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# A FACILE SYNTHESIS OF 3-UNSUBSTITUTED 4-ISOXAZOLINES

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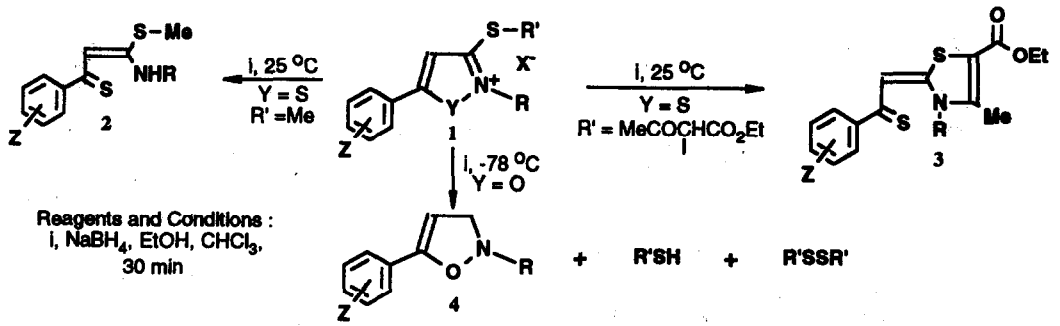
**Abstract:** Treatments of 3-alkylthio-5-aryl-2-arylmethylisoxazolium halides with sodium borohydride in a mixture of ethanol and chloroform at -78℃ afforded the corresponding 3-unsubstituted 4-isoxazolines in excellent yields.

Recently 4-isoxazolines have received considerable attention partly because of the mechanistic interests on their thermal decompositions and potential in new synthetic method for heteroatom compounds[1]. Although a number of 4-isoxazolines have been found in the literature, they have various substituents at 2, 3, 4, and/or 5-positions.[2] Furthermore, the synthetic methods reported might not be utilized for the synthesis of 3-unsubstituted 4-isoxazolines because of inaccessibility of proper starting materials. We are aware of only one report for the synthesis of 3-unsubstituted 4-isoxazolines[2f]. That is, treatments of 2-alkyl-5-phenylisoxazolium salts with $NaBH_4$ in aqueous acetonitrile at -5 ℃ afforded the corresponding 4-isoxazolines along with 4-isoxazoline-borane complex, and ring-opened compounds. The reported yields of 4-isoxazolines were in the range of 23 to 29 % except for 97 % of 2,5-diphenyl-4-methyl-4-isoxazoline.

In the course of pursuing ongoing project for the development of new synthetic method for 2-thiophenacylidene-1,3-thiazolines (3), 2-alkyl-3-alkylthio-5-phenylisothiazolium salts (1, Y=S, R=Me, Et, Z=H) were treated with $NaBH_4$ in a mixture of ethanol and chloroform at room temperature. It was found that when 1 (Y=S, R=Me, Et, Z=H) had simple alkylthio groups (R'=Me, Et, $CH_2CH=CH_2$, $C_6H_5CH_2$) at 3-position, thiobenzoylketene S, N-acetals (2) were formed whereas those with dioxoalkylthio groups, e.g., R'=$MeCOCHCO_2Et$, gave 3 in good yields.[3]




We have applied the same method to 3-alkylthio-5-aryl-2-arylmethylisoxazolium halides (1, Y=O)[4] at -78 ℃ and found that 1 (Y=O) were excellent precursors for 5-aryl-2-arylmethyl-4-isoxazolines (4).[5]

When the reductions of 1 (Y=O) with $NaBH_4$ performed at room temperature, yields of 4 decreased drastically with the increased formations of unidentifiable compounds. The reason for the addition of chloroform to ethanol ($CHCl_3$ : EtOH, 1:2, v:v) was to increase the solubilities of 1. Yields of 4 were essentially independent on the solvent whether it was an ethanol-chloroform mixture or not when 1 were soluble in ethanol. Aluminum oxide (basic) was better adsorbent for the chromatographic separations of the reaction mixtures than silica gel (70-230 mesh, Merck) which caused the decomposition of 4 to form β-aminoketones. The results are summarized in Table 1.

Table 1. Yields of 5-Aryl-2-arylmethyl-4-isoxazolines (4), o-Bromobenzylthiol and o-Bromobenzyl Disulfide.

| | 1 (Y=O) R | Z | R' | Molar Ratio $NaBH_4$ : 1 | 4 | Yield (%) R'SH | R'SSR' |
|---|---|---|---|---|---|---|---|
| (a) | $C_6H_5CH_2$ | H | o-$BrC_6H_4CH_2$ | 1:1 | 92 | 53 | 40 |
| | | | | 1:2 * | 62 | 18 | 46 |
| | | | | 1.5:1 | 89 | 51 | 40 |
| | | | | 1.5:1 | 79† | 52† | 19† |
| | | | | 1:1 | 75† | | 75† |
| (b) | $C_6H_5CH_2$ | H | $CH_2$=$CHCH_2$ | 1:1 | 100 | | |
| (c) | $C_6H_5CH_2$ | H | $EtO_2CCH_2$ | 1:1 | 82 | | |
| (d) | $C_6H_5CH_2$ | p-Cl | o-$BrC_6H_4CH_2$ | 1.5:1 | 94 | | 97 |
| (e) | $C_6H_5CH_2$ | o-Cl | o-$BrC_6H_4CH_2$ | 1:1 | 87 | | |
| (f) | o-$FC_6H_4CH_2$ | H | Me | 1:1 | 100 | | |
| (g) | o-$ClC_6H_4CH_2$ | p-Me | o-$BrC_6H_4CH_2$ | 1:1 | 94 | 31 | 60 |

Isolated yields by column chromatography. * When molar ratio of $NaBH_4$ to 1 was 1:2, 1a was recovered (33%). †Yields under $N_2$ atmosphere. †Yields at -23 ℃ otherwise at -78 ℃.

Unexpectedly 1 (Y=O, R=$C_6H_5CH_2$, Z=H, R'=$MeCOCHCO_2Et$) gave 2-benzyl-5-phenyl-4-isoxazolin-3-thione (59 %) whereas 1 (Y=O, R=$C_6H_5CH_2$, Z=H, R'=$C_6H_5COCH_2$) afforded 2-benzyl-5-phenyl-4-isoxazolin-3-one (81 %) under the same conditions.

Table 1 shows that the same molar amounts of $NaBH_4$ to 1 are needed for the completion of the reactions. Isolations of o-bromobenzylthiol and o-bromobenzyl disulfide in the reactions with 1a at -78 ℃ and only o-bromobenzyl disulfide at -23 ℃ coupled with markedly decreased yield of disulfide under $N_2$ atmosphere indicate the involvement of a radical mechanism for the formation of 4.

It is very interesting to note that no 4-isoxazoline-borane complexes were detected in all cases although reductions of 5-aryl-2-arylmethylisoxazolium ions by $NaBH_4$ are assumed to be involved in the course of the reactions as in the previous report.[2f]

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4. Compounds 1 (Y=O) were prepared from the reactions of 2-alkyl-5-aryl-4-isoxazolin-3-thiones with alkyl bromides in $CH_2Cl_2$ at 30 ℃. Methyl iodide was used for 1f.
5. Typical procedure : To a solution of 1d (85 mg, 0.154 mmol) in a mixture of EtOH (10 ml) and $CHCl_3$ (5 ml) at -78 ℃ was added $NaBH_4$ (9 mg, 0.231 mmol). After being stirred for 30 min, the solvent was removed *in vacuo*. The residue was extracted with $CH_2Cl_2$ and dried ($MgSO_4$). After removal of the solvent *in vacuo*, the residue was chromatographed ($Al_2O_3$, basic, 70-230 mesh, 1.5 x 7 cm). Elution with n-hexane and $CH_2Cl_2$ (v:v, 2:1, 60 ml) gave o-bromobenzyl disulfide (30 mg, 0.074 mmol, 97 %). After removal of unidentifiable mixtures (11 mg) with the same solvent mixture (v:v, 1:1, 100 ml), 4d (39 mg, 0.145 mmol, 94 %) was eluted by using $CH_2Cl_2$ (200 ml). 4d: liquid; $^1H$ NMR ($CDCl_3$, 60 MHz) δ 4.13 (m, 4H, $CH_2$-N-$CH_2$), 5.33 (t, 1H, -CH=), 7.20-7.68 (m, 9H, ArH); IR (KBr) 3070, 3040, 2760, 2940, 1720, 1680, 1590, 1495, 1460, 1280, 1095, 1020, 840 ; MS m/e 271.

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