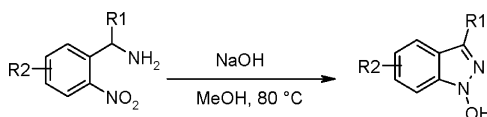


A Versatile New Synthetic Route to  
1*N*-HydroxyindazolesFredrik Lehmann,<sup>†,§</sup> Tobias Koolmeister,<sup>†</sup> Luke R. Odell,<sup>‡</sup> and Martin Scobie<sup>\*,†,¶</sup>*Biovitrum AB, Discovery Research, 112 76 Stockholm, Sweden and Department of Medicinal Chemistry, Uppsala Biomedical Center, Uppsala University, 751 23, Uppsala, Sweden*

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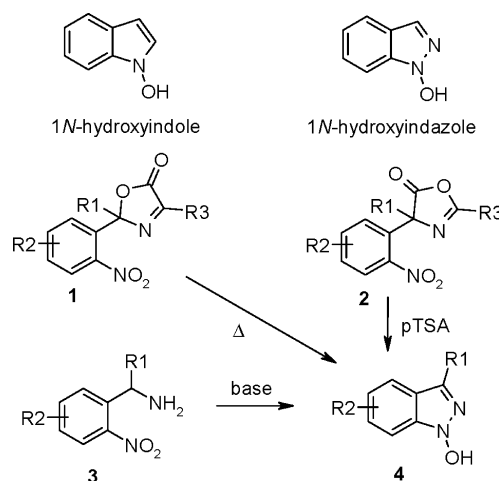
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## ABSTRACT



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,<sup>1</sup> coproveridine,<sup>2</sup> and the potent antibiotic nocathiacin I<sup>3</sup> has prompted development of a wealth of new synthetic methods facilitating access to this unusual indole oxidation level.<sup>4</sup>

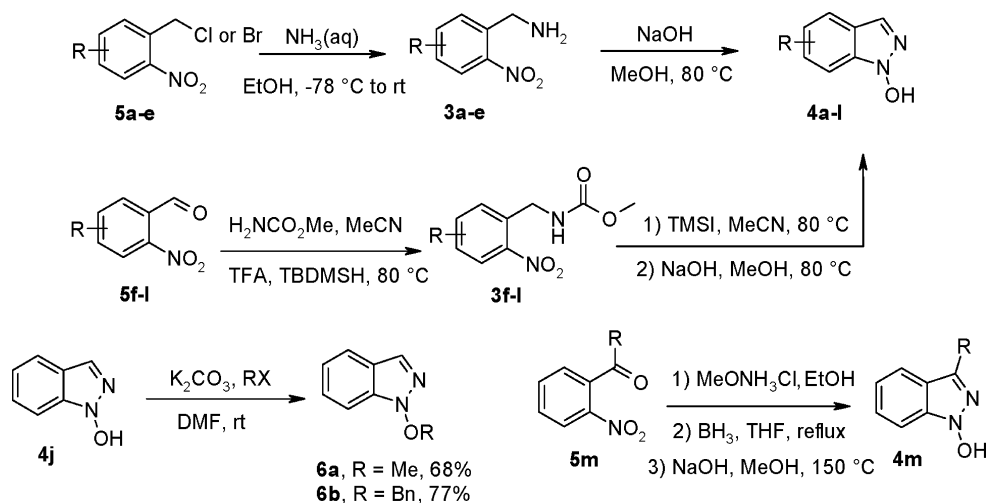
Scheme 1. Synthesis of 1*N*-Hydroxyindazoles<sup>a</sup>

<sup>a</sup> Known thermal or acid-catalyzed rearrangement of isoxazalone 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 oxazalone intermediates **1** and

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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.<sup>5</sup> 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,<sup>6</sup> peptide-coupling reagents,<sup>7</sup> optoelectronic materials, and dye additives.<sup>8</sup> Recently related *N*-hydroxypyrazole-containing compounds were found to display potent antitumor activity in rodent models.<sup>9</sup>

Our interest in N–N bond-forming processes that involve interaction of aromatic nitro groups with ortho-substituents<sup>10</sup> 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.<sup>11</sup>

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 hydroxyindazoles 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).<sup>12</sup>

(5) Steglich, W.; Kubel, B.; Gruber, C. *Chem. Ber.* **1973**, *106*, 2870. (b) D'Anello, M.; Erba, E.; Gelmi, M. L.; Pocar, D. *Chem. Ber.* **1987**, *121*, 67.

(6) Bhagwat, S. S.; Satoh, Y.; Sakata, S. T.; Buhr, C. A.; Albers, R.; Sapienza, J.; Plantevin, V.; Chao, Q.; Sahasrabudhe, K.; Ferri, R. U.S. Patent 2004/127536. (b) Hagihara, M.; Komori, K.; Sunamoto, H.; Nishida, H.; Matsugi, T.; Nakajima, T.; Hatano, M.; Kido, K.; Hara, H. WO 2005/035506. (c) Wei, C. C.; Huang, P.; Xia, Y. WO 2004/014368.

(7) Horiki, K.; Murakami, A.; Chomei, N. *React. Polym.* **1987**, *6*, 127.

(8) (a) Ishikawa, T.; Elman, J. F.; Massa, D. J.; Montbach, E. N.; Teegarden, D. M. U.S. Patent 2005/089676. (b) Lim, M. U.S. Patent 2006/0156486. (c) Glenn, R. W.; Lim, M.; Murphy, B. P. U.S. Patent 2006/042026.

(9) Wenckens, M.; Jakobsen, P.; Vedso, P.; Huusfeldt, P. O.; Gissel, B.; Barfoed, M.; Brockdorff, B. L.; Lykekesfeldt, A. E.; Begtrup, M. *Bioorg. Med. Chem. Lett.* **2003**, *11*, 1883.

(10) (a) Slevin, A.; Koolmeister, T.; Scobie, M. *Chem. Commun.* **2007**, *24*, 2306. (b) Scobie, M.; Tennant, G. *Chem. Commun.* **1994**, *21*, 2451. (c) Scobie, M.; Tennant, G. *Chem. Commun.* **1993**, *23*, 1756.

(11) (a) Mills, A. D.; Nazer, M. Z.; Haddadin, M. J.; Kurth, M. J. *J. Org. Chem.* **2006**, *71*, 2687. (b) Butler, J. D.; Solano, D. M.; Robins, L. I.; Haddadin, M. J.; Kurth, M. J. *J. Org. Chem.* **2008**, *73*, 234. (c) Bouillion, I.; Zajicek, J.; Pudelova, N.; Krchnak, V. *J. Org. Chem.* **2008**, *73*, 9027.

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

<sup>a</sup> All yields are isolated yields. <sup>b</sup> Used as trifluoroacetate salt. <sup>c</sup> 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<sub>3</sub> and CH<sub>2</sub> carbon signals resonate at 64.9 and 80.0, respectively, which is consistent with the formation of the *O*-alkylated products.<sup>13</sup> 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  $\alpha$ -substituted benzylamines would also be cyclized, allowing convenient access to 3-substituted 1*N*-hydroxyindazoles. The acetophenone **5m** was converted into the known  $\alpha$ -methylbenzylamine **3m**.<sup>14</sup> 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.

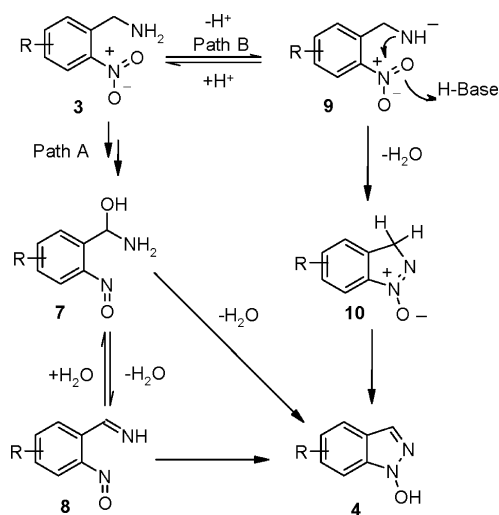
Mechanistically (Scheme 3), cyclization is readily explained by minor adaptation of a mechanism recently proposed by Kurth.<sup>11</sup> Oxygen transfer from nitro to the benzylic position followed by collapse of the resulting aminal **7** affords a nitroso-imine **8**, which is then poised to cyclize under basic conditions, affording a 1*N*-hydroxyindazole **4**.<sup>15</sup> 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.<sup>16</sup> 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.<sup>5</sup> 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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**Scheme 3.** Possible Mechanistic Pathways for Formation of 1*N*-Hydroxyindazoles **4** from 2-Nitrobenzylamines **3**



(12) (a) Lehmann, F.; Scobie, M. *Synthesis* **2008**, 11, 1679. (b) Dube, D.; Scholte, A. A. *Tetrahedron Lett.* **1999**, 40, 2295.

(13) Vedso, P.; Begtrup, M. *J. Org. Chem.* **1995**, 60, 4995.

(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<sub>2</sub>) 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.