ChemComm
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View Article Online
DOI: 10.1039/D0CC05862A

COMMUNICATION

Efficient synthesis of 2-aryl-2*H*-indazoles by base-catalyzed benzyl C–H deprotonation and cyclization

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

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A straightforward and efficient method for the preparation of 2-aryl-2*H*-indazoles from *ortho*-alkyl substituted azoxybenzenes is presented. The reaction proceeds through base-catalyzed benzyl C-H deprotonation and cyclization to afford 2-aryl-2*H*-indazoles in good yields. This synthetic strategy can be applied to the construction of several fluorescent and bioactive molecules.

Indazole is recognized as an important diazole compounds[1] given its paramount importance in modern drug discovery.[2] Particularly, 2-aryl-2*H*-indazoles are important synthetic intermediates[3] and crucial scaffolds found in various biologically active molecules[4] as well as fluorescent reagents cellular imaging[5] (Fig 1). Over the years, much attention has been devoted to the development of methods for the preparation of 2-aryl-2*H*-indazoles to address the ever-increasing demands. One of classic approaches was the [3+2] cycloaddition of benzynes with sydnones or diazocarbonyl species.[6] Another synthetic route involved condensation/cyclization sequence was established, but it is ineffective for the preparation of 3-substituted 2*H*-indazoles and requires excessive explosive hydrazoates or tri-*n*-butylphosophine.[7] Recent advances demonstrated that azobenzenes could serve as the starting material or key intermediate in the synthesis of 2-aryl-2*H*-indazoles.[8]

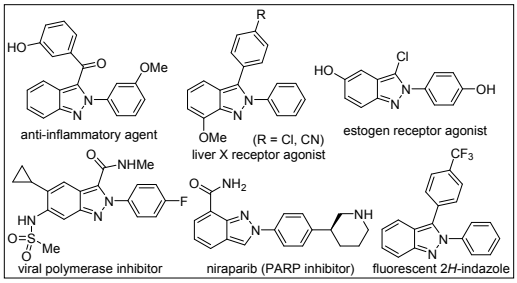

Fig 1. Some bioactive and fluorescent 2-aryl-2*H*-indazoles.

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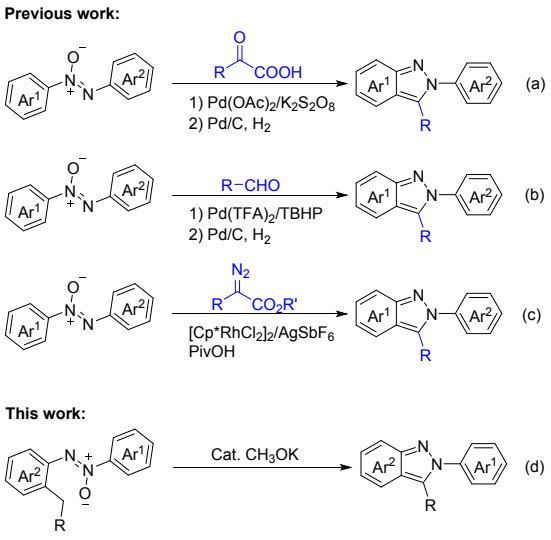
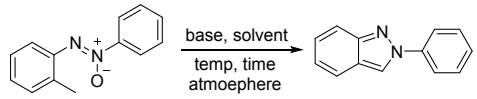


Scheme 1. The synthesis of 2-aryl-2*H*-indazoles from azoxybenzenes.

Transition-metal-catalyzed C-H functionalization has emerged as a powerful tool to construct 2-aryl-2*H*-indazoles. A variety of transition metal catalysts including Rh,[9] Co,[10] Re,[11] Pd[12] have been successfully applied to the reactions between azobenzenes and aldehydes to provide a straightforward method to access this useful skeleton. In addition to aldehydes, acrylates could also react with azobenzenes in the presence of 5 mol% of Rh catalyst and two equivalents of $Cu(OAc)_2$.[13] Despite its high efficiency, this protocol involving direct C–H functionalization was limited to symmetrical azobenzenes and often produced a mixture of regioisomers in case of unsymmetrical azobenzenes. To address the selectivity issues, azoxybenzenes have been chose as a substitute for azobenzenes, enabling site-selective *ortho*-C–H bond functionalization (Scheme 1). For instance, wang's group disclosed a palladium-catalyzed selective *ortho*-C–H acylation of azoxybenzenes with α-oxocarboxylic acids, followed by reductive cyclization to furnish 2*H*-indazoles (Scheme 1a).[14] A similar two-step synthetic route involving selective *ortho*-C–H acylation of azoxybenzenes with aldehydes and reductive

cyclization was also reported (Scheme 1b).[15] Recently, You's group developed a one-pot synthesis of 2-aryl-2*H*-indazoles through Rh-catalyzed selective C–H alkylation/decarboxylative cyclization of azoxybenzenes with diazoesters (Scheme 1c).[16] Despite its high efficiency and wide applicability, this protocol involving *ortho*-C–H functionalization suffered from the use of precious metals. To eliminate the need for precious metals, we envisage the presence of a strong base would trigger the nucleophilic cyclization of *ortho*-alkyl substituted azoxybenzenes, leading to a wide range of 2-aryl-2*H*-indazoles along with the release of H_2O (Scheme 1d).

Table 1 Reaction optimization.[a]



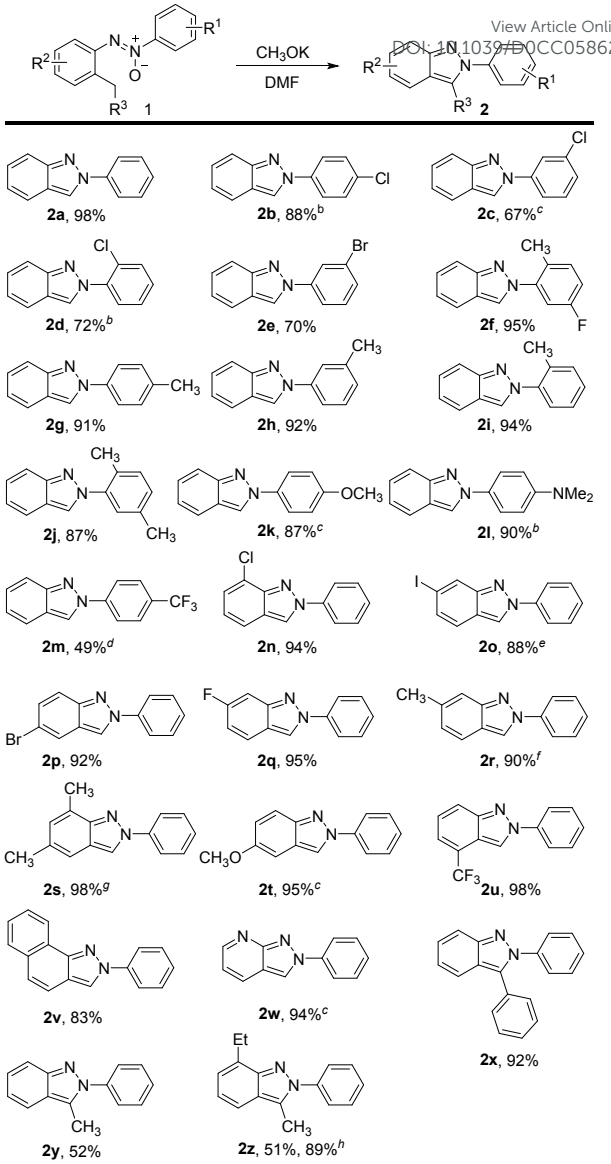
1a 2a

entry	base	solvent	temp (°C)	yield (%)
1	*t*BuOK	DMF	90	70
2	*t*BuONa	DMF	90	35
3	KOH	DMF	90	54
4	NaOH	DMF	90	28
5	LiOH	DMF	90	0
6	K_2CO_3	DMF	90	0
7	Cs_2CO_3	DMF	90	0
8	CH_3OK	DMF	90	98
9	CH_3ONa	DMF	90	16
10	CH_3OLi	DMF	90	trace
11	CH_3OK	CH_3CN	90	42
12	CH_3OK	DMSO	90	83
13	CH_3OK	THF	90	45
14	CH_3OK	CCl_4	90	0
15	CH_3OK	n-hexane	90	0
16	CH_3OK	DMF	80	86
17	CH_3OK	DMF	70	75
18[b]	CH_3OK	DMF	90	54
19[c]	CH_3OK	DMF	90	trace
20[d]	CH_3OK	DMF	90	73

[a]Reaction conditions unless specified otherwise: **1a** (0.3 mmol), base (20 mol%), solvent (2 mL), 90 °C, under N_2 atmosphere, 8 h, isolated yields. [b]Under air atmosphere. [c]Under O_2 atmosphere. [d]CH_3OK (10 mol%).

We initiated our investigations by employing 1-phenyl-2-(*o*-tolyl)diazene 1-oxide (**1a**) as a model substrate to evaluate the feasibility of direct nucleophilic cyclization to access 2-aryl-2*H*-indazole (Table 1). Delightfully, we found that 70% yield of the targeted product (**2a**) was obtained when the model reaction was conducted in the presence of 0.2 equiv *t*BuOK in DMF at 90 °C under argon for 8 h (entry 1). Systematical screening for

Scheme 2. Scope for synthesis of 2-aryl-2*H*-indazoles.[a]



[a]Reaction conditions: **1** (0.3 mmol), CH_3OK (20 mol%), DMF (2 mL), 90 °C, under N_2 atmosphere, 8 h, isolated yields. [b]CH_3OK (100 mol%). [c]CH_3OK (50 mol%). [d]CH_3OK (100 mol%), 100 °C. [e]CH_3OK (50 mol%), 100 °C. [f]CH_3OK (150 mol%), 120 °C. [g]CH_3OK (30 mol%), 100 °C. [h]DMSO as the solvent.

bases (entries 2-8) revealed that the basicity of the base served as an important factor in the reaction efficiency, and the use of CH_3OK as the base proved to be the best choice (entry 8). The nature of the cation of the base was found to be another significant factor (entries 9 and 10). Other polar solvents such as CH_3CN, THF and DMSO could also promote this transformation, yet delivering inferior yields (entries 11-13). However, switching the solvent to nonpolar CCl_4 and n-hexane completely shut down the reaction (entries 14 and 15). Reducing the reaction temperature lowered the reaction efficiency (entries 16 and 17). Control experiments demonstrated that the presence of oxygen dramatically depressed the yield (entries 18 and 19). Moreover, less CH_3OK led to low yield of **2a** (entry 20).

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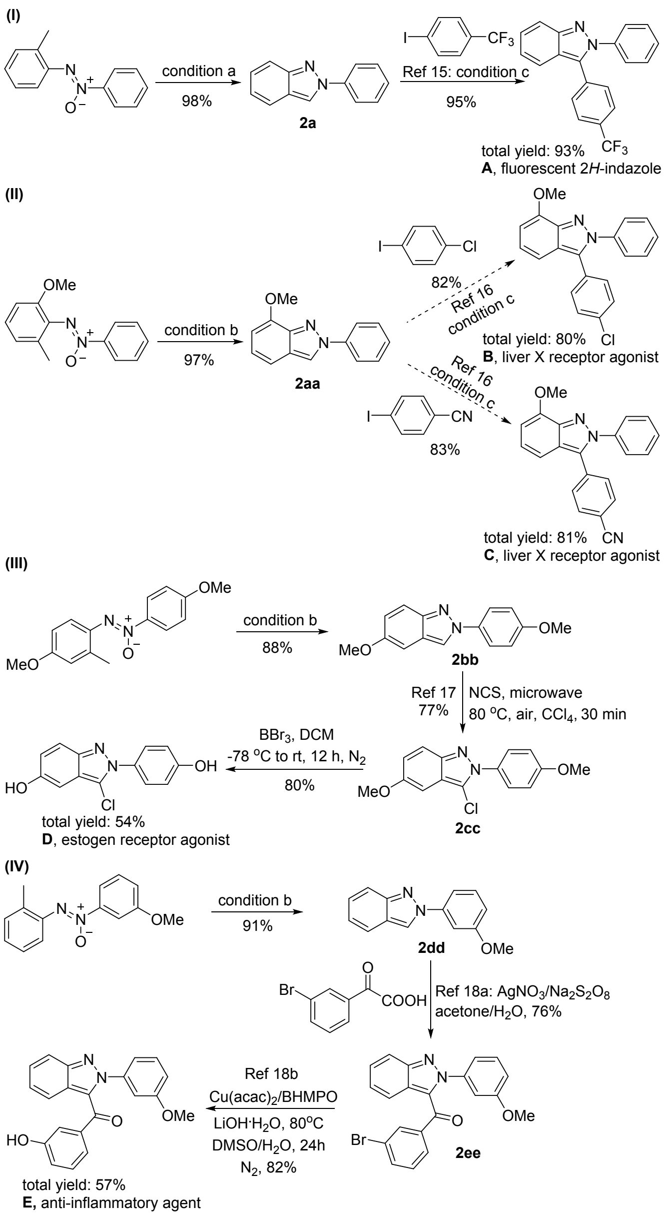
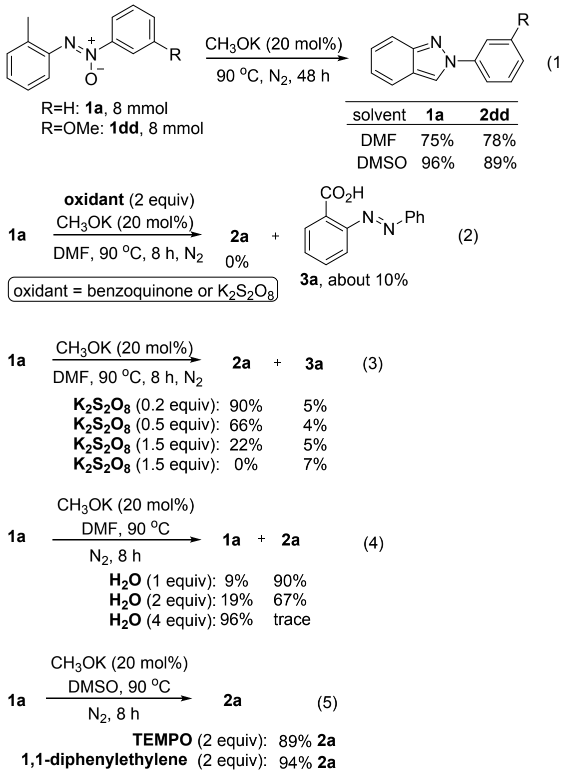
Having optimized the reaction conditions in hand, we started to investigate the substrate scope of the intramolecular cyclization (Scheme 2). Various R^1 substituents such as halogens, electron-neutral methyl, electron-donating groups or electron-withdrawing group were all well tolerated at different positions on the phenyl ring (products **2a**-**2m**). Steric hindrance showed no significant influence on the efficacy of this transformation, as illustrated in the generation of products **2f**, **2i** and **2j**. On the other hand, a survey of R^2 substituents was also investigated. The R^2 substituents could be halogens (products **2n**-**2q**), methyl



Scheme 3. The synthesis of several fluorescent and bioactive molecules. Condition a: CH_3OK (20 mol%), DMF (2 mL), 90 °C, N_2, 8 h. Condition b: CH_3OK (20 mol%), DMSO (2 mL), 90 °C, N_2, 8 h. Condition c: $Pd(dppf)Cl_2{\cdot}DCM$ (5 mol%), PPh_3 (10 mol%), Ag_2CO_3 (1 equiv), 50 °C, air, 16 h.

group (products **2r** and **2s**), methoxy (product **2t**) or trifluoromethyl group (product **2u**). Interestingly, a fused ring or a heterocycle was found to be was compatible with the reaction conditions (products **2v** and **2w**). In addition, 3-substituted 2*H*-indazoles (products **2x**-**2z**) could be also accessed by replacing the methyl with benzyl (R^3= Ph) or ethyl group (R^3= CH_3). It should be pointed out that higher CH_3OK loading or higher temperature was required for complete conversion in some cases.



Scheme 4. Gram-Scale reactions and control experiment.

The important synthetic value of this protocol was further illustrated by its application in the synthesis of several fluorescent and bioactive molecules. For example, our method, serving as a key step, enabled the synthesis of important molecules including fluorescent 2*H*-indazole **A**, liver X receptor agonist **B** and **C**,[17] estogen receptor agonist **D**[18] and anti-inflammatory agent **E**[19] (Scheme 3, I-IV). Furthermore, the gram-scale synthesis of product **2a** and **2dd** demonstrated its potential practicability (Scheme 4.1). Different from small-scale reaction, gram-scale reaction required the extended reaction time in DMSO instead of DMF as the solvent for complete conversion. In addition to oxygen, the use of other oxidants such as benzoquinone and $K_2S_2O_8$ could suppress the formation of the desired product (Scheme 4.2). The examination on the amount of oxidant showed that the product could not be completely inhibited until 1.5 equivalents of oxidant was added (Scheme 4.3). It should be noted that the presence of oxidants not only led to the formation of oxidation product **3a** but also inactivated the base CH_3OK, thus accounting for the low yield of **2a**. The amount of water has a significantly negative influence on the reaction conversion

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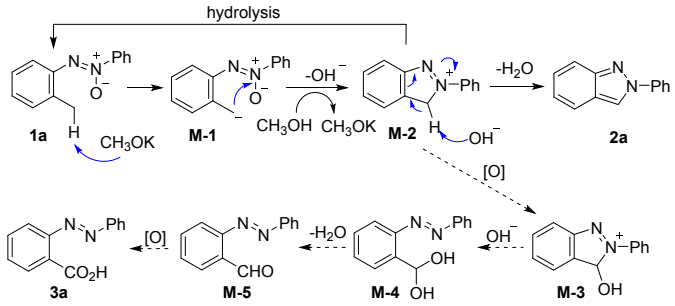
(Scheme 4.4). Control reaction showed that this cyclization are more likely to proceed via an anionic way (Scheme 4.5).

Based on above observations, a plausible mechanism for this CH_3OK-catalyzed cyclization of **1a** is depicted in Scheme 5. CH_3OK deprotonates **1a** to generate carbanion intermediate **M-1**. The intramolecular nucleophilic cyclization of **M-1** produces the intermediate **M-2**, followed by dehydration isomerization reaction to provide the desired product **2a**. Obviously, **M-2** hydrolyzes readily to starting material **1a**, accounting for the reaction why the reaction is sensitive to water. On the other hand, **M-2** can be oxidized to **M-3** by oxidant. Subsequently, nucleophilic attack of hydroxyl ion toward **M-3** to form acetal **M-4** that is converted to **M-5** with elimination of water. Finally, **M-5** was further oxidized to product **3a**.



Scheme 5. Proposed mechanism.

In summary, we have successfully disclosed a green and efficient method for the synthesis of 2-aryl-2*H*-indazoles through base-catalyzed benzyl C-H deprotonation and cyclization of *ortho*-alkyl substituted azoxybenzenes. In contrast to previous transition-metal-catalyzed strategy, this protocol employs cheap CH_3OK as the base, eliminates the need for oxidants and transition-metal catalysts. Remarkably, the synthetic value and potential practicability of this protocol are demonstrated by the synthesis of several fluorescent, bioactive molecules and gram-scale reactions respectively.

We are grateful for financial support from the National Natural Science Foundation of China (21901187, 21672164 and 21372177).

Conflicts of interest

There are no conflicts to declare.

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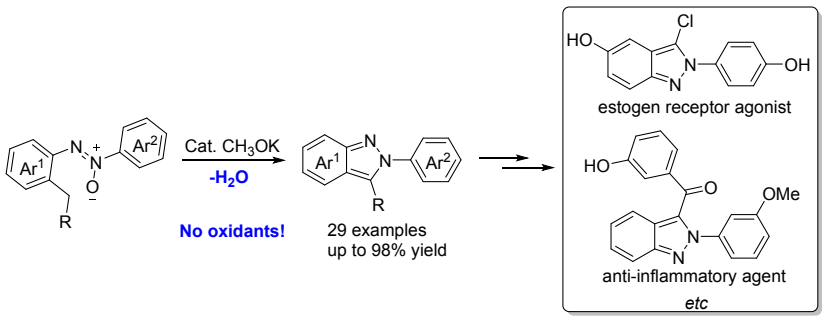

A facile method for the synthesis of 2-aryl-2*H*-indazoles by base-catalyzed benzyl C–H deprotonation and cyclization is developed.