a reactive intermediate useful in the synthesis of nitrogen heterocycles. Previous strategies for using *o*-nitrosobenzaldehyde involve its isolation *via* chromatography and/or formation under harsh conditions. Herein, this intermediate was photochemically generated *in situ* from *o*-nitrobenzyl alcohols in a mild, efficient manner for the construction of 1,2-dihydro-3*H*-indazol-3-ones using an aqueous solvent at room temperature. This convenient reaction offers several advantages over reported methods. The commercially available photoreactor employed 3 × 18 W bulbs outputting broad emission above 365 nm.

Graphical Abstract



Expanding the toolkit for 1,2-dihydro-3*H*-indazol-3-one (indazolone) construction is highly desirable because these heterocycles afford a plethora of interesting biological activities with valuable pharmaceutical applications (Figure 1).[1] For example, **1** and **2** have antiviral and antibacterial activities,[2] **3** has shown antihyperglycemic properties,[3] **4** is an antitumor agent,[4] **5** is an angiotensin II receptor antagonist,[5] and other cases in the literature.[6]

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Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.8b02356.

Characterization data: ^{1}H and ^{13}C NMR spectra (PDF)

The authors declare no competing financial interest.

Our group recently modified the Davis–Beirut reaction[1,7] to exploit the fact that suitably strong bases facilitate the formation of *aci*-nitronate intermediates[8] and developed this chemistry for the direct synthesis of indazolones from *o*-nitrobenzyl alcohol and proposed that the reaction proceeded *via o*-nitrosobenzaldehyde **7** as the key intermediate (Scheme 1; R^1 = H).[9] However, that reported protocol required quite forcing conditions: 20 equiv of KOH at 100 °C.[9] The *o*-nitrobenzyl moiety (cf., **6**) is a photolabile protecting group for heteroatoms[10] where the key role of light in the deprotection is generation of an *aci*-nitro species. The most commonly cited disadvantage of this group's photodeprotection is that cargo release is accompanied by the generation of highly reactive **7**.[10]

Despite this, the deprotection of **6** is generally accomplished under mild conditions suitable for studying various biological systems.[10] Therefore, we envisioned that an indazolone forming reaction (**6** → **7** → indazolone) could potentially also be realized under gentle photochemical conditions; this UV-mediated strategy would be one of the most mild and convenient indazolone synthetic methods reported.[11] Herein, we detail the development and implementation of a photochemical route to indazolones from *o*-nitrobenzyl alcohols and primary amines.

We first attempted to synthesize indazolone **1** by simply treating a mixture of *o*-nitrobenzyl alcohol and *n*-butylamine with UV light. This reaction was initially carried out in deionized water but resulted in a complex mixture. We reasoned that employing conditions more favorable for the formation of **7** would give better results, since the mechanism of **6** → **7** is pH dependent.[10,12] Therefore, the experiment was repeated using aqueous phosphate-buffered saline (PBS) solution, which is known to stabilize the pH and has been shown to be suitable for the generation of **7**.[10] To our delight, indazolone **1** was the major product observed by LCMS under these reaction conditions.

Next, the effectiveness of multiple light sources was investigated, including a Rayonet RMR-600 equipped with either eight lamps outputting single wavelength (254, 300, or 350 nm) light, a ThermalSpa 49135 equipped with three 18 W UVA bulbs outputting light above 365 nm,[13] and a 500 W halogen lamp outputting broad spectrum light. Regardless of the wavelength, the Rayonet reactor resulted in a lower indazolone yield compared to the ThermalSpa (Table 1; entries 1–3 vs 4) and the 500 W halogen lamp gave indazolone **1** in only 11% yield (entry 5). In addition, the temperature of the reaction mixture with the halogen lamp was difficult to control and the bulb had a much higher operating wattage requirement. Using sunlight as the light source was not considered due to standard operating procedure constraints. Therefore, the ThermalSpa was selected for further optimization for its relative low cost, moderate operating temperature, and ease of use.[13]

After selecting the photoreactor, optimization of the reaction began. Since the reaction mixture was not homogeneous after irradiation, the PBS solution was diluted with 5% or 10% DMSO to improve solubility; however, this did not result in more indazolone formation (Table 2, entries 2 and 3). At this point, the air-cooling system was adjusted (see Supporting Information (SI)) so that the solution's final temperature did not exceed 30 °C, which resulted in a modest increase in yield (entry 4). ^{i}PrOH and THF were used as solvents and gave comparable yields to PBS (entries 5 and 6). Next, the amount of amine was

investigated (entries 7–10); the reaction is most successful when the amine equivalence was between 2 and 5. Although some *o*-nitrobenzyl systems can be transformed to *o*-nitrosobenzaldehyde quite rapidly,[14] the conversion of *o*-nitrobenzyl alcohol to reactive intermediate **7** is not as fast. Indeed, when the reaction was stopped after 2 h, indazolone was formed in only 21% yield with 64% recovered starting alcohol (entry 12). The effect of concentration was studied (entries 13–16), and it was found that the reaction performed best with increased volumes of solvent. That said, it is interesting that the reaction delivers indazolone with only a modest decrease in yield when carried out under neat conditions (entry 13 vs 17). Lowering the temperature to 0 °C (8 h) resulted in a 48% yield with 24% starting alcohol (entry 18). In contrast, the reaction gave indazolone in 55% yield with 29% starting alcohol at 30 °C (entry 19). Using quartz reaction vessels was effective but not required for product formation (entries 20 and 21).

With optimized conditions in hand (Table 2, entry 13), the substrate scope of this photochemical indazolone-forming reaction was explored (Table 3). As hoped, various alkyl amines gave the corresponding alkyl indazolones (**1**, **2**, **8**, **9**, **10**, **11**, **12**, **18**, and **19**) in good yield. The synthesis of 9 was accomplished in 53% yield even though *n*-heptylamine is not soluble in PBS solution. Photocleavage of aryl halide bonds is known to be radical-mediated.[15] As a result, reaction of (5-chloro-2-nitrophenyl)methanol with *n*-butylamine gave indazolone **14** in only 10% yield with indazolone **1** as a side product in 9% yield (note: three side-products having $m/z < 100$ were found by LCMS with each accounting for <10% of the recovered mass). Under strongly alkaline conditions,[9] (3-methyl-2-nitrophenyl)methanol provided the corresponding indazolone **15** in marginal yields after 48 h of reaction time, presumably due to issues related to benzylic proton acidity affecting *aci*-nitronate anion formation. In contrast, this problem was eliminated under the reaction conditions reported here and **15** was obtained in 69% yield. Similarly, the reaction of (3-methyl-2-nitrophenyl)methanol with cyclopentylamine gave indazolone **16** in 55% yield and cyclohexylamine gave indazolone **17** in 56% yield. Unfortunately, aniline failed to provide **20** (LCMS suggests that *N*,2-diphenyl-2*H*-indazol-3-amine was formed in low yield, but this preliminary observation could not be verified due to isolation issues).

Another challenging class of substrates for base-mediated indazolone formation[9] is reactions of benzylic amines, due to side reactions associated with the benzylic hydrogen's acidity. Here, in the absence of base, benzylamine gave **21** in 69% yield. α-Substituted benzylic amines gave **22** in 56% yield and **23** in 51% yield. Finally, although the light source selected is known to promote [2 + 2] cycloaddition,[13] we were delighted to find that allylamine gave **24a** in 63% yield and did not have dimerization issues. Likewise, propargylamine gave indazolone **24b** in 60% yield and using amines containing heterocycles resulted in indazolones **25** and **26** in 83% and 62% yield, respectively.

The proposed mechanistic model for this reaction is as follows (Scheme 2). The reaction begins by generation of *aci*-nitro intermediate **A** from *o*-nitrobenzyl alcohol.[10] The *aci*-nitro intermediate then undergoes a 6π electrocyclization to generate *N*-hydroxy anthranil species **B**. Ring fragmentation occurs to form **C**, and subsequent loss of water gives *o*-nitrosobenzaldehyde **7**. The primary amine then undergoes condensation with **7** at the nitroso and/or the aldehyde to give **D** and/or **E**, respectively.[9] Intermediates **D** and **E** can

both lead to indazolone ring formation through events involving cyclization/dehydration/tautomerization.

In summary, we report a green photochemical route to indazolones from *o*-nitrobenzyl alcohols and primary amines in an aqueous solvent at room temperature using an affordable, low-power, and easy to operate photoreactor. These reactions proceed through *o*-nitrosobenzaldehyde as the key reactive intermediate. Although exploiting this intermediate in base-mediated indazolone synthesis was previously demonstrated by our group, the protocol reported here significantly reduces the overall harshness of the reaction conditions and this UV-mediated route overcomes several established substrate scope limitations.

EXPERIMENTAL SECTION

All chemicals were purchased from standard commercial suppliers and used without further purification. Anhydrous solvents were dispensed from a solvent purification system utilizing dry neutral alumina or prepared using dry molecular sieves. Analytical TLC was performed using precoated plates (silica gel 60 F254) and visualized with UV light or an I_2 chamber. Flash chromatography in glass columns was performed using 60 Å 230–400 mesh silica gel (Fisher). ^{1}H NMR spectra and proton decoupled ^{13}C NMR spectra were obtained on a 400 MHz Bruker, a 600 MHz Varian, or an 800 MHz Bruker NMR spectrometer. ^{1}H and ^{13}C chemical shifts (δ) are reported in parts per million (ppm) relative to residual solvent peaks or TMS. Multiplicities are given as s (singlet), d (doublet), t (triplet), q (quartet), p (pentet), hex (hextet), h (heptet), and m (multiplet). Coupling constants (J) are given in Hz. For HRMS analysis, samples were analyzed by flow-injection analysis with a Thermo Fisher Scientific LTQ Orbitrap (San Jose, CA) operated in the centroided mode. Samples were injected into a mixture of 50% MeOH/H_2O and 0.1% formic acid at a flow of 0.2 mL/min. Source parameters were set to 5.5 kV spray voltage, a capillary temperature of 275 °C, and a sheath gas setting of 20. Spectral data were acquired at a resolution setting of 100 000 fwhm with the lockmass feature, which typically results in sufficient mass accuracy. Uncorrected melting point values were gathered using a Stanford Research Systems OptiMelt MPA100. LCMS analysis was carried out using a Waters 2695 equipped with an Ascentis Express C18, 2.7 μm HPLC column using a gradient of MeCN/H_2O with 0.1% formic acid. The HLPC was also equipped with an inline Water 996 photodiode array detector operating between 250 and 800 nm and a Waters micromass ZQ mass spectrometer in ESI+ mode. Photochemical reactions were carried out in Rayonet RQV-5 quartz reaction vessels. Light sources used were a Globe Electric 500 W portable yellow work light equipped with 1 × 500 W halogen T3 double-ended clear RSC base light bulbs (The Home Depot), a Rayonet RMR-600 with fan and merry-go-round unit using 8 × RMR-2537A, 8 × RMR-3000A, and 8 × RMR-3500A lamps (The Southern New England Ultraviolet Co.), or a ThermalSpa 49135 UV Auto Gel Light Nail Dryer equipped with 3 × PL-18W/UVA bulbs operating in continuous mode (Amazon).[13] Pictures and description of the photoreactor setups are shown in the SI.

General Procedure for Indazolone Synthesis.

A stir bar, *o*-nitrobenzyl alcohol (0.5 mmol), amine (1.0 mmol), and PBS solution (10 mL) were added to a 16 × 125 mm quartz test tube. The top of the test tube was covered and sealed using Parafilm. This reaction mixture was then suspended inside the ThermalSpa UV source, with an approximately 2.5 cm distance between the light source and irradiation vessel (no filters were employed). House air cooling delivered via Tygon tubing was used for the duration of the 24 h reaction to maintain the reaction temperature at 30 °C (the reaction mixture temperature was measured by thermometer at the end of the reaction). The reaction mixture was transferred using dichloromethane to a solution of HCl (30 mL, 1 M) and then extracted using dichloromethane (3 × 50 mL). The organic layers were combined, dried using magnesium sulfate, and filtered. Dichloromethane was removed using rotatory evaporation, and the crude mixture was purified by flash column chromatography on silica gel with a gradient of dichloromethane and methanol; generally, the gradient was with 50 mL of 1% methanol in dichloromethane followed by 200 mL of 2.5% methanol in dichloromethane followed by 50 mL of 5% methanol in dichloromethane. Compounds **14** and **25** were purified using a CombiFlash Rf+ (Teledyne Isco). Note: **25** remained in the acidic aqueous layer, which was dried and subjected to purification directly.

Procedure for Large Scale Synthesis of 1.

A stir bar, *o*-nitrobenzyl alcohol (0.77 g, 5 mmol), amine (0.99 mL, 10 mmol), and PBS solution (100 mL) were added to a 125 mL Chemglass recovery flask. This reaction mixture was then suspended inside the ThermalSpa UV source, with an approximately 0.5 cm distance between the light source and irradiation vessel (no filters were employed). House air cooling delivered via Tygon tubing was used for the duration of the 24 h reaction to maintain the reaction temperature at 30 °C (the reaction mixture temperature was measured by thermometer at the end of the reaction). The reaction mixture was transferred using dichloromethane to a solution of aq. HCl (300 mL, 1 M) and then extracted using dichloromethane (3 × 100 mL). The organic layers were combined, dried using magnesium sulfate, and filtered. The dichloromethane was removed using rotatory evaporation, and the crude mixture was purified by flash column chromatography on silica gel with a 2.5% methanol in dichloromethane solution. Yield: 524 mg (55%) as brown oil.

2-Butyl-1,2-dihydro-3H-indazol-3-one (1).—Yield: 64 mg (67%), brown oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.26 (s, 1H), 7.73 (d, J = 1H), 7.45 (t, J = 7.6, 1H), 7.22 (d, J = 8.2, 1H), 7.11 (t, J = 7.6, 1H), 3.89 (t, J = 7.2, 2H), 1.73 (q, J = 7.4, 2H), 1.29 (h, J = 7.4, 2H), 0.86 (t, J = 7.2, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 161.8, 146.1, 131.5, 123.3, 121.7, 118.1, 112.1, 43.9, 30.4, 19.9, 13.6; HRMS (Orbitrap): Calcd for $[C_{11}H_{15}N_2O^+, M + H]^+$, 191.1179; found, 191.1176. Data match literature values.[2]

2-Isopropyl-1,2-dihydro-3H-indazol-3-one (2).—Yield: 57 mg (65%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.38 (s, 1H), 7.75 (d, J = 7.9, 1H), 7.50–7.41 (m, 1H), 7.23 (d, J = 8.2, 1H), 7.13 (t, J = 7.5, 1H), 4.79 (hept, J = 6.8, 1H), 1.36 (d, J = 6.8, 6H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 162.0, 146.9, 131.5, 123.5, 122.1, 119.1, 112.5, 46.0, 20.4; HRMS (Orbitrap): Calcd for $[C_{10}H_{13}N_2O^+, M + H]^+$, 177.1022; found, 177.1019. Data match literature values.[2]

2-(tert-Butyl)-1,2-dihydro-3H-indazol-3-one (8).—Yield: 70 mg (74%) as a tan solid; mp: decomposes at 190 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, J = 7.8, 1H), 7.45 (t, J = 7.7, 1H), 7.30 (s, 1H), 7.22–7.09 (m, 2H), 1.63 (s, 9H); $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 163.9, 146.7, 131.5, 123.5, 122.3, 121.0, 112.3, 58.4, 27.5; HRMS (Orbitrap): Calcd for $[C_{11}H_{15}N_2O^+, M + H]^+$, 191.1179; found, 191.1178. Data match literature values.[9]

2-Heptyl-1,2-dihydro-3H-indazol-3-one (9).—Yield: 62 mg (53%) as a brown oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (s, 1H), 7.80 (d, J = 7.9, 1H), 7.49 (t, J = 7.7, 1H), 7.24 (d, J = 8.3, 1H), 7.21–7.12 (m, 1H), 3.88 (t, J = 7.3, 2H), 1.76 (p, J = 7.3, 2H), 1.34–1.21 (m, 10H), 0.86 (t, J = 6.7, 3H); $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 161.8, 146.2, 131.5, 123.4, 121.8, 118.2, 112.1, 44.3, 31.7, 28.9, 28.4, 26.7, 22.5, 14.0; HRMS (Orbitrap): Calcd for $[C_{14}H_{21}N_2O^+, M + H]^+$, 233.1648; found, 233.1644.

2-Cyclopentyl-1,2-dihydro-3H-indazol-3-one (10).—Yield: 75 mg (74%) as a dark orange solid; mp: 102–104 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.12 (s, 1H), 7.70 (d, J = 7.9, 1H), 7.42 (t, J = 7.7, 1H), 7.22 (d, J = 8.2, 1H), 7.09 (t, J = 7.5, 1H), 4.88 (p, J = 7.9, 1H), 2.00–1.72 (m, 6H), 1.65–1.51 (m, 2H); $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 162.08, 146.55, 131.43, 123.26, 121.80, 118.49, 112.38, 54.86, 30.16, 24.44; HRMS (Orbitrap): Calcd for $[C_{12}H_{15}N_2O^+, M + H]^+$, 203.1179; found, 203.1176. Data match literature values.[9]

2-Cyclohexyl-1,2-dihydro-3H-indazol-3-one (11).—Yield: 77 mg (71%) as a yellow foam. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.06 (s, 1H), 7.73 (d, J = 7.9, 1H), 7.43 (t, J = 7.6, 1H), 7.23 (d, J = 8.2, 1H), 7.09 (t, J = 7.6, 1H), 4.44–4.27 (m, 1H), 1.88–1.60 (m, 7H), 1.38–1.22 (m, 2H), 1.16–1.02 (m, 1H); $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 161.6, 146.5, 131.4, 123.4, 121.7, 118.6, 112.3, 53.5, 31.0, 25.5, 25.2; HRMS (Orbitrap): Calcd for $[C_{13}H_{17}N_2O^+, M + H]^+$, 217.1335; found, 217.1334. Data match literature values.[9]

2-Phenethyl-1,2-dihydro-3H-indazol-3-one (12).—Yield: 70 mg (59%) as a yellow solid; mp: 156–158 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.64 (s, 1H), 7.79 (d, J = 7.9, 1H), 7.49 (t, J = 7.7, 1H), 7.28–7.11 (m, 7H), 4.17 (t, J = 7.5, 2H), 3.10 (t, J = 7.5, 2H). $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 162.2, 146.5, 138.1, 131.7, 128.71, 128.69, 126.7, 123.5, 122.1, 118.5, 112.3, 45.8, 34.7. HRMS (Orbitrap): Calcd for $[C_{15}H_{15}N_2O^+, M + H]^+$, 239.1179; found, 239.1185. Data match literature values.[9]

2-Butyl-6-methoxy-1,2-dihydro-3H-indazol-3-one (13).—Yield: 76 mg (69%) as a beige powder; mp: 101–103 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (s, 1H), 7.65 (d, J = 8.7, 1H), 6.74 (d, J = 8.8, 1H), 6.62 (d, J = 2.1, 1H), 3.81 (s, 3H), 3.80 (t, J = 7.4, 2H), 1.69 (p, J = 2H), 1.38–1.23 (m, 2H), 0.89 (t, J = 7.4, 3H); $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 163.2, 162.5, 148.5, 124.6, 112.2, 112.0, 95.0, 55.6, 44.1, 30.3, 19.9, 13.6; HRMS (Orbitrap): Calcd for $[C_{12}H_{17}N_2O_2^+, M + H]^+$, 221.1285; found, 221.1281.

2-Butyl-5-chloro-1,2-dihydro-3H-indazol-3-one (14).—Yield: 12 mg (10%) as a tan solid; mp: 172–174 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (s, 1H), 7.76 (s, 1H), 7.53–7.40 (m, 1H), 7.15 (d, J = 8.6, 1H), 3.87 (t, J = 7.3, 2H), 1.73 (q, J = 7.4, 2H), 1.34 (p, J = 7.4, 2H), 0.92 (t, J = 7.3, 3H); $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 161.2, 144.8, 132.0, 128.1,

123.3, 120.4, 113.6, 44.2, 30.3, 19.9, 13.6; HRMS (Orbitrap): Calcd for $[C_{11}H_{14}ClN_2O^+$, M + H$]^+$, 225.0789; found, 225.0784. Data match literature values.[9]

2-Butyl-7-methyl-1,2-dihydro-3H-indazol-3-one (15).—Yield: 72 mg (69%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.73 (s, 1H), 7.56 (d, J = 7.8, 1H), 7.26 (d, J = 7.3, 1H), 7.04 (t, J = 7.5, 1H), 3.85 (t, J = 7.4, 2H), 2.38 (s, 3H), 1.71 (p, J = 7.4, 2H), 1.27 (h, J = 7.4, 2H), 0.85 (t, J = 7.4, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 162.4, 145. 8, 131.8, 122.2, 120.8, 118.2, 118.1, 44.0, 30.4, 19.9, 15.9, 13.6; HRMS (Orbitrap): Calcd for $[C_{12}H_{17}N_2O^+$, M + H$]^+$, 205.1335; found, 205.1333. Data match literature values.[9]

2-Cyclopentyl-7-methyl-1,2-dihydro-3H-indazol-3-one (16).—Yield: 60 mg (55%) as a red amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, J = 7.8, 1H), 7.27 (d, J = 7.5, 1H), 7.26 (s, 1H), 7.09 (t, J = 7.5, 1H), 4.88 (q, J = 9.2, 6.3, 1H), 2.38 (s, 3H), 2.06–1.92 (m, 2H), 1.89–1.76 (m, 4H), 1.71–1.56 (m,2H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 163.2, 146.3, 132.0, 122.8, 122.5, 121.0, 119.5, 55. 0, 29.9, 24.4, 15.8; HRMS (Orbitrap): Calcd for $[C_{13}H_{17}N_2O^+$, M + H$]^+$, 217.1335; found, 217.1334.

2-Cyclohexyl-7-methyl-1,2-dihydro-3H-indazol-3-one (17).—Yield: 65 mg (56%) as a brown oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (s, 1H), 7.60 (d, J = 7.8, 1H), 7.28 (d, J = 7.2, 1H), 7.08 (t, J = 7.5, 1H), 4.37–4.26 (m, 1H), 2.41 (s, 3H), 1.87–1.76 (m, 5H), 1.72–1.66 (m, 2H), 1.37–1.30 (m, 2H), 1.19–1.13 (m, 1H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 162.5, 146.3, 132.0, 122.54, 122.46, 121.0, 119.2, 53.5, 30.8, 25.5, 25.2, 15.9; HRMS (Orbitrap): Calcd for $[C_{14}H_{19}N_2O^+$, M + H$]^+$, 231.1492; found, 231.1490.

2-Butyl-5-methyl-1,2-dihydro-3H-indazol-3-one (18).—Yield: 76 mg (74%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (s, 1H), 7.52 (s, 1H), 7.29 (d, J = 8.4, 1H), 7.11 (d, J = 8.4, 1H), 3.84 (t, J = 7.3, 2H), 2.37 (s, 3H), 1.77–1.66 (m, 2H), 1.39–1.23 (m, 2H), 0.89 (t, J = 7.4, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ = 162.4, 145.0, 133.0, 132.0, 123.0, 119.3, 112.1, 44.0, 30.3, 21.0, 19.9, 13.6; HRMS (Orbitrap): Calcd for $[C_{12}H_{17}N_2O^+$, M + H$]^+$, 205.1335; found, 205.1334.

2-(Cyclopropylmethyl)-1,2-dihydro-3H-indazol-3-one (19).—Yield: 59 mg (63%) as red crystals; mp: 139–141 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (d, J = 7.8, 1H), 7.78 (s, 1H), 7.50 (t, J = 7.8, 1H), 7.24 (d, J = 8.2, 1H), 7.18 (t, J = 7.5, 1H), 3.74 (d, J = 7.1, 2H), 1.19–1.13 (m, 1H), 0.64–0.56 (m, 2H), 0.44–0.37 (m, 2H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 162.2, 146.8, 131.7, 123.8, 122.5, 119.4, 112.4, 48.7, 9.6, 3.6; HRMS (Orbitrap): Calcd for $[C_{11}H_{13}N_2O^+$, M + H$]^+$, 189.1022; found, 189.1022.

2-Benzyl-1,2-dihydro-3H-indazol-3-one (21).—Yield: 77 mg (69%) as black crystals; mp: 170–172 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (d, J = 7.5, 1H), 7.46 (t, J = 7.7, 1H), 7.35–7.23 (m, 6H), 7.22–7.09 (m, 2H), 5.00 (s, 2H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 162.5, 146.94, 146.88, 135.5, 131.91, 131.89, 128.96, 128.93, 128.84, 128.38, 128.30, 128.27, 128.19, 128.17, 124.00, 123.95, 122.71, 122.59, 119.1, 112.51, 112.49, 47.99, 47.97; HRMS (Orbitrap): Calcd for $[C_{14}H_{13}N_2O^+$, M + H$]^+$, 225.1022; found, 225.1016. Data match literature values.[7]

2-(1-Phenylethyl)-1,2-dihydro-3H-indazol-3-one (22).—Yield: 66 mg (56%) as a black oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, J = 7.6, 1H), 7.48–7.23 (m, 7H), 7.19–7.13 (m, 2H), 5.85 (q, J = 7.0, 1H), 1.74 (d, J = 7.1, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 162.2, 147.97, 146.95, 139.4, 139.34, 139.31, 131.7, 128.8, 128.1, 128.0, 127.33, 127.26, 123.9, 123.83, 123.81, 122.41, 122.37, 122.34, 119.22, 119.17, 112.6, 52.2, 17.6, 17.52, 17.49; HRMS (Orbitrap): Calcd for [$C_{15}H_{15}N_2O^+$, M + H]$^+$, 239.1179; found, 239.1174.

2-(1,2,3,4-Tetrahydronaphthalen-1-yl)-1,2-dihydro-3H-indazol-3-one (23).—Yield: 68 mg (51%) as a brown foam. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, J = 7.9, 1H), 7.55–7.49 (m, 1H), 7.27–7.11 (m, 6H), 6.51 (s, 1H), 5.89 (t, J = 7.4, 1H), 2.98–2.81 (m, 2H), 2.29–2.21 (m, 1H), 2.15–2.04 (m, 2H), 1.96–1.86 (m, 1H); ^{13}C{^{1}H} NMR (201 MHz, $CDCl_3$) δ 162.7, 146.8, 139.0, 133.3, 131.7, 129.7, 127.8, 127.4, 126.7, 124.0, 122.7, 119.6, 112.6, 52.4, 29.3, 28.6, 21.2; HRMS (Orbitrap): Calcd for [$C_{17}H_{17}N_2O^+$, M + H]$^+$, 265.1335; found, 265.1334.

2-Allyl-1,2-dihydro-3H-indazol-3-one (24a).—Yield: 55 mg (63%) as a red solid; mp: 116–118 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.94 (s, 1H), 7.82 (d, J = 7.8, 1H), 7.55–7.46 (m, 1H), 7.27–7.14 (m, 2H), 5.99–5.83 (m, 1H), 5.37–5.24 (m, 2H), 4.51 (dd, J = 5.9, 2H); ^{13}C{^{1}H} NMR (201 MHz, $CDCl_3$) δ = 162.2, 146.7, 131.8, 131.7, 123.7, 122.4, 119.3, 118.9, 112.3, 46.6; HRMS (Orbitrap): Calcd for [$C_{10}H_{11}N_2O^+$, M + H]$^+$, 175.0866; found, 175.0865.

2-(prop-2-yn-1-yl)-1,2-dihydro-3H-indazol-3-one (24b).—Yield: (60%) as a pale pink amorphous solid. ^{1}H NMR (400 MHz, CD_2Cl_2) δ = 7.78 (d, J = 7.8, 1H), 7.57 (t, J = 7.8, 1H), 7.29 (d, J = 8.2, 1H), 7.24 (t, J = 7.5, 1H), 7.17 (s, 1H), 4.63 (d, J = 2.3, 2H), 2.43 (t, J = 2.3, 1H). ^{13}C{^{1}H} NMR (101 MHz, CD_2Cl_2) δ 162.7, 147.9, 132.4, 123.8, 123.0, 119.3, 112.8, 77.0, 73.0, 34.2; HRMS (Orbitrap): Calcd for [$C_{10}H_9N_2O$, M + H]$^+$, 173.0709, found 173.0700.

2-(2-(Pyrrolidin-1-yl)ethyl)-1,2-dihydro-3H-indazol-3-one (25).—Yield: 96 mg (83%) as yellow fibers. ^{1}H NMR (400 MHz, CD_3OD) δ = 7.71 (d, J = 7.8, 1H), 7.53 (t, J = 7.5, 1H), 7.29 (d, J = 8.2, 1H), 7.15 (t, J = 7.3, 1H), 4.33 (broad, 2H), 3.11 (broad, 2H), 2.10 (broad, 4H), 1.95 (broad, 4H); ^{13}C{^{1}H} NMR (201 MHz, CD_3) δ = 162.3, 146.7, 132.5, 122.6, 122.1, 116.2, 112.2, 54.4, 52.5, 40.8, 22.6; HRMS (Orbitrap): Calcd for [$C_{13}H_{18}N_3O^+$, M + H]$^+$, 232.1444; found, 232.1446.

2-((Tetrahydrofuran-2-yl)methyl)-1,2-dihydro-3H-indazol-3-one (26).—Yield: 68 mg (62%) as a dark orange solid; mp: 121–123 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (s, 1H), 7.84 (d, J = 7.9, 1H), 7.48 (t, J = 7.7, 1H), 7.24–7.12 (m, 2H), 4.35–4.25 (m, 1H), 4.22–4.11 (m, 1H), 3.99–3.87 (m, 1H), 3.84–3.66 (m, 2H), 2.13–1.99 (m, 1H), 1.97–1.84 (m, 2H), 1.73–1.60 (m, 1H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 161.7, 146.5, 131.6, 123.8, 122.1, 118.7, 112.1, 78.9, 68.4, 46.7, 28.6, 25.7; HRMS (Orbitrap): Calcd for [$C_{12}H_{15}N_2O_2^+$, M + H]$^+$, 219.1128; found, 219.1124.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENTS

The authors gratefully acknowledge financial support from the National Institutes of Health (DK072517 and DK067003). Funding for NMR spectrometers was provided by National Science Foundation (DBI722538 and CHE9808183) and National Institute of Environmental Health (ES005707-13) grants. The authors thank Dr. Ping Yu (UC Davis) for assistance with NMR spectroscopy and Prof. Jared T. Shaw (UC Davis) for helpful discussions. J.S.Z. is supported by the UC Davis Tara K. Telford CF Fund, UC Davis Dissertation Year Fellowship, and R. Bryan Miller Graduate Fellowship. N.K. is supported by the UC Davis Provost's Undergraduate Fellowship.

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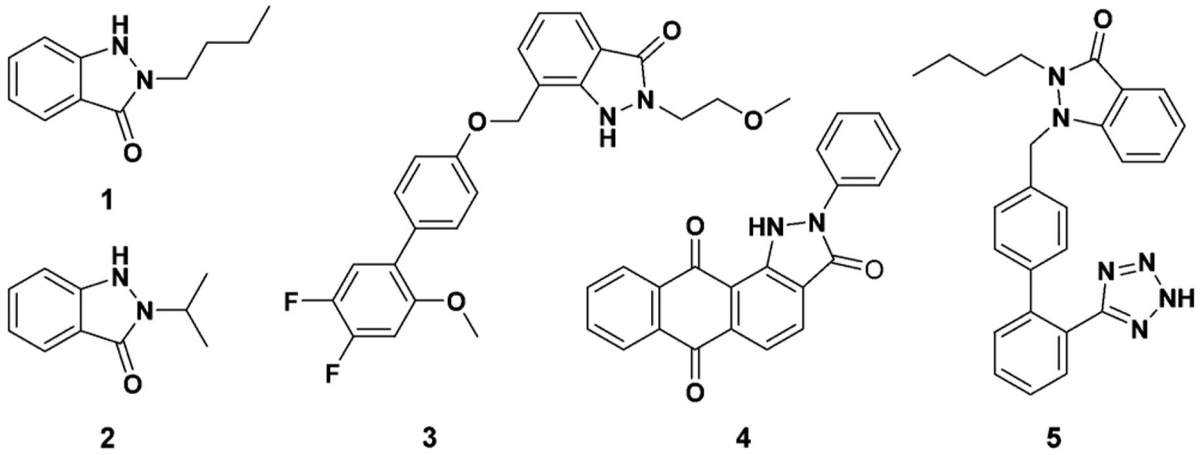
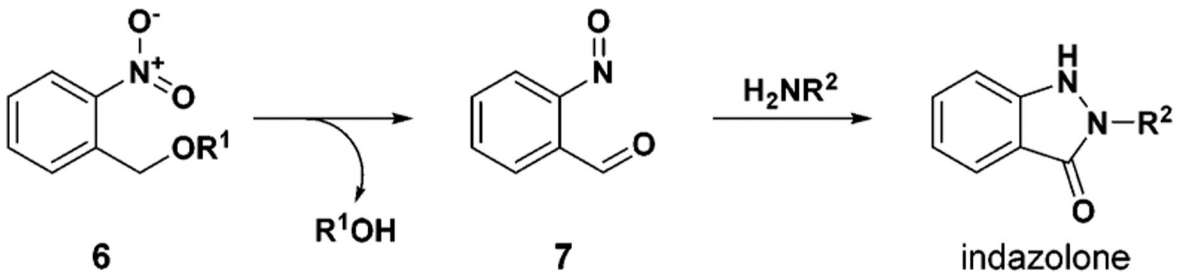
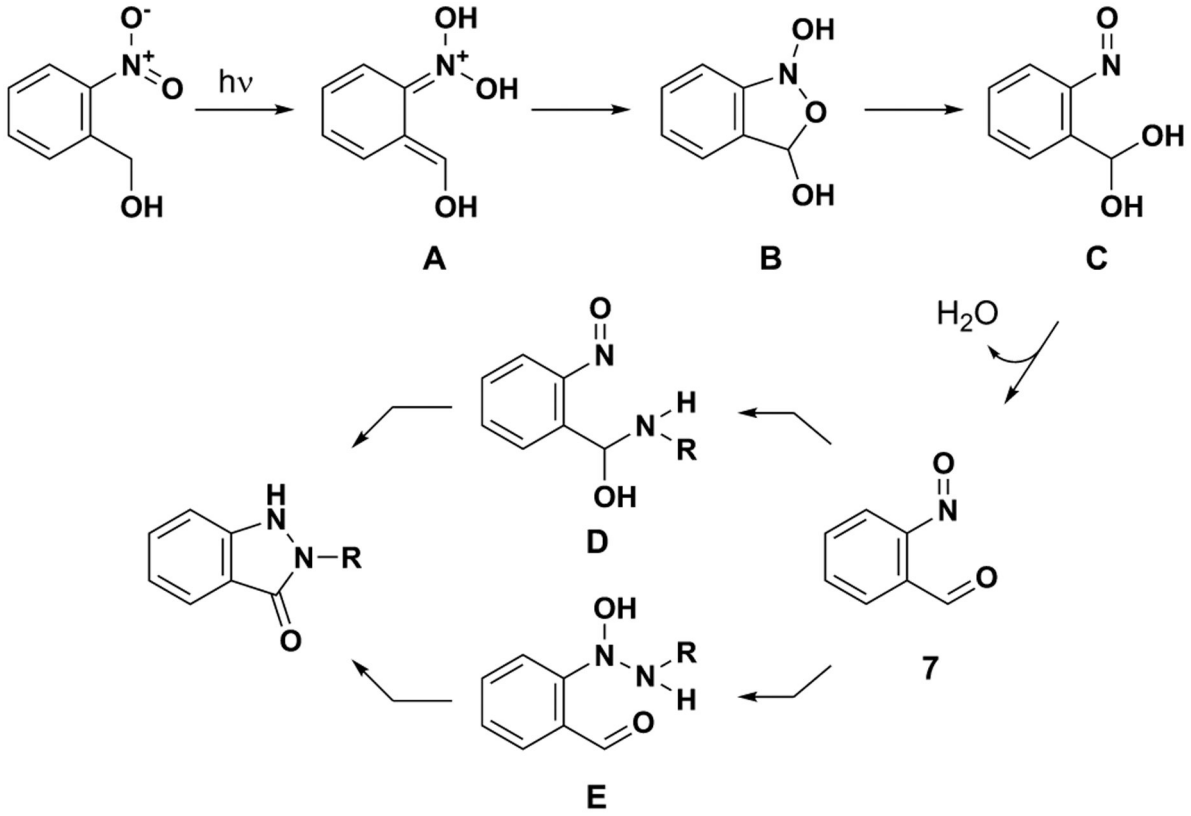


Figure 1.
Biologically relevant indazolones.



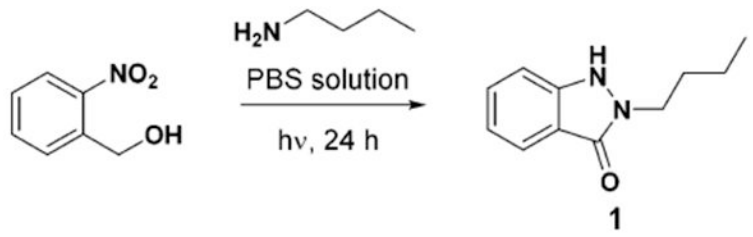
Scheme 1.
Generation of 7 *in Situ* for Indazolone Synthesis



Scheme 2.
Proposed Reaction Mechanism

Table 1.

Light Source Optimization[a]



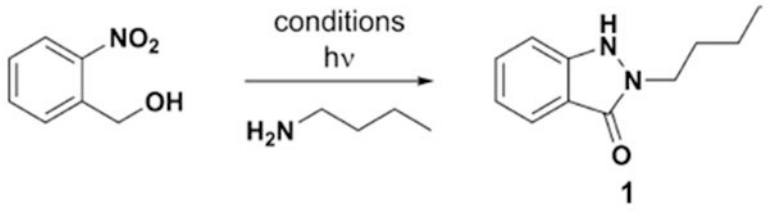
1

entry	light source	operating temp (°C)	yield (%)
1	Rayonet 2537A	r.t.	12
2	Rayonet 3000A	r.t.	32
3	Rayonet 3500	r.t.	23
4	ThermalSpa	45	59
5	500 W halogen	70	11

[a]Reaction conditions: *o*-nitrobenzyl alcohol (0.5 mmol, 1 equiv), primary amine (2.5 mmol, 5 equiv), PBS solution (6.5 mL), 24 h. Isolated yields are reported.

Table 2.

Reaction Optimization[a]



1

entry	solvent	amine (equiv)	temp (°C)	time (h)	yield (%)
1	6.5 mL of PBS	5	45	24	59
2	6.5 mL of PBS[b]	5	45	24	57
3	6.5 mL of PBS[c]	5	45	24	57
4	6.5 mL of PBS	5	30	24	66
5	6.5 mL of ^{i}PrOH	5	30	24	63
6	6.5 mL of THF	5	30	24	55
7	6.5 mL of PBS	2	30	24	62
8	6.5 mL of PBS	1	30	24	17
9	6.5 mL of PBS	0.5	30	24	n.d.[d]
10	6.5 mL of PBS	10	30	24	35
11	6.5 mL of PBS	2	30	18	56
12	10 mL of PBS	2	30	2	21[e]
13	10 mL of PBS	2	30	24	67
14	4 mL of PBS	2	30	24	62
15	2 mL of PBS	2	30	24	33
16	0.5 mL of PBS	2	30	24	19
17	neat	2	30	24	60
18	10 mL of PBS	2	0	8	48[e]
19	10 mL of PBS	2	30	8	55[e]
20[f]	10 mL of PBS	2	30	24	54[e]
21[g]	10 mL of PBS	2	30	24	50[e]

[a] Reaction carried out in a ThermalSpa photoreactor on 0.5 mmol scale in solvent unless otherwise noted. Isolated yields are reported.

[b] 5% DMSO.

[c] 10% DMSO.

[d] Complex mixture.

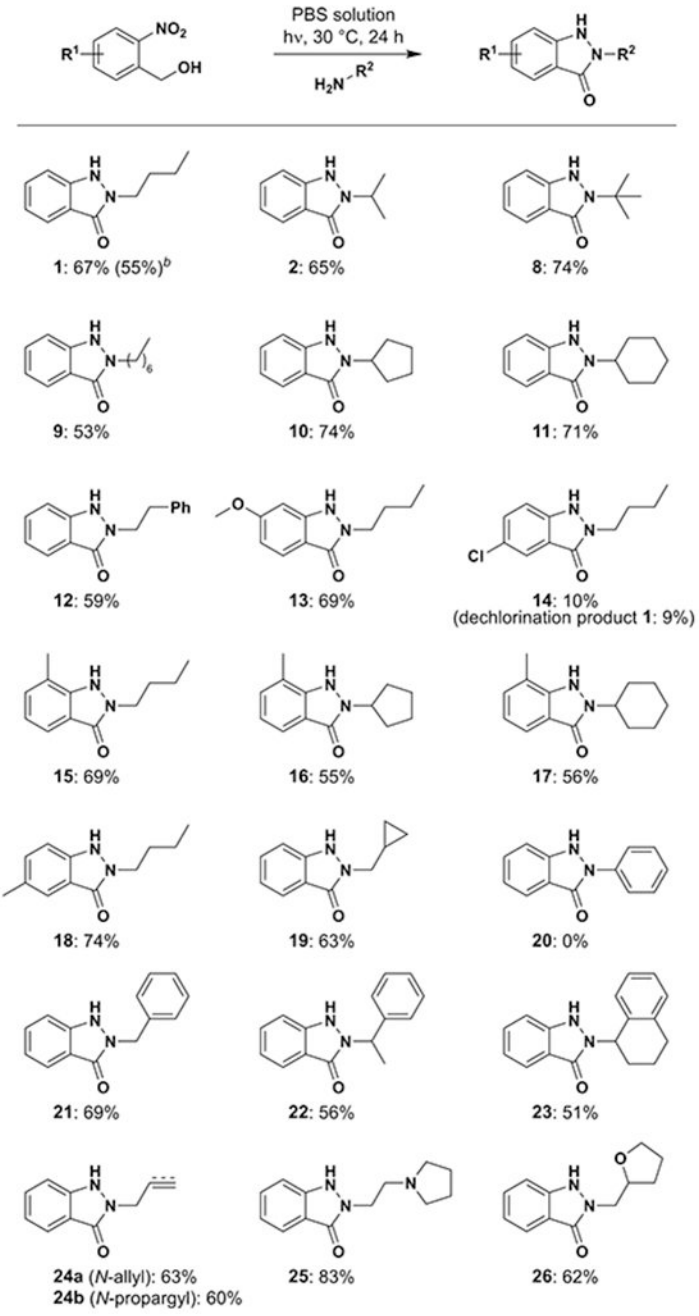
[e] Starting material recoverable.

[f] In a 20 mL Biotage microwave vial.

[g] In a 25 mL Chemglass recovery flask.

Table 3.

Indazolone Substrate Scope[a]



[a]Reaction conditions: ThermalSpa photolysis of *o*-nitrobenzyl alcohol (0.5 mmol, 1 equiv), primary amine (1.0 mmol, 2 equiv), PBS solution (10 mL), 30 °C, 24 h. Isolated yields are reported.

[b]5 mmol scale reaction.