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Solid-Phase Synthesis of Pyrazolines and Isoxazolines with Sodium Benzenesulfinate as a Traceless Linker

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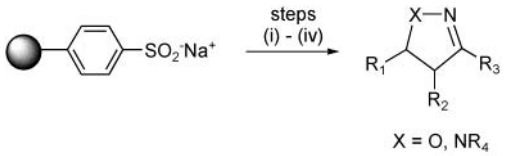
ABSTRACT



The preparation of pyrazoline and isoxazoline derivatives with traceless solid-phase sulfone linker strategy is described. Key steps involved in the solid-phase synthetic procedure include (i) sulfinate *S*-alkylation, (ii) sulfone anion alkylation, (iii) γ-hydroxy sulfone → γ-ketosulfone oxidation, and (iv) traceless product release via elimination–cyclization. A library of 12 pyrazolines and isoxazolines was synthesized.

An important feature of solid-phase organic synthesis (SPOS) is the linker that attaches the compounds being synthesized onto the solid support.[1] Methods of immobilizing compounds to the solid phase for combinatorial synthesis initially rely upon traditional solid-phase peptide linkers, which resulted in the release of carboxylic acids, esters, or amides from the ester- or amide-bound substrate.[2] The presence of these appendages is acceptable if the final products embody these functional groups. However, complications may arise if these vestigial functionalities are redundant and affect the activities of the compounds. In this regard, one of our interests is to develop the sulfone linker via polystyrene/1% divinylbenzene sodium sulfinate (**1**) as a traceless linker and explore new applications for it in SPOS. Earlier reports from other laboratories[3,4] and ours[5] have demonstrated the use of **1** as a solid support for SPOS and shown the resulting sulfone linker derived from **1** to be a versatile and robust tether that offers a variety of on-resin functionalization or cleavage with additional changes.

Compounds containing the pyrazoline or isoxazoline moieties have diverse activities[6] and have been developed as antiinflammatory agents,[7] human leukocyte elastase inhibitors,[8] optical brighteners,[9] fluorescent switches,[10] and intermediates of various biologically important compounds.[11] Although the solid-phase synthesis of isoxazoline with 1,3-dipolar cycloaddition has been extensively studied,[3b,12] examples of their solid-phase synthesis with α,β-unsaturated

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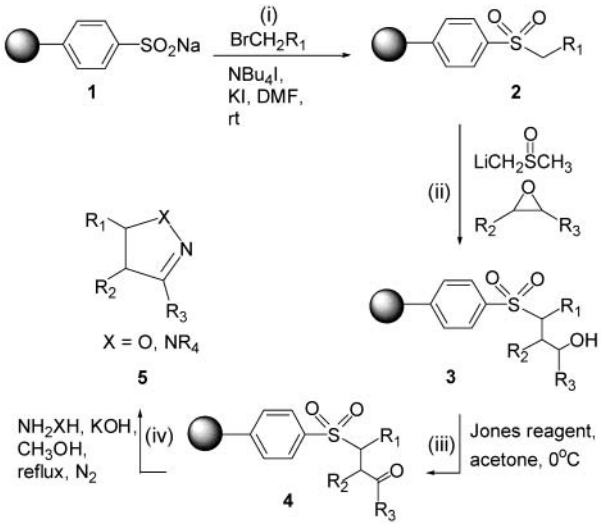
ketone and hydroxylamine are unknown. In addition, to our knowledge, there have been no reports on the traceless synthesis of pyrazolines. Herein, we report the extension of this sulfone-based chemistry to a convenient, traceless synthesis of pyrazoline or isoxazoline derivatives using α,β-unsaturated ketone and hydrazine/hydroxylamine.

Key steps in the synthesis of pyrazolines or isoxazolines from **1** include (i) sulfinate *S*-alkylation, (ii) sulfone anion alkylation with an epoxide, (iii) γ-hydroxyl sulfone → γ-ketosulfone oxidation, and (iv) traceless product release by a one-pot elimination−cyclization reaction (Scheme 1).

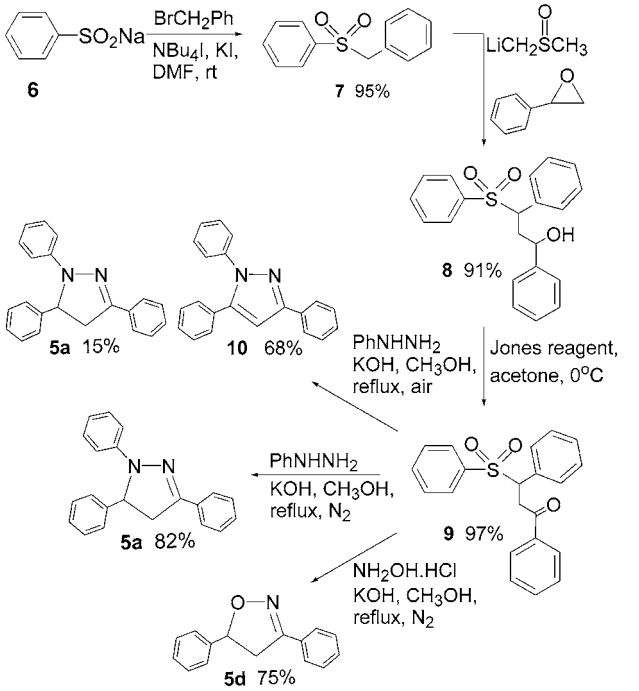
Scheme 1. Sulfinate SPOS to Pyrazoline and Isoxazoline



Since a variety of reagents can be used in steps i, ii, and iv, the overall strategy appears to be applicable for library generation.

Solution-Phase Synthesis of Pyrazoline and Isoxazoline. Prior to the solid-phase synthesis, preliminary solution-phase studies were carried out to survey the requisite reaction conditions and establish the modifications required for SPOS. To begin our investigation, γ-ketosulfone, 3-benzenesulfonyl-1,3-diphenylpropan-1-one (**9**) was prepared by treating sodium benzenesulfinate (**6**) with benzyl bromide in the presence of NBu_4I/KI/DMF at room temperature to give phenylsulfonylmethylbenzene (**7**) in 95% yield (Scheme 2). Subsequent alkylation of **7** with styrene oxide according to a procedure from Kurth and co-workers[3c] provided 3-benzenesulfonyl-1,3-diphenylpropan-1-ol (**8**) in good yield (91%). Oxidation of **8** with Jones reagent[13] gave **9** in quantitative yield (97%).

Scheme 2. Solution-Phase Study



Attempts to cyclize **9** by refluxing it with phenyl hydrazine and KOH/CH_3OH in air gave mainly 1,3,5-triphenyl-1*H*-pyrazole (**10**, 68%) and only 15% of 1,3,5-triphenyl-4,5-dihydro-1*H*-pyrazole (**5a**). However, when the reaction was carried out under nitrogen condition, **5a** was formed in 82%

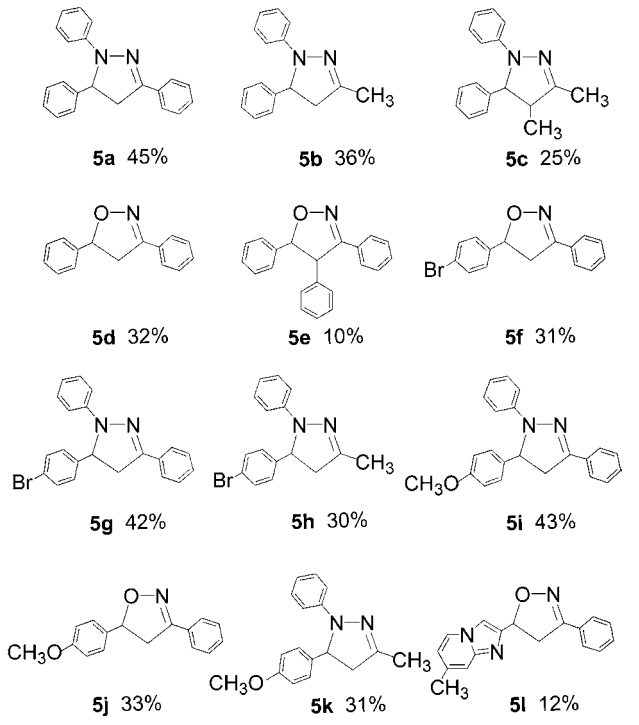


Figure 1. Library of pyrazoline and isoxazoline.

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yield and **10** was not observed at all. Similarly, reaction of **9** with hydroxylamine hydrochloride in nitrogen atmosphere gave the desired 3,5-diphenyl-4,5-dihydroisoxazole (**5d**) in 75% yield.

Solid-Phase Synthesis of Pyrazoline and Isoxazoline. With the solution-phase pathway to pyrazoline and isoxazoline established, we proceeded to develop the solid-phase route to these compounds. Polystyrene/1% divinylbenzene sodium sulfinate (**1**, 100−200 mesh) in NBu_4I/KI/DMF was allowed to react with benzyl bromide at room temperature (Scheme 1). The formation of **2** was amenable to KBr FTIR monitoring (i.e. appearance of the sulfone stretch at 1316, 1151 cm^{-1}). Alkylation of **2** with epoxides gave resin **3**, which could not be reliably analyzed with FTIR. Hence we proceeded to oxidize resin **3** with Jones reagent (we have also examined the oxidation of resin **3a** with Dress−Martin reagent and found that the overall yield was comparable to that obtained from the Jones reagent; since the Jones reagent was easier to handle, it was used for our library synthesis). This transformation was monitored by FTIR for the appearance of a new carbonyl stretch (ν_{max} 1687 cm^{-1}). Subsequent treatment of resin **4** with substituted hydrazine or hydroxylamine in KOH/CH_3OH under nitrogen condition gave **5**. To illustrate the versatility of this chemistry, a library of 12 compounds (**5a**−**5l**) was prepared (Figure 1). Except for **5e**, the overall yields of **5a**−**d** and **5f**−**k** were 25−45% (purities of >95% by NMR), indicating an average yield of greater than 70% for each step of the four solid-phase reactions. The lower yield observed for **5e** may be attributed to the greater steric hindrance in the molecule. **5l** was prepared via a five-step reaction from polymer-supported 2-benzenesulfonylmethyl-6-methylimidazo[1,2-*a*]pyridine.[5a]

The structures of the pyrazolines and isoxazolines were confirmed by NOESY experiments performed on representative compounds **5c**, **5f**, and **5i**. The observed data indicate that **5c** has the trans configuration.

In summary, we have demonstrated a traceless solid-phase synthesis of pyrazoline and isoxazoline that accommodates four points of diversification (R_1 to R_4 in **5**). The chemistry used is suitable for combinatorial library preparation.

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Supporting Information Available: Detailed experimental procedure, NMR and MS data for all compounds, ^1H and ^{13}C NMR spectra for **5a**−**c**, and NOESY data for **5c**,**f**,**i**. This material is available free of charge via the Internet at http://pubs.acs.org.

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