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Solid-Phase Synthesis of Novel Isoxazolocyclobutanones and Isoxazolinocyclobutenones

Wei-Chieh Cheng, Melissa Wong, Marilyn M. Olmstead, and Mark J. Kurth*

Department of Chemistry, University of California, One Shields Avenue, Davis, California 95616-5295

mjkurth@ucdavis.edu

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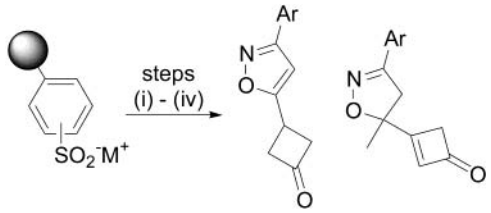
ABSTRACT



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 → 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 → 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 others[6] 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] → sulfone alkylation, (ii) four-member ring formation by sulfone dianion alkylation of epichlorohydrin,[8] (iii) heterocycle formation by nitrile oxide 1,3-dipolar cycload-

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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 K_2CO_3(aq) in DMF after the polymer was washed with THF, MeOH, THF/H_2O (80:20), THF, and ether.

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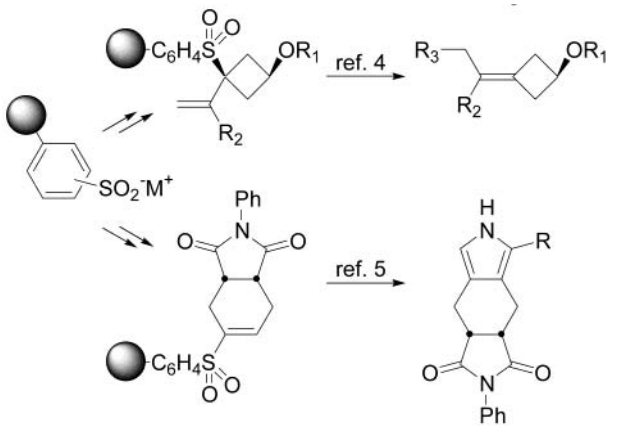


Figure 1. Traceless sulfone linker strategies.

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

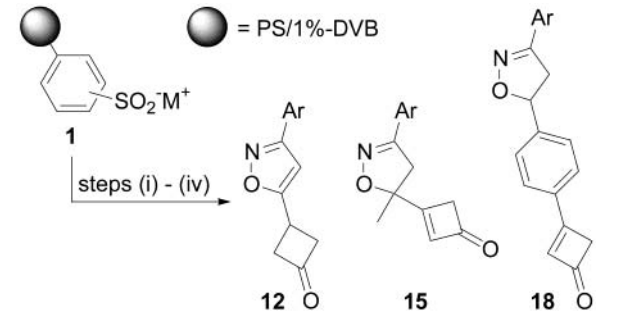
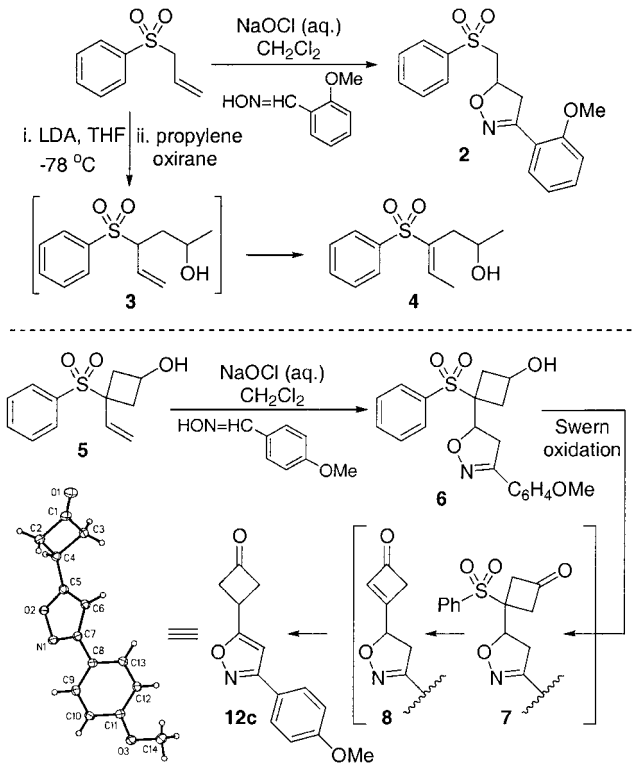


Figure 2. Sulfinate SPOS route to cyclobutanones and cyclobutenones.

(**12**/**15**/**18**) may provide useful molecular scaffolds for library production[10] 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 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

Scheme 1. Solution-Phase Studies



allyl phenyl sulfone with *o*-methoxybenzaldehyde oxime and NaOCl (the Huisgen method[13] for in situ nitrile oxide generation) gave isoxazolinosulfone **2** in good yield (80%). Attempts to α-alkylate this isoxazolinosulfone (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 experience[14] and others,[15] we were not surprised to find that 1,3-dipolar cycloaddition

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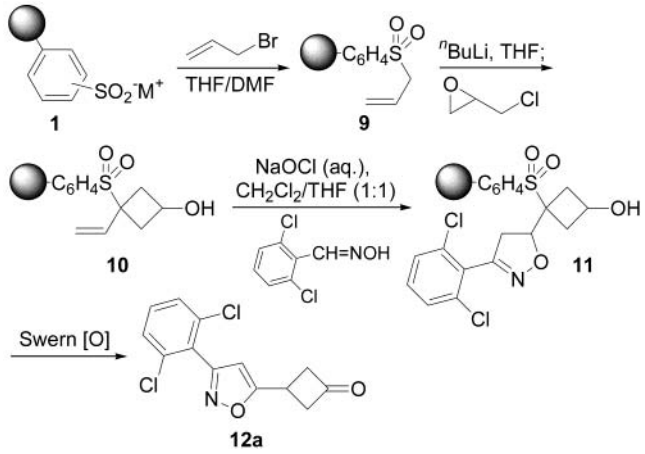
(13) Huisgen, R. *Angew. Chem., Int. Ed. Engl.* **1963**, *2*, 565.

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** → **7** was accompanied by concomitant sulfinate elimination[17] (**7** → **8**). Likewise, given the relative energetics of placing the C,C-double bond in the cyclobutyl vs isoxazolo rings, we fully expected isoxazolinocyclobutenone **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 isoxazolocyclo-butanone **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 (→ **9**) and α,α-dialkylation with epichlorohydrin[4] (Scheme 2). Treatment of resin **10** with 2,6-dichlorobenzaldehyde oxime in the presence of NaOCl (aq) in CH_2Cl_2/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.

Scheme 2. Solid-Phase Synthesis



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-

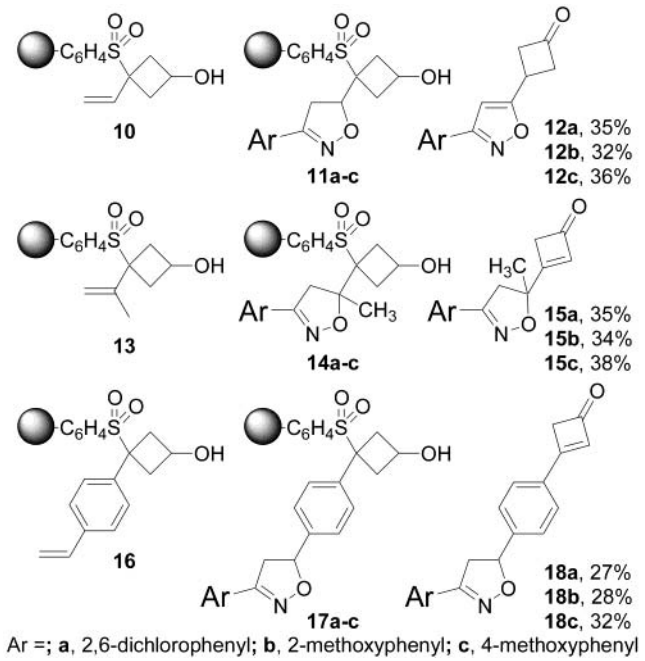


Figure 3. Product diversity.

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 cyclobutenone 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** → **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** → **12**, **13** → **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** → **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 isoxazolinocyclobutenones 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 ^{1}H 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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