N-Acylsulfonamide Linker Activation by Pd-Catalyzed Allylation

Yi He,† Jesse P. Wilkins,‡ and Laura L. Kiessling*†‡

Departments of Chemistry and Biochemistry, University of Wisconsin—Madison, Madison, Wisconsin 53706

kiessling@chem.wisc.edu

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Abstract

N-Acylsulfonamide safety-catch linkers are versatile tools in solid-phase organic synthesis because of their stability. This stability necessitates linker activation prior to compound cleavage. Here, we demonstrate that the N-acylsulfonamide group can react with a π-allyl palladium complex and that these mild and neutral conditions can be exploited for linker activation. The advantages of this process are illustrated by its use in the efficient synthesis of thioesters. We anticipate that this activation method will extend the utility of the N-acylsulfonamide group.

A key component in solid-phase synthesis is the linker, which serves as the anchor between the product and the solid support.1 The utility of a linker depends on the range of conditions it can tolerate. One strategy to achieve high linker stability is to employ a “safety-catch” linker.2,3 With a safety-catch linker, the release of a compound from the support must be facilitated by linker activation.

Kenner and co-workers introduced the first safety-catch linker.2,4 Composed of an N-acylsulfonamide group, it is stable under either strongly basic or acidic conditions. This stability stems from the low pKa (ca. 2.5) of the N-acylsulfonamide moiety. Linker activation is accomplished via alkylation. When N-alkylated, the acylsulfonamide group becomes susceptible to nucleophilic attack; therefore, it can react to afford carboxylic acids and their derivatives, such as amides, esters, hydrazides, and thioesters.

The N-acylsulfonamide safety catch resin is especially valuable for the synthesis of peptide thioesters.5-7 These species are critical components in the assembly of natural and nonnatural proteins using native-chemical ligation,8 expressed protein ligation, and Staudinger ligation.9 Peptide thioesters have been synthesized from the methylated acylsulfonamide linker.5 To obtain high yields of the desired thioester products, sodium benzenethiolate is needed. The

1 Department of Chemistry.
2 Department of Biochemistry.


† Department of Chemistry.
‡ Department of Biochemistry.


2 For a review on the N-acylsulfonamide linker, see the following: Heidler, P.; Link, A. Bioorg. Med. Chem. 2005, 13, 585–599.
initial cleavage product is presumably a thiophenyl ester, which then undergoes transthiosterification to afford the target thioester. Although the addition of thiophenol improves yields, its inclusion in the cleavage reaction has drawbacks. It is difficult to remove from the thioester products, and its presence can result in mixed disulfide side products.

To avoid these drawbacks, the N-acylsulfonamide linker can be converted into a more activated species.6 Ellman and co-workers demonstrated that the cyanomethylated linker is more electrophilic.10 Accordingly, when cyanomethylation is used for linker activation, no thiophenol additive is required; the thioester is generated directly.4 The disadvantage of cyanomethylation is that the conditions are basic and side reactions can occur.4,11 Moreover, N-acylsulfonamide cyanomethylation typically proceeds in lower yield than methylation. Thus, there remains a need for alternative methods for N-acylsulfonamide linker activation.

We anticipated that mild and neutral activation conditions could be developed by exploiting the “softness” of the delocalized N-acylsulfonamide anion.12 We further postulated that a π-allyl Pd complex might serve as an appropriate electrophile.13–15 This metal-catalyzed functionalization reaction would allow N-acylsulfonamide activation under neutral conditions.

To test the feasibility of the proposed activation method, we first examined the propensity of tosylsulfonamide 1 to undergo Pd-catalyzed allylation. Sulfonamides have been shown to undergo Pd-catalyzed allylation reactions;16 the reactivity of acylsulfonamides, however, had not been explored. On the basis of their acidity and delocalization, we anticipated that they would be excellent substrates. Indeed, when 1 was treated with allyl ethyl carbonate in the presence of a catalytic amount of palladium tetrakistriphenylphosphine (Pd(PPh3)4), it underwent allylation in high yield (95%, Figure 1).

![Figure 1. Pd-catalyzed allylation of tosylsulfonamide 1 with allyl ethyl carbonate.](image)

The efficiency of the Pd-catalyzed allylation of tosylsulfonamide 1 prompted us to investigate its utility for activating N-acylsulfonamide linkers derived from arylsulfonamide 3 (Table 1). Arylsulfonamides tend to be better leaving groups than alkylsulfonamides, but their use is limited by difficulties in alkylating the acylsulfonamide products.10 Thus, we reasoned that derivatives of 3 would serve as challenging substrates for activation via allylation.

Table 1. Activation of the Arylsulfonamide Linker and Cleavage with n-Propylamine

<table>
<thead>
<tr>
<th>Activation conditions</th>
<th>4d: % yieldb</th>
<th>5d: % yieldb</th>
</tr>
</thead>
<tbody>
<tr>
<td>1% Pd(OAc)2b</td>
<td>13 (75)</td>
<td>11 (75)</td>
</tr>
<tr>
<td>5% Pd(OAc)2b</td>
<td>46 (84)</td>
<td>36 (80)</td>
</tr>
<tr>
<td>10% Pd(OAc)2b</td>
<td>54 (85)</td>
<td>40 (78)</td>
</tr>
<tr>
<td>20% Pd(OAc)2b</td>
<td>62 (80)</td>
<td>38 (78)</td>
</tr>
<tr>
<td>TMSCHN2e</td>
<td>90 (75)</td>
<td>78 (83)</td>
</tr>
<tr>
<td>ICH3CN</td>
<td>29 (74)</td>
<td>16 (79)</td>
</tr>
</tbody>
</table>

* Yields are crude and calculated using the experimentally determined amino acid loadings; the % purities are calculated from the LC traces. The triangle in compounds 4 and 5 denotes that the immobilized peptides are protected using the groups employed in standard Fmoc synthesis. R = allyl, 200 equiv of allyl ethyl carbonate, 50% PBS, THF; R = methyl, 300 equiv of TMSCHN2, THF; R = CH2CN, 300 equiv of ICH3CN, 60 equiv of DIPEA, NMP.

We tested whether the compounds 4 and 5 could be activated for cleavage using a Pd-catalyzed allylation reaction. We employed an alternative to the air-sensitive Pd(PPh3)4, the catalyst used in our test reaction. We reasoned that the combination of the more robust palladium(II) acetate
and triphenylphosphine would be more useful in solid-phase synthesis. The utility of the activation conditions was evaluated by treatment with excess \( n \)-propylamine; amines will cleave only the \( N \)-alkyl acylsulfonamide linker. For evaluation of the activation efficiency, we removed the peptide protecting groups and analyzed the products using liquid chromatography–mass spectrometry (LCMS) (Table 1).

From the allylated substrates 4a and 5a, crude peptides 4d and 5d were generated in high purities (> 75%, Table 1). These results indicate that the Pd-catalyzed allylation is efficient. From a comparison of the results obtained using different catalyst loadings, there is little influence on yield as long as \( \geq 5\% \) Pd(OAc)\(_2\) is employed. We conducted subsequent allylation experiments using 10% Pd(OAc)\(_2\) because these conditions afforded the products in good yields and with high purities. A comparison of our optimized activation conditions and cyanomethylation indicates that the yields from the former are superior.\(^{19}\) Given these results, our next goal was to determine whether this allylation could be used in thioester synthesis in the absence of any thiophenol additive.

To evaluate the allylation activation method in thioester synthesis, we compared the ability of ethyl 3-mercaptopro-