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Dimsyl anion in the monoalkylation of solid-phase alkyl sulfones

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Abstract—Polymer-bound α-sulfonyl monocarbanions can be generated very effectively with dimsyl anion. The highly efficient and convenient protocols presented here report the preparation of α,β-unsaturated ketones and vinylaryl compounds using dimsyl anion to achieve the key solid-phase α-sulfonyl monocarbanion alkylation step.

The solution-phase geminal dialkylation of α,α-sulfonyl dicarbanions with various electrophiles has been studied by Kaiser[1] and others.[2] According to those protocols,[1,2] the α,α-dilithiosulfone is typically generated by two equivalents of ^{n}BuLi in THF and subsequently undergoes smooth geminal dialkylation. In solid-phase organic synthesis (SPOS), excess reagents are often employed to drive reactions to completion; thus, polymer-bound α,α-dilithiosulfones can be readily prepared with excess ^{n}BuLi.[3] In contrast, given the vagaries of stoichiometry and reaction rates on solid-phase, it is difficult to perform a controlled generation of an α-monolithiosulfone on resin using ^{n}BuLi (Fig. 1). Moreover, functional groups such as amides and aryl halides are incompatible with the use of ^{n}BuLi. Even though the solution-phase preparation of α-sulfonyl monocarbanions can be accomplished by the use of stoichiometric ^{n}BuLi or LDA,[4] the efficient solid-phase production of α-monolithiosulfones for use in monoalkylations has not been explored.

As part of an investigation of the feasibility of solid-phase sulfone monoalkylation, we set out to prepare α,β-unsaturated ketones[5] via a four-step process consisting of (i) sulfinate *S*-alkylation; (ii) sulfone monoalkylation with epoxides; (iii) γ-hydroxy sulfone→γ-ketosulfone oxidation, and (iv) polymer-bound benzenesulfinate[6] elimination with release of the desired α,β-unsaturated ketone product from the resin (Fig. 2). While these α,β-unsaturated ketones can be prepared via the Claisen–Schmidt base-catalyzed aldol condensation,[7] they have not, to our knowledge, been prepared via SPOS using a traceless sulfone linker[3,7] strategy.

Preliminary solution-phase studies were undertaken to survey reaction conditions and establish the modifications required for SPOS. LDA was the first base employed in our trial and, to mimic solid-phase conditions, excess base (2 equiv.) and electrophile (epoxide, 3 equiv.) were employed at various temperatures to perform the epoxide-alkylation reactions (Scheme 1, Table 1).[8,9] At lower temperature (e.g. −78°C), the reaction proceeds best (78% yield of **4**), but the yield was poor at room temperature (18%) and unreacted starting material (**3**) was recovered (50% recovery; presumably due to LDA decomposition at room temperature in THF). These results led us to select LDA at −78°C for our investigation of solid-phase monoalkylation.

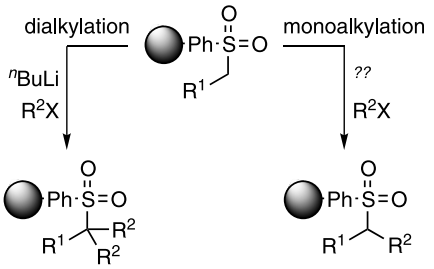

Figure 1.

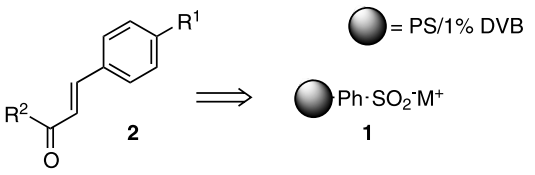

Figure 2. Benzenesulfinate **1**→α,β-unsaturated ketones **2**.

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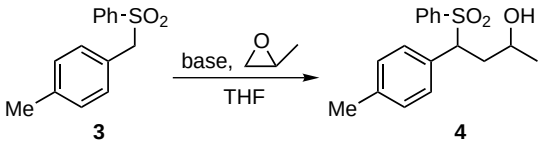


Scheme 1. Solution-phase monoalkylation with propylene oxide.

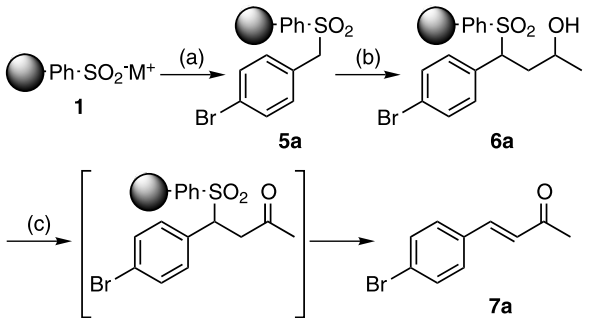
Table 1.

Entry	Base[a]	Temp.	Yield of **4** (%)
1	LDA[b]	Rt	18
2	LDA[b]	−30°C	67
3	LDA[b]	−78°C	78
4	Dimsyl[c]	Rt	93

[a] Two equivalents of base and three equivalents of propylene oxide were used.
[b] LDA = $(^{i}Pr)_2NLi$.
[c] Dimsyl = $CH_3S(O)CH_2Li$.

In the event, treatment of sulfone resin **5a** (see Scheme 2; **1**→**5a**) with LDA (now, 5 equiv.) at −78°C followed by addition of propylene oxide (now, 7 equiv.) gave resin **6a**. Since this transformation exhibited no reliably diagnostic absorption peaks in the single bead FTIR spectrum, we decided to release the target molecule from the solid support via Swern oxidation[10] of **6a** with concomitant linker cleavage by sulfinate elimination following our published protocol.[11] The resulting α,β-unsaturated ketone (**7a**) was produced smoothly in 72% overall yield from starting resin **1**.

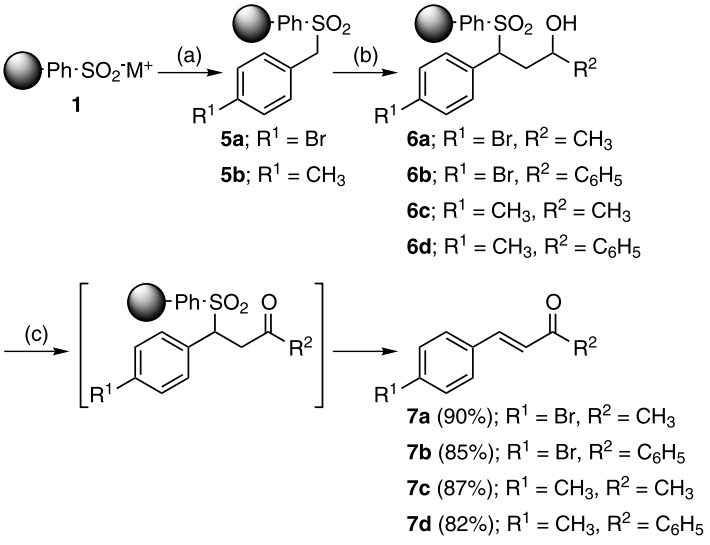
Although the solid-phase monoalkylation of **5a** using LDA was viable, we realized that the low temperature (−78°C) requirement as well as the relative instability of LDA would be inconvenient in combinatorial library production. These considerations led us to investigate



Scheme 2. Loading of **1** = 0.5 mmol/g. *Reagents and conditions*: (a) 4-bromobenzyl bromide, THF/DMF, 80°C. (b) Base (5 equiv.), THF; propylene oxide (7 equiv.), THF. (c) Swern oxidation.

the use of dimsyl anion[12] [$CH_3S(O)CH_2^-M^+$; DMSO, $pK_a = 35$] in place of LDA [$(^{i}Pr)_2NH$, $pK_a = 36$] for the generation of solid-phase α-sulfonyl monocarbanions.[13] In solution-phase studies, treatment of **3** with dimsyl anion[14] (2 equiv.) at room temperature followed by addition of propylene oxide gave **4** in 93% yield (Scheme 1). We next extended this encouraging result to solid-phase, now employing dimsyl anion for α-sulfonyl monocarbanion formation—now at room temperature. Following the protocol outlined in Scheme 2,[15] monocarbanion formation and alkylation of **5a** with propylene oxide followed by oxidation of intermediate **6a** led to the α,β-unsaturated ketone via concomitant linker cleavage by sulfinate elimination. Enone **7a** was obtained in 90% overall yield for this three-step process.

To further illustrate the merits of employing dimsyl anion for solid-phase sulfone monoalkylation, polymer-bound benzyl phenyl sulfones **5a** (R = Br) and **5b** (R = Me) together with propylene and styrene oxides were utilized to build a small library of enones (**7a**–**d**),[16] as illustrated in Scheme 3. Monocarbanion formation and alkylation delivered resins **6a**–**d** which, upon Swern

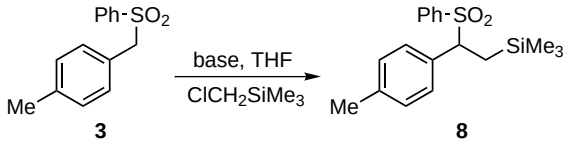


Scheme 3. Loading of **1** = 0.5 mmol/g. *Reagents and conditions*: (a) 4-bromobenzyl bromide or 4-methylbenzyl chloride, THF/DMF, 80°C. (b) $CH_3S(O)CH_2Li$ (5 equiv.), THF; propylene or styrene oxide (7 equiv.), THF. (c) Swern oxidation.

oxidation with concomitant sulfinate elimination, delivered α,β-unsaturated ketones **7a–d** in excellent overall yields from starting resin **1** (82–90%).

In addition to sulfone aninon opening of epoxides, we also examined the use of chloromethyltrimethylsilane as our alkylation reagent. We again started in solution-phase by reacting **3** with bases (2 equiv.) followed by addition of chloromethyltrimethylsilane to afford **8** (Scheme 4, Table 2). As hoped, monoalkylation produced **8** in high yield (95%) when dimsyl anion was used as base. In contrast, the conversion was sluggish with LDA as base at −78°C (entries 1 and 2), but improved in the presence of added crown ether (15-crown-5; entry 3).[17]

Following the solid-phase monoalkylation protocols shown in Schemes 2 and 3, monocarbanions of resins **5a–c** were generated by treatment with dimsyl anion at room temperature. Subsequent monoalkylation by treatment with chloromethyltrimethylsilane generated resins **9a–c**. This transformation exhibited reliably diagnostic absorption peaks in the single bead FTIR spectrum (Si–C bond at 1250 cm^{-1}). To release our target molecules from the resin, we chose a new cleavage strategy that employed the silane moiety at the β position to trigger elimination of polymer-bound benzenesulfinate. Thus, treating resin **9** with floride anion (TBAF)[18] in THF for 6 h delivered the target molecules—vinylaryl compounds **10a–c**—in high yields (80–89%; Scheme 5).



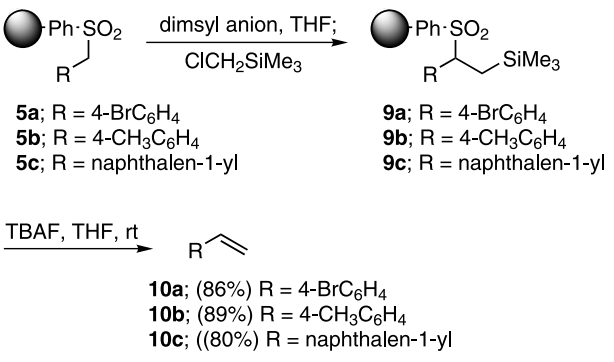
3 **8**

Scheme 4. Solution-phase monoalkylation with propylene oxide.

Table 2.

Entry	Base[a]	Temp./time	Yield of **8**[b] (%)
1	LDA	−78°C/2 h	55
2	LDA	−78°C/5 h	75
3	LDA[c]	−78°C/3 h	89
4	Dimsyl	Rt/2 h	95

[a] Two equivalents of base and three equivalents of $ClCH_2SiMe_3$ were used.
[b] Isolated yield.
[c] With added 15-crown-5 (3 equiv.).



Scheme 5. Solid-phase monoalkylation with $ClCH_2SiMe_3$.

In summary, polymer-bound α-sulfonyl monocarbanions can be generated by LDA (−78°C) or dimsyl anion (room temperature) and undergo alkylation with epoxides to generate γ-hydroxy sulfones (**6**) or chloromethyltrimethylsilane to generate β-silyl sulfones (**9**). In each case, the more convenient and efficient protocol employs dimsyl anion as base.

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8. Similar epoxide opening reactions have been reported by Julia and Uguen with the use of ^{n}BuLi (1 equiv., −78°C) as base. See: Julia, M.; Uguen, D. *Bull. Soc. Chim. Fr.* **1976**, 513.
9. Attempts to separate the diastereomeric mixture of **4** are not feasible with flash column chromatography. Oxidation (Jones' reagent) of **4** delivers 4-benzenesulfonyl-4-(*p*-tolyl)butan-2-one in quantitative yield: IR (neat) 1718, 1314, 1145 cm^{-1}; ^{1}H NMR δ 2.13 (s, 3H), 2.27 (s, 3H), 3.24 (dd, 1H, $J=18$, 9 Hz), 3.56 (dd, 1H, $J=18$, 4.2 Hz), 4.69 (dd, 1H, $J=9$, 4.2 Hz), 6.95–7.54 (m, 9H); ^{13}C NMR δ 203.0, 138.6, 136.6, 133.5, 129.3, 129.0, 128.8, 128.5, 65.7, 41.4, 30.5, 21.1.
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14. Dimsyl anion was prepared by addition of ^{n}BuLi to DMSO (1/2 molar ratio) in THF at 0°C.
15. Typical procedure for the transformation (**5a→6a**) with dimsyl anion as base: ^{n}BuLi (5 equiv., 1.2 mL, 1.6 M) was added to DMSO (10 equiv., 0.3 g) in THF (10 mL) at 0°C and stirred for 5 min. The resulting dimsyl anion solution was transferred to a suspension of polymer **5a** (0.8 g, 0.38 mmol) in THF (6 mL) at room temperature; the resin color changed from pale yellow to yellow. After 30 min, propylene oxide (7 equiv., 0.16 g) was added to this mixture; the color turned light orange. The reaction was quenched with 10% HCl (aq.) after 1 h and the resin was filtrated, washed, and dried to afford resin **6a** as pale yellow beads: IR (single bead reflectance) 1600, 1492, 1452, 1310, 1138 cm^{-1}.
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