Available online at www.sciencedirect.com
ScienceDirect
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

Yi-Fan Chang, Yi-Rui Jiang and Wei-Chieh Cheng*

The Genomics Research Center, Academia Sinica, No. 128, Academia Road Sec. 2, Nankang District, Taipei 11529, Taiwan

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).

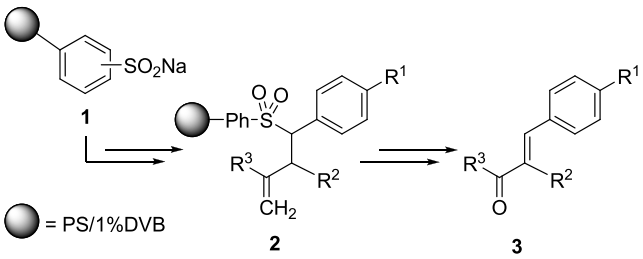


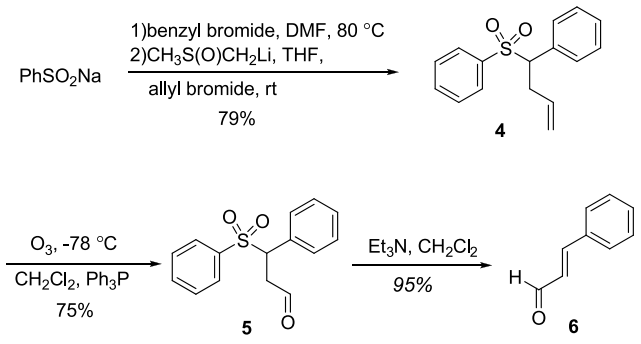
Figure 1. α,β-Unsaturated carbonyl compounds from polymer-bound benzenesulfinate **1**.

Keywords: Solid-phase organic synthesis; Sulfone linker; Ozonolysis; α-β-Unsaturated carbonyl compounds.
* Corresponding author. Tel./fax: +886 2 2789 9931; e-mail: wcheng@gate.sinica.edu.tw

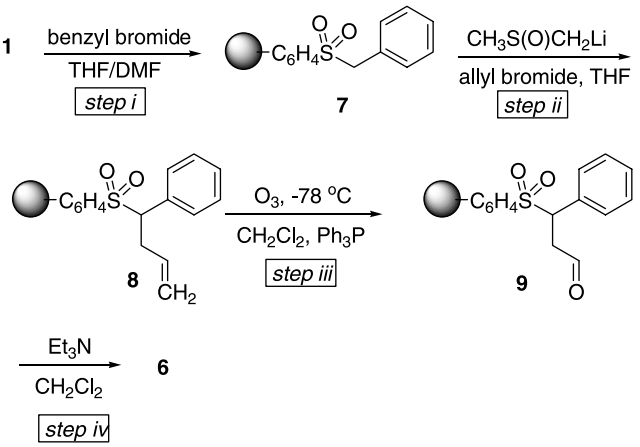
0040-4039/$ - see front matter © 2007 Published by Elsevier Ltd.
doi:10.1016/j.tetlet.2007.11.064

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.