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Abnormal Pummerer Cyclizations on the Indole Ring

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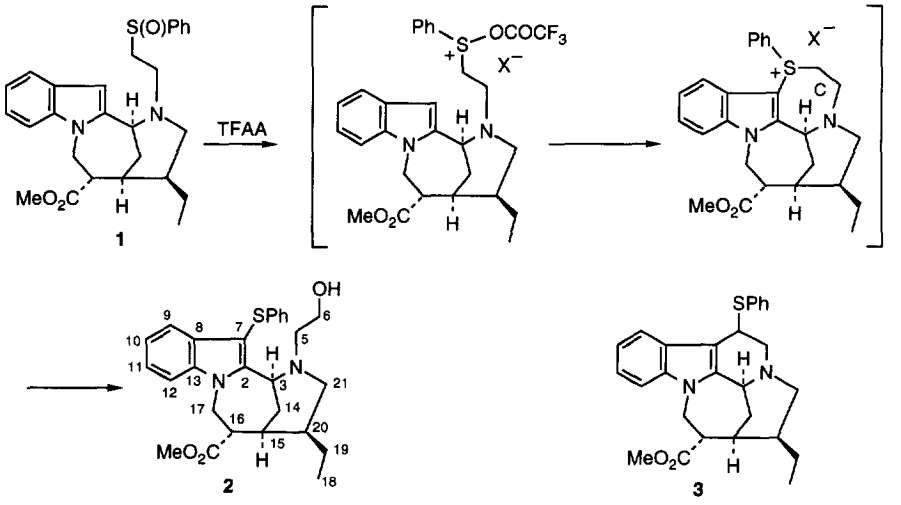
Abstract : Sulfides **2** and **7** are formed from sulfoxides **1** and **4a**, respectively, under Pummerer reaction conditions. The process involves the formation of a positively charged seven-membered ring intermediate by nucleophilic attack of the indole nucleus on the initially formed acyloxysulfonium salt.

The Pummerer reaction constitutes a versatile and effective method for the generation of α-thiocarbocations (thionium ions) from sulfoxide precursors.[1] In general, the initial step of the reaction involves acylation of the sulfoxide oxygen to form an acyloxysulfonium salt, thus converting this oxygen to a good leaving group. Removal of a proton from the α-carbon, with elimination of the acyloxy group, generates a thionium ion, which is trapped by one of the nucleophilic species present in the medium. The Pummerer reaction has proved to be useful in natural product synthesis, in particular indole alkaloids.[2]

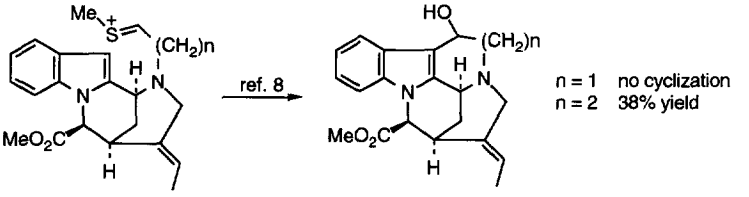
In spite of its general applicability, some side reactions can competitively occur, depending on the substrate and the reaction conditions:[1] elimination of sulfenic acid, fragmentation reactions, formation of vinyl sulfides, formation of dithioacetals,[3] or reduction to a sulfide via a sulfurane.[4] In other cases, the acyloxy group in the initially formed acyloxysulfonium salt can undergo displacement by an internal nucleophile to give a new positively charged sulfur species, from which several pathways are open for the subsequent reaction.[1b]

In the context of our studies[5] on the synthesis of pentacyclic apogeissoschizine-type systems by closure of the C ring in the last steps by cyclization on the indole nucleus, we have observed an abnormal course of the Pummerer reaction. Thus, treatment of sulfoxide **1** under standard Pummerer reaction conditions (TFAA, CH_2Cl_2, rt, 3 h) led to sulfide **2**[6] as the major product (43%). A similar result was obtained when operating at higher temperature or in the presence of $BF_3.Et_2O$. Formation of **2** can be rationalized by considering the nucleophilic displacement of the acyloxy group by the indole ring in the initially formed acyloxysulfonium intermediate. Subsequent attack of an external nucleophile (CF_3COO^- or OH^-) on the α-carbon gives sulfide **2** (Scheme 1). This process involves the formation of a seven-membered C ring intermediate rather than the expected closure of a six-membered ring (leading to **3**) by electrophilic cyclization of the intermediate thionium ion on the indole 3-position.[7]



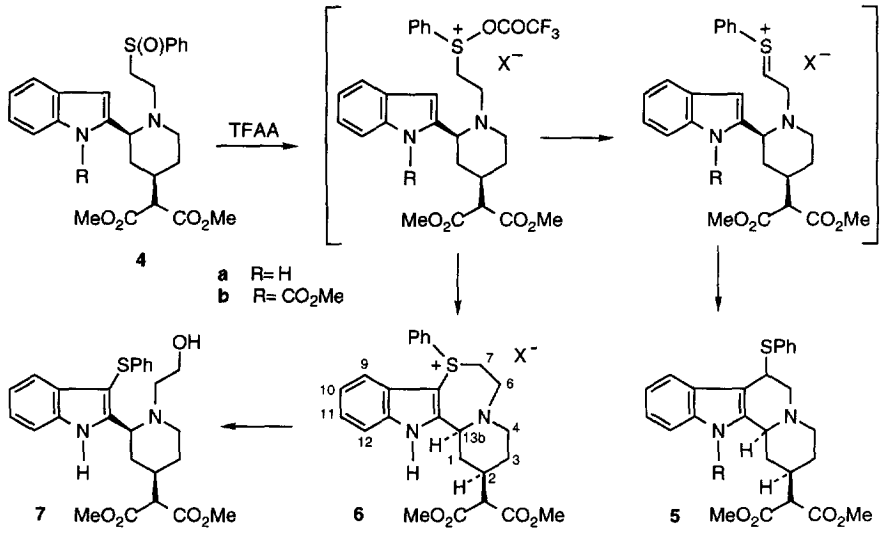
Scheme 1

This result was initially related to the reluctance of tetracyclic derivatives in the C-mavacurine series to close the six-membered C ring by cyclization of a thionium ion on the indole 3-position and, in contrast, to the success of a similar cyclization leading to a seven-membered C ring (Scheme 2).[8] This differing behaviour was rationalized on steric grounds because the piperidine ring is included in a rigid bridged system.



Scheme 2

However, in the present case this interpretation does not seem to be completely true because a similar sulfide **7** was obtained under Pummerer reaction conditions from sulfoxide **4a**, in which the above steric constraints do not exist. Previously we had observed[9] that treatment of sulfoxide **4a** with TFAA at room temperature led to the expected cyclized product **5a** in modest (28%) yield. A careful reinvestigation of this reaction allowed us to isolate a polar compound, identified as the sulfonium salt **6**,[10] which was subsequently converted into sulfide **7**[11] upon heating. Interestingly, sulfide **7** was directly obtained in 73% yield as the only isolable product by treatment of sulfoxide **4a** under the usual Pummerer reaction conditions (TFAA, rt, 2 h) followed by heating in chlorobenzene for 2 h.



Scheme 3

The above results are noteworthy because, although nucleophilic substitution reactions on the heterosulfonium cation initially formed in the Pummerer reaction have previously been reported,[1b] there are very few examples[12] in which the resulting sulfonium ion undergoes cleavage of the C-S bond by nucleophilic substitution at the carbon atom. Two factors could explain the abnormal course of the above Pummerer reactions: a) substrates **1** and **4** are β-amino sulfoxides,[13] in which the generation of the thionium ion by abstraction of an α-proton from the acyloxysulfonium intermediate is slower than in activated sulfoxides such as β-keto sulfoxides; b) the indole ring is not protected (deactivated) by an electron-withdrawing group that diminishes its nucleophilic character. Substitution at sulfur in the acyloxysulfonium intermediate by attack of the indole ring is faster than generation of the thionium ion required in the normal Pummerer cyclization. In accordance with this interpretation, the process was not observed from sulfoxide **4b**, which bears a methoxycarbonyl substituent on the indole nitrogen. In this case the Pummerer reaction follows a normal course, leading to tetracycle **5b** as the major product.[9,14]

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2. (a) Gallagher, T.; Magnus, P.; Huffman, J. C. *J. Am. Chem. Soc.* **1983**, *105*, 4750-4757. (b) Amat, M.; Linares, A.; Bosch, J. *J. Org. Chem.* **1990**, *55*, 6299-6312.
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4. Cardwell, K.; Hewitt, B.; Ladlow, M.; Magnus, P. *J. Am. Chem. Soc.* **1988**, *110*, 2242-2248.

5. Bennasar, M.-L.; Zulaica, E.; Sufi, B. A.; Bosch, J. *Tetrahedron*, in press.

6. **2**: IR (film) 1737 (CO), 3400 (OH); ^{1}H-NMR (300 MHz): 1.05 (t, J = 7.1 Hz, 3H, 18-H), 1.49 (m, 2H, 19-H), 1.93 (dt, J = 14.3, 1 Hz, 1H, 14-H), 2.26 (m, 3H, 5-H, 14-H and 20-H), 2.56 (t, J = 12.4 Hz, 1H, 21-H), 2.87 (m, 1H, 15-H), 2.98 (m, 2H, 21-H and 5-H), 3.18 (m, 1H, 16-H), 3.44 and 3.61 (2m, 2H, 6-H), 3.58 (s, 3H, OCH_3), 4.38 (dd, J = 14.8, 2.7 Hz, 1H, 17-H), 4.83 (d, J = 3.7 Hz, 1H, 3-H), 5.13 (dd, J = 14.8, 3.5 Hz, 1H, 17-H), 6.90-7.40 (m, 7H, Ar), 7.45 (d, J = 8 Hz, 1H, 12-H), 7.53 (d, J = 8 Hz, 1H, 9-H); ^{13}C-NMR 11.6 (C-18), 23.7 (C-19), 31.6 (C-14), 32.0 (C-15), 39.7 (C-20), 42.6 (C-16), 45.0 (C-17), 51.8 (C-3), 52.3 (OCH_3), 52.4 (C-21), 56.2 (C-5), 57.5 (C-6), 110.2 (C-12), 119.9 (C-9), 120.9 (C-10), 123.5 (C-11), 124.7, 125.1, 128.7 (C_6H_5), 128.9 (C-8), 138.7 (C-2), 138.9 (C-13), 172.7 (CO); MS, m/e (rel intensity) 464 (M^+, 39), 433 (M-31, 100); HRMS calcd for $C_{27}H_{32}N_2O_3S$ 464.2133, found 464.2149.

7. Pentacycle **3** was only isolated, although in very low yield (6%), when the Pummerer reaction was effected with trimethylsilyl triflate in the presence of diisopropylethylamine: see reference 5.

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9. Amat, M.; Hadida, S.; Sathyanarayana, S.; Bosch, J. *Tetrahedron Lett.* **1996**, *37*, 3071-3074.

10. **6**: ^{13}C-NMR (75 MHz, $CDCl_3$) 29.5 (C-3), 35.5 (C-2), 36.7 (C-1), 48.4 (C-7), 51.9 (C-4), 52.9 (CH_3O), 53.1 (CH_3O), 54.0 (C-6), 56.7 (CH), 63.4 (C-13b), 81.8 (C-8a), 114.4 (C-12), 116.5 (C-9), 123.1 (C-10), 124.3 (C-11), 127.4 (C-*o*), 128.7 (C-*ipso*), 129.6 (C-8b), 130.8 (C-*m*), 132.1 (C-*p*), 133.7 (C-12a), 136.8 (C-13a), 168.8 (CO).

11. **7**: IR (film) 3100 (OH), 1736 (C=O) cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) 1.50 (qd, J = 12.0, 3.5 Hz, 1H, 5-Hax), 1.64 (q, J = 12.0 Hz, 1H, 3-Hax), 1.72-1.88 (m, 2H, 3-Heq and 5-Heq), 2.30 (dm, J = 13.5 Hz, 1H, NCH), 2.23 (td, J = 12.0, 3.0 Hz, 1H, 6-Hax), 2.30 (m, 1H, 4-H), 2.72 (ddd, J = 13.5, 10.0, 4.5 Hz, 1H, NCH), 3.18 (d, J = 8.5 Hz, 1H, CH), 3.28 (dm, J = 12.0 Hz, 6-Heq), 3.41 (dt, J = 11.8, 4.0 Hz, 1H, OCH), 3.55 (s, 3H, CH_3O), 3.68 (s, 3H, CH_3O), 3.71 (dm, J =11.8 Hz, 1H, OCH), 4.03 (dd, J = 11.5, 2.8 Hz, 1H, 2-H), 6.98-7.22 (m, 7H, Ar), 7.33 (dm, J = 8.0 Hz, 1H, 7´-H), 7.55 (dm, J = 7.6 Hz, 1H, 4´-H), 9.90 (br s, 1H, NH); ^{13}C-NMR (75 MHz, $CDCl_3$) 29.4 (C-5), 35.9 (C-4), 37.6 (C-3), 52.3 (C-6), 52.4 (CH_3O), 56.4 (NCH_2), 56.7 (CH), 58.4 (OCH_2), 59.3 (C-2), 99.7 (C-3'), 111.6 (C-7'), 119.1 (C-4'), 120.6 (C-5'), 122.8 (C-6'), 124.6 (C-*p*), 125.5 (C-*o*), 128.7 (C-*m*), 129.7 (C-3'a), 135.8 (C-7'a), 139.0 (C-2'), 144.3 (C-*ipso*), 168.2 (CO), 168.4 (CO); MS, m/e (rel intensity) 482 (M^+, 27), 451 (36), 342 (39), 341 (100), 238 (18), 200 (21).

12. Kaneko, T. *J. Am. Chem. Soc.* **1985**, *107*, 5490-5492.

13. There are very few examples of Pummerer reactions from β-amino sulfoxides: (a) Takano, S.; Iida, H.; Inomata, K.; Ogasawara, K. *Heterocycles* **1993**, *35*, 47-52. (b) Catena, J. L.; Valls, N.; Bosch, J.; Bonjoch; J.; *Tetrahedron Lett.* **1994**, *35*, 4433-4436. (c) Amat, M.; Bosch, J. *J. Org. Chem.* **1992**, *57*, 5792-5796.

14. To our knowledge, the Pummerer reaction leading to **5b** constitutes the first example of a synthetically useful Pummerer cyclization on the indole 3-position in 3-unsubstituted indoles: Oikawa, Y.; Yonemitsu, O. *J. Org. Chem.* **1976**, *41*, 1118-1124. See also reference 1.

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