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Regioselective Synthesis of Multi-substituted Phenylselenomethyl Isoxazolines

Wei Ming XU, Lu Ling WU, Xian HUANG*

Department of Chemistry, Zhejiang University (Xixi Campus), Hangzhou 310028

Abstract: A mild, regioselective 1, 3-dipolar cycloaddition protocol for the preparation of phenylselenomethyl isoxazolines through substituted allyl phenyl selenides and nitrile oxides was reported.

Keywords: 1, 3-Dipolar cycloaddition, isoxazolines, selenides.

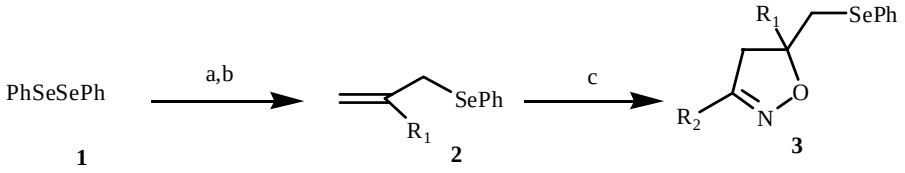
1,3-Dipolar cycloaddition reactions are very important in the construction of five-membered heterocycles[1]. Nitrile oxides are effective 1, 3-dipoles and can undergo reactions with substituted alkynes and alkenes smoothly to give substituted isoxazoles and isoxazolines, respectively. Both classes of heterocycles are versatile intermediates for the synthesis of natural products and biologically active compounds[2]. But to date, no 1,3-dipolar cycloaddition on selenium-substituted alkynes and alkenes has been reported.

Diorganic selenides have attracted considerable interest because of their potential use as anticancer and antioxidant agents[3]. Our research group[4] has been interested in the application of selenium in organic synthesis for several years. Here we reported a mild protocol to prepare multi-substituted phenylselenomethyl isoxazolines regioselectively. ß-Substituted allyl phenyl selenide **2** (1.0 mmol), easily prepared from diphenyl diselenide and ß-substituted allyl bromide, was mixed with hydroximoyl halide (1.0 mmol). To the mixture, Et_3N (1.1 mmol in 5 mL CH_2Cl_2) was slowly added dropwise to afford multi-substituted phenylselenomethyl isoxazolines (**Scheme 1**). It is noteworthy that the reactivity of allyl phenyl selenide and ß-phenylallyl phenyl selenide in this reaction are higher than ß-methylallyl phenyl selenide. The results are summarized in **Table 1**.

In summary, we report a mild 1,3-dipolar cycloaddition protocol through substituted allyl phenyl selenides and nitrile oxides to prepare phenylselenomethyl isoxazolines which have potential use as anticancer and antioxidant agents.

* E-mail: huangx@mail.hz.zj.cn

Scheme 1



Reagents and conditions: (a) $NaBH_4$, THF, DMF, rt, 1h; (b) substituted allyl bromide, THF, rt, 2 h; (C) $R_2C(Cl)=NOH$, CH_2Cl_2, Et_3N, rt, 6 h

Table 1 Synthesis of multi-substituted phenylselenomethyl isoxazolines

Product	R_1	R_2	Yield (%)[a]
3a	H	4-$CH_3C_6H_4$	85
3b	H	4-$CH_3OC_6H_4$	88
3c	H	4-BrC_6H_4	83
3d	H	COOEt	97
3e	CH_3	4-$CH_3C_6H_4$	61
3f	CH_3	C_6H_5	62
3g	CH_3	4-BrC_6H_4	59
3h	CH_3	4-FC_6H_4	53
3i	C_6H_5	4-ClC_6H_4	83
3j	C_6H_5	COOEt	95

[a] Isolated yield.

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