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Active and Recyclable Catalytic Synthesis of Indoles by Reductive Cyclization of 2-(2-Nitroaryl)acetonitriles in the Presence of Co−Rh Heterobimetallic Nanoparticles with Atmospheric Hydrogen under Mild Conditions

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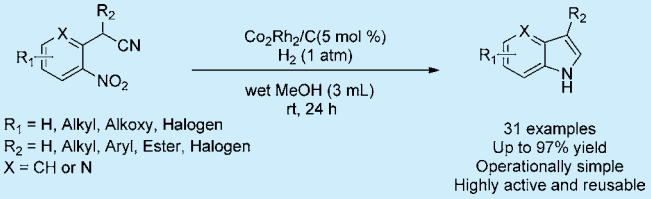
Supporting Information

ABSTRACT: A cobalt−rhodium heterobimetallic nanoparticle-catalyzed reductive cyclization of 2-(2-nitroaryl)-acetonitriles to indoles has been achieved. The tandem reaction proceeds without any additives under the mild conditions (1 atm H_2 and 25 °C). This procedure could be scaled up to the gram scale. The catalytic system is significantly stable under these reaction conditions and could be reused more than ten times without loss of catalytic activity.

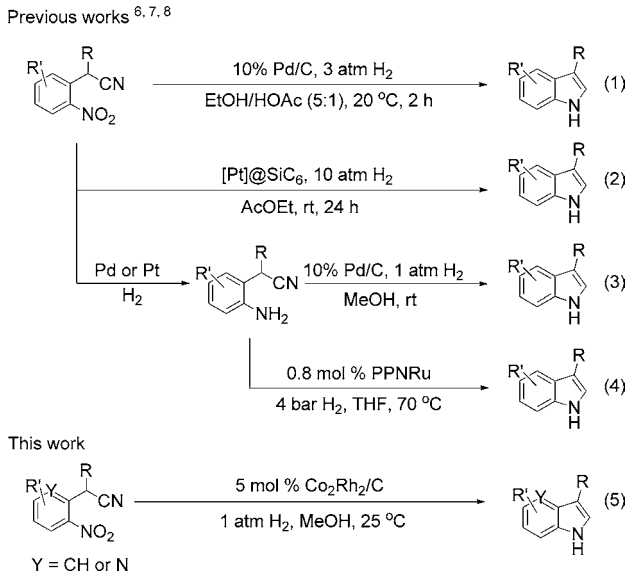


Indoles[1] are ubiquitous structural units of biologically active natural products and pharmaceutical compounds. The synthesis of indoles has attracted substantial attention, and a number of useful synthetic methods for indoles have been developed, established, and reviewed.[2] However, the scope and generality of the synthesis of a particular indole have sometimes been restricted owing to the lack of substrate availability. Consequently, the development of efficient and atom-economical methods for the synthesis of indoles from readily available starting materials is still challenging. From this perspective, 2-(2-nitroaryl)acetonitriles[3] could be good candidates because they are easily obtained from commercially available starting materials and thus might be suitable substrates for the synthesis of 3- to 7-substituted indoles. It has been especially reported[4] that C3-arylindoles exhibit important biological responses. In fact, the use of 2-(2-nitroary1)acetonitriles in the synthesis of indoles has been well-established.[5] For example, Mąkosza reported[6] the reduction of 2-(2-nitroaryl)acetonitriles in the presence of palladium on activated charcoal to the corresponding indoles in moderate to high yields (Scheme 1, eq 1). However, the reaction was very complicated and sensitive to the reaction conditions because the reaction should be carried out in an acidic condition and relatively high pressure where mixture solvent of ethanol and acetic acid (5:1) and 3 atm of hydrogen gas were used together. Nagashima also reported[7] the reaction of 2-nitrophenylacetonitriles with the heterogeneous platinum catalyst [Pt]@SiC_6 affording a reductive cyclization product, indole, with 52% yield (Scheme 1, eq 2), but the reaction required 10 atm of hydrogen, which is much higher than the pressure used for Mąkosza's reaction.

Although the use of (2-nitroaryl)acetonitriles as substrates has been revealed as an attractive method for the synthesis of indoles, nevertheless, it has been rarely used for the purpose of indole synthesis in a direct way. Instead, as an indirect way, 2-(2-aminoaryl)acetonitriles, prepared by the reduction of 2-(2-nitroaryl)acetonitriles, has been most commonly used in the conversion to indoles (Scheme 1, eqs 3 and 4).[8] Therefore, we were interested in reevaluation for a direct way of use of 2-nitrophenylacetonitriles in the synthesis of indoles by simple hydrogenation.

Recently, the use of heterobimetallic nanoparticles as catalysts has attracted much attention because of their superior catalytic performance compared to that of heteromonometallic nano-

Scheme 1. Catalytic Synthesis of Indoles



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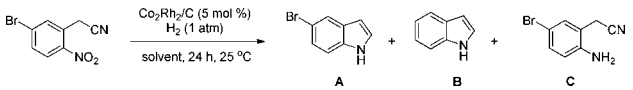
particles.[9] We reported that cobalt/rhodium heterobimetallic nanoparticles (Co_2Rh_2, derived from $Co_2Rh_2(CO)_{12}$) immobilized on charcoal (Co_2Rh_2/C) showed wide usefulness for Pauson–Khand reaction[10] and hydrogenation of nitroarenes.[11] Hoping to find a new catalytic reaction, we found that Co_2Rh_2/C could be used for reductive cyclization of 2-(2-nitroaryl)-acetonitriles under atmospheric hydrogen at room temperature, leading to the isolation of indoles with high yields (eq 5). We herein present our results that the reductive cyclization with Co_2Rh_2/C could be conducted under substantially lower pressure and atmospheric hydrogen and could be reused more than ten times without loss of catalytic activities. As far as we are aware, this is the first report of indoles and azaindoles under only 1 atm of hydrogen at room temperature.

Initially, we studied the hydrogenation of aryl nitriles under 1 atm of hydrogen (a balloon of hydrogen) at ambient temperature in the presence of Co_2Rh_2/C. Benzonitrile was easily converted to benzyl amine, *N*-benzyl-1-phenylmethanimine, and dibenzyl amine (see SI). It is notable that the easy formation of secondary amine or imine under mild reaction conditions is remarkable.[12]

Encouraged by these observations, we began to investigate the reductive cyclization of 2-(2-nitroaryl)acetonitriles. The reaction conditions were optimized using 0.25 mmol of substrate with 5 mol % Co_2Rh_2/C under 1 atm H_2 (using a balloon of hydrogen) at 25 °C.

Using 2-(5-bromo-2-nitrophenyl)acetonitrile as a substrate, we screened the reaction medium (Table 1, entries 1–6), and

Table 1. Screening the Reductive Cyclization of 2-(5-Bromo-2-nitrophenyl)acetonitrile



entry	solvent[a]	isolated yield (%) (**A**/**B**/**C**)
1	MeOH	75 (68/7/0)
2	THF	57 (57/0/0)
3	CH_2Cl_2	54 (54/0/0)
4	benzene	24 (24/0/0)
5	toluene	57 (57/0/0)
6	*p*-xylene	60 (60/0/0)
7[b]	MeOH	62 (10/0/52)
8[c]	MeOH	70 (34/36/0)
9[d]	MeOH	42 (42/trace/0)
10[e]	MeOH	61 (57/4/0)
11[f]	MeOH	69 (62/7/0)
12[g]	MeOH	68(63/5/0)
13	wet MeOH	76 (70/6/0)

[a]3 mL used. [b]1 mol % catalyst used. [c]10 mol % catalyst used. [d]Reaction time was 3 h. [e]Reaction time was 8 h. [f]Reaction time was 16 h. [g]Reaction temperature was 50 °C.

reasonable yields were observed for all solvents used. The highest total yield of reductive cyclization products (75%) was observed with methanol and a debromination product, 1*H*-indole (**B**), was isolated in no more than 7% yield. Using methanol as a representative reaction solvent, we examined how the reaction depended on the amount of Co_2Rh_2/C used (entry 1 vs 7 and 8). Decreasing the amount of the catalyst from 5 to 1 mol % led to the formation of a mixture of 5-bromoindole (**A**) and 2-(2-aminophenyl)acetonitrile (**C**) in 10% and 52% yield, respectively (entry 7). When the amount of the catalyst increased from 5 to 10 mol %, formation of **A** and **B** in 34% and 36% yield, respectively, was observed (entry 8). Decreasing the reaction time from 24 h to 3, 8, and 16 h resulted in the isolation of cyclization product in 42%, 61%, and 69% yields, respectively (entries 9–11). When a reaction was conducted at 50 °C, **A** and **B** were isolated in 63% and 5% yields, respectively (entry 12). To our delight, when the reaction was conducted in wet methanol, a similar high yield, 76%, to the reaction conducted in dry methanol was observed (entry 13). This means that the solvent (MeOH) could be used without purification, allowing the catalytic system to be operationally simple. Other metal nanoparticles, such as Co/C and Rh/C, were examined as a catalyst using 2-(2-nitrophenyl)acetonitrile as a substrate (see SI). In the case of Co/C, no reaction was observed. Interestingly, Rh/C showed a high catalytic activity in the reductive cyclization of 2-(2-nitrophenyl)acetonitrile, but no desirable product was obtained in the reaction of 2-(6-methoxy-3-nitropyridin-2-yl)acetonitrile. Among the catalysts studied, no other case gave a higher yield and wider substrate scope than Co_2Rh_2/C. Thus, the optimum reaction conditions for the reductive cyclization were temporarily established as follows: 0.25 mmol of substrates and 5 mol % Co_2Rh_2/C in 3.0 mL MeOH at 25 °C for a reaction time of 24 h.

With the optimized reaction conditions in hand, the substrate scope of the reaction was next examined (Table 2). The reductive cyclization reaction showed excellent generality for a variety of 2-(2-nitroaryl)acetonitriles substrates. In some cases, sublimation, dehalogenation, and steric hindrance might have a slightly unfavorable effect on the yield. For example, because some indoles suffered from sublimation while drying *in vacuo*, their isolated yields were not as great as we expected. With regard to dehalogenation, bromo-substituted starting materials were merely undergone (entries 17–19). Chloro group at the α position to the nitrile was intolerant likewise under our reaction conditions (entry 10), yielding 1*H*-indole as the sole product. 3-Benzyl-1*H*-indole showed low yield (27%), but this could be overcome and approximately doubled by lengthening the reaction time (entry 9, 48 h). This result presumably occurred due to the benzyl group, hampering coordination to the nanoparticles as proposed by Sajiki et al.[8a] Beside these observations above, for overall α-substituted 2-(2-nitrophenyl)-acetonitrile, the corresponding indoles were isolated in high to excellent yields (71–97%) (entries 2–8). Moreover, the halo (F and Cl) substituents in 2-(5-halo-2-nitrophenyl)acetonitriles and 2-(6-halo-2-nitrophenyl)acetonitriles were generally survived (entries 11–16). The corresponding products were isolated in reasonable to high yields (71–91%). In general, both electron-donating (OMe) and -withdrawing (F, Cl, Br, CF_3) groups on the aromatic substituents of the substrates are tolerated (entries 11–25). When 2,2-bis(2-nitrophenyl)acetonitrile was used as a substrate, 2-(1*H*-indol-3-yl)aniline, widely used in the synthesis of indolo[2,3-*c*]quinolines,[13] was isolated in 79% yield (entry 26). Treatment of 2-(1-nitronaphthalen-2-yl)acetonitrile with hydrogen afforded 1*H*-benzo[*g*]indole in 77% yield. This presents the first synthesis of 1*H*-benzo[*g*]indole from the substrate having both a nitrile and a nitro group via the reductive cyclization (entry 27). In addition, the reaction could be conducted on a gram-scale. A total of 1.58 g of 1*H*-indole was isolated in 65% yield from 2-(2-nitrophenyl)acetonitrile. Thus, it was proven that scale-up of the procedure resulted in no reduction in the yield.

To test electronic effects, (5-methoxy-2-nitrophenyl)-2-(2-nitrophenyl)acetonitrile and 2-(5-chloro-2-nitrophenyl)-2-(2-nitrophenyl)acetonitril were prepared and reacted under our

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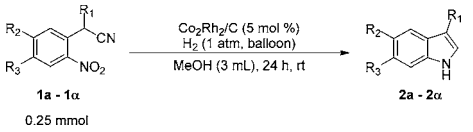
Table 2. Synthesis of Indoles[a]

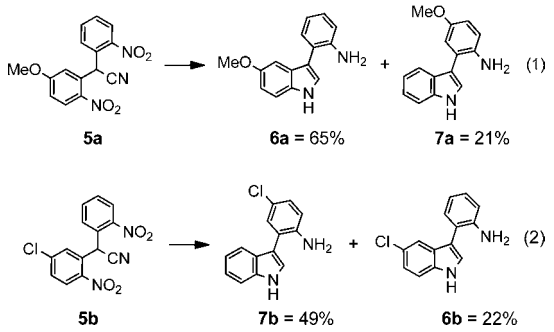


	reactant			
entry	R_1	R_2	R_3	yield (%)[a]
1	H	H	H	68 (**2a**)
2	Me	H	H	80 (**2b**)
3	Et	H	H	97 (**2c**)
4	Pr	H	H	81 (**2d**)
5	Ph	H	H	83 (**2e**)
6	4-FC_6H_4	H	H	86 (**2f**)
7	4-ClC_6H_4	H	H	71 (**2g**)
8	4-$MeOC_6H_4$	H	H	78 (**2h**)
9	CH_2Ph	H	H	27 (49)[b] (**2i**)
10	Cl	H	H	56[c] (**2j**)
11	H	F	H	71 (**2k**)
12	H	Cl	H	73 (**2l**)
13	Me	Cl	H	76 (**2m**)
14	Pr	Cl	H	89 (**2n**)
15	H	H	Cl	71 (**2o**)
16	(CO)OEt	H	Cl	91 (**2p**)
17	Me	Br	H	78 (**2q**)
18	Pr	Br	H	53 (**2r**)
19	(CO)OEt	H	Br	92 (**2s**)
20	H	CF_3	H	49 (**2t**)
21	H	H	CF_3	73 (**2u**)
22	H	OMe	H	68 (**2v**)
23	Me	OMe	H	90 (**2w**)
24	Pr	OMe	H	73 (**2x**)
25	H	OMe	OMe	59 (**2y**)
26	2-NO_2-C_6H_4	H	H	79[d] (**2z**)
27	2-(1-nitronaphthalen-2-yl)acetonitrile			77 (**2α**)

[a]Isolated yield. [b]When the reaction proceeded for 48 h, a yield was 49%. [c]1*H*-indole was isolated. [d]An isolated product was 2-(1*H*-indol-3-yl)aniline.

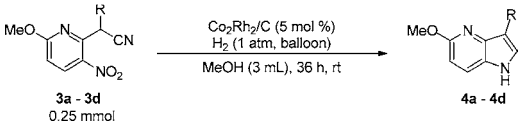
reaction conditions (Scheme 2). In the first reaction, 2-(5-methoxy-1*H*-indol-3-yl)aniline and 2-(1*H*-indol-3-yl)-4-methoxyaniline were isolated in 65% and 21% yield, respectively. In the second reaction, 2-(5-chloro-1*H*-indol-3-yl)aniline and 4-chloro-2-(1*H*-indol-3-yl)aniline were isolated in 22% and 49% yields, respectively. This observation clearly demonstrated that the electron-richness of substituent favors the intramolecular nucleophilic attack of the amine group, helping cyclization.

Scheme 2. Competition Experiments



Azaindoles possess remarkable pharmacological and physicochemical properties, although their direct functionalization at the C3 position is not straightforward.[14] Thus, we investigated the reductive cyclization of 2-(3-nitropyridin-2-yl)acetonitrile derivatives under our mild conditions (Table 3). Pyridine derivatives were then hydrogenated to provide the corresponding C3-substituted 4-azaindoles in high yields (61−72%).

Table 3. Synthesis of Azaindoles



entry	reactant	yield (%)[a]
1	R = H	61 (**4a**)
2	R = Me	72 (**4b**)
3	R = Pr	67 (**4c**)
4	R = CH_2(CO)OEt	65 (**4d**)

[a]Isolated yield.

Thus, the catalytic reaction process developed in this study revealed a greatly easy and simple way to make indoles and azaindoles under the user-friendly condition (1 atm H_2 and 25 °C).

The reusability of Co_2Rh_2/C was examined for the reductive cyclization of 2-(2-nitrophenyl)acetonitrile (see SI). The catalyst maintained a high level of activity even after being reused ten times. After ten runs, the recovered catalyst was reused in the reductive cyclization of 2-(2-nitrophenyl)butanenitrile under the same reaction conditions, and 3-ethyl-1*H*-indole was isolated in 94% yield. The catalytic system showed a great capability of reuse and a significant air-stability under the reaction conditions. Moreover, plausible reaction pathways were proposed based on GC−MS data.[15]

In conclusion, we have developed an operationally simple, highly active, and recyclable method for the Co_2Rh_2 nanoparticles/charcoal-catalyzed cascade reductive cyclization of (2-nitroaryl)acetonitriles to indoles and 2-(3-nitropyridin-2-yl)-acetonitrile to azaindoles. To the best of our knowledge, this is the first report of indoles and azaindoles synthesis under only 1 atm of hydrogen at room temperature. Advantageously, no complicated ligands or additional acid or base is needed. The experimental simplicity and reusability (more than ten times) are especially attractive features of the catalytic system and should encourage its use among synthetic chemists. Further investigations of the present catalytic system for other reactions are currently ongoing in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02659.

Experimental procedures, characterization data, reduction of benzonitrile, reductive cyclization in the presence of monometallic nanoparticles, reuse of Co_2Rh_2/C in the synthesis of indoles, and plausible reaction pathway (PDF)

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Notes

The authors declare no competing financial interest.

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(15) See the Supporting Information for plausible reaction pathways.

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