A new and convenient benzyloxyalkylating agent induced by samarium diiodide

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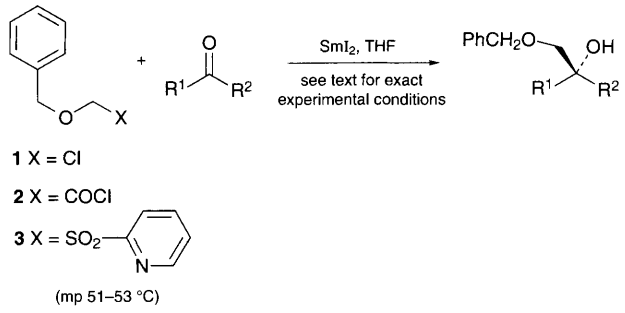
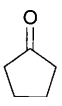
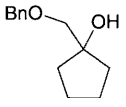
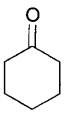
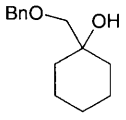
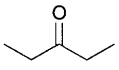
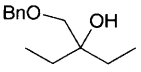
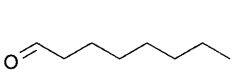
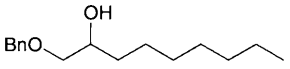
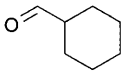
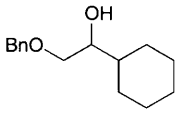
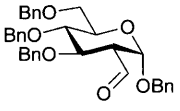
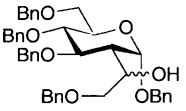
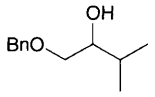
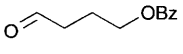
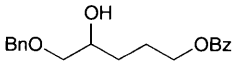
Benzyloxymethyl 2-pyridylsulfone reacts instantaneously and efficiently with aliphatic ketones or aldehydes by simple titration with 2 equiv. of SmI_2 to give the corresponding monoprotected vicinal diols in high yields.

Benzyloxymethylation provides a convenient approach for a one-carbon homologation of carbonyl compounds affording monoprotected vicinal diols.[1–4] Of the few benzyloxymethylation reactions known, two previous methods promoted by samarium diiodide have been reported (Scheme 1) making use of either benzyloxymethyl chloride **1**[2] or α-benzyloxyacetyl chloride **2**.[3,5] The former, now only available from Fluka in 60% purity, undergoes reductive samariation slowly with SmI_2 (1–2 h) giving modest to good yields of the coupled products with ketones, whereas for aldehydes, reduction is the major competing pathway leading to high yields of pinacol coupling products. Moderate yields (46–66%) could nevertheless be obtained by employing the unstable benzyloxymethyl iodide or



Scheme 1

Table 1 SmI_2 promoted benzyloxymethylation of carbonyl compounds with pyridylsulfone **3**

Entry	Carbonyl compound	Product	Yield (%)[a]
1			91
2			86
3			87
4			84
5			75
6			86[b]
7			81
8			76

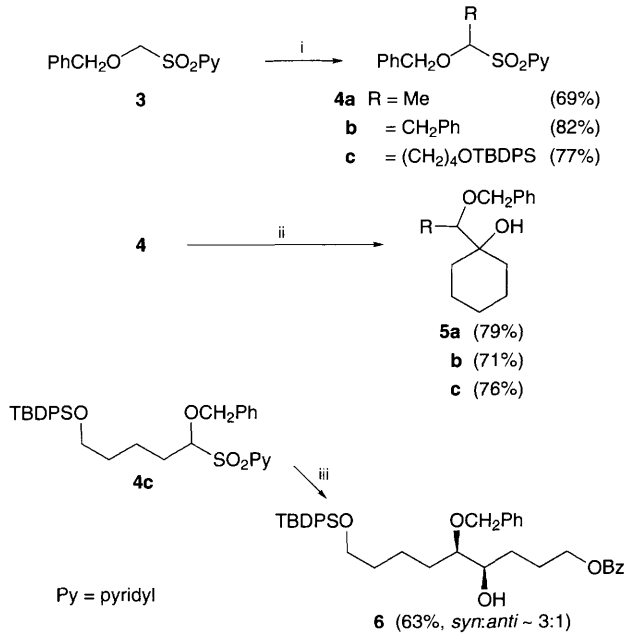
[a] Based on isolated, chromatographically pure material. [b] 1 : 1 diastereoisomeric mixture.

a cosolvent, such as tetraglyme, although with similar reactions times. In the latter case involving a SmI_2-mediated decarbonylation of **2**, only two examples with ketones have been provided so far with yields of approximately 60%.

We,[6] as well as others,[7] have found the important role played by nitrogen in heteroatom ring-substituted arylsulfones for their effective reduction by samarium diiodide in the absence of a cosolvent, whereas phenylsulfones were practically inert under identical conditions, requiring HMPA for activation.[6–9] Here and in conjunction with our earlier results in *C*-glycoside synthesis, we present a new and stable substitute, benzyloxymethyl 2-pyridylsulfone **3**[10] displaying greater versatility as well as simplicity, in comparison to all previously reported benzyloxymethylation reactions.[1–3]

Pyridylsulfone **3** was easily prepared in two steps. 2-Sulfanyl pyridine was treated with commercially available benzyloxymethyl chloride in 60% purity, in the presence of diisopropylethylamine at 0 °C and allowed to stir for 3 h,[11] after which purification afforded a 92% yield of the corresponding benzyloxymethyl pyridylsulfide. Further oxidation with MCPBA gave uneventfully the sulfone **3** in 92% yield, which unlike its predecessors **1** and **2**, is a stable crystalline solid (mp 51–53 °C, ether/pentane).

When an approx. 0.5 mol dm^{-3} THF solution of sulfone **3** (1.3 equiv.) and cyclopentanone (1.0 equiv.) was subjected to 2 equiv. of a 0.1 mol dm^{-3} solution of SmI_2 in THF at 23 °C, an instantaneous reaction ensued leading to a 91% yield of the product of benzyloxymethylation after work-up and chromatographic purification (Table 1, entry 1), representing in a 34% increase to the previous method employing benzyloxymethyl chloride.[2] The salient feature of our procedure is that the immediate reaction of the pyridylsulfone with SmI_2 allows one to simply perform these coupling reactions by titrating with the blue-coloured divalent samarium in THF at room temperature, such that excess SmI_2 signals the completion of the reaction. Other examples are indicated in Table 1 with either aliphatic ketones (entries 2 and 3, 86–87%) or aldehydes (entries 4–8, 75–86%) representing a notable improvement over the above-mentioned methods. The good yields obtained with aldehydes (entries 4–8) are explained by the quick and preferred reduction of the arylsulfone moiety by SmI_2 then of the carbonyl group, in contrast to those observed for chloride **1**. In addition, we have been able to perform these reactions on scales as low as 0.1 mmol without noteworthy decreases in coupling yields, hence making this method suitable for quick small scale benzyloxymethylation attempts.



Scheme 2 *Reagents and conditions*: i, BuLi (1.1 equiv.), THF, −78 °C, 15 min then HMPA (5 equiv.) and MeI or BnBr or $I(CH_2)_4OTBDPS$ (1.1 equiv.), −78 °C, 2 h; ii, cyclohexanone (1.5 equiv.), SmI_2 (2 equiv.), THF, 23 °C; iii, $BzO(CH_2)_3CHO$ (0.8 equiv.), SmI_2 (2 equiv.), THF, 23 °C

The greater versatility of our reagent may be demonstrated by its alkylation as shown in Scheme 2 prior to carbonyl coupling. Lithiation of **3** in THF could easily be performed by treatment with BuLi at −78 °C for 15 min followed by addition of the alkyl halide and HMPA.[10] Subsequently these new sulfones **4a–c**† could be treated in a similar fashion, as with **1** with cyclohexanone and SmI_2 providing alcohols **5a–c**. Compound **4c** was also reacted with 4-benzoyloxybutanal giving tetrol **6**, in which each of the four hydroxy groups were differentiated. A modest *syn*-selectivity was noted for this last example, tentatively assigned through similar selectivities with previous *C*-glycosylations.[12]

In summary, we have introduced a new and versatile benzyloxymethylating agent, which because of the quick reaction of the pyridylsulfone group with SmI_2 allows for the convenient benzyloxymethylation of carbonyl compounds *via* a simple titration with SmI_2 at room temperature.

Footnote

†Attempted alkylation of **4c** by first lithiation with lithium diisopropylamide and then addition of benzyl bromide did not lead to the desired dialkylated derivative of **3**, but to the hydrolysis product 6-*tert*-butyldiphenylsilyl-1-phenylhexan-2-one in 54%. For a similar observation with alkoxy phenylsulfones, see reference 10.

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