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Reduction of α-aryloxy carbonyl compounds with samarium(II) iodide. A new traceless linker for the solid phase synthesis of carbonyl compounds

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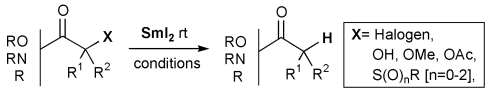
A new linker for the solid phase synthesis of functionalised carbonyl compounds which is cleaved under mild, neutral conditions using samarium(II) iodide has been developed; the manipulation of an immobilised γ-butyrolactone has been carried out to illustrate the utility of the linker.

The design of powerful new linker strategies is crucial to the continued advancement of solid phase technology and combinatorial chemistry.[1,2] The most useful linkers are often described as being *traceless*, the most common definition of this being when an aliphatic or aromatic proton is introduced at the point of cleavage.[3,4] Here we describe a new linker which can be cleaved in a simple *traceless* sense and which, we believe is the first member of a potential family of linkers cleaved using electron-transfer reagents such as samarium(II) iodide.[5]

Cleavage of the linker described here, relies on the well established reduction of α-heteroatom substituted carbonyl compounds. This transformation is most often carried out in solution using samarium(II) iodide[6] due to the neutral conditions and the low temperatures which can be employed (Scheme 1).[7]

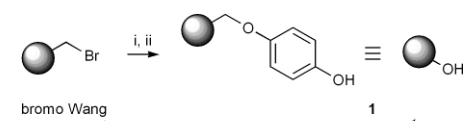
In Scheme 1, if the 'X' group represents a heteroatom linkage to solid support, then the overall reaction represents cleavage from the support and introduction of a proton at the point of cleavage.[8] We refer to this new type of linker as an α-**H**etero-**A**tom **S**ubstituted **C**arbonyl or **HASC** linker.[9] In this communication we report the realisation of this linker approach and illustrate its application in the solid-phase synthesis of functionalised carbonyl compounds from an immobilised γ-butyrolactone.



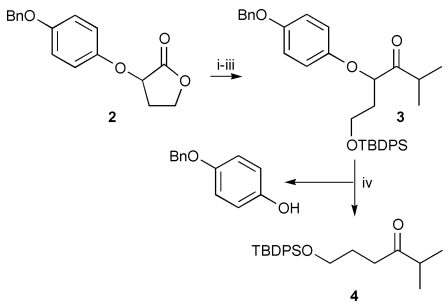
Scheme 1 Reduction of α-heteroatom substituted carbonyl compounds with samarium(II) iodide.

We chose to establish the linkage through the reaction of phenol resin **1** with α-halo carbonyl compounds.[10] This immobilisation approach was selected due to the ready availability of α-halo carbonyl compounds and the predicted ease of the etherification reaction with phenols. Importantly, we predicted that the cleavage step would lead to the direct regeneration of the phenol resin **1** which could be reused without the need for chemical re-activation. Phenol resin **1** was readily prepared from commercially available bromo Wang resin in two steps and in good overall yield[11] (Scheme 2).

Reaction of resin **1** with chloroacetone, methyl bromoacetate, or α-bromo-γ-butyrolactone all proceeded well (K_2CO_3, DMF, 18-crown-6, (KI for chloroacetone), 60 °C, 24 h) to give the corresponding alkylated resins containing the key α-aryloxy carbonyl linkage in good yield (60–78%).[12] To assess the feasibility of the proposed linker, we carried out solution model studies using benzyloxyphenol as a model for resin **1**. One such study is outlined in Scheme 3. The reaction of benzyloxyphenol with α-bromo-γ-butyrolactone under the conditions already outlined gave lactone **2** in 72% yield. Ring-opening and Weinreb amide formation, TBDPS protection and reaction with ^{i}PrMgCl gave ketone **3** in good overall yield, which represents a model substrate for the samarium(II) cleavage reaction. Pleasingly, treatment of **3** with samarium(II) iodide at 0 °C resulted in complete conversion to ketone **4** (97% isolated yield) and benzyloxyphenol (94% isolated yield) in less than 5 min. This clearly showed the potential of our linker approach and illustrated the compatibility of the linkage with strongly basic and Lewis acid conditions. In addition, the link proved to be stable during the addition of Grignard reagents to the amide carbonyl group. The solution model studies also suggested the possibility of recovering and reusing the phenol resin **1**.



Scheme 2 Reagents and conditions: i, 4-TBDMSOC$_6$H$_4$OH 4 eq, NaH 5 eq, DMF, rt, 18 h; ii, TBAF (1 M in THF) 6 eq, THF, rt, 15 h (resin retreated under the same conditions): overall yield ~80%.



Scheme 3 Reagents and conditions: i, $AlMe_3$ 3 eq, NH(Me)(OMe)·HCl 3eq, toluene, 0 °C–rt; ii, TBDPSCl 2 eq, imidazole 4 eq, DMF, rt, 79% (2 steps); iii, ^{i}PrMgCl 2.5 eq, THF, 0 °C–rt, 67%; iv, SmI_2 3 eq, THF, 0 °C, <5 min: ketone **4** 97%, benzyloxyphenol 94%.

To explore the utility of our linker we devised routes from **5** to simple, functionalised carbonyl compounds which embraced a variety of reaction conditions. The key aspects of the route are illustrated in Scheme 4. Lewis acid catalysed ring-opening of **5** with a variety of secondary amines was carried out followed by subsequent silylation or acetylation of the resultant alcohol **6** (see Scheme 4). In addition, *tert*-butyldiphenylsilyl-protected morpholine amides were converted to ketones **9** by reaction with Grignard reagents. Cleavage of the linkage in amide substrates was found to be more difficult than for analogous ketone linkages. In the only previous example of the reduction of α-alkoxy amides, Simpkins reported that LiCl[13] was an efficient promoter of the reaction.[7b] In our system, the use of LiCl often led to incomplete cleavage of the linker. The use of the additive DMPU was subsequently found to give excellent results in the cleavage reaction. Crucially, we have found that the link can be cleaved in the presence of ester groups (**8d** and **8e**), thus clearly illustrating the mild and neutral nature of the cleavage conditions (Table 1).

No aqueous work up is necessary on completion of the reduction. Products were conveniently separated from DMPU and inorganic by-products by simple filtration through a short column of silica gel,[14] after which they were found to give satisfactory ^{1}H and ^{13}C NMR spectra.

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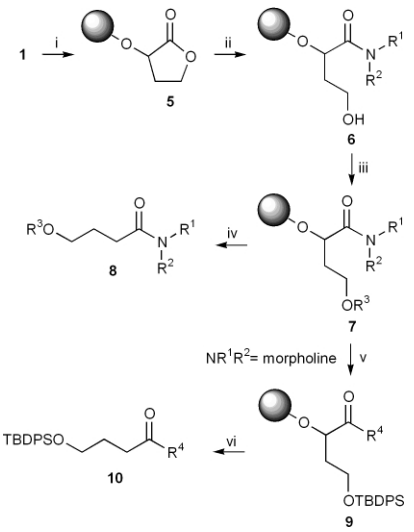
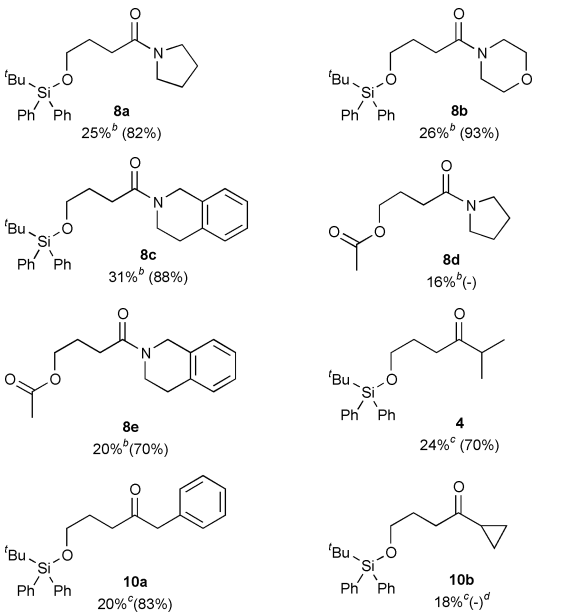


Scheme 4 Reagents and conditions: i, α-bromo-γ-butyrolactone 10 eq, K_2CO_3 16 eq, DMF, 60 °C, 18 h; ii, pyrrolidine/morpholine/1,2,3,4-tetrahydroisoquinoline 6 eq, $AlMe_3$ (2 M in hexanes) 6 eq, toluene, 50 °C, 20–24 h; iii, TBDPSCl 4 eq, imidazole 8 eq, DMF, rt, 16 h or Ac_2O 10 eq, pyridine, rt, 20 h; iv, SmI_2 5 eq, DMPU 16 eq, THF, rt or 50 °C, 6–12 h; v, ^{i}PrMgCl/BnMgCl/^{c}PrMgBr 6 eq, THF, 0 °C–rt; 20 h; vi, SmI_2 1–4 eq, THF, rt, 4–6 h.

Table 1 Yields and purities for carbonyl compounds prepared



[a] All compounds were characterised by ^{1}H and ^{13}C NMR, IR and HRMS. HPLC purities (254 nm) are given in parentheses after chemical yields. [b] Overall yield for 4 steps from **1**. [c] Overall yield for 5 steps from **1**. [d] Obtained as a 6 : 1 mixture of ring-closed and ring-opened products.[15]

The solid phase synthesis of cyclopropyl ketone **10b** was designed to probe the mechanism of cleavage from the resin. The isolation of **10b**, where the cyclopropyl ring is intact,[15] suggests that a radical is not formed at the carbonyl carbon during cleavage.[16] This indicates that cleavage occurs by direct reduction of the carbon–oxygen link rather than by elimination of the α-heteroatom substituent after reduction of the carbonyl.[6a,b] To the best of our knowledge, direct reduction of an α-substituent in ketone substrates, has not previously been proposed.

In conclusion, we have described a new linker whose cleavage is based on the samarium(II)-mediated reduction of α-heteroatom substituted carbonyl compounds. The key features of the linker are its stability to a range of reaction conditions and its mild, neutral, chemoselective cleavage. The use of different heteroatom links and the *in situ* trapping of reactive intermediates formed upon cleavage are extensions of this methodology currently under investigation in our laboratory.

We thank the Engineering and Physical Sciences Research Council (EPSRC) and OSI Pharmaceuticals for support of F. M.

Notes and references

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9 (*a*) Janda has reported a single, sulfone example of this linkage as a member of a different, general class of sulfone linker. Cleavage of the linker is achieved using sodium mercury amalgam: X. Zhao, K. W. Jung and K. D. Janda, *Tetrahedron Lett.*, 1997, **38**, 977; (*b*) Ellman has used immobilisation *via* an ether link α- to a carbonyl group but cleaves the linker at a different site using conventional conditions: C. E. Lee, E. K. Kick and J. A. Ellman, *J. Am. Chem. Soc.*, 1998, **120**, 9735; (*c*) Nicolaou has described attachment of substrates to a support through an α-sulfonate group: K. C. Nicolaou, P. S. Baran and Y.-L. Zhong, *J. Am. Chem. Soc.*, 2000, **122**, 10246; (*d*) Bradley has described sulfur and selenium-based links which are cleaved by oxidation and thermal syn-elimination: H. E. Russell, R. W. A. Luke and M. Bradley, *Tetrahedron Lett.*, 2000, **41**, 5287.

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11 The loading of phenol resin **1** was determined by cleavage with TFA–CH_2Cl_2 (1 : 1) and isolation of hydroquinone, in conjunction with bromine elemental analysis of the resin.

12 Yields were determined by treatment of the product resins with TFA–CH_2Cl_2 (1 : 1) and determination of the yield of the corresponding α-(4-hydroxyphenoxy) carbonyl compounds.

13 R. S. Miller, J. M. Sealy, M. Shabangi, M. L. Kuhlman, J. R. Fuchs and R. A. Flowers II, *J. Am. Chem. Soc.*, 2000, **122**, 7718.

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15 The small amount of ring-opened product observed has been shown to arise from over-reduction of cleaved ketone **10b**.

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