Pergamon

Tetrahedron Letters, Vol. 36, No. 24, pp. 4315-4318, 1995
Elsevier Science Ltd
Printed in Great Britain
0040-4039/95 $9.50+0.00

0040-4039(95)00748-2

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

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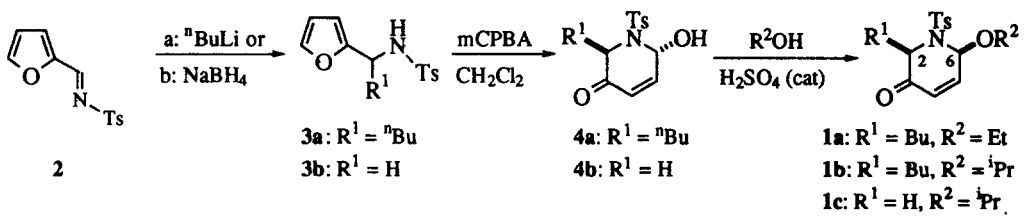
Abstract: *N*-Tosyl-6-alkoxy-2,6-dihydro-1*H*-pyridin-3-ones **1** were found to react stereoselectively with various nucleophiles under the influence of $BF_3{\cdot}OEt_2$ yielding 2,6-*cis*-disubstituted dihydropyridinones.

The use of *N*-acyliminium ions in natural product synthesis has been thoroughly investigated in the last two decades.[2] More recently, *N*-sulfonyliminium ions have also been applied in the synthesis of natural products such as anatoxin-a,[3] sarain-a,[4] dihydropinidine[5] and swainsonine.[6] 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.[7] Here we wish to report stereoselective reactions of allylic *N*-sulfonyliminium ions derived from *N*-tosyl-6-alkoxy-2,6-dihydro-1*H*-pyridin-3-ones **1**.

Although the oxidation and subsequent rearrangement of furfuryl alcohols was known for some time,[8] the first report on this reaction sequence of furfurylamides was published by Ciufolini and Wood in 1986.[9] Using the *aza*-Achmatowicz reaction they could synthesize 2-alkyl-6-alkoxypiperidin-3-ones. It was shown to be possible to obtain stable dihydropyridinones **4** using *N*-furfurylsulfonamides **3** in the Lefebvre oxidation.[10] The synthesis of **1** is a modification of this method (Scheme 1).

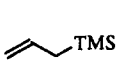
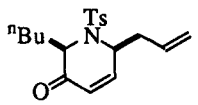
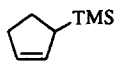
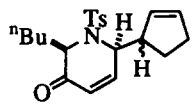
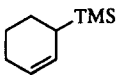
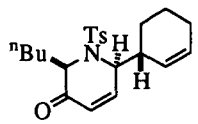
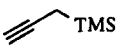
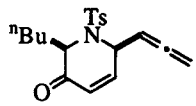
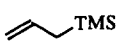
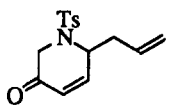


Scheme 1. Synthesis of 6-alkoxy-2,6-dihydropyridin-3-ones.

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.[11] 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 CH_2Cl_2 for 2 h at room temperature yielded 2-butyl-6-hydroxy-2,6-dihydro-1*H*-pyridin-3-one **4a** as a single diastereomer.[12] 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 isopropoxy derivatives **1a** and **1b** in 83% and 82% yield, respectively, after flash chromatography and recrystallization. Alternatively, imine **2** was reduced with $NaBH_4$ 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.

Compound **1a** reacted under the influence of $BF_3{\cdot}OEt_2$ in high to nearly quantitative yields with various allylic silanes at C6 (Table 1).[13] 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 1. Reactions of **1** with Allylic Silanes.

entry	s.m.	nucleophile[a]	product (yield)[b]
1	**1a**		 **5a** (99%)
2	**1a**		 **5b** (82%)
3	**1a**		 **5c** (79%)
4	**1a**		 **5d** (98%)
5	**1b**		**5a** (98%)
6	**1c**		 **5e** (86%)

a) *Reagents and conditions*: allylic silane (2 equiv), $BF_3{\cdot}OEt_2$ (2 equiv), CH_2Cl_2, 0 °C→rt. b) After column chromatography.

Attempts to determine the stereochemistry of **5a-5d** by ^{1}H-NMR and NOE measurements were unsuccessful. Fortunately, **5c** gave crystals which were suitable for an X-ray crystal structure determination.[14] 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.

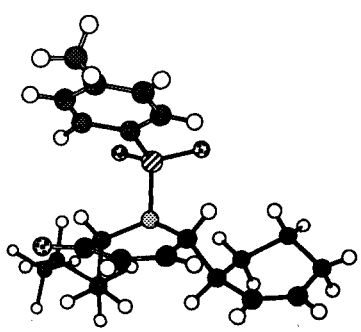
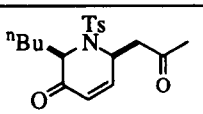
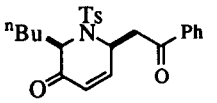
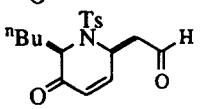
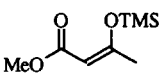
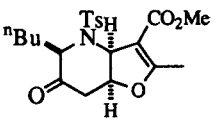


Figure 1. Chem 3D™ view of **5c**.

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 $BF_3{\cdot}OEt_2$ 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 β-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.

entry	nucleophile	conditions[a]	product (yield)[b]
1		A	 **6a** (78%)
2		A	 **6b** (60%)
3		A	 **6c**[c]
4		B	**6a** (79%)
5		B	 **7** (58%)

a) *Reagents and conditions:* A: enol acetate (2 equiv), $BF_3{\cdot}OEt_2$ (2 equiv), CH_2Cl_2, 0 °C→rt; B: silyl enol ether (2 equiv), TMSOTf (2 x 2 equiv), CH_2Cl_2, -20 °C→rt, 2 h. b) After column chromatography. c) The aldehyde was too unstable to be isolated; crude *ca.* 80%.

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 $A^{(1,3)}$ strain[17] 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 $BF_3{\cdot}OEt_2$.[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 Zhou[5,6,10] and our own suggests that H4 can be used as a probe. In *cis* products, the chemical shift of H4 in $CDCl_3$ 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 S_E2' 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 (*ul* transition state) would lead to the observed product **5c**. The *lk*-transition state suffers from severe steric interactions (Figure 2). Therefore, the major diastereomer of **5b** is likely to be the *u*-product and the minor the *l*-product.

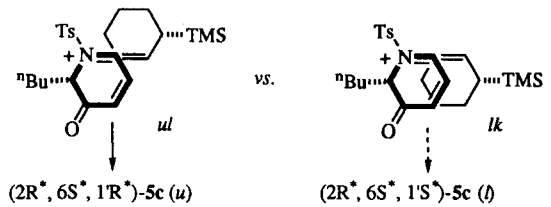


Figure 2. The preferred formation of **5c** from the *ul* transition state.

In conclusion, we have shown that 6-alkoxy-2,6-dihydro-1*H*-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 **3**.[10]

Acknowledgements:
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).

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13. Spectral data for **5a**: IR ($CHCl_3$): 3010, 2920, 2860, 1680, 1590, 1355, 1165 cm^{-1}; ^{1}H-NMR ($CDCl_3$): 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), 5.93 (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); ^{13}C-NMR ($CDCl_3$): δ 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, R_w = 0.071. Data deposited at the Cambridge Cystallographic Data Centre.
15. With BF_3·OEt_2 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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(*Received in UK* 15 *March* 1995; *revised* 19 *April* 1995; *accepted* 21 *April* 1995)