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An Oxazolo[3,2-*b*]indazole Route to 1*H*-Indazolones†

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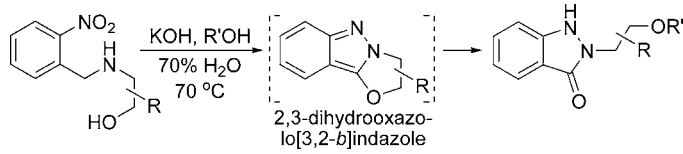
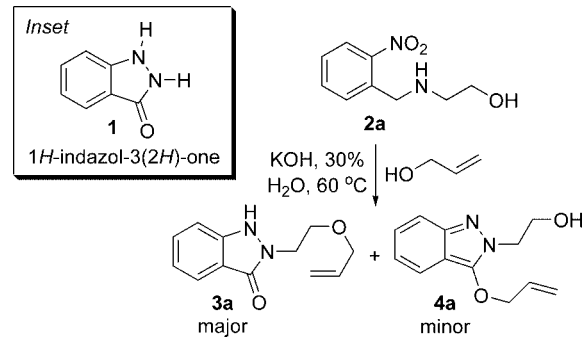
ABSTRACT



The novel heterocycle 2,3-dihydrooxazolo[3,2-*b*]indazole has been synthesized and utilized to provide easy access to 1*H*-indazolones, particularly the previously unreported 2-(2-alkoxyethyl)-1*H*-indazol-3(2*H*)-ones. Mechanistic as well as optimization and reaction scope studies are reported.

1*H*-Indazol-3(2*H*)-ones (**1**, Scheme 1 inset) are known to exhibit a wide range of biologically and pharmaceutically relevant properties and are reported to exhibit analgesic,[1] antitumor,[2] anticancer,[3] and anti-inflammatory activities.[4] Due in part to these wide ranging biological implications, a number of techniques for synthesizing indazolones have been reported.[5] These include such strategies as base-mediated ring opening of pyrazoles,[4] base-mediated intramolecular *ipso* substitution of 2-fluorobenzohydrazides,[3] PIFA-mediated intramolecular *N*-acylnitrenium trapping,[6] acid-induced rearrangement of azobenzenes,[7] *o*-azidobenzanilide treatment with thionyl chloride followed by base-mediated hydrolysis,[1] zinc/sodium hydroxide reductive cyclization of 2-nitrobenzamides,[8] copper-mediated C−N bond-forming heterocyclization of 2-halohydrazides,[9] protection of the N-2 position followed by alkylation/deprotection,[8b] CuO-catalyzed cou-

Scheme 1. Formation of 1*H*-Indazolone **3a** along with 2*H*-Indazole **4a**



† Dedicated to the memory of Professor Aaron Mills (University of Idaho), deceased May 2009.

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pling of 2-haloarylcarboxylic acids with methylhydrazine,[10] and other methods reported from this laboratory.[11]

En route to the 3-allyloxy-2*H*-indazole **4a** (Scheme 1) via our previously reported one-step heterocyclization of *o*-nitrobenzylamines (e.g., **2a**),[12] it was surprising to observe that **4a** was only a minor reaction product. As indazolones have been observed in reactions that form indazoles,[11] it was suspected that the unidentified major product could be a 1*H*-indazolone. Indeed, spectral data corroborated this suspicion, and subsequent X-ray crystallography (Figure 1) identified

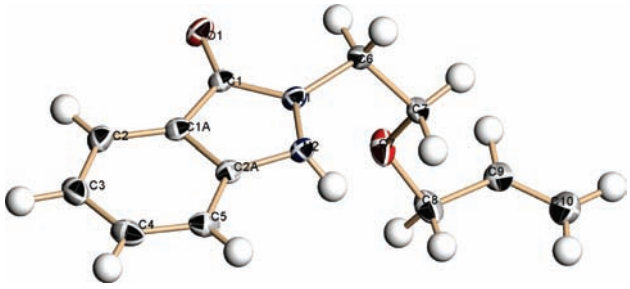
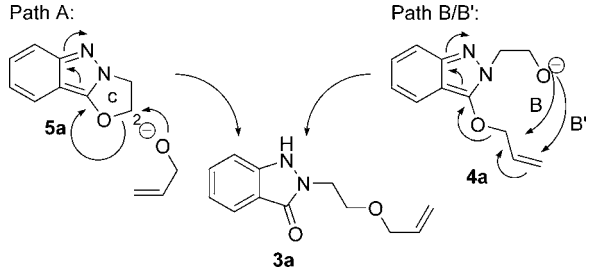


Figure 1. X-ray crystal structure of 1*H*-indazolone **3a**.

the major reaction product as 2-(2-(allyloxy)ethyl)-1*H*-indazol-3(2*H*)-one (**3a**).

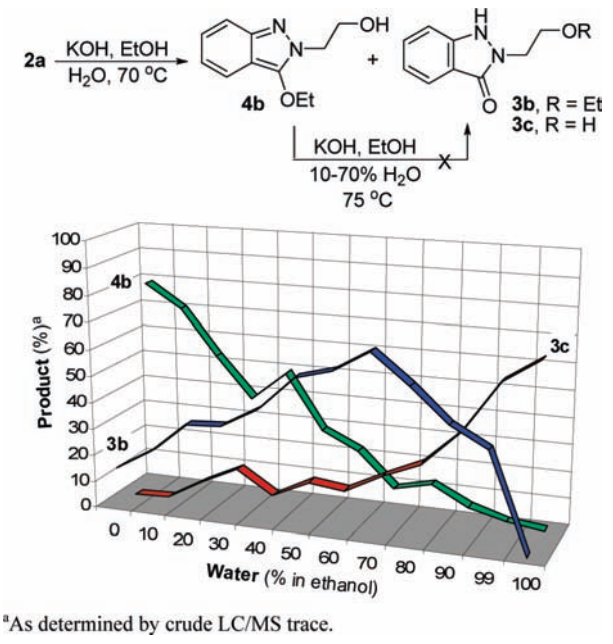
This intriguing result (**2a** → **3a**) called into question the possible reaction mechanism for the formation of indazolone **3a** and led to the consideration of two options (Scheme 2).

Scheme 2. Mechanistic Options for the Formation of 1*H*-Indazolone **3a**



Path A involves the formation of a 2,3-dihydrooxazolo[3,2-*b*]-indazole (**5a**) by intramolecular alkoxide addition with subsequent intermolecular allyloxide attack at C2 to open the C-ring and form indazolone **3a**. Path A appeared quite feasible given our recent report that "intramolecular C-ring" 2*H*-indazole formation can occur to give six-membered rings (i.e., 3,4-dihydro-2*H*-[1,3]oxazino[3,2-*b*]indazoles).[13] However, other mechanistic routes were also considered. For example, in Path B/B′, formation of the 2*H*-indazole **4a** would occur first and subsequent intramolecular S_N2 (Path B) or S_N2' (Path B′) reaction would afford the 1*H*-indazolone (**3a**).

In support of Path A, attempts were made to synthesize **5a** from **2a** under a variety of conditions, but the isolation of **5a** proved to be unsuccessful. Consequently, tactics were changed and evidence was sought to eliminate Path B/B′ as possible reaction mechanisms. The reaction of *o*-nitrobenzylamine **2a** in ethanol with no added water (Figure 2)



[a]As determined by crude LC/MS trace.

Figure 2. Effect of the concentration of water on 1*H*-indazolone formation.

resulted in formation of indazolone **3b** as a product (80%) along with the corresponding 2*H*-indazole **4b** (15%); these observations eliminated Path B′ as a viable option. Isolated and purified indazole **4b** was then resubjected to the reaction conditions for an extended period of time in varying concentrations of water (Figure 2). No conversion of **4b** to indazolone **3b** was observed, thus effectively eliminating Path B as a possible mechanism for indazolone formation.

Earlier observations demonstrated that 2*H*-indazole formation is highly dependent on the percentage of water present in the reaction;[14] this insight led us to analyze the effects of water concentration on indazolone formation. As summarized in Figure 2, a series of reactions were performed in which only the percentage of water in alcohol was varied. The clear trend was observed in which increasing the percentage of water results in a decreased yield of indazole **4b** with a corresponding increase in the yield of indazolone **3b**. These

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results are consistent with Path A in that as the percentage of alcohol present in the reaction mixture decreases, oxazoloindazole **5a** (presumed precursor of **3b**) would be formed over the competing reaction to form indazole **4b**. Optimal conditions for indazolone formation (e.g., **3b**) appear to be 70% water in alcohol. Furthermore, at particularly high concentrations of water, formation of 2-(2-hydroxyethyl)-1*H*-indazol-3(2*H*)-one (**3c**) becomes the dominant path: **3c** could arise by either hydroxide attack at C2 of **5a** or by direct addition of water during the initial heterocyclization reaction (giving **3c** instead of indazole **4b**).

In an attempt to further support Path A, 3,4-dihydro-2*H*-[1,3]oxazino[3,2-*b*]indazole (**7**) was synthesized from *o*-nitrobenzylamine **6** (Scheme 3). Indazolone **8** was not observed en route to **7**, nor was it observed when isolated and purified **7** was resubjected to the reaction conditions. Thus, although the ready formation and isolation of **7** lends credence to the formation of **5a**, its lack of reactivity vis-à-vis formation of **8** left the intermediacy of **5a** still in question.

Scheme 3. Synthesis of 3,4-Dihydro-2*H*-[1,3]oxazino[3,2-*b*]indazole (**7**)

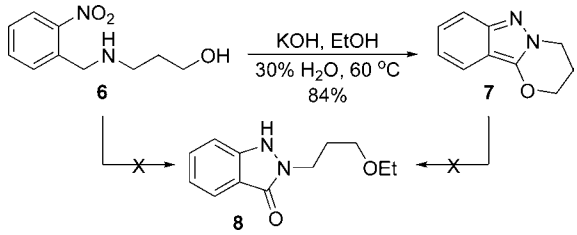
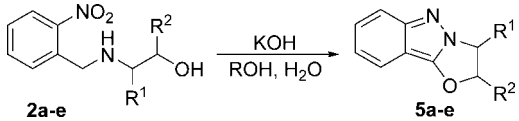


Table 1. Formation of 2,3-Dihydrooxazolo[3,2-*b*]indazoles



entry	R^1	R^2	ROH/H_2O (%)	time (h)	temp (°C)	reaction	yield (%)
1	H	H	*i*-PrOH/10	4	60	**2a** → **5a**	24[b]
2	H	H	*i*-PrOH/10	24	60	**2a** → **5a**	5[c]
3	H	Me	MeOH/70	32	70	**2b** → **5b**	30[c]
4	H	Me	EtOH/30	12	70	**2b** → **5b**	65[a]
5	H	Me	*i*-PrOH/10	32	70	**2b** → **5b**	67[a]
6	Me	H	*i*-PrOH/10	18	60	**2c** → **5c**	84[a]
7	Bn	H	*i*-PrOH/0	18	70	**2d** → **5d**	10[c]
8	Bn	H	*i*-PrOH/10	18	60	**2d** → **5d**	88[a]
9	*i*-Pr	H	*i*-PrOH/10	18	60	**2e** → **5e**	80[a]

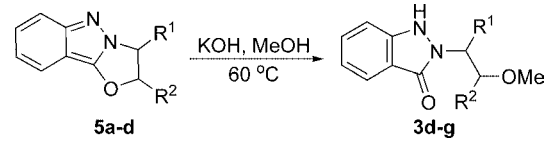
[a] Isolated yield after silica gel chromatography. [b] Reaction was prematurely evaluated. Isolated yield after silica gel chromatography; starting material was recovered in 53% yield. [c] Yield as determined by crude LC/MS trace.

At this point, the addition of R groups to the ethanolamine moiety of **2a** (see **2a** in Table 1) was investigated in an attempt to mitigate the reactivity of presumed intermediate **5a**. Indeed, we were gratified to find that modification led to 2,3-dihydrooxazolo[3,2-*b*]indazoles **5b**−**e** as the major reaction products under a variety of reaction conditions (see Table 1). These confirming results led to intensified efforts to isolate the novel parent system **5a**. Ultimately, we found that interrupting the reaction of **2a** (entry 1) prior to complete consumption of starting material resulted in the isolation of **5a** in an overall yield of 24% (53% recovery of **2a**); complete consumption of starting material **2a** resulted in only evidence of trace amounts of **5a** (LC/MS data; see Table 1, entry 1 vs entry 2).

When thus isolated 2,3-dihydrooxazolo[3,2-*b*]indazole **5a** was subjected to base-mediated methanolysis, indazolone **3d** was obtained in 97% yield (Table 2, entry 1). Similar treatment of indazoles **5c** and **5d** also proceeded smoothly to give the corresponding indazolones **3f** and **3g**. However, the steric hindrance of **5b** significantly reduced the reactivity of this indazole leading to a decreased yield of indazolone **3e**. Taken together, these results clearly support Path A as the most probable mechanistic explanation of **2a** → **3a**.

Having this support of Path A as the operative process, attention was next turned to evaluating the scope of this

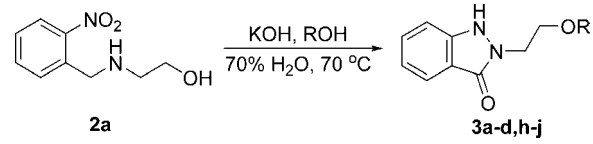
Table 2. Oxazoloindazoles React To Give Indazolones



entry	R^1	R^2	time (h)	Reaction	yield (%)[a]
1	H	H	8	**5a** → **3d**	97
2	H	Me	144	**5b** → **3e**	40
3	Me	H	14	**5c** → **3f**	92
4	Bn	H	18	**5d** → **3g**	72

[a] Isolated yield after silica gel chromatography.

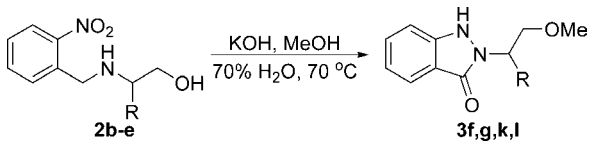
Table 3. Formation of 1*H*-Indazolones Utilizing Different Alcohols



entry	ROH	R^a	reaction	product ratio[b]
1	allyl alcohol	$CH_2CH{=}CH_2$	**2a** → **3a** + **3c**	56:22
2	ethanol	CH_2CH_3	**2a** → **3b** + **3c**	67:18
3	methanol	CH_3	**2a** → **3d** + **3c**	80:−
4	isopropyl alcohol	$CH(CH_3)_2$	**2a** → **3h** + **3c**	38:46
5	*tert*-butyl alcohol	$C(CH_3)_3$	**2a** → **3i** + **3c**	−:85
6	ethylene glycol	CH_2CH_2OH	**2a** → **3j** + **3c**	77:−

[a] **3c**; R = H. [b] Yield determined by crude LC/MS trace.

Table 4. Formation of 1*H*-Indazolones Utilizing Different *o*-Nitrobenzylamines



entry	stereochemistry	R	reaction	yield (%)[a]
1	S	CH_3	**2b** → **3f**	89[a]
2	R	CH_2Ph	**2c** → **3g**	48[a]
3	S	$CH(CH_3)_2$	**2d** → **3k**	60[b]
4	R	$CH_2CH(CH_3)_2$	**5e** → **3l**	59[b]

[a] Yield determined by crude LC/MS trace. [b] Isolated yield after silica gel chromotography.

transformation under one-pot reaction conditions. As detailed in Table 3, *o*-nitrobenzylamine **2a** was subjected to heterocyclization/alcoholysis with a variety of alcohols employing the optimal conditions for indazolone formation (70% water in alcohol). Primary alcohols performed well, delivering indazolones **3a**, **3b**, **3d**, and **3j** in good yield, while isopropyl alcohol (Table 3, entry 4) delivered **3h** in decreased yield. *tert*-Butyl alcohol (Table 3, entry 5) gave only trace amounts of alkoxide-incorporated indazolone, instead favoring formation of 2-(2-hydroxyethyl)-1*H*-indazol-3(2*H*)-one (**3c**). With these non-nucleophilic alcohols indazolone **3c** most probably occurs via a mechanism similar to Path A, but indazole **5a** is opened by hydroxide rather than alkoxide.

It was further demonstrated that a variety of *o*-nitrobenzylamines can successfully undergo indazolone formation (Table 4). From *o*-nitrobenzylbromide, several new ethanolamine-substituted *o*-nitrobenzylamines were prepared from amino acid derived aminoalcohols. Each of these 2-(2-nitrobenzylamino)alkan-1-ols underwent heterocyclization/alcoholysis to give indazolones **3f**, **3g**, **3k**, and **3l** using methanol as a solvent.

In summary, a new method for the formation of indazolones has been demonstrated. This unique process works with a variety of alcohols and *o*-nitrobenzylamines. Evidence suggests that these reactions proceed via the intermediacy of a 2,3-dihydrooxazolo[3,2-*b*]indazole. A study of related indazoles and their reactivity with various nucleophiles is currently underway and will be reported in due course.

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Supporting Information Available: Experimental procedures and characterization data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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