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Indium mediated reductive heterocyclization of 2-nitroacylbenzenes or 2-nitroiminobenzenes toward 2,1-benzisoxazoles in aqueous media

Byeong Hyo Kim,[a,*] Youngoo Jin,[a] Young Moo Jun,[a] Rongbi Han,[a] Woonphil Baik [b] and Byung Min Lee [c]

[a] *Department of Chemistry, Kwangwoon University, Seoul 139-701, South Korea*
[b] *Department of Chemistry, Myong Ji University, Kyung Ki Do, South Korea*
[c] *Korea Research Institute of Chemical Technology, Taejon, South Korea*

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Abstract

2-Nitro-substituted acylbenzenes or iminobenzenes such as 2-nitrobenzaldehydes, 2′-nitroacetophenone, and *N*-(2-nitrobenzylidene)anilines were cyclized toward 2,1-benzisoxazoles in the presence of 2-bromo-2-nitropropane and indium in an MeOH/H_2O solution in excellent yields.

Keywords: benzisoxazoles; cyclization; electron transfer; indium and compounds.

Compared to other metals, indium has not been explored much in organometallic reactions. Recently, studies on indium-mediated reactions in aqueous media have focused on synthetic applications because of environmental issues and the ease of reactions, obviating the need for inflammable anhydrous organic solvents and an inert atmosphere.[1] Indium has been applied to various reactions in aqueous conditions without an inert atmosphere: alkylation of aldehydes and ketones,[2] reductive coupling of aldimines,[3] Reformatsky and aldol reactions,[4] allenylation of aldehydes,[5] and ring expansion of carbocycles.[6]

Without doubt, indium metal can be a suitable candidate for an electron donor in single electron transfer (SET) processes and has some striking advantages over other metals, i.e., indium metal is unaffected by air or oxygen at ordinary temperatures and is practically unaffected by water. Of special interest to us was the possibility of utilizing an indium-promoted reaction for the preparation of various nitrogen-containing heterocyclic compounds as an extension of studies on reductive cyclization reaction of 2-nitroarenes,[7] since the application of indium to other than carbon–carbon bond formation was unprecedented elsewhere. Herein, we wish to report the utilization of indium for the preparation of 2,1-benzisoxazoles, which are very useful in the pharmaceuticals.

* Corresponding author. E-mail: bhkim@daisy.kwangwoon.ac.kr (B. H. Kim)

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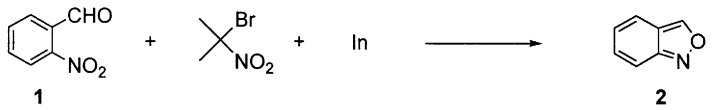
As control experiments, various reaction conditions were attempted to examine the use of indium for the reductive cyclization of 2-nitrobenzaldehyde and the results are summarized in Table 1. The reactions of 2-nitrobenzaldehyde (**1**) with indium (5 equiv.) in methanol (Table 1, entry 1), in water (entry 2), or in a methanol/water co-solvent (entry 3) at 50°C did not exhibit any effective cyclizations and 2-nitrobenzaldehyde was recovered completely in every case. However, addition of BNP to the reaction mixture made the reductive cyclization of 2-nitrobenzaldehyde possible and the formation of 2,1-benzisoxazole was observed as expected.

Table 1
Reactions of 2-nitrobenzaldehyde in the presence of BNP/indium under the various reaction conditions



1 **2**

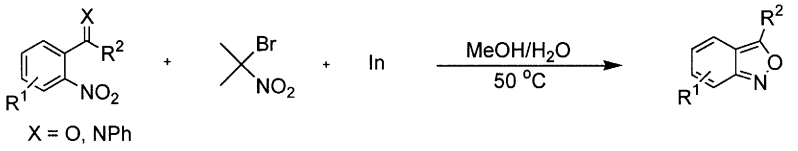
entry	molar ratio **1** : BNP : In	solvent	temp. (°C)	Time (min)	yield (%, **2**)[a]
1	1 : 0 : 5	MeOH	50	240	0
2	1 : 0 : 5	H_2O	50	240	0
3	1 : 0 : 5	MeOH/ H_2O (v/v = 1 : 2)	50	240	0
4	1 : 2 : 5	MeOH	50	240	80
5	1 : 2 : 5	H_2O	50	30	70
6	1 : 2 : 5	MeOH/ H_2O (v/v = 1 : 6)	50	10	80
7	1 : 1 : 5	MeOH/ H_2O (v/v = 1 : 2)	50	50	91
8	1 : 2 : 2	MeOH/ H_2O (v/v = 1 : 2)	50	120	75
9	1 : 2 : 3	MeOH/ H_2O (v/v = 1 : 2)	50	10	85
10	1 : 2 : 4	MeOH/ H_2O (v/v = 1 : 2)	50	10	90
11	1 : 2 : 5	MeOH/ H_2O (v/v = 1 : 2)	50	10	98 (93)[b]
12	1 : 2 : 5	MeOH/ H_2O (v/v = 1 : 2)	rt	50	76
13	1 : 2 : 5	MeOH/ H_2O (v/v = 1 : 1)	50	20	90
14	1 : 2 : 5	THF/ H_2O (v/v = 1 : 1)	50	60	37
15	1 : 2 : 5	Tol/ H_2O (v/v = 1 : 6)	50	240	23

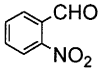
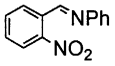
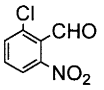
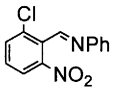
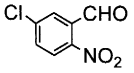
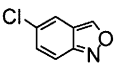
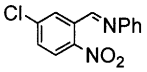
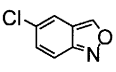
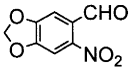
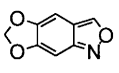
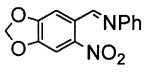
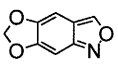
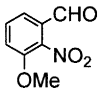
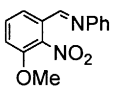
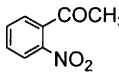
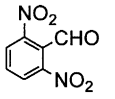
[a]GC yield with an internal standard. [b]Isolated yield.

As shown in Table 1, reactions both in methanol and in water worked well when proper amounts of BNP and indium were present. Usually, the reaction in an aqueous solution completed much faster than in methanol. The optimum condition was obtained when 2 equiv. of BNP and 5 equiv. of indium were applied in methanol/water (v:v=1:2) with 2-nitrobenzaldehyde at 50°C (entry 11) and the reaction time was diminished dramatically compared to our previous zinc-mediated reaction.[7a] It produced almost a quantitative yield of desired 2,1-benzisoxazole within 10 min!

The role of BNP is to be an electron acceptor due to its low-lying antibonding π-orbital and the utility of BNP has been described by Russell et al.[8] and by us.[7] To ensure the electron accepting ability of BNP, the cyclic voltammetric behavior of BNP was examined. BNP [−0.26 V, Pt cathode, 0.3 M $LiClO_4$/MeOH/H_2O (v:v=1:2) 40 mV/s] exhibited quite lower reduction potential compared to 2-nitrobenzaldehyde [−0.64 V, Pt cathode, 0.3 M $LiClO_4$/MeOH/H_2O (v:v=1:2), 40 mV/s] in the aqueous co-solvent medium. Furthermore, addition of di-*tert*-butyl nitroxide or *m*-dinitrobenzene has shown strong inhibitory effects. Compared to the normal reaction of nitrobenzaldehyde in MeOH (entry 4), the reactions of nitrobenzaldehyde/BNP/indium in MeOH in the presence of 10 mol% of di-*tert*-butyl nitroxide or *m*-dinitrobenzene had shown about 1 h initial retardation for each and completion time

Table 2
The reactions of substituted 2-nitrobenzaldehydes, 2′-nitroacetophenone, or *N*-(2-nitrobenzylidene)anilines in the presence of BNP (2 equiv.)/indium (5 equiv.) in MeOH/H_2O (v:v=1:2) at 50°C[a]



entry	substrate	reaction time (min)	product	isolated yield (%)	entry	substrate	reaction time (min)	product	isolated yield (%)
1		10		93	7		20		93
2		25		85	8		10		81
3		50		95	9		60		93
4		60		83	10		30		97
5		10		61	11		60		50
6		20		95	12		20		tr

[a]All reactions were carried out with 0.3 mmol of reactant.

was delayed with decrement of yields (6 h, 75% and 62% each). This indicates that radical and radical anion are involved during the reductive cyclization. Thus, BNP, a good electron acceptor, can easily take the electron from indium to form BNP radical anion that dissociates immediately to 2-nitropropan-2-yl radical and bromide anion. We believe 2-nitropropan-2-yl radical reacts with a nitro group to generate a nitroso intermediate.

In order to test the synthetic utility of BNP/In conditions, we examined the reductive cyclizations of various substituted 2-nitrobenzaldehydes, 2′-nitroacetophenone, and *N*-(2-nitrobenzylidene)anilines under the optimized condition. Our works concerning the reductive cyclizations using BNP/In are summarized in Table 2. A trial for the Pd-catalyzed reduction of halogenated aromatic nitro compound was reported to provide a dehalogenated product.[9] In most of our cases, cyclizations were completed within 10–60 min with excellent yields independent of the electronic effect of the substituent. However, in the case of 3-methoxy-2-nitrobenzaldehyde which has an *ortho*-methoxy group relative to the nitro group, the yield of the reductive cyclization toward 7-methoxy-2,1-benzisoxazole was drastically reduced

to 61% and formation of the by-product, 2-amino-3-methoxybenzaldehyde, was observed in a large amount (~30%) which was not formed in other reactions (Table 2, entry 5). A similar trend was observed for 3-methoxy-substituted *N*-(2-nitrobenzylidene)aniline (entry 11). This strongly indicates that steric hindrance of the methoxy group retards the reaction between the nitro group and the 2-nitropropan-2-yl radical generated from BNP radical anion, which will be a key step for the heterocyclization. Consequently, a simple reduction of the nitro group can compete with the heterocyclization reaction because electron and proton transfer processes are relatively free from the steric requirement. Despite its accompanying low yielding problem with 3-substituted 2-nitroarenes, the reductive cyclization of nitroarenes substituted with acid labile alkoxy functional groups using BNP/In in our neutral condition provides an efficient and selective method for the synthesis of 2,1-benzisoxazole derivatives. Reductive cyclization of 2,6-dinitrobenzaldehyde failed to obtain 4-nitro-2,1-benzisoxazole although all the starting substrate was consumed (entry 12).

A typical procedure for the BNP-mediated reductive cyclization reaction is as follows. To a stirred solution of 2-nitroarene derivative (1 mmol) and indium dust (0.574 g, 5 mmol) in MeOH/H_2O (v:v=1.5:3 mL, for acylbenzenes, or v:v=0.75:1.5 mL, for imines) was added 2-bromo-2-nitropropane (0.336 g, 2 mmol) at 50°C. After the reaction was completed, the reaction mixture was taken up in CH_2Cl_2/10% aqueous NH_4Cl solution and extracted with CH_2Cl_2 (3×50 mL). The combined organic layer was dried over $MgSO_4$ and concentrated. If necessary, GC yield was determined with an internal standard. Products were isolated by flash column chromatography with ethyl acetate:hexane (5:95–1:99) and are fully characterized. For the full spectral data of products, see our previous reports.[7]

It is quite clear that the neutral condition in aqueous medium for the reductive heterocyclization overwhelms any other methods shown in the literature, since our condition is mild and the reaction is completed in a short reaction time. Further study of the application of BNP/In in an aqueous medium to the heterocyclization reaction is underway.

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