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A Versatile New Synthetic Route to 1*N*-Hydroxyindazoles

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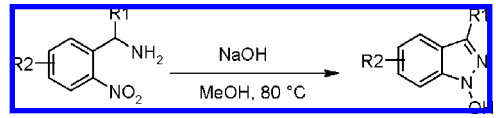
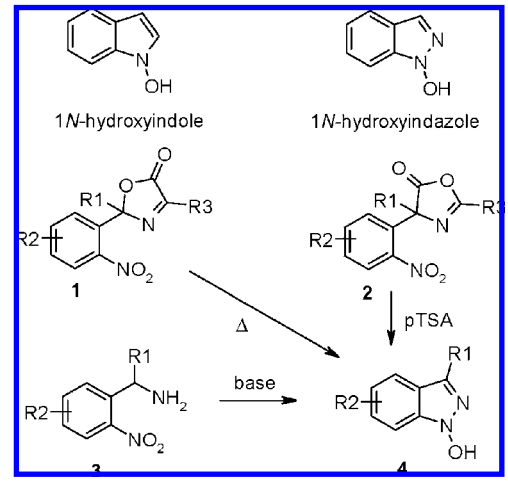
ABSTRACT



A new and versatile cyclization reaction affording rare 1*N*-hydroxyindazoles is presented. Treatment of 2-nitrobenzylamines with methanolic sodium hydroxide furnishes 1*N*-hydroxyindazoles regioselectively and in high yield. The reaction tolerates a range of functional groups and electronic effects.

A number of bioactive natural products containing the unusual 1*N*-hydroxyindole motif (Scheme 1) have recently been described. Discovery of the antitumor alkaloids stephacidin B,[1] coproverdine,[2] and the potent antibiotic nocathiacin I[3] has prompted development of a wealth of new synthetic methods facilitating access to this unusual indole oxidation level.[4]

Scheme 1. Synthesis of 1*N*-Hydroxyindazoles[a]



[a] Known thermal or acid-catalyzed rearrangement of isoxazolone derivatives and our postulated base-catalyzed cyclization of 2-nitrobenzylamines.

In sharp contrast, the closely related 1*N*-hydroxyindazole system is much less studied. Viable access to this very rare class of compounds is achieved only by thermal or acid-catalyzed rearrangement of oxazolone intermediates **1** and

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(1) Qian-Cutrone, J.; Huang, S.; Shu, Y.-Z.; Vyas, D.; Fairchild, C.; Menendez, A.; Krampitz, K.; Dalterio, R.; Khlor, S. E.; Gao, Q. *J. Am. Chem. Soc.* **2002**, *124*, 14556.

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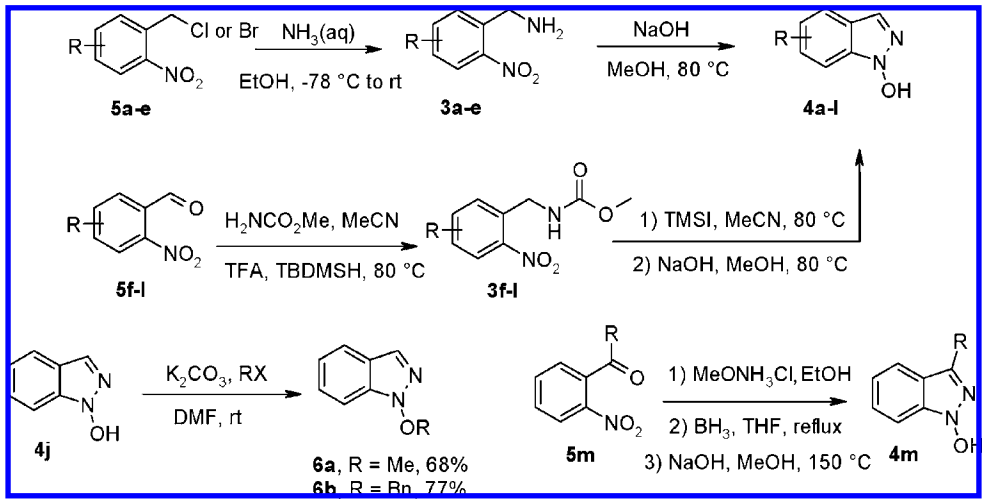
Scheme 2. Conversion of Benzylic Halides **5a**−**e**, Benzaldehydes **5f**−**l**, or Acetophenones **5m** into 1*N*-Hydroxyindazoles **4a**−**m**



2.[5] Unfortunately, unfavorable atom economy and lengthy synthetic sequences required for construction of isoxazolone intermediates detract from the synthetic utility of these approaches.

Despite the paucity of useful synthetic methods, 1*N*-hydroxyindazole derivatives have nonetheless been claimed in patent applications as kinase inhibitors,[6] peptide-coupling reagents,[7] optoelectronic materials, and dye additives.[8] Recently related *N*-hydroxypyrazole-containing compounds were found to display potent antitumor activity in rodent models.[9]

Our interest in N−N bond-forming processes that involve interaction of aromatic nitro groups with ortho-substituents[10] led us to speculate that intramolecular base-catalyzed condensation of 2-nitrobenzylamine derivatives **3** could provide a valuable and concise route to 1*N*-hydroxyindazoles **4**. Importantly, 2-nitrobenzylamines **3** were expected to be conveniently prepared from readily available starting materials (Scheme 2). Formal dehydrations between aromatic nitro groups and aliphatic primary amine-containing side chains are to our knowledge unknown. However, related base-promoted condensations in systems containing secondary amine side chains were recently described during the course of this study.[11]

Treatment (Scheme 2) of 2-nitrobenzyl halides **5a**−**d** with ammonia furnished the corresponding amines **3a**−**d** in satisfactory yields (56−83%; see Table 1). We were delighted to find that these were smoothly cyclized on exposure to hot methanolic sodium hydroxide. The products **4a**−**d**, whose NMR spectra and HRMS data were consistent with a 1*N*-hydroxyindazole structure, were obtained in good to excellent yields (75−95%; see Table 1). To avoid the potentially problematic isolation of amino acid derivative **3e**, a one-pot amination−cyclization procedure was developed. After amination, the crude reaction mixture was evaporated and then treated with methanolic sodium hydroxide to give the indazole **4e** directly and in good overall yield (74% from **5e**). That several useful functionalities capable of undergoing further manipulation were readily incorporated into the final products (**4a**,**c**,**e**) was particularly pleasing.

To increase the scope and utility of this novel cyclization process (Scheme 2), we then incorporated a range of commercial 2-nitrobenzaldehydes as starting materials **5f**−**l**. Reductive amination of these substrates with methyl carbamate was anticipated to afford 2-nitrobenzyl carbamates **3f**−**l**. We hoped that treatment of carbamates **3f**−**l** with base would result in concomitant deprotection and cyclization, providing hyroxyindazoles in one pot. In practice, treatment of the carbamates **3f**−**l** with methanolic sodium hydroxide led only to formation of complex mixtures. Fortunately, we found that trimethylsilyl iodide (TMSI) was effective in unmasking the amine cleanly, and after acid−base workup, they could be cyclized directly.

Thus, carbamates **3f**−**l** were prepared (Table 1) by reductive amination of 2-nitrobenzaldehydes **5f**−**l** with methyl carbamate and *tert*-butyldimethylsilane (TBDMSH).[12]

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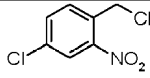
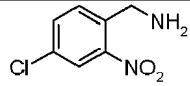
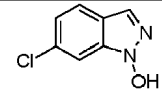
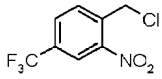
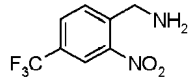
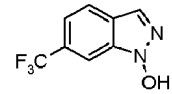
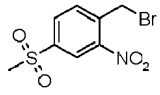
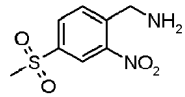
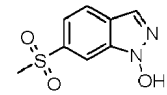
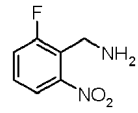
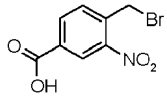
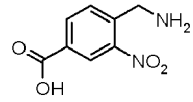
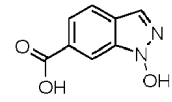
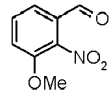
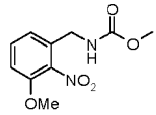
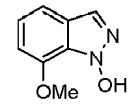
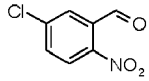
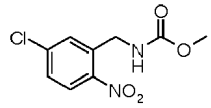
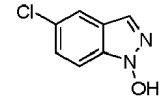
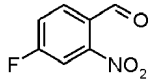
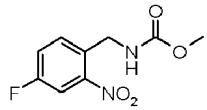
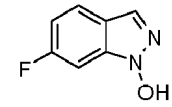
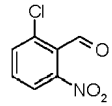
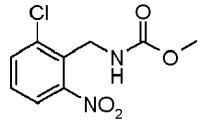
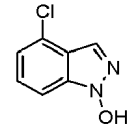
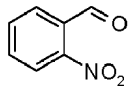
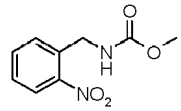
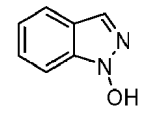
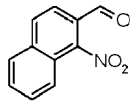
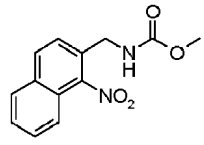
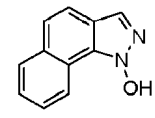
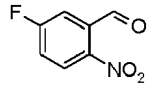
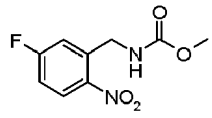
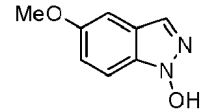
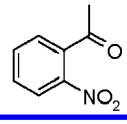
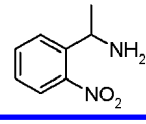
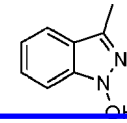
Table 1. Synthesis of 1*N*-Hydroxyindazoles **4a**−**m** from 2-Nitrobenzyl Halides **5a**−**e**, 2-Nitrobenzaldehydes **5f**−**l**, or 2-Nitroacetophenone **5m**

entry	starting material **5**	amine or carbamate **3**	yield %[a]	1*N*-hydroxyindazole **4**	yield %[a]
a			83[b]		85
b			56[b]		94
c			69		87
d			69		75
e			Not Isolated		74 from **5e**
f			81[c]		75
g			62[c]		78
h			65[c]		80
i			33[c]		70
j			95[c]		97
k			12[c]		70
l			20[c]		75
m			41		68

[a] All yields are isolated yields. [b] Used as trifluoroacetate salt. [c] Converted to amine hydrochloride salt and cyclized directly.

Deprotection and cyclization furnished the *N*-hydroxy compounds **4f**−**l** in 70−97% yields.

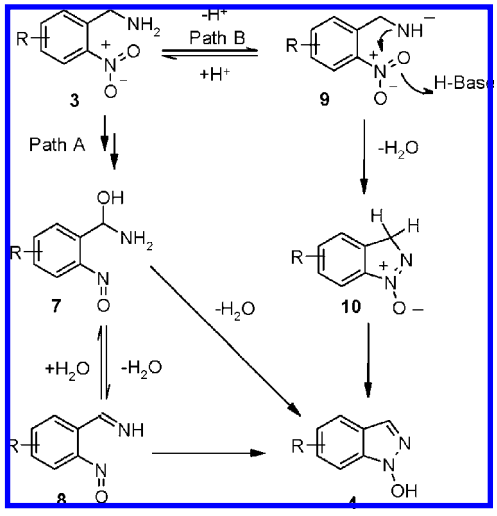
Cyclization of substrates containing both electron withdrawing or donating substituents was well tolerated, and little

detrimental effect was observed with substitution patterns containing proximal groups to either nitro- or aminomethyl moieties (entries **4f**,**i**,**k**). Interestingly, the fluorobenzyl carbamate **3l** was converted into 1*N*-hydroxy-5-methoxyindazole **4l**. This is readily explained by nucleophilic aromatic substitution of fluoride by methoxide prior to, or during, cyclization. No analogous substitution was observed with chlorobenzyl carbamate **3g**, which afforded the expected chloroindazole **4g** in high yield.

Treatment of the parent hydroxyindazole **4j** with methyl iodide or benzyl bromide and potassium carbonate in DMF (Scheme 2) afforded the *O*-methyl and *O*-benzyl derivatives **6a** and **6b**, respectively. The CH_3 and CH_2 carbon signals resonate at 64.9 and 80.0, respectively, which is consistent with the formation of the O-alkylated products.[13] Furthermore, an NMR study on **6a** revealed an NOE between the *O*-methyl substituent and the ring proton at C7 in good agreement with the proposed structure.

Last, we investigated whether α-substituted benzylamines would also be cyclized, allowing convenient access to 3-substituted 1*N*-hydroxyindazoles. The acetophenone **5m** was converted into the known α-methylbenzylamine **3m**.[14] However, treatment of the latter with methanolic sodium hydroxide under our standard conditions failed to give appreciable quantities of the desired product **4m**, even after heating at 80 °C for 48 h. Heating the reaction mixture at 150 °C for 30 min, using microwave irradiation, gave **4m** in good yield (68%), illustrating the potential benefits of microwave heating for this type of cyclization process.

Scheme 3. Possible Mechanistic Pathways for Formation of 1*N*-Hydroxyindazoles **4** from 2-Nitrobenzylamines **3**



Mechanistically (Scheme 3), cyclization is readily explained by minor adaptation of a mechanism recently proposed by Kurth.[11] Oxygen transfer from nitro to the benzylic position followed by collapse of the resulting aminal **7** affords a nitroso-imine **8**, which is then poised to cyclize under basic conditions, affording a 1*N*-hydroxyindazole **4**.[15] Alternatively, the aminal **7** could cyclize directly and then dehydrate to give the product. In path B, initial base-catalyzed deprotonation of the amine, followed by condensation with the pendant nitro group results in formation of an azoxy intermediate **10**, which can then tautomerize to give the *N*-hydroxyindazole **4** directly.[16] While both mechanisms are consistent with the decreased reactivity observed in cyclization of compound **3m**, the strongly deactivating effect of benzylic substitution probably favors a mechanism similar to that outlined in path A. Other possibilities involving electron transfer or pericyclic processes cannot be ruled out.

In summary, we have developed a useful and concise synthesis of rare 1*N*-hydroxyindazoles. This compound class has received comparatively little attention when compared to related 1*N*-hydroxyindoles or 1*N*-hydroxybenzotriazole. The route is operationally simple and employs readily accessible starting materials which can accommodate a range of synthetically useful functionalities. Although the cyclization conditions are not particularly mild, the route nicely complements the existing acid-catalyzed or thermal methods which have been previously described.[5] Use of microwave heating, while presently not fully explored, is expected to further enhance the utility of this methodology.

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

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(14) Salerno, C. P.; Magde, D.; Patron, A. P. *J. Org. Chem.* **2000**, *65*, 3971.
(15) Interestingly, Kurth's study employed N-substituted secondary 2-nitrobenzylamines (**3**; NHR for NH_2) as substrates these give 3-alkoxy-2*H*-indazoles. For a related process, see: Hurst, J.; Wibberley, D. G. *J. Chem. Soc. C* **1968**, 1487.
(16) For potentially related processes, see for example: (a) ref 11c. (b) Arndt, F. *Chem. Ber.* **1913**, *46*, 3522. (c) Muth, C. W.; Abraham, N.; Linfield, M. L.; Wotring, R. B.; Pacovsky, E. A. *J. Org. Chem.* **1960**, *25*, 736.