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Tetrahedron Letters 44 (2003) 7821–7824

TETRAHEDRON LETTERS

Oxidation of aromatic and aliphatic triisopropylsilanylsulfanyls to sulfonyl chlorides: preparation of sulfonamides

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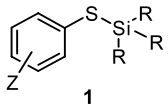
Received 11 May 2003; accepted 14 August 2003

Abstract—A series of aromatic and aliphatic triisopropylsilanylsulfanyls were prepared and oxidized to the sulfonyl chlorides with KNO_3/SO_2Cl_2. The sulfonyl chlorides were characterized via their conversion to sulfonamides.

In medicinal chemistry, sulfonamides are important functional groups. Structure–activity relationship (SAR) has demonstrated their valuable role in drug design and their utility as surrogate in amide replacement. They are encountered in many natural products as well as in therapeutic molecules used today. In the synthesis of organic molecules, aromatic sulfonamides can be used in Direct *ortho* Metallation (D*o*M) reaction to obtain more complex compounds.[1] Ammonia, primary and secondary amines react readily with sulfonyl chlorides in high yields to furnish sulfonyl amides. In turn, there are many ways to prepare sulfonyl chlorides on an aromatic ring. Direct chlorosulfonation of a suitable electron rich phenyl ring with $ClSO_3H$[2] will afford the desired product. They can also be prepared from aromatic thioethers,[3] amines,[4] trialkyl tins[5] and halides,[6] with the later case being the method of choice. In this particular route, the halogen is first converted to the anion via a lithium–halogen exchange. This is usually done with a strong base such as *n*-butyllithium and the resulting phenyl anion treated with SO_2 to form a sulfinate. Finally, the sulfinate is oxidized with NCS or SO_2Cl_2 to yield the sulfonyl chloride. One major disadvantage of this approach obviously comes from the use of a strong base in the metal–halogen exchange reaction which precludes the presence of numerous sensitive functional groups in the starting material. This is one of the reasons why milder methods that can either use electron rich or electron poor substrates would be of great interest. We wish to describe herein our work in this field.



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We envisioned that trialkylsilyl thioethers such as **1**, which possess a weak silicon–sulfur bond, would be a group of choice to obtain sulfonyl chlorides in a simple manner. Typically, this would be equivalent to running a thiol oxidation. Compounds of type **1** can easily be prepared from an aromatic thiol and a trialkylsilyl halide[7] but this would be pointless since one can directly oxidize the thiol to the sulfonyl chloride. The thioether can also be prepared from a palladium catalyzed coupling reaction between potassium triisopropylsilanethiolate **2** and an aromatic halide (Z = Br, I)[8] or triflate.[9] This approach is much more interesting and broadens considerably the scope of the methodology. In addition, the conditions used for the coupling reaction are rather mild thus allowing the presence of functional groups.

We used 4-iodo anisole as a model substrate to study the feasibility of the oxidation on the trialkylsilyl mercaptide. Compound **3** (Z = *p*-OMe) was obtained as an oil in 85% isolated yield after filtration over a pad of silica gel. We then turned our attention in the selection of a method for the oxidation. Accordingly, we looked at the oxidation of **3** with the KNO_3/SO_2Cl_2 system.[10] To a solution of **3** in acetonitrile at 0°C was added 2.5 equiv. of KNO_3 followed by the dropwise addition of sulfuryl chloride. After stirring 20–40 min the reaction mixture was filtered and the solvent removed under vacuum. The crude material was diluted in THF at 0°C and an excess of diluted ammonia was added. From this, we obtained the desired sulfonamide **5** in 66% isolated yield for two steps. The conditions for the oxidation step were briefly investigated. For example,

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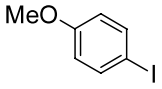
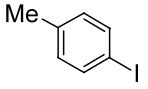
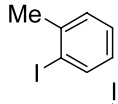
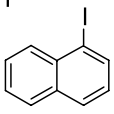
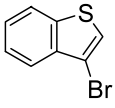
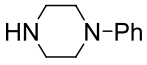
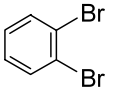
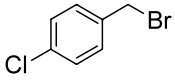
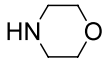
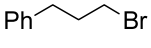
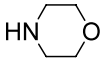
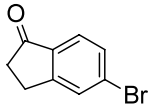
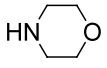
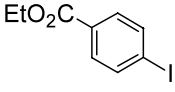
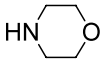
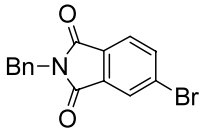
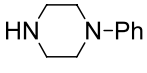
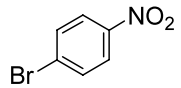
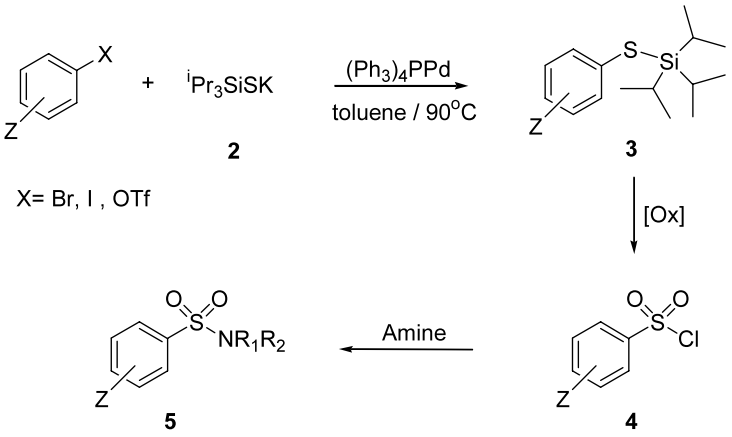
doi:10.1016/j.tetlet.2003.08.073

the addition of a tertiary amine to the reaction mixture or lowering the temperature to −78°C resulted only in a slight change in yield.[11] We also looked at other systems for the oxidation. For instance, a combination of bleach and $HCl_{conc.}$ on 3-triisopropylsilanylsulfanyl toluene also worked well. Having recognized the practicality of this methodology, we chose not to isolate the sulfonyl chloride but to carry on with the crude mixture up to the more stable sulfonamide. In only one instance, the sulfonyl chloride **4** (Z=*p*-OMe) has been isolated to make sure of the integrity of the compound. The sulfonyl chloride prepared in this manner was identical to a commercially available sample.

Table 1. Formation of triisopropylsilanylsulfanyls (**3**) and sulfonamides (**5**)[12]

Entry	Substrate	Yield of (3)[a]	Amine	Yield of (5)	Total yield
1-		85% (5h)	NH_4OH H_2NPr $HNEt_2$	66% 73% 73%	56%
2-		95%[b] (3h)	NH_4OH $HNEt_2$	75% 72%	71% 68%
3-		81% (16h)	NH_4OH	67%	54%
4-		97% (4h)	NH_4OH $HNEt_2$	61% 57%	59% 55%
5-		- (18h)		-	25%
6-		79% (14h)	$HNEt_2$	58%[c]	46%
7-		71% (5h)		13% 32%[d,e]	9% 23%
8-		86% (6h)		59%[d,f]	51%
9-		79% (4h)	NH_4OH 	61% 82%[d]	48% 65%
10-		- (5h)		-	53%
11-		81% (4.5h)		31%	25%
12-		- (1h)	$HNEt_2$	-	55%

[a] Time of reaction in parenthesis; [b] 5% $PdCl_2$dppf was used instead of $(Ph_3P)_4Pd$; [c] bis-sulfonamide; [d] Purified *via* trituration; [e] Run at -75° C; [f] Run at -20° C.



These results encouraged us to determine the scope and limitations of this new sequence. Therefore, a series of silylmercaptides were prepared with minor modifications from the original procedure. The palladium tetrakistriphenylphosphine coupling reaction with **2** was run in a 0.2 M solution of toluene at 90°C for the period of time indicated in Table 1. The adducts **3** were purified over a pad of silica gel and generally obtained in high yields and in good purity (>95%) for spectral characterization (^{1}H and ^{13}C NMR). In some cases, the purity was lower and the exact yield was not determined. This does not imply that the coupling reaction is problematic but rather indicates a more difficult purification. In those particular examples we carried out the sequence and calculated a global yield for the three steps (entries 5, 10, and 12).

Nonetheless, the coupling reaction with either electron-rich or electron-poor aryl halides proceeded rather nicely with yields ranging from 80 to 97% (see Table 1). Other palladium catalysts could be used as well. For example, $PdCl_2$dppf (entry 2) gave after 3 h of heating an excellent isolated yield (95%) of **3** (Z=*p*-Me). We also examined non-aromatic substrates. Those were prepared by S_N2 displacement of the thiolate **2** on 4-chlorobenzyl bromide (entry 7) and on 1-bromo-3-phenylpropane (entry 8) to yield the corresponding trialkylsilylmercaptide in 71 and 86%, respectively.

In the next step, the adducts were subjected to the oxidation conditions described earlier and the purification was done either on silica gel or by a trituration in hexane. Therefore, the sulfonamides are obtained in two steps (oxidation and treatment with amine) from **3** in good yield (57–82%). The phthalimide (entry 11) was an exception with only 31%. The benzylic substrate of entry 7 with an isolated yield of only 13% was also problematic. In this case, a side reaction took place and the major product was the corresponding benzyl chloride. We could increase the yield of sulfonamide to 32% by running the oxidation in proprionitrile instead of acetonitrile at −75°C.

Since we are forming a sulfonyl chloride, this implies that we are not restricted in preparing only RSO_2NH_2 like many other methods. To illustrate this, we have condensed the sulfonyl chloride with four different amines during the study. Diethyl amine, *n*-propyl amine, morpholine and *n*-phenyl piperazine were consider. Only the piperazine seemed to be less reactive toward the sulfonyl chloride in entries 5 and 11. They both gave an overall yield of 25%.

Finally, we have shown that aromatic sulfonamides with electron donating and electron withdrawing groups can be prepare in good yields from triisopropylsilanylsulfanyls **3**. Aliphatic substrates can also be used as well to prepare sulfonamides. Ketone, ester, nitro and phthalimide groups are compatible with our methodology. We also avoided the use of strong bases such as *n*-BuLi to prepare the Ar–Li.

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11. With diethyl amine, a 65% yield of sulfonamide was obtained when the oxidation was run at −78°C and 76% yield with the addition of Hünig's base.
12. Each compound was characterized by ^{1}H and ^{13}C NMR and either by elemental analysis or HRMS. Melting point was obtained on solid compounds. Once pure, the trialkylsilanylsulfanyls are reasonably air-stable and only have a slight odor if any. They are usually kept at 0°C for many weeks.