

Solid-Phase Synthesis of Novel Isoxazolocyclobutanones and Isoxazolinocyclobutenones

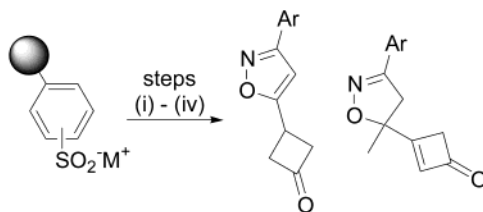
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ABSTRACT



The preparation of novel isoxazolocyclobutanone and isoxazolinocyclobutenone derivatives via a traceless solid-phase sulfone linker strategy is described. Key steps in the solid-phase protocol reported here include (i) sulfinate \rightarrow sulfone alkylation, (ii) four-member ring formation by sulfone dianion alkylation, (iii) heterocycle formation by nitrile oxide 1,3-dipolar cycloaddition, and (iv) traceless product release by cyclobutanol \rightarrow cyclobutanone oxidation with concomitant linker cleavage by sulfinate elimination.

An important objective in solid-phase organic synthesis (SPOS)¹ is the development of chemistries applicable to combinatorial techniques not limited by the tether and where target molecules can be efficiently cleaved from the resin by a specialized reagent or transformation.² In this regard, one of our goals has been to develop sulfone linkers for SPOS and to explore sulfone-based chemical transformations and cleavage strategies.^{3–5} Previous reports from our

laboratories^{3a,4,5} as well as others⁶ have detailed the use of a sulfinate-functionalized resin (styrene/divinyl benzene copolymer beads = ●) as the starting point for these strategies. The sulfone linkers derived from this sulfinate resin provide tethers robust to various chemical transformations and “traceless” when cleaved under appropriate conditions (Figure 1).^{4,5} Herein, we report extension of this sulfone-based chemistry to the synthesis of isoxazolocyclobutanones and isoxazolinocyclobutenones.

Key steps in the protocol reported here include (i) sulfinate (1)^{4,7} \rightarrow sulfone alkylation, (ii) four-member ring formation by sulfone dianion alkylation of epichlorohydrin,⁸ (iii) heterocycle formation by nitrile oxide 1,3-dipolar cycloadd-

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(7) The preparation of PS/DVB sulfinate (1) was similar to that in ref 4 except the reaction was quenched by HCl (6 N) and the polymer was treated with K₂CO₃(aq) in DMF after the polymer was washed with THF, MeOH, THF/H₂O (80:20), THF, and ether.

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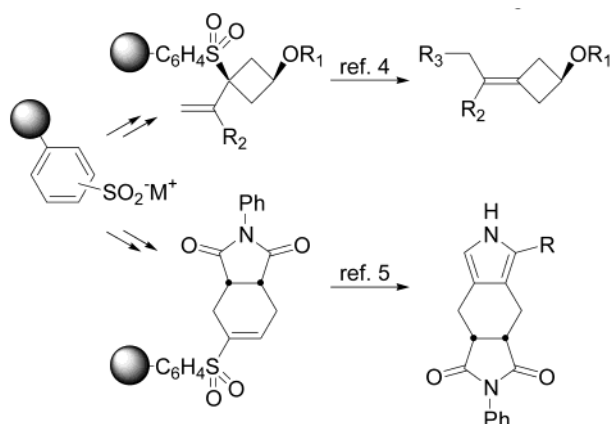


Figure 1. Traceless sulfone linker strategies.

dition,⁹ and (iv) traceless product release by cyclobutanol \rightarrow cyclobutanone oxidation with concomitant linker cleavage by sulfinate elimination (Figure 2). The resulting products

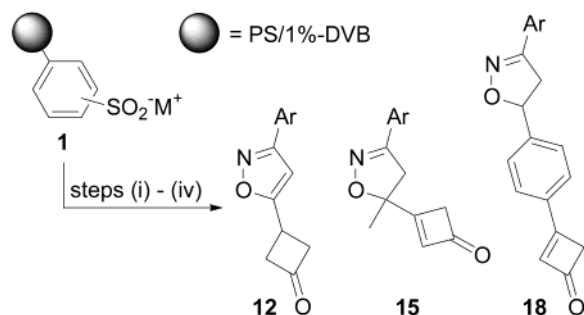


Figure 2. Sulfinate SPOS route to cyclobutanones and cyclobutenones.

(12/15/18) may provide useful molecular scaffolds for library production¹⁰ as four-member ring-containing compounds are both prevalent in nature and useful as building blocks for further transformations.¹¹ Moreover, these SPOS products contain isoxazoline or isoxazole heterocycles, which have

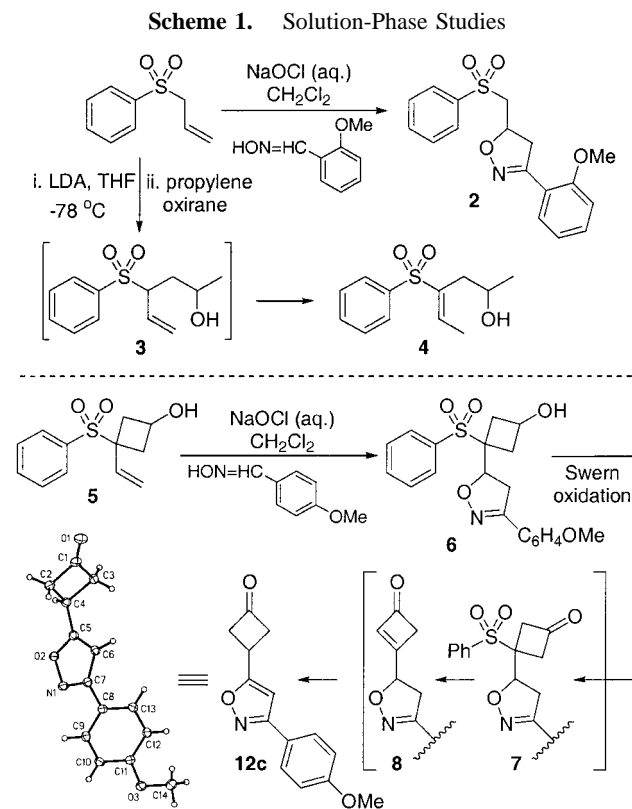
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been used extensively to modulate various biologically active motifs.¹² As reported here, we have also demonstrated reagent versatility in steps (i) and (iii) suggesting this protocol is suitable for library generation.

Solution-Phase Isoxazolocyclobutanone Synthesis. In a preliminary solution-phase study (Scheme 1), treatment of



allyl phenyl sulfone with *o*-methoxybenzaldehyde oxime and NaOCl (the Huisgen method¹³ for in situ nitrile oxide generation) gave isoxazolinyl sulfone **2** in good yield (80%). Attempts to α -alkylate this isoxazolinyl sulfone (LDA or *n*-BuLi in THF) resulted only in decomposition. Likewise, treating allyl phenyl sulfone with LDA followed by addition of propylene oxide resulted in vinyl sulfone **4** as the sole product instead of the anticipated allyl sulfone **3**. These observations led us to investigate first effecting sulfone α,α -dialkylation (i.e., cyclobutyl formation) and then proceeding with the 1,3-dipolar cycloaddition. Thus, 3-benzensulfonyl-3-vinylcyclobutanol (**5**)⁴ was reacted with *p*-methoxybenzaldehyde oxime and NaOCl to give 1,3-dipolar cycloadduct **6** in 81% yield. On the basis of our experience¹⁴ and others,¹⁵ we were not surprised to find that 1,3-dipolar cycloaddition

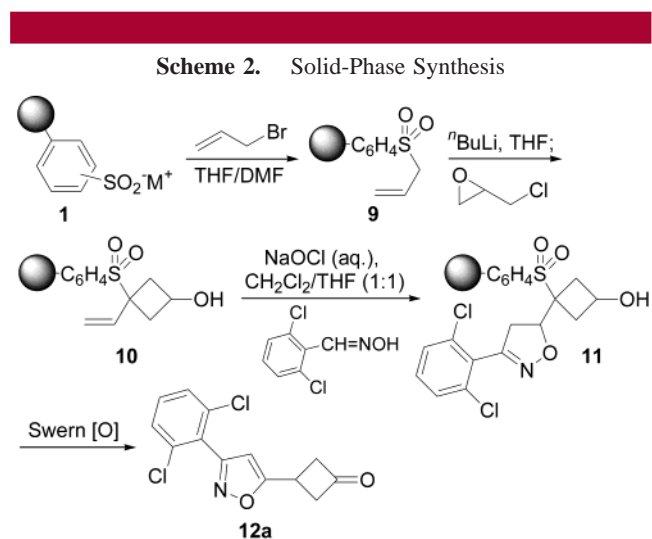
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to olefin **5** proceeded to give isoxazolinocyclobutanol **6** with complete regioselectivity.

The chemical shifts of the C4 and C5 isoxazolino protons in **6** appeared at δ 3.4 and 4.6, respectively, and were diagnostic in judging its conversion to the isoxazolo ring of “sulfone released” product **12c**. To effect this transformation—the equivalent of substrate release when performed on resin—the cyclobutanol moiety of **6** was oxidized (Swern)¹⁶ to the corresponding cyclobutanone (**7**). We were not surprised to find that, under the basic conditions of this reaction, oxidation **6** \rightarrow **7** was accompanied by concomitant sulfinate elimination¹⁷ (**7** \rightarrow **8**). Likewise, given the relative energetics of placing the C,C-double bond in the cyclobutyl vs isoxazolo rings, we fully expected isoxazolinocyclobutanone **8** to isomerize into isoxazolocyclobutanone **12c**. We were surprised at the ease with which this isomerization occurred, giving **12c** (the C5 methine at δ 4.6 in **6** had disappeared and the two proton signal at δ 3.4 now appeared as a one proton singlet at δ 6.3) in a one-pot overall yield of 82% from **6**. The observed C=O stretch at 1799 cm^{-1} is fully consistent with the unconjugated cyclobutanone of **12c**; a computer generated X-ray structure of **12c** is depicted in Scheme 1.

Solid-Phase Isoxazolocyclobutanone Synthesis. With a successful solution-phase route to isoxazolocyclobutanone **12c** in hand, we turned to the development of a viable solid-phase protocol and began with the preparation of polymer-bound benzenesulfinate **1** following our published protocol^{4,5} (Scheme 2). This resin (0.8 mmol/g) was converted to 3-(PS/



DVB-sulfonyl)-3-vinylcyclobutanol **10** via *S*-allylation with allyl bromide (\rightarrow **9**) and α,α -dialkylation with epichlorohydrin⁴ (Scheme 2). Treatment of resin **10** with 2,6-dichlorobenzaldehyde oxime in the presence of NaOCl (aq) in

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$\text{CH}_2\text{Cl}_2/\text{THF}$ (1:1) effected the 1,3-dipolar cycloaddition to give isoxazolino resin **11**. Since this transformation exhibited no reliably diagnostic absorption peaks in the IR spectrum, the oxidative release step was undertaken with some trepidation. Fortunately, Swern oxidation of resin **11** successfully delivered the isoxazolocyclobutanone **12a** in 35% overall yield from starting resin **1**, an average yield of >75% for each of the four solid-phase reactions.

We next employed the nitrile oxides generated in situ from *o*- and *p*-methoxybenzaldehyde oximes in the 1,3-dipolar cycloaddition reaction with resin **10** to deliver resin **11b** and **11c**, respectively (Figure 3). Oxidative elimination of resin-

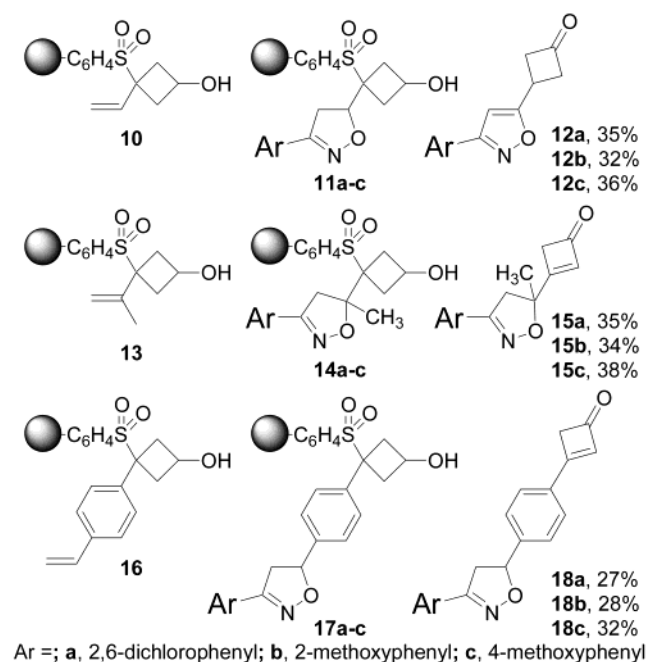


Figure 3. Product diversity.

ous sulfinate from these intermediates delivered isoxazolocyclobutanones **12b** and **12c**.

To further illustrate the versatility of this chemistry, 3-chloro-2-methylpropene and 4-vinylbenzyl (this alkylating agent introduces a phenyl “spacer” between the isoxazolino and cyclobutanone moieties) chloride were used to *S*-alkylate polymeric sulfinate **1** giving polymer-bound sulfones, which were then α,α -dialkylated with epichlorohydrin to give polymers **13** and **16**, respectively. Subsequent conversions to isoxazolinocyclobutanols **14a–c** and **17a–c** were ac-

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complished as described for **10** \rightarrow **11**. Oxidation of these cyclobutanols with concomitant cleavage of the sulfone linker produced isoxazolinocyclobutenones **15a–c** and **18a–c**, respectively. Obviously, olefin isomerization is unlikely in these case, and as expected, the IR spectra of these products displayed C=O absorptions between 1753 and 1769 cm^{-1} indicating that cyclobutenones and not cyclobutanones were obtained.

Finally, it is noteworthy that the procedures developed for **10** \rightarrow **12**, **13** \rightarrow **15** gave reduced overall yields of the liberated isoxazoline products (18–23% range). This led us to further scrutinize the solid-phase reaction conditions for **13** \rightarrow **14**. We discovered that performing the 1,3-dipolar cycloaddition reactions twice (i.e., after first treatment with 3 equiv of oxime plus NaOCl for 12 h, the reaction was filtered and then an additional 3 equiv of oxime plus NaOCl were added a second time for an additional 12 h) significantly improved the yields of **15a–c** (34–38% range). Presumably, the disubstituted olefin in **14** is less reactive in the solid-phase 1,3-dipolar cycloaddition than the monosubstituted olefin in **10**.

In summary, we have developed a traceless solid-phase route to isoxazolocyclobutanones and isoxazolinocyclobuten-

ones with diversity in the aryl, isoxazolo/isoxazolino, cyclobutanone/cyclobutenone, and “spacer” moieties (see Figure 2). The solid-phase chemistry proceeds with formation of three C,C-bonds—two by sulfone α,α -dialkylation and one by nitrile oxide 1,3-dipolar cycloaddition—as well as a novel sulfinate oxidative elimination step. The solid-phase preparation of nine diverse isoxazolocyclobutanones and isoxazolinocyclobutenones in 27–38% overall yield from polymer-bound benzenesulfinate **1** demonstrates the versatility of this chemistry.

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Supporting Information Available: Experimental procedures, full characterization for compounds for **12a–c** and **15a–c**, and ^1H and ^{13}C NMR spectra for **18a–c**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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