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One Pot Solid Phase Synthesis of Isoxazolines

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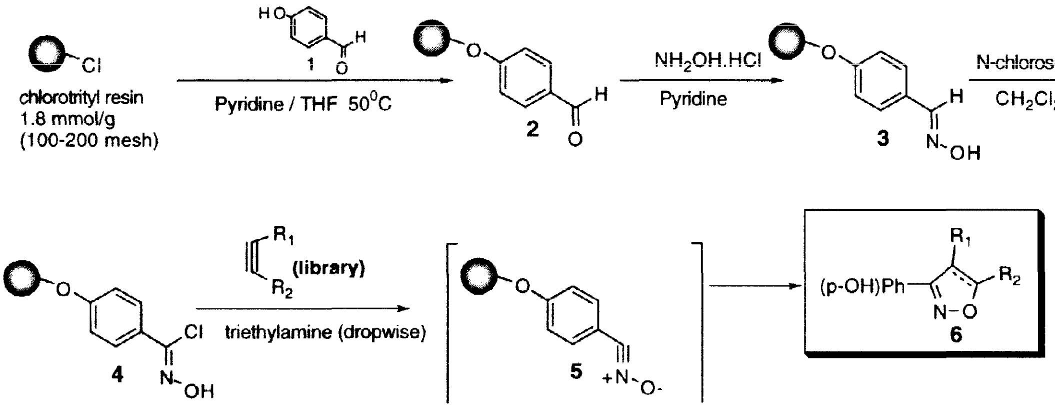
Abstract: *1,3 Dipolar cycloadditions of nitrile oxides generated in situ on solid phase in the presence of a variety of dipolaraphiles provided a library of isoxazolines and isoxazoles.* © 1998 Elsevier Science Ltd. All rights reserved.

Nitirile oxides undergo [3+2] cycoladditions with olefins and acetylenes to provide isoxazolines and isoxazoles respectively.[1] These products, besides being potential pharmaceutical agents, are also precursors to useful intermediates such as γ-amino alcohols and β-hydroxy ketones enroute to other natural products.[2] The major limitation of this chemistry is the propensity of nitrile oxides to undergo rapid dimerization to furoxan N-oxide.[3] One can circumvent this problem by generating the nitrile oxide species *in situ* under high dilution conditions in the presence of multifold excess of the olefinic trap. However, purification and isolation of the desired product becomes an issue.

The temptation to exploit the virtues of Solid Phase Organic Chemistry (SPOC)[4] to overcome these limitations was compelling. Accordingly, our plan was to anchor a nitrile oxide precursor on to the solid phase thereby simulating high dilution by virtue of inherent loading factor, and then generate the reactive species in the presence of excess trap, preferably all in one pot. Finally, washing off all of the surplus reagents followed by cleavage would provide the cycloadducts. Our efforts at generating a representative library of isoxazolines and isoxazoles using this strategy are presented below.

para-Hydroxy benzaldehyde **1** was attached on chlorotrityl resin.[5] The aldehyde functionality was converted to aldoxime by treating with excess hydroxylamine hydrochloride in pyridine at room temperature, monitored by Infrared spectroscopy[6] for the disappearance of the aldehyde stretch at 1693 cm^{-1}. After washing and drying, the oxime resin **3** was chlorinated with 4 eq. N-chlorosuccinimide in methylene chloride for two hours to provide chloro oxime **4**, a precursor to the nitrile oxide. To this was added a ten fold excess of dipolaraphile (olefin/acetylene) as a methylene chloride solution before generating the nitrile oxide **5** by slow addition of triethylamine over a period of two hours.[7] The resulting mixture was shaken overnight. The resin was filtered, washed, and dried.[5] The cycloadducts were cleaved off the resin with 1% TFA in methylene chloride.



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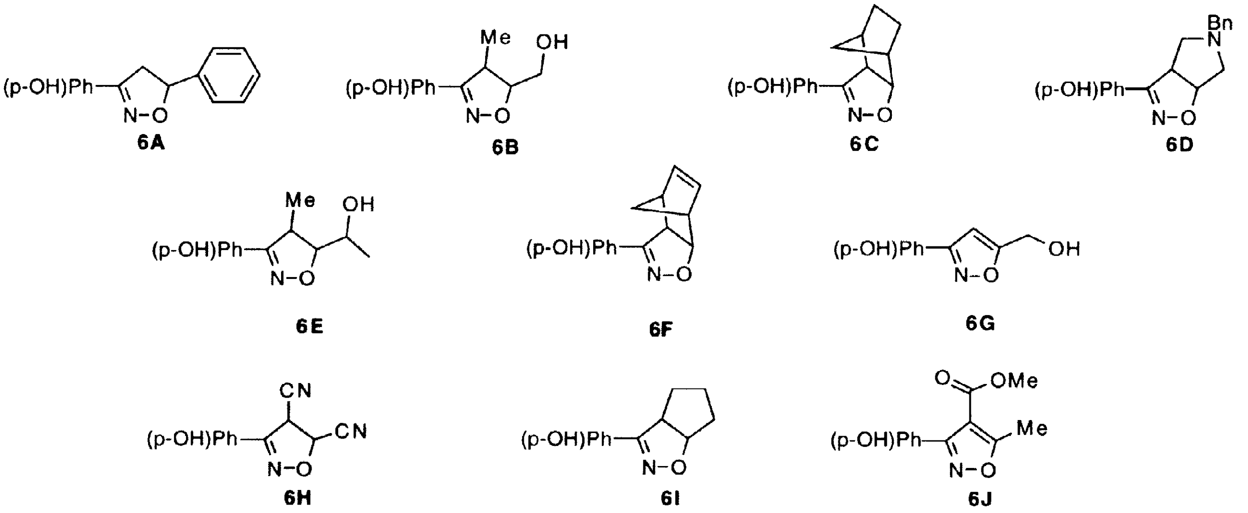
A library of isoxazolines and isoxazoles (**6A**-> **6J**)[1] was thus generated by trapping in situ generated nitrile oxide with appropriate olefins and acetylenes in a Diversomer Kit[8] in a practical and efficient one pot operation . The yields were in the range of (60 -> 80%) and greater than 90% purity.[9] In case of unsymmetrical dipolaraphiles the major regioisomer is shown.[1]

Library



The oxime **3** is a versatile intermediate and can potentially be used to generate nitrones to provide isoxazolidine libraries. These studies will be the subject of future communication.

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References and Notes:

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5. Novabiochem; The combinatorial chemistry catalog Feb. **1997**, S29. Workup: Filtered resin was washed sequentially with CH_2Cl_2, DMF, DMF / water (1:1), water, EtOH, and diethyl ether.
6. Sample of the resin was washed and dried. The resin was ground into fine powder and a pellet was made after mixing with KBr.
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9. The yields are based on p-hydroxy benzaldehyde loading and the purity was determined by LCMS and NMR. ^{1}H-NMR **6A** : (300 MHz, $CDCl_3$) 3.35 (dd, J = 16.0, 7.5 Hz, 1H), 3.8 (dd, J = 16.0, 10.0 Hz, 1H), 5.78 (dd, J = 10.0, 7.5 Hz, 1H), 6.9 (d, J = 7.5 Hz, 2H), 7.4 (m, 5H), 7.65 (d, J = 7.5 Hz, 2H).