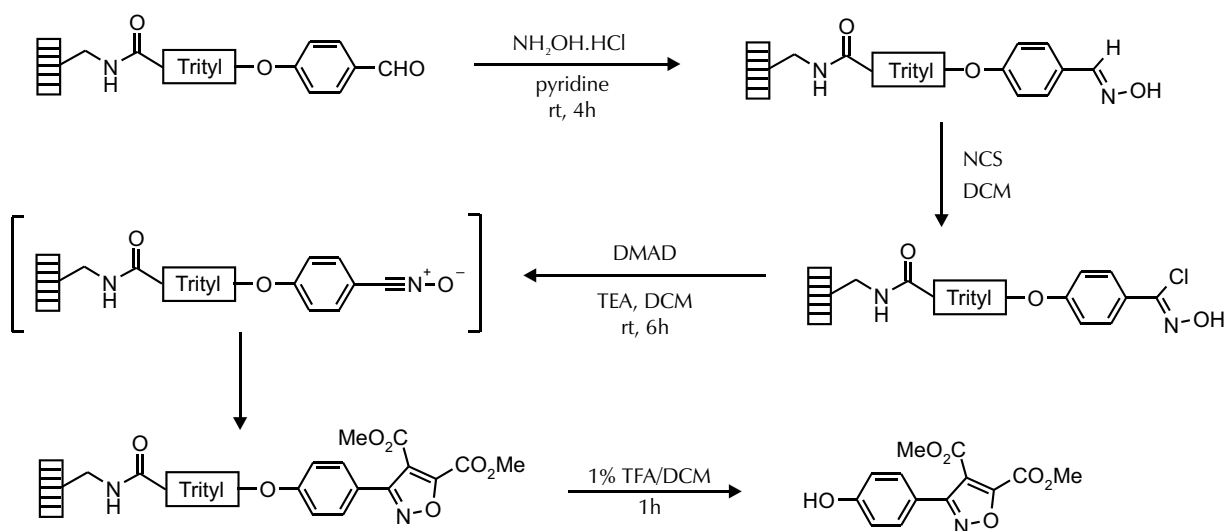


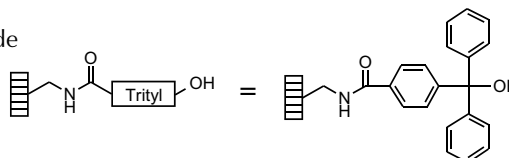


Preparation of Isoxazoles or Isoxazolines

The [3 + 2] cycloaddition of a support bound nitrile oxide with an alkyne or alkene is a useful synthetic route to isoxazoles or isoxazolines respectively.¹ In the following example, an oxime is generated from a support-bound aldehyde. The oxime is converted to the chloro-oxime and then treated with TEA to form a nitrile oxide *in situ*. The nitrile oxide is then trapped by a dipolarophile, such as DMAD to afford an isoxazole. In this example, 4-hydroxybenzaldehyde had previously been coupled to SynPhase™ PS trityl alcohol Lanterns.^{2,3}



NCS: N-chlorosuccinimide DMF: dimethylformamide
DCM: dichloromethane rt: room temperature
TFA: trifluoroacetic acid TEA: triethylamine
DMAD: dimethylacetylene dicarboxylate



Aldoxime Reaction

Each D-Series Lantern previously derivatized with 4-hydroxybenzaldehyde (initial specified loading: 36 μmol) is treated with 0.6 mL of a solution of hydroxylamine hydrochloride (1.0M,

600 μmol, 16.5 mole equivalents) in anhydrous pyridine at rt for 4h. The reagent solution is decanted and the Lanterns washed with DMF (3 × 3min) and DCM (3 × 3min) then air dried.

Chloro-oxime Reaction

The Lanterns are added to a vial containing a solution of NCS (0.6M, 0.57 mL per Lantern, 342 μmol, 9.4 mole equivalents) in DCM at rt for 3h.⁴ The reagent solution is decanted and

the Lanterns washed with DMF (3 × 3min) and DCM (3 × 3min) then dried. Lanterns should then be used immediately.

Cycloaddition Reaction

Each Lantern is treated with 0.5mL of a solution of DMAD (0.75M, 375 μ mol, 10.3 mole equivalents) in DCM. To this solution is added TEA (52 μ L, 0.75M, 375 μ mol, 10.3 mole equivalents).

The Lanterns are then allowed to react at rt for 6h. The reagent solution is decanted and the Lanterns washed with DMF (3 \times 3min) and DCM (3 \times 3min) then air dried.

Cleavage

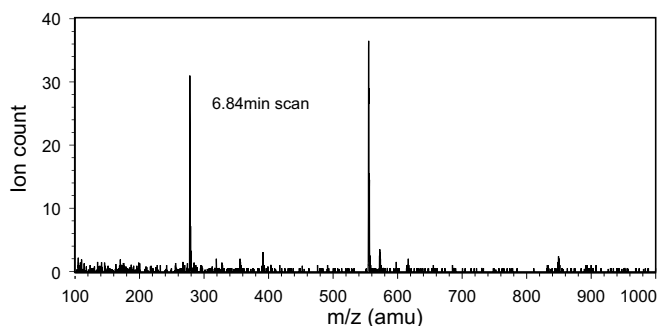
Individual Lanterns are placed in polypropylene tubes and treated with 1% TFA in DCM (0.6-0.8mL) for 1h. The Lanterns are removed and the cleaved products are concentrated using a

centrifugal evaporator. The yield of crude isoxazole is 68% (based on the initial loading). Samples are dissolved in 90% CH₃CN/H₂O for HPLC and ES-MS analysis.

Analytical Data

400MHz ¹H NMR spectrum of crude Isoxazole (CDCl₃)

(x) Residual TEA



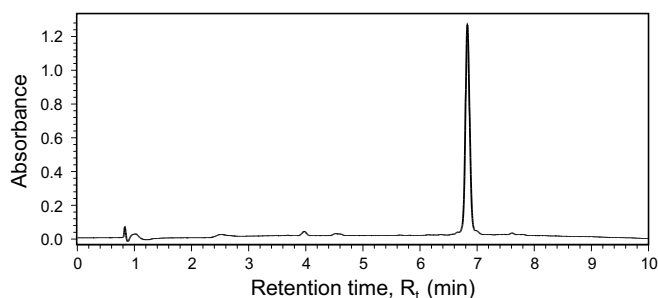
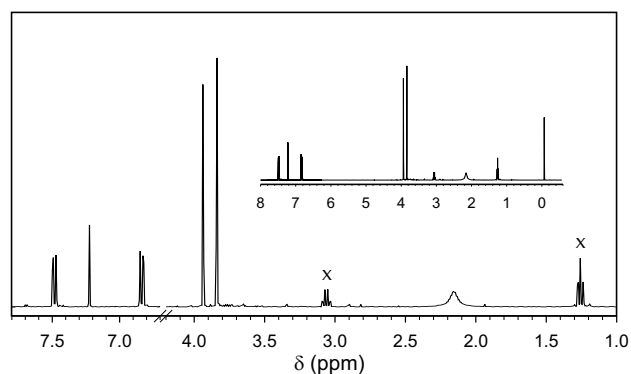
Electrospray MS trace of LC peak at R_t=6.84min

Molecular Formula: C₁₃H₁₁NO₆

Monoisotopic Mol. Weight: 277.24amu

[M+1]⁺ peak at 278.2amu

[2M+1]⁺ peak at 555.5amu



Reverse-phase HPLC trace of the crude Isoxazole

Detection at 214nm

References and Notes

- 1 Shankar, B.B., Yang, D.Y., Girton, S. and Ganguly, A.K., *Tetrahedron Lett.*, 1998, **39**, 2447.
- 2 See SynPhase Chemistry Note SCN 009-3.
- 3 The chemistry described here was performed using SynPhase PS Lanterns but is readily adaptable to SynPhase PA Lanterns.
- 4 The NCS may not completely dissolve.



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