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Supporting Information

ABSTRACT: A concise, one-step route to indazolones from primary alkyl amines and *o*-nitrobenzyl alcohols is reported. The key step in this readily scalable indazolone forming process involves base-mediated *in situ o*-nitrobenzyl alcohol \rightarrow *o*-nitrosobenzaldehyde conversion. Although this functional group interconversion is known to be useful for 2*H*-indazole synthesis, its reactivity was modulated for indazolone formation.



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Titrogen heterocycles are highly privileged structures, and due to their exceptional properties, the development of safe, efficient, and operationally convenient methods for nitrogen heterocycle synthesis is of paramount importance. Our group pioneered the development of the Davis-Beirut reaction¹ for 2*H*-indazole synthesis, and we have also employed the acid or electrophile mediated hydrolysis of 2H-indazoles to 1,2-dihydro-3H-indazolones (herein referred to as indazolones).² These N–N bond containing heterocycles have demonstrated considerable potential as therapeutic agents.¹ The construction of N-N bonds commonly involves electrochemical methods,³ oxidative protocols,⁴ or reductive conditions.⁵ Consequently, the syntheses of 2H-indazoles and indazolones are generally accomplished with the N-N bond already in place (Scheme 1); for example, through the use hydrazine and its derivatives.⁶ Hydrazines are known to present considerable hazards, and there have been attempts to improve safety at scale through flow chemistry.^{6d} There is currently no literature precedent for direct access to substituted indazolones from safe, diverse, and commercially available building blocks. Herein, we report a one-step, transition-metal-free, redox-neutral, and scalable synthesis of indazolones from relatively benign starting materials-primary alkyl amines and o-nitrobenzyl alcohols.

The *o*-nitrobenzyl moiety is known for its utility as a photolabile protecting group.⁷ However, its deprotection generates highly reactive *o*-nitrosobenzaldehyde (**2**; Scheme 2) and this is often cited as a significant disadvantage.⁷ Reactive **2** is a reagent for 2*H*-indazole synthesis, and its generation involves a straightforward photochemical transformation from *o*-nitrobenzyl alcohol **1**.⁸ That said, practical applications of **2** are limited because of poor bench stability; i.e., it is prone to air oxidation to *o*-nitrobenzoic acid.⁹ Recently, we discovered that base treatment can deprotect *o*-nitrobenzyl compounds, generating *o*-nitrosobenzaldehyde (**2**).⁹





This discovery affords a method to generate **2** *in situ* where its reactivity can then be exploited. We envisioned that the reaction of **2** with a primary amine could potentially yield both 2*H*-indazoles (4) and indazolones (5; Scheme 2) by formation of nitrosoimine **3** via pathways A and B, respectively. When **1** was heated at 100 °C with KOH and butylamine in EtOH/ H_2O (5 mL/0.5 mL), both 2*H*-indazole (4) and indazolone (5) were obtained in a 76:24 ratio. Although this 4/5 mixture was generated under these reaction conditions, pathway A was easy to shut down since secondary alcohols fail to participate in the Davis–Beirut reaction to effectively form 2*H*-indazoles;¹⁰ thus, switching the solvent to isopropanol was expected to

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Scheme 2. Reactivity of 2 with Butylamine



greatly skew product distribution in favor of **5**. Indeed, when the reaction was carried out with isopropanol instead of ethanol as the solvent, **5** was formed with complete selectivity (Table 1, entry 1).

Table 1. Optimizing Indazolone Formation



This indazolone forming process was then optimized by systemically varying the reaction conditions (Table 1). Optimal conditions employ 5 equiv of amine and 20 equiv of KOH (entry 9) at 100 °C. Further increases in amine (entry 8) or KOH (entry 10) do not increase yields. The yield of the reaction decreased sharply when suboptimal amounts of either KOH (entry 1) or amine (entry 11) were employed. Excluding either amine or water from the reaction resulted in a complex mixture (entries 4 and 5), and attempts to accelerate the reaction by elevating the temperature to 150 °C also resulted in a complex mixture (entry 15).

With these optimized reaction conditions in hand, the substrate scope of this indazolone-forming process was explored (Scheme 3). The reaction tolerates a wide range of o-nitrobenzyl alcohols and alkylamines. The scaled up (15 g of o-nitrobenzyl alcohol) synthesis of **5** presented no problems, and in fact, the reaction proceeded better than expected with an 89% yield. The reaction to form **6** was not complete after 24 h, and starting materials could be isolated. Prolonging the heating time to 48 h did not improve the yield significantly.

Scheme 3. Scope of This Indazolone Forming Reaction^a



^aReaction conditions: *o*-nitrobenzyl alcohol (0.5 mmol, 1 equiv), primary amine (2.5 mmol, 5 equiv), KOH (10 mmol, 20 equiv), ⁱPrOH/H₂O (5 mL/1.5 mL, 0.077 M), 100 °C, 24 h. Isolated yields are reported. ^bScaled up reaction from 15 g of starting alcohol. ^cRecovered starting material (57%).

However, this was not a problem for 7. Yield comparisons for 6 vs 7 and 17 vs 18 further highlight the steric demands of the nitrosoimine intermediate, which was perhaps already obvious due to the failure of isopropoxide to add to 3. Bulky *tert*-butylamine can be utilized for indazolone formation (see 8, Scheme 3), which is a significant advantage because 8 cannot be accessed through *N*-alkylation of unsubstituted indazolones.⁶ Indazolone 12 spontaneously crystallized to large cubic crystals upon routine purification, and the X-ray structure was obtained (see Scheme 3). Interestingly, the starting material for indazolones 19, 20, and 21 features a chlorine *para* to the

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nitro group and, importantly, S_NAr was not a competing side reaction-a clear advantage compared to many hydrazinebased indazolone synthetic methods.⁶ Some exceptions to the generality of this indazolone-forming protocol were found during substrate scope studies, and the rationale for these cases are given, as follows. The yield of 13 is lower than average because the electron-donating methoxy impacts the rates of base-mediated aci-nitronate anion formation and imine formation. It was disappointing to find that anilines were not effective for indazolone formation and p-anisidine only provided indazolone 15 in 17% yield. This is perhaps due to the reduced nucleophilicity of aniline vs alkylamine nitrogens. Finally, benzylic, allylic, and propargylic amines result in complex reaction mixtures that do not contain the targeted indazolones (22-24) due to side reaction or stability issues (vide infra).

Indeed, it was surprising that 22 was not isolated from the reaction of 1 + benzylamine because the reaction of 2 + benzylamine is a known route to 22 (Scheme 4). Due to the

Scheme 4. Reaction of 22 in KOH



suspicion that perhaps the product was decomposing, authentic 22 was synthesized using a literature route¹¹ and subjected to the optimized indazolone-forming reaction conditions. After 12 h, 22 did not decompose; therefore, 22-24 are presumably not formed in the reaction. Indeed, careful evaluation of the reaction mixture from 1 + benzyl-amine led to the isolation of side products 3-phenylcinnoline (25) and 2-phenylquinazoline (26) in 15% and 13% yield, respectively.

A mechanistic model for indazolone formation from 1 is formulated on the basis of the following considerations (Scheme 5). The possibility of amine attacking the nitro group (i.e., $27a \rightarrow 27b$; Scheme 5A) as the initiating step is challenging because, although intramolecular heteroatom additions to a nitro group are known,¹² intermolecular additions are less likely; for example, base-mediated H2O18 oxygen exchange at the nitro groups does not occur.¹³ Also, as a backdrop, the typical Davis-Beirut reaction (blue structures in Scheme 5B; o-nitrobenzylamine $28 \rightarrow 2H$ -indazole) proceeds by aci-nitronate anion 29 formation followed by internal oxidation of the benzylic carbon with concomitant reduction of the nitro to deliver nitrosoimine intermediate 30. Subsequent addition of primary alkoxide to the imine of 30 gives hemiaminal ether 31, and heterocyclization (i.e., N-N bond formation) gives heterocycle 32. Loss of water from 32 completes the Davis-Beirut reaction, giving the 2H-indazole product.11





In the present work (red structures in Scheme 5B), onitrobenzyl alcohol (1) is converted to *o*-nitrosobenzaldehyde (2) by heating with KOH in isopropanol. Addition of an amine to give 2-nitrosoimine $(2 \rightarrow 33 \rightarrow 30)$ is a nonproductive pathway because it is well established that the Davis-Beirut reaction fails to deliver 2H-indazoles when isopropanol is employed as the solvent.¹⁰ Indeed, when heating under KOH/ isopropanol conditions. 30 and 2 are known to be in equilibrium.¹⁴ With conversion of o-nitrosobenzaldehyde (2) to 2H-indazole blocked by the steric demands of isopropanol, the productive reaction pathway becomes hemiaminal heterocyclization $(33 \rightarrow 34)$ with subsequent dehydration and tautomerization to give the observed indazolone product. The fact that the Davis-Beirut reaction delivers the 2Hindazole product in quite high yield in methanol or ethanol (with 10% added water-optimized Davis-Beirut conditions) suggests $33 \rightarrow 34$ is less effective than $31 \rightarrow 32$. In the indazolone protocol reported here, the isopropoxy analog of 31 does not form, which causes the reaction to proceed via heterocyclization of 33 (\rightarrow 34) to deliver the indazolone product. While this mechanistic model explains the formation of 26 (Scheme 4) from reaction of 1 + benzylamine (i.e., the acidic benzylic hydrogens cause benzylic anion to intercept the nitroso moiety of 30), it does not explain the isolation of 25 (Scheme 4). This side product offers evidence for the formation of intermediate 35 (Scheme 5B), which arises from amine condensation with the nitroso moiety of 2. While 2 is expected to react kinetically with the amine via the aldehyde to form an imine, DFT calculations show that amine

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condensation at the nitroso to form a diazene is favored thermodynamically by >25 kcal/mol. With alkyl amines lacking acidic methylene hydrogens, cinnoline products like **25** are not expected to form and this might allow **35** to provide an additional pathway to indazolones [via o-(diazinyl)-benzaldehyde heterocyclization].

In summary, we have developed a concise, operationally simple method for the synthesis of indazolones from safe and readily available starting materials. Reaction insights gained from this work and the Davis–Beirut reaction were utilized for proposing the mechanistic model outlined in Scheme 5B. The key step in this transformation involves *in situ* generation of *o*nitrosobenzaldehyde. Subsequent condensation with primary amine results in N–N bond forming heterocyclization.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.or-glett.8b01655.

Experimental procedures, characterization data, ¹H and ¹³C NMR spectra, and details of quantum chemical calculations (PDF)

Accession Codes

CCDC 1838472 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

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