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A general carbometalation, three component coupling strategy for the synthesis of α,β-unsaturated γ-sultines including thio-rofecoxib, a selective COX-2 inhibitor

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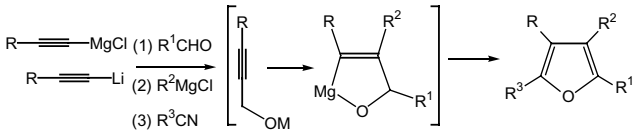
Abstract—Magnesium mediated carbometalation (Grignard addition) to appropriate propargyl alcohols to synthesize a cross-section of variably substituted α,β-unsaturated γ-sultines is described. Thio-rofecoxib, a selective COX-2 inhibitor (**12**), is synthesized by this method and its IC_{50}, μM COX-1 and COX-2 inhibition, and whole blood stability values reported.

Cyclic sulfinates (sultines) constitute a class of heterocyclic compounds whose chemistry continues to be of interest.[1] There appears to be only one report of a sultine natural product, 3-propyl-γ-sultine from the yellow passion fruit (*Passiflora edulis f. flavicarpa*).[2] Nevertheless sultines have a long chemical history[3] and several methods exist for their synthesis.[1,4] Sultines are versatile synthetic intermediates, applications include ring-opening reactions (to generate *ortho*-quinodimethanes[5] or biradicals[6]), alkylation,[7] and oxidation at sulfur to give sultones.[8] In addition, the stereogenic center at sulfur has the potential to play a role in subsequent asymmetric transformations. More recently, there has been increased interest in five membered sulfur heterocycles such as sultines because of their cancer chemopreventative effects. They function as glutathione *S*-transferase inducers and may have medicinal potential.[9] Additional reports suggest that thio-acetals such as 1,2-dithiolanes and 1,2-dithianes hold promise as HIV type 1 replication inhibitors.[10]

We have previously described some of the attributes and versatility of the magnesium mediated carbometalation of propargyl alcohols[11] to assemble several diverse compounds generated in a single reaction, for a variety of objectives. These reactions have included the regio- and stereoselective generation of diene–halides, diene–diols, enediynes, furans, furanones, taxo intermediates, and palladium(0) cross-couplings for dienes, and the stereospecific synthesis of (*Z*)-tamoxifen.[12]

The common feature of this chemistry is the reaction of a propargyl alcohol either directly or in situ with a Grignard reagent, subsequent generation of the magnesium chelate, followed by reaction with an appropriate electrophile. In the case of furans the substitution pattern may be controlled for all the ring substituents and five bonds are formed in one reaction vessel (Scheme 1).

We wish to report an extension of this chemistry for the synthesis of 3,4-disubstituted α,β-unsaturated γ-sultines. It was anticipated that the putative chelate **3** that arises from addition of the Grignard reagent **2** to the propargylic alcohol **1** could be trapped with thionyl chloride to



Scheme 1. Magnesium mediated carbometalation route to furans.

Keywords: Carbometalation; Propargyl alcohols; Sultines; Cox-2 inhibitor.
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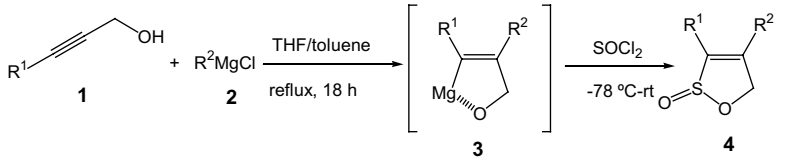


Scheme 2. Carbometalation of propargyl alcohols with thionyl chloride quench to sultines.

yield variably disubstituted γ-sultines of type **4** (Scheme 2).

The carbometalation of several propargylic alcohols (**1**) were conducted with a variety of Grignard reagents **2**. However, initial attempts to trap the intermediate chelate **3** at 0 °C with thionyl chloride resulted in complex product mixtures. This difficulty was overcome by conducting the quench at −78 °C to afford the desired γ-sultines cleanly with minimal contamination. These results are summarized in Table 1. The yields were reproducible and the products were of sufficient purity, determined by ^{1}H NMR analysis, that further purification was usually not required.

The cyclooxygenases (COX-1 and COX-2) play an important role in human health due to their important role as catalysts for the conversion of arachidonic acid to initiate the prostaglandin cascade. It is now established that cyclooxygenages exist as two isoforms with different functions. COX-1, via prostaglandins, helps mediate gastric cytoprotection and platelet aggregation. In contrast COX-2 is up-regulated in response to inflammatory stimuli. This has led to a new family of COX-2 selective inhibitors that are potent anti-inflammatory agents with improved gastrointestinal features compared to non-selective drugs (NSAIDS) (Fig. 1). The potential of more efficient drugs for the treatment of osteoarthritis and reduction of acute pain with less acute gastrointestinal problems stimulated the discovery of several novel coxib drugs with improved efficacy. Prominent among these were refecoxib (**5**, Vioxx®), celecoxib (**6**, Celebrex®) valdecoxib (**7**, Bextra®), and etoricoxib (**8**, Arcoxia®). In a very short time frame these became billion dollars drugs. It is interesting to note the similarity in structures, particularly of the first generation, based on a five membered ring heterocyclic framework that contained both phenyl and most importantly a phenylsulfonyl methyl or phenylsulfonamide functionality.

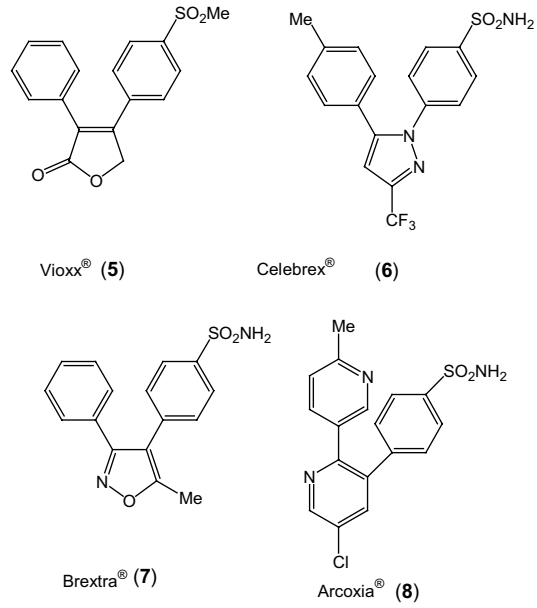


Figure 1. Selective COX-2 inhibitor drugs.

Our research was completed before the current controversy regarding heart complications with Vioxx® was verified. However, further research and human ingenuity will eventually generate compounds with improved therapeutic profiles. Previously we developed a two-step synthesis of the COX-2 anti-inflammatory drug Vioxx® (**5**) with our carbometalation strategy (Scheme 3).[11c] In view of the widespread interest in COX-2 inhibitors and the success of the results above the opportunity to synthesize a C2 sulfur analog of the butenolide nicknamed ''thio-Vioxx'' (**12**) was particularly appealing.[13]

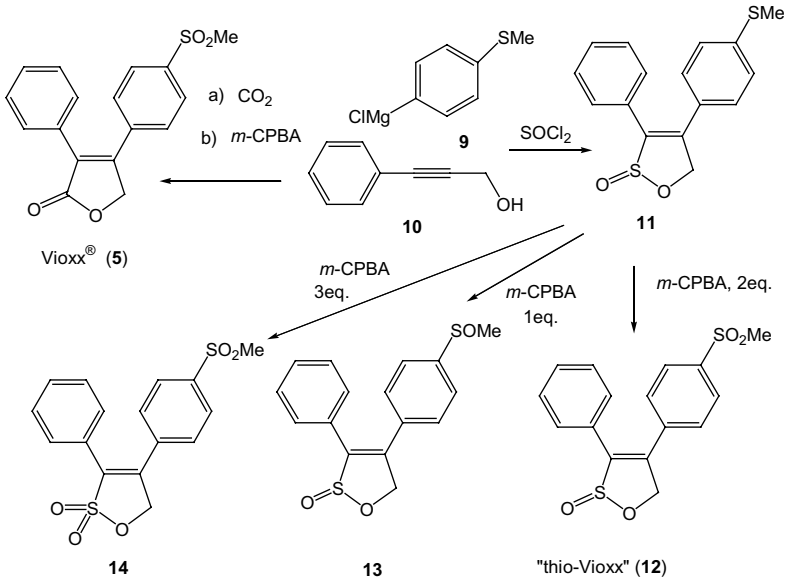
Standard quenching conditions at −78 °C afforded the sultine **11** from addition of thioanisole magnesium chloride (**9**) to phenylpropargyl alcohol (**10**) in modest yield (29%). Oxidation of sultine **11** with exactly 2 equiv of *m*-CPBA afforded **12** in 99% yield. The differentially oxidized analogs **13** and **14** were prepared via modification of the oxidation conditions.

Treatment of **11** with 1 equiv of *m*-CPBA afforded the methyl sulfoxide **13**, while with 3 equiv of oxidant **14** was produced. The preferential oxidation of the thiomethyl ether **11** is noteworthy, as no competing oxidation of the intra-annular sulfur was observed in the preparation of either **12** or **13**.

Table 1. Sultine **4** substitution patterns and yields

Compound	R^1	R^2	Yield[a] (%)
4a	Me	Allyl	57
4b	Me	Ph	60
4c	Ph	Me	82
4d	Ph	Vinyl	95
4e	Ph	Isopropenyl	92
4f	Ph	Allyl	89
4g	Ph	Ph	86
4h	TMS	Vinyl	82
4i	TMS	Vinyl	83
4j	TMS	Ph	91

[a] Yields are for isolated products.



Scheme 3. Synthesis of 'thio-rofecoxib' = 'thio-Vioxx' **12**.

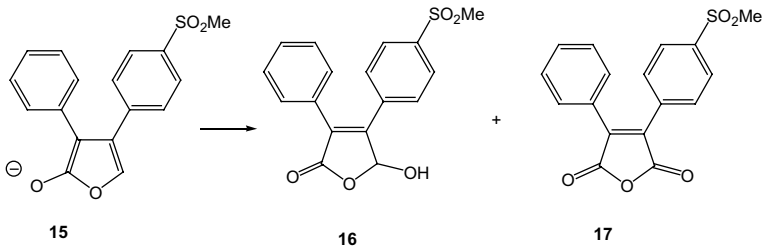
At the outset, we wanted to evaluate the metabolic stability of sultine **12**. This was accomplished by incubating **12** in rat plasma at room temperature and subsequently analyzing the incubations for levels of parent drug. Thus, at different time points, the rat plasma incubation sample was treated with acetonitrile to precipitate the plasma proteins and, after centrifugation, the resulting materials were analyzed by HPLC–UV. We were pleased to note that the concentration of **12** in the plasma samples, as measured by LC–UV, remained unchanged even after 24 h incubation. Encouraged by this finding, we next evaluated the in vitro coxib profile of **12** in a microsomal enzyme assay. Results of this assay revealed that sultine **12** is a selective COX-2 inhibitor. The IC_{50} of **12** on COX-1 was found to be >100 μM (13% inhibition at 100 μM). Interestingly, the titration curve for the COX-2 assay plateaued at approximately 40% inhibition with an inflection point of 0.86 μM. The reason for this plateau effect in the COX-2 assay is unclear, although this phenomenon with other classes of COX-2 inhibitors has been reported in the literature.[14]

A select number of 3,4-disubstituted α,β-unsaturated γ-sultines have been reported.[15] However, our magnesium mediated carbometalation approach offers a very flexible 3-component coupling method for efficient access to previously unavailable γ-sultines with novel substitution patterns. In addition, thio-rofecoxib, which displays selective COX-2 inhibitor was prepared in a straightforward manner. Based on these results, extension of this chemistry to the synthesis of glutathione peroxidase catalysts such as 1,2-oxaselenane Se-oxide[16] may be feasible.

After submission of this manuscript it was suggested that the conjugate base of rofecoxib was a possible contributor to the human toxicity observed during long term treatment with rofecoxib.[17] Air oxidation of anion **15**, generated from rofecoxib on treatment with either *n*-BuLi or LiOH in THF, afforded a small amount of **16** and the corresponding maleic anhydride **17** (Scheme 4). If anhydride **17** were to be generated in vivo and if it was a long live metabolite, it was speculated that nucleophilic attack from amino groups would be possible.[17]

A reviewer asked us to comment on the potential relationship with these observations and the anticipated behavior of thio-rofecoxib **12**.

These are very different molecules and the sultine is not capable of enolization in the manner of the butenolide. Indeed, the most likely oxidation product from **12** is



Scheme 4. Possible in vitro oxidation pathway from rofecoxib alkoxide.

the sultone **14**. Consequently the metabolic oxidative pathways will share little in common.

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