ORGANIC LETTERS

2001
Vol. 3, No. 15
2301−2303

N-Methylated 5-Alkenyloxazolium Salt Transformations

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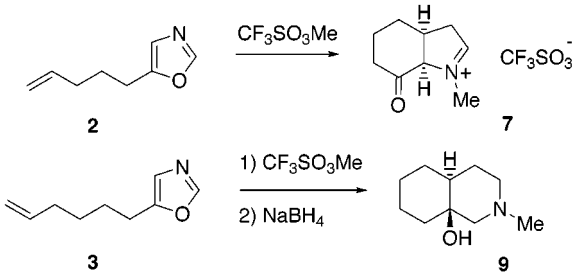
Received May 9, 2001

ABSTRACT



In the course of natural product synthetic studies, 5-(4-pentenyl)oxazole and 5-(5-hexenyl)oxazole were *N*-methylated. The initial *N*-methylated 5-alkenyloxazolium salt adducts were found to be only intermediates and were ultimately transformed into hydroindole and hydroisoquinoline compounds, respectively.

We had need of *N*-methylated 5-alkenyloxazolium salts during a study of methods for alkaloid synthesis. In the preparation of these compounds, unexpectedly facile cycloaddition chemistry was observed, leading to compounds from which hydroindole and hydroisoquinoline derivatives were ultimately obtained.

The required starting 5-substituted oxazoles **1**−**5** were synthesized in 40−87% yields from methyl esters [e.g., **1** from methyl 4-pentenoate] upon reaction with 1 equiv [2 equiv for the preparation of oxazole **4**] of lithiated methyl isocyanide using the method of Schöllkopf and Schröder.[1] [Oxazole **6** was obtained in 70% yield from **5** after acid hydrolysis and reaction with (carbomethoxymethylene)-triphenylphosphorane] (Figure 1.) *N*-Methylation of oxazoles **1**−**4** and **6** could be achieved quantitatively upon reaction

1 R = -$CH_2CH_2CH{=}CH_2$
2 R = -$CH_2CH_2CH_2CH{=}CH_2$
3 R = -$CH_2CH_2CH_2CH_2CH{=}CH_2$
4 R = -$CH_2CH_2CH_2CH{\equiv}CH$
5 R = -$CH_2CH_2CH_2CH(OMe)_2$
6 R = -$CH_2CH_2CH_2CH{=}CHCO_2Me$ (trans)

Figure 1. Synthesized 5-substituted oxazoles.

with an equivalent of methyl triflate at room temperature in dry $CHCl_3$ for 5 min. Whereas the *N*-methylated oxazolium triflates of **1**, **4**, and **6** were stable at room temperature (as well as at 90 °C after 3 h), those of oxazoles **2** and **3** underwent further transformation.[2]

Examination of the ^1H NMR spectrum of the room-temperature $CDCl_3$ solution of oxazole **2** 10 min after

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(1) Schöllkopf, U.; Schröder, R. *Angew. Chem., Int. Ed. Engl.* **1971**, *10*, 333.

10.1021/ol016088i CCC: $20.00
Published on Web 06/21/2001

treatment with methyl triflate confirmed that *N*-methylation had occurred.[3] After a 36 h reaction period, a white, crystalline product **7** (mp 94−95 °C) was obtained in 60% yield (based on a 1:1 oxazole−methyl triflate adduct) (Figures 2 and 3).

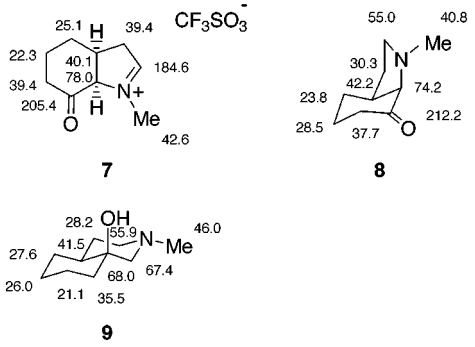

Figure 2. Structures and ^{13}C NMR assignments of **7**−**9**.

Spectral data and an X-ray diffraction study identified the product derived from **2** as (±)-1-methyl-7(6*H*)-oxo-*cis*-hexahydroindoleninium triflate (**7**). The IR spectrum revealed strong absorptions at 1715 and 1665 cm^{-1}, and the ^{1}H NMR spectrum (CD_3CN) included peaks at δ 8.65 (s, N=CH), 5.01 (d, J = 9.7, COCHN), and 3.71 (s, N-CH_3). The ^{13}C NMR spectra[4] (chemical shifts are recorded on the structural representations) of **7** and its product **8** from hydrogenation over 10% Pd on charcoal (70% yield) were in accord with the assigned stereochemistry. Carbon shifts for C-4 (δ 23.8) and C-6 (δ 37.7) of **8** are shielded strongly when compared with those of sterically unencumbered cyclohexanones,[5] implying a γ-effect of an axially disposed pyrrolidine nitrogen atom on these centers and thereby restricting the compound to a *cis*-configuration.[6] The constitution of **7** was verified by X-ray crystallography,[7] but the precision of the analysis is low due to the paucity of diffraction data as a consequence of the somewhat disordered nature of the triflate anion which represents the major fraction of the scattering matter. A view of the asymmetric crystal unit is provided in Figure 3. The cation has the conformation expected for such a strained *cis*-fused ring system.[8] Thus, the five-membered ring has an envelope form with C-3a as the out-of-plane atom, and the cyclohexanone ring is in a flattened chair conformation.

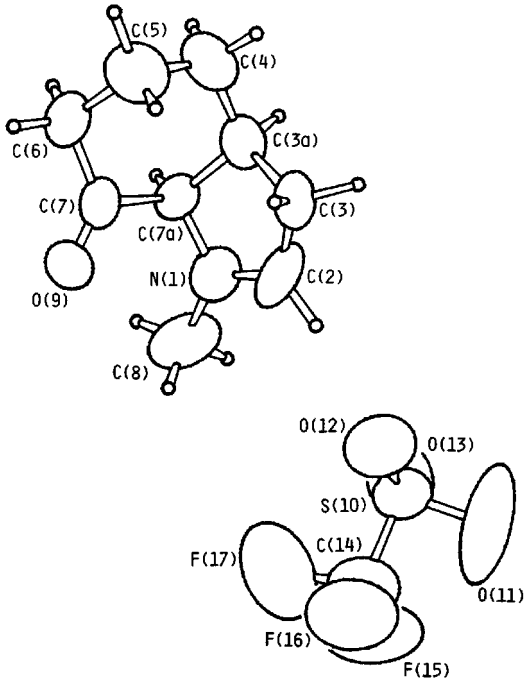

Figure 3. X-ray structure of **7**.

Treatment of oxazole **3** with an equivalent of methyl triflate gave its *N*-methyloxazolium salt, which also underwent further transformation at room temperature. Evidence for the initial formation of the oxazolium salt was provided at 8 min of reaction time by the ^{1}H NMR spectrum ($CDCl_3$).[9] After 22 h, a strong peak at δ 3.78 (d, J = 1 Hz) was present as well as two downfield absorptions [δ 9.10 (d, J = 1 Hz) and 6.19 (d, J = 3 Hz)][10] of slightly increased intensity compared to those of the diminishing oxazolium salt ring hydrogen atoms. By 6 days, these latter-appearing signals were the most prominent, while those of the oxazolium salt

(2) Satisfactory analytical and spectroscopic data were obtained for all new compounds.

(3) Selected absorptions include δ 9.73 (s, H-2), 7.65 (s, H-4), and 4.05 (s, N-CH_3).

(4) All ^{13}C NMR spectra were obtained in $CDCl_3$ except that of **7** which was obtained in CD_3CN.

(5) (a) Fringuelli, F.; Pizzo, F.; Taticchi, A.; Halls, T. D. J.; Wenkert, E. *J. Org. Chem.* **1982**, *47*, 5056. (b) Grover, S. H.; Marr, D. H.; Stothers, J. B.; Tan, C. T. *Can. J. Chem.* **1975**, *53*, 1351. (c) Weigert, F. J.; Roberts, J. D. *J. Am. Chem. Soc.* **1970**, *92*, 1347.

(6) In contrast, compound **7** and 1-methyl-2-phenyl-2a,3,3ab,4,5,7ab-hexahydro-7(6*H*)-indolone (Wenkert, D.; Ferguson, S. B.; Porter, B.; Qvarnstrom, A.; McPhail, A. T. *J. Org. Chem.* **1985**, *22*, 4114) have the nitrogen in an equatorial position in the other of the two possible conformations of the ring system.

(7) Crystal data. [$C_9H_{14}NO^+$][$CF_3SO_3^-$] **7**, M = 301.29, monoclinic, space group $P2_1/c$, a = 7.057(1), b = 16.398(2), and c = 11.497(2) Å, β = 95.64(1)° (from 25 orientation reflections, 32° < θ < 44°), V = 1324.0(6) Å^3, Z = 4, D_c = 1.511 g cm^{-3}, μ(Cu Kα radiation, λ = 1.5418 Å) = 26.1 cm^{-1}; crystal size 0.20 × 0.24 × 0.40 mm (sealed under N_2 inside a thin-walled glass capillary). Intensity data ($+h,+k,\pm l$, θ_{max} = 67°, 2359 nonequivalent reflections) were recorded on an Enraf-Nonius CAD-4 diffractometer (Cu Kα radiation, graphite monochromator; $\omega-2\theta$ scans) and they were corrected for the usual Lorentz and polarization effects. An empirical absorption correction was also applied. Those 1084 reflections with $I > 2.0\sigma(I)$ (46%) were retained for the analysis. The crystal structure was solved by direct methods. Full-matrix least-squares refinement [anisotropic C, F, N, O, S; fixed H contributions; $\sum w\Delta^2$ minimized, $w = 1/\sigma^2(|F_o|)$] converged at R = 0.106 (R_w = 0.144). Crystallographic calculations were performed by use of the Enraf-Nonius Structure Determination Package (SDP 3.0).

(8) Endocyclic torsion angles ($\omega_{i,j}$ ±1°) for the enantiomer shown follow: $\omega_{1,2}$ −2, $\omega_{2,3}$ −18, $\omega_{3,3a}$ 28, $\omega_{3a,7a}$ −29, $\omega_{7a,1}$ 20° in the five-membered ring; $\omega_{3a,4}$ 45, $\omega_{4,5}$ −56, $\omega_{5,6}$ 62, $\omega_{6,7}$ −57, $\omega_{7,7a}$ 47, $\omega_{7a,3a}$ −39° in the cyclohexanone ring.

(9) Selected data include the singlet for N-CH_3 at δ 4.06 and the downfield absorptions at δ 9.76 (s, H-2) and 7.56 (s, H-4).

(10) These absorptions were subsequently assigned to the methyl, iminium, and bridgehead hydrogens of **10**, respectively.

were only of ca. 10% relative intensity (similar results were obtained by heating a CD_3CN solution of the oxazolium salt for 1 h at 74 °C).

As the evaporated reaction mixture from the *N*-methylation of oxazole **3** was not amenable to ready purification, it was subjected to further reaction. Treatment with an excess of sodium borohydride led to crystalline product **9** (mp 36−38 °C) in 30% yield. Spectral analysis of this product showed it to be (±)-8a-hydroxy-2-methyl-*trans*-decahydroisoquinoline. The ^{1}H NMR ($CDCl_3$) coupling constants of the bridgehead hydrogen H4a[11] and ^{13}C NMR data[12] were consistent with a *trans* ring fusion (Figure 2).

The transformation of the methylated oxazolinium salt of **3** is consistent with an intramolecular Diels−Alder reaction with *exo* stereoselectivity leading to **10**[13] (Figure 4). Sodium

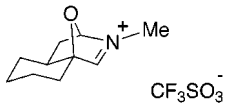

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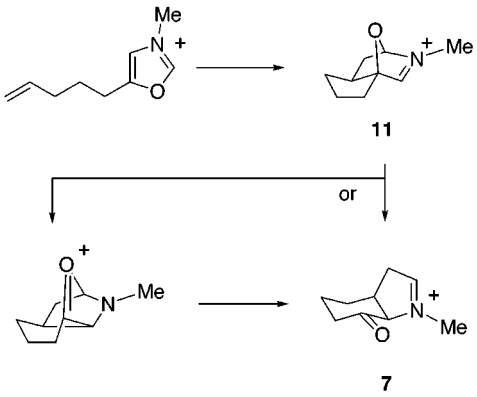
Figure 4. Intermediate **10**.

borohydride reduction of **10** would lead first to a dihydro compound which is a carbinolamine ether whose solvolysis leads to a hydroxyiminium salt. Further sodium borohydride reduction of the latter leads to **9**.

With regard to the transformation of the methylated oxazolinium salt of **2**, a possible mechanism is illustrated in Scheme 1. Cyclization of the salt of **2** results in strained

Scheme 1



adduct **11**,[14] assuming that the unusual changes of the oxazolium salt proceed initially also via an intramolecular Diels−Alder reaction. However, the adduct thus formed then undergoes rearrangement to the hydroindoleninium salt **7**.

Acknowledgment. This work was supported in part by the Petroleum Research Fund and the Welch Foundation. Acquisition and interpretation of some of the spectral data by Peter D. R. Moeller and Ming Guo are appreciated.

Supporting Information Available: Crystallographic data for **7**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) δ 1.02, dddd, $J_{H-4a-H-5\alpha} = J_{H-4a-H-4\alpha} = 4$ Hz, $J_{H-4a-H-5\beta} = J_{H-4a-H-4\beta} = 12$ Hz).

(12) The $\Delta\delta$ [*trans*-decalin (Dalling, D. K.; Grant, D. M.; Paul, E. G. *J. Am. Chem. Soc.* **1973**, *95*, 3718) minus 8a-hydroxy-*trans*-decalin (Ayer, W. A.; Browne, L. M.; Fung, S.; Stothers, J. B. *Org. Magn. Reson.* **1978**, *11*, 73)] values when applied to 2-methyl-*trans*-decahydroisoquinoline (Bailey, J. M.; Booth, H.; Al-Shirayda, J. A. R. Y. *J. Chem. Soc., Perkin Trans. 2* **1984**, 583) gave calculated carbon shifts almost identical with the experimental values shown on structural formula **9**.

(13) Although Diels−Alder reactions of oxazoles are well-known (see Chapter 1, pp 1−342, by Turchi, I. J., and Chapter 5, pp 963−1018, by Maryanoff, B. E. In *The Chemistry of Heterocyclic Compounds*, Vol. 45; Weissberger, A., Taylor, E. C., Eds.; John Wiley and Sons: New York, 1986, and references therein), the only published accounts for *N*-substituted oxazolium salts are of the 5-heteroatom-substituted type, i.e., "munchnones" (see Chapter 4, pp 731−962, Gingrich, H. L.; Baum, J. S. In *The Chemistry of Heterocyclic Compounds*, Vol. 45; Weissberger, A., Taylor, E. C., Eds.; John Wiley and Sons: New York, 1986, and references therein).

(14) Consistent with the formation of the intermediate adduct **11** were the temporarily observed ^{1}H NMR ($CDCl_3$) absorptions of δ 9.38 (d, J = 2 Hz) and 6.29 (s) that could be ascribed to the iminium methine and bridgehead (OCH-N) hydrogens, respectively. These absorptions were of equal prominence at 1.5 h at room temperature with those of the methylated oxazole but had disappeared by 21 h reaction time.