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A Practical, Metal-Free Synthesis of 1*H*-Indazoles

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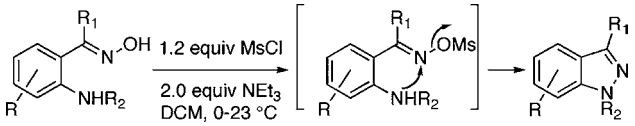
ABSTRACT



The synthesis of 1*H*-indazoles is achieved from *o*-aminobenzoximes by the selective activation of the oxime in the presence of the amino group. The reaction occurs with a variety of substituted *o*-aminobenzoximes using a slight excess of methanesulfonyl chloride and triethylamine at 0–23 °C and is amenable to scale-up. The synthesis of 1*H*-indazoles under these conditions is extremely mild compared with previous synthetic approaches and affords the desired compounds in good to excellent yields.

The diverse pharmacological properties exhibited by 1*H*-indazoles have sparked the emergence of novel methods toward their synthesis. The use of 1*H*-indazoles as anti-cancer, -inflammatory, and -microbial agents has been documented in recent patents and publications.[1] Although many new methodologies have been reported to synthesize 1*H*-indazoles, a mild, general method still remains an ongoing challenge.

Classical routes to 1*H*-indazoles typically require harsh or inconvenient conditions such as diazotizations and nitrosation reactions.[2] The large number of recently published methods that aim to improve the traditional routes to 1*H*-indazole signifies the importance of these compounds.

Condensation reactions of *o*-fluorobenzaldehydes and excess hydrazine provide a metal-free synthesis of 1*H*-indazoles; however, the method is limited in scope and requires the use of the *o*-fluoroarenes.[3] The palladium-catalyzed synthesis of 1*H*-indazoles from aryltosylhydrazones requires high catalyst loadings and only provides tosyl-protected indazoles.[4] Other recent metal-catalyzed routes to 1*H*-indazoles employ low catalyst loadings of CuO but give *N*-methylindazoles in moderate yields,[5] and an iron-catalyzed route to 1*H*-indazoles from *o*-nitrooximes requires 150 °C and a high pressure of CO.[6] Most recently, Yamamoto reported the synthesis of 1*H*-indazoles via the 1,3-dipolar cycloaddition of arynes and diazoalkanes.[7] We report a simple, metal-free synthesis of substituted 1*H*-indazoles that occurs from readily available aminobenzoximes under mild conditions.

Recently, practical syntheses of tertiary amines have been developed using electrophilic amination strategies involving

(1) (a) Cerecetto, H.; Gerpe, A.; Gonzalez, M.; Aran, V. J.; Ocariz, C. O. *Mini-Rev. Med. Chem.* **2005**, *5*, 869. (b) Feng, Y.; Cameron, M. D.; Frackowiak, B.; Griffin, E.; Lin, L.; Ruiz, C.; Schroeter, T.; LoGrasso, P. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 8, 2355. (c) Goodman, K. B.; Cui, H.; Dowdell, S. E.; Gaitanopoulos, D. E.; Ivy, R. L.; Sehon, C. A.; Stavenger, R. A.; Wang, G. Z.; Viet, A. Q.; Xu, W.; Ye, G.; Semus, S. F.; Evans, C.; Fries, H. E.; Jolivette, L. J.; Kirkpatrick, R. B.; Dul, E.; Khandekar, S. S.; Yi, T.; Jung, D. K.; Wright, L. L.; Smith, G. K. *J. Med. Chem.* **2007**, *50*, 1, 6. (d) Zhu, G.-D.; Gandhi, V. B.; Gong, J.; Thomas, S.; Woods, K. W.; Song, X.; Li, T.; Diebold, R. B.; Luo, Y.; Liu, X.; Guan, R.; Klinghofer, V.; Johnson, E. F.; Bouska, J.; Olson, A.; Marsh, K. C.; Stoll, V. S.; Mamo, M.; Polakowski, J.; Campbell, T. J. *J. Med. Chem.* **2007**, *50*, 13, 2990. (e) Sun, J.-H.; Teleha, C. A.; Yan, J.-S.; Rodgers, J. D.; Nugiel, D. A. *J. Org. Chem.* **1997**, *62*, 5627.

(2) Eicher, T.; Hauptmann, S. *The Chemistry of Heterocycles*; Wiley-VCH: Weinheim, 2003.

(3) Lukin, K.; Hsu, M. C.; Fernando, D.; Leanna, M. R. *J. Org. Chem.* **2006**, *71*, 8166.

(4) Inamoto, K.; Katsuno, M.; Yoshino, T.; Arai, Y.; Hiroya, K.; Sakamoto, T. *Tetrahedron* **2007**, *63*, 2695.

(5) Vina, D.; Olmo, E. d.; Lopez-Perez, J. L.; Feliciano, A. S. *Org. Lett.* **2007**, *9*, 525.

(6) O'Dell, D. K.; Nicholas, K. M. *Heterocycles* **2004**, *63*, 373.

(7) Jin, T.; Yamamoto, Y. *Angew. Chem., Int. Ed.* **2007**, *46*, 3323−3325.

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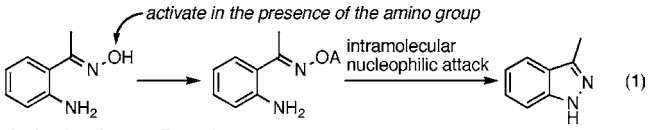
the use of carbanions as nucleophiles.[8] The idea to use electrophilic amination to synthesize indazoles was inspired by a report from Hassner in 1962, which described the synthesis of a pyrazole ring via N−N bond formation between an amine and an oxime from a β-aminooxime using DCC.[9] We hypothesized that selective activation of an oxime can occur over an arylamino group, which would then prompt an intramolecular attack onto this activated oxime by the amino group and produce the desired 1*H*-indazole (eq 1).



Activating Agents Tested:
acetyl chloride, Boc_2O, methyl chloroformate, MsCl, TsCl

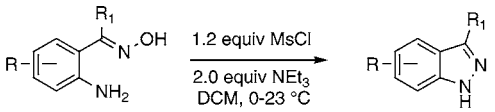
We attempted to isolate protected *o*-aminophenyl oxime compounds by combining a number of activating agents and bases in the presence of the oxime of *o*-amino acetophenone (eq 1). Initial experiments toward this goal involved screening reagents that could activate the hydroxyl group of the oxime, while leaving the arylamine untouched. Among this group, *o*-aminophenyl oxime protected as the carbonate was isolated. However, the formation of the corresponding 1*H*-indazole from this compound occurred in low yields in the presence of various bases. Ultimately, the combination of methanesulfonyl chloride (MsCl) and triethylamine (NEt_3) directly formed the desired 1*H*-indazole. Initially, the reaction occurred in unpredictable yields that ranged from 11% to 30%. We soon discovered that the concentration and stoichiometry of each reaction component greatly determined the amount and identity of indazole product.

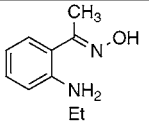
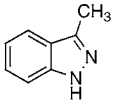
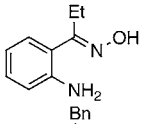
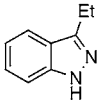
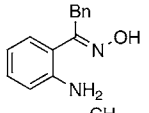
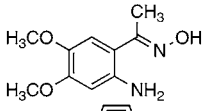
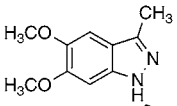
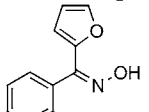
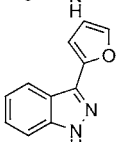
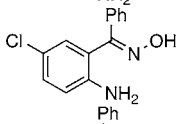
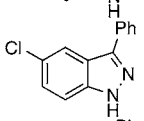
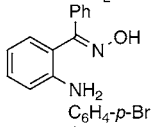
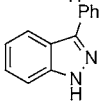
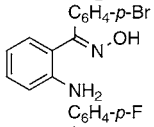
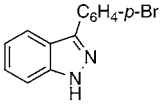
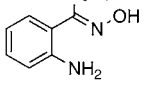
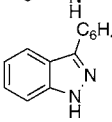
By adjusting the reagent concentrations of MsCl and NEt_3 and the reaction temperature, we found a fast and reliable route to 1*H*-indazoles. Table 1 shows the oxime starting materials[10] and corresponding 1*H*-indazole products obtained under our conditions. The primary use of oximes occurs in their formation of amides or nitriles via the Beckmann rearrangement. The propensity of similar substrates to undergo this rearrangement was a concern as this reaction can occur at ambient temperature.[11] However, we observed little or no Beckmann rearrangement product in entries 1−9.

Another concern was the use of oximes with α-protons, such as entries 1−4, because similar substrates have been shown to undergo facile Neber rearrangement at these temperatures,[12] but products related to this reaction were not observed. Despite these potential side reactions, the conversion of oximes to 1*H*-indazoles under these conditions is facile and avoids most of the issues described above. This method is also amenable to larger scale reactions, as 5 g of *o*-aminoacetophenone oxime was converted to the corresponding 3-methylindazole in 70% yield.

(8) Campbell, M. J.; Johnson, J. S. *Org. Lett.* **2007**, *9* (8), 1521−1524.
(9) Hassner, A.; Michelson, M. J. *J. Org. Chem.* **1962**, *27*, 298−301.
(10) Starting ketones and aldehydes were bought or prepared by the addition of a Grignard reagent to *o*-aminobenzonitrile or Friedel−Crafts acylations of *o*-nitrobenzoyl chlorides (see Supporting Information).
(11) Luca, L. D.; Giacomelli, G.; Porcheddu, A. *J. Org. Chem.* **2002**, *67*, 6272−6274.
(12) Taber, D. F.; Tian, W. *J. Am. Chem. Soc.* **2006**, *128*, 1058.

Table 1. Synthesis of 1*H*-Indazoles from Oximes



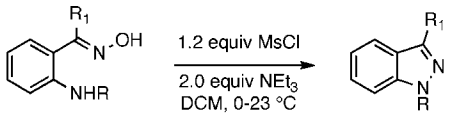
entry	oxime	indazole	yield(%)[a]
1			70
2			81
3			86
4			75
5			86
6			82
7			82
8			81
9			86

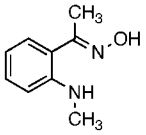
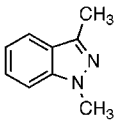
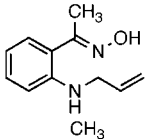
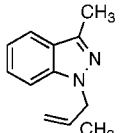
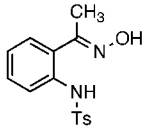
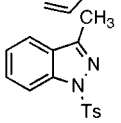
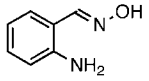
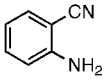
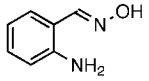
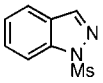
[a] Isolated yields are an average of two reactions. Refer to Supporting Information for detailed procedures.

Because of the success of the reactions conducted in Table 1, we subjected several secondary aniline oxime derivatives to the optimized conditions. *N*-Methylaniline oxime gave high yields (Table 2, entry 1); however, other substitution on the aryl nitrogen provided reactions that gave lower yields. In the case of an *N*-phenyl oxime derivative (not shown), a complex mixture of products was observed in the ^{1}H NMR spectrum. Other aryl anilines, such as entry 3 in Table 2, provided a low yield of the desired indazole. Upon treatment of o-aminobenzaldoxime (Table 2, entry 4) using our optimized conditions, we recovered 69% of o-aminobenzonitrile, whereas alternative reagents such as TsCl/pyridine provided a mixture of products. However, exposure of the *o*-aminobenzaldoxime to 2.0 equiv of MsCl and NEt_3 at −20 °C gave the mesylated indazole in 52% yield.

The mechanism of this reaction is thought to proceed via initial mesylation of the oxime, followed by the nucleophilic attack of the arylamine at the sp^2-nitrogen center. Thus, for

Table 2. Synthesis of 1*H*-Indazoles from Oximes

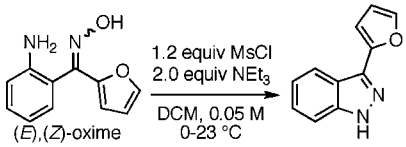


entry	oxime	indazole	yield(%)[a]
1			87
2			70
3			35
4			69
5			52[b]

[a] Isolated yields are an average of two reactions. [b] Reaction conducted at −20 °C with 2 equiv of MsCl.

this intramolecular nucleophilic substitution mechanism to be plausible, the geometry of the oxime would have to be consistent with the hydroxyl group of the oxime distal to the amino group, which is the (*Z*)-isomer in this case. To investigate this hypothesis, isomeric mixtures of (2-aminophenyl)(furan-2-yl) methanone oxime were subjected to our standard reaction conditions (Scheme 1).

Scheme 1



z-oxime(%)	prod.(%)
0	<5
22.5	18.6
51.5	38.4
75.2	59.1
100.0	86.0

The reaction containing 100% of the (*E*)-oxime gave less than 5% of the corresponding 1*H*-indazole, whereas the increase of (*Z*)-oxime corresponded to an increase in the desired product. Under these conditions, it is unlikely that the oximes are isomerizing, since partial isomerization of oximes has been shown to occur under acidic conditions or at elevated temperatures.[13]

In summary, we report a facile strategy toward the synthesis of 1*H*-indazoles. This mild method affords a broad range of substituted 1*H*-indazoles and is amenable to scale-up. The application of this strategy toward the synthesis of other *N*-heterocycles is currently being explored. Additional future studies will employ monoarylated anilines, which would provide an alternative route to the metal-catalyzed arylation of indazoles.

Acknowledgment. This work was generously supported by The Ohio State University.

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

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