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One-pot Synthesis of Isoxazolines Using Soluble Polymer-supported Acrylates

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Abstract: An efficient and rapid parallel liquid-phase synthesis of isoxazolines has been reported. The one-pot three-component reaction of polyethylene glycol-supported acrylates, aldehydes and hydroxylamine hydrochloride in the presence of chloramine-T in methanol gave the corresponding PEG-supported isoxazolines, which can be cleaved from the support under mild condition to afford isoxazolines in good yields (>80%) and high purities (>86%).

Keywords: Isoxazolines, 1, 3-dipolar cycloaddition, soluble polymer, liquid-phase synthesis, polythylene glycol.

In recent years, the liquid-phase synthesis of small heterocyclic molecules has been a subject of intense research activity[1]. Since it represents one of the most promising ways to generate small molecular libraries in the field of combinatorial chemistry[2]. It profits from both the advantageous features of homogeneous solution chemistry (high reactivity, lack of diffusion phenomena and ease of analysis without following the cleavage and check technique) and of solid-phase methods (use of excess reagents and easy isolation and purification of products). Among the various soluble polymers, polyethylene glycol (PEG) is the most optimum[3].

1, 3-Dipolar cycloaddition is a useful method to obtain varieties of heterocyclic compounds which are versatile intermediates in medical chemistry[4]. The liquid-phase synthesis of substituted pyrazolines[5], oxadiazoles[6] and isoxazoles[7] *via* 1, 3-dipolar cycloaddition of nitrile oxides were well documented. The liquid-phase synthesis of isoxazolines by trapping the *in situ* generated nitrile oxides with soluble polymer-supported acrylate has been tentatively studied previously[8].

In this paper, we would like to report the parallel synthesis of isoxazolines *via* 1, 3-dipolar cycloaddition of nitrile oxides, initiating from aldehydes, with PEG-supported acrylates in one-pot procedure, and to obtain a representative library of isoxazolines. Commercially available difunctional PEG_{4000} was chosen as soluble polymer support.

The ready availability of aldehydes from commercial sources allows the preparation of large heterocyclic compounds library. The structures of the isoxazolines were provided by ^1H NMR, GC-MS spectra.

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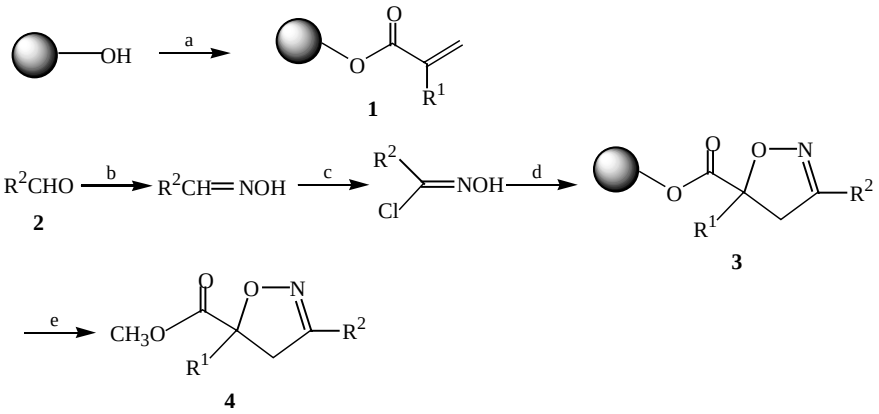
Scheme 1



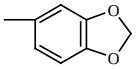
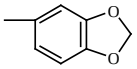
a) CH_2=CHR^{1}COCl / TOA / CH_2Cl_2 b) NH_2OH·HCl / TOA / MeOH c) CAT d) **1**
e) MeONa / MeOH

Experimental

Typical procedure for isoxazoline synthesis: PEG-supported acrylates **1** were easily obtained as illustrated in **Scheme 1** and the convertion of terminal hydroxyl groups on PEG was determined by ^{1}HNMR analysis to be quantitative. Aldehydes (2.0 mmol) **2** were reacted with hydroxylamine hydrochloride (2.0 mmol) and trioctylamine (TOA) (2.0 mmol) in MeOH (10 mL) at room temperature for 10 min. PEG-supported acrylate (0.25 mmol) and chloramine-T (CAT) (2.0 mmol) were added and the mixture was stirred over night at the temerature of 45°C. Upon completion of the reaction, Et_2O (80 mL) was added to the reaction mixture on cooling to precipitate the PEG-bound isoxazoline **3**. The precipitate **3** was then cleaved by 0.1 mol/L MeONa in MeOH (5 mL) at room temperature for 6 hours. Et_2O (80 mL) was added to precipitate the detached PEG-OH. The polymer was filtered and the solvent was removed to give the desired isoxazolines **4**. All compounds listed in **Table 1** were analyzed by ^{1}H NMR, GC-MS spectra. The data of compound **3j** are as follows: ^{1}H NMR (500 MHz, $CDCl_3$, δ ppm): 7.54 (d, 2H, *J*=8.1Hz), 7.21 (d, 2H, *J*=7.9Hz), 4.35 (m, PEG-2H), 3.88 (d, 1H, *J*=16.9Hz), 3.79~3.50 (PEG), 3.23 (d, 1H, *J*=16.9Hz), 2.38 (s, 3H), 1.71 (s, 3H). Compound **4j**: ^{1}H NMR (500 MHz, $CDCl_3$, δ ppm): 7.55 (d, 2H, *J*=8.1Hz), 7.21 (d, 2H, *J*=8.0Hz), 3.87 (d, 1H, *J*=16.9Hz), 3.81 (s, 3H), 3.21 (d, 1H, *J*=16.9Hz), 2.38 (s, 3H), 1.72 (s, 3H). MS *m*/*z* (%): 233 (M^+, 16), 174 (42), 132 (100), 91 (18).

In summary, we have demonstrated that liquid-phase methodology can be applied efficiently in parallel one-pot synthesis of isoxazoline library. All reactions involved here are highly efficiently in giving the desired compounds at mild condition. Crude products are usually obtained in high purity and high yield by simple precipitation and washings. They can be used directly in primary biological assays without further purification.

Table 1 Liquid-phase synthesis of isoxazolines on PEG support

Compd.	R^1	R^2	MS (*m/z*, M^+)	Yield (%)[a]	Purity (%)[b]
4a	H	C_6H_5	205	92	97
4b	H	4-CH_3-C_6H_4	219	94	96
4c	H	4-CH_3O-C_6H_4	235	95	98
4d	H	4-Cl-C_6H_4	239	93	90
4e	H	2-Cl-C_6H_4	239	93	98
4f	H		249	95	95
4g	H	CH_2CH_3	157	86	91
4h	H	$CH_2CH_2CH_3$	171	85	86
4i	Me	C_6H_5	219	90	94
4j	Me	4-CH_3-C_6H_4	233	91	99
4k	Me	4-CH_3O-C_6H_4	249	90	95
4l	Me	4-Cl-C_6H_4	253	80	94
4m	Me	2-Cl-C_6H_4	253	86	98
4n	Me		263	92	99
4o	Me	CH_2CH_3	171	85	95
4p	Me	$CH_2CH_2CH_3$	185	89	96

[a] Yields by gravimetric analysis were based on isolated material following cleavage from support.
[b] Purities were based on GC-MS analysis of cleaved samples. GC-MS purities were consistent with the purities measured by ^{1}H NMR spectra.

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