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A NEW ATTACHMENT/CLEAVAGE STRATEGY: POLYMER-BOUND ALLYLIC SULFONES IN A SOLID-PHASE ROUTE TO TRISUBSTITUTED OLEFINS

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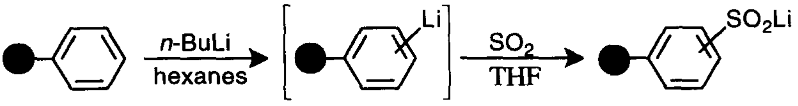
Abstract: *By tethering allyl sulfone to polystyrene (3-steps from polystyrene beads consisting of lithiation, sulfination, and allylation), trisubstituted olefins can be generated by Cα-sulfone alkylation and subsequent resin cleavage by S_N2' nucleophilic displacement of sulfinate.* © 1997 Elsevier Science Ltd.

Over the past several years, the focus of solid-phase synthetic chemistry has been shifting from the generation of peptide[1] and oligonucleotide[2] libraries to the construction of small organic molecules on polymer supports.[3] Derivatization of insoluble resins and subsequent chemical modifications (solid-phase organic synthesis = SPOS) have allowed organic chemists to generate a wide variety of compound classes with high efficiency. One of our goals in this field has been to examine new tethering strategies for the attachment of small molecule building blocks to insoluble resins and to explore new applications of these tethers in SPOS.[4] Here we report the preparation of a sulfinate-functionalized resin (prepared from styrene/2% divinyl benzene co-polymer beads) which by sulfinate *S*-allylation, Cα-sulfone alkylation, and nucleophilic S_N2' sulfinate displacement delivers resin-free trisubstituted olefins. By varying the sulfone alkylation and sulfinate displacement reagents, this three-step procedure accommodates reagent diversity and appears suitable for library generation.

Following the pioneering work of Leznoff,[5] Fréchet,[6] and Camps,[7] we reasoned that lithiated polystyrene beads would react with sulfur dioxide to deliver polymer-bound lithium phenyl sulfinate.[8] Indeed, this derivatization works nicely on a multi-gram scale to give **1** by treating cyclohexane-immersed polystyrene beads (20-115 g) with *n*-BuLi followed by 3 washes with THF, and finally infusion of excess SO_2 to the THF swelled resin.



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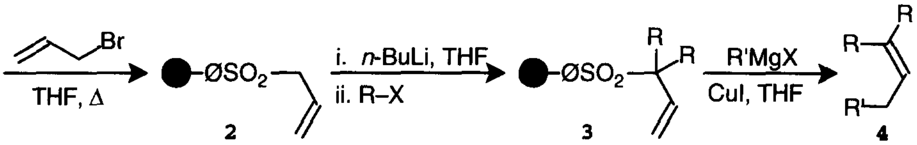
• **Preparation of 1**: Cyclohexane (400 mL) was distilled directly into a flask containing polystyrene (40 g). Under an argon atmosphere, TMEDA (60 mL) was introduced, the mixture was cooled to 0 °C with gentle stirring (overhead mechanical), and *n*-BuLi (1.6M, 250 mL) was added. The resin changed from off-white to orange after stirring overnight and the resulting lithiated polymer was washed with anhydrous THF (3x), cooled to -78 °C, and $SO_2(g)$ was bubbled through the THF-swollen polymer for 1 h using a fritted glass bubbler. The reaction was quenched by addition of H_2O (1 h), the polymer was washed with THF, THF/H_2O (80:20), THF, and ether, and the collected resin was dried in a vacuum oven overnight at 30 °C.

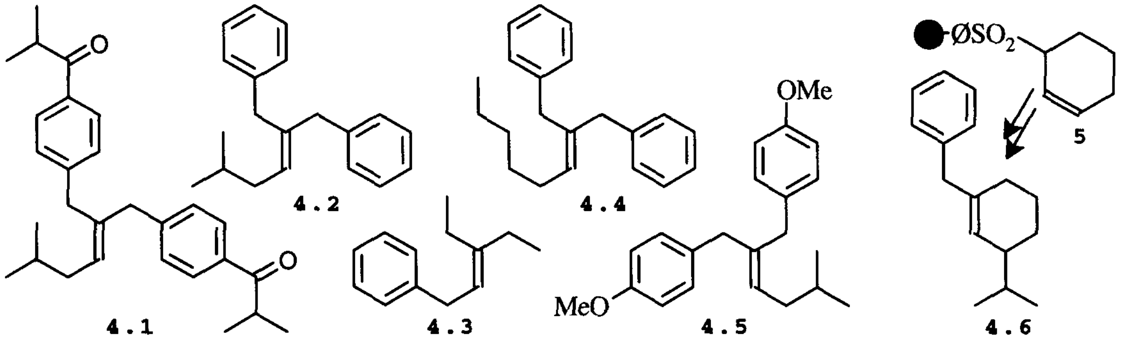
In parallel with solution results,[9] reaction of this THF-swollen, air-stable sulfinate resin (**1**) with allyl bromide gives allyl phenyl sulfone beads (**2**) in a reaction which can be monitored by KBr FT-IR.[10] This transformation to **2** is key in that it also sets the stage for our planned strategic release of targeted trisubstituted olefins by S_N2' displacement of sulfinate from C=C-C-SO_2–RESIN.



Sulfone dianion formation[11] with *n*-BuLi in THF followed by addition of excess alkylating agent delivered α,α'-dialkylated sulfone **3**. Typically **2** → **3** was not amenable to IR analysis but, by employing 4-cyanobenzyl bromide as the alkylating agent, conversion could be monitored by appearance of a cyano stretch in the KBR FT-IR (**3** where $-R = -CH_2C_6H_4CN$; 2227 cm^{-1}). Soft nucleophiles such as lithium-dialkylcuprates [$(R')_2CuLi$] or copper-mediated Grignards are known to react with solution allylic sulfones[12] to deliver sulfinate and an olefin. Our resin-bound allyl sulfone performs similarly, regenerating the starting sulfinate resin **1** and liberating the targeted trisubstituted olefin **4**.[13] When $-R = -CH_2C_6H_4CN$ in **3**, $(CH_3)_2CHMgCl$/CuI delivers **4.1** where the Grignard not only displaces the sulfinate but also adds to each cyano group.

- **Preparation of 4.1**: Resin **1** (2 g) in THF was treated with allyl bromide (20 mmol) and refluxed overnight. After filtration, the polymer was subjected to *n*-BuLi (1.6M, 16 mmol) at 0 °C for 30 min and then 4-cyanobenzyl bromide (16 mmol) was added along with $(Bu)_4NI$ and stirring continued for an additional 5 h. The resulting resin, having now been exposed to four synthetic transformations (lithiation, sulfination, allylation, and dialkylation), was swollen in THF and isopropylmagnesium chloride (20 mmol) and CuI (4 mmol) were added. The reaction was stirred at 0 °C under argon for 4 h (a dark purple color indicated formation of the active cuprate) and ammonium chloride (saturated aqueous) was added (20 mL). The polymer was collected by filtration and the filtrate was concentrated (rotary evaporation) to give **4.1** which was isolated by eluting from silica gel with hexanes (clear oil, 27% overall yield from **1**; based on titration of polymer-bound sulfinic acid).[14]

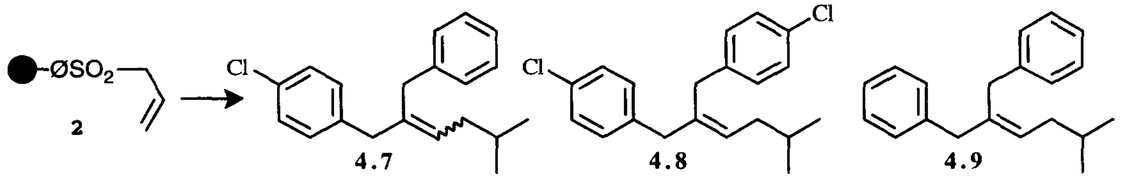
As an indication of the synthetic versatility of this three step solid-phase route to trisubstituted olefins, alkenes **4.1** [$BrCH_2C_6H_4CN$ & $(CH_3)_2CHMgCl$], **4.2** [$BrCH_2C_6H_5$ & $(CH_3)_2CHMgCl$], **4.3** [ICH_2CH_3 & C_6H_5Li], **4.4** [$BrCH_2C_6H_5$ & $CH_3(CH_2)_3Li$], and **4.5** [$MeOC_6H_4CH_2Br$ & $(CH_3)_2CHMgCl$] were prepared from polymer-bound sulfinate **1** (20-30% overall yield). In preliminary solution studies, we found that the choice of solvent in the sulfinate displacement step was important with THF giving superior results when compared to diethyl ether. THF has the added advantage during reactions on the resin in that it swells the polymer to a much greater extent than diethyl ether.



4.1 **4.2** **4.3** **4.4** **4.5** **4.6**

Sulfinate resin **1** can also be allylated with 3-bromocyclohexene (in place of allyl bromide) to give resin **5**. Here, monoalkylation ($BrCH_2C_6H_5$) followed by copper-mediated sulfinate displacement [$(CH_3)_2CHMgCl$, CuI] gave cyclohexenyl derivative **4.6** (20% overall yield from **1**).

This latter example establishes that unsymmetrical trisubstituted olefins can be prepared from sulfinate **1** via monoalkylation of an allylic 2⁰-sulfone (i.e., **5**). However, as illustrated above, bisalkylation of the dianion formed from allylic



4.7 4.8 4.9

1^0-sulfone **2** with two different alkylating agents (1:1 mixture of $C_6H_5CH_2Cl$ and *p*-$ClC_6H_4CH_2Cl$) with Bu_4NI (0.1 equiv.) in THF leads to an ≈2:1:1 mixture of products **4.7** (unresolved (*E*/*Z*)-mixture) **4.8**, and **4.9**, respectively.

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[9] Allylation of phenylsulfinic acid sodium salt with 3 eq. of allyl bromide and 5 mol-% of $N(Bu)_4I$ in refluxing THF proceeded cleanly in 92% yield.

[10] FT-IR data: sulfinate **1** (1374, 1068, 1027 cm^{-1}); sulfone **2** (1638, 1322, 1142, 1087, 1027 cm^{-1}).

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[13] All compounds were characterized by ^1H NMR, ^{13}C-HMR, IR, and MS. Isolated yields are as reported and crude product purities were >80%.

[14] The loading of sulfinate on the polymer was calculated by titration of sulfinic acid by NaOH in THF (0.3 meq/g). Allylation gave polymer-bound allyl sulfone with approximately 0.3 meq./g (ASTM E 441-90).

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