Heterocycles

Lithium-Catalyzed Thiol Alkylation with Tertiary and Secondary Alcohols: Synthesis of 3-Sulfanyl-Oxetanes as Bioisosteres

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Abstract: 3-Sulfanyl-oxetanes are presented as promising novel bioisosteric replacements for thioesters or benzyl sulfides. From oxetan-3-ols, a mild and inexpensive Li catalyst enables chemoselective C–OH activation and thiol alkylation. Oxetane sulfides are formed from various thiols providing novel motifs in new chemical space and specifically as bioisosteres for thioesters due to their similar shape and electronic properties. Under the same conditions, various N-activated secondary and tertiary alcohols are also successful. Derivatization of the oxetane sulfide linker provides further novel oxetane classes and building blocks. Comparisons of key physicochemical properties of the oxetane compounds to selected carbonyl and methylene analogues indicate that these motifs are suitable for incorporation into drug discovery efforts.

Organosulfur functional groups are often present in pharmaceutical compounds, found in a quarter of the top 200 drugs (branded drugs by US retail sales in 2011).[1,2] Benzylic sulfides, sulfoxides and sulfones are particularly prevalent, such as in AstraZeneca’s blockbuster antiulcerant Nexium, Figure 1.[3] Thioester-containing compounds have also been disclosed, but are often used as a pro-drug due to limited metabolic stability.[4] Thioesters are 100× more reactive to amine nucleophiles than esters.[5] However, to date there are no suitable bioisosteres for these functional groups to provide improved stability at the C-center, limiting this design space for medicinal chemists.

Oxetanes have emerged as valuable motifs in medicinal chemistry that can confer improved physicochemical and metabolic properties.[6] Oxetanes can act as suitable polar replacements for gem-dimethyl linkers and as bioisosteres for carbonyl functionality.[7] In recent years, oxetane isosteres have been presented for amide,[8] ketone,[9] and carboxylic acid derivatives.[10] These developments continue to accelerate the exploration of oxetanes in medicinal chemistry.[11, 6a]

We were interested in the potential of 3-sulfanyloxetane derivatives as isosteres for sulfides or thioesters (Figure 1). This little explored class of compounds would offer similar features to thioesters, based on the dipole and lone pair position of the oxetane, but without the electrophilic center. Indeed, our DFT studies indicated that while the thioester C–O bond length is calculated to be 0.8 Å shorter than the oxetany sulfide, their electrostatic mapping is very similar.[12, 13] Additionally, these motifs may offer a protected benzylic center for sulfides or oxidized derivatives. Encouragingly, Bernardes recently reported a mono-substituted 3-sulfanyloxetane as part of a modified protein which was stable under incubation with blood plasma and with glutathione.[14] However, synthetic access to these motifs remains limited,[15–18] particularly towards 3,3-disubstituted ex-
amperes; Ellman[19] and Sun[20] reported 3-alkyl-3-sulfanyloxetanes through conjugate addition of a sulfide to oxetanemic- 

We envisaged an S₈1 process for the formation of oxetane sulfides from 3-aryloxetan-3-ols (Figure 1). We recently report-
ed a Li-catalyzed Friedel–Crafts reaction using oxetanols to form diaryloxetanes, invoking an oxetane carbocation.[9] The catalytic activation of alcohols through C–O activation has become an attractive alternative to replace more toxic alkyl halides.[21,22] However, there are only infrequent examples of catalytic thiol alkylation on functionalized substrates, which often require high catalyst loadings with acidic reagents.[23] Furthermore, ring opening of oxetanes by S-nucleophiles under acidic conditions[24] presents a significant chemoselectivity concern. Here we report a high yielding Li-catalyzed alkylation 

Building on our prior studies and with the above considera-
tions in mind, we investigated the alkylation of benzylmercap-
tan with oxetanol 1 (Table 1).

| Table 1. Selected optimization for the reaction of 1 with benzylmercap-
tan. | | |
|---|---|---|
| Change from the “standard” conditions | Yield 2a Yield 3 [7%][24] [9%][24] |
| 1 none | 81(67) < 5 |
| 2 FeCl₃ (5 mol %), instead of Li(N(Tf)₂) BuNPF₆ | 18 0 |
| 3[21] Ca(N(Tf)₂) (5 mol %), BuNPF₆ (5 mol %) instead of Li(N(Tf)₂) | 62 0 |
| 4 Ga(OTf)₃ (5 mol %), instead of Li(N(Tf)₂) BuNPF₆ | 21 11[21] |
| 5 Bi(OTf)₃ (5 mol %), instead of Li(N(Tf)₂) BuNPF₆ | 4 0[21] |
| 6 TiOH.H₂O (5 mol %), instead of Li(N(Tf)₂) BuNPF₆ | 0 0[24] |
| 7 toluene, instead of CHCl₃ | 61 16 |
| 8 No Li(N(Tf)₂) | 0 0 |
| 9 No BuNPF₆ | 0 0 |
| 10 3 equiv BnSH, 10 min reaction time | 0 0 |
| 11 3 equiv BnSH | 75 9 |
| 12 6 equiv BnSH, 6 h | 0 97 |

[a] Yield determined by ¹H NMR using 1,3,5-trimethoxybenzene as internal 

standard. Yield of isolated product in parentheses. [b] See reference [24a] 

development of Ca reagents. [c] 45% recovered 1. [d] Trace amount of 

We optimized the reaction to form oxetane sulfide 2a, and to minimize ring-opened side product 3 in which all alkyl C–O 

of sulfides 2c–2l with the reaction insensitive to the electronic and steric nature of the substituents. 4-Hydroxythiophenol 
gave complete selectivity for the S-alkylated product 2j with no Friedel–Crafts or O-alkylated product observed. Aliphatic 
thiols such as tertialyl 1-adamantanethiol (2m) and primary butyl-3-mercaptropriionate (2n) were also successful. However, 
NBoc-cysteine methyl ester and 2-(Boc-amino)ethanethiol did not afford the corresponding 3-sulfanyloxetanes, giving 
complete recovery of starting material. The comparison to butyl-3-meraptropriionate suggests that coordination of the 
NHBOC group to the catalyst causes deactivation. Other prein-

Scheme 1. Scope of oxetanylsulfides using aryl, benzyl and alkyl thiols.
stalled electron-rich aromatic groups were successful in stabilizing the oxetane-carbocation intermediate. A TIPS-protected phenol gave oxetane sulfide 8 in 66% yield. A 3,4,5-trimethoxybenzene group yielded oxetane sulfide 9 in a low yield (23%) due to increased oxetane ring opening. Furan and indole substituted oxetanes gave the corresponding oxetane sulfides 10 and 11 in excellent yields of 86% and 91% respectively.

Other varied π-activated secondary and tertiary alcohols (12) were explored to demonstrate the wider applicability of these reaction conditions. Excellent yields were obtained of tertiary benzylc sulfides bearing tetrahydropyran, cyclohexane and cyclobutane linkers as well as secondary and tertiary propargylic and allylic sulfides (see Supporting Information page S18, for full details; 10 examples 13 a–j).

Next, we explored functionalization of the oxetane sulfides. Deprotection of the TIPS group of oxetane sulfide 8, followed by formation of the triflate 14 occurred in high yields, providing a building block for further reaction (Scheme 2A). Biaryl 15 was formed by Suzuki–Miyaura cross-coupling in 95% yield. The high yield demonstrated the excellent stability of the oxetane sulfide unit to the reaction conditions. Oxidation of the oxetane sulfides with mCPBA formed selectively 3-sulfinyloxetanes 16 c, d, f or 3-sulfonyloxetanes 17 c, d, f as new oxetane structural classes (Scheme 2B).

Oxetane–cysteine derivatives continued to make an attractive target as alkylated cysteines feature in several marketed drugs. As protected cysteine did not react with oxetanol 1 directly, an alternative route via oxetane thiol 18 was devised (Scheme 3). Typically, conversion of a tertiary alcohol to a thiol involves Lawesson’s reagent or heating under acidic conditions with thiourea. From oxetanol 1, a mild and convenient two step, one pot procedure was developed using tritylthiol under thiol alkylation conditions. In situ deprotection (trifluoroacetic acid (TFA) and triethylsilane) gave 53% of oxetane thiol 18. Reaction of 18 with a protected dehydroalanine derivative yielded sulfide 19 in quantitative yield. Ester hydrolysis and Boc deprotection afforded the racem target unnatural amino acid 20.

In the context of drug discovery, the distribution coefficient of a compound strongly affects how effectively the drug can reach its intended target, as well as efficacy and pharmacokinetic properties. Hence, LogD is often used by medicinal chemists in pre-clinical drug discovery to consider the drug-likeness of an intended target molecule. To understand the effect of oxetane sulfides on this key parameter, LogD was measured for compounds 21, 2 d, and 17 d. Replacing the thioester functionality with the oxetane thiol had the positive effect of lowering the LogD by approximately 1 Log unit (Figure 2). Furthermore, oxidizing the sulfide to the sulfone fur-
tans, over competing oxetane ring opening. The use of the mild and inexpensive Li catalyst was crucial and careful control of the reaction conditions gave high yields of the oxetane sul- fides. The oxetane sulfides were compatible with palladium catalyzed cross-coupling and were converted to sulfoxide, sulfone, and thiol derivatives; themselves providing new classes of oxetane containing compounds. Measurement of key physicochemical properties: LogD, clearance and cell permeability, indicated that oxetane sulfides and sulfones are attractive for medicinal chemistry applications.

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Conflict of interest

The authors declare no conflict of interest.

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