Tetrahedron Letters, Vol. 33, No. 23, pp. 3289-3292, 1992
Printed in Great Britain

0040-4039/92 $5.00 + .00
Pergamon Press Ltd

# β-Lactams from 5,5-Difluoroisoxazolidines

**Suzanne T. Purrington* and Kuen-Wanq Sheu**

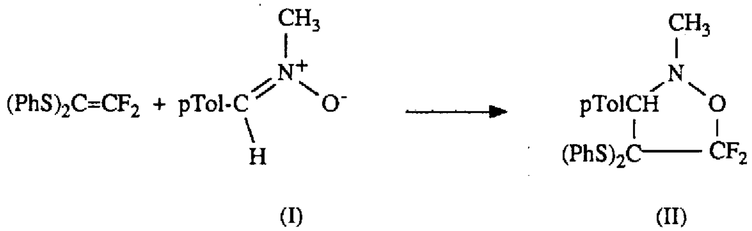
Department of Chemistry
North Carolina State University
Raleigh, NC 27695-8204

*Keywords: 1,1-difluoroolefins; nitrones; [3+2]cycloaddition; 5,5-difluoroisoxazolidines, β-lactams*

***Abstract:*** *1,3-Dipolar cycloaddition of nitrones with 1,1-difluoroolefins gives rise to fluorinated isoxazolidines in 85% yield; subsequent Raney nickel reduction of the cycloadducts produces β-lactams.*

β-Lactams have been important synthetic target molecules particularly because of their presence in the penicillin family of antibiotics. The four-membered ring in these compounds is strained, hard to form and also susceptible to either acidic or basic hydrolysis. A number of syntheses of β-lactams have been devised.[1] Although ring-expansion reactions, ring-contraction reactions and the oxidation of azetidines have been used to prepare these compounds, the major routes are cycloaddition and ring closure reactions. The cycloaddition reaction used is necessarily a [2+2] cycloaddition since the desired product is a four-membered ring. We have devised a novel synthesis for the formation of β-lactams. It is a two-step process involving a [3+2] cycloaddition reaction of a nitrone and a fluoroolefin followed by a ring-contracting reduction reaction. β-Lactams, such as thienamycin, have been prepared by [3+2] cycloaddition of a nitrone and an acrylate. Hydrogenolysis followed by a condensation gives rise to the desired azetidinone.[2]

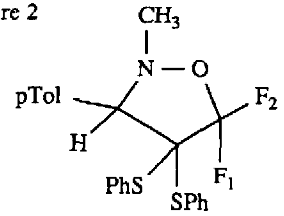
In this letter we report the formation of two 5,5-difluoroisoxazolidines by nitrone cycloaddition with 1,1-difluoroolefins and the β-lactams derived from their Raney nickel reduction. While investigating means for introducing fluorine into organic compounds, we looked at the addition of nitrone I to $(PhS)_2C{=}CF_2$[3] which formed heterocycle II in 85% yield as shown in equation 1. The NMR



(1)

spectrum of II is quite interesting. In the $^1H$ NMR a doublet is observed at $\delta = 4.42$ ppm which is indicative of long range coupling to one of the fluorines. In THF, the $^{19}F$ NMR spectrum of II, a pair of doublets between -65 and -76 ppm with $J = 141$ Hz was observed. The chemical shift difference between the fluorine signals was dramatically solvent dependent. When the solvent polarity was increased, as measured by its dielectric constant, the chemical shift difference also increased as shown in Table I. This effect is presumably due to an anomeric effect on the fluorine anti to the lone pair of electrons on the adjacent oxygen, as shown in Figure 2.

Figure 2



II

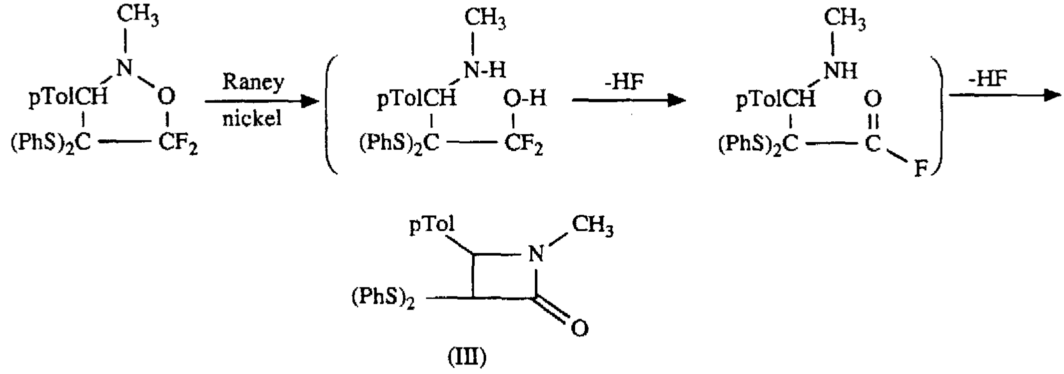
Table 1: $^{19}F$ NMR Chemical Shift Data for (II)

| Solvent | $F_1$ ppm | $F_2$ ppm | $\Delta F_1$-$F_2$ ppm | Dielectric Constant, $\varepsilon$ |
|---|---|---|---|---|
| Hexane | -67.2 | -74.4 | 7.2 | 1.9 |
| Benzene | -65.3 | -74.3 | 9.0 | 2.3 |
| Chloroform | -65.6 | -75.5 | 9.9 | 4.8 |
| THF | -65.5 | -76.2 | 10.7 | 7.6 |
| DMF | -63.7 | -76.2 | 12.5 | 36.7 |
| DMSO | -62.5 | -75.8 | 13.3 | 46.7 |

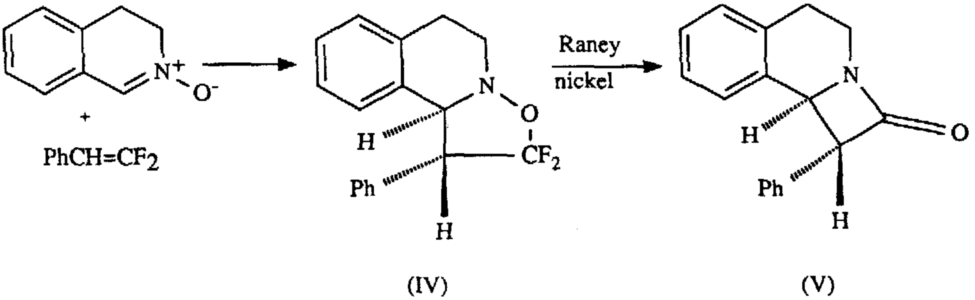
In the course of determining the structure of the isoxazolidine, a Raney nickel reduction of II was undertaken and the resulting product was found to be the ring contracted β-lactam III. The presumed course of the cleavage reaction is shown in Scheme 1. It should be noted that the carbon-sulfur bond is not cleaved by the Raney nickel.

Another example of this new β-lactam synthesis begins with the cycloaddition of 3,4-dihydroisoquinoline N-oxide with β,β-difluorostyrene is diastereoselective, as shown in equation 2. The 5,5-difluoroisoxazolidine IV is formed in 64% yield. Reduction with Raney nickel in acetone gives the corresponding β-lactam V in 46% yield. It should be noted that during the reduction the relationship of the protons in the lactam ring is retained.

Scheme 1



This is the first report of the participation of 1,1-difluoroolefins in a [3+2] cycloaddition reaction with nitrones. The interesting 5,5-difluoroisoxazolidines that result are readily reduced and provide a new route to β-lactams. We are currently probing this sequence in more detail.



(2)

**Experimental.** The $^1H$ and $^{13}C$ NMR spectra were obtained on a GE GN-300 NMR spectrometer operating at 300.52 MHz for $^1H$ and 75.57 MHz for $^{13}C$. Spectra were obtained in $CDCl_3$ with chemical shifts reported in ppm relative to internal TMS. $^{19}F$ NMR spectra were obtained on a Bruker AR-100 spectrometer operating at 95.52 MHz for $^{19}F$. Spectra were obtained in $CDCl_3$ with chemical shifts reported in ppm relative to external $CFCl_3$. Negative chemical shifts indicate that the resonances are upfield relative to $CFCl_3$.

Synthesis of II: $CF_2=C(SPh)_2$[3] (1.10 g, 3.93 mmol) and α-tolyl-N-methylnitrone(I) (0.44 g, 2.95 mmol) were refluxed in THF overnight. The product was purified by column chromatography on silica gel. mp: 75-77°C. $^1H$-NMR (300 MHz, $CDCl_3$): δ 2.35 (s, 3 H), 2.59 (s, 3 H), 4.42 (d, 1 H, J = 2.2 Hz), 7.13-7.67 (m, 14 H). $^{13}C$-NMR (300 MHz, $CDCl_3$): δ 21.22, 43.96, 74.47 (dd, J = 21.92, 31.74 Hz), 80.08, 126.87 (dd, J = 261.6, 275.9 Hz), 128.26, 128.81, 128.97, 129.39, 129.52, 129.71, 129.84, 130.20, 136.17, 136.92, 139.24. $^{19}F$-NMR (100 MHz, THF): δ -65.55 (d, J = 141 Hz), -76.2 (d, J = 141 Hz). Anal. Calcd. for $C_{23}H_{21}F_2NOS_2$: C, 64.31; H, 4.93. Found: C, 64.37; H, 4.97.

Synthesis of III: An aqueous Raney-Nickel solution (2.22 g, Aldrich) was refluxed in acetone (20 mL) under $N_2$ for 2 h, then II (0.42 g, 0.98 mmol) was added. After refluxing for 9 hr, the solution was filtered through celite, extracted with $CH_2Cl_2$ and chromatographed. The product was recrystallized from hexanes and ethyl acetate. The yield was 40-50%. mp: 91-92°C. $^1$H-NMR (300 MHz, $CDCl_3$): δ 2.36 (s, 3 H), 2.69 (s, 3 H), 4.65 (s, 1 H), 6.97-7.65 (m, 14 H). $^{13}$C-NMR (300 MHz, $CDCl_3$): δ 21.24, 27.05, 68.54, 73.32, 128.11, 128.18, 128.34, 128.92, 129.02, 129.24, 129.73, 130.18, 130.92, 134.57, 135.51, 139.00, 166.33. IR (Nujol): υ = 1743 cm$^{-1}$. Anal. Calcd. for $C_{23}H_{21}NOS_2$: C, 70.54; H, 5.41; N, 3.58; S, 16.38. Found: C, 70.65; H, 5.42; N, 3.62; S, 16.44.

Synthesis of IV: 3,4-Dihydroisoquinoline N-oxide (2.00 g, 13.6 mmol) and $CF_2$=CHPh (1.00 g, 7.14 mmol) were refluxed under $N_2$ in dry THF (15 mL) for 3 h and IV was purified by chromatography. 64% yield. mp: 150-152°C. $^1$H-NMR (300 MHz, $CDCl_3$): δ 2.81-2.97 (m, 1 H), 3.06-3.16 (m, 1H), 3.49-3.67 (m, 2 H), 4.06 (q, 1H, J = 10.99 Hz), 5.13 (d, 1H, J = 11.00 Hz), 6.34-7.45 (m, 9 H). $^{13}$C-NMR (300 MHz, $CDCl_3$): 28.25, 49.99, 59.71 (dd, J = 22.67, 31.74 Hz), 68.40 (d, J = 5 Hz) 126.27, 126.40, 127.60, 128.40, 128.57, 128.73, 128.86, 129.08, 129.95, 132.38, 132.44, 132.67, 135.77. The weak doublet of doublets expected for the fluorine containing carbon are buried under the other peaks; only the peak at 135.77 is visible. $^{19}$F-NMR (100 MHz, THF): δ -65.0 (dd, $J_{FF}$ = 143, $J_{HF}$ = 11 Hz), -72.6 (dd, $J_{FF}$ = 144, $J_{HF}$ = 10 Hz) Calcd. for $C_{17}H_{15}F_2NO$ ($M^+$) m/z 287.1122, found 287.1120.

Synthesis of V: An aqueous Raney-Nickel solution (3.00 g, Aldrich) in acetone (15 mL) was refluxed under $N_2$ for 2 h and IV (0.51 g, 1.74 mmol) was added. After refluxing overnight, the solution was filtered through celite, extracted with $CH_2Cl_2$ and chromatographed. 46% yield. mp 107-109°C. $^1$H-NMR (300 MHz, $CDCl_3$) δ 2.72-2.82 (m, 1 H), 3.08-3.23 (m, 2 H), 3.98-4.07 (m, 1 H), 4.18 (d, 1 H, J = 2.2 Hz), 4.55 (s, 1 H), 7.16-7.44 (m, 9 H) $^{13}$C-NMR (300 MHz, $CDCl_3$: 28.12 37.62, 56.87, 63.66, 126.01, 126.92, 127.34, 127.40, 127.60, 128.89, 129.47, 133.73, 134.99, 135.12, 169.21. IR (Nujol): υ = 1725 cm$^{-1}$. Calcd for $C_{17}H_{15}NO$ ($M^+$) m/z 249.1154, found 249.1154.

**Acknowledgment.** Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this research. Mass spectra were obtained at the Mass Spectrometry Laboratory for Biotechnology Research at North Carolina State University, established by a grant from the North Carolina Biotechnology Center.

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(Received in USA 11 February 1992)