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Soluble polymer-supported synthesis of isoxazoles

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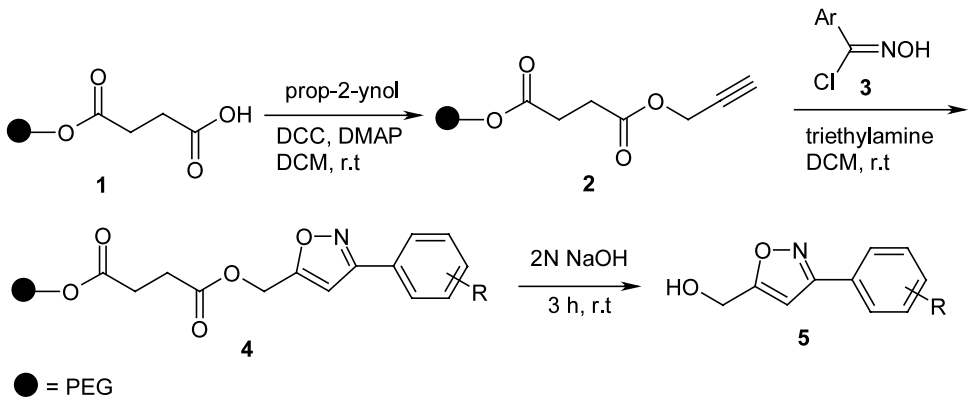
Abstract—The first soluble polymer-supported synthesis of isoxazoles through a 1,3-dipolar cycloaddition is described. A soluble polymer-supported alkyne reacts with nitrile oxides generated in situ to give isoxazoles in good yield. © 2002 Published by Elsevier Science Ltd.

1,3-Dipolar cycloaddition of alkynes and alkenes with nitrile oxides is useful for the synthesis of isoxazoles and isoxazolines, which are versatile intermediates for the synthesis of a wide variety of complex natural products[1] and important pharmacophores in medicinal chemistry. Solution methods for their preparation are well documented, and several examples of dipolar cycloaddition to insoluble polymer-supported dipolarophiles have been reported recently.[2] These polymer-supported syntheses offer potential in the combinatorial synthesis of small heterocycle libraries, since the established advantages of solid-phase organic chemistry can be readily applied. General difficulties in solid phase work, however, include the possibility of lower reactivity at the polymer-solvent interface and characterization of intermediate products while still attached to the polymer. Some problems can be alleviated with the use of a soluble polymer support.[3] In this letter we would like to describe a facile liquid-phase synthesis of isoxazoles.[4]

For development of dipolar cycloaddition chemistry we chose to employ polyethylene glycol (PEG) with an average molecular weight of 4000. 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 solubility allow for solution reactivity but also intermediate products can be adequately characterized by proton NMR.

The synthesis of isoxazoles is described in Scheme 1. PEG_{4000} succinate **1**[5] was condensed with propargyl alcohol (3.0 mol equiv.) in the presence of dicyclohexylcarbodiimide (DCC, 4.0 mol equiv.) and 4-dimethylaminopyridine (DMAP, 0.2 mol equiv.) to afford the polymer supported alkyne **2**.[6] This material was reacted with aryl hydroxyminoyl chlorides **3** by slow addition of triethylamine over a period of 2 h in methylene chloride.[7] The resulting mixture was shaken at room temperature overnight. To this was added five equiva-



Scheme 1.

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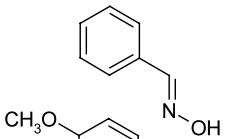
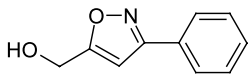
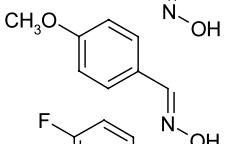
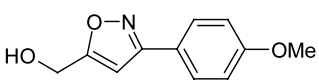
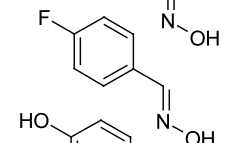
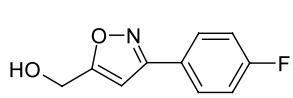
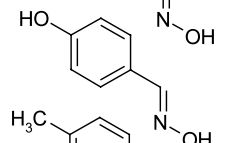
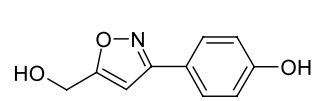
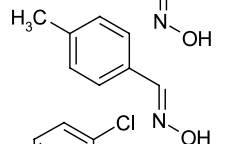
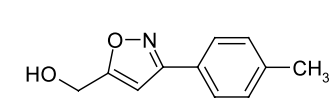
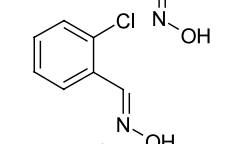
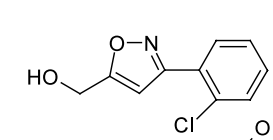
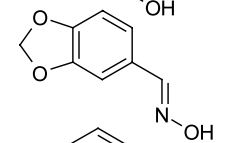
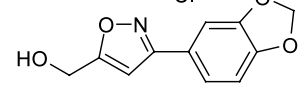
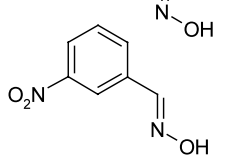
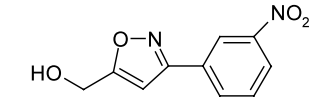
Table 1. Liquid-phase synthesis of isoxazoles

Entry	Oxime	Isoxazole	M^+	purity(%)[a]	yield(%)[b]
3a			175	98.6	91
3b			205	100	86
3c			193	97.8	80
3d			191	95.6	62
3e			189	100	89
3f			209	99.0	54
3g			219	96.4	87
3h			220	95.3	48

[a] Purity determined by GC/MS analysis of crude products. [b] The crude yields are based on weight of crude samples and relative to the initial loading.

lents of benzene to remove triethylamine hydrochloride. The solution was concentrated and diethyl ether was added to afford the polymer supported isoxazoles **4**.[8] Substrate cleavage was accomplished by treating **4** with aqueous 2N NaOH at room temperature and monitored for the disappearance of the polymeric isoxazoles (3 h) (Table 1).[9]

Using this procedure, a variety of isoxazoles can be synthesized by trapping in situ generated nitrile oxides with the polymer-supported alkyne in a practical and efficient one-pot operation. The products are of excellent purity (>95%) and isolated in 48–91% yields, as shown in Table 1.

Acknowledgements

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5. Compound **1** was prepared in 96% yield by treatment of PEG_{4000} with succinic anhydride and catalytic DMAP in refluxing CH_2Cl_2.

6. The polymer supported alkyne was characterised by 500 MHz ^{1}H NMR analysis in $CDCl_3$ (δ 2.50 [t, $J=2.3$ Hz, alkyne proton], 2.69 [m, 4H, -$OCCH_2CH_2CO$], 4.25 [t, $J=4.2$ Hz, 2H, -PEG$OCH_2\underline{CH_2}OCO$], 4.70 [d, $J=2.4$ Hz, propargylic CH_2]).
7. Paton, R. M.; Young, A. A. *J. Chem. Soc., Chem. Commun.* **1994**, 993.
8. Typical procedure for isoxazole synthesis: *N*-Chlorosuccinimide (NCS, 2 mmol) was stirred in a flask containing dry methylene chloride. The oxime (2 mmol) was added at 25°C in one portion. The polymer-supported alkyne (0.5 mmol) was added in one portion after the chlorination was over. Usually after ca. 30 min, triethylamine (0.14 mL in 2 mL of CH_2Cl_2) was added dropwise 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 diethyl ether was added to afford the polymer-supported isoxazoles **4**, which were characterised by ^{1}H NMR spectroscopy. Compound **4b**: ^{1}H NMR (500 MHz $CDCl_3$): δ 7.74 [d, $J=8.7$ Hz, 2H], 6.97 [d, $J=8.7$ Hz, 2H], 6.58 [s, 1H], 5.24 [s, 2H], 4.25 [t, $J=4.7$ Hz, 2H], 3.85 [s, 3H], 2.71 [br., 4H]. The resin was then cleaved with aqueous 2N NaOH at room temperature to give the desired isoxazoles. Compound **5b**: ^{1}H NMR ($CDCl_3$): δ 7.72 [d, $J=8.7$ Hz, 2H], 6.97 [d, $J=8.8$ Hz, 2H], 6.50 [s, 1H], 4.79 [s, 2H], 3.84 [s, 3H]); GC/MS: m/z 205 (M^+, 59%), 174 (100%).
9. Purity was determined by GC/MS analysis of the crude products. All products showed satisfactory NMR and MS data, which were consistent with the proposed structures.