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Tetrahedron Letters
Tetrahedron Letters 49 (2008) 543–547

Traceless sulfone linker cleavage triggered by ozonolysis: solid-phase synthesis of diverse α-β-unsaturated carbonyl compounds

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Received 28 September 2007; revised 8 November 2007; accepted 13 November 2007
Available online 17 November 2007

Abstract—The highly efficient and convenient protocol to prepare diverse α,β-unsaturated aldehydes, ketones, and acids via the parallel solid-phase synthesis is developed. The key sulfone linker cleavage strategy is performed by ozonolysis to generate a carbonyl moiety followed by base-mediated polymer-bound sulfinate elimination to release our desired molecules from the resin. All α,β-unsaturated carbonyl compounds are prepared in good purities and yields without further purification.

Sulfinate-functionalized resins have been efficiently prepared and utilized in solid-phase organic synthesis (SPOS)[1] and the resulting sulfone linker has been found to be both a robust and a versatile linker.[2] In this regard, one of our goals is to develop sulfone linkers for SPOS and to explore sulfone-based chemical transformations and cleavage strategies. Among various sulfone linker cleavage strategies,[2c,d,3] the most convenient way is to generate an α,β-unsaturated carbonyl moiety spontaneously released from the resin via the oxidation–elimination procedure. Previous reports from Kurth and co-workers[4] and Lam and co-workers[5] have detailed the use of a sulfinate-functionalized resin as the starting point for this strategy.

Small molecules containing α,β-unsaturated carbonyl groups are popular in nature[6] and show versatile biological activities such as antitumor, antiinflammatory, and antimalarial properties.[7] In addition, they are key intermediates[8] of various biologically important compounds such as flavanones,[9] pyrroles,[10] and pyrimidines.[11]

Previous reports showed a straightforward method for the solid-phase synthesis of α,β-unsaturated ketones employing the sulfone as a linker via sulfone monoalkylation with epoxides as a key step.[4a,5] However, to extend this method to more diverse α,β-unsaturated ketones, commercially available epoxides are limited. In addition, this protocol is not suitable for the preparation of α,β-unsaturated aldehydes and acids, which are both prevalent in nature and useful as building blocks for further transformations.[6,12] To circumvent these limitations, new synthetic methods and cleavage strategies are needed. Based on our preliminary study, ozonolysis has been utilized in SPOS[13] but no cleavage conditions triggered by ozonolysis have been reported. Herein, we report sulfone-based chemistry for the synthesis of diverse α,β-unsaturated carbonyl compounds including aldehydes, ketones, and acids via SPOS as well as a new traceless ozonolysis–elimination cleavage strategy to release the desired products from the solid-support (Fig. 1).

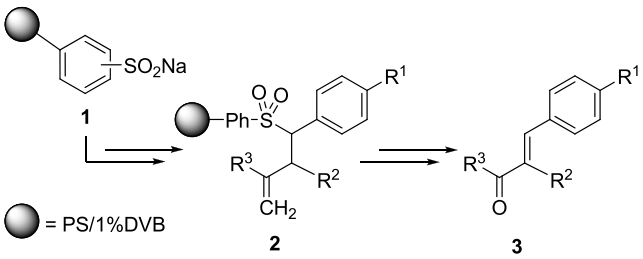

Figure 1. α,β-Unsaturated carbonyl compounds from polymer-bound benzenesulfinate **1**.

Keywords: Solid-phase organic synthesis; Sulfone linker; Ozonolysis; α-β-Unsaturated carbonyl compounds.
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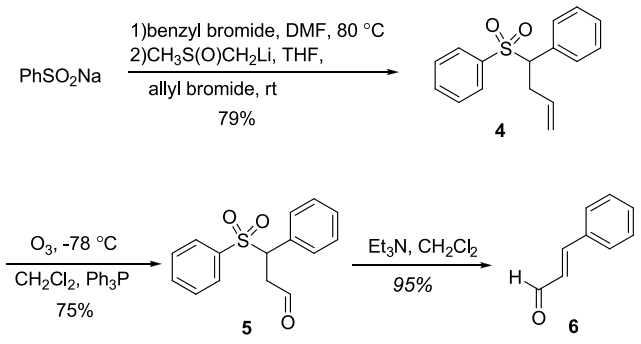
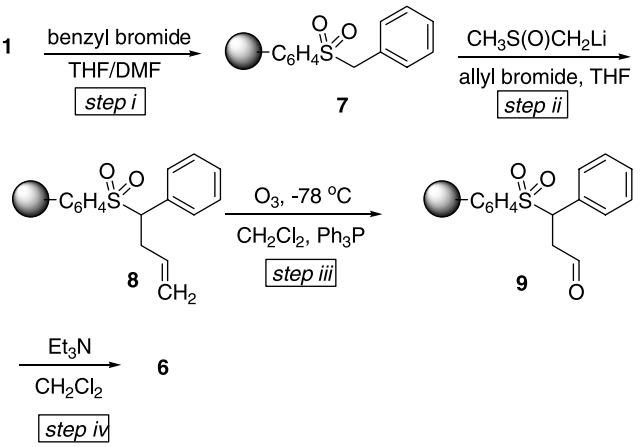
0040-4039/$ - see front matter © 2007 Published by Elsevier Ltd.
doi:10.1016/j.tetlet.2007.11.064

As part of an investigation of the feasibility of ozonolysis–elimination cleavage strategy in solid-phase sulfone linker chemistry, we initially set out to develop a procedure to prepare α,β-unsaturated aldehyde via a four-step process consisting of (i) sulfinate S-alkylation with alkyl halide; (ii) sulfone monoalkylation with allyl halide; (iii) ozonolysis, and (iv) polymer-bound benzenesulfinate elimination with release of the desired product from the resin. Once the cleavage condition has been established, various highly diverse α,β-unsaturated acids and ketones can also be prepared following this similar protocol.

Preliminary solution-phase studies were undertaken to survey the requisite reaction conditions and establish modifications needed for SPOS. To begin our investigation, compound **4** was prepared from sodium benzenesulfinate in two steps [S-alkylation with benzyl bromide and sulfone α-monoalkylation with allyl bromide by using dimsyl anion (2 equiv) as the base] in an overall yield of 79%.[14] Subsequent ozonolysis[15] of **4** in CH_2Cl_2 at −78 °C generated the carbonyl moiety in **5** (75%). To our delight, under these reaction conditions no β-elimination was observed. Finally our desired product, cinnamaldehyde (**6**), was obtained smoothly under basic conditions (Et_3N/CH_2Cl_2) via β-elimination of sulfinate in 95% yield (Scheme 1). The newly formed double bond was in the *E*-form, as assigned from the ^1H NMR coupling constant (15.9 Hz) between the two of olefinic protons. The successful solution-phase transformations encouraged us to explore this protocol on solid-phase.



Scheme 1. The model study of solution-phase synthesis.



Scheme 2. The model study of solid-phase synthesis.

Our attention was next directed at development of a solid-phase protocol (Scheme 2) and the work began with step i—the S-alkylation of the sulfinate moiety of resin**1**[16] (sulfinate loading = 0.8 mmol/g) with benzyl bromide. Monoalkylation of resin **7**, prepared by treatment with dimsyl anion (3–5 equiv) as the base at room temperature followed by addition of allyl bromide gave resin **8** in step ii. While step i was amenable to FTIR monitoring (e.g., disappearance of sulfinate absorption at 1028 cm^{-1}; appearance of sulfone absorption at ~1320 and ~1130 cm^{-1}), it was not possible to monitor the next transformation (step ii) since this reaction exhibited no reliably diagnostic absorption peaks in the single bead FTIR spectrum. Subsequent ozonolysis of resin **8** in step iii was successfully carried out at −78 °C to deliver the corresponding resin **9** bearing a carbonyl group, which was readily monitored by FTIR (~1650 cm^{-1}). However, the prolonged reaction time in step iii did not enhance the carbonyl absorption peak in the FTIR spectrum but reduced the overall yield of **6** from 89% to 70%. Perhaps, partial decomposition of resin **9** resulted from the prolonged reaction time of ozonolysis. On the other hand, the inconvenience of low temperature (−78 °C) prompted us to further

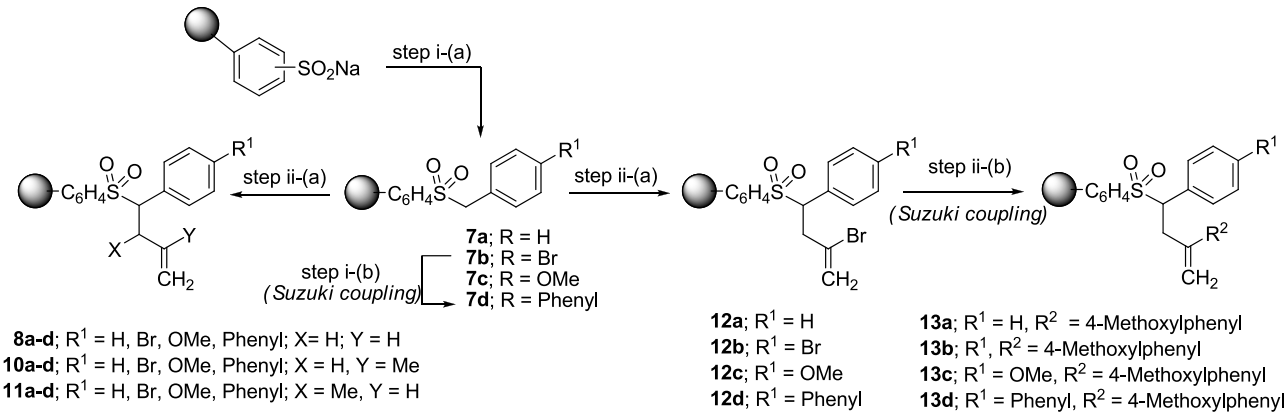
Table 1. A model study for optimization of solid-phase ozonolysis/elimination

resin **8** —ozonolysis (step iii)→ resin **9** —β-elimination (step iv)→ **6**

Entry	Step iii solvent/temp/time	Step iv base/solvent/temp/time	Overall yield[a] (%)
1	CH_2Cl_2/−78 °C/5 min	Et_3N/CH_2Cl_2/rt/3 h	89[b]
2	CH_2Cl_2/−78 °C/30 min	Et_3N/CH_2Cl_2/rt/3 h	70[b]
3	CH_2Cl_2/0 °C/5 min	Et_3N/CH_2Cl_2/rt/3 h	91[b]
4	CH_2Cl_2/0 °C/5 min	Et_3N/CH_2Cl_2/rt/3 h	89[b]
5	CH_2Cl_2/0 °C/5 min	NaOMe[d]/CH_2Cl_2/rt/3 h	96[c]
6	CH_2Cl_2/0 °C/5 min	NaOH/H_2O–THF/rt/3 h	83[b]

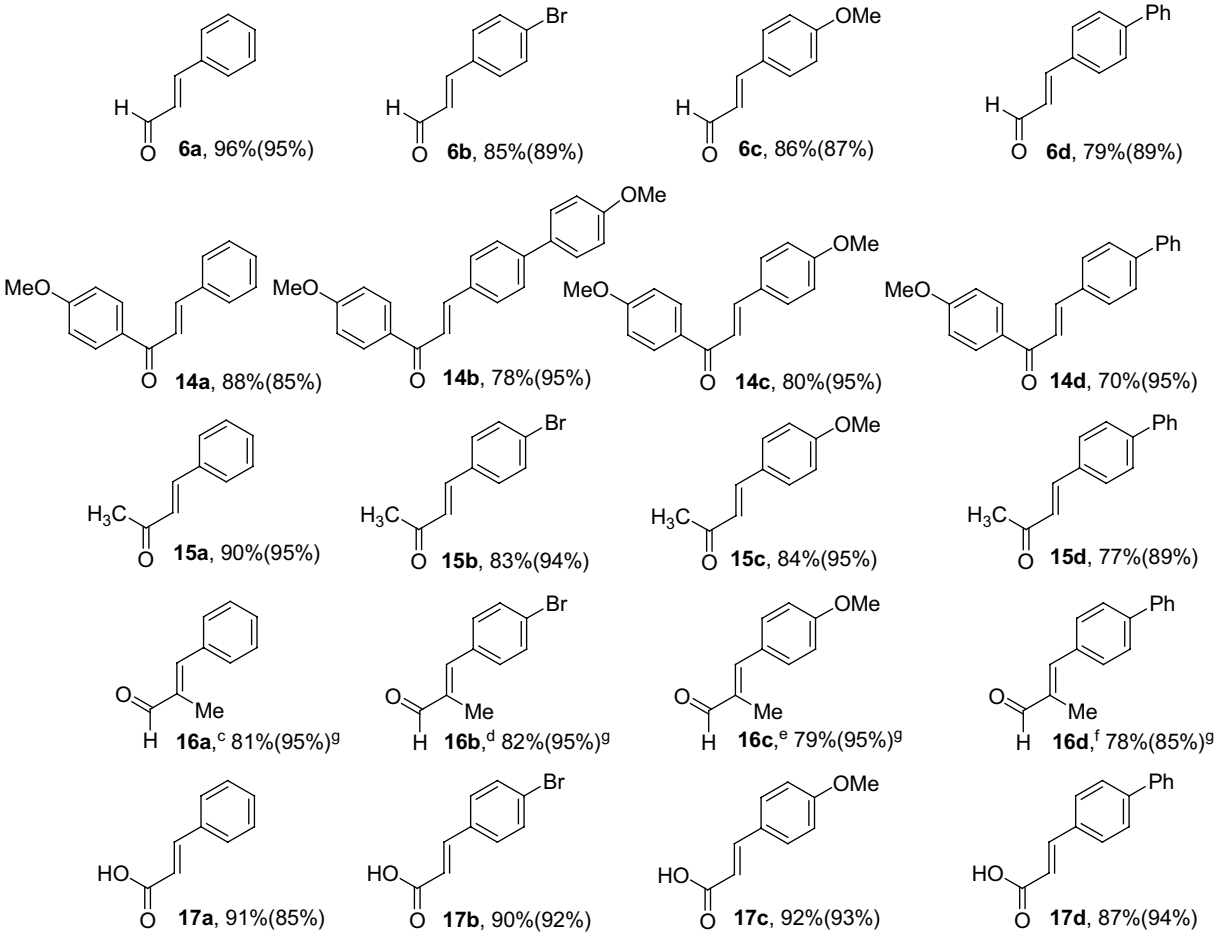
[a] Overall yield calculated on the basis of the loading of resin **1**. Over 95% purities as evaluated by NMR.
[b] Purified by column chromatography.
[c] Without any purification or extraction.
[d] 30 wt% solution in methanol.

scrutinize various ozonolysis conditions on solid-phase. Indeed, we discovered this transformation could also be performed at 0 °C instead of lower temperature (Table 1). Subsequent treatment of resin **9** under basic conditions



Scheme 3. Loading of **1** = 0.8 mmol/g. Reagents and conditions: Step i-(a) substituted benzyl halides, DMF/THF, 60 °C; step i-(b) 4-methoxyphenylboronic acid, K_2CO_3(aq), $Pd(PPh_3)_4$, DME, 90 °C; step ii-(a) $CH_3S(O)CH_2Li$, substituted allyl halides, THF, rt; step ii-(b) 4-methoxyphenylboronic acid, K_2CO_3(aq), $Pd(PPh_3)_4$, DME, 90 °C.

Table 2. Structures and yield[a] (purity)[b] data of α,β-unsaturated carbonyl compounds



[a] Yields were based on the weight of crude material and relative to the initial loading of resin **1**.
[b] The purity of the crude material was determined by HPLC.
[c] The yield and purity represented a mixture of two products (major **16a**/minor **6a** = 80:20).
[d] The yield and purity represented a mixture of two products (major **16b**/minor **6b** = 85:15).
[e] The yield and purity represented a mixture of two products (major **16c**/minor **6c** = 78:22).
[f] The yield and purity represented a mixture of two products (major **16d**/minor **6d** = 75:25).
[g] See Ref. 17.

(Et_3N/CH_2Cl_2) promoted β-elimination of polymer-bound sulfinate and liberated cinnamaldehyde (**6**) from the resin. After chromatographic purification, compound **6** was obtained in 91% overall yield from starting resin **1** for this four-step process. Although this solid-phase protocol was viable, we realized that the final purification or extraction requirement would be inconvenient or tedious in combinatorial library production. These considerations led us to further investigate various base-mediated conditions (see in Table 1). Screening of reaction conditions was performed by tuning all the main factors: reaction time and temperature in step iii; base and solvent in step iv. The best results for step iv were presented by using NaOMe/MeOH in CH_2Cl_2 at room temperature for 3 h. In the FTIR spectrum, no sulfone peaks were observed in the residue resin indicating this cleavage step was complete. Fortunately, without purification or extraction, our model compound **6** was directly obtained in high purity (>95%) and overall yield (96%) from starting resin **1** (Table 1, entry 5). In contrast, other conditions such as Et_3N in CH_2Cl_2 or NaOH(aq) in THF, less clean products were obtained and purification was needed.[4a]

With the optimal conditions in hand, we set out to prepare a small library of diverse α,β-unsaturated carbonyl compounds. As illustrated in Scheme 3, benzyl bromide, 4-bromobenzyl bromide, and 4-methoxybenzyl bromide were employed in step i as well as four allyl halides (allyl bromide, 2-bromo allyl bromide, 3-bromo-2-methyl-1-propene, and 3-chloro-1-butene)[17] were exemplified for monoalkylation in step ii. To increase the library diversity, resins **7b** and **12a–d**, containing an aryl bromide or a vinyl bromide moiety, were efficiently transformed to the corresponding **7d** and **13a–d** via solid-phase Suzuki coupling reactions, which have been extensively applied in modern combinatorial library synthesis.[18] Notably, resin **13b** was prepared by introducing two 4-methoxylphenyl groups via double Suzuki coupling reactions.

Following the optimal ozonolysis/β-elimination cleavage conditions outlined in Table 1, all polymer-bound intermediates **8a–d**, **10a–d**, **11a–d**, and **13a–d** were successfully transformed to the corresponding aldehydes and ketones in 70–96% overall yields from starting resin **1** (Table 2). The stereochemistry of the final products **6a–d**, **14a–d**, and **15a–d** was determined by ^1H NMR spectroscopy. As expected, all the coupling constants (15.5–16.3 Hz) of the two olefinic protons indicated the exclusive production of *E*-isomers.[19] Significantly, products **6a–d**, **14a–d**, **15a–d**, and **16a–d** all showed high purities (85–95%). In addition, oxidation of aldehydes **6a–d** in $NaClO_2/H_2O_2$ conditions[20] gave the corresponding acids **17a–d** in good yields (87–92%) and high purities (85–94%). Our library of 20 compounds is shown in Table 2.

In summary, this work further demonstrates the durability and chemical versatility of the sulfone moiety as a linker for SPOS. The new mild cleavage strategy of ozonolysis followed by base-mediated (NaOMe) β-elimination provides ready access to the resin-free target with high yield and high purity. Moreover, the solid-phase synthetic route presented here benefits from the fact that only molecules having successfully negotiated the entire reaction sequence (step i–v) can be released from the solid-support. To increase structural diversity, Suzuki coupling reactions on solid-phase as well as oxidation of aldehydes to acids in solution phase have been applied. The preparation of conjugated enones with three diversities has been developed and is suitable for large library generation.

Acknowledgments

This work is supported by National Science Council (NSC 95-2113-M-001-019) and Academic Sinica.

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14. *Typical procedure for the preparation of compound* **4**: Sodium benzenesulfinate (1.05 equiv, 0.50 g, 3.0 mmol) and benzyl bromide (0.50 g, 2.9 mmol) were dissolved in DMF (5 mL) and the reaction mixture was stirred at 80 °C for 4 h. After removal of organic solvent the solid was

collected by filtration, washed with H_2O, and dried to give benzyl phenyl sulfone (0.64 g, 2.75 mmol, 95%) as a white solid. Subsequently, *n*-BuLi (2 equiv, 2.2 mL, 2.5 M) was added to DMSO (4 equiv, 0.78 mL) in THF (10 mL) and stirred for 5 min at room temperature. This dimsyl anion was transferred to benzyl phenyl sulfone (0.64 g, 2.75 mmol) in THF (10 mL) at room temperature. After 30 min, ally bromide (1.5 equiv, 0.50 g, 4.13 mmol) was added to this mixture and stirred for further 1 h. The reaction mixture was extracted with ethyl acetate and water. The combined organic extracts were dried ($MgSO_4$), concentrated, and the residue was purified by recrystallization to give **4** (0.62 g, 2.28 mmol, 83%) as a white solid: ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.53–7.06 (m, 10H), 5.55–5.48 (m, 1H), 5.04 (d, 1H, $J = 17.0$ Hz), 4.95 (d, 1H, $J = 10.1$ Hz), 4.08 (dd, 1H, $J = 11.5$ Hz, $J = 3.7$ Hz), 3.19–3.14 (m, 1H), 2.92–2.87 (m, 1H). ^{13}C NMR (600 MHz, $CDCl_3$) δ 137.40, 133.71, 133.17, 132.05, 130.20, 129.29, 129.00, 128.84, 128.63, 118.70, 71.31, 32.03; HRMS: $[M+Na]^+$ cacld for $C_{16}H_{16}O_2S$, 295.0769; found, 295.0761.

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16. The preparation of PS/DVB sulfinate (**1**) was similar to that in Ref. 3c.
17. Monoalkylation of resin **7a** with 3-chloro-1-butene gave two expected polymer-bound regioisomers via an S_N2 or S_N2' process. After cleavage from the resin, two products **16a** (major) and **6a** (minor) were generated. Likewise, major products **16b–d** were released from the solid-support with concomitant minor products **6b–d**, respectively.
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