2-BROMO-2-NITROPROPA/NZn PROMOTED REDUCTIVE CYCLIZATIONS OF ORTHO-SUBSTITUTED NITROARENES TOWARD 2,1-BENZISOXAZOLE DERIVATIVES

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Abstract - Under the mild conditions, reductive cyclizations of 2-nitrobenzaldehydes or 2'-nitroacetophenone towards 2,1-benzisoxazoles were accomplished in the presence of 2-bromo-2-nitropropane/Zn in methanolic solution. The synthetic utility and the role of 2-bromo-2-nitropropane were investigated.

2,1-Benzisoxazole (Anthranil) has been known for more than 100 years, and a modest number of 2,1-benzisoxazole derivatives have a patented usage, i.e. antiinflammatory, antituberculotic, lipodemia, and analogs of psilocene and muscomal.1a Some of 2,1-benzisoxazole derivatives are also useful key intermediates for the synthesis of biologically active molecules such as quinazolinones and 1,4-benzodiazepines.2 The utilized methods of preparation include some of the earliest recorded examples of nitro group side chain interaction in ortho-substituted nitrobenzene derivatives,1b namely, reductive transformations by zinc and acetic acid,3 triethyl phosphite,4 thionyl chloride,2b and catalytic hydrogenation1 have been suggested. However, useful methods for synthesizing 2,1-benzisoxazoles have not been well established.

In the course of our study on reductive cyclization reaction of 2-nitroarenes,9 we found an efficient synthetic method for 2,1-benzisoxazoles by using 2-bromo-2-nitropropane (BNP) and Zn dust. Herein we wish to report unique reductive cyclizations of 2-nitrobenzaldehyde derivatives or 2'-nitroacetophenone
towards 2,1-benzisoxazoles which were accomplished in the presence of BNP/Zn dust in methanolic solution.

The reaction of 2-nitrobenzaldehyde (1) with BNP (1.2 equiv.) and Zn (5 equiv.) in methanol at 50 °C produced 2,1-benzisoxazole (2) in 98% yield. Surprisingly, only a small amount (1 - 2%) of 2-aminobenzaldehyde was observed and acetal of 2-nitrobenzaldehyde was not formed. Increased amount of BNP did not affect too much (2 equiv.; 94%, 3 equiv.; 92%) for the yield of 2. However, the reaction was not effective with a catalytic amount of BNP [1/BNP(0.5 equiv.)/MeOH/50 °C/5 h, 37%]. In all cases, a trace amount of 2,3-dimethyl-2,3-dinitrobutane, the dimer from BNP radical, and easily removable 2-nitropropane were observed.

![Chemical Reaction](image)

In control experiments, without BNP it produced 2 in a trace amount while retaining most of the reactant. In the absence of Zn [1/BNP (3 equiv.)/MeOH/50 °C/12 h], it gave rise to a trace amount of acetal, $\alpha$-O$_2$NC$_3$H$_4$CH(OMe)$_2$ and 93% of starting material (1) was recovered. In acidic conditions (aq. 35% HCl/Zn/MeOH) which is similar to known procedure, the yield of 2 was relatively low and some by-products including 2-aminobenzaldehyde were observed. Even with an optimum condition [aq. 35% HCl (5 equiv.)/Zn (5 equiv.)/MeOH], only 74% of cyclized product (2) was obtained along with more than 23% of 2-aminobenzaldehyde by-product which was not easy to separate from the reaction mixture. Obviously, both BNP and zinc dust were essential for the reductive cyclization of 2-nitrobenzaldehyde under the neutral conditions. Furthermore, it was much better than the acidic condition reaction as far as the by-product formation concerned. The role of BNP is likely to be an electron acceptor due to its low lying antibonding $\pi$-orbital which has been employed in $S_{\pi n}$ process, and the utility of BNP has been described by G. A. Russell et al. In order to test the synthetic utility of the BNP/Zn condition, we examined the reductive cyclizations of various substituted 2-nitrobenzaldehydes and 2'-nitroacetophenone under the optimized condition. Results are summerized in Table I. In most cases, cyclization was successful with excellent yields independent of
Table I. The reactions of substituted 2-nitrobenzaldehydes or 2'-nitroacetophenone in the presence of 2-bromo-2-nitropropane (BNP, 1.2 equiv.)/Zn (5 equiv.) in MeOH at 50 °C.

<table>
<thead>
<tr>
<th>entry</th>
<th>substrate</th>
<th>time (h)</th>
<th>product</th>
<th>yield (%)*</th>
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*GC yield with an internal standard. **No 2-bromo-2-nitropropane was added. ***Starting material was recovered.

the position and the character of the substituent.
In case of chloro-substituted o-nitrobenzaldehydes, the corresponding chloro-substituted 2,1-benzisoxazole product was obtained in high yield without giving any dechlorinated products (Table I, entries 3, 4). Trial for the Pd-catalyzed reduction of halogenated aromatic nitro compound was reported to provide dehalogenated products.12 Moreover, the reductive cyclization of nitroarenes substituted with acid labile alkoxy functional groups using BNP/Zn provides an efficient and selective method for the synthesis of 2,1-benzisoxazole derivatives (Table I, entries 5, 6). Additionally, the reductive cyclization of 2'-nitroacetophenone under our mild conditions yielded more than 90% of the desired 2,1-benzisoxazole derivative (Table I, entry 7).
while it produced about 1:1 mixture of cyclized product and 2'-aminoacetophenone under the acidic condition [aq. 35% HCl (5 equiv.)/Zn (5 equiv.)/MeOH]. It is clear that our neutral conditions give better results than the acidic conditions for the conversion of 2'-nitroacetophenone to corresponding 2,1-benzisoxazole derivative.

The reductive cyclization of 2,6-dinitrobenzaldehyde was strongly retarded because of dinitro functionality (Table I, entry 8). However, it is worth mentioning that 2,6-dinitrobenzaldehyde was selectively converted to 5-nitro-2,1-benzisoxazole without reduction of 5-nitro groups.

For mechanistic purposes, some inhibition experiments were carried out. Under O₂ atmosphere, the reactions of 1/BNP/Zn/O₂ at 50 °C for 5 hours gave nothing and the reactant was fully recovered (Table II, entry 2). In the presence of 10 mol% of m-dinitrobenzene, the reductive cyclization reaction was retarded and the yield of cyclized product (2) decreased to 39% at 50 °C (Table II, entry 3). Also, the reactions in the presence of di-tert-butyl nitroxide resulted in effective inhibition (Table II, entries 4, 5). Apparently electron transfer processes are involved during the reductive cyclization reaction resulting in 2,1-benzisoxazole.

### Table II. The reactions of 2-nitrobenzaldehyde with 2-bromo-2-nitropropane (1.2 equiv.) and Zn (5 equiv.) in the presence of inhibitors in MeOH at 50 °C.

<table>
<thead>
<tr>
<th>entry</th>
<th>Inhibitor</th>
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<th>1 (% yield)</th>
<th>2 (% yield)</th>
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<td>0</td>
<td>98</td>
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<td>5</td>
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<tr>
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<td>DBN⁶</td>
<td>5</td>
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<td>17</td>
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</table>

a GC yield with an internal standard.  
b m-Dinitrobenzene, 10 mol%.  
c Di-tert-butyl nitroxide, 5 mol%.  
d Di-tert-butyl nitroxide, 10 mol%.

BNP (-0.13 V, Hg cathode, 0.1 M LiClO₄/MeOH, Ag/AgCl, 20 mV/s) could be a good electron acceptor but not an electrophile, and may more like assist the reaction by enhancing the electron transfer ability. Electron transfer from Zn or BNP radical anion to o-nitrobenzaldehyde (-0.59 V, -0.84 V, Hg cathode, 0.1 M LiClO₄/MeOH, Ag/AgCl, 20 mV/s) may lead to nitrosobenzaldehyde intermediate. Additional controlled
experiments are currently under way to prove pathways of the reaction mechanism in detail.

In conclusion, we have now established a mild and novel reaction route for 2,1-benzisoxazole derivatives by using 2-bromo-2-nitropropane and Zn dust which would be a new synthetic methodology.

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References and Notes


11. 2-Bromo-2-nitropropane (0.403 g, 2.4 mmol) at 50 °C was added to a stirred solution of 2-nitroarene derivative (2 mmol) and zinc dust (0.654 g, 10 mmol) in deoxygenated MeOH (6 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$_2$Cl$_2$/aqueous 10% NH$_4$Cl solution. The separated organic layer was dried over MgSO$_4$ and concentrated. The product was isolated by flash column chromatography (silica gel) with ethyl acetate/hexane (5/95) co-solvent and was fully characterized.


14. Detailed measurements of kinetic chain length with 5 mol% or 10 mol% of di-tert-butyl nitrooxide were exhibited less than 1.

15. Nitrosobenzaldehyde intermediacy was conformed by GCMS analysis of the reaction mixture.

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