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DIMETHYL(METHYLTHIO)SULFONIUM FLUOROBORATE INDUCED CYCLIZATION OF DITHIOACETALS UPON 2,3-DISUBSTITUTED INDOLES

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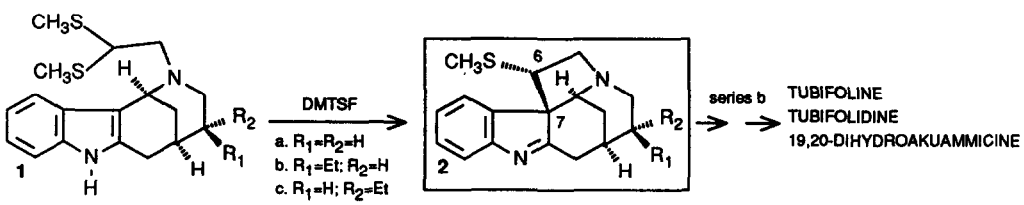
Treatment of dithioacetals **1a-c**, **3**, and **4** with DMTSF accomplishes cyclization upon the indole 3-position to give the *Strychnos*-type pentacycles **2a-c**, **10**, and **11**, respectively.

Dimethyl(methylthio)sulfonium fluoroborate (DMTSF)[1] is an excellent initiator for the chemoselective generation of thionium ions (thiocarbocations) from dithioacetals.[2-4] This reagent has widened the range of applications of thionium ions as reactive carbonyl equivalents for the formation of C-C bonds.

Our interest in DMTSF arises from our studies on the synthesis of pentacyclic *Strychnos* indole alkaloids:[5] we focused our attention on a strategy based on the construction of the pentacyclic ring system of these alkaloids by cyclization upon the indole 3-position of appropriate tetracyclic derivatives (the ABCD substructure of *Strychnos* alkaloids) having a functionalized two-carbon chain at the piperidine nitrogen (bond formed C_6-C_7).[6] After several unsuccessful attempts[7,8] to induce closure of the five membered E ring, this cyclization was satisfactorily achieved in approximately 50% yield[9] by treatment of dithioacetals **1a-c** with DMTSF, thus establishing a new synthetic entry to the pentacyclic ring system of the *Strychnos* alkaloids.[8,10] Pentacycle **2b** was further converted into the *Strychnos* alkaloids of the Strychnan-type tubifolidine,[10] tubifoline,[11] and 19,20-dihydroakuammicine.[12]

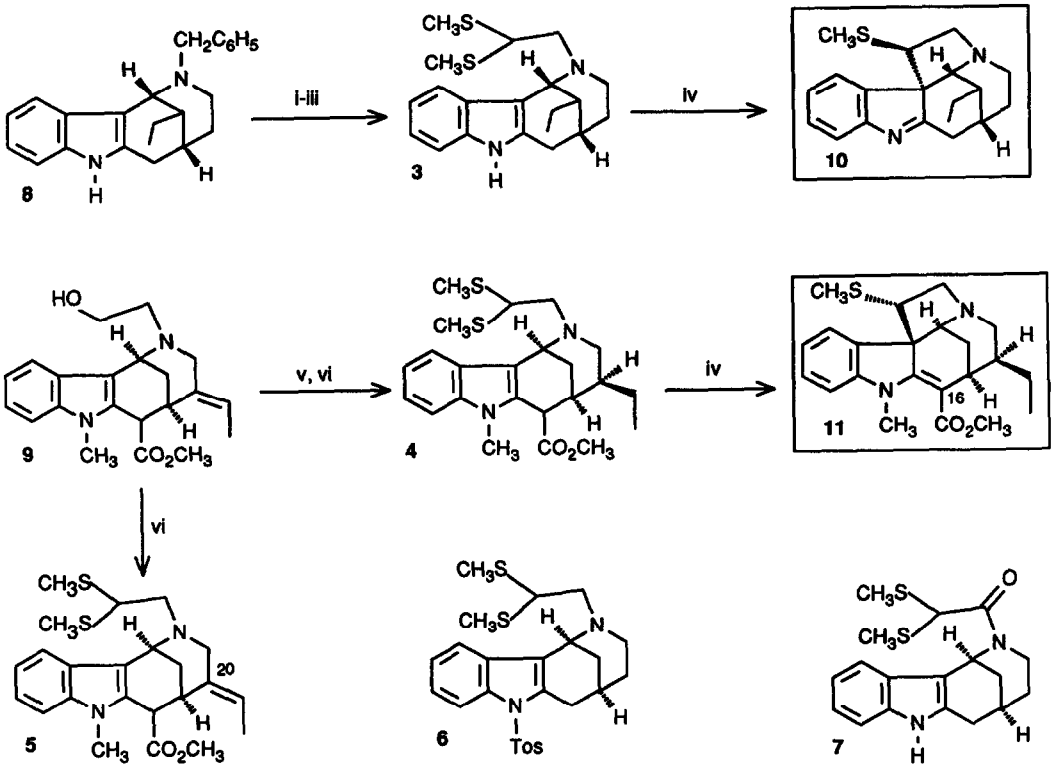


Scheme 1

In order to assess the scope and limitations of this approach to *Strychnos* alkaloids and to evaluate the usefulness of these DMTSF-induced cyclizations upon 2,3-disubstituted indoles we decided to apply the same procedure to dithioacetals **3-7**.

Dithioacetals **3**, **4**, and **5** were conveniently prepared[13] as shown in Scheme 2 from the previously reported tetracycles **8**[14] and **9**,[15] whereas dithioacetal amide **7**[13] was obtained by acylation of the corresponding secondary amine[7] with bis(methylthio)acetyl chloride.

Treatment of dithioacetals **3** and **4** with DMTSF (CH_2Cl_2, 0°C, 3 h) afforded, although in moderate yields, the expected pentacycles **10**[16] and **11**,[17] respectively. The former possesses the ethyl substituent at the bridge carbon, so it can be considered a synthetic precursor of the *Strychnos* bases having the Aspidospermatan skeleton (condyfoline, tubotaiwine), whereas the latter incorporates both a methyl substituent upon the indole nitrogen and a C-16 oxidized one-carbon appendage, which are characteristic of strychnofluorine.



Reagents and Conditions: (i) H_2, activated $Pd(OH)_2$, MeOH, 80%; (ii) $BrCH_2CH(OEt)_2$, Na_2CO_3, dioxane, rt, 15h, 68%; (iii) CH_3SH, $BF_3.Et_2O$, CH_2Cl_2, 0°C, 48 h, 79%; (iv) DMTSF, CH_2Cl_2, 0°C, 3 h, 23% for **10**, 15% for **11** (not optimized); (v) H_2, PtO_2, MeOH, 90%; (vi) $(COCl)_2$-DMSO, THF, -60°C, 30 min; then CH_3SH, $BF_3.Et_2O$, benzene, 0°C, 16 h, 42% for **4**, 53% for **5**.

Scheme 2

The above results show that the strategy developed provides a general synthetic entry to the *Strychnos* alkaloids, of both the Strychnan and the Aspidospermatan type and having or not an N_a-alkyl substituent and a C-16 oxidized one-carbon substituent.

In contrast, a similar DMTSF treatment of the ethylidene-bearing tetracyclic dithioacetal **5** did not result in the desired cyclization: non identifiable material was recovered. Although the addition of DMTSF and related salts to alkenes is a known process[18] which allows the activation of olefins for nucleophilic attack,[19] it was

expected that the high thiophilicity of DMTSF would allow to accomplish the desired cyclization. In fact, DMTSF has been successfully used for the chemoselective generation of thionium ions from dithioacetals in the presence of olefins,[4] even activated as vinyl silanes,[2] enol silyl ethers[2,3] or allylstannates.[4] The above failure constitutes a limitation of our strategy since the C-20 ethylidene substituent is present in some pentacyclic *Strychnos* alkaloids.

Finally, we examined the DMTSF-induced cyclization of dithioacetals **6**[8] and **7**, which incorporate two different structural features: a tosyl substituent upon the indole nitrogen and an exocyclic amide carbonyl group, respectively. In the former case, the aldehyde resulting from hydrolysis of the intermediate thionium ion was the only product detected from the reaction mixture, thus revealing the deactivating effect of the tosyl group.[20] Dithioacetal amide **7** did not cyclize either, a result that can be accounted for by considering that cyclization upon the indole 3-position would imply the loss of planarity of the amide bond.

In conclusion, DMTSF provides a valuable tool for the cyclization of dithioacetals, by way of a thionium ion, upon 2,3-disubstituted indoles, thus expanding the application of this reagent in synthesis.[21]

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9. The not optimized reported yields for **2a** (25%)[8] and **2c** (not specified)[10] have been improved to 50% (DMTSF 2 eq, CH_2Cl_2, 0°C, 3 h).
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16. **10**: unstable oil; IR: 1565 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.56 (deformed t, 3H, H-18), 0.80 (m, 2H, H-19), 1.60 (s, 3H, CH_3S), 1.70 (m, 1H, H-20), 1.93 (m, 2H, H-14), 2.40 (m, 1H, H-15), 2.73 (d, *J*=15.0 Hz, 1H, H-16α), 3.05 (t, *J*=11.5 Hz, 1H, H-5β), 3.13 (dd, *J*=15.0, 6.0 Hz, 1H, H-16β), 2.9-3.2 (masked, 1H, H-3α), 3.28 (dm, *J*=12.0 Hz, 1H, H-3β), 3.44 (dd, *J*=11.5, 6.0 Hz, 1H, H-5α), 3.98 (br s, 1H, H-21),

3.99 (dd, *J*=11.5, 6.0 Hz, 1H, H-6α), 7.15 and 7.24 (2t, 2H, H-10 and H-11), 7.36 (d, *J*=7.5 Hz, 1H, H-9), 7.45 (d, *J*=7.5 Hz, 1H, H-12).

17. **11**: ^{13}C NMR (50.6 Mz, $CDCl_3$) δ 11.5 (C-19), 16.3 (CH_3S), 27.5 (C-18), 28.9 (C-14), 35.5 (CH_3N), 35.6 (C-15), 39.2 (C-20), 50.9 (C-21), 50.9 (CH_3O), 62.7 (C-5), 63.7 (C-3), 64.4 (C-6), 96.2 (C-16), 108.6 (C-12), 120.6 (C-9), 123.6 (C-10), 128.9 (C-11), 161.2 (C-2), 167.6 (C=O); ^1H NMR (200 MHz, $CDCl_3$) δ 0.88 (t, *J*=7.2 Hz, 3H, H-18), 1.01 and 1.21 (2m, 2H, H-19), 1.36 (dm, *J*=13.7 Hz, 1H, H-14*R*), 1.76 (s, 3H, CH_3S), 2.21 (dt, *J*=13.7, 3.0 Hz, 1H, H-14*S*), 2.85 (m, 1H, H-5α), 3.05 (s, 3H, CH_3N), 3.24 (dd, *J*=14.0, 6.5 Hz, 1H, H-5β), 3.31 (m, 1H, H-15α), 3.68 (s, 3H, CH_3O), 3.84 (dd, *J*=14.0, 6.5 Hz, 1H, H-6β), 4.00 (br s, 1H. H-3α), 6.70 (d, *J*=7.3 Hz, 1H, H-12), 6.87 (t, *J*=7.3 Hz, 1H, H-10), 7.08 (d, *J*=7.3 Hz, 1H, H-9), 7.20 (t, *J*=7.3 Hz, 1H, H-11)
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21. There are no precedents of DMTSF-induced cyclizations of dithioacetals on aromatic nucleus. For a similar DMTSF-promoted cyclization from a tris(phenylthio)alkyl derivative, *via* a bis(phenylthio)carbocation, see: A. R. bin Manas and R. A. J. Smith, *Tetrahedron*, **1987**, *43*, 1847.

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