Communication

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

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An efficient liquid-phase synthesis of isoxazolines through a 1,3-dipolar cycloaddition is described. Soluble polymer-supported acrylate reacted with nitrile oxides generated *in-situ*, followed by cleavage from the support giving corresponding isoxazolines in high yields and excellent purities.

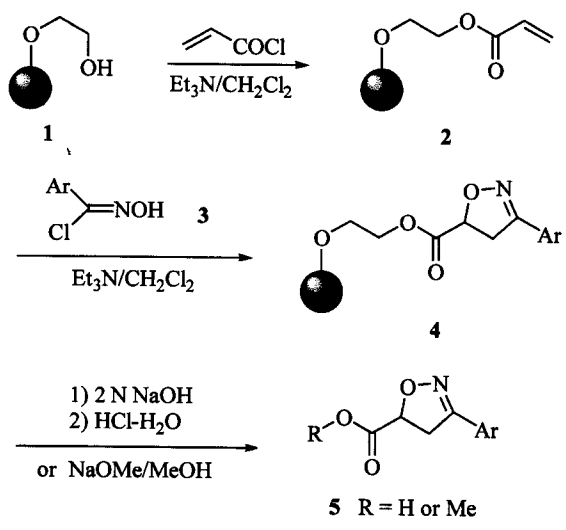
Keywords poly(ethylene glycol) (PEG), isoxazoline, cycloaddition, liquid-phase

Cross-linked polymer supports are now widely used in the fields of combinatorial chemistry, organic synthesis, catalysts and reagents.[1] However, due to the emerging problems associated with the heterogeneous nature of the ensuing chemistry and with "on-bead" spectroscopic characterization, soluble polymers are being developed as alternative matrices for combinatorial library production[2] and organic synthesis.[3] Synthetic approaches that utilize soluble polymers, termed "liquid-phase" chemistry, couple the advantages of homogeneous solution chemistry with those of solid-phase methods. In liquid-phase synthesis, the separation of the functionalized matrix could be easily achieved by either solvent or heat precipitation, membrane filtration or size-exclusion chromatography.[4]

Isoxazoles and isoxazolines are versatile scaffolds for the synthesis of a wide variety of complex natural products and important pharmacophores in medicinal chemistry.[5] Solution methods for their preparation via 1,3-dipolar cycloaddition of nitrile oxide with alkyne or alkene are well documented.[6] The solid-phase synthesis of isoxazoles has been described earlier using either polymer-supported nitrile oxide precursors[7] or polymer-supported alkynes.[8] In our previous paper,[9] we have described the liquid-phase synthesis of isoxazoles by trapping the *in-situ* generated nitrile oxide with the polymer-supported alkyne. We herein disclose a practical and efficient liquid-phase synthesis of isoxazolines using soluble polymer-supported acrylate (Scheme 1).

We chose the soluble polymer support, polyethylene glycol (PEG) (average molecular weight of 4000), to perform our reactions. This inexpensive polymer is attractive as a support since it is soluble in many organic solvents, with the notable exception of ethers and hexane, and is a solid at room temperature. Not only does its good solubility allow to have enough reactivity in solution, but also intermediate products can easily be adequately characterized by ^{1}H NMR spectra. Our work presented here shows that the use of PEG-bound substrates can help to rapidly evaluate the substrate spectrum of a multistep sequence.

Scheme 1



Our investigation began with the anchor of acryloyl chloride on PEG_{4000} to obtain polymer-supported acrylate **2** in a quantitative yield (Scheme 1). The nitrile oxides[10] generated *in-situ* from aryl hydroximinoyl chlorides **3** and triethylamine in methylene chloride reacted with the PEG-bound acrylate **2** to afford the polymer-supported isoxazoles **4**.[11] Cleavage of products with aqueous 2 N NaOH gave free acids **5** (R = H) in good yields and high purities (Table 1, compounds **5a**, **5c** and **5e—5h**). Treatment of **4** with CH_3ONa/CH_3OH resulted in the ester exchange products **5** (R = Me) in high yields and excellent purities (compounds **5b**, **5d**, **5i** and **5j**).[11]

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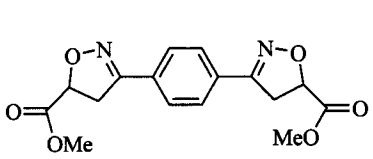
Table 1 Isoxazolines **5a**—**5j** prepared via the procedure as shown in Scheme 1

Compound	Ar	R	MS (m/z, M^+)	Yield (%)[a]	Purity (%)[b]
5a	C_6H_5	H	191	90	97
5b	4-MeC_6H_4	Me	219	95	96
5c	4-MeC_6H_4	H	205	93	99
5d	4-$MeOC_6H_4$	Me	235	95	95
5e	4-$MeOC_6H_4$	H	221	94	96
5f	4-FC_6H_4	H	209	90	98
5g	4-$O_2NC_6H_4$	H	236	85	95
5h	2-ClC_6H_4	H	225	86	95
5i	3,4-$(OCH_2O)C_6H_3$	Me	249	92	98
5j	3-$O_2NC_6H_4$	Me	250	95	95

[a] Yields by gravimetric analysis were based on isolated material following cleavage from support. [b] Purities were based on LCMS or GCMS analysis of cleaved samples. LCMS or GCMS purity was consistent with the purity measured by ^1H NMR spectra.

To extend the scope of this methodology, we have also investigated the synthesis of bis(isoxazoline) heterocycle system. Treating PEG-bound acrylate **2** with terephthaldinitrile oxide and isophthaldinitrile oxide, followed by cleavage from the resin with CH_3ONa/CH_3OH, afforded two bis(isoxazoline) heterocycles **6** and **7** in high yields (92% and 91%, respectively) and high purities (97% and 95%, respectively), which could be readily converted into β-hydroxy ketone moieties by a reductive cleavage.[12]



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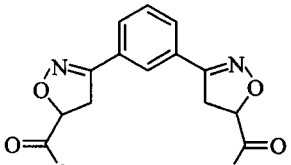

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In summery, we have developed a practical and efficient liquid-phase synthetic methodology for preparation of isoxazolines via 1, 3-dipolar cycloaddition. This one-pot protocol works reliable in good to high yields (>85%) and excellent purities (>95%) using a commercially available PEG_{4000} as support.

References and notes

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5 A search in MDDR (MDL data base) revealed the presence of more than 250 structures based on the isoxazole scaffold and endowed with several pharmacological activities used for analgesia, inflammation, immunology and CNS diseases (such as anxiety, memory impairment, depression, Parkinson's and stroke).

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11 Typical procedure for the synthesis of isoxazolines: *N*-chlorosuccinimide (NCS, 2 mmol) and the oxime (2 mmol) were stirred at 25 ℃ in a flask containing dry methylene chloride. The polymer-supported acrylate (0.5 mmol) was added in one portion after the chlorination was over (usually after *ca.* 30 min) and triethylamine (0.14 mL in 2 mL of CH_2Cl_2) was added drop by drop over *ca.* 2 h. The reaction mixture was stirred overnight at room temperature. To this was added a five fold excess of dry benzene to remove triethylamine hydrochloride. The solution was concentrated and diethylether was added to afford the polymer-supported isoxazolines **4**. The resin **4** is then cleaved with CH_3ONa/CH_3OH at room temperature to give the desired isoxazolines **5**. Compound **4b**: ^1H NMR (500 MHz, $CDCl_3$) δ: 7.57 (d, 2H), 7.21 (d, 2H), 5.17—5.23 (m, 1H), 4.36 (t, 2H), 3.50—3.78 (PEG), 3.09—3.11 (m, 2H), 2.38 (s, 3H). Compound **5b**: m.p. 45 ℃; ^1H NMR (500 MHz, $CDCl_3$) δ: 7.57 (d, 2H), 7.21 (d, 2H), 5.19—5.23 (m, 1H), 3.81 (s, 3H), 3.64 (m, 2H), 2.38 (s, 3H); IR ν: 1767 (C=O), 1611 (C=N) cm^{-1}; GC/MS m/z (%): 219 (M^+, 100), 160 (46). Anal. calcd for $C_{12}H_{13}NO_3$: C 65.75, H 5.94, N 6.39; found C 65.86, H 5.75, N 6.37.

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