A Novel and Efficient Synthesis of 2-Aryl-2*H*-indazoles via $SnCl_2$-Mediated Cyclization of 2-Nitrobenzylamines

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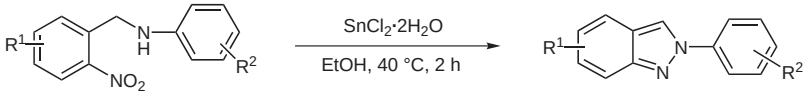
Abstract: A mild, efficient, and novel synthesis of 2-aryl-2*H*-indazoles via cyclization of 2-nitrobenzylamines promoted by $SnCl_2{\cdot}2H_2O$ has been described. This method applies to a wide scope of substrates containing electron-donating and electron-withdrawing substituents.

Key words: 2-aryl-2*H*-indazole, 2-nitrobenzylamine, $SnCl_2$

Indazole is well known as an aza analogue of indole, and a number of indazole derivatives have powerful pharmacological activities including anti-inflammatory,[1] antitumor,[2] anti-HIV,[3] antidepressant,[4] contraceptive activities,[5] anti-aggregatory, and vasorelaxant activity by NO release.[6] Recently, Aran reported some new 5-nitroindazole derivatives have trichomonacidal, antichagasic, and antineoplastic activities.[7] Different approaches to the synthesis of 2-substituted indazoles have been proposed.[8] The reduction of secondary 2-nitrobenzyl amines with Sn, Zn, or Fe in acidic medium,[9] produced 2-substituted indazole byproduct in low yields. The direct N-alkylation[10] and N-arylation[11] of indazole yielded mixtures of 1- and 2-substituted indazole with poor selectivities. The reaction of 2-nitrobenzylidenamines with trivalent organophosphorous reagents as deoxygenating agents resulted in 2-aryl-2*H*-indazoles with high yields, but the drastic conditions of the reaction restrict application.[12] The reduction of 2-nitrobenzylamines and subsequent cyclization to 2-substituted indazoles were achieved by an electrochemical method, but this method requires special equipment.[13] Transition-metal-complex-catalyzed N–N bond formation via reductive carbonylation of *N*-(2-nitrobenzylidene)amine yielded 2*H*-indazoles, but this reaction performed under drastic conditions (i.e., at 100 °C under 20 kg cm^{-2} of CO pressure).[14] The palladium-catalyzed intramolecular amination of the corresponding *N*-aryl-*N*-(*o*-bromobenzyl)hydrazines yielded 2-substituted-2*H*-indazoles, however, the yield of this reaction is low and the time of the reaction is long.[15] A one-step heterocyclization of 2-nitrobenzylamines in the presence of KOH and alcohol produced 3-alkoxy-2*H*-indazoles, however, only one 2-aryl-2*H*-indazole was mentioned with low yield.[16] Recently, Huo reported a novel synthesis of 5,6-dihydroindazolo[3,2-*a*]isoquinolines and their relative compounds via $SnCl_2{\cdot}2H_2O$ as reducing agent.[17] Although these methods have successfully led to a large repertoire of 2*H*-indazole synthetic routes, many of these still suffer from drawbacks such as unsatisfactory yields, long reaction time, occurrence of side reactions, use of an expensive catalyst, high temperature, and inaccessible starting materials. Therefore, the development of more efficient methods for the preparation of this kind of compounds is still an active research area and there is room for further improvement toward milder reaction conditions and improved yields with a greener nature. In this paper, we wish to describe a new route to 2-aryl-2*H*-indazoles through the creation of the N–N bond via a $SnCl_2$-mediated cyclization of 2-nitrobenzylamines (Scheme 1).

In a preliminary study, *N*-(4-fluorophenyl)-2-nitrobenzylamine (**1a**, Table 1), which was readily prepared by a literature procedure,[16] was used to define the reaction conditions for the reductive cyclization sequence. When compound **1a** was reduced with different reagents (entries 1–4, Table 1), only the $SnCl_2{\cdot}2H_2O$/EtOH system gave the desired product **2a** (50% yield). Further optimization of the reaction conditions revealed that the use of two equivalents $SnCl_2{\cdot}2H_2O$ at 40 °C gave superior results (entries 5–11, Table 1).



1 2

Scheme 1

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Table 1 Optimization of Reductive Reagent, Ratio, and Temperature in the Synthesis of 2-(4-Fluorophenyl)-2*H*-indazole (**2a**)

Entry	Reductive reagent	Ratio (**1a**:reductive reagent)	Temp (°C)	Yield (%)
1	$TiCl_4$-Zn, THF	1:2	reflux	0
2	Zn-NH_4Cl, EtOH	1:2	reflux	0
3	$SnCl_2{\cdot}2H_2O$, HCl–EtOH	1:2	reflux	0
4	$SnCl_2{\cdot}2H_2O$, EtOH	1:2	reflux	50
5	$SnCl_2{\cdot}2H_2O$, EtOH	1:2	60	56
6	$SnCl_2{\cdot}2H_2O$, EtOH	1:2	40	65
7	$SnCl_2{\cdot}2H_2O$, EtOH	1:2	r.t.	47
8	$SnCl_2{\cdot}2H_2O$, EtOH	1:1	40	56
9	$SnCl_2{\cdot}2H_2O$, EtOH	1:3	40	39
10	$SnCl_2{\cdot}2H_2O$, EtOH	1:4	40	22
11	$SnCl_2{\cdot}2H_2O$, EtOH	1:5	40	23

In order to apply this reaction to a library synthesis, various 2-nitrobenzylamines were subjected to the reaction conditions and representative examples are shown in Table 2. Most of the 2-nitrobenzylamines gave the expected 2-aryl-2*H*-indazole products in moderate to good yields, either bearing electron-withdrawing groups (such as halides) or electron-donating groups (such as alkyl or alkoxyl groups) under the same reaction conditions. Therefore, we concluded that the electronic nature of the substituents has no significant effects on this reaction. However, when the aromatic groups were 2-methylphenyl, 2-naphthyl and 5-quinolyl, the reactions did not take place and the desired products were not obtained, suggesting that steric hindrance plays a critical role in this reaction.

All the structures of the products were characterized by ^{1}H NMR, ^{13}C NMR, IR, MS spectra, and elemental analysis.[19] In addition, the structure of compound **2i** was further confirmed by X-ray diffraction analysis (Figure 1).[20]

Table 2 Synthesis of 2-Aryl-2*H*-indazole via $SnCl_2$-Mediated Cyclization of 2-Nitrobenzylamine[18]

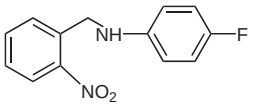
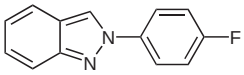
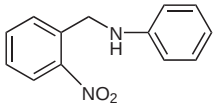
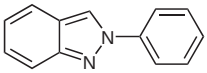
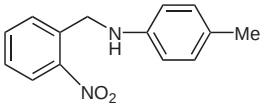
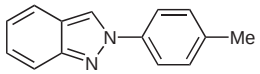
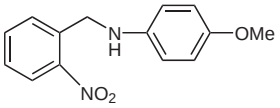
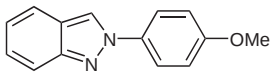
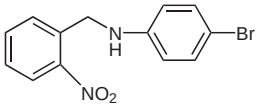
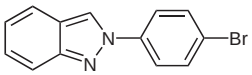
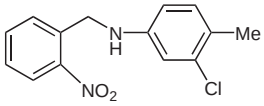
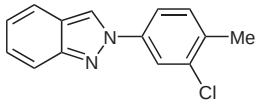
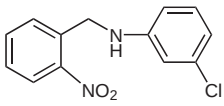
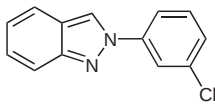
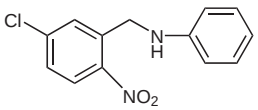
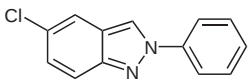
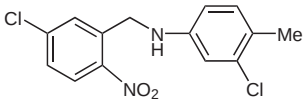
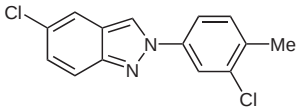
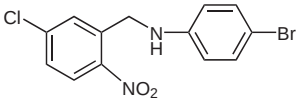
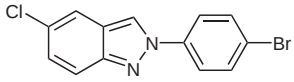
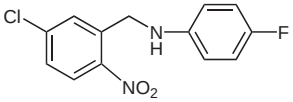
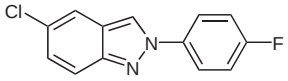
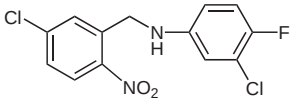
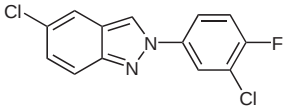
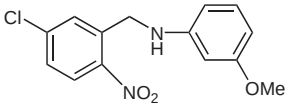
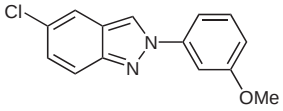
Entry	Substrate[a]	Product	Yield (%)[b]
2a			65
2b			88
2c			40
2d			46
2e			85
2f			71
2g			75
2h			65

Table 2 Synthesis of 2-Aryl-2*H*-indazole via $SnCl_2$-Mediated Cyclization of 2-Nitrobenzylamine[18] (continued)

Entry	Substrate[a]	Product	Yield (%)[b]
2i			72
2j			70
2k			68
2l			60
2m			61

[a] All substrates were prepared according to the literature procedure.[16]
[b] Isolated yields by crystallization.

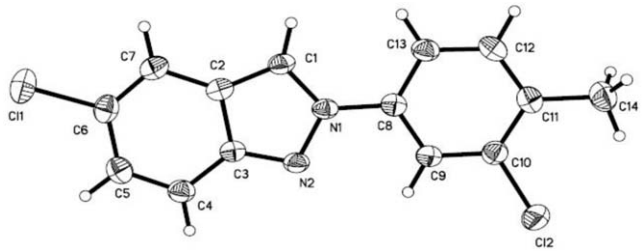
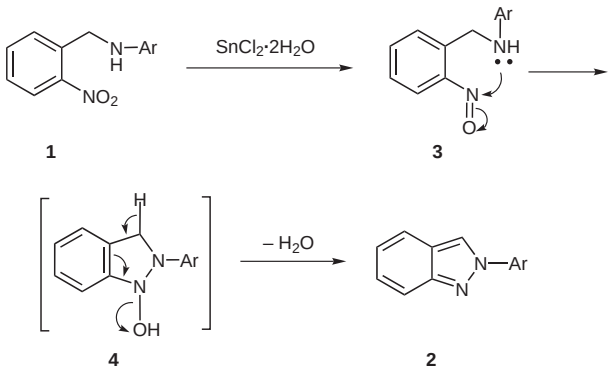


Figure 1 The molecular structure of compound **2i**

We propose the following possible mechanism (Scheme 2) to account for the reaction. At the first step, **1** was reduced by $SnCl_2$ to **3**. This nitroso compound then cyclized by the nucleophilic attack of the NH group onto the nitroso group giving intermediate **4**. Finally, the expected product **2** was produced by elimination of water.



Scheme 2

In summary, a series of 2-aryl-2*H*-indazoles were synthesized via cyclization of 2-nitrobenzylamines promoted by $SnCl_2$. The advantages of this new method are the easily accessible starting materials, convenient manipulation, short reaction time, and moderate to high yields.

Acknowledgment

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(17) Kuo, C. Y.; Wu, M. J. *J. Chin. Chem. Soc.* **2005**, *52*, 965.
(18) **General Procedure for the Synthesis of 2-Aryl-2*H*-indazoles**
A solution of 2-nitrobenzylamine (3 mmol) and $SnCl_2 \cdot 2H_2O$ (6 mmol) in 95% EtOH (20 mL) was allowed to stir at 40 °C for 2 h. The reaction mixture was quenched with 3% HCl (100 mL), filtrated, the crude product was purified by crystallization from 95% EtOH to give the pure products **2**.
(19) **Representative Spectral Data for 2b**
^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.12 (s, 1 H, H-3), 8.10 (d, 2 H, *J* = 8.0 Hz, ArH), 7.78 (d, 2 H, *J* = 8.4 Hz, ArH), 7.72 (d, 2 H, *J* = 8.4 Hz, ArH), 7.46 (t, 1 H, *J* = 7.2 Hz, ArH), 7.32 (t, 1 H, *J* = 8.0 Hz, ArH), 7.11 (t, 1 H, *J* = 7.6 Hz, ArH) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ = 149.12, 140.12, 129.86, 128.02, 126.96, 122.64, 122.28, 121.74, 121.11, 120.42, 117.65 ppm. IR (KBr): ν = 3131, 3066, 1626, 1593, 1518, 1494, 1464, 1407, 1378, 1349, 1314, 1250, 1231, 1201, 1143, 1129, 1073, 1044, 950, 907, 820, 780, 754, 685 cm^{-1}. MS: *m/z* (%) = 194 (100) [M$^+$]. Anal. Calcd for $C_{13}H_{10}N_2$: C, 80.39; H, 5.19; N, 14.42. Found: C, 80.55; H, 5.29; N, 14.26.
(20) Crystallographic data for the structure of **2i** has been deposited at the Cambridge Crystallographic Data Centre under the deposit number CCDC-655981. Copies of available material can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 (1223)336033; e-mail: deposit@ccdc.cam.ac.uk]. Crystal data for **2i**: $C_{14}H_{10}Cl_2N_2$; *M* = 277.14, colorless block crystals, 0.43 × 0.40 × 0.32 mm, monoclinic, space group $P2_1/c$, *a* = 14.234(3) Å, *b* = 14.438(3) Å, *c* = 6.0511(15) Å, *α* = 90°, *β* = 92.338(7)°, *γ* = 90°, *V* = 1242.5(5) Å^3, *Z* = 4, D_c = 1.481 g cm^{-1}, *F*(000) = 568, *μ* (Mo Kα) = 0.503 mm^{-1}. Intensity data were collected on a diffractometer with graphite monochromated Mo Kα radiation (λ = 0.71073 Å) using *ω* scan mode with 1.43° < θ < 25.00°; 2183 unique reflections were measured and 1532 reflections with $I > 2\sigma(I)$ were used in the refinement. The structures were solved by direct methods and expanded using Fourier techniques. The final cycle of full-matrix least squares technique to *R* = 0.0460 and *wR* = 0.1283.