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An Efficient Deselenenylation Reaction to the Synthesis of 3, 5-Disubstituted Isoxazoline and Isoxazole

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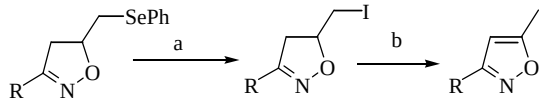
Abstract: A mild deselenenylation reaction protocol for the preparation of 3, 5-disubstituted isoxazolines and their further application to 3-methyl-5-substituted isoxazoles both in solution phase and solid phase was reported.

Keywords: Deselenenylation reaction, isoxazoline, isoxazole.

The development of organoselenium chemistry[1] has been expanding rapidly during the last decades. Among them, organic selenides are key intermediates, for that they can be efficiently introduced, manipulated, and removed through selenoxide *syn*-elimination[2]. Our research group[3] has been interested in the application of selenium in organic synthesis for several years. Isoxazolinyl substituted phenyl selenide **1**[3a], although a β-H exists in the molecule, did not undergo selenoxide *syn*-elimination even they were mixed with H_2O_2 in THF and stirred at 50 °C for 1 h. In order to solve this problem, here we reported a mild deselenenylation protocol to prepare 3,5-disubstituted isoxazolines and their further application to prepare 3-methyl-5-substituted isoxazoles as an important complementarity of selenoxide *syn*-elimination.

Isoxazolinyl substituted phenyl selenide (1.0 mmol), NaI (1.0 g), CH_3I (1.0 mL) and 5 mL DMF were mixed together (**Scheme 1**). The mixture was stirred at 80°C for 20 h to afford 3-substituted-5-iodomethyl isoxazoline in good yield. 3-Substituted-5-iodomethyl isoxazoline was then treated with the organic base 1,5-diazabicyclo[5,4,0]-undec-5-ene (DBU) or NaCN both to afford 5-methyl-3-substituted isoxazole almost quantitatively. The results are summarized in **Table 1**.

Scheme 1



1 **2** **3**

a. CH_3I, NaI, DMF, 80°C, 20 h b. DBU or NaCN, DMF, 80°C, 12 h

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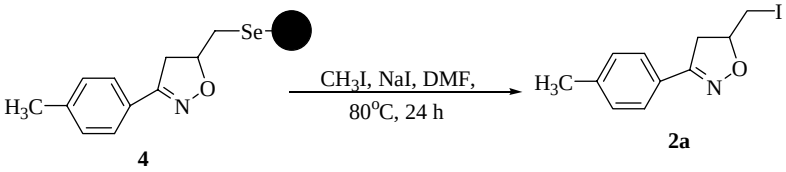
Table 1 Synthesis of 3, 5-disubstituted isoxazolines and isoxazoles

Product	R	Yield (%)[a]
2a	4-$CH_3C_6H_4$	85
2b	4-FC_6H_4	85
2c	4-BrC_6H_4	84
2d	COOEt	90
2e	4-$NO_2C_6H_4$	87
2f	C_6H_5	88
3a[b]	4-BrC_6H_4	97
3b[c]	4-$CH_3C_6H_4$	96

[a] Isolated yield, [b] DBU was used as base, [c] NaCN was used as base

Scheme 2



4 **2a**

Yield: 80%, Purity : 95%

In connection with our previous work, polymer supported 3-(4-methylphenyl)-isoxazolinyl substituted selenide **4**[4], which could not undergo selenoxide *syn*-elimination either, reacted smoothly with NaI and CH_3I using the same procedure. And 3-(4-methylphenyl)-5-iodomethyl isoxazoline **2a** was obtained in good yield and high purity (**Scheme 2**).

In summary, we have developed a mild deselenenylation reaction protocol for the preparation of 3, 5-disubstituted isoxazolines both in solution phase and solid phase. And they reacted further with a base to afford 3-methyl-5-substituted isoxazoles almost quantitatively.

Acknowledgment

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