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Synthesis of *N*-Arylindazoles and Benzimidazoles from a Common Intermediate

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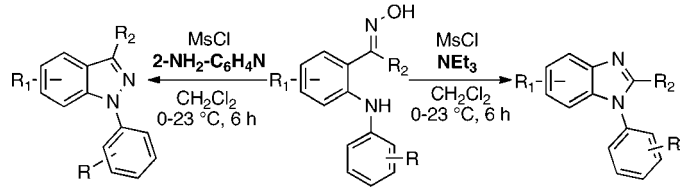
ABSTRACT



A variety of *N*-aryl-1*H*-indazoles and benzimidazoles were synthesized from common arylamino oximes in good to excellent yields. The product selectivity depends upon the base used in the reaction, as triethylamine promoted the formation of benzimidazoles, whereas 2-aminopyridine promoted the formation of *N*-arylindazoles. This method is valuable to the synthetic community because both indazoles and benzimidazoles are prevalent in pharmaceuticals.

The 1*H*-indazole nucleus is rarely found in nature[1] but is a common moiety in the pharmaceutical industry.[2] Indazoles exhibit anticancer, antimicrobial, and other important therapeutic properties. *N*-arylindazoles also elicit interesting biological responses as anti-inflammatories and Hedgehog pathway antagonists (Figure 1).[3] The prevalence of indazoles in many pharmaceuticals may also be caused by the fact that the indazole moiety is a bioisostere of phenol.[4]

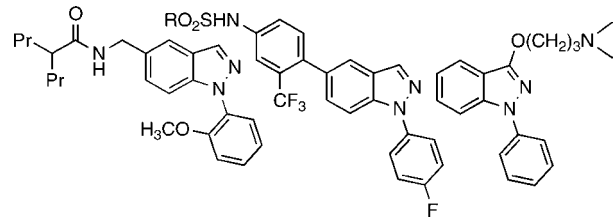


Figure 1. Some biologically active *N*-arylindazoles.

The lack of methods to prepare indazoles has recently inspired several groups to develop routes to these com-

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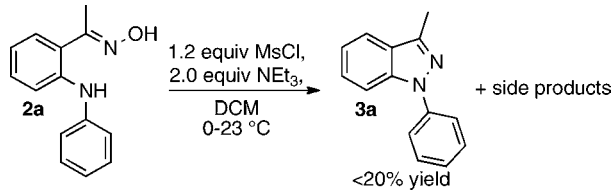
pounds.[5] Previously, our group reported a practical, metal-free synthesis of a variety of 1*H*-indazoles.[6] This method provided several 1*H*-indazoles in good yields. The mechanism of this process is thought to proceed via chemoselective mesylation of the oxime, followed by nucleophilic attack of the arylamino group to the sp^2-nitrogen center.[7] Although the formation of an *N*-methylated indazole was reported in good yield, the syntheses of *N*-arylindazoles proceeded in low yields and were not reported. For example, ^{1}H NMR spectroscopic analysis of the crude reaction mixture consisting of *N*-phenyl *o*-aminoacetophenone oxime (**2a**), MsCl, and NEt_3 in DCM gave the desired indazole (**3a**) product in ~20% yield along with several products that included the parent ketone from hydrolysis of the oxime and the *N*-mesylated oxime starting material (Scheme 1). Because of

Scheme 1



the difficulty in preparing *N*-arylindazoles by direct arylation of 1*H*-indazole, further investigation into conditions that provide *N*-arylindazoles were undertaken. Herein, we report these investigations and the synthesis of a variety of *N*-arylindazoles from the corresponding *N*-aryl oxime compounds. Moreover, we have discovered that benzimidazoles can be produced from the same *o*-aminobenzoximes that form *N*-arylindazoles, and the selectivity of this process largely depends upon the identity of the base employed in these reactions.

The synthesis of *N*-substituted 1*H*-indazoles remains an ongoing challenge. With the development of metal-catalyzed carbon−nitrogen bond forming reactions, new methodologies for forming 1-aryl-1*H*-indazoles have been developed. For example, palladium-catalyzed intramolecular cyclization of *N*-aryl-*N*′(o-bromobenzyl) hydrazines as well as [*N*-aryl-*N*′-(o-bromobenzyl)-hydrazinato-*N*′]-triphenylphosphonium bromides are converted to 1-aryl-1*H*-indazoles.[8] An intramolecular amination reaction from commercially available 2-bromobenzaldehydes and arylhydrazines also provides 1-aryl-1*H*-indazoles but uses harsher conditions.[9] A drawback to both of these methods is the inability to synthesize 2-substituted 1-aryl-1*H*-indazoles directly. Voskoboynikov overcame this by employing a palladium-catalyzed intramolecular cyclization using arylhydrazones of 2-bromoaldehydes and 2-bromoacetophenones.[10] However, the yields are poor for ketones and require high temperatures (120 °C) and long reaction times (160 h). In addition to palladium, copper can also be employed as a catalyst. Buchwald utilized a copper-diamine catalyzed *N*-arylation reaction of indazoles.[11] When aryl bromides are employed, mixtures of the 1*H*- and 2*H*-indazoles are produced. A single example using copper(I) oxide to promote the cyclization of *o*-fluoro hydrazone to give *N*-phenylindazole in 40% yield has been reported.[12]

Because of the lack of mild methods to prepare *N*-arylindazoles, a closer examination of our previously reported *N*-arylindazole attempt was undertaken. The reaction of *N*-phenyl *o*-aminoacetophenone oxime (**1a**) (prepared by a Cu-catalzyed amination of the *o*-amino acetophenone with the corresponding aryl iodide followed by standard oxime forming conditions, see Supporting Information) was reinvestigated under the standard conditions developed in our lab (Scheme 1).[6] During chromatographic separation of this reaction mixture, a compound with an increased polarity relative to the corresponding indazole was isolated. This side product was determined to be a structural isomer of 1*H*-indazole after ^{1}H NMR spectroscopic and mass spectrometric analysis. The compound was thought to contain a benzimidazole ring, which was confirmed by independent preparation of this product. This was an exciting discovery because benzimidazoles are extremely important components in pharmaceuticals as two of the top 25 selling drugs in the world (esomeprazole and lansoprazole) contain the benzimidazole core structure.[13] Therefore, conditions that would selectively provide indazole or benzimidazole from a common intermediate would be extremely useful to synthetic chemists.

Initial attempts to selectively produce *N*-arylindazoles over benzimidazoles were unsuccessful. Varying the temperature, concentration, or solvent did not lead to a substantial increase in the ratio of indazole to benzimidazole.[14] The identity of the base was then investigated. Exposure of oxime (**2b**) to 2.0 equiv of base and 2.0 equiv of MsCl in DCM for 6 h provided the corresponding *N*-arylindazole (**3b**) and benzimidazole products (**4b**) (Table 1). In many cases, the choice of base had a large influence on the outcome of the reaction. The highest ratio of indazole (**3b**) to benzimidazole (**4b**) was observed using 2-aminopyridine (entry 1). Alternatively, the highest ratio of benzimidazole to indazole was observed using NEt_3, NBu_3, or *N*,*N*-diisopropylethylamine (entries

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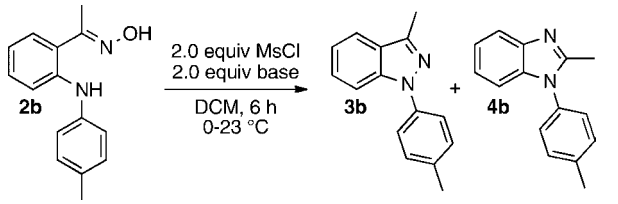
(14) Please refer to the Supporting Information.

Table 1. Effect of Base on the Ratio of Indazole to Benzimidazole Products[a,b]

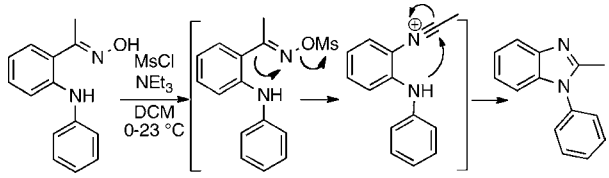


entry	base (pK_a (H_2O))	indazole: benzimidazole
1	2-aminopyridine (6.8)	9.2
2	2,6-diaminopyridine (6)	5.8
3	1-methylimidazole (7.4)	2.5
4	pyridine (3.4)	1.7
5	DBU (12)	0.41
6	NEt_3 (10.8)	0.32
7	NBu_3 (10.9)	0.28
8	DIPEA (11.4)	0.26

[a] Ratio of indazole to benzimidazole was determined using gas chromatography with 1,3,5-trimethoxybenzene as an internal standard. [b] All reactions proceeded to >70% conversion except for entry 4.

6−8). The ratio of indazole to benzimidazole did not correlate to the pK_a values of the bases (although the complete pK_a values of all bases were only available in water) but in general, weaker bases favored the formation of indazole, while stronger bases favored benzimidazole products. The formation of the benzimidazole product may arise from the pathway in Scheme 2. Upon mesylation of the

Scheme 2

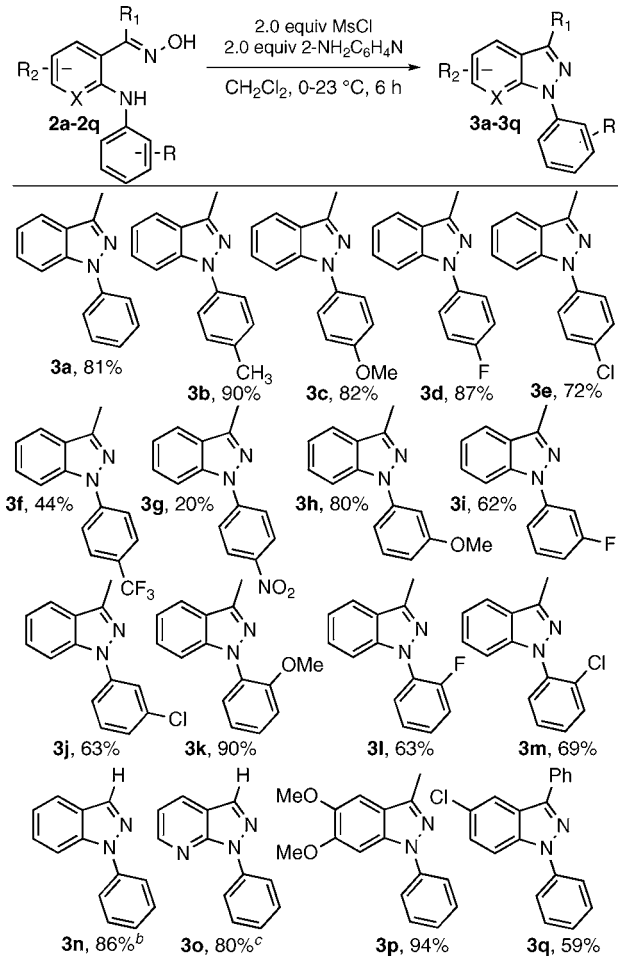


oxime, a Beckmann rearrangement occurs with intramolecular trapping of the formed nitrilium ion by the arylamine. It is currently unclear why stronger bases would promote the Beckmann rearrangement pathway that forms benzimidazoles over the nucleophilic subsitution pathway to form indazoles.[15]

Several substituted arylamino oximes were prepared (see Supporting Information) and examined under the optimized reaction condtions (Scheme 3). High yields were obtained for most substrates that contained arenes with electron-donating or electron-withdrawing groups at the ortho, meta, or para positions. However, lower yields of indazoles were obtained with *p*-CF_3 (**3f**, 44%) and *p*-NO_2 (**3g**, 20%)

(15) We thank the reviewer who suggested that the formation of benzimidazole may occur through a deprotonation, migration, ketenimine formation, and cyclization sequence.

Scheme 3. Synthesis of Indazoles Using 2-Aminopyridine as Base[a]



[a] Isolated yields are an average of two 1 mmol reactions. [b] This reaction was conducted at −78 to 23 °C. [c] This reaction was conducted at −20 °C.

substituted aryl amines. When aldoximes were employed as starting materials (entries **3n**, **3o**), the reactions were conducted at lower temperatures to avoid elimination of the

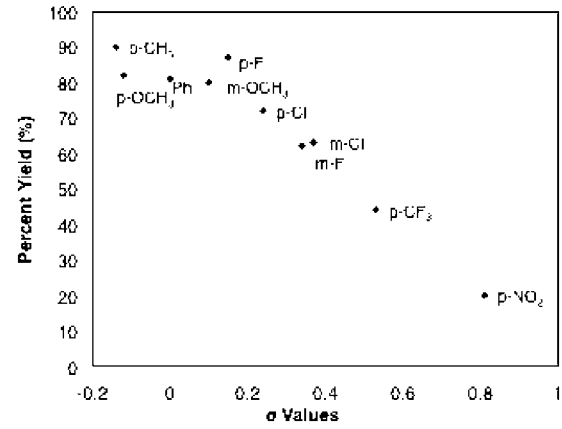
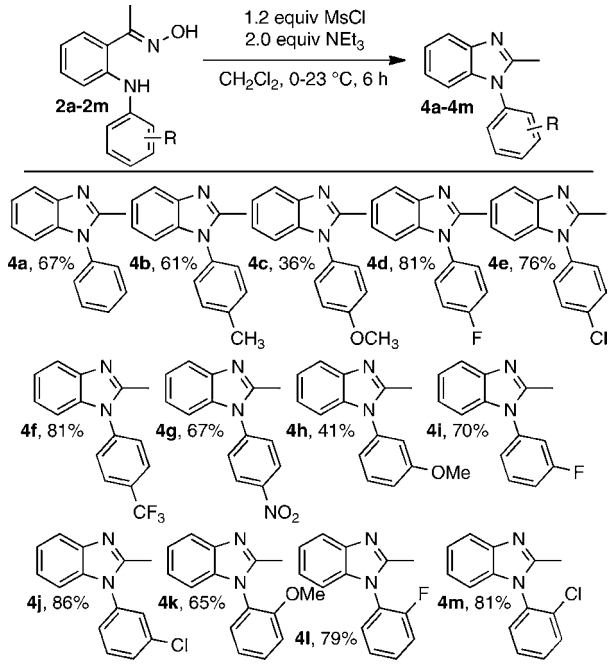


Figure 2. Percent yield of indazole vs σ values of arenes.

Scheme 4. Synthesis of Benzimidazoles Using Triethylamine as Base[a]



[a] Isolated yields are an average of two 1 mmol reactions.

aldoximes to the corresponding nitriles. The method was also amenable to substitution on the aromatic ring containing the oxime. The dimethoxy product **3p** and the chloro product **3q** were isolated in 94 and 59% respectively.

In addition to the influence of base, the electronics of the group attached to the arene influenced the reaction outcome. A linear relationship exists between the yield of indazole and the σ values of the aryl substituents (Figure 2).[16] A general trend was that the stronger σ donors produce a larger amount of indazole product. The relationship is likely caused by the increased nucleophilicity of the arylamine that attacks the oxime nitrogen. This rate increase lessens the delay time needed to allow the Beckmann rearrangement to occur.

We next investigated the selective formation of benzimidazoles using the conditions uncovered in the reaction screening from Table 1. The conditions employed are the same conditions that produced 1*H*-indazoles in our previous work. Surprisingly, benzimidazole was not observed in any appreciable yields in reactions of primary aromatic amines. Nonetheless, exposure of the same substrates that formed indazoles in the presence of 2-aminopyridine gave benzimidazoles with triethylamine (Scheme 4). Lower yields were obtained with a methoxy group present at the *para* or *meta* positions (**4c**, 36%; **4h**, 41%). However, moderate to high yields were obtained for electron-withdrawing substituents at the *ortho*, *meta*, or *para* positions. Currently, this method is not amenable to strongly electron-rich arenes, as treatment of dimethoxy (**2p)** with MsCl and NEt_3 gave the corresponding *N*-arylindazole.

In summary, we report the synthesis of both *N*-aryl-1*H*-indazoles and benzimidazoles through a common oxime intermediate. Product selectivity of these reactions was achieved through selection of the base. The reactions that produce indazoles correlate well to the σ values of the groups on the *N*-aromatic ring. This method affords a broad range of indazoles and benzimidazoles from good to excellent yields and should provide synthetic chemists an additional avenue to prepare indazoles and benzimidazoles. More significant is the fact that two diverse heterocycles can be generated from a common intermediate by simply changing the identity of the base in the reaction.

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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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