Ionization of Pyrido[3,4-*b*]pyrrolizidine and Pyrrolo[1,2-*a*]indole Triflate Derivatives. A Novel Approach to the Mitosene Skeleton

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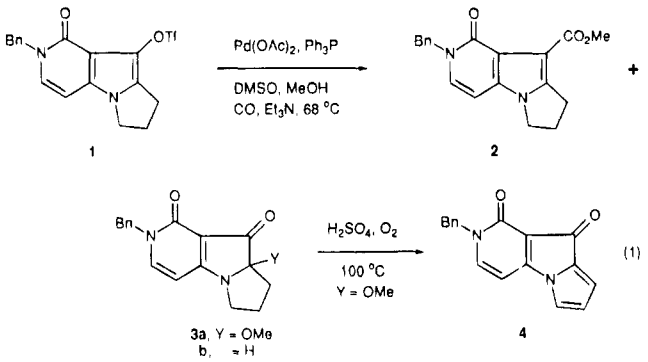
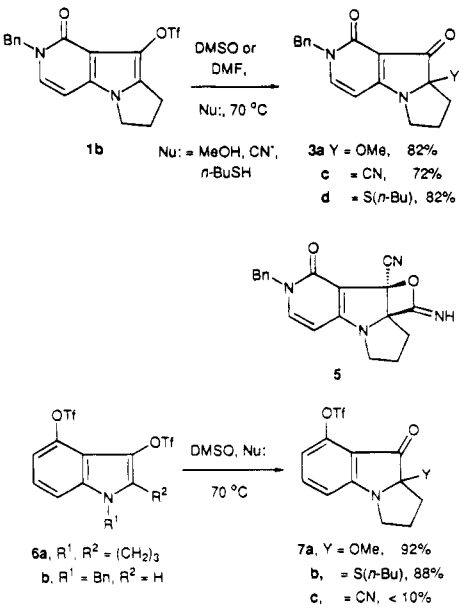
In recent years the advent of heteroaromatic triflates[1] as building blocks for the synthesis of more elaborate heterocyclic structures through palladium-catalyzed carbon–carbon bond-forming reactions[2] has become well recognized. Our program has a major interest in the use of annulated pyrrole-3-triflates for the construction of various pyrrole-containing molecules.[3] While a new route to pyrrolo[3,2-*c*]pyridin-2-ones and pyrido[3,4-*b*]pyrrolizidin-1-ones, an undetermined side product was noticed during the palladium-catalyzed methoxycarbonylation of triflate **1** to ester **2**. It was noted that this process only occurred with the pyrido[3,4-*b*]pyrrolizidine triflate having an alkyl substituent at the 2-position on the pyrrole ring. In contrast, a simplified pyrrolo[3,2-*c*]pyridine triflate having a hydrogen at this position readily underwent the desired carbonylation. We now report the discovery of an unprecedented form of reactivity for pyrrole-3-triflates based on the structure assignment of this compound as **3a**. This unexpected byproduct appeared to be the overall result of hydrolysis of the triflate-bearing carbon leading to formation of a 3-keto group and oxidative addition of methanol to the α-position of the pyrrole ring. In order to define the elements required for this reaction and determine the applicability of such a process as a novel approach to the mitomycin skeleton, the following study was carried out.



Compound **3a** revealed the following spectral characteristics. The ^{1}H NMR showed sets of diastereomeric proton signals for each of the ring and the benzyl methylene protons. The IR spectrum for **3a** showed the presence of two carbonyl groups at 1713 and 1646 cm^{-1} which was consistent with two signals in the ^{13}C NMR at 194.0 and 172.7 ppm. To further support the structure

Scheme 1



assigned to **3a**,[4] exposure of this material to hot sulfuric acid in the presence of air resulted in elimination of methanol and *in situ* oxidation of the pyrroline intermediate to afford the aromatic compound **4** in 90% yield.[5] Furthermore, hydrolysis of C-9 acetoxy derivative **1a** (Na_2CO_3, MeOH, 60 °C, 5 min) afforded the C-8a unsubtituted compound **3b**. This confirmed the location of the methoxy substituent in **3a** as based on the appearance of a ^{1}H NMR signal for the C-8a methine proton in **3b** at δ 3.90 (1H, br s).

To determine the necessary elements needed for this transformation, each of the key reaction components was systematically left out. It was noticed that an absence of base led to a greatly increased yield of compound **3a**. In fact, the only required components are a polar aprotic solvent (DMSO or DMF), methanol, and gentle heating. In this way a high yield of **3a** could be obtained (Scheme 1). Although the palladium(II) salt in solution was not found to be necessary for the reaction to proceed, the reaction rate was approximately doubled in its presence. Methanol acts as a nucleophile in this process. To test this proposal, the reaction was run in the presence of other nucleophiles. Gentle heating of a solution of compound **1** and a slight excess of KCN in DMF or butanethiol in DMSO resulted in the isolation of adducts **3c** and **3d** in good yield. Interestingly, treatment of **1b** with an excess of NaCN in DMSO afforded a new compound **5**[6] in 55% yield which incorporated two moles of cyanide.[7] A likely mechanistic rational accounting for the formation of this compound would have the second

(1) For recent examples utilizing heterocyclic triflates, see: (a) Gribble, G. W.; Conway, S. C. *Synth. Commun.* **1992**, *22*, 2129. (b) Gribble, G. W.; Conway, S. C. *Heterocycles* **1990**, *30*, 627. (c) Crisp, G. T.; Flynn, B. L. *Tetrahedron Lett.* **1990**, 1347. (d) Hirota, K.; Kitade, Y.; Isobe, Y.; Make, Y. *Heterocycles* **1987**, *26*, 355.

(2) For a review, see: Ritter, K. *Synthesis* **1993**, 735.

(3) (a) Edstrom, E. D. *Synlett* **1995**, 49. (b) Edstrom, E. D.; Yu, T. *Tetrahedron Lett.* **1994**, *35*, 6985. (c) Edstrom, E. D.; Wei, Y. *J. Org. Chem.* **1994**, *59*, 6902. (d) Edstrom, E. D.; Wei, Y. *J. Org. Chem.* **1993**, *58*, 403.

(4) As further evidence, compound **3a** was also found to undergo a ready exchange reaction with water under gentle heating or acid catalyst. The resulting hemiketal was partially characterized by ^{1}H and ^{13}C NMR.

(5) The spectral data for compound **4** revealed a straightforward set of five heteroaromatic protons at δ 7.62 (d, J = 7.0 Hz), 6.92 (dd, J = 2.8, 0.8 Hz), 6.74 (dd, J = 3.5, 0.8 Hz), 6.32 (dd, J = 3.5, 2.8 Hz), and 6.21 (d, J = 7.0 Hz).

(6) Key spectral features of **5** which suggested the assigned structure are: IR (KBr) 3449, 1781, 1653 cm^{-1}; ^{1}H NMR (DMSO) δ 9.95 (s, 1 H, D_2O disappear); ^{13}C NMR (DMSO) δ 160.3, 155.0, 115.2.

(7) We attribute this change in product distribution to the greater concentration of cyanide in solution. TLC analysis of this reaction after short periods of time revealed the presence of **3c** which disappeared with time. In an independent experiment, treatment of **3c** with NaCN in DMSO resulted in its clean conversion into **5**.

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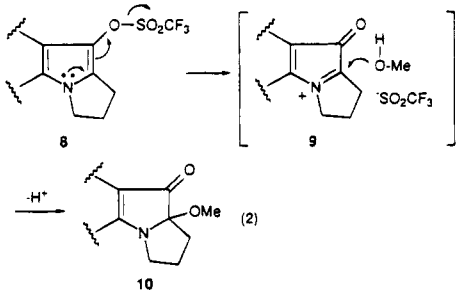
equivalent of cyanide adding to the C-9 carbonyl group of **3c**, forming a cyanohydrin intermediate. It can be imagined that the newly formed hydroxy group then adds across the adjacent *cis*-orientated nitrile group at C-8a leading to the formation of the cyclic imidate ring.[8] To test the generality of this reaction the indole systems **6a,b**[9] were subject to the same solvolytic reaction conditions. The pyrrolo[1,2-*a*]indole **6a** was found to react cleanly and afford adducts **7a,b** in good yield. In contrast, the 2-unsubstituted indole system **6b** did not react under these conditions.[10]

A mechanistic rational for the ionization of pyrrole-3-triflates is shown in eq 2. Heterolytic cleavage of the



sulfonate ester bond would result in loss of the triflinate ion[11] and give rise to the acyliminium ion intermediate **9**. This process is facilitated by donation of the lone pair from the nitrogen atom and the stabilizing effect of a polar aprotic solvent. An external nucleophile, such as a solvent molecule of methanol, then attacks at the α-carbon of **9** and results in the observed product **10**, following proton loss. The overall process can be seen as a solvolysis reaction with a concomitant internal redox reaction, i.e., reduction of the S–O bond and oxidation at the pyrrole α-carbon. This form of reactivity for aryl triflates is unprecedented. Normally, aryl and vinyl triflates form aryl or vinyl carbocation intermediates through loss of the triflate ion.[12]

We have documented a novel form of reactivity for heteroaromatic based organotriflates. Thus, pyrrole-3-triflates bearing an alkyl group in the α-position are seen to undergo an overall oxidative hydrolysis process in polar aprotic solvents, which leads to the synthesis of α-substituted 3-ketopyrroles. Synthetically useful functional groups can be introduced to the α-position including methoxy, cyano, and alkylthio. The further application of this methodology for the synthesis of azamitosene[13] and mitomycin precursors[14] is currently being investigated.

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Supporting Information Available: Experimental procedures for the preparation of compounds **3a–d**, **4**, **5**, **6a,b**, and **7a–c**. ^{1}H and ^{13}C NMR spectra of compounds **3a,c**, **5**, and **7a,b** (27 pages).

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(8) This type of reaction has some precedence; i.e., cyanohydrin formation (KCN, DMSO) followed by intramolecular displacement of a tosylate by the incipient alkoxide leads to the formation of a 2-cyanooxetane system. Furthermore, KCN in MeOH results in the addition of methanol across a nitrile group. Nerdel, F.; Weyerstahl, P.; Lucas, K. *Tetrahedron Lett.* **1965**, 5751.

(9) Compounds **6a,b** were obtained from their 4-keto-4,5,6,7-tetrahydroindole precursors, prepared as described in a recent communication. Edstrom, E. D. *Synlett.* **1995**, 49. The details for the transformation of 3-acetoxy-4-ketoindoles into 3,4-ditriflates **6a,b** are provided in the supporting information.

(10) We attribute this to the need to stabilize the developing positive charge on the α-carbon atom.

(11) For the use of the use of potassium triflinate in synthesis, see: Hendrickson, J. B.; Skipper, P. L. *Tetrahedron* **1976**, *32*, 1627.

(12) Stang, P. *Acc. Chem. Res.* **1978**, *11*, 107.

(13) For examples of ring-modified mitosene or mitomycin analogues, see: Köhler, B.; Su, T. L.; Chou, T. C.; Jiang, X. J.; Watanabe, K. A. *J. Org. Chem.* **1993**, *58*, 1680. Bhuyan, P.; Boruah, R. C.; Sandhu, J. S. *Ind. J. Chem.* **1990**, *29B*, 901.

(14) For a synthetic approach to mitomycins using 9-ketopyrrolo-[1,2-*a*]indole intermediates, see: Benbow, J. W.; McClure, K. F.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1993**, *115*, 12305. Jimenez, L. S.; Wang, Z. *J. Am. Chem. Soc.* **1994**, *116*, 4977.