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# Solid-phase synthesis of 3-hydroxymethyl isoxazoles via resin bound nitrile oxides

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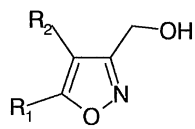
**Abstract**—[3+2] Cycloaddition of alkynes to resin bound nitrile oxides gives after cleavage of 3,4,5 trisubstituted isoxazoles in acceptable yields and fair to good purity, depending on the alkyne substituents. The reaction has been automated on the ACT 496 synthesiser. 

Solid-phase synthesis is gaining more importance since its scope has been extended from the preparation of peptide compounds, as originally pioneered by Merrifield, to the synthesis of small organic molecules.[1] The development of new synthetic procedures suited to solid-phase synthesis continues to be a major focus for chemistry. The methods amenable to automation for the parallel production of compounds are of particular value.

The combinatorial libraries are generally built around a scaffold decorated at the available positions with substituents able to impart the requested drug like properties.[2] From this point of view, isoxazole appears well suited possessing three positions to be exploited for diversity. This scaffold (and the related isoxazoline) represents a pharmacophore itself as it has been observed in several substances showing activity against a broad range of therapeutic targets.[3]

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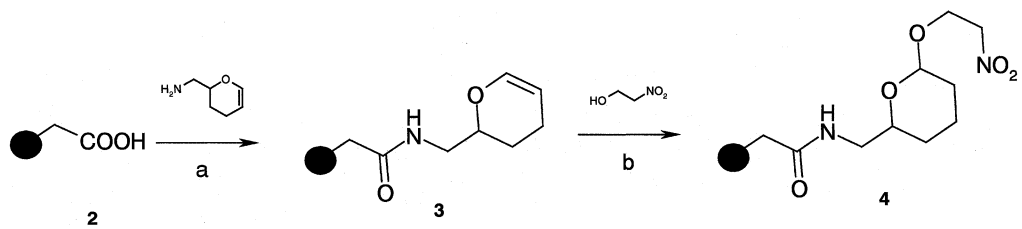
A small library of 3-hydroxymethyl-4,5-disubstituted isoxazoles **1** was designed to be prepared on solid phase through the well known [3+2] cycloaddition of a nitrile oxide to a triple bond. Mono and disubstituted alkynes, easily available,[4] served as diversity precursors and the 3-hydroxymethyl group as a tethering point on the resin. Examples of isoxazoles synthesis on solid phase through a dipolar cycloaddition have already been reported by Kurth[5] and Pei,[6] but carrying out the [3+2] cycloaddition the opposite way. Indeed, they reacted polymer bound acetylenes with nitrile oxides generated in solution, which is similar to the method of Curran[7] who tethered the alkynes to a fluorous phase.




2 3 4

**Scheme 1.** (a) DCC (4 equiv.), HOBT (4 equiv.), DMF, rt, 16 h. (b) Nitro ethanol (5 equiv.), *p*-TsOH (1 equiv.), $CH_2Cl_2$, rt, 24 h.

*Keywords*: solid-phase synthesis; combinatorial chemistry; isoxazoles; [3+2] cycloadditions.

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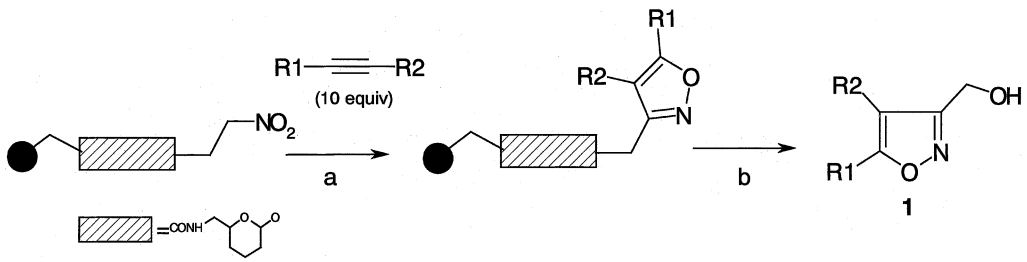
We describe herein a strategic alternative which complements the previous methods. The nitrile oxide is generated directly on the resin, being the cycloadducting alkynes in solution. The poor stability of the reactive species would be increased on a solid support leading to final compounds of good quality. Indeed under solid-phase conditions the formation of dimers (in the present case furoxane which is present as a by-product in the nitrile oxide cycloadditions carried out in solution) is generally avoided. Among several nitrile oxide precursor species,[8] the nitro group was selected based on the available building blocks. A modified tetra hydropyranyl[9] linker **3** was first prepared by tethering aminomethyl tetrahydropyrane to a Merrified carboxylic acid resin **2** under traditional coupling conditions. Nitro ethanol was then added under acid catalysis to afford the resin bound intermediate **4** (Scheme 1).

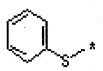
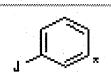
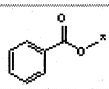
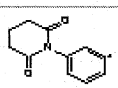
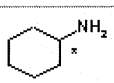
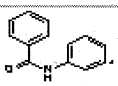
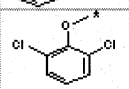
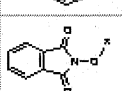
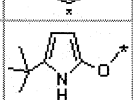
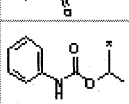
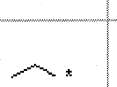
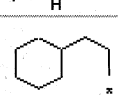
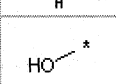
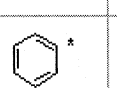
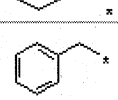
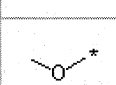
The reaction progress was followed by FT-IR spectroscopy (formation of the carboxamide signal at 1700 $cm^{-1}$) and the resin loading was determined by nitrogen elemental analysis. The cycloaddition step was carried out by generating the resin bound nitrile oxide from intermediate **4** under Mukayiama conditions[10] in the presence of the reacting alkynes. The final compounds **1** were obtained after mild TFA cleavage from solid support. (Scheme 2). The conditions set up for manual synthesis were optimised for automated synthesis to be carried out on the ACT Multiple Organic Synthesiser Model 496 (manufactured by Advanced ChemTech, Louisville KY).

The intermediate **4** was made available in a 15 g batch and the library was prepared following a defined protocol.[11] Basing on the load of the resin bound intermediate **4** (1.08 mmol/g) the amount of the compounds was spread over a 15–35 mg range, as expected. From the total weight of the 96 well plate an average amount of 15 mg was estimated for each well and this indicates a 60% average yield. The yields of the isoxazoles obtained by the present method with parallel automated synthesis are indeed satisfactory and similar to or better than those reported with traditional solution phase chemistry.[12] In Table 1 are listed 24 compounds which represent a selected pool (25%) of the whole library in




**Scheme 2.** (a) PhNCO (20 equiv.), TEA (10 equiv.), DMF, 50°C, 5 h. (b) 20% TFA, $Cl_2H_2$.

**Table 1.** Selected compounds from the isoxazole library **1**

| Cp | R1 | R2 | Yield | Cp | R1 | R2 | Yield | Cp | R1 | R2 | Yield |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 # |  | H | 75 | 9 |  | H | 59 | 17 |  | H | 68 |
| 2 |  | H | 89 | 10 |  | H | 72 | 18 |  | H | 65 |
| 3 |  | H | 74 | 11 |  | H | 81 | 19 |  | H | 75 |
| 4 |  | H | 58 | 12 |  | H | 93 | 20 # |  | COOEt | 51 |
| 5 |  | H | 80 | 13 |  | H | 82 | 21 |  | COOEt | — |
| 6 |  | H | 64 | 14 |  | H | 60 | 22 |  | | — |
| 7 |  | H | 33 | 15 § |  | H | 60 | 23 |  | | — |
| 8 |  | H | 82 | 16 |  | H | 72 | 24 | COOEt | COOEt | 70 |

# Compounds also prepared by manual synthesis to set up synthetic and analytical methods. § Compound obtained from tetrahydro pyranylether protected alkyne.

terms of substituent type and compound purity. The quality of the library was automatically checked on an LC/MS system equipped with a Gilson 215 autosampler.

The compounds were injected directly from the plate into the HPLC; then the flow was split both to a UV detector and an MS spectrometer.[13] This latter confirmed the presence of the expected compound according to the ion corresponding to the protonated molecule $[M+H]^+$, whereas the purity was determined according to the relative HPLC peak area under UV detection ($\lambda$ 240 nm). The isoxazoles were considered absent either when the $[M+H]^+$ was not detected or when their purity was less than 20%. A few representative compounds, manually prepared and fully purified on a semi preparative HPLC, were submitted to NMR for structure confirmation.[14]

The overall quality of the library is fair to good taking into account that the LC purity refers to 'crude' substances, devoid of any post synthesis purification process. The major pool comprises about 60% of the compounds showing a purity higher than 50%, which is believed acceptable for initial screening purposes. A second pool representing about 20% of the library includes compounds with purity ranging from 20 to 50%. The remaining 20% refers to substances not detected at all by MS or showing a purity lower than 20%: these latter come mainly from alkynes disubstituted with electron withdrawing groups which are weak dipolarophiles.

Of note was the confirmed regioselectivity of the cycloaddition reaction even when carried out on solid-phase. This is substantiated by NMR spectra of selected manually prepared compounds, and by the absence in LC/MS of couples of peaks possessing identical molecular weight. Finally, as anticipated in the initial strategy, the presence of dimer furoxane was never detected.

In conclusion we have set up a reliable method for solid-phase synthesis of 3-hydroxymethyl isoxazoles through a [3+2] cycloaddition of alkynes to a resin bound nitrile oxide. This method is robust enough to be carried out in a parallel and automated fashion by an automated synthesiser.

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4. ACD (MDL data base) contains more than 1000 alkynes commercially available and about 200 of them are suited for the preparation of drug-like substances.
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11. Protocol of the synthesis: Polystyrene carboxylic acid resin (Novabiochem, 15 g, 1.24 mmol/g loading, 18.6 mmol) was reacted for 16 h with 2-aminomethyl 3,4-dihydro-2*H*-pyran (4.2 g, 37 mmol), in the presence of HOBT (12.5 g, 81 mmol) and DCC (16.9 g, 81 mmol) in DMF (100 ml) under gentle stirring. After washings (DMF×5, $CH_2Cl_2$×5, MetOH×3, $CH_2Cl_2$×5, 100 ml each), a solution of nitroethanol (8.7 g, 93 mmol) in $CH_2Cl_2$ (150 ml) was added and the mixture was stirred gently for 24 h. The resin was washed ($CH_2Cl_2$×5, MetOH×3, $Et_2O$×3, $CH_2Cl_2$×5, 100 ml each), desiccated and dispensed into the ACT 496 block (100 mg/well, calculated loading 1.01 mmol/g). 1 M DMF solutions of PhNCO (20 equiv.) TEA (20 equiv.) and the alkyne (10 equiv.) were sequentially added to the reaction chambers. The reaction conditions were set up at 50°C for 5 h under stirring. After several washings (DMF×7, $CH_2Cl_2$×7, $Et_2O$×5, MetOH×5, $CH_2Cl_2$×7, 1.5 ml each) a 20% solution of TFA in $CH_2Cl_2$ was dispensed and the block stirred for 30 minutes. The solutions of the cleaved compounds were collected by filtration into a 96 well plate and evaporated to dryness in a speed-vac.
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13. LC/MS analysis: C8 reverse phase column (Alltech Nucleosil 4.6×15 cm) isocratic method (solvent A $H_2O$/0.2% formic acid; solvent B $CH_3CN$/0.2% formic acid) 1 ml/min for 20 min; mass spectrometry was performed on a Finnigan Navigator instrument in APCI+ mode, Temp. 450°C.
14. $^1H$ NMR (Varian 200 MHz, $CDCl_3$). Compound **1** 4.82 (2H, s, $\underline{CH_2}OH$); 6.59 (1H, s, $\underline{H}(4)$); 7.45–7.79 (5H, m, $\underline{Ph}$). Compound **20** 1.25–1.33 (3H, t, $\underline{CH_3}CH_2$); 4.21–4.24 (1H, d, $CH_2\underline{OH}$); 4.28–4.39 (2H, q, $CH_3\underline{CH_2}O$); 4.90 (2H, s, $\underline{CH_2}OH$); 7.49–7.85 (5H, m, $\underline{Ph}$).