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A Synthesis of 1*H*-Indazoles via a $Cu(OAc)_2$-Catalyzed N−N Bond Formation

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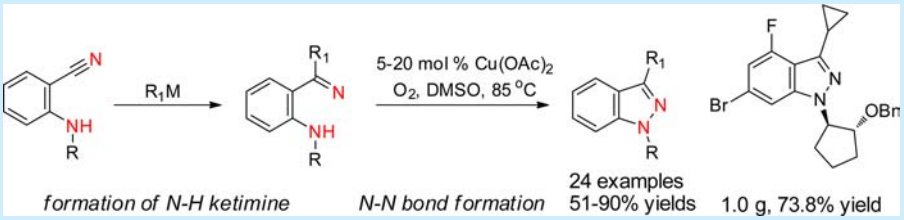
Supporting Information



ABSTRACT: A facile synthesis of 1*H*-indazoles featuring a $Cu(OAc)_2$-catalyzed N−N bond formation using oxygen as the terminal oxidant is described. The reaction of readily available 2-aminobenzonitriles with various organometallic reagents led to *o*-aminoaryl N−H ketimine species. The subsequent $Cu(OAc)_2$-catalyzed N−N bond formation in DMSO under oxygen afforded a wide variety of 1*H*-indazoles in good to excellent yields.

1*H*-Indazoles are ubiquitous in the realms of pharmacologically active agents even though their occurrence in nature is scarce (Figure 1).[1] A number of important drugs containing 1*H*-indazole pharmacores such as granisetron, gamendazole, and benzydamine have been developed.[2] In addition, a few structurally interesting tricyclic indazoles have been isolated from *Nigella glandulifera* and display diverse biological activities.[3] The importance of this class of heterocycles as medicinal agents has continued to inspire the pursuit of their general and efficient syntheses. Many existing approaches to 1*H*-indazoles rely on the formation of a C_{7a}−N_1 bond employing condensation of highly toxic hydrazine or organohydrazines with *o*-haloaryl aldehyde or aryl ketone derivatives under fairly harsh conditions.[4] Other methods employing organoazide reagents and utilizing precious transition metals as catalysts are less attractive.[5] Herein, we report a facile synthesis of 1*H*-indazoles via a $Cu(OAc)_2$-catalyzed N−N bond formation employing oxygen as the terminal oxidant.[6,7] We envisioned that addition of Grignard or organolithium reagents to readily available *o*-aminobenzonitriles would form *o*-aminoaryl N−H ketimines. The subsequent intramolecular N−N bond formation using copper catalysts under aerobic oxidation conditions would then lead to the formation of 1*H*-indazoles. To the best of our knowledge, this approach to make 1*H*-indazoles has not been reported.[5a,8]

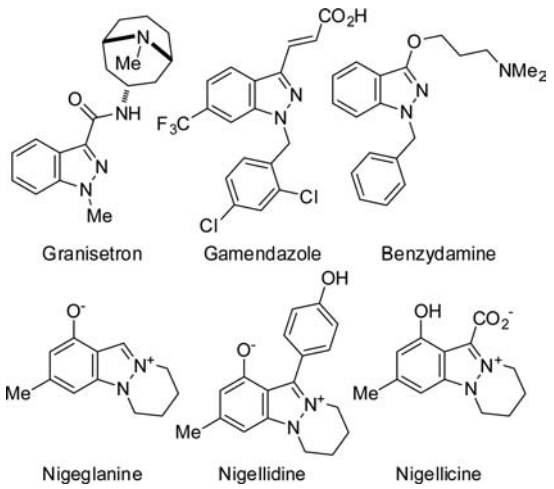


Figure 1. 1*H*-Indazoles as medicinal agents and natural products.

Two metal-free syntheses of a variety of 1*H*-indazoles featuring an intramolecular N−N bond formation have been reported.[9] As shown in Scheme 1, these syntheses rely on the selective activation of the oxime in the presence of the amino group followed by an intramolecular displacement reaction to form the indazole ring. In this approach, the oximes were derived from *o*-aminoaryl ketones **4**, which, in turn, were prepared from *o*-aminobenzonitriles **1** and organometallic reagents through the hydrolysis of the ketimine intermediates **2**.[10,11] Taking into account atom and step economy, we envisioned that a direct N−N bond formation from the ketimine species **2** should be a viable and attractive approach to this important class of compounds. We further anticipated that such transformations could be facilitated via a metal-catalyzed

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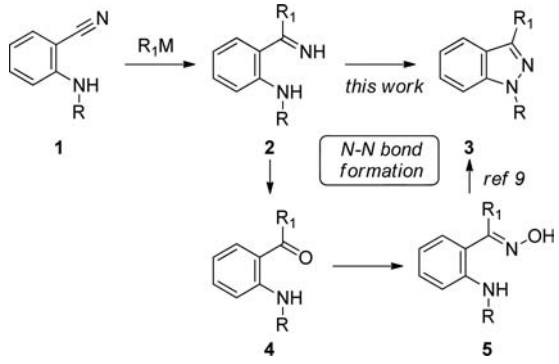
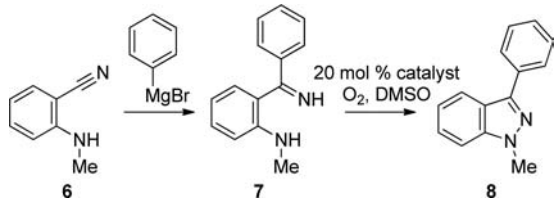
Scheme 1. Synthetic Strategy for 1*H*-Indazoles via Direct N−N Bond Formation



N−N bond formation using oxygen as the terminal oxidant. Our strategy, therefore, relies on generation of *o*-aminoaryl ketimine species and its subsequent usage in the N−N bond formation to 1*H*-indazoles.

We started our work by preparing ketimine **7**[12] from nitrile **6** and phenylmagnesium bromide and explored its metal-catalyzed N−N bond formation to form the indazole ring. We were delighted to find that this conceptually simple approach worked very well when prepared 2-methylaminoaryl N−H ketimine **7** was treated with a catalytic amount of $Cu(OAc)_2$ (20 mol %) in DMSO under oxygen to afford 1*H*-indazole **8** in 77.8% yield (Table 1, entry 1). Continued catalyst screening indicated that $Cu(OAc)_2$ is superior to other catalysts in facilitating the N−N bond formation (Table 1, entries 2−7). Neither Pd nor Ni catalysts are effective in the catalysis with only a trace amount of 1*H*-indazole **8** formed. This preliminary yet exciting lead prompted us to develop a versatile method for the direct access to various 1*H*-indazoles from *o*-aminoaryl ketimines.

Table 1. Catalyst Screening for the N−N Bond Formation

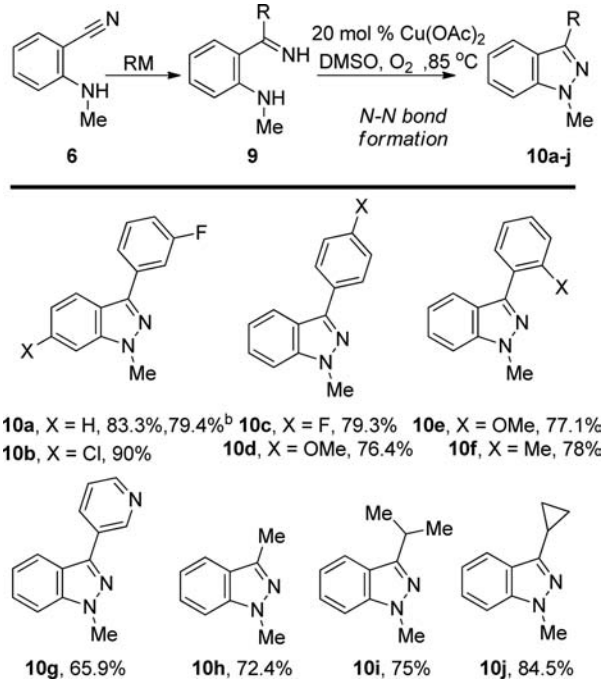


entry[a]	catalyst	yield[b] (%)
1	$Cu(OAc)_2$	77.8[c]
2	$Cu(OTf)_2$	42.5
3	$CuBr_2$	53.3
4	CuCl	69.4
5	CuI	58.6
6	CuBr	68.7
7	CuO	30.7
8	$Pd(OAc)_2$	1.0
9	$Ni(dppe)Cl_2$	0.10
10	$Pd(dppf)Cl_2/PPh_3$	0.10

[a]All screening experiments were carried out on 0.5 g scale under oxygen in DMSO (10 g) at 85 °C for 3 h. [b]All the yields except entry 1 were based on HPLC assay against the standard sample of **8**. [c]Isolated yield.

Next, we explored the generality of the defined conditions in the synthesis of indazoles from ketimines **9** which were readily prepared from addition of various organometallic reagents to nitrile **6**. As shown in Scheme 2, all the N−N bond formations occurred smoothly to afford a wide variety of 3-substituted 1*H*-indazoles (**10a−j**) under mild conditions. The N−N bond formation is independent of the arylmagnesium as several 3-aryl 1*H*-indazoles (**10a−f**) were obtained in good to excellent yields. The reaction also tolerated chloride moiety such that **10b** was obtained in excellent yield through this two-step sequence. The reaction also tolerated a pyridinyl group to afford 1*H*-indazole **10g** in 65.9% yield. Furthermore, alkyl groups and cyclopropyl group can be incorporated in the indazole framework to give 1*H*-indazole **10h−j** in 72.4−84.5% yields. All of these reactions were carried out in gram quantities in good yields, demonstrating the efficiency and practicality of this methodology. The catalyst loading of $Cu(OAc)_2$ can be reduced to 5 mol % as illustrated in the preparation of 1*H*-indozole (**10a**, 79.4%) on a 5 g scale without compromising the efficiency of the N−N bond formation.

Scheme 2. Synthesis of 1*H*-Indazoles from 2-Methylaminobenzonitriles[a]



[a]All reactions were run under oxygen in DMSO (20 g/g substrate) at 85 °C for 3−6 h, and products were isolated in gram quantities after SiO_2 column chromatography. [b]5 mol % of the catalyst was used on a 5 g scale.

Having successfully prepared a range of 3-substituted *N*-Me indazoles (**10**) from *o*-methylaminoaryl N−H ketimines (**2**) employing $Cu(OAc)_2$-catalyzed N−N bond formation, we decided to extend this protocol to *N*-aryl-substituted ketimines for the preparation of *N*-aryl-substituted indazoles.[13] Delightfully, this extension was rather straightforward, and a wide array of 3-substituted *N*-arylindazoles (**11a−h**) were obtained from the corresponding *o*-aminoaryl ketimines as summarized in Scheme 3. While most reactions were carried out under oxygen, the N−N bond formation was also feasible under air with 1*H*-indazole **11a** obtained in 70.4% yield. In addition to the installation of the aromatic groups at the 3-position of 1*H*-indazoles, both propenyl and cyclopropyl groups can be

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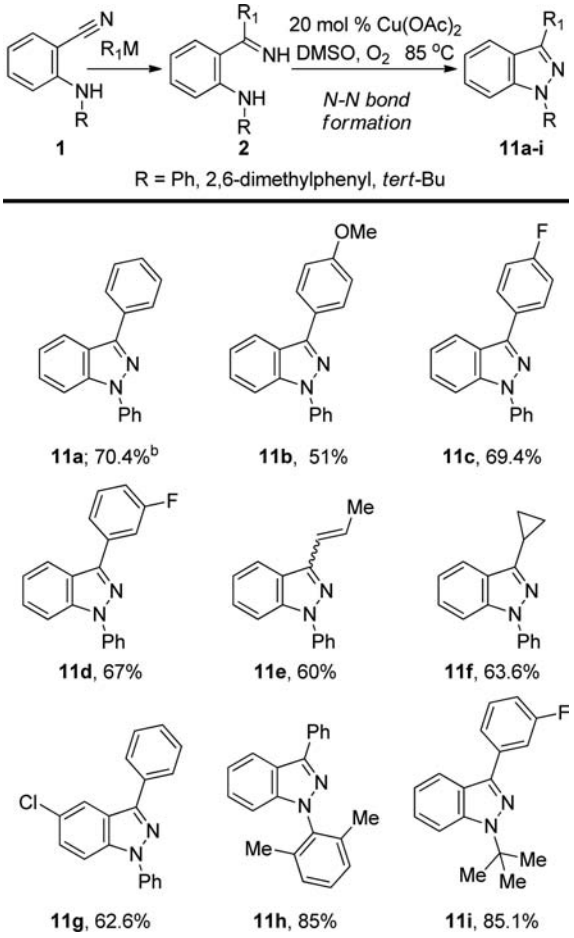
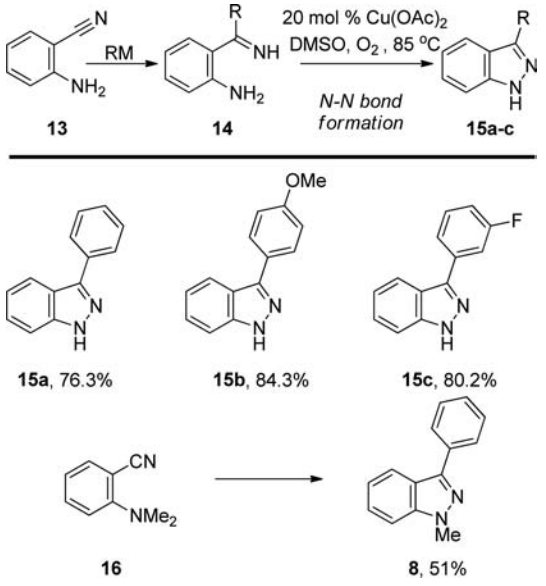
Scheme 3. Synthesis of 1*H*-Indazoles from 2-Aryl- or *tert*-Butylaminobenzonitriles[a]



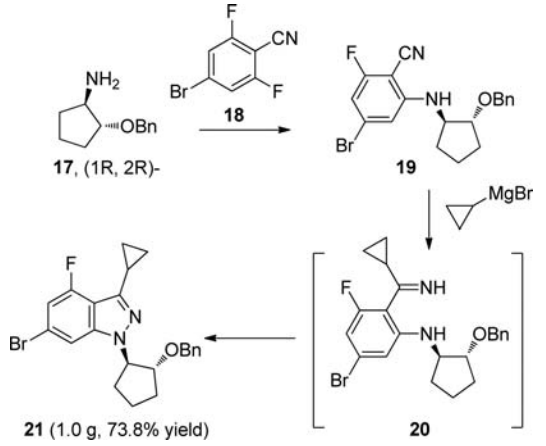
[a]All reactions were run under oxygen in DMSO (20 g/g of the substrate) at 85 °C for 3−6 h, and products were isolated in gram quantities after SiO_2 column chromatography. [b]Reaction was carried out under air.

Scheme 4. Synthesis of 1*H*-Indazoles from 2-Aminobenzonitrile[a]



[a]All reactions were run under oxygen in DMSO (20 g/g substrate) at 85 °C for 3−6 h and compounds were isolated in gram quantity after SiO_2 column chromatography.

Scheme 5. Preparation of Chiral 1*H*-Indazole



introduced (**11e** and **11f**) to these molecules. Compound **11g** was prepared in a much more straightforward manner than with the literature protocol.[9] We noticed that the reaction gave a higher yield of 1*H*-indazoles with the bulky substituted group attached to the amino moiety (**11h** and **11i**). This observation warrants further examination to gain more understanding of the steric effect on the efficiency of the N−N bond formation.

Furthermore, the methodology can be extended to the preparation of 3-substituted 1*H*-indazoles from 2-aminobenzonitrile (**13**). Three 2-aminobenzonitrile-derived 1*H*-indazoles (**15a−c**) were prepared in 76.3−84.3% yields (Scheme 4). Moreover, the *N*,*N*-dimethylamino nitrile **16** was subjected to the reaction sequence to afford *N*-methylindazole **8** in 51% yield. Interestingly, demethylation occurs during the N−N bond formation.

A highlight of this N−N bond formation protocol is shown in Scheme 5, where a chiral amino moiety can be readily incorporated into the indazole ring. Addition of cyclopropylmagnesium bromide to nitrile **19** followed by N−N bond formation of ketiminium species **20** afforded 1*H*-indazole **21** in 73.8% yield. We believe this is a unique example of preparation of a 1*H*-indazole-bearing chiral moiety in the molecule. This example also proved the tolerance of bromide moiety of this protocol. This shows that molecular complexity can be readily built through this versatile methodology.

On the basis of literature reports,[5a,6a,b] we speculate that the reaction proceeds with the coordination of $Cu(OAc)_2$ with *o*-aminoketimine **14** to form species **22**, which could also be oxidized further to species **23**. Reductive elimination leads to N−N formation to afford the desired 1*H*-indazole and reduced copper species, CuOAc. The copper(I) acetate, in turn, is oxidized by oxygen to regenerate the $Cu(OAc)_2$ catalyst. Oxygen plays a critical role in the catalytic cycle to reoxidize presumably the CuOAc species (Scheme 6). For example, the N−N bond formation reaction was performed using 20 mol % of $Cu(OAc)_2$ but under argon stalled at 23% conversion to the desired 1*H*-indazole. However, removal of argon and reintroduction of oxygen allowed the reaction proceed to completion.

In conclusion, we have developed a new and efficient synthetic method for the construction of 1*H*-indazoles based on

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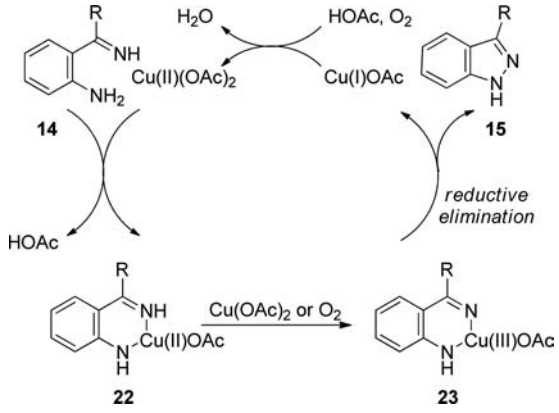
Scheme 6. Mechanistic Hypothesis for the N−N Bond Formation



$Cu(OAc)_2$-catalyzed N−N bond formation using oxygen as the terminal oxidant. This protocol takes advantage of the readily accessible ketimine precursors prepared from *o*-aminobenzonitriles and organometallic reagents. The simplicity and high efficiency of this protocol renders it attractive when compared to the others reported in the literature. Importantly, both nitrogen atoms in the starting material were conserved. The method demonstrated here allows easy access to structurally diverse 1*H*-indazoles and could serve as a versatile tool for the modular synthesis of 1*H*-indazole containing medicinal agents. We hope this work will prompt others to explore application of the N−N bond formation methodology using *o*-amino ketimines in the arena of heterocycle syntheses.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00611.

Experimental details, characterization data, and NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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