Pergamon

Tetrahedron Letters 41 (2000) 5287–5290

TETRAHEDRON LETTERS

Thermally cleavable safety-catch linkers for solid phase chemistry

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Received 5 April 2000; accepted 16 May 2000

Abstract

Safety-catch linkers based on the sulfoxide/selenoxide *syn* elimination have been developed. Clean and efficient oxidation of the sulfide to the sulfoxide was achieved with the homogeneous oxidising system comprising of hexafluoroisopropanol (HFIP) and hydrogen peroxide. Elimination of the sulfoxide was only possible with the most activated of substrates, while the selenoxide underwent cleavage under much milder conditions. © 2000 Elsevier Science Ltd. All rights reserved.

Solid phase synthesis usually requires the use of a linker[1] to attach the compound of interest to the solid support. This linker must be stable to the synthetic conditions used to prepare the target compound but should be cleavable under relatively mild conditions at the end of the synthesis to yield the target molecule. Safety-catch linkers[2–6] require some pre-determined activation step prior to final compound cleavage. The advantage of this class of linkers is that the cleavage step may be effected under very mild conditions, possibly with the product being cleaved directly into an aqueous solution for immediate biological screening,[7–9] while the ultimate cleavage process does not have to be orthogonal to the preceding synthesis.

Here we describe the synthesis of linkers cleaved by sulfoxide and selenoxide pericyclic elimination reactions[10] (Scheme 1). We also describe a versatile, homogeneous solid phase oxidation method for the selective oxidation of thioethers to sulfoxides. This follows initial reports by Michels[11] in 1976, who co-polymerised 4-styreneselenol with 1,4-divinylbenzene to generate seleno-PS resin which was then used for the introduction of unsaturation into carbonyl compounds. More recent reports by ourselves in the area of sulfoxide linkers[12] and a variety of other solid phase selenium based chemistries have also been published by a number of groups.[13]

The synthetic methodology was developed using *t*-butyl-*p*-bromomethylbenzoate (**1**), synthesised in two steps from *p*-toluoyl chloride in 74% overall yield.[14] This allowed preliminary studies to be carried out in solution prior to resin attachment. Thus, bromide **1** was alkylated with thiourea or

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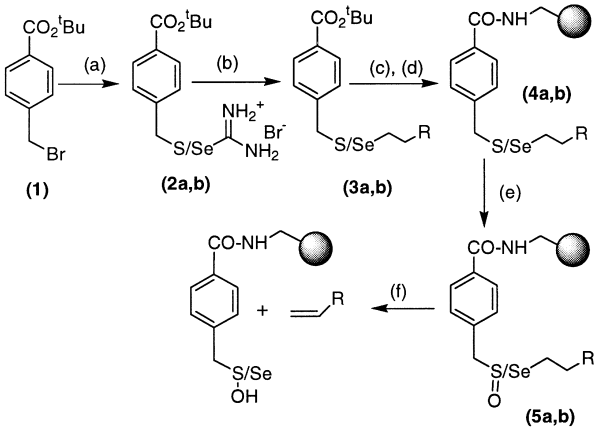
PII: S0040-4039(00)00807-8

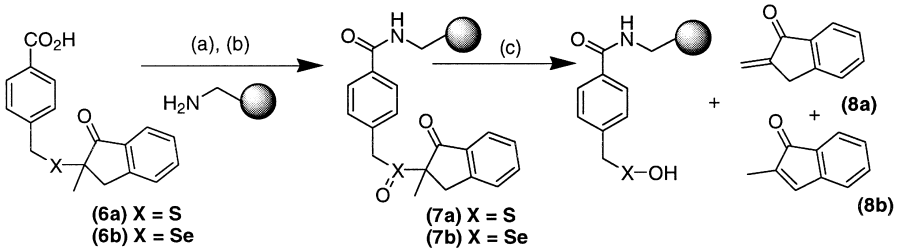


Scheme 1. (a) Thiourea or selenourea (1 equiv.), EtOH, 65°C, quantitative; (b) 4% aq. NaOH, RBr (1.2 equiv.), EtOH:water (1:1) or 20% aq. NaOH, TEBA; then 1.1 equiv. R-Br, 60°C, 33–60%; (c) TFA, DCM (thio analogue), HCO_2H, (seleno analogue), 85–100%; (d) aminomethyl polystyrene resin, DIC, HOBt, DMF; (e) H_2O_2, HFIP, DCM (2:1); (f) dioxane, reflux, (sulfoxide only)

selenourea in refluxing EtOH for 7 h, to give the isothiouronium/isoselenouronium salts (**2a**,**b**), respectively, in quantitative yields. These salts were subsequently hydrolysed with 4% aq. NaOH, then alkylated in situ to give the desired thio/seleno ethers **3a**,**b**, ready for solid phase attachment or solution chemistry. Oxidation of the thioether **4a** to the sulfoxide **5a** was achieved in very good yield using an excess of H_2O_2 in 1,1,1,3,3,3-hexafluoroisopropanol/DCM (2:1) as previously described.[15]

There was no evidence of over-oxidation to the sulfone (reactions on the solid phase were monitored both by gel phase ^{13}C NMR and analysis following cleavage of model compounds attached to the solid phase via the Rink linker) thus allowing a very controlled solid phase synthesis of the sulfoxides. The HFIP was not just acting as an acid catalyst since the addition of other acids led to mixtures of both sulfones and sulfoxides and thus it may be that HFIP co-ordinates the sulfoxide thereby preventing over-oxidation to the sulfone.[15]

Initially the indenones **8a**,**b** were viewed as suitable synthetic targets, since the precursors **7a**,**b** were highly activated towards elimination (Scheme 2). Thus **6a**,**b** were prepared from **2** and 2-bromo-2-methylindanone in yields of 27 and 22%, respectively, and coupled to aminomethyl polystyrene resin (negative ninhydrin test). Compound **7a** was thermally eliminated to give predominantly the *exo*-indenone **8a** (the ratio of *exo*/*endo* indenones was 13:1 by reverse phase



Scheme 2. (a) DIC, HOBt, DMF; (b) 30% aq. H_2O_2, HFIP, DCM (2:1); (c) compound **7a**: 100°C, dioxane; compound **7b**, room temperature

HPLC, Fig. 1) in excellent purity (> 95% by HPLC) and in reasonable purified yields (45% based on initial resin loading). The identity of the indenones **8a**,**b** were confirmed by comparison with pre-synthesised standards which were prepared according to literature methods.[16,17] The dominance of the *exo* isomer was surprising based on literature expectations.[18]

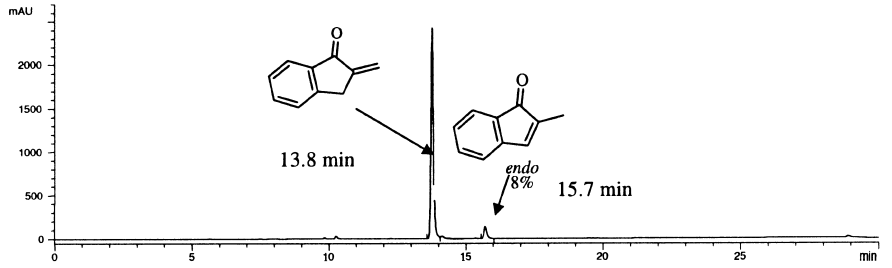
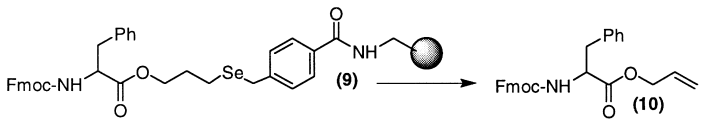


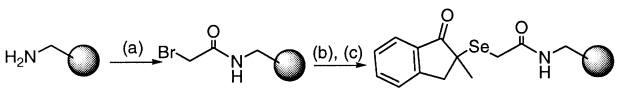
Figure 1. Crude RP-HPLC analysis of indenone elimination from **7a**

Numerous other thioethers were prepared in an analogous manner. However upon oxidation and thermolysis using a range of solvents (dioxane, toluene, *N*-methylformamide) no unsaturated products were obtained. A typical example was 4-{[(3-phenylpropyl)sulfinyl]methyl}benzoate which was refluxed in MeOH, dioxane or *N*-methylformamide (bp 199°C), but in no case was the desired elimination product obtained. Since Moghaddam[19] had successfully obtained allylbenzene in 30% yield using an analogous system and had increased the yield by the use of microwaves, a purpose designed microwave reactor with a CO_2 cooled condenser was used. Unfortunately, the only product obtained in this reaction was the phenyl disulfide. It was clear that the sulfoxide linkers could only be used for highly activated substrates and thus the analogous seleno-ether based linker constructs were prepared. The selenium indanone conjugates were prepared in an identical manner (Schemes 1 and 2), except for the use of formic acid to remove the *tert*-butyl ester from **3b** (TFA led to the reductive cleavage of the C–Se bond to give methylindanone). The indenones were prepared in a straightforward manner (Scheme 2) following oxidation with hydrogen peroxide and thermal elimination. The selenol was also alkylated with 3-bromopropanol, which was esterified with Fmoc-Phe-OH to give **9** (Scheme 3). Oxidation and elimination gave the allyl ester Fmoc-Phe-OAllyl **10** with a purity of 96% in 31% yield based on initial resin loading.



Scheme 3. $NaIO_4$, dioxane:water (1:1), 0°C, filtered, add dioxane, 18 h, 20°C

An alternative method of direct attachment was also successful (Scheme 4). Thus aminomethyl TentaGel resin was reacted with bromoacetic acid/DIC (25% $BrC^{13}H_2CO_2H$ was used for reaction analysis by ^{13}C NMR),[20] the bromide was displaced with selenourea, the isoselenouronium salt hydrolysed (NaOH) and the resulting selenol immediately alkylated. The use of 2-bromo-2-methylindanone as the alkylating agent and oxidation ($NaIO_4$) as previously described led to a 21:1 ratio of the *exo*:*endo* indenones in 32% isolated overall yield based on the starting loading of the aminomethyl TentaGel resin.



Scheme 4. (a) $BrCH_2CO_2H$, DIC, DCM; (b) selenourea, EtOH, 2% then 10% aq. NaOH; (c) 2-bromo-2-methylindanone, Cs_2CO_3, DMF

In summary, we have developed a series of linker constructs which can be cleaved by oxidation followed by elimination. In the case of the sulfoxides this process requires an activated substrate and relatively high temperatures, while in the case of selenoxides much reduced temperatures are required and much less activated materials are required. One particularly useful new prospect is a method of synthesising peptide allyl esters by solid phase synthesis.

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