ORGANIC LETTERS

2004
Vol. 6, No. 6
921−923

# Reactivity of β-Lactamido *N*-Sulfonyl Radicals

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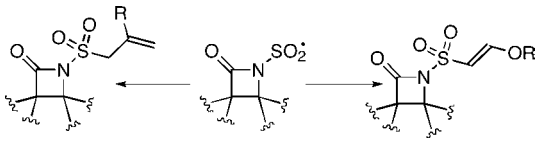
**Received December 5, 2003**

## ABSTRACT



**A new class of *N*-substituted radical has been studied. Obtained from the corresponding chlorides, β-lactamido *N*-sulfonyl radicals were allylated and added onto electron-rich olefins. It has been shown that the radicals do not undergo desulfonylation and are electrophilic in nature.**

After having been out of mainstream organic chemistry for the better part of the last century, synthetic radical chemistry has witnessed a tremendous blossoming since the early 1980s. Yet, even if the favorable features of radical chemistry are more widely recognized and are increasingly used to solve difficult synthetic problems, the quest for new tools and reactions available to the chemical community is far from over.[1]

Sulfur-centered radicals are prominent among the extended radical family.[2] In particular, sulfonyl radicals are especially valuable because they can undergo a reversible α-scission reaction, which releases or introduces sulfur dioxide.[3] This allows a versatility that has been used in very efficient and elegant processes. Formal acylation,[4] tin-free alkylation[5] or azidation,[6] and activation of C−H bonds can be achieved via extrusion of $SO_2$,[7] while sulfonylation of alkyl radicals plays an essential role in the copolymerization of olefins with sulfur dioxide.[8]

Contrary to sulfonyl radicals, the parent *N*-substituted sulfonyl radicals have attracted comparatively very little attention (Figure 1). Kharasch was the first to report their existence: when submitted to atom-transfer conditions (the Kharasch addition), *N*-chlorosulfonylphthalimides led to the β-chloro sulfonyl adducts in good yields.[9] Similarly, di-

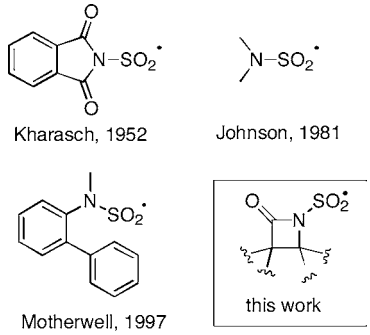



**Figure 1.** Reported N-substituted sulfonyl radicals.

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10.1021/ol0363725 CCC: $27.50 
**Published on Web 02/14/2004**

methylaminosulfonyl radicals were allylated with no sign of desulfonylated products.[10] More recently, Motherwell used the known elimination of $\beta$-sulfonyl radicals to prepare biarylic compounds. In this case, loss of $SO_2$ was observed.[11]

To the best of our knowledge, no amide-derived sulfonyl radicals were examined although desulfonylation would lead to nitrogen-centered amidyl radicals and establish a new way to prepare these important intermediates. Because our group has been involved in asymmetric radical synthesis involving sulfoxides[12] and in the chemistry of nitrogen-containing oxidized sulfur functions such as sulfoximines and sulfonimidates,[13] we decided to look more closely to this former field. As they are biologically highly relevant, we chose $\beta$-lactams as target amides.

We report herein the data we gathered along the way. To examine the scope of the reaction, we selected an array of four different precursors (Figure 2), which were prepared by [2 + 2] cycloaddition of the corresponding olefins with *N*-chlorosulfonylisocyanate.

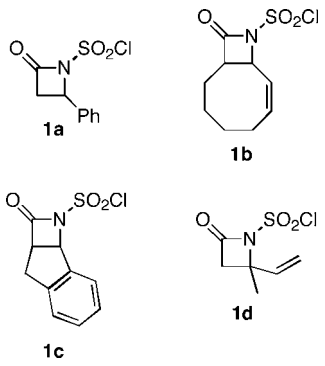
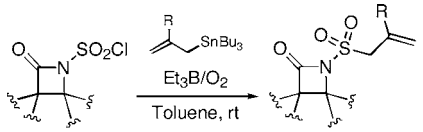



**Figure 2.** Radical precursors.

When submitted to standard radical conditions (tributyltin hydride, cat. AIBN in refluxing benzene), phenyl derivative **1a**[14] led to the corresponding desulfonylated amide. However, when the same reaction was carried out without AIBN, the same product was obtained. This shows that the chlorosulfonamide is reduced to the amide in a nonradical way. This is not a great surprise because tin hydride is a hydrido−metal compound and thus can be a reducing agent.[15] We decided to use allylstannanes instead. At high temperature, allylstannanes substitute the chlorine atom on sulfur, but this reaction is low yielding and barely reproducible. Lowering of the temperature totally shut off this ionic substitution. So we decided to drop AIBN and use the triethylborane/oxygen system to trigger the radical reaction at low temperature.[16] Except where indicated, room temperature proved to be the optimum temperature. We were able to isolate the allyl derivatives **2**−**4** in good yields. The results are presented in Table 1.

**Table 1.** Allylation of $\beta$-Lactamido *N*-Sulfonyl Chlorides




**2a-d**, R = H
**3a-d**, R = Me
**4a-c**, R = $CO_2$Me

| entry | precursor | R | product, yield (%) |
|---|---|---|---|
| 1 | **1a** | H[a] | **2a**, 73 |
| 2 | **1a** | Me | **3a**, 100 |
| 3 | **1a** | $CO_2$Me | **4a**, 40 |
| 4 | **1b** | H[a] | **2b**, 72 |
| 5 | **1b** | Me | **3b**, 99 |
| 6 | **1b** | $CO_2$Me | **4b**, 75 |
| 7 | **1c** | H[a] | **2c**, 92 |
| 8 | **1c** | Me | **3c**, 77 |
| 9 | **1c** | $CO_2$Me | **4c**, 44 |
| 10 | **1d**[c] | H[a] | **2d**, 36 |
| 11 | **1d**[c] | Me | **3d**, 32 |
| 12 | **1d**[c] | $CO_2$Me | —[b] |

[a] Allyltriphenylstannane was used. [b] Only degradation was observed. [c] The reaction was carried out at −78 °C.

We examined first the allylation with allyltributyltin, but the reaction was more efficient with the triphenyl derivative (entries 1, 4, and 7). Precursor **1d**[17] is extremely temperature sensitive. The reactions had to be carried out at low temperature but the yields remained low (entries 10 and 11). In this series, retro-[2 + 2] was very problematic. Use of the methyl substituted allyltin mediator[18] led to the corresponding products in very good yields (entries 2, 5, and 8), except in the case of **1d** (entry 11). To get data on the philicity of the *N*-substituted sulfonyl radicals, we checked their reaction with the carbomethoxy-substituted allyltin

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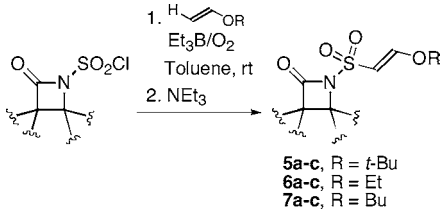
reagent. In those cases, the products were obtained in generally lower yields (entries 3, 6, and 9), and not at all with **1d** (entry 12). This shows that the radicals we are studying are electrophilic and thus react better with electron-rich olefins. However, allylstannanes being very reactive mediators, mismatched reagents still led to the desired final products.

The apparent electrophilicity of *N*-substituted sulfonyl radicals suggested that they could be used in atom transfer addition reactions, which are quite attractive transformations.[19] Moreover, in our case, the halogen was a chlorine atom. Relatively few chlorine—as opposed to bromine, iodine, or phenylseleno—transfer reactions have been reported, and this particular reaction remains a challenging task. The previous report by Kharasch featured *N*-sulfonylphthalimido derivatives.[9] Although our radicals were presumably less stabilized, we were confident that this reaction could be performed. The use of triethylborane instead of hexabutylditin would ensure no tin at all was used.

Reactions of precursors **1a**, **1b**,[20] and **1c**[21] with various enol ethers led to adducts which proved very difficult to isolate and purify. Precursor **1d** gave only decomposition. Atom transfer radical additions onto enol ethers are known to be difficult because of the inherent lack of stability of the products. One solution is to trap the chloroether adducts either by nucleophiles or by bases.[22] When we used this technique and treated the crude materials with triethylamine, we were able to isolate the vinylsufonamides **5**−**7** in acceptable to good yields (Table 2). The overall process is a radical vinylation of *N*-sulfonyl radicals, which is made possible by the sulfur-promoted activation of a C−H bond.

The products were reasonably stable for characterization purposes. However they are quite sensitive, especially on silica. Upon very careful control of the purification conditions, and by focusing on purification by precipitation in petroleum ether, the yields reached 70%. They dropped when the product did not precipitate, thus forcing us to purify by chromatography (entries 1 and 7). The nature of the substituent on oxygen seems to alter the stereochemical outcome of the reaction: switching from ethyl to *n*-butyl does not change the diastereoselectivity (compare entries 2−3, 5−6, and 8−9). But when *tert*-butyl vinyl ether was used, a considerable increase in the minor *Z*-isomer was observed (entry 4). Unfortunately, this could not be further confirmed, since both **5a** and **5c** did not precipitate in petroleum ether and had to be purified over silica. In those cases, only the *E*-isomers were isolated and the yields were modest (entries 1 and 7). It is likely that some selective degradation occurred. As expected, no reaction took place with acrylonitrile. This fits with an electrophilic character of the radical, which does not easily react with electron-poor olefins.

**Table 2.** Vinylation of $\beta$-Lactamido *N*-Sulfonyl Chlorides




| entry | precursor | R | product, yield (%) | *E*/*Z* ratio |
|---|---|---|---|---|
| 1 | **1a** | *t*-Bu | **5a**, 34[a] | 100:0 |
| 2 | **1a** | Et | **6a**, 52 | 94:6 |
| 3 | **1a** | Bu | **7a**, 68 | 92:8 |
| 4 | **1b** | *t*-Bu | **5b**, 70 | 69:31 |
| 5 | **1b** | Et | **6b**, 69 | 98:2 |
| 6 | **1b** | Bu | **7b**, 71 | 96:4 |
| 7 | **1c** | *t*-Bu | **5c**, 42[a] | 100:0 |
| 8 | **1c** | Et | **6c**, 69 | 98:2 |
| 9 | **1c** | Bu | **7c**, 70 | 93:7 |

[a] Product did not precipitate and was purified by flash column chromatography. Following this method, partial degradation occurred and the *Z* isomer was lost.

To conclude, we were able to prepare $\beta$-lactamido *N*-sulfonyl radicals. Upon using triethylborane as the radical initiator, those radicals could be allylated and showed an electrophilic nature. We thus could use them in atom transfer radical additions with electron-rich olefins. In this process, activation of C−H bonds is possible via a tin-free pathway. For this class of sulfonyl radicals, desulfonylation is a slow process. Work aiming at finding conditions to achieve this α-elimination, at establishing the exact scope and limitations of the reaction, at further functionalizing the isolated $\beta$-lactams (in particular to take advantage of the sulfonyl moiety to prepare nonclassical lactams) is in progress. It will be reported in due course. Furthermore, the modified 2-azetidinones and sulfonamides might have interesting antibiotic properties. This point is also currently being pursued.

**Acknowledgment.** We thank UPMC and CNRS for financial support.

**Supporting Information Available:** Detailed descriptions of experimental procedures and characterizations of compounds **2**−**7**. This material is available free of charge via the Internet at http://pubs.acs.org.

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