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The Synthesis of Cerpegin

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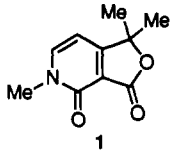
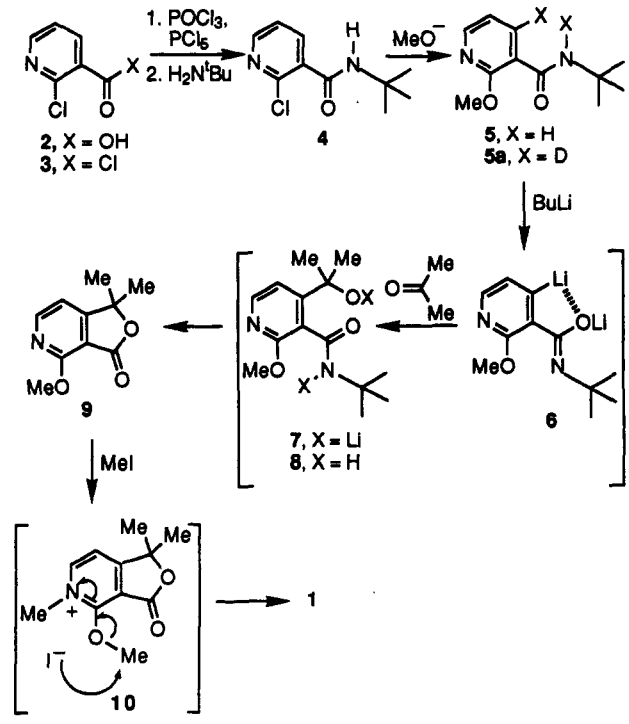
The structure of the pyridone alkaloid cerpegin was recently established as **1**.[1] Apart from some metabolites of pyridoxal,[2] to our knowledge cerpegin is the only naturally occurring example of the bicyclic furo[3,4-*c*]pyridine ring system. Because of the novelty of its structure and our continuing interest in the synthesis of pyridine-containing natural products,[3] we undertook the synthesis of **1**. We now report the first synthesis of cerpegin; the synthesis uses a reaction sequence that requires only about five steps from commercially available starting materials.



1

Thus (Scheme I) 2-chloronicotinic acid (**2**) was converted to its *tert*-butyl amide **4** via the acid chloride **3**.[4] Replacement[5] of the chloride by methoxide then afforded methoxy amide **5**. It had been our hope that **5** could be ortho lithiated[6] to give **6** and that **6** could be condensed with acetone to introduce the dimethylcarbinol side chain. Attempts to achieve that end in tetrahydrofuran using *n*-BuLi for ortho metalation followed by addition of acetone led only to recovery of starting material **5** after workup. In order to establish whether the absence of apparent reaction was due to a failure to ortho metalate **5** or to the quenching of **6** by proton transfer from the acetone, the putative **6** was quenched with D_2O; the deuterated derivative **5a** was isolated in high yield. Evidently, the problem was not in the ortho metalation step but in the quenching of anion **6** by proton transfer from acetone. Buhler[7] had previously established that in the reaction of alkyllithiums with ketones, enolization is diminished by using ether instead of THF as the reaction solvent. Accordingly, we attempted the preparation and reaction of **6** in ether rather than THF. Although some **5** was still

Scheme I



recovered, substantial amounts of **8** and **9** were produced. In the optimized procedure the crude product mixture is treated with acid prior to purification to complete the conversion of **8** to **9**. The overall isolated yield of **9** from **5** is 35%. That the recovery of **5** is due to quenching of **6** rather than incomplete metalation was shown, as before, by monitoring the progress of the metalation by quenching small aliquots of the reaction mixture with D_2O.

With a route to **9** in hand, it remained only to transpose the methyl group from the oxygen to the nitrogen to complete the synthesis. That manipulation was accomplished cleanly by heating a solution of **9** in CH_3I at 140 °C in a sealed tube. The conversion presumably proceeds via **10**.[8] The **1** so produced is identical by direct comparison (including mixed melting point) to a sample of naturally derived cerpegin.

Experimental Section[9]

***N*-*tert*-Butyl-2-chloronicotinamide (4).** 2-Chloronicotinic acid (5.00 g, 31.7 mmol) and PCl_5 (7.28 g, 34.9 mmol) were vigorously stirred in $POCl_3$ (25 mL) at 0 °C under N_2 for 30 min. The mixture was allowed to warm to room temperature and was then heated at reflux with stirring for 60 min during which time a clear solution resulted. The solution was allowed to cool to ambient temperature, and the volatiles were removed in vacuo. The resultant, resinous residue (crude **3**[4]) was cooled to 0 °C, and neat *tert*-butylamine (20 mL, 0.19 mol) was added dropwise over a period of approximately 15 min with vigorous stirring. The suspension was warmed to ambient temperature and then heated at reflux for 30 min. The reaction mixture was cooled to ambient temperature, water (25 mL) was added, and the mixture was partitioned between $CHCl_3$ and water. The aqueous phase was removed and extracted twice with $CHCl_3$. The organic phases were combined, washed with brine, dried over $MgSO_4$, and concentrated to dryness in vacuo to give a yellow solid. Recrystallization was achieved by heating the solid on a steam bath with

(1) (a) Adibatti, N. A.; Thirugnanasambantham, P.; Kulothungan, C.; Viswanathan, S.; Kameswaran, L.; Balakrishna, K.; Sukumar, E. *Phytochemistry* **1991**, *30*, 2449. (b) Sivakumar, K.; Eswaramurthy, S.; Subramanian, K.; Natarajan, S. *Acta Crystallogr.* **1990**, *C46*, 839.

(2) For a recent reference, see: Jong, Y.-J.; Snell, E. E. *J. Biol. Chem.* **1986**, *261*, 15112.

(3) Kelly, T. R.; Echavarren, A.; Chandrakumar, N. S.; Köksal, Y. *Tetrahedron Lett.* **1984**, *25*, 2127. Kelly, T. R.; Maguire, M. P. *Tetrahedron* **1985**, *41*, 3033. Kelly, T. R.; Liu, H.-t. *J. Am. Chem. Soc.* **1985**, *107*, 4998. Kelly, T. R.; Echavarren, A.; Whiting, A.; Weibel, F. R.; Miki, Y. *Tetrahedron Lett.* **1986**, *27*, 6049. Kelly, T. R.; Field, J. A.; Li, Q. *Tetrahedron Lett.* **1988**, *29*, 3545. Kelly, T. R.; Bell, S. H.; Ohashi, N.; Armstrong-Chong, R. J. *J. Am. Chem. Soc.* **1988**, *110*, 6471. Kelly, T. R.; Jagoe, C. T.; Gu, Z. *Tetrahedron Lett.* **1991**, *32*, 4263. Kelly, T. R.; Kim, M. H. *J. Org. Chem.* **1992**, *57*, 1593.

(4) Sliwa, H. *Bull. Soc. Chim. Fr.* **1970**, *5*, 631.

(5) For somewhat related reactions, see: Ames, D. E.; Dodds, W. D. *J. Chem. Soc., Perkin Trans. 1* **1972**, 705.

(6) For a recent review of the directed metallation of pyridines and some other π-deficient aza aromatics, see: Queguiner, G.; Marsais, F.; Snieckus, V.; Epsztajn, J. *Adv. Heterocycl. Chem.* **1991**, *52*, 187.

(7) Buhler, J. D. *J. Org. Chem.* **1973**, *38*, 904.

(8) For a leading reference, see: Beak, P.; Bonham, J.; Lee, J. T., Jr. *J. Am. Chem. Soc.* **1968**, *90*, 1569.

(9) For general experimental procedures, see: Kelly, T. R.; Bridger, G. J.; Zhao, C. *J. Am. Chem. Soc.* **1990**, *112*, 8024. In all cases $CHCl_3$ was used as received (which means that the ~0.75% ethanol stabilizer was not removed).

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ca. 20 mL of $CHCl_3$, adding 2-propanol dropwise (ca. 2–3 mL) until the solid dissolved, diluting, while still hot, with ca. 10 mL of petroleum ether, and slowly cooling to −20 °C to give 6.11 g (90%) of **4** as white crystals: mp 97–100 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 1.48 (9 H, s), 6.19 (1 H, br s), 7.33 (1 H, apparent dd, J = 7.5, 5.1 Hz), 8.03 (1 H, dd, J = 7.5, 1.8 Hz), 8.44 (1 H, dd, J = 5.1, 1.8 Hz). Anal. Calcd for $C_{10}H_{16}N_2O_2$: C, 56.47; H, 6.12; N, 13.18. Found: C, 56.59; H, 5.83; N, 13.27.

***N*-*tert*-Butyl-2-methoxynicotinamide (5).** A solid mixture of anhydrous copper(II) acetate (80 mg) and *N*-*tert*-butyl-2-chloronicotinamide (**4**, 3.75 g, 17.6 mmol) was added portionwise at room temperature to a stirring methanolic sodium methoxide solution which was prepared from 25 mL of anhydrous methanol and 2.0 g (87 mmol) of sodium metal. The resultant, deep-blue mixture was stirred at reflux for 60 min and cooled to 0 °C. Approximately 5 mL of glacial acetic acid was added dropwise to the stirring mixture, which was then partitioned between $CHCl_3$ and water. The organic phase was removed, washed with water (2×), 1 N aqueous $NaHCO_3$, and brine, dried over $MgSO_4$, and concentrated to dryness in vacuo to yield a yellow oil. Flash chromatography[10] on a 2.5-cm × 23-cm silica gel column eluting with 15:85 ethyl acetate/petroleum ether afforded a clear oil that solidified to a white, waxy solid upon standing at 0 °C (2.71 g, 74%): mp 22–24 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 1.47 (9 H, s), 4.09 (3 H, s), 7.05 (1 H, apparent dd, J = 7.5, 5.1 Hz), 7.91 (1 H, br s), 8.24 (1 H, dd, J = 5.1, 1.8 Hz), 8.49 (1 H, dd, J = 7.5, 1.8 Hz). Anal. Calcd for $C_{11}H_{16}N_2O_2$: C, 63.46; H, 7.69; N, 13.46. Found: C, 63.74; H, 7.71; N, 13.24.

1,1-Dimethyl-4-methoxyfuro[3,4-*c*]pyridin-3(1*H*)-one (9). To a stirred solution of *N*-*tert*-butyl-2-methoxynicotinamide (**5**, 219 mg, 1.05 mmol) in 3 mL of dry (from sodium benzophenone ketyl) diethyl ether at −78 °C under a nitrogen atmosphere was added 0.94 mL (2.2 mmol) of a 2.36 M solution of *n*-butyllithium in hexanes dropwise over a period of approximately 5 min to give a yellow suspension. The cooling bath was removed; the mixture gradually (ca. 30 min) warmed to ambient temperature and was stirred at that temperature an additional 45 min. The mixture was recooled to −78 °C, and dry, HPLC-grade acetone (0.085 mL, 1.2 mmol) was added in one portion. The cooling bath was removed, and the mixture was stirred an additional 2 h after it had reached room temperature. The reaction was quenched with water, and the resultant mixture was partitioned between ethyl acetate and water. The aqueous phase was separated and extracted with ethyl acetate (2×). The organic layers were combined, washed with brine, dried over $MgSO_4$, and concentrated to dryness in vacuo to yield an amber oil which was taken up in $CHCl_3$ (5 mL) and treated with *p*-toluenesulfonic acid (ca. 15 mg) at reflux for 2 h (to convert residual **8** to **9**). The solution was cooled back to room temperature, quenched with water, washed with 1 N aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated to dryness in vacuo to afford 248 mg of a pale-yellow oil whose ^1H NMR showed it to be principally a ~1:1 mixture of **5** and **9**. Flash chromatography on a 2-cm × 25-cm silica gel column eluting with 30:70 ethyl acetate/petroleum ether afforded 56 mg (26%) of recovered **5** and 70 mg (35%, 47% based on unrecovered **6**) of **9** as a white, crystalline solid: mp 111–113 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 1.62 (6 H, s), 4.13 (3 H, s), 6.94 (1 H, d, J = 5.1 Hz), 8.39 (1 H, d, J = 5.1 Hz). Anal. Calcd for $C_{10}H_{11}NO_3$: C, 62.18; H, 5.70; N, 7.25. Found: C, 62.32; H, 6.01; N, 7.41.

1,1,5-Trimethylfuro[3,4-*c*]pyridine-3,4(1*H*,5*H*)-dione (Cerpegin, 1). A portion of **9** (100 mg, 0.52 mmol) was dissolved in neat iodomethane (1 mL) and heated at 140 °C for 24 h in a sealed tube. The burgundy mixture that resulted was diluted with CH_2Cl_2, washed successively with 1 N aqueous HCl and brine, dried over $MgSO_4$, and concentrated to dryness to yield 90.3 mg (90%) of **1**: mp 268–271 °C (lit.[1a] mp 268–270 °C), which was pure as judged by ^1H NMR. The melting point of a mixture of synthetic and natural **1** is undepressed, the two are identical by TLC using cospotting and a variety of solvent systems, and the spectra of synthetic **1** are identical to those of natural **1**.[11]

(10) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

(11) Due to a faulty calibration, the ^1H NMR chemical shifts reported in ref 1a are incorrect. The correct ^1H NMR spectral data are as follows: (300 MHz, $CDCl_3$) δ 1.59 (6 H, s) 3.64 (3 H, s), 6.23 (1 H, d, J = 6.9 Hz), 7.68 (1 H, s, J = 6.9 Hz).

Acknowledgment. We thank Dr. P. Thirugnanasambantham[1a] for a sample of **1** and its spectra.

Registry No. **1**, 129748-28-3; **3**, 2942-59-8; **4**, 144084-34-4; **5**, 144084-35-5; **9**, 144084-36-6.

Ring Expansion of Halo Dithiolanes and Dithianes: A Facile Synthesis of Medium-Ring Dithiacycloalkenes

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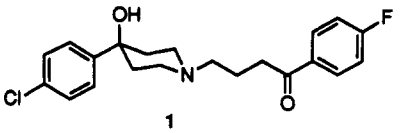
Medium ring containing compounds have long attracted the attention of synthetic chemists as they are generally resistant to attempts to prepare them via standard cyclization methodologies.[1] This difficulty is thought to be essentially due to an enthalpic effect caused by the high intrinsic strain of medium-ring systems.[2] Fragmentation of a bicyclic system containing smaller, more easily synthesized rings is a well-recognized strategy for the construction of these systems.[3] We have developed such an approach in which the bicyclic intermediate, derived from the cyclization of a halo thioketal, is generated in situ and fragments to a 1,4- or 1,5-dithiacycloalkene.

While investigating the synthesis of a number of analogs of haloperidol (**1**),[4,5] a promising lead compound for the development of nonpeptidic HIV-1 protease inhibitors,[6] we attempted the alkylation of a piperidine moiety with the dithiolane-containing γ-halobutyrophenone **2a**.



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Surprisingly, the desired product was not formed. Instead, we isolated a small amount of the 1,5-dithiacyclooctene **3a**, derived from ring expansion of the starting thioketal. We report here an optimized version of this reaction that provides a facile entry into medium ring 1,4- and 1,5-dithiacycloalkenes *for which no general synthesis is currently available* (see Table I). A brief survey of the literature reveals that while oxidative ring expansions of cyclic thioketals are relatively common,[7] few are driven by an alkylation reaction and most are limited to only one or two carbon ring enlargements.[8] There is only one report of a related reaction in which a thioketal sulfur interacts

(1) Illuminati, G.; Mandolini, L. *Acc. Chem. Res.* **1981**, *14*, 95–102.

(2) Evans, P. A.; Holmes, A. B. *Tetrahedron* **1991**, *47*, 9131–9166.

(3) Fuhrhop, J.; Penzlin, G. *Organic Synthesis Concepts, Methods, Starting Materials*; Verlag Chemie: Weinheim, 1983; p 80–82.

(4) Sui, Z., De Voss; J. J.; Ortiz de Montellano, P. R. Unpublished.

(5) De Voss, J. J.; Sui, Z.; Ortiz de Montellano, P. R. Unpublished.

(6) DesJarlais, R. L.; Seibel, G. L.; Kuntz, I. D.; Furth, P. S.; Alvarez, J. C.; Ortiz de Montellano, P. R.; DeCamp, D. L.; Babé, L. M.; Craik, C. S. *Proc. Natl. Acad. Sci. U.S.A.* **1990**, *87*, 6644–6648.

(7) See, for example: Tani, H.; Inamasu, T.; Tamura, R.; Suzuki, H. *Chem. Lett.* **1990**, 1323–1326. Francisco, C. G.; Freire, R.; Hernández, R.; Salazar, J. A.; Suárez, E. *Tetrahedron Lett.* **1984**, *25*, 1621–1624. Hiroi, K.; Sato, S.; Matsuo, K. *Chem. Pharm. Bull.* **1980**, *28*, 558–566.

(8) Nikkon, A.; Rodriguez, A. D.; Shirhatti, V.; Ganguly, R. *J. Org. Chem.* **1985**, *50*, 4218–4226. Weintraub, P. M. *J. Heterocycl. Chem.* **1979**, *16*, 1081–1082.

0022-3263/92/1957-6658$03.00/0