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Reductive heterocyclizations via indium/iodine-promoted one-pot conversion of 2-nitroaryl aldehydes, ketones, and imines

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Abstract—2-Nitroaryl aldehydes, ketones, and imines were reductively cyclized to 2,1-benzisoxazoles with good yields in the presence of indium and iodine in MeOH. Under a similar condition, *N*-(2-nitrobenzylidene)anilines were produced mixtures of 2,1-benzisoxazoles and 3-anilino-2-phenyl-2*H*-indazoles.

Since the past decade, indium has been receiving increasing interest due to its applications in organic transformations.[1] In particular, indium-mediated reactions in aqueous media have been focused on synthetic applications because of environmental issues and the ease of reactions that obviate the need for inflammable anhydrous organic solvents and inert atmosphere.[1b] Indium can be used in various reactions in aqueous conditions without requiring inert atmosphere: in alkylation of aldehydes and ketones,[2] reductive coupling of aldimines,[3] Reformatsky and aldol reactions,[4] allenylation or allylation of aldehydes and ketones,[5] and ring expansion of carbocycles.[6]

Of special interest to us is the possibility of utilizing the indium-promoted reaction for the preparation of various nitrogen-containing heterocyclic compounds as an extension of the study on reductive cyclization reaction of 2-nitroarenes,[7] as only a limited number of applications of indium, other than carbon–carbon bond formation, are found in the literature.[1a,8] In our study of heterocyclic compound formation via reductive cyclization reaction of nitroarenes,[7,9] we have found that the nitro group can be reduced by chemical or electrochemical method, and it can initiate the heterocyclization toward nitrogen-containing heterocycles such as 2,1-benzisoxazoles and benzotriazoles when it has a proper functional group at the *ortho* position. Moreover, reductive heterocyclizations using indium were also successfully transformed into heterocyclic compounds such as 2,1-benzisoxazoles,[10a] benzimidazoles,[10b] and quinolines.[10c]

In recent years, iodine has been used for various organic transformations including Lewis acid catalyst.[11] Furthermore, iodine has been known to make a reactive intermediate reacting with indium metal under proper conditions.[12] A combination of indium and iodine has been recently used for atom-transfer cyclizations such as the reductive cyclizations of iodoalkyne to the 5-exo cyclized product.[13] Therefore, it would be interesting to apply and make use of the environmentally favorable indium and iodine. Thus, we examined the combined use of indium and additives such as iodine to develop useful reductive condition for the heterocyclization in terms of green chemistry. We hereby report on the utilization of indium and iodine for the preparation of 2,1-benzisoxazoles, which can be useful in pharmaceuticals.

Prior to the study of reductive cyclization reaction, the reduction of nitrobenzene was attempted to examine the reductive power of some indium-related reagents. As we somehow expected, no reaction occurred at

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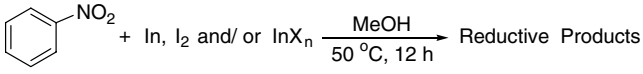
all when indium (Table 1, entry 1), iodine (entry 2) or indium(III) iodide (entry 3) was used as the only reagent. Although the indium itself did not reduce the nitro group, indium(I) iodide showed a reasonable reductive power and the reaction produced a mixture of aniline and azoxybenzene (entries 4 and 5). Unlike indium(I) iodide reactions, the combined use of indium and iodine in MeOH produced aniline as a major product with hydrazobenzene and a trace amount of azo- or azoxybenzene by-products (entry 6), which was a good indication for the possibility of reductive cyclization of *o*-nitro-substituted arenes.

As indium and related reagents turned out to have reasonable reductive power, reductive conditions that were attempted with nitrobenzene were applied for the reductive cyclization of 2-nitrobenzaldehyde, which was expected to produce 2,1-benzisoxazoles similar to the results of our previous studies. The representative indium-mediated reductive cyclizations are summarized in Table 2. The reaction of 2-nitrobenzaldehyde using indium(I) iodide in MeOH gave 76% of 2,1-benzisoxazole, along with 9% of 2-aminobenzaldehyde (Table 2, entry 1). The addition of indium(III) iodide to the reaction mixture did not help to increase the 2,1-benzisoxazole product; instead, it facilitated the acetal formation (entry 2). However, the reaction of 2-nitrobenzaldehyde in the presence of indium and iodine in MeOH at 50 °C gave better results, that is, it produced the 2,1-benzisoxazole as a predominant product (entries 3 and 4). Both a combined use of indium/iodine and the use of indium(I) iodide showed comparable reductive abilities. However, the combined use of indium/iodine was proved to be better for synthetic utility as it produced better yield with much less by-products and is relatively cheap and easy to handle compared with indium(I) iodide. The role of iodine would be both acting as Lewis acid[11] and acting as an activating reagent for the electron transferring ability of indium.[12]

To test the synthetic utility of the indium/iodine-promoted reductive reaction for the synthesis of 2,1-benzisoxazole derivatives, heterocyclizations of substituted 2-nitrobenzaldehydes, 2′-nitroacetophenone, and 2-nitrobenzophenones were examined using the optimized reaction conditions (Table 3, entries 1–11). In most cases, cyclization reaction appears to be generally

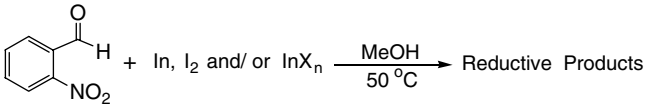
Table 1. Indium-mediated reductive reaction of nitrobenzene under various reaction conditions at 50 °C in MeOH

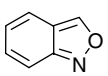
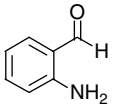
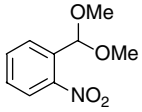


Entry	Molar equivalent In:I_2:InI:InI_3	Product (yield, %)[a]		
		$PhNH_2$	Ph—N(H)—N(H)—Ph	Ph—N(O⁻)=N⁺—Ph
1	3:0:0:0		No reaction	
2	0:1:0:0		No reaction	
3	0:0:0:2		No reaction	
4[b]	0:0:2:0	16	—	75
5[b]	0:0:2:2	17	—	70
6[b]	3:1:0:0	69	~20	Trace

[a] GC yield with an internal standard.
[b] Trace amount of azobenzene was observed on GCMS.

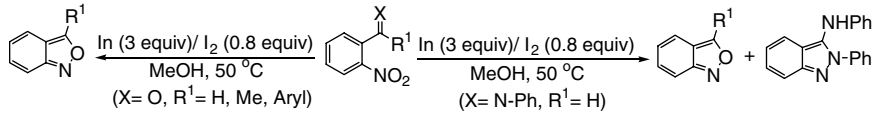
Table 2. Indium-mediated reductive reaction of 2-nitrobenzaldehyde under various reaction conditions at 50 °C in MeOH

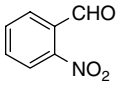
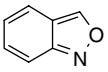
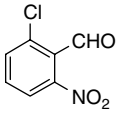
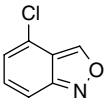
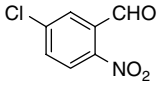
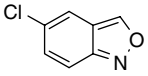
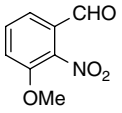
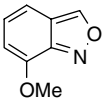
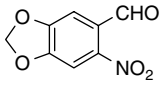
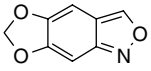
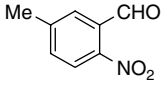
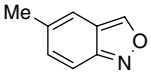
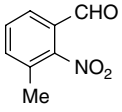
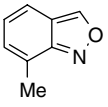
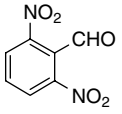
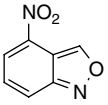
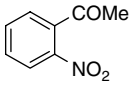
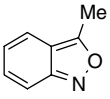
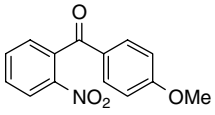
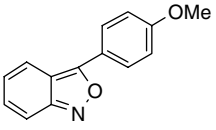
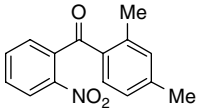
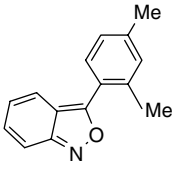
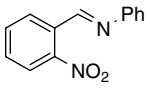
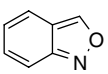
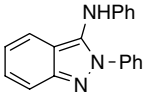


Entry	Molar equivalent In:I_2:InI:InI_3	Time (h)	Product (yield, %)[a]		
					
1	0:0:2:0	2	76	9	Trace
2	0:0:2:2	2	55	10	21
3	3:1:0:0	1	83	Trace	—
4	3:0.8:0:0	1	87	—	—
5	0:0:0:2	2	—	Trace	94
6	0:1:0:0	12	—	—	72

[a] Isolated yield.

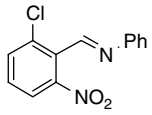
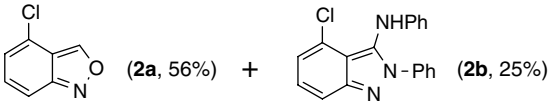
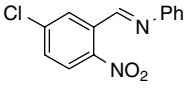
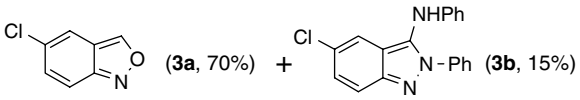
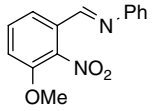
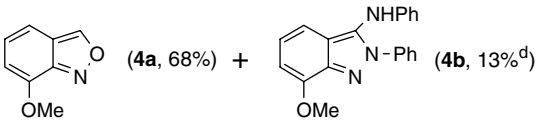
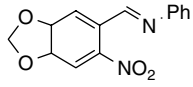
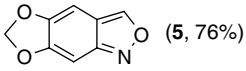
Table 3. Reductive cyclization of 2-nitroacylbenzenes or 2-nitroiminobenzenes (1.0 mmol) in the presence of indium (3.0 equiv)/I_2 (0.8 equiv) in MeOH (3 mL) at 50 °C



Entry	Substrate	Time (h)	Product(s) (yield, %)[a]
1		1.5	 (**1a,** 87%)
2		6	 (**2a**, 85%)
3		2	 (**3a**, 95%)
4		5	 (**4a**, 50%[b])
5		5	 (**5**, 80%)
6		6	 (**6**, 87%)
7		5	 (**7**, 42%)
8		24	 (**8**, 18%[c])
9		4	 (**9**, 88%)
10		4	 (**10**, 81%)
11		6	 (**11**, 88%)
12		4	 (**1a**, 56%) +  (**1b**, 27%)

(*continued on next page*)

Table 3 (*continued*)

Entry	Substrate	Time (h)	Product(s) (yield, %)[a]
13		6	 (**2a**, 56%) + (**2b**, 25%)
14		6	 (**3a**, 70%) + (**3b**, 15%)
15		6	 (**4a**, 68%) + (**4b**, 13%[d])
16		6	 (**5**, 76%)

[a] Isolated yield.
[b] 2-Amino-3-methoxybenzaldehyde was formed (16%).
[c] Substrate was remained.
[d] Trace amount of *N*-[(2-amino-3-methoxyphenyl)methylene]benzenamine was observed.

applicable, as all of the substrates were consumed within 1.5–6 h to give the corresponding 2,1-benzisoxazoles in 80–95% yields independent of the electronic effect of the substituents. In the case of chloro-substituted 2-nitrobenzaldehydes, the corresponding chloro-substituted 2,1-benzisoxazole was obtained in high yield (entries 2 and 3) without giving any of the dechlorinated product, which was a promising indication of its mild reductive condition. Moreover, the indium/iodine-promoted reductive reaction could also be useful for the reductive cyclization of nitroarenes substituted with acid labile alkoxy groups as well. In addition, similar to the reactions of 2-nitrobenzaldehydes, the indium/iodine-promoted reductive reaction of 2-nitroaryl ketones such as 2′-nitroacetophenone and 2-nitrobenzophenones worked well giving the corresponding 3-substituted 2,1-benzisoxazoles in 81–88% yields (entries 9–11). However, 3-substituted 2-nitroarenes, that is, ortho-substituted arenes relative to the nitro group (entries 4 and 7), produced relatively low yields of the desired product compared with others, presumably because of the steric effect of the groups that may interfere with the reductive reaction of the nitro group. The reductive cyclization of 2,6-dinitrobenzaldehyde (entry 8) was strongly retarded possibly because of the inhibitory effect of the secondary nitro functionality that may inhibit the single electron transfer processes.

As an extension of the indium/iodine-promoted reductive cyclization reaction, heterocyclizations of *N*-(2-nitrobenzylidene)aniline derivatives were examined (entries 12–16). In our previous study, the reductive cyclizations of both 2-nitrobenzoyls and *N*-(2-nitrobenzylidene)anilines produced the same products, 2,1-benzisoxazoles, with similar yields.[7a,b] Interestingly, reductive cyclization of *N*-(2-nitrobenzylidene)aniline in the presence of indium/iodine in MeOH produced a mixture of 2,1-benzisoxazole (56%) and 3-anilino-2-phenyl-2*H*-indazole (27%) (entry 12). The formation of 3-anilino-2-phenyl-2*H*-indazole was somehow unexpected and the reactions of halo or methoxy substituted *N*-(2-nitrobenzylidene)anilines also exhibited similar results, producing mixtures of 2,1-benzisoxazoles and 3-anilino-2-phenyl-2*H*-indazoles (entries 13–15). We presumed that 3-anilino-2-phenyl-2*H*-indazoles might come from the effect of in situ formed anilines, which are leaving groups when 2,1-benzisoxazoles are formed. As indazole derivatives have also attracted much attention for their pharmaceutical activities, such as anti-inflammatory, anti-tumor, and anti-HIV properties, and our indazole derivatives are unknown compounds, it would be valuable to investigate the reductive reactions of *N*-(2-nitrobenzylidene)aniline derivative with the indazole derivative as a major product. Thus, we are now focusing on the 3-anilino-2-phenyl-2*H*-indazole formation reaction to develop as a new synthetic methodology for the indazole synthesis and to solve mechanistic considerations.

A typical procedure for the reductive heterocyclization is as follows: 2-nitrobenzaldehyde derivative or *N*-(2-nitrobenzylidene)aniline derivative (1.0 mmol) was added to a mixture of indium powder (345 mg, 3.0 mmol) and iodine (203 mg, 0.8 mmol) in MeOH (3 mL). The reaction mixture was stirred at 50 °C under a nitrogen atmosphere. After the reaction was complete, the reaction mixture was diluted with CH_2Cl_2 (30 mL), filtered through Celite, and poured into 10% NH_4Cl solution and extracted with CH_2Cl_2 (30 mL × 3). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated. The residue was eluted with ethyl acetate/hexane (v/v = 2/98–20/80) through a silica gel column to give the corresponding 2,1-benzisoxazoles and indazoles. Structures of 2,1-benzisoxazoles and

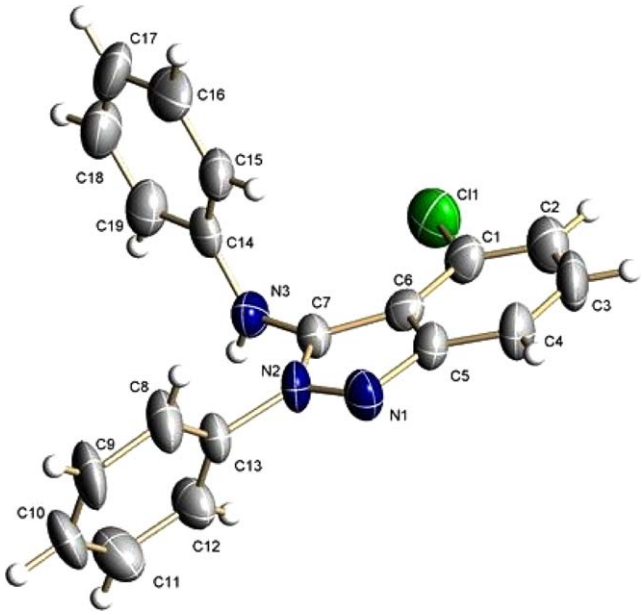


Figure 1. The molecular structure of (4-chloro-2-phenyl-2*H*-indazol-3-yl)phenylamine (**2b**) with an atom-labeling scheme.

indazoles were fully characterized by ^{1}H NMR, ^{13}C NMR, FTIR, MS, and HRMS. X-ray crystal structure of (4-chloro-2-phenyl-2*H*-indazol-3-yl)phenylamine (one of the indazoles) was obtained for the decisive structure determination (Fig. 1).[14]

In conclusion, we have described a simple and efficient method for a one-pot preparation of 2,1-benzisoxazoles from nitroarenes using indium/iodine in MeOH under mild conditions. Under a similar condition, *N*-(2-nitrobenzylidene)anilines produced mixtures of 2,1-benzisoxazoles and 3-anilino-2-phenyl-2*H*-indazoles. The development of a new methodology for the indazole synthesis from *N*-(2-nitrobenzylidene)anilines is now under investigation.

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14. *Spectroscopic data of (4-chloro-2-phenyl-2H-indazol-3-yl)phenylamine*: TLC (30% ethyl acetate/hexane) R_f 0.46; mp 178–180 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.67–7.58 (m, 3H), 7.40–7.29 (m, 3H), 7.21–7.11 (m, 3H), 7.00 (d, 1H, $J = 7.2$ Hz) 6.82 (t, 1H, $J = 7.2$ Hz) 6.57 (d, 2H, $J = 7.7$ Hz) 5.92 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.2, 145.5, 138.6, 132.5, 129.2, 129.0, 128.5, 127.1, 125.3, 124.5, 121.8, 120.3, 116.8, 115.1, 114.7; IR (nujol) 3225, 3036, 1601, 1256, 749, 690 cm^{-1}; GC–MS *m/z* (rel intensity) 319 (M^+, 100), 283 (11), 207 (9), 178 (7), 77 (23); HRMS (EI) calcd for $C_{19}H_{14}ClN_3$ 319.0876, found 319.0874. The crystallographic data for the structure of (4-chloro-2-phenyl-2*H*-indazol-3-yl)phenylamine in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 614941.