Pergamon

Tetrahedron Letters 40 (1999) 2039–2040

TETRAHEDRON LETTERS

A novel Fremy's salt-mediated oxidation and rearrangement of anilines into amino ortho-diketones. Applications to the synthesis of pyrrolobenzodiazepines

George A. Kraus* and Natesan Selvakumar

Department of Chemistry, Iowa State University, Ames, IA 50011

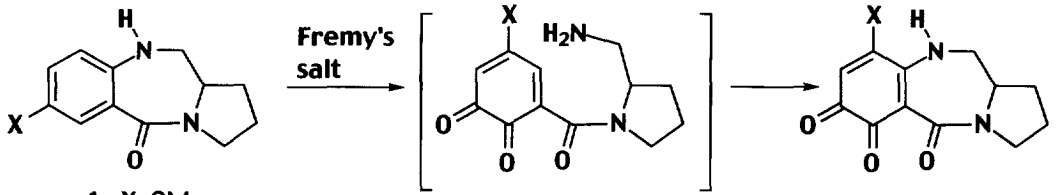
Received 24 November 1998; revised 5 January 1999; accepted 7 January 1999

Abstract

The reaction of anilines **1**, **3**, and **5** with 4.4 equivalents of Fremy's salt affords ortho-quinones in good yields via a one-pot five-step sequence.

Pyrrolobenzodiazepine natural products have shown promise in the treatment of disease.[1] The ability of these compounds to intercalate into specific sequences in DNA may make them more broadly useful in the treatment of genetic diseases.[2] DC-81[3] and tomaymycin[4] are representative members of this class. The availability of analogs bearing a variety of aromatic substitution patterns would not only enable researchers to better define structure-activity relationships but would also facilitate the preparation of conjugates linked to the aromatic ring.

Functionalization of a number of anilines using Fremy's salt has been reported by Teuber[5,6] and Horner.[7] The products were either quinones or quinone imines. Compound **1**, available by a three-step route from 5-methoxy-2-nitrobenzoic acid by amide formation (DCC, prolinol), aldehyde formation (Dess-Martin ox.) and nitro group reduction followed by reductive amination,[8] was treated with 4.5 equivalents of Fremy's salt in 1:1 acetonitrile:pH 7 buffer at 25 °C for 3 hours to afford ortho-quinone **2** in 82% yield. This structure was supported by the UV spectrum (λmax = 295, 462.5 nm) and NMR (aromatic H at 5.95).[9] Quinone **2** is the product of a five-step sequence involving hydroxylation ortho to the amine, oxidation to the quinone imine, hydrolysis of the imine to an amino ortho-quinone, Michael addition of the amine and oxidation of the resulting hydroquinone to the ortho quinone. In like manner, aniline **3** produced quinone **4** in 88 % yield, based on recovered starting material.



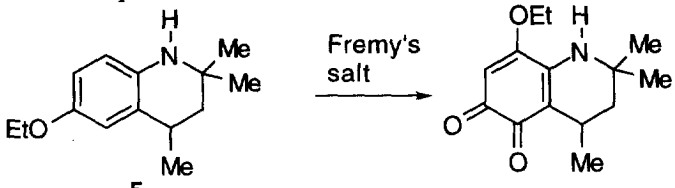
1: X=OMe
3: X=Me

2: X=OMe
4: X=Me

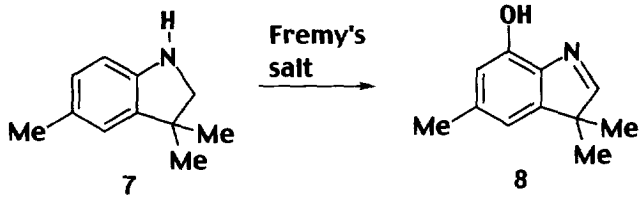
* e-mail: gakraus@iastate.edu

0040-4039/99/$ - see front matter
PII: S0040-4039(99)00087-8

In order to determine the scope of this novel one-pot reaction sequence, amines **5** and **7** were studied.[10] The reaction of amine **5** with Fremy's salt (4.4 equiv., 25 °C) produced ortho-quinone **6** in 68% isolated yield.[11] However, the reaction of **7** afforded the hydroxy imine **8** as the major product in 56% yield. Imine **8** is probably produced as a result of tautomerization of an iminoquionone intermediate.



5 **6**



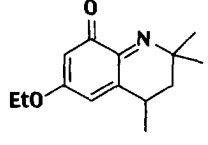
7 **8**

The Fremy's salt mediated oxidation of **1**, **3**, and **5** produces highly substituted ortho quinones.[12] Quinones **1** and **3** represent novel analogs that will be useful as analogs or for the synthesis of conjugates via Michael addition reactions.

Acknowledgement. We thank ISU for a postdoctoral fellowship for NS. We thank Alex Melekhov for a sample of **1**.

References

[1] Thurston, D. E.; Bose, D. S. *Chem. Rev.* **1994**, *94*, 433.
[2] Thurston, D. E. "Molecular Aspects of Anticancer Drug-DNA Interactions", Neidle, S.; Waring, M. J. Eds. The Macmillan Press Ltd **1993**, *1*, 54-88.
[3] Bose, D.S.; Jones, G. B.; Thurston, D. E. *Tetrahedron* **1992**, *48*, 751.
[4] Nishioka, Y.; Beppu, T. *J. Antibiot* **1972**, *25*, 660.
[5] Teuber, H.-J.; Staiger, G. *Chem. Ber* **1954**, *87*, 1251.
[6] Teuber, H.-J.; Waider, H. *Chem Ber* **1958**, *91*, 2341. Teuber, H.-J.; Hasselbach, M. *Chem. Ber*, **1959**, *92*, 674.
[7] Horner, L.; Sturm, K. *Chem. Ber* **1955**, *88*, 329.
[8] Thurston, D. E.; Langley, D. R. *J. Org. Chem* **1986**, *51*, 705. Kraus, G. A.; Melekhov, A. *Tetrahedron* **1998**, *54*, 11749.
[9] Wanzlick, H.-W.; Jahnke, U. *Chem. Ber* **1968**, *101*, 3744.
[10] Compound **5** was commercially available. Compound **7** was prepared from p-toluidine by a sequence involving acetylation, alkylation with methallyl chloride in K_2CO_3 and cyclization using $AlCl_3$ in PhCl at 110 °C followed by 6N HCl.



9

[11] At short reaction time, quinone imine **9** could be isolated.
[12] **2**: 300 MHz NMR acetone-D_6 δ 1.70-1.98 (m, 3 H), 2.30-2.40 (m, 1 H), 3.38-3.47 (m, 2 H), 3.55-3.64 (m, 1 H), 3.74-3.82 (m, 1H), 3.85 (s, 3 H), 3.98-4.05 (m, 1 H), 5.95 (s, 1 H), 7.43 (brs, 1 H). ^{13}C NMR ($CDCl_3$) δ 22.8, 30.7, 47.3, 52.5, 54.7, 57.0, 103.1, 104.2, 142.9, 162.5, 162.7, 177.4, 182.1. IR (neat) 1665, 1612, 1573 cm^{-1}. UV (CH_3CN) 295, 462.5 nm. MS m/z 262, 247, 193, 82, 70. HRMS m/z for $C_{13}H_{14}N_2O_4$: calcd: 262.09536. found: 262.09530.