Novel Heterocyclic Cage Compounds from 2-Methylthiofurans

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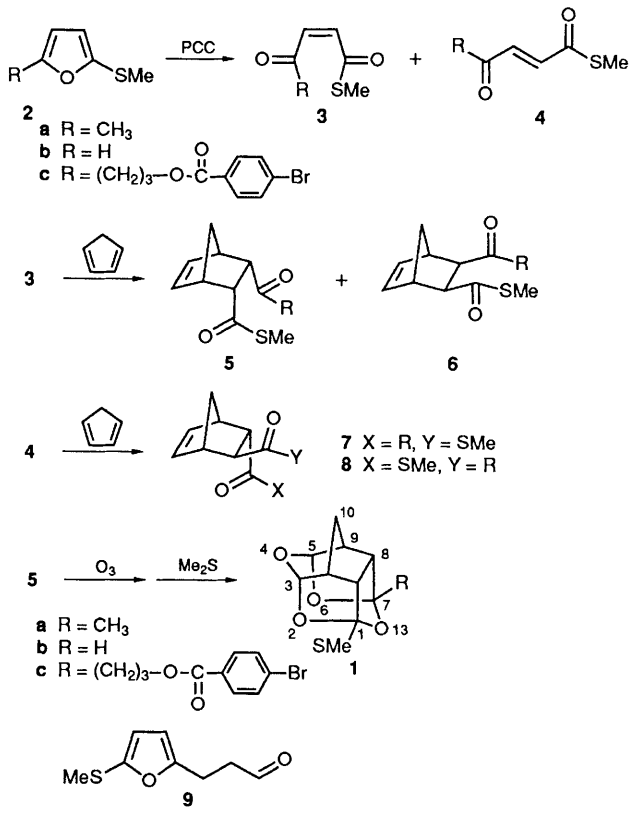
Some novel heterocyclic cage compounds **1a–1c** were synthesized from the corresponding 2-methylthiofurans **2a–2c** in a short sequence.

There is considerable interest in the synthesis of cage compounds,[1] including heterocyclic cage compounds.[2] We report here the synthesis of some novel heterocyclic cage compounds **1a–1c**, which possess four oxygen atoms in the framework, in three steps from the corresponding 2-methylthiofurans **2a–2c**.

Metallation[3] of 2-methylfuran with n-butyllithium followed by addition of dimethyldisulphide gave 2-methylthio-5-methylfuran **2a** in 85% yield. Oxidation of **2a** with two equivalents of pyridinium chlorochromate (PCC) in CH_2Cl_2 at room temperature for 2 h gave a single product **3a** in 70% yield. A longer oxidation reaction time (24 h) gave the *cis*-isomer **3a** and the *trans*-isomer **4a** in a ration of 1:2. Reaction of the *cis*-isomer **3a** with cyclopentadiene at room temperature gave the *endo* adduct **5a** as the major product and the *exo* adduct **6a** as the minor product in a ratio of 6:1 in 80% yield. Reactions of the *trans*-isomer **4a** with cyclopentadiene at room temperature gave the adducts **7a** and **8a** in a ratio of 1:1 in 80% yield. Compounds **5b**, **6b**, **7b** and **8b** were synthesized from 2-methylthiofuran **2b** in a similar sequence, Scheme 1.

Reaction of **2b** with acrolein in glacial acetic acid at 60 °C gave the Michael adduct **9**, which following reduction with $NaBH_4$ and esterification with *p*-bromobenzoyl chloride gave



Scheme 1

compound **2c** in 55% overall yield. Compound **5c** was synthesized from **2c** *via* a similar sequence as **5a** from **2a** and **5b** from **2b**, Scheme 1.

Ozonolysis of compounds **5a**, **5b** and **5c**, all of which have *cis-endo* stereochemistry, in CH_2Cl_2 at −78 °C followed by reduction with dimethylsulphide gave the corresponding novel heterocyclic cage compounds **1a**, **1b** and **1c** in 60–68% yields, Scheme 1. The IR spectra lacked the carbonyl absorptions. The ^1H NMR spectrum† of **1a** showed two doublets at δ 5.58 and 5.52 for the two acetal protons on C-3 and C-5, and a singlet at δ 2.21 for the methylthio protons. The absorption at δ 2.09 singlet for the methyl ketone protons of **5a** shifted to δ 1.57 for the angular methyl protons of **1a**. The ^{13}C NMR spectrum lacked any carbonyl absorption and displayed two singlets at δ 121.9 and 117.7 for the quaternary carbons C-1 and C-7 of compound **1a**. The ^1H and ^{13}C NMR spectra of **1b** and **1c** revealed that both compounds **1b** and **1c** possess the same skeleton as **1a**.†

In order to understand the effect of the stereochemistry of the Diels–Alder adducts **5–8** on the formation of cage compounds **1**, ozonolysis reactions of compounds **6a**, **7a** and **8a** were also performed. No detectable amount of cage compound **1a** was formed in either ozonolysis reactions of **6a** or the mixture of **7a** and **8a**. Thus, only the isomers with *cis-endo* stereochemistry could give the corresponding heterocyclic cage compounds.

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† *Spectral data* for cage compounds **1a**: highly viscous liquid, IR, ν_{max} (neat) 1050 cm^{-1}; ^1H NMR ($CDCl_3$, 100 MHz), δ 5.58 (1H, d, *J* 6.6 Hz), 5.52 (1H, d, *J* 6.6 Hz), 3.59 (1H, dd, J_1 7.9, J_2 7.6 Hz), 3.23 (1H, dd, J_1 7.9 Hz, J_2 7.8 Hz), 2.95 (2H, m), 2.21 (3H, s), 1.95–1.85 (2H, m), 1.57 (3H, s); ^{13}C NMR $CDCl_3$, 25.0 MHz), δ 121.9(s), 117.7(s), 103.4(d), 102.6(d), 59.5(d), 56.5(d), 45.4(d), 45.1(d), 28.6(t), 24.2(q), 12.6(q); high resolution mass ($C_{11}H_{14}O_4S$) 242.0609 (calcd. 242.0613). **1b**: IR, ν_{max} (neat) 1050 cm^{-1}; ^1H NMR ($CDCl_3$, 100 MHz), δ 5.88 (1H, d, *J* 4.9 Hz), 5.58 (1H, d, *J* 6.6 Hz), 5.52 (1H, d, *J* 6.6 Hz), 3.52 (2H, m), 2.92 (2H, m), 2.27 (3H, s), 1.92 (2H, m); ^{13}C NMR ($CDCl_3$, 25.0 MHz), δ 122.6(s), 110.0(d), 104.0(d), 102.7(d), 58.6(d), 53.4(d) 45.3(d), 44.9(d), 28.9(t), 12.6(q); high resolution mass ($C_{10}H_{12}O_4S$) 228.0463 (calcd. 228.0456). **1c**: IR, ν_{max} (KBr)1720, 1595, 1280, 1050 cm^{-1}; ^1H NMR ($CDCl_3$, 100 MHz), δ 7.89 (2H, d, *J* 8.5 Hz), 7.57 (2H, d, *J* 8.5 Hz), 5.60 (1H, d, *J* 6.5 Hz), 5.54 (1H, d, *J* 6.5 Hz), 4.36 (2H, t, *J* 3.2 Hz), 3.55 (1H, dd, J_1 8.3 Hz, J_2 7.5 Hz), 3.24 (1H, dd, J_1 8.3H, J_2 7.6 Hz), 2.95 (2H, m), 2.23 (3H, s), 2.05–1.80 (6H, m); ^{13}C NMR ($CDCl_3$, 25.0 MHz), δ 165.1(s), 131.1(d)(2C), 130.6(d)(2C), 128.6(s), 127.4(s), 122.1(s), 119.4(s), 103.6(d), 102.7(d), 64.5(t), 59.4(d), 55.4(d), 45.6(d), 45.3(d), 33.9(t), 28.8(t), 23.4(t), 12.7(q); high resolution mass ($C_{20}H_{21}O_6SBr$) 470.0245, 468.0240 (calcd. 470.0218, 468.0240).