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N—N Bond Formation between Primary Amines and Nitrosos: Direct Synthesis of 2-Substituted Indazolones with Mechanistic Insights

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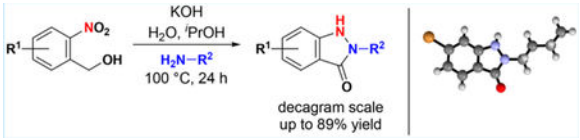
Abstract

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 → *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.

Graphical Abstract



Nitrogen 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 reaction[1] for 2*H*-indazole synthesis, and we have also employed the acid or electrophile mediated hydrolysis of 2*H*-indazoles to 1,2-dihydro-3*H*-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

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Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b01655. Experimental procedures, characterization data, ^{1}H and ^{13}C 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.

Notes

The authors declare no competing financial interest.

bonds commonly involves electrochemical methods,[3] oxidative protocols,[4] or reductive conditions.[5] Consequently, the syntheses of 2*H*-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 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).

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. 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 nitro group and, importantly, S_NAr was not a competing side reaction—a clear advantage compared to many hydrazine-based 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 suspicion that perhaps the product was decomposing, authentic **22** was synthesized using a literature route[11] 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** + benzylamine 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** → **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 H_2O^{18} 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** → 2*H*-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 2*H*-indazole product.[11]

In the present work (red structures in Scheme 5B), *o*-nitrobenzyl alcohol (**1**) is converted to *o*-nitrosobenzaldehyde (**2**) by heating with KOH in isopropanol. Addition of an amine to give 2-nitrosoimine (**2** → **33** → **30**) is a nonproductive pathway because it is well established that the Davis–Beirut reaction fails to deliver 2*H*-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 2*H*-indazole blocked by the steric demands of isopropanol, the productive reaction pathway becomes hemiaminal heterocyclization (**33** → **34**) with subsequent dehydration and tautomerization to give the observed indazolone product. The fact that the Davis–Beirut reaction delivers the 2*H*-indazole product in quite high yield in methanol or ethanol (with 10% added water-optimized Davis–Beirut conditions) suggests **33** → **34** is less effective than **31** → **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** (→ **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 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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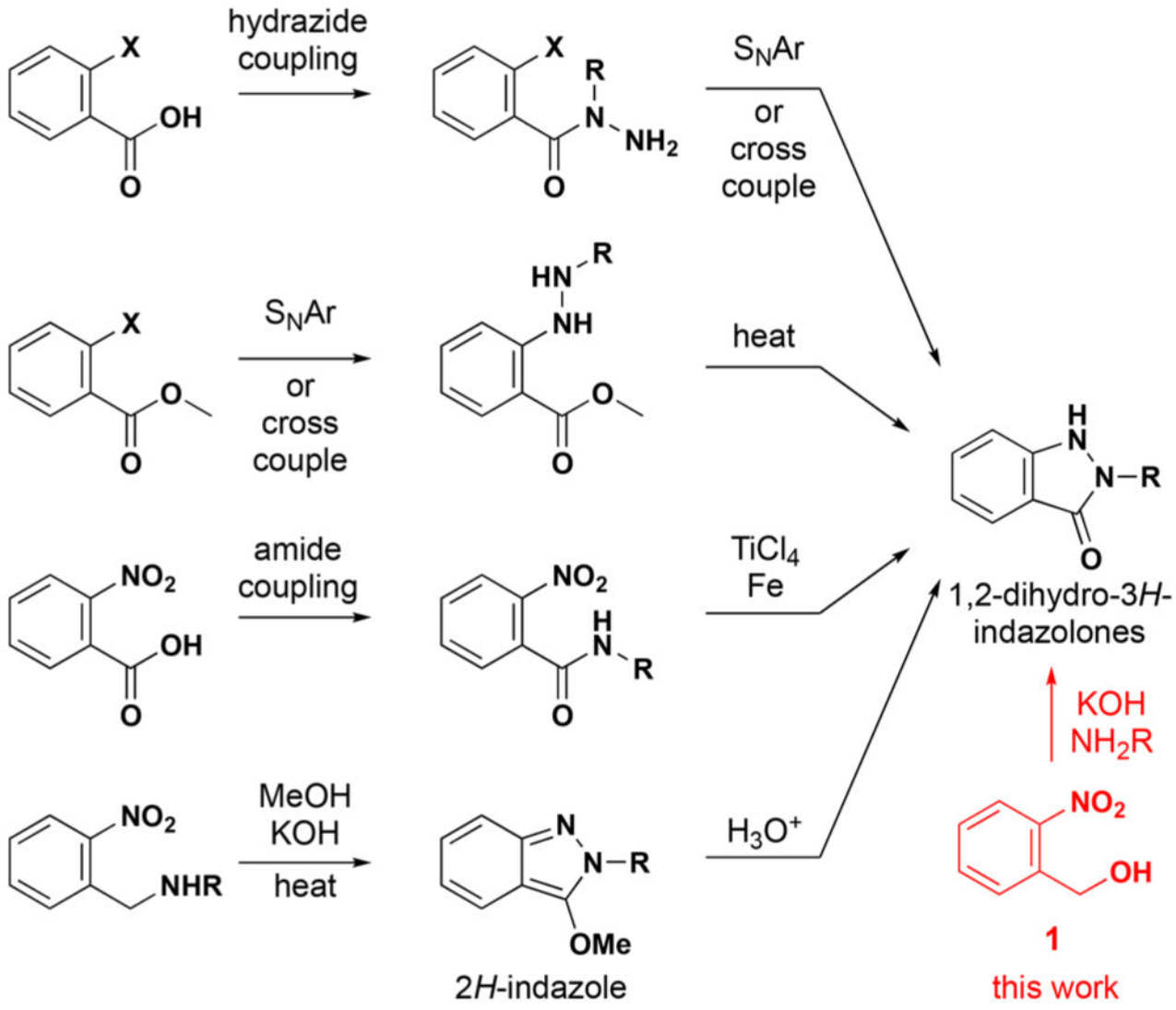
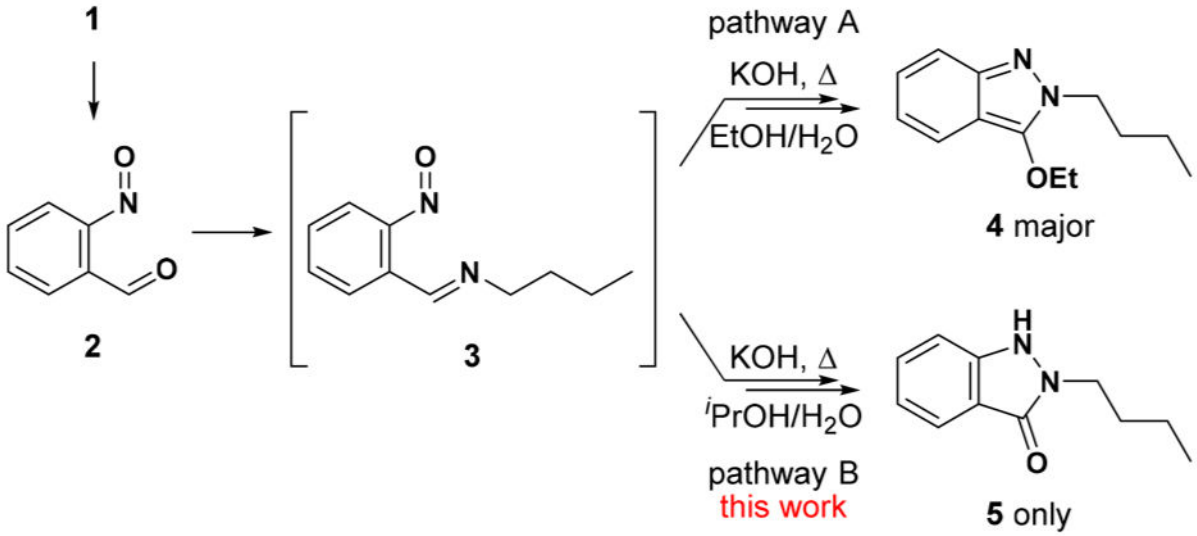
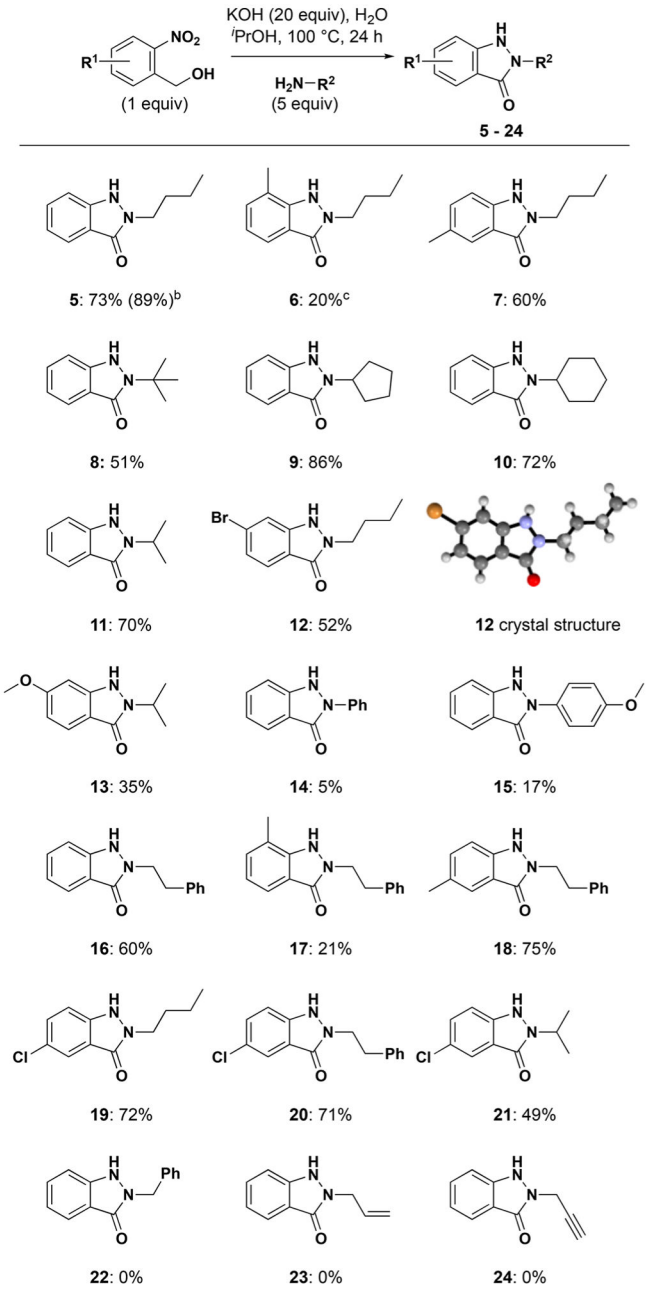


Scheme 1.
Representative Indazolone Synthetic Methods



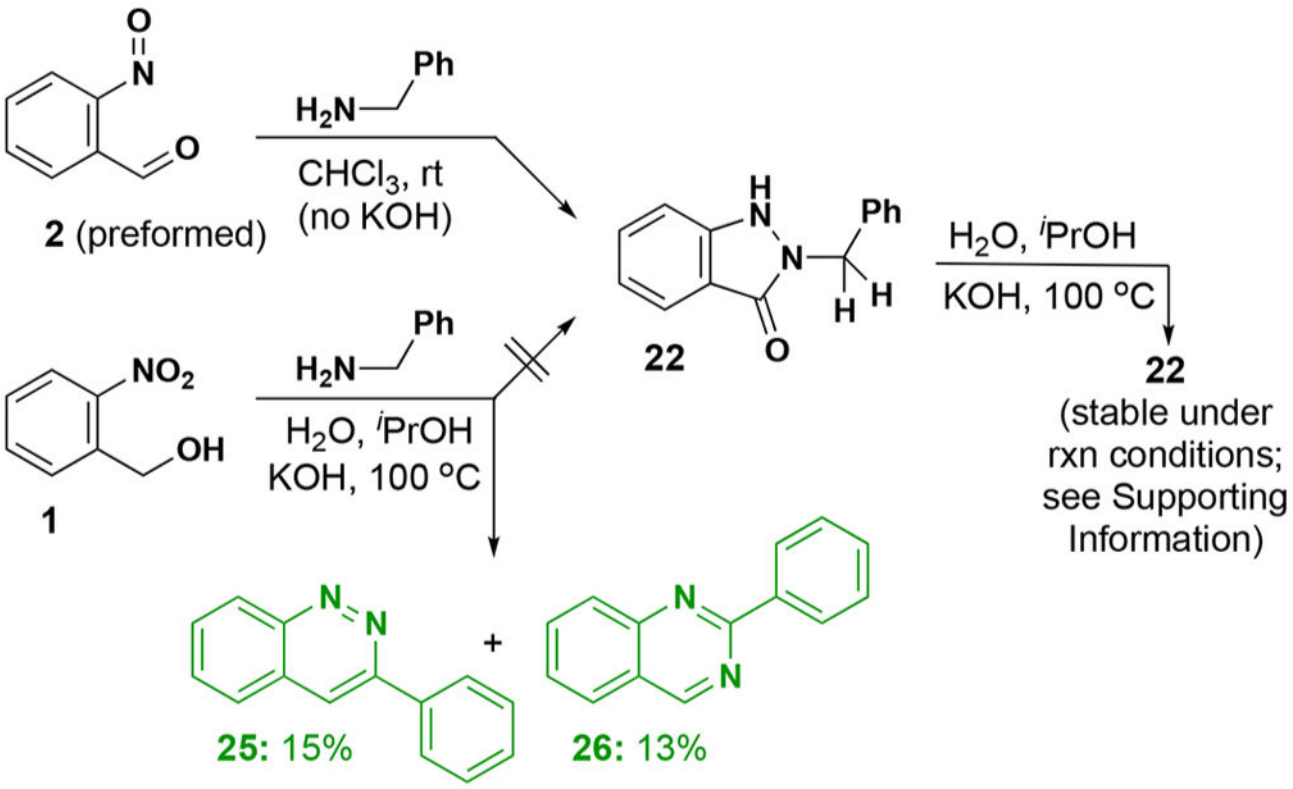
Scheme 2.
Reactivity of 2 with Butylamine



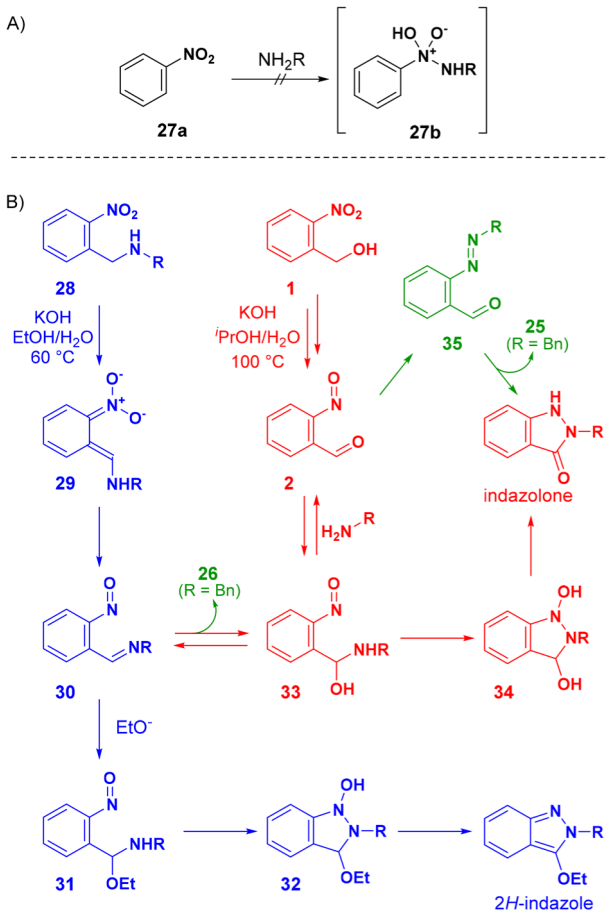
Scheme 3.

Scope of This Indazolone Forming Reaction[a]

[a]Reaction conditions: *o*-nitrobenzyl alcohol (0.5 mmol, 1 equiv), primary amine (2.5 mmol, 5 equiv), KOH (10 mmol, 20 equiv), ^{i}PrOH/H_2O (5 mL/1.5 mL, 0.077 M), 100 °C, 24 h. Isolated yields are reported. [b]Scaled up reaction from 15 g of starting alcohol. [c]Recovered starting material (57%).



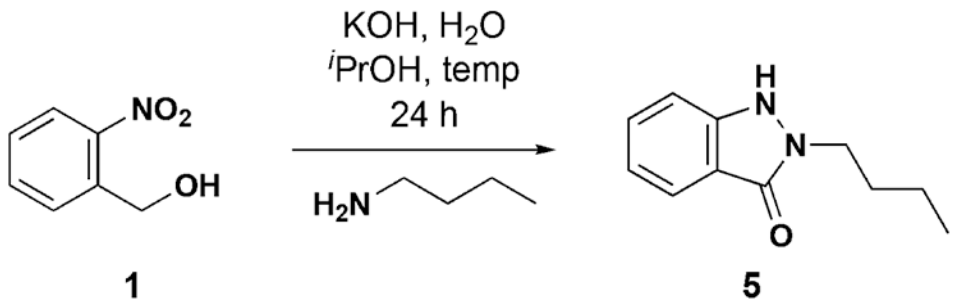
Scheme 4.
Reaction of 22 in KOH



Scheme 5.
Reaction Mechanism and Rationale

Table 1.

Optimizing Indazolone Formation



1 5

entry	KOH (equiv)	^{i}PrOH (mL)	H_2O (mL)	amine (equiv)	temp (°C)	yield (%)[a]
1	10	5	1.5	5	100	54
2	10	5	1.5	10	100	40
3	5	5	1.5	5	100	56
4	10	5	1.5	0	100	n.d.[b]
5	10	6.5	0	10	100	n.d.[b]
6	10	5	1.5	10	60	42
7	10	5	1.5	10	90	54
8	20	5	1.5	10	100	73
9	20	5	1.5	5	100	73
10	30	5	1.5	5	100	72
11	20	5	1.5	2	100	25
12	8	5	1.5	2	100	28
13	20	4.5	2	5	100	71
14	20	3.5	2.5	5	100	58
15[c]	20	5	1.5	5	150	n.d.[b]

[a] Isolated yield.

[b] Complex mixture.

[c] 2 h reaction time.