CHEMISTRY
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To be cited as: *Chem. Eur. J.* 10.1002/chem.201902242

Link to VoR: http://dx.doi.org/10.1002/chem.201902242

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Room-Temperature, Metal-Free and One-Pot Preparation of 2*H*-Indazoles *via* Mills Reaction and Cyclization Sequence

Masaru Kondo,*[a] Shinobu Takizawa,[a,b] Yuzhao Jiang,[a] Hiroaki Sasai[a]

Abstract: The Mills reaction and cyclization of readily available 2-aminobenzyl alcohols and nitrosobenzenes using thionyl bromide provided 2*H*-indazoles in up to 88% yields. In the metal-free process, acetic acid played a crucial role for the both Mills reaction and cyclization. A brominated 2*H*-indazole could also be obtained *via* the one-pot sequence.

Indazoles are a useful class of *N*-heteroaromatic compounds because they are crucial structural motifs of unnatural pharmaceuticals and biologically active compounds,[1] particularly, bioisosteres for indoles and benzimidazoles.[1e] A large number of 2*H*-indazole derivatives have been demonstrated for use as important biologically active compounds[1c-h] such as niraparib (PARP inhibitor)[2] and liver X receptor agonist,[3] in addition to fluorescent agents for cellular imaging in the field of chemical biology (Figure 1). [4] Because of the high utility of *N*-substituted indazoles, much attention has been devoted to establish novel and efficient strategies for their preparation. However, *N*-functionalization of indazoles often results in a mixture of 1*H*- and 2*H*-indazoles because the latter is thermodynamically disfavored in comparison with the former (energy difference between them is 2.3 kcal/mol).[1e,5,6] Therefore, regioselective construction of the 2*H*-indazole skeleton remains a challenging task in organic synthesis.[4a,7]

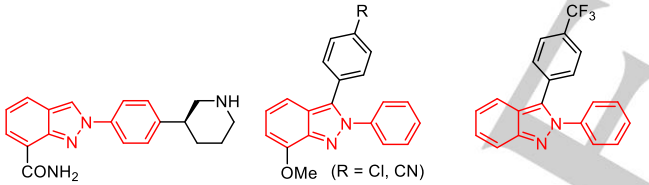
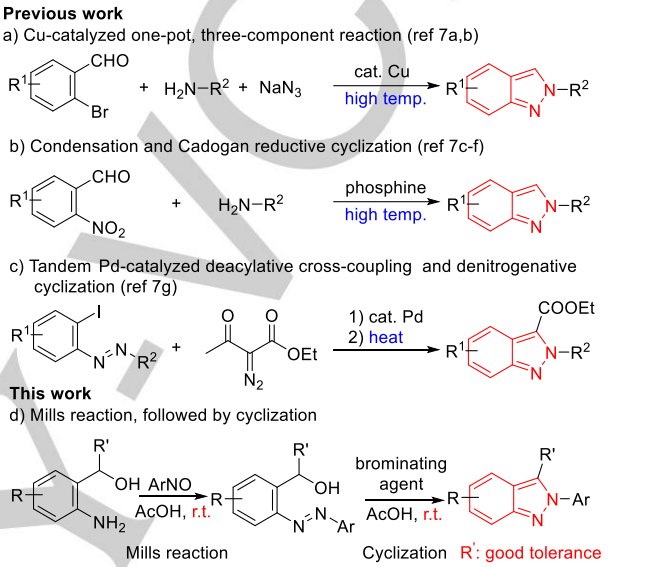


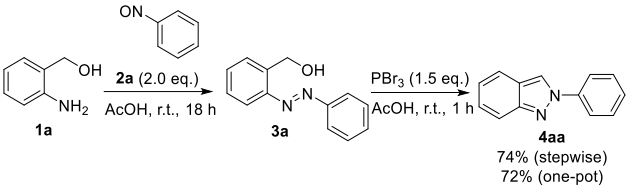
Figure 1. Examples of biologically active compounds and fluorophore bearing a 2*H*-indazole backbone.

Recently, there have been a few remarkable reports on the one-pot syntheses of 2*H*-indazoles. The synthesis involves a copper-catalyzed three-component reaction (Scheme 1a),[7a,b] condensation, and Cadogan reductive cyclization using organophosphorus reagents (Scheme 1b),[7c-f] or tandem palladium-catalyzed deacylative cross-coupling and denitrogenative cyclization (Scheme 1c).[7g] However, these reactions have inherent limitations such as the need for elevated temperatures and transition-metal reagents in addition to the narrow substrate scope (in particular, the difficulty in introducing various substituents at the C3 position of indazole). Herein, we demonstrate an operationally simple, one-pot, and metal-free synthesis of 2*H*-indazoles using 2-aminobenzyl alcohols, nitrosobenzenes, and brominating agents such as PBr_3 or $SOBr_2$ in acetic acid at room temperature.



Scheme 1. One-pot syntheses of 2*H*-indazoles.

We envisioned that the Mills reaction of 2-aminobenzyl alcohols with nitrosobenzenes would efficiently furnish an azobenzene intermediate in acetic acid, [8] which would be converted into 2*H*-indazole *via* cyclization by a brominating agent, with easily removable side products such as H_2O, SO_2, or HBr (Scheme 1d).



Scheme 2. Preliminary result for synthesis of 2*H*-indazole **4aa** using Mills reaction/cyclization

We preliminarily examined the Mills reaction of commercially available 2-aminobenzyl alcohol **1a** with nitrosobenzene **2a** (2.0 eq.) in acetic acid, and cyclization of azobenzene **3a** using PBr_3 (1.5 eq.) at room temperature in a stepwise manner. These reactions provided azobenzene **3a** in 93% yield and 2-phenyl-2*H*-indazole **4aa** in 80% yield with high purity, respectively (74% yield in 2 steps). This result encouraged us to investigate a one-pot sequence combining the Mills reaction and cyclization. Fortunately, the desired product **4aa** was obtained in 72% overall yield in this tandem reaction, without detrimental effects (Scheme 2).

On the basis of the abovementioned finding, we optimized the reaction conditions (the type of additive and its ratio) to improve

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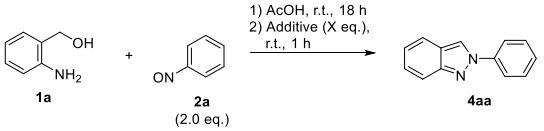
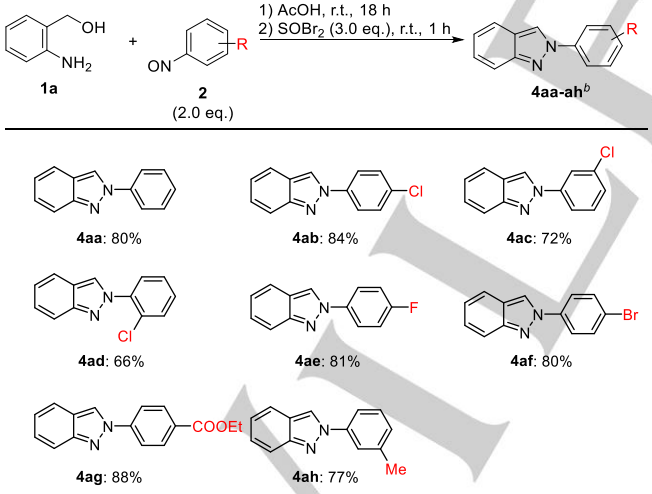
the yield in the cyclization step (Table 1). In the absence of the additive, 2*H*-indazole **4aa** was not formed (entry 1). When PBr_3 or $SOBr_2$ was used as the brominating reagent, **4aa** was obtained in good yield (entries 2 and 3). Chlorinating agents (entries 4 and 5: PCl_3, $SOCl_2$), Appel reaction conditions[9] (entry 6: I_2/PPh_3), and a strong acid[10] (entry 7: trifluoroacetic acid) were less effective for this procedure. Increasing the amount of $SOBr_2$ to 3.0 eq. improved the yield of **4aa** slightly (entry 8). In order to demonstrate the scalability of this methodology, a gram-scale reaction was carried out under the optimal conditions to obtain **4aa** in 80% yield (entry 9).

Table 1. Optimization of reaction conditions[a]



Entry	Additive	Eq.	Yield [%] in 2 steps[b]
1	-	-	-
2	PBr_3	1.5	72
3	$SOBr_2$	1.5	75
4	PCl_3	1.5	66
5	$SOCl_2$	1.5	61
6[c]	I_2 + PPh_3	1.5	-
7	TFA[g]	1.5	-
8[d]	$SOBr_2$	3.0	82 (80)[e]
9[d,f]	$SOBr_2$	3.0	80[e]

[a]General reaction conditions: **1a** (0.1 mmol), **2a** (0.2 mmol) in AcOH (0.5 mL) at r.t. for 18 h, followed by treatment with additive (0.15 mmol) at r.t. for 1 h. [b]^{1}H NMR yield using trimethoxybenzene as an internal standard. [c]I_2 (0.15 mmol), PPh_3 (0.15 mmol), 1*H*-imidazole (0.2 mmol) were used. [d]$SOBr_2$ (0.3 mmol) was used. [e]Isolated overall yield. [f]One gram of **1a** was used. [g]Trifluoroacetic acid.

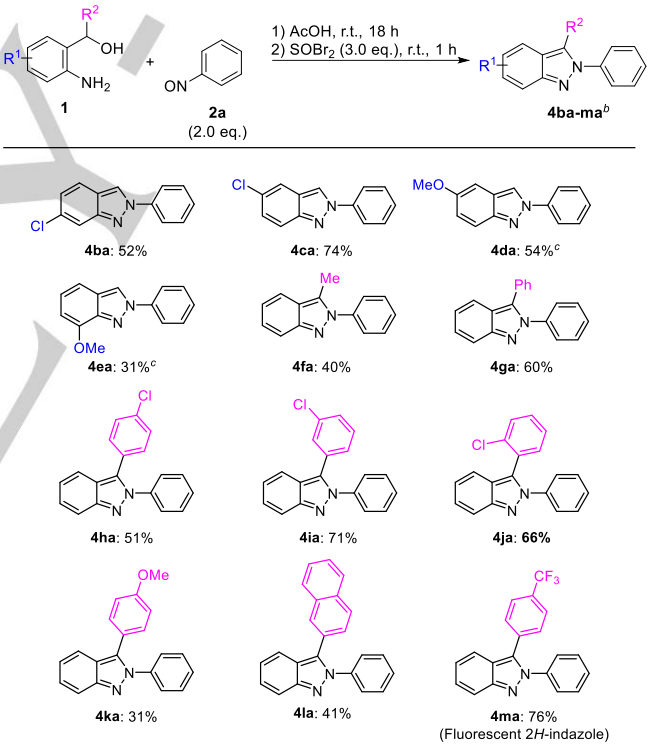


[d]Reaction conditions: **1a** (0.1 mmol), **2** (0.2 mmol) in AcOH (0.5 mL) for 18 h at r.t., followed by treatment with $SOBr_2$ (0.3 mmol) for 1 h at r.t. [b]Isolated overall yield.

Scheme 3. Scope of nitrosobenzenes

With the optimized reaction conditions in hand, we next investigated the scope of substrates for this reaction system. Initially, we evaluated a wide range of nitrosobenzenes **2** (Scheme 3). *p*-Chloronitrosobenzene **2b** reacted with 2-aminobenzyl alcohol **1a** to give the desired product **4ab** in 82% yield. Nitrosobenzene **2c** and **2d**, which has chloro substituent at *meta*- or *ortho*- position, furnished the corresponding products **4ac** and **4ad** in 72% and 66% yields, respectively. Other 4-halonitrosobenzenes **2e** and **2f** having a fluoro or a bromo group were also effectively transformed into the desired 2*H*-indazoles **4ae** and **4af** (81% and 80% yields, respectively). Treatment with another electron-deficient nitrosobenzene **2g** bearing an ethoxycarbonyl group provided **4ag** in the highest yield (88%). The use of **2h** with an electron-donating methyl group as the substrate under the optimal conditions led to the formation of 2*H*-indazole **4ah** in 77% yield.

Next, we then turned our attention to the scope of 2-aminobenzyl alcohols **1b-1j** bearing various substituents on the aromatic ring (Scheme 4). 2-Aminobenzyl alcohols with an electron-withdrawing chloro group at the 4- and 5-positions afforded the desired 2*H*-indazoles **4ba** and **4ca** in 52% and 74% yields, respectively. The reaction of nitrosobenzene **2a** with electron-rich 2-aminobenzyl alcohols [R^1 = 4-MeO (**1d**); 3-MeO (**1e**)] gave **4da** and **4ea**, which was converted into liver X receptor agonist **5** by arylation at the C3 position, as shown in Scheme 5.[11] To suppress undesired side reactions when using **1d** and **1e**, the less reactive PBr_3 was preferred over $SOBr_2$.

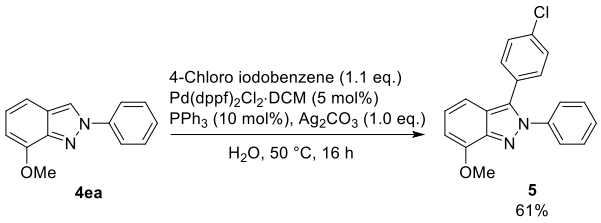


[a]Reaction conditions: **1** (0.1 mmol), **2a** (0.2 mmol) in AcOH (0.5 mL) at r.t. for 18 h, followed by treatment with $SOBr_2$ (0.3 mmol) at r.t. for 1 h. [b]Isolated overall yield. [c]PBr_3 (0.4 mmol) was used instead of $SOBr_2$.

Scheme 4. Scope of 2-aminobenzyl alcohols[a]

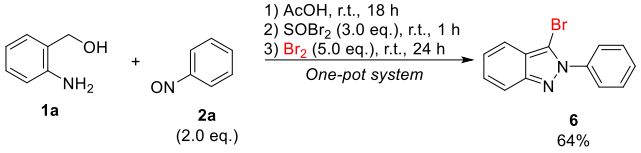
Notably, various C3-substituted indazoles could be synthesized by utilizing commercially available 1-(2-aminophenyl)ethanol **1f** and 2-aminobenzhydrol **1g**; in these cases, C3-methyl and phenyl 2*H*-indazoles **4fa** and **4ga** were obtained in moderate yields. Moreover, the reaction of nitrosobenzene **2a** with electron-deficient 2-aminobenzhydrols **1h-1j** [R^2 = 4-ClC_6H_4 (**1h**); 3-ClC_6H_4 (**1i**); 2-ClC_6H_4 (**1j**)] gave the corresponding products **4ha**-**4ja** (51-71% yields). Additionally, electron-rich and sterically bulky starting materials **1k** and **1l** [R^2 = 4-$MeOC_6H_4$ (**1k**); 2-

naphtyl (**1l**)] were converted into desired 2*H*-indazoles **4ka** and **4la** in acceptable yields. Finally, the use of **1m** bearing a CF_3 group allowed the formation of fluorescent 2*H*-indazole **4ma** in 76% yield.[12]



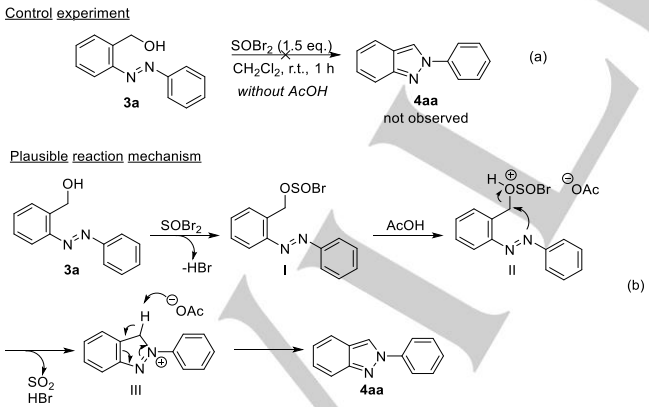
Scheme 5. Synthesis of liver X receptor agonist **5**

To increase the utility of this reaction, we investigated the one-pot synthesis of 3-bromo-2*H*-indazole, which can be transformed into a variety of 3-functionalized 2*H*-indazoles (Scheme 6).[13] As expected, 2*H*-indazole **4aa** was obtained first, which upon subsequent treatment with bromine provided 3-bromo-2*H*-indazole **6** in 64% overall yield over 3 steps.



Scheme 6. One-pot synthesis of 3-bromo-2*H*-indazole **6**

To gain mechanistic insight into the key cyclization step, the following control experiment was performed. When cyclization of the intermediate azobenzene **3a** was carried out in dichloromethane using $SOBr_2$, 2*H*-indazole **4aa** was not formed. This result indicated that acetic acid would also play a crucial role in the cyclization step as well as the Mills reaction (Scheme 7a). Judging from the reaction outcome, the cyclization would proceed *via* intramolecular S_N2 cyclization, as shown in Scheme 7b. Initially, bromosulfinilation of the OH group by $SOBr_2$ occurs,



Scheme 7. Control experiment and plausible mechanism of the cyclization step by $SOBr_2$/AcOH

with the evolution of HBr. Acetic acid protonates intermediate I to produce intermediate II. Subsequently, intermediate II is cyclized to provide intermediate III *via* intramolecular S_N2 cyclization with the release of SO_2 and HBr. Finally, 2*H*-indazole **4aa** is obtained by deprotonation of cyclized intermediate III, with dearomatization of the benzene ring by the acetate anion.In conclusion, we have developed a metal-free and operationally simple method for the synthesis of 2*H*-indazoles *via* Mills reaction and cyclization. The present reaction is applicable to both non-substituted 2*H*-indazoles and C3-substituted 2*H*-indazoles, which has been a long-standing challenge in synthetic chemistry. The one-pot 2*H*-indazole synthesis, followed by bromination, provides synthetically useful 3-brominated 2*H*-indazoles. Further investigation into the reaction mechanism and the practical application of this protocol for other *N*-heteroaromatic compounds are in progress.

Experimental Section

General procedure for one-pot synthesis of 2*H*-indazole *via* Mills reaction and cyclization sequence

A solution of 2-aminobenzyl alcohol **1a** (12.3 mg, 0.1 mmol) and nitrosobenzene **2a** (21.4 mg, 0.2 mmol) in acetic acid (0.5 mL) was stirred for 18 h, then treated with $SOBr_2$ (23 µL, 0.3 mmol) for 1 h. The reaction mixture was neutralized with saturated $NaHCO_3$ aq. solution and extracted with AcOEt. The combined organic layer was dried over Na_2SO_4, filtrated, and evaporated under vacuum. The crude residue was purified by silica column chromatography (Hexane/AcOEt = 95/5) to afford 2*H*-indazole **4aa** (15.5 mg, 80%) as a white solid.

Acknowledgements

This work was supported by JSPS KAKENHI Grant Numbers JP18K14221 in Grant-in-Aid for Young Scientists, JP16K08163 in Grant-in-Aid for Scientific Research (C), JP18H04412 in Middle Molecular Strategy, Iketani Science and Technology Foundation. We acknowledge the technical staff of the Comprehensive Analysis Center of ISIR, Osaka University (Japan).

Keywords: indazole · one-pot reaction · nitrogen heterocycles · metal-free· cyclization

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[12] We also examined various other R^2 on **1** groups by using this procedure. Starting materials with a strongly electron-withdrawing group ($R^2 = CF_3$ and COOEt) and allyl group ($R^2 = CH_2CH{=}CH_2$) did not provide any desired products. Additionally, the reaction of substrate **1** bearing a heteroaromatic such as 2-pyridyl and 2-thienyl gave the trace amount of 2*H*-indazole (< 10%).

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Layout 2:

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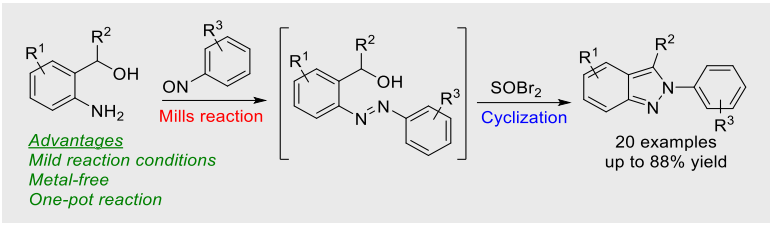

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