Traceless Solid Phase Synthesis with Polystyrene-Bound Tellurium and in Comparison with Polystyrene-Bound Selenium

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Abstract: A novel traceless linking strategy by use of polystyrene-bound tellurium is described. The application of the tellurium linker is demonstrated by the solid phase synthesis of a small library of single alkyl aryl ethers containing two points of diversity. Polystyrene-bound tellurium and polystyrene-bound selenium are compared by their cleavage performance under radical conditions (homolysis) at different temperatures. In addition, polystyrene-bound substrates were analysed by the use of high-resolution magic angle spinning (HR–MAS) NMR spectroscopy.

Key words: combinatorial chemistry, solid phase synthesis, traceless linker, polystyrene-bound chalcogenes, HR–MAS NMR spectroscopy

Introduction

Solid phase organic synthesis (SPOS) of combinatorial libraries of non-peptidic compounds with low molecular weight and suitable physicochemical properties has become an established tool in pharmaceutical companies for the discovery of biologically active compounds. Traceless SPOS is of high importance in particular for the design of biologically active target molecules since the cleaved target compounds have no memory of their former attachment point and therefore are bearing exclusively those functionalities that have been chosen for their biological activity. Examples of traceless linkers which enables the cleavage of products under aliphatic C(sp^3)-H bond formation are rare compared with traceless linkers, from which products are released under aromatic C(sp^2)-H bond formation.

We and others have recently reported that the chalcogen tellurium takes place smoothly under radical conditions at elevated temperature (using tributyltin hydride and catalytic amounts of AIBN) by C(sp^3)-H bond formation.

The first library synthesised on polystyrene-bound selenium was a library consisting of six alkyl aryl ethers with two points of diversity. Within the last few years, publications from K. C. Nicolaou et al. and others have initiated impressive demonstrations of application possibilities of polystyrene-bound selenium in the SPOS of e.g. carbohydrates (2-deoxy glycosides), glycopeptides (vancomycin derivatives) and heterocycles (indoles, benzopyrans, furanones and others). Obviously, compounds attached to polystyrene-bound selenium are allowed to bear a broad range of functional groups and are also allowed to undergo diverse chemical transformations prior to cleavage.

However, cleavages from polystyrene-bound selenium under radical conditions have so far been performed at elevated temperature (90–100 °C, toluene). The high temperature is a drawback for temperature-sensitive compounds and it complicates parallel synthesis in automation routines since reaction vessels (generally made of polypropylene) are not resistant to toluene at this temperature. Since literature reports suggested that homolysis of phenyl alkyl tellurides could take place at lower temperature in comparison to phenyl alkyl selenides, we have extended our linker-strategy towards the chalcogen atom, tellurium. Only a few tellurium-containing polymers have found applications in organic synthesis. For instance, polystyrene-bound diaryl telluroxides are reported as mild and selective oxidation agents and very recently soluble poly(ethylene glycol)-bound tellurides have been used as catalysts for Wittig-type olefination reactions. In solution-phase organic synthesis, tellurium plays generally only a minor and exotic role.

In the present paper, the element tellurium is given an important role as linking element for traceless SPOS. To the best of our knowledge we herein describe for the first time the preparation of polystyrene-bound tellurium as a suitable solid support for SPOS. In the following, we compare the cleavage performance of polystyrene-bound tellurium with polystyrene-bound selenium in the synthesis of a library of single aryl alkyl ethers using the Mitsunobu reaction. In addition, each step of the synthesis can be monitored by high-resolution magic angle spinning (HR–MAS) 1H NMR spectroscopy.

Results and discussion

The preparation of polystyrene-bound tellurium was achieved in analogy to the synthesis protocol for the preparation of polystyrene-bound selenium (Scheme 1). Commercially available polystyrene (100–200 mesh, cross-linked with 1% divinylbenzene) was brominated...
under thallium acetate catalysis to obtain bromopolystyrene 1 (loading: 3.67 mmol/g). Bromine-lithium exchange (with excess n-BuLi) in hexane–toluene (1:1) generated lithiated polystyrene 2 which was treated with tellurium powder (approximately 350 mesh) under reflux to generate polystyrene-bound tellurium 3. Excess tellurium was liberated from resin 3 by reduction with NaBH₄ in MeOH.

In order to determine the loading of polystyrene-bound tellurium resin 3, the polystyrene-bound sodium telluro(triethyl)borate complex 4 was converted by alkylation with 2,4-dichlorobenzyl chloride to the almost colourless resin 4. No bromine was found by elemental analysis indicating that the bromine–tellurium exchange on resin 1 must have gone to completion. The alkylation of resin 4 with chloro-N,N-dimethylacetamide, which has been used previously to determine the loading of polystyrene-bound selenium, failed and the starting resin 3 was recovered due to re-oxidation of the polystyrene-bound sodium telluro(triethyl)borate complex 4.

The solid-phase synthesis of a [2 × 3] sized alkyl aryl ether library is outlined in Scheme 3. In order to compare the cleavage results of polystyrene-bound tellurium with polystyrene-bound selenium, identical building blocks and reaction conditions were chosen. The first point of diversity was introduced by alkylation of resin 4 (after activation of polystyrene-bound tellurium 3) with 2-[2-(2-chloroethoxy)ethoxy]ethanol and 6-bromohexanol, respectively, yielding the polystyrene-bound alcohols 6 and 7. The second point of diversity was introduced by ether formation with phenols under Mitsunobu reaction conditions. Coupling of each of the polystyrene-bound alcohols 6 and 7 with 4-phenyl-, 2-fluoro-, and 3-methoxy phenol furnished the six polystyrene-bound alkyl aryl ethers 8–c and 9–c. Cleavage by homolysis of the resins 8–c and 9–c furnished the aryl alkyl ethers 10–c and 11–c, respectively.

In order to compare the cleavage performance of polystyrene tellurium and selenium at different temperatures, identical cleavage conditions for both resins were used (4.2 equiv of tributyltin hydride and 0.1 equiv of AIBN in toluene). Cleavages were performed at 90 °C and 60 °C (for all members 8–c and 9–c of the library, Table 1) and exemplarily at 50 °C and 40 °C (for compound 10a). The results (yields and purities after column chromatography) are shown in Table 1.

As mentioned earlier, we expected that cleavage for polystyrene-bound tellurium would be more efficient compared with polystyrene-bound selenium. To our surprise, this was not the case. By use of polystyrene-bound selenium (loading: 2.34 mmol/g) yields for the cleaved products 10a–c and 11a–c were similarly high at both 90 °C and 60 °C and (not significantly different from those earlier reported). However, the yields obtained by use of polystyrene-bound tellurium were approximately 20–30% lower at 60 °C in comparison to cleavage at 90 °C. In addition, yields after cleavage from polystyrene-bound tellurium are in general significantly lower in comparison with polystyrene-bound selenium at all temperatures (approximately 10–20% and 25–30% lower yields at 90 °C and 60 °C, respectively; (exception: 11b entry 9, Table 1)). In addition, cleavage of the alkyl aryl ether 10a from polystyrene-bound selenium and tellurium was performed at 50 °C and 40 °C, respectively. With polystyrene-bound selenium a yield of 78% (GC–MS purity: 93%) for 10a was obtained, which is slightly lower in comparison to cleavage performed at 60 °C (entry 1, Table 1). With polysty-
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Scheme 3

Polystyrene-bound tellurium a yield of 58% (GC–MS purity: 93%) for 10a was obtained, which is similar in comparison to cleavage performed at 60 °C (entry 2, Table 1). However, yields are dropping dramatically when cleavage is performed below 50 °C. Only traces of the product 10a were isolated after cleavage at 40 °C for both, polystyrene-bound selenium (yield: 9%, GC–MS purity: 14%), and polystyrene bound tellurium (yield: 11%, GC–MS purity: 9%).

It is not obvious to us why the reactivity of polystyrene-bound tellurium towards homolysis is lower in comparison to polystyrene-bound selenium. A possible explanation could be that traces of elemental tellurium (still remaining within the resin) are interfering with the radical chain process in the cleavage step at lower temperature (<90 °C).

Recently, we have demonstrated that HR–MAS NMR spectroscopy is a very powerful tool in analysing substrates attached to polystyrene-bound selenium. In analogy we are able to monitor the synthesis and cleavage (at 90 °C) of substrates attached to polystyrene-bound tellurium, as exemplified by resins 8a and 12 (Scheme 4).

Figure 1 shows the 1H HR–MAS spectra of polystyrene-bound tellanyl ether 8a and, after its cleavage, of the resulting polystyrene-bound tributylstannyl telluride 12.

Assignments of the proton chemical shifts of 8a in Figure 1a are based on the gradient COSY spectra (Figure 2a). Although the signals from protons of the methylene group adjacent to the Te-atom (labelled a in Figure 1) are invisible in the Carr–Purcell–Meiboom–Gill (CPMG) spectrum (due to the poor T2 relaxation properties), they are clearly visible in the COSY spectrum (Figure 2a). Figure 1b shows the 1H HR–MAS spectra of polystyrene-bound tributylstannyl telluride 12. Thus we clearly demonstrate that the cleavage reaction went to completion. The assignments of 1H-signals are (in analogy to polystyrene-bound tributylstannyl selenide) based on multiplicity and line shape without the need of the COSY spectrum. As expected, the NMR spectra of 8a and 12 show a strong resemblance to those of the corresponding Se-analogues. Only the methylene groups, adjacent to the linking heteroatom, display significant chemical shift differences. In the case of 8a, the chemical shift of the methylene protons a (Figure 1a) is 3.0 ppm while it is 3.1 ppm in the Se-analogue. For 12, the chemical shift for protons l (Figure 1b) is 1.0 ppm while it is 1.1 ppm in the Se-analogue.
Conclusions

We have described the preparation of polystyrene-bound tellurium and its first application in traceless SPOS. Additionally we demonstrated that substrates attached to this linker could be analysed by HR–MAS NMR spectroscopy. The preparation of polystyrene-bound tellurium by the described procedure is very tenacious compared with polystyrene-bound selenium. Cleavages were performed under radical conditions using tributyltin hydride and AIBN in toluene. Polystyrene-bound tellurium and selenium were compared by their cleavage performance at different temperatures. Cleavages at 90 °C and 60 °C from polystyrene-bound selenium furnished comparable and

Table 1  Cleavage Performance of Polystyrene-Bound Selenium vs. Polystyrene-Bound Tellurium

<table>
<thead>
<tr>
<th>Entry</th>
<th>Product</th>
<th>Cleavage from 90 °C\textsuperscript{a,b}</th>
<th>Yield (%)</th>
<th>Purity (%)</th>
<th>Yield (%)</th>
<th>Purity (%)</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>10a Se</td>
<td>Yield (%)</td>
<td>96</td>
<td>96</td>
<td>95</td>
<td>98</td>
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<tr>
<td>2</td>
<td>Te</td>
<td>73</td>
<td>100</td>
<td>55</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>10b Se</td>
<td>97</td>
<td>96</td>
<td>91</td>
<td>97</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Te</td>
<td>83</td>
<td>99</td>
<td>60</td>
<td>100</td>
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</tr>
<tr>
<td>5</td>
<td>10c Se</td>
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<td>95</td>
<td>87</td>
<td>96</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Te</td>
<td>74</td>
<td>99</td>
<td>56</td>
<td>99</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>11a Se</td>
<td>86</td>
<td>80</td>
<td>86</td>
<td>96</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>Te</td>
<td>86</td>
<td>99</td>
<td>57</td>
<td>100</td>
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<tr>
<td>9</td>
<td>11b Se</td>
<td>51</td>
<td>96</td>
<td>57</td>
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</tr>
<tr>
<td>10</td>
<td>Te</td>
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<td>11</td>
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</tr>
<tr>
<td>12</td>
<td>Te</td>
<td>84</td>
<td>96</td>
<td>62</td>
<td>95</td>
<td></td>
</tr>
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</table>

\textsuperscript{a} Yields are reported for the individual and isolated compound after purification by solid phase extraction (silica gel) and are based on the initial loading of resins 8a–c and 9a–c.

\textsuperscript{b} Purities are measured by GC–MS.

Figure 2  Magnitude gradient COSY spectrum of 8a (a) and 12 (b). The relaxation delay was 1.5 s. In both cases, 512 × 64 point matrices with 4 scans per increment were acquired. In the \textit{o}_2-dimension, linear prediction to 256 complex points was applied. The data were sine-bell weighted in both dimensions and zero-filled to a final size of 2048 × 512 complex points.
high yields. In comparison, yields obtained from polystyrene-bound tellurium are generally lower and are also dropping significantly when temperature is changed from 90 °C to 60 °C. Yields for cleavages below 50 °C are dropping dramatically for both, polystyrene-bound selenium and tellurium, and only traces of the cleaved products were found at 40 °C. In our hands and under the reported conditions, polystyrene-bound selenium has shown to be superior to polystyrene-bound tellurium for its use in SPOS. All reactions were carried out under positive pressure of N2. Unless otherwise noted, starting materials were obtained from commercial suppliers and used without further purification. THF and toluene were distilled under N2 from sodium/benzophenone immediately prior to use. For solid-phase extraction, Scharlau 60 (230–400 mesh) silica gel (sorbil) was used. TLC was performed on Merck 60 prior to use. For solid-phase extraction, Scharlau 60 (230–400 mesh) crosslinked with 1% divinylbenzene). Bromopolystyrene

Preparation of Resin-Bound Tellurium; General Procedure

Polymer-bound tellurium (50 mg) was suspended in EtOH–MeOH (10:1, 0.5 mL) and treated with NaBH4 (50 mg, 1.3 mol) at r.t. After approximately 1 h, gas and heat generation occurred and the resin became swollen and almost colourless. The mixture was stirred for approximately 5 h until the gas evolution stopped. The resin was washed with EtOH (1 × 20 mL) under argon and treated with 2,4-dichloro benzyl chloride (352 mg) in EtOH (0.5 mL). After stirring for 12 h at r.t., the resin was washed with EtOH (1 × 25 mL), EtOH (1 × 25 mL), water (2 × 25 mL), acetone (1 × 25 mL), and CH3Cl, (3 × 25 mL) and dried in vacuo at r.t.

According to the elemental analysis for tellurium, a loading of 1.71 mmol/g was calculated for resin 5, which corresponds to a loading of 2.36 mmol/g for the initial loading of polystyrene-bound tellurium, assuming that the alkylation went to completion. The resins 6 and 7 were prepared according to the procedure described above by alkylation with 2-(2-chloroethoxy)ethoxyethanol and 6-bromo-hexanol, respectively.

Alkylation of Resin-Bound Tellurium: 2,4-Dichloro Benzyl Tel-lanyl Polystyrene 5; Typical Procedure

According to the elemental analysis for tellurium, a loading of 1.71 mmol/g was calculated for resin 5, which corresponds to a loading of 2.36 mmol/g for the initial loading of polystyrene-bound tellurium, assuming that the alkylation went to completion. The resins 6 and 7 were prepared according to the procedure described above by alkylation with 2-(2-chloroethoxy)ethoxyethanol and 6-bromo-hexanol, respectively.

Alky1 A ryl Ether Synthesis by Mitsuobu Reaction: 2-[2-(2-(3-Methoxyphenoxy)ethoxy)ethoxy]ethyltellanyl Polystyrene 8e; Typical Procedure

Polystyrene-bound alkyl alcohol 6 (650 mg, 1.16 mmol) was pre-swollen for 5 min in a solution of triphenylphosphine (1.57 g, 6.0 mmol) and 3-methoxyphenol (745 mg, 6.0 mmol) in 4-methylmorpholine (8 mL). neat diisopropyl azodicarboxylate (1.22 g, 6.0 mmol) was added in small portions over a period of 20 min at r.t. After the suspension was stirred for 12 h at r.t., the resin was filtered and subsequently washed with THF (3 × 10 mL), DMSO (2 × 10 mL), THF (2 × 10 mL), water (2 × 10 mL), MeOH (2 × 10 mL), and CH3Cl, (3 × 10 mL) and dried in vacuo at r.t. for 12 h. An almost colourless resin 8e (730 mg) was obtained which was calculated to have a loading of 1.51 mmol/g, assuming the Mitsuobu reaction went to completion. The resins 8a, 8b, 9a, 9b and 9c were prepared according to the procedure described above.

Cleavage by Homolysis: 1-[2-(2-Ethoxyethoxy)ethoxy]-3-meth-oxylbenzene 10c; Typical Procedure

Resin 8e (0.60 g, 0.91 mmol) was pre-swollen for 5 min in a freshly prepared solution of tributyltin hydride (1.11 g, 3.82 mmol) and AIBN (10 mg, 61 mmol) in anhyd toluene (6 mL). The mixture was heated in a sealed tube to 90 °C for 12 h. After cooling to r.t., the
resin was filtered and washed with THF (2 × 2 mL), acetone (2 × 2 mL), and CH₂Cl₂ (2 × 2 mL). The filtrates were combined, and the solvents removed in vacuo. The residue was purified by solid-phase extraction. Non-polar tin impurities were removed by washing the column with pure hexane. Subsequently, elution with heptane–EtOAc (15:1) gave 161 mg (74%; GC–MS purity: 99%) of 10c. The same experiment, carried out at 60 °C instead of 90 °C, furnished 122 mg (56%, GC–MS purity: 99%). The aryl alkyl ethers 10a, 10b, 11a, 11b and 11c were prepared (at 60 °C and 90 °C) and purified by solid phase extraction, according to the procedure above. Yields and GC–MS purities are given in Table 1. 1H NMR and 13C NMR data were identical to those given in the literature.3

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References


