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Stereoselective Carbon-Carbon Bond Formation via Allylic N-Sulfonyliminium Ions

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Abstract: N-Tosyl-6-alkoxy-2,6-dihydro-1H-pyridin-3-ones 1 were found to react stereoselectively with various nucleophiles under the influence of BF₃·OEt₂ yielding 2,6-disubstituted dihydropyridinones.

The use of N-acyliminium ions in natural product synthesis has been thoroughly investigated in the last two decades. More recently, N-sulfonyliminium ions have also been applied in the synthesis of natural products such as anatoxin-a, sarain-a, dihydropinidine and swainsonine. In some cases the use of N-sulfonyliminium ions offers advantages over N-acyliminium ions in terms of reactivity, stability and crystallinity of starting materials and products. Here we wish to report stereoselective reactions of allylic N-sulfonyliminium ions derived from N-tosyl-6-alkoxy-2,6-dihydro-1H-pyridin-3-ones 1.

Although the oxidation and subsequent rearrangement of furfuryl alcohols was known for some time, the first report on this reaction sequence of furfurylamides was published by Ciufolini and Wood in 1986. Using the aza-Achmatowicz reaction they could synthesize 2-alkyl-6-alkoxy-piperidin-3-ones. It was shown to be possible to obtain stable dihydropyridinones using N-furfurylsulfonamides in the Lefebvre oxidation. The synthesis of 1 is a modification of this method (Scheme 1).

Heating tosylamide and furfural with Si(OEt)₄ at 160 °C for 6 h while distilling off ethanol yielded imine 2 in 83% after trituration. Reaction of 2 with n-butyllithium in THF at -20 °C gave N-furfurylsulfonamide 3a in 80% yield. Oxidative rearrangement of 3 by treatment with 2 equiv of pure mCPBA in CH₂Cl₂ for 2 h at room temperature yielded 2-butyl-6-hydroxy-2,6-dihydro-1H-pyridin-3-one 4a as a single diastereomer. In our hands 4a was rather unstable and was therefore reacted directly with ethanol or isopropanol containing a catalytic amount of sulfuric acid to give the ethoxy and isopropanoxy derivatives 1a and 1b in 83% and 82% yield, respectively, after flash chromatography and recrystallization. Alternatively, imine 2 was reduced with NaBH₄ in isopropanol to sulfonamide 3b, which was transformed into dihydropyridinone 1c by oxidative rearrangement and isopropanolysis in 54% overall yield. The corresponding ethoxy derivative and alcohol 4b were quite sensitive and could be isolated in low yields only.

Scheme 1. Synthesis of 6-alkoxy-2,6-dihydropyridin-3-ones.
Compound 1a reacted under the influence of BF₃·OEt₂ in high to nearly quantitative yields with various allylic silanes at C6 (Table 1). Only one diastereoisomer with respect to C2 and C6 was obtained in all cases. The cyclopentenyl substituted product 5b was formed with a high preference for one diastereoisomer (9:1, entry 2), while the cyclohexenyl dihydropyridinone 5c was formed as one diastereoisomer exclusively (entry 3). From the reaction of 1a with propargyltrimethylsilane, the allenyl substituted product 5d was obtained in excellent yield (entry 4). The reaction of 1b with allyltrimethylsilane shows that 1b is equally suitable for N-sulfonyliminium reactions as 1a, although 1b can be stored without decomposition for a longer period of time than 1a. The monosubstituted dihydropyridinone 1c also reacted readily with allyltrimethylsilane (entry 6).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Nucleophile</th>
<th>Product (Yield)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>la</td>
<td><img src="image1" alt="Structure of 5a" /> (99%)</td>
</tr>
<tr>
<td>2</td>
<td>la</td>
<td><img src="image2" alt="Structure of 5b" /> (82%)</td>
</tr>
<tr>
<td>3</td>
<td>la</td>
<td><img src="image3" alt="Structure of 5c" /> (79%)</td>
</tr>
<tr>
<td>4</td>
<td>la</td>
<td><img src="image4" alt="Structure of 5d" /> (98%)</td>
</tr>
<tr>
<td>5</td>
<td>lb</td>
<td><img src="image1" alt="Structure of 5a" /> (98%)</td>
</tr>
<tr>
<td>6</td>
<td>lc</td>
<td><img src="image5" alt="Structure of 5e" /> (86%)</td>
</tr>
</tbody>
</table>

*Reagents and conditions: allylic silane (2 equiv), BF₃·OEt₂ (2 equiv), CH₂Cl₂, 0 °C → rt. b) After column chromatography.*

Attempts to determine the stereochemistry of 5a-5d by ¹H-NMR and NOE measurements were unsuccessful. Fortunately, 5e gave crystals which were suitable for an X-ray crystal structure determination. The X-ray analysis (Figure 1) showed the cis-stereochemistry with respect to the substituents on C2 and C6, the relative configuration of the whole molecule being (2R*,6S*,1'R*). All spectral data being comparable, we assume all products 5a-5d to be 2,6-cis-disubstituted.

![Chem 3D™ view of 5e](image6)
To examine its synthetic utility further, 1a was reacted with enol acetates and silyl enol ethers. These reactions yielded the expected carbonyl compounds in good yields (Table 2, entries 1-4). In the case of silyl enol ethers, TMS triflate was used as the Lewis acid as BF₃·OEt₂ led to decomposition of the nucleophile (entries 4 and 5). Again, only 2,6-cis-disubstituted products were obtained. An interesting result was obtained from the coupling with a \( \beta \)-ketoester (entry 5). The expected product was shown to be present in the crude reaction mixture, but after column chromatography the cyclised product 7 was isolated in 58% yield.¹⁵

Table 2. Reactions of 1a with Enolate Equivalents.

<table>
<thead>
<tr>
<th>entry</th>
<th>nucleophile</th>
<th>conditions¹</th>
<th>product (yield)²</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>OAc</td>
<td>A</td>
<td>6a (78%)</td>
</tr>
<tr>
<td>2</td>
<td>Ph</td>
<td>A</td>
<td>6b (60%)</td>
</tr>
<tr>
<td>3</td>
<td>H</td>
<td>A</td>
<td>6c</td>
</tr>
<tr>
<td>4</td>
<td>OTMS</td>
<td>B</td>
<td>6a (79%)</td>
</tr>
<tr>
<td>5</td>
<td>MeO</td>
<td>B</td>
<td>7 (58%)</td>
</tr>
</tbody>
</table>

¹) Reagents and conditions: A: enol acetate (2 equiv), BF₃·OEt₂ (2 equiv), CH₂Cl₂, 0 °C→rt; B: silyl enol ether (2 equiv), TMSOTf (2 x 2 equiv), CH₂Cl₂, -20 °C→rt, 2 h. ²) After column chromatography.

The preference for the formation of 2,6-cis-disubstituted products is seen in similar systems lacking the double bond.⁵,¹⁶ These observations can be explained by the \( A^{(1,3)} \) strain¹⁷ present between the tosyl and the butyl group, forcing the latter to adopt a pseudo-axial orientation and causing the tosyl group to shield the opposite face of the molecule. The crystal structure of 5c gives an idea how the tosyl group bends over the molecule.¹⁸ The steric bulk of the tosyl group directs the attack of the nucleophile on the intermediate N-sulfonyliminium ion to the side of the butyl group, resulting in the formation of the cis-products. For this reason we believe the products of alcoholysis 1a and 1b to be cis-substituted as well, contrary to Zhou et al., who report the formation of trans ethoxy derivatives from 4 and (EtO)₃CH under the influence of BF₃·OEt₂.⁵,⁶ Unfortunately, there is no easy way of determining the stereochemistry in 2,6-dihydropyridin-3-ones, because \( J_{5,6} \) is 4.1-4.7 Hz both in cis and trans products and the NOE between H2 and H6 was not observed owing to the conformation of the cis compounds. However, a comparison of the NMR data published by Zhou⁵,⁶,¹⁰ and our own suggests that H4 can be used as a probe. In cis products, the chemical shift of H4 in CDCl₃ is 5.65-5.72, whereas in trans products it ranges from 5.84-5.92. However, there are some borderline cases as well.

The high diastereoselectivity in the formation of 5b and 5c can be explained by assuming that the attack of the allylsilane will proceed via the preferred conformation for this type of S₂' reaction,¹⁹ i.e. with the TMS group in axial position. The transition state for the reaction of the Re face of the iminium ion and the Si face of the allylsilane (\( \sigma \) transition state) would lead to the observed product 5c. The \( \pi \)-transition state suffers from severe steric interactions (Figure 2). Therefore, the major diastereomer of 5b is likely to be the \( \sigma \)-product and the minor the \( \pi \)-product.
In conclusion, we have shown that 6-alkoxy-2,6-dihydro-1H-pyridin-3-ones are excellent precursors of allylic N-sulfonyliminium ions, which react with various nucleophiles to give 2,6-cis-disubstituted products. The stereochemistry was proven by X-ray analysis and is believed to arise from A(1,3) strain between the N-tosyl and the 2-butyl group. The compounds described herein should be available in enantiopure form by starting from the enantiopure dihydropyridinones, which is available via a modified Sharpless kinetic resolution of N-furfuryl sulfonamides.

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We thank J. Fraanje and K. Goubitz of the AIMS’ Laboratory of Crystallography for the X-ray structure determination. This study was supported by the Netherlands’ Foundation for Chemical Research (SON) with financial aid from the Netherlands’ Organisation for the Advancement of Pure Research (NWO).

References and Notes
1. ERASMUS-exchange student from the University of Santiago de Compostela, January-June 1995.
(b) Åhman, J.; Somfai, P. Tetrahedron 1992, 48, 9537-9544.
12. In the oxidative rearrangement of furfuryl alcohols mixtures of diastereomers are usually obtained: see e.g. ref. 8b; Martin, S. F.; Guinn, D. E. J. Org. Chem. 1987, 52, 5588-5593.
13. Spectral data for 5a: IR (CHCl3): 3010, 2920, 2860, 1680, 1590, 1355, 1165 cm⁻¹; 1H-NMR (CDCl3): δ 0.91 (t, 3 H, J = 7.3), 1.25-1.74 (m, 6 H), 2.37 (s, 3 H), 2.48 (m, 1 H), 2.78 (m, 1 H), 4.36 (dd, 1 H, J = 6.1, 9.3), 4.52 (m, 1 H), 5.19 (dd, 1 H, J = 17.0, 1.3), 5.21 (dd, 1 H, J = 8.4, 1.0), 5.73 (dd, 1 H, J = 10.6, 2.0), 5.95 (m, 1 H), 6.71 (dd, 1 H, J = 4.3, 10.6), 7.22 (d, 2 H, J = 8.1), 7.57 (d, 2 H, J = 8.1); 13C-NMR (CDCl3): 8 13.8, 21.4, 22.1, 27.7, 34.5, 41.1, 53.8, 61.7, 116.8, 125.0, 126.8, 129.8, 133.4, 136.3, 143.7, 146.6, 194.3.
14. Compound 5c is orthorhombic, space group Pcab, a = 13.250(1) Å, b = 15.5228(8) Å, c = 20.647(1) Å, Z = 8, R = 0.076, Rw = 0.071. Data deposited at the Cambridge Crystallographic Data Centre.
15. With BF₃·OEt₂ as the Lewis acid a small amount of the 2,5/6-trans-trisubstituted product was formed (combined yield 63%, diastereomeric ratio 1:6).

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