REDUCTIVE REACTIONS OF NITROARENES IN THE PRESENCE OF ALLYL BROMIDE AND ZINC DUST

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Abstract - Under the mild condition, allyl bromide/Zn mediated reductive *N,O*-diallylation of nitrobenzene was observed. In case of *o*-nitroarenes such as 2-nitrobenzaldehyde derivatives, 2'-nitroacetophenone, and *N*-(2-nitrobenzylidene)anilines, reductive cyclizations were accomplished in good to excellent yields. Synthesis and mechanistic details are discussed.

INTRODUCTION

Metal-mediated transformations are among the most powerful tools in organic chemistry. Particularly the use of allyl bromide and zinc for the Barbier-type C-C bond formation with carbonyl or imino group was studied extensively.[1] However, the use of allyl bromide and zinc for the reductive reaction of nitro compounds has never been reported. During our continuous studies on various metal-mediated reductive reactions of nitro compounds,[2] we found that allyl bromide and zinc could be applied for the reductive allylation of nitro group or nitro group reduction initiated heterocyclization as well as the Barbier-type C-C bond formation.

The *N*-containing 5-membered heterocyclic compounds are of great importance in organic synthesis, medicinal chemistry, and industry. Among them, 2,1-benzisoxazole (anthranil) has been known for a long time, and a modest number of 2,1-benzisoxazole derivatives have a patented usage, *i.e.* anti-inflammatory, antituberculotic, lipodemia, and analogs of psilocene and muscomal.[3a] Some of 2,1-benzisoxazole derivatives are also known to be useful key intermediates in the synthesis of biologically active molecules such as quinazolinones and 1,4-benzodiazepines.[4] The utilized methods of preparation of 2,1-benzisoxazoles include some of the earliest recorded examples of nitro and acyl group side chain

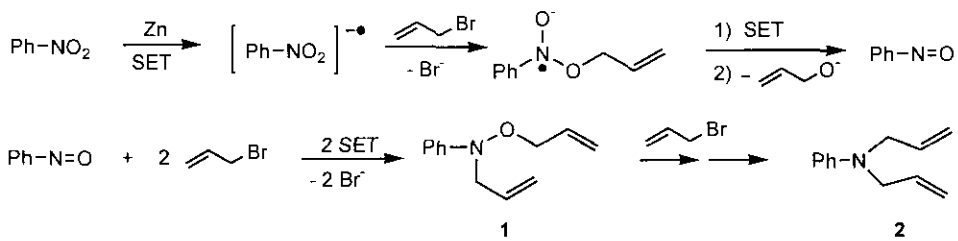
interaction in *o*-nitroacylbenzene derivatives,[3-10] *i.e.* catalytic hydrogenation,[3] reductive transformations by zinc/acetic acid,[5] triethyl phosphite,[6] thionyl chloride,[4b] and electrolysis reaction.[11]

Herein we wish to report reductive allylation of nitroarenes and unique reductive cyclizations of 2-nitrobenzaldehydes, 2'-nitroacetophenone, and *N*-(2-nitrobenzylidene)anilines toward 2,1-benzisoxazoles which were accomplished in the presence of allyl bromide and zinc.

RESULTS AND DISCUSSION

Nitrobenzene (1 mmol), when was treated with allyl bromide (4 mmol) and Zn (5 mmol) in MeOH at 50 °C for 5 hours, gave *N,O*-diallylated phenylhydroxylamine, $PhN(CH_2CH{=}CH_2)OCH_2CH{=}CH_2$ in 50% along with 8% of *N,N*-diallylaniline and 6% of aniline. The more allyl bromide (5 equiv.) was employed, the more of allylated products, $PhN(CH_2CH{=}CH_2)OCH_2CH{=}CH_2$ (61%) and *N,N*-diallylaniline (33%) were obtained. The radical anions, $PhNO_2^{-\bullet}$ or $PhNO^{-\bullet}$ generated by a single electron transfer (SET) process seemed to react readily with allyl bromide electrophile. The following is a plausible reaction path for the formation of the substituted phenylhydroxylamines (Scheme 1).

Scheme 1



To support the intermediacy of the nitroso stage, we examined the similar reaction with nitrosobenzene in place of nitrobenzene (nitrosobenzene : allyl bromide : Zn = 1 : 3 : 5, in MeOH, 50 °C for 2 hours). However, the products obtained were azobenzene (28%) and azoxybenzene (34%) instead of allylated products. Presumably, the fast dimerization of nitrosobenzene radical anion led to radical coupling reaction that was predominated over the reaction between nitrosobenzene radical anion and the electrophile (allyl bromide). Nitroarenes have been shown the ability to form radical anions spontaneously in the presence of electron donors.[12] In fact, the LUMO energy level of nitroarenes lies in a relatively low, thus the formation of $ArNO_2^{-\bullet}$ can be explained by a SET process. In addition, nitrosoarenes are also capable of accepting an electron. Russell reported that the SET process of nitrosobenzene in the presence of hydroxide ion occurs in <0.5 sec to give nitrosobenzene radical anion.[13]

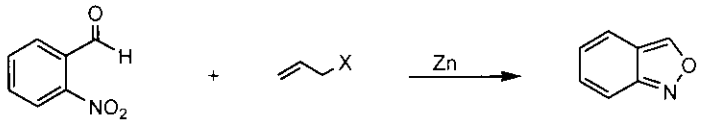
Generally, nitroso compounds, which are often postulated as intermediates, are too reactive to be isolated, even if indeed they are intermediate. Thus if a sufficient amount of electrophile is presented in the reaction mixture at lower temperature, the allylated products rather than azo- or azoxybenzene can be obtained. To confirm this postulation, we tried the reaction in the presence of a large excess of allyl bromide. To a solution of allyl bromide (3 mL, 35 mmol)/Zn (5 mmol), nitrosobenzene (1 mmol) in MeOH (15 mL) was added dropwisely at -20 °C for 2 hours using a syringe pump. Surely enough, the amount of azobenzene (10%) and azoxybenzene (18%) was decreased and allylated products such as $PhNHOCH_2CH=CH_2$ (36%) and $PhN(CH_2CH=CH_2)OCH_2CH=CH_2$ (5%) were observed by GC analysis.

From the above experiments, it was quite clear that allyl bromide could stimulate the deoxygenation of nitro group toward nitroso functionality as described in Scheme 1. If it happens prior to Barbier-type allylation with carbonyl or imino group, it can be utilized for heterocyclization reaction in a mild condition by using proper substrates such as *ortho*-nitrated acylbenzenes or iminobenzenes. To manifest the direction of allylation, *i.e.* nitro versus carbonyl or imino group, competition reaction between nitrobenzene and benzaldehyde was carried out. In the reaction of nitrobenzene/benzaldehyde (nitrobenzene : benzaldehyde : allyl bromide : Zn = 1 : 1 : 4 : 5 mmol, in MeOH (5 mL), room temperature for 7 hours), products originated from nitrobenzene reduction such as PhNO (4%), $PhN(CH_2CH=CH_2)OCH_2CH=CH_2$ (2%), PhCH=NPh (21%), PhCH(OH)NHPh (36%), and PhCONHPh (11%) were superior to allyl alcohol formation (2%) on GC analysis (area%). Undoubtedly, the reduction of nitro group occurs first prior to the Barbier-type allylation reaction. In consequence of the competition reactions, we are quite confident of the utilization of allyl bromide and Zn combination for the heterocyclization reaction.

Heterocyclization was examined with 2-nitrobenzaldehyde that was expected to form 2,1-benzisoxazole if our postulation was correct. Extensive exploration of the various reaction conditions (Table 1) allows us to come up to the optimum condition for the reductive cyclization of 2-nitrobenzaldehyde. The reaction of 2-nitrobenzaldehyde in the presence of allyl bromide (2 - 3 equiv.) and Zn (5 equiv.) in MeOH at room temperature produced 2,1-benzisoxazole in 95 - 96% yield (Table 1, entries 8, 9).

In order to prove the synthetic utility of the developed reaction condition, we examined the reductive cyclizations of several substituted 2-nitroacylbenzenes under this optimized condition. Results are summarized in Table 2 (entries 1, 3, 5, 7, 9, 11, 12). In most cases, cyclizations were successful with fair to excellent yields independent of the position and the electronic effect of the substituents. Our reaction condition was so mild that reductive cyclizations of chlorinated 2-nitrobenzaldehydes were able to transform smoothly to the corresponding chlorinated 2,1-benzisoxazoles without giving any dechlorinated

Table 1. Reactions of 2-nitrobenzaldehyde in the presence of allyl halide/Zn under various reaction conditions.



3 4a

entry	X	molar equiv. 3 : RX : Zn	solvent	temp. (°C)	time (h)	Yield (%)[a]
1	none	1 : 0 : 5	MeOH	50	36	2[b]
2	Cl	1 : 2 : 5	MeOH	50	24	23[b]
3	Br	1 : 3 : 5	THF	50	48	tr[b]
4	Br	1 : 3 : 5	THF/H_2O (5/1)	50	1	50[c]
5	Br	1 : 3 : 5	MeOH/H_2O (5/1)	50	1.5	54[c]
6	Br	1 : 3 : 5	$PhCH_3$/H_2O (5/1)	50	1	50[c]
7	Br	1 : 1 : 5	MeOH	rt	24	49[b]
8	Br	1 : 2 : 5	MeOH	rt	10	96
9	Br	1 : 3 : 5	MeOH	rt	9	95

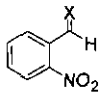
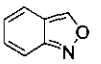
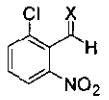
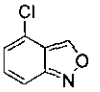
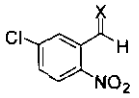
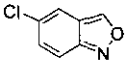
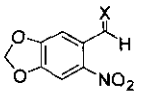
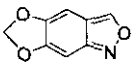
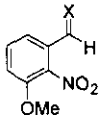
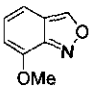
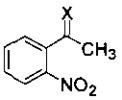
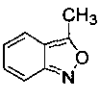
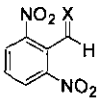
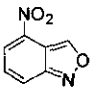
[a]GC yield with an internal standard. [b]Starting substrate was recovered. [c]By-products were formed.

products (Table 2, entries 3, 5). Trial experiment for the Pd-catalyzed reduction of halogenated nitroarene was reported to provide dehalogenated products,[14] and dechlorination was also reported for the electrochemical reductive reactions.[15] Moreover, for the substituted nitroarenes with acid labile alkoxy functional group, our mild reductive reaction provided an efficient method for the preparation of 2,1-benzisoxazole derivatives (Table 2, entries 7, 9). The reductive cyclization of 2,6-dinitrobenzaldehyde was strongly retarded probably because of the inhibitory effect of the second nitro functionality.

For the extension of synthetic utility, we examined the reductive cyclizations of several substituted *N*-(2-nitrobenzylidene)anilines by using allyl bromide and Zn dust under the optimized condition that was obtained from the reactions of acylnitrobenzenes. And it turned out to be worked well for *N*-(2-nitrobenzylidene)anilines toward 2,1-benzisoxazoles as well as 2-nitroacylbenzenes (Table 2, entries 2, 4, 6, 8, 10, 13).

For mechanistic purpose, some inhibition experiments were carried out. Under O_2 atmosphere, the reactions of 2-nitrobenzaldehyde/allyl bromide/Zn at room temperature for 10 hours gave only 1% of 2,1-benzisoxazole with 99% of 2-nitrobenzaldehyde recovered (Table 3, entry 2). In the presence of 10 mol% of 1,3-dinitrobenzene, the reductive cyclization was retarded and the yield of cyclized product decreased to 3% (Table 3, entry 3). Apparently, electron transfer processes through the radical anion species are involved during the reductive cyclization reaction. However, the reactions of 2- nitrobenzaldehyde/allyl bromide/Zn at room temperature in the presence of 20 mol% of di-*tert*-butyl nitroxide resulted in

Table 2. The reactions of substituted 2-nitrobenzaldehydes, 2'-nitroacetophenone, or *N*-(2-nitrobenzylidene)anilines in the presence of allyl bromide (2 equiv.)/Zn (5 equiv.) in MeOH at room temperature.

entry	substrate	X	time (h)	product	yield (%)[a]
1		O	10	 **4a**	96
2		NPh	24		99
3		O	6	 **4b**	86
4		NPh	30		70
5		O	8	 **4c**	76
6		NPh	25		77
7		O	4	 **4d**	82
8		NPh	15		99
9		O	12	 **4e**	50
10		NPh	25		63
11		O	4	 **4f**	86
12		O	48	 **4g**	23[b]
13		NPh	10		10[b]

[a]GC yield with an internal standard. [b]Starting material was recovered.

Table 3. The reactions of 2-nitrobenzaldehyde (**3**, 1 equiv.)/allyl bromide (2 equiv.)/Zn (5 equiv.) in MeOH in the presence of inhibitors at room temperature for 10 h.

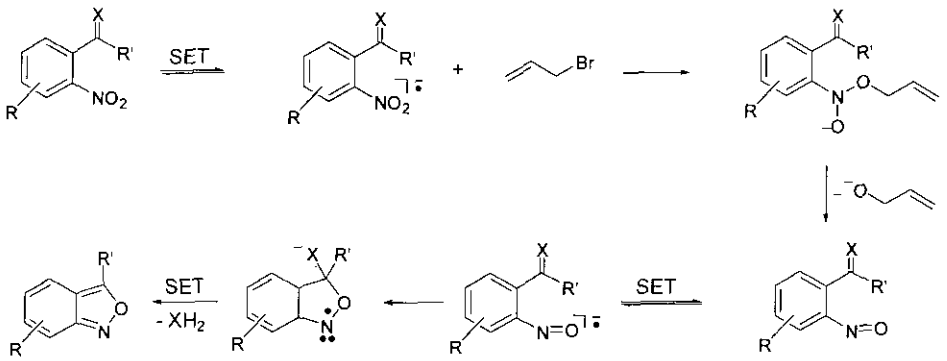
entry	Inhibitor	**3** (% yield)[a]	**4a** (% yield)[a]
1	none	-	96
2	O_2	99	1
3	10 mol% *m*-dinitrobenzene	85	3
4	20 mol% di-*tert*-butyl nitroxide	-	94

[a]GC yield with an internal standard.

ineffective inhibition (Table 3, entry 4). Thus, we eliminated the possibility of allyl radical participation for the heterocyclization that was observed in the reaction of 2-bromo-2-nitropropane/Zn mediated reductive cyclization.[2a,c] To exclude the possibility of ionic participation of *in situ* formed allylic anion

CH_2=CH-CH_2ZnBr, we examined the reactions of 2-nitrobenzaldehyde/CH_2=CH-CH_2MgBr/(with or without Zn) at room temperature under various conditions and none of the reactions was successful at all. Plausible mechanism is presented in Scheme 2 based on the results of our various control experiments.

Scheme 2



In conclusion, we have now established a mild and novel reaction route for 2,1-benzisoxazoles using allyl bromide and Zn dust that would be a useful synthetic methodology along with reductive *N,O*-diallylation of nitrobenzene.

EXPERIMENTAL

1. General consideration

Chemical reagents were purchased from Aldrich and used without further purification in most cases. Solvents were purchased and dried by a standard method. Analytical gas chromatography (GC) was performed on a Donam 6200 gas chromatograph equipped with a DB-1 column and Hitachi D-2500 integrator. ^{1}H NMR spectra were recorded on 300 or 500 MHz Bruker instrument and ^{13}C NMR spectra were recorded on 75 MHz Bruker instrument. Chemical shifts are in ppm from tetramethylsilane (TMS). High-resolution MS were recorded on a Jeol JMS-DX 303 mass spectrometer. IR spectra were recorded on a Nicolet 205 FT-IR. Analytical data were obtained with an EA-1110, CHNS-O CE instruments. Melting points were determined on an Electrothermal apparatus and are uncorrected.

Products were isolated by flash column chromatography on silica gel (70 - 230 mesh ATSM, purchased from Merck) with eluents of mixed solvents (hexane and ethyl acetate). GC yields were determined by using an internal standard (toluene or decane) and were corrected with predetermined response factors.

Spectroscopic data of 2,1-benzisoxazole derivatives were identical with those previously reported in all aspects.[11]

2. General procedure for the reductive allylation or cyclization

Allyl bromide (2 – 4 mmol) at rt was added to a stirred solution of 2-nitroarene derivative (1 mmol) and zinc dust (5 mmol) in deoxygenated MeOH (3 mL). Stirring was continued until the reaction was completed under Ar atmosphere. The solid residue was then filtered off, and the filtrate was concentrated which was followed by normal extraction with CH_2Cl_2/10% aqueous NH_4Cl solution. The separated organic layer was dried over $MgSO_4$ and concentrated. The GC yield was determined by using an internal standard and, if necessary, the products were isolated by flash column chromatography with ethyl acetate-hexane (5/95) co-solvent and was fully characterized. Solid products were recrystallized from a drop of ethyl acetate/hexane co-solvent.

***N,O*-Diallylphenylhydroxylamine (1)** Liquid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31-7.25 (m, 2H), 7.08-7.05 (m, 2H), 6.99-6.95 (m, 1H), 6.03-5.92 (m, 2H), 5.34-5.16 (m, 4H), 4,31-4.28 (m, 2H), 3.94-3.91 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.2, 133.6, 133.5, 128.7, 122.1, 118.2, 116.7, 74.4, 61.3; IR (nujol) 3057, 2981, 2829, 1606, 1502, 1431, 1267 cm^{-1}; GC-MS m/z (rel. intensity) 189 (15, M^+), 148 (100), 77 (31), HRMS(EI) calcd for $C_{12}H_{15}NO$ 189.1154, found 189.1136. *Anal.* Calcd for $C_{12}H_{15}NO$: C, 76.16; H, 7.99; N, 7.40. Found: C, 75.95; H, 8.08; N, 7.63.

2,1-Benzisoxazole (4a) Liquid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.13 (s, 1H), 7.64-7.56 (m, 2H), 7.36-7.27 (m, 1H), 7.04-6.99 (m, 1H).

4-Chloro-2,1-benzisoxazole (4b) White solid, mp 51 - 53 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.20 (d, 1H, J = 0.9 Hz), 7.54 (dd, 1H, J = 0.9, 9.0 Hz), 7.22 (dd, 1H, J = 6.9, 9.0 Hz), 7.00 (d, 1H, J = 6.9 Hz). *Anal.* Calcd for C_7H_4NOCl: C, 54.75; H, 2.62; N, 9.12. Found: C, 54.72; H, 2.64; N, 9.09.

5-Chloro-2,1-benzisoxazole (4c) Pale yellowish solid, mp 80 - 82 °C (lit.[5] mp 78 °C). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.10 (s, 1H), 7.61-7.56 (m, 2H), 7.28-7.21 (m, 1H). *Anal.* Calcd for C_7H_4NOCl: C, 54.75; H, 2.62; N, 9.12. Found: C, 54.82; H, 2.60; N, 9.10.

2,5,7-Trioxa-1-aza-*s*-indacene (4d) White solid, mp 115 - 117 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.77 (d, 1H, J = 0.7 Hz), 6.80 (d, 1H, J = 0.7 Hz), 6.68 (s, 1H), 5.99 (s, 2H). *Anal.* Calcd for $C_8H_5NO_3$: C, 58.90; H, 3.09; N, 8.59. Found: C, 58.82; H, 3.15; N, 8.57.

7-Methoxy-2,1-benzisoxazole (4e) Liquid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.07 (s, 1H), 7.11 (d, 1H, J = 8.7 Hz), 6.93 (dd, 1H, J = 7.2, 8.7 Hz), 6.48 (d, 1H, J = 7.2 Hz), 4.01 (s, 3H). *Anal.* Calcd for $C_8H_7NO_2$: C, 64.42; H, 4.73; N, 9.39. Found: C, 64.19; H, 4.88; N, 10.08.

3-Methyl-2,1-benzisoxazole (4f)[16] Liquid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51 (d, 1H, J = 8.8 Hz), 7.43 (d, 1H, J = 8.8 Hz), 7.28-7.24 (m, 1H), 6.91 (dd, 1H, J = 6.4, 8.8 Hz), 2.79 (s, 3H).

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