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Facile Synthesis Of 1H-Indazoles Through Iodobenzene-Catalyzed C–H Amination Under Mild And Metal-Free Conditions

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Abstract:
The transition-metal- and halogen-free synthesis of N-aryl substituted 1H-indazole and derivatives was accomplished on the basis of the iodobenzene-catalyzed intramolecular C -H amination of hydrazones under mild conditions. Reactions of hydrazones derived from ketones and hydrazines with a catalytic amount of iodobenzene in the presence of Oxone as an oxidant in trifluoroacetic acid took place to afford 1H indazoles in moderate to good yields.

Keywords: *Hypervalent compounds, Amination, Cyclization, oxidant.*

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I. Introduction:

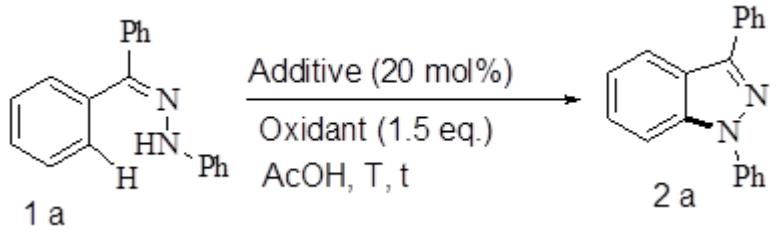
1H-Indazole and its derivatives are known to be important structural units for the development of pharmaceutically important molecules.[1] For instance, they present an tiarthritic,[2] anti-inflammatory,[3] and antifertility activities.[4] Traditional syntheses of 1H-indazoles often require harsh reaction conditions, toxic reagents, and unstable intermediates, all of which have restricted their substrate scope and their industrial application.[5] Recently, the transition-metal-catalyzed synthesis of 1*H*-indazoles was documented on the basis of intramolecular Buchwald–Hartwig type coupling reactions and/or C–H amination.[6] Although these methods are effective under milder reaction conditions than those required for the traditional synthesis,[5] the high cost and toxicity of the transition metals restrict their practical use. Accordingly, the development of a new protocol for the formation of 1*H*-indazole scaffolds under transition-metal-free conditions is highly desirable.[7] Recently, the use of hypervalent iodine reagents in oxidative reactions as metal-free reagents has received much attention owing to their low toxicity and the fact that they can be used under mild reaction conditions.[8] Many useful carbon–carbon[9] and carbon–heteroatom[10] bond-forming reactions have been documented in which a stoichiometric amount of the hypervalent iodine reagent is used. More recently, a catalytic process involving the use of m-chloroperoxybenzoic acid (m-CPBA) as a terminal oxidant to avoid the formation of undesired iodoarenes in an equimolar amount was reported.[11] On the basis of this concept, a variety of methods have been developed for the transformation of organic molecules.[12] We now report iodobenzene-catalyzed oxidative C–H amination for the construction of 1*H*-indazoles from arylhydrazones by using Oxone ($2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$) as a terminal oxidant under mild reaction conditions .

II. Results And Discussion:

The reaction conditions were optimized by using phenyl hydrazone 1a as a model substrate (Table 1). Treatment of 1a with iodobenzene (1eq) and m-CPBA (1.5 equiv.) as the oxidant in (DCM, 2 ml) as the solvent for 4-5 h at room temperature afforded target 1*H*-indazole 2a in 10% yield (Table 1, Entry 1). Screening of the solvents, including carbon tetrachloride(CCl_4), DMF, dichloromethane, methanol, acetic acid, and DMSO, proved unsuccessful (Table 1, Entries 2–5). Fortunately, target 2a was obtained in 85 % yield by using acetic acid (AC) as the solvent (Table 1, Entry 10). Employing other substituted iodoarenes, such as p-iodotoluene and p iodoanisole, and also iodine sources, such as iodine and tet rabutylammonium iodide, produced inferior results (Table 1, Entries 6–8). Additionally, reactions performed with oxidants such as, hydrogen peroxide, and potassium persulfate were unsuc cessful (Table 1, Entries 9–10). To our delight, upon employing Oxone (potassium peroxymonosulfate) as the oxi dant, 2a was obtained in 85% yield (Table 1, Entry 10). Lowering the temperature to–10 °C led to isolation of the product in 90% yield (Table 1, Entry 10).

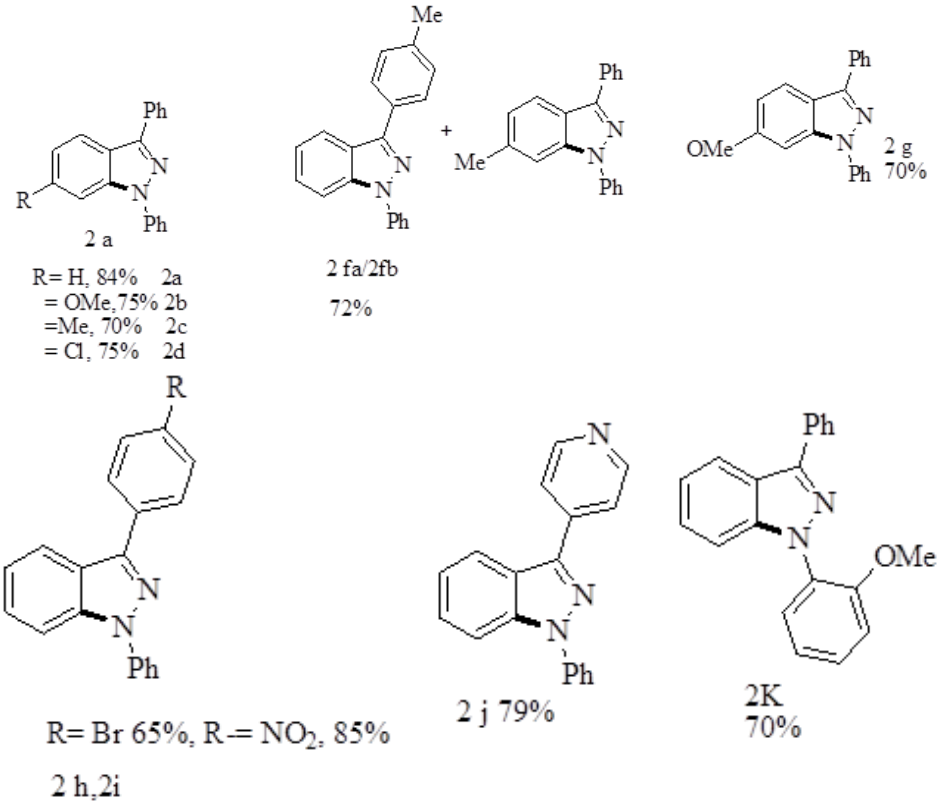
Table1.Optimization of the reaction conditions for the cyclization of phenylhydrazone1a.[a]

Entry	Oxidant	Additive	Solvent	T(^{0}C)	t (h)	Yield (%)
1	**mCPBA**	**PhI**	**DCM**	**r.t.**	**24**	**10**
2	**mCPBA**	**PhI**	**CCl4**	**r.t.**	**24**	**5**
3	**mCPBA**	**PhI**	**AcOH**	**r.t.**	**24**	**oo**
4	**mCPBA**	**PhI**	**DMF**	**r.t.**	**24**	**5**
5	**mCPBA**	**PhI**	**DMSO**	**r.t.**	**24**	**oo**
6	**mCPBA**	**p-MeC_6H_4I**	**TFA**	**r.t.**	**10**	**25**
7	**mCPBA**	**p-$MeoC_6H_4I$**	**TFA**	**r.t.**	**10**	**20**
8	**H_2O_2**	**p-$NO_2C_6H_4I$**	**Oxalic acid**	**r.t.**	**5**	**30**
9	**Oxone**	**I_2**	**Oxalic acid**	**r.t.**	**2**	**40**
10	**Oxone**	**PhI**	**AcOH**	**-10**	**1**	**85**



Scheme :1

With the optimized conditions in hand, we next investigated the scope of the cyclization of a series of substituted hydrazones (Scheme 1). Hydrazones 1b and 1c with methoxy and methyl substituents on both benzene rings reacted to give corresponding substituted 1H-indazoles 2b and 2c in 77 and 71% yield, respectively. Substrates 1d and 1e bearing halogen substituents also gave target products 2d and 2e in 75 and 71% yield, respectively. As can be anticipated, the substrate singly substituted with a methyl group provided a mixture of regioisomeric products 2fa and 2fb. Interestingly, if phenylhydrazone 1g with a methoxy group was employed as the substrate, the reaction proceeded with high regioselectivity to afford 2g throughout the cyclization from the electron-rich benzene ring. However, cyclization of bromoand nitro-substituted pyridine-ring-containing substrates 1h, 1i, and 1j preferentially occurred from the electron-rich benzene ring to afford 2h, 2i, and 2j. Substrate 1k with a substituent at the hydrazine-derived benzene ring also underwent cyclization to afford 1H-indazole 2k in moderate yield.



III. Conclusions:

We synthesis of multisubstituted 1Hindazoles with an N-aryl substituent from readily available hydrazones on the basis of iodobenzene-catalyzed oxidative C–H aminations by using Oxone as a stable and inexpensive oxidant under mild conditions within a short reaction time. The scope and limitations of this transformation and also valuable information with regard to the reaction mechanism were partially elucidated. This transformation avoids the use of a toxic transition-metal catalyst and leaving groups, which require additional steps for prefunctionalization. A range of functional groups [methoxy, methyl, halogen (Br, Cl, and F), ester, and 4-pyridyl] were accepted for this transformation to provide a series of functionalized 1H-indazoles in moderate to good yields.

Experimental Section: General Procedure: Oxone (0.60 mmol, 1.5 equiv.) was added to a stirred solution of hydrazone 1 (0.40 mmol, 1.0 equiv.) and iodobenzene (10 mol-%) in Acetic acid (2 mL) at –10 °C. The mixture was stirred for 30 min and then quenched with water, diluted with DCM, and washed with water (3 10 mL). The combined organic layers were dried (Na_2SO_4), and the solvents were removed under reduced pressure. The residue was purified by column chromatography (hexane/ethyl acetate) to afford pure substituted 1H-indazole.

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