



Pergamon

Tetrahedron Letters 41 (2000) 9181–9184

TETRAHEDRON  
LETTERS

# A photolabile ‘traceless’ linker for solid-phase organic synthesis

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Received 14 August 2000; accepted 20 September 2000

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## Abstract

A photolabile linker based on a thiohydroxamic acid has been shown to be an efficient ‘traceless’ linker, revealing an aliphatic CH bond on photolysis at 350 nm. Methods for the synthesis, loading and photolytic cleavage of the linker are described. © 2000 Elsevier Science Ltd. All rights reserved.

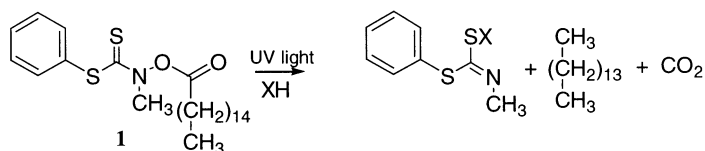
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The synthesis of combinatorial libraries on solid-phase has experienced a rapid expansion in the last five years and is now routine in drug discovery. Critical to the success of any solid-phase synthesis is the linker, which attaches the substrate to the support. There are numerous linkers currently available<sup>1</sup> and judicious choice can result in a successful library synthesis. Almost all linkers are designed to reveal a polar functionality on release of the substrate from the resin. In contrast, there are few linkers designed to reveal a CH bond on cleavage. The majority of these so-called ‘traceless’ linkers are designed to create an aromatic CH bond. These are often based on arylsilane handles that are cleaved via acid-mediated protodesilylation.<sup>2,3</sup> There are scant examples of linkers that reveal aliphatic CH bonds and all have major limitations such as harsh/unsuitable cleavage reagents or poor yields.<sup>4–9</sup> The use of photolabile linkers in solid-phase synthesis is an attractive strategy as photolysis can provide an orthogonal non-invasive method of cleavage. To this end we have designed a new linker, which will reveal an aliphatic CH bond upon photolytic cleavage. Work by Barton has shown that irradiation of the stable thiohydroxamic ester **1**, in the presence of a suitable chain carrier, initiates a rapid decarboxylative radical rearrangement releasing an alkane (Scheme 1).<sup>10</sup>

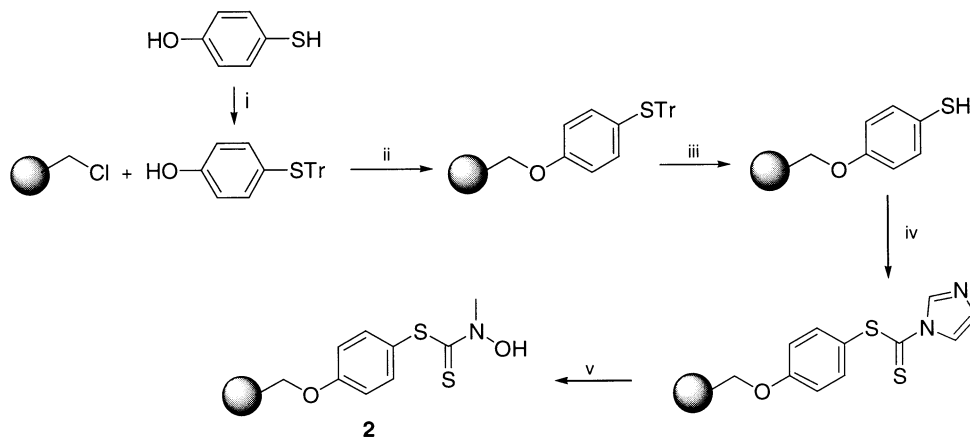
To study the utility and scope of this thiohydroxamic acid as a photolabile ‘traceless’ linker for solid-phase synthesis, the linker was assembled on resin (Scheme 2). Trityl protected 4-hydroxymercaptophenol was attached to chloromethylpolystyrene (0.8 mmol/g, Novabiochem) by alkylation. The resin was deprotected and immediately reacted with 1,1-thiocarbonyldiimidazole. Subsequent displacement of imidazole with *N*-methylhydroxylamine

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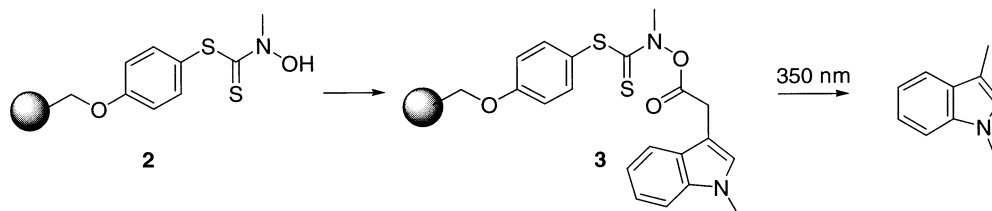
Scheme 1.



Scheme 2. (i) trityl chloride (1 equiv.), pyridine (1 equiv.),  $\text{CH}_2\text{Cl}_2$ , ambient temp., 4 h, 97%. (ii) chloromethylpolystyrene (0.8 mmol/g), NaH (60% dispersion in oil) (3 equiv.), DMF,  $60^\circ\text{C}$ , 18 h, 98%.<sup>12</sup> (iii) TFA: $\text{CH}_2\text{Cl}_2$ :triethylsilane, (9:10:1), ambient temp., 1 h. (iv) 1,1-thiocarbonyldiimidazole (3 equiv.),  $\text{CH}_2\text{Cl}_2$ , ambient temp., 18 h, 78%.<sup>13</sup> (v) *N*-methyl hydroxylamine hydrochloride (3 equiv.), triethylamine (6 equiv.),  $\text{CH}_2\text{Cl}_2$ , ambient temp., 18 h, 73%.<sup>13</sup>

furnished the resin-bound linker **2**.<sup>11</sup> The loading of the resin was determined to be 0.39 mmol/g by elemental analysis of nitrogen.

Various coupling methods were investigated in order to optimise the attachment of *N*-methylindole-3-acetic acid to linker **2** (Scheme 3). Aliquots of resin were treated with various coupling reagents and the results shown in Table 1.



Scheme 3.

The optimum coupling was achieved using *N,N*-diisopropylcarbodiimide (DIC) and 1-hydroxybenzotriazole (HOBt) in the presence of dimethylaminopyridine (DMAP).<sup>14</sup> The capacity of resin **3** to release 1,3-dimethylindole was investigated.<sup>15</sup> The results are illustrated in Table 2.

The nature of any photoproducts remaining on the resin were not investigated (loss of the stretch at  $1805\text{ cm}^{-1}$  in the FTIR was noted, indicating complete consumption of the thiohydroxamic ester moiety). Photolysis of **3** in the presence of 2-methyl-2-propanethiol gave a low

Table 1  
Coupling of *N*-methylindole-3-acetic acid to resin **2**

Method	Yield of <b>3</b> (%) <sup>b</sup>
Acid (2 equiv.), <sup>a</sup> DIC (2 equiv.), HOBT (2 equiv.), DMAP (0.2 equiv.)	85
Acid (2 equiv.), DIC (2 equiv.), HOBT (2 equiv.)	80
Acid (3 equiv.), MSNT (3 equiv.), MeIm (2.5 equiv.)	70
Acid (2 equiv.), TBTU (2 equiv.), HOBT (2 equiv.), <sup>t</sup> Pr <sub>2</sub> EtNH (4 equiv.)	73

<sup>a</sup> Based on the loading of resin **2** (0.39 mmol/g).

<sup>b</sup> The percentage yield is based on the theoretical 100% loading of resin **3** and is determined by elemental analysis for nitrogen and the amount of *N*-methylindole-3-acetic acid methyl ester released on treatment with excess NaOMe.

Table 2  
Release of 1,3-dimethylindole from resin **3**

Conditions	Yield of 1,3-dimethylindole (%) <sup>a</sup>
THF: MeOH (4:1), 30 min, 350 nm	8
THF: (TMS) <sub>3</sub> SiH (40:1), 30 min, 350 nm	44
THF: Bu <sub>3</sub> SnH (40:1), 30 min, 350 nm	55
THF: Bu <sub>3</sub> SnH (40:1), 60 min, 350 nm	47
THF: <sup>t</sup> BuSH (40:1), 30 min, 350 nm	31
Toluene: Bu <sub>3</sub> SnH (40:1), AIBN (1 equiv.), <sup>b</sup> 18 h, 70°C	38

<sup>a</sup> The yield of released 1,3-dimethylindole is determined by HPLC analysis using diode array detection and indole as an internal standard.

<sup>b</sup> Based on the loading of resin **3** (0.31 mmol/g).

yield of 1,3-dimethylindole but this reaction had the advantage of facile removal of excess thiol via evaporation under reduced pressure. Although in all cases the yield of the photolytic release was slightly disappointing we were gratified to note the purity of the released 1,3-dimethylindole was >90% (Fig. 1).

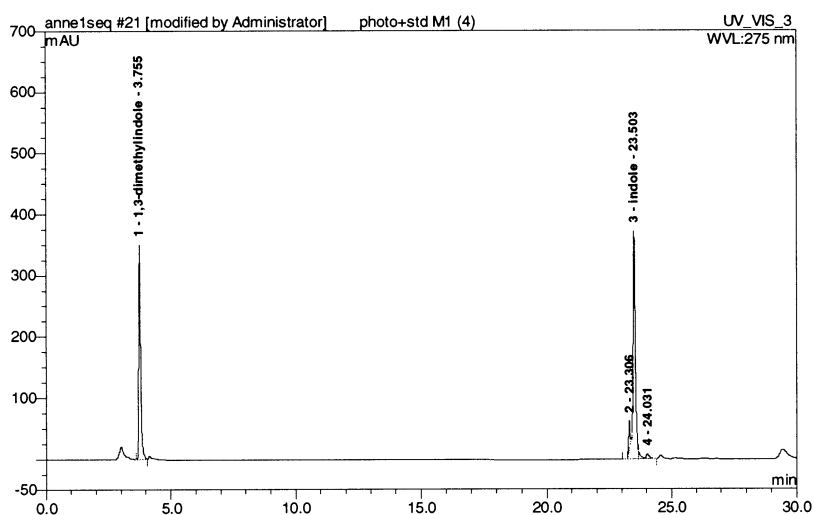


Figure 1. HPLC trace (275 nm detection) of released 1,3-dimethylindole with added indole as an internal standard

In this letter we have illustrated the potential of a thiohydroxamic acid as a photolabile 'traceless' linker for solid-phase organic synthesis. We are currently optimising photolytic release from the resin and exploring the chemical stability of the linker.

## Acknowledgements

We would like to thank The University of Leeds, The Royal Society (for a research grant), Pfizer Central Research and GlaxoWellcome (Dr. S. McKeown) for financial support. We also thank Dr. Maria Fiorini (University of Cambridge) for some preliminary studies.

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11. The signals that could be distinguished from the polystyrene resin backbone were;  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , ppm) 115.9(–OCCH–), 67.9(–CH<sub>2</sub>O–).
12. Yield determined by elemental analysis for sulphur.
13. Yield determined by elemental analysis for nitrogen and sulphur.
14. **Procedure for loading resin 2 with *N*-methylindole-3-acetic acid.** Resin 2 (0.5 g, 0.195 mmol) was swollen in a minimum of  $\text{CH}_2\text{Cl}_2$ . *N*-methylindole-3-acetic acid (73 mg, 0.39 mmol), HOBt (53 mg, 0.39 mmol) and DMAP (4.8 mg, 0.039 mmol) were dissolved in anhydrous DMF (2 ml). This solution was added to the resin mixture, DIC (49 mg, 0.39 mmol) was added dropwise and the reaction was agitated at ambient temperature for 18 h. The resin was filtered and washed with DMF (3×5 ml), THF (3×5 ml) and  $\text{CH}_2\text{Cl}_2$  (3×5 ml). The resin was dried under vacuum until a constant weight was achieved (72 h). Gel phase FTIR showed a stretch at  $1805\text{ cm}^{-1}$  (C=O). Gel phase  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , ppm) 168.7(C=O), 68.5(–CH<sub>2</sub>O–), 33.3(–NCH<sub>3</sub> of indole), 29.2(–CH<sub>2</sub>COO–).
15. **Typical procedure for the photolysis of resin 3.** The resin 3 (0.05 g, 0.0155 mmol of loaded *N*-methylindole-3-acetic acid) was swollen in THF:XH (40:1) and the solution degassed with nitrogen for 10 min. The solution was photolysed at 350 nm using a Rayonet photochemical reactor for 30 min. The resin was removed by filtration and the solution made up to 10 ml. Indole was added and an aliquot of the solution was removed and analysed by HPLC (diode array detection).