19. Synthesis of 4,6,8-Trisubstituted Methyl Azulene-2-carboxylates

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(21.X.94)

It is shown that sodium (methoxycarbonyl)cyclopentadienide (**1**), which is easily accessible from sodium cyclopentadienide and dimethyl carbonate in THF, reacts with 2,4,6-trisubstituted pyrylium tetrafluoroborates **2a–d** in boiling MeOH to afford the corresponding methyl azulene-2-carboxylates **4a–d** in good yields. The corresponding 1-carboxylates **3** were not found (*cf. Schemes 1* and *2*).

Whereas the synthesis of azulenes, substituted at the seven-membered ring, can easily be accomplished by the reaction of 2,4,6-trisubstituted pyrylium salts with sodium cyclopentadienide in THF (*cf.* [1] [2]) or of *N*-alkylpyridinium salts with sodium cyclopentadienide in DMF (*cf.* [1] [3]), it is much more problematic to react substituted cyclopentadienides under the above mentioned conditions, since, in general, mixtures of the 1- and 2-substituted azulenes are obtained which are difficult to separate (*cf.* [1] [4]). The reaction of 2,4,6-trimethylpyrylium perchlorate with sodium methylcyclopentadienide under carefully controlled conditions in THF leads to the formation of 2,4,6,8-tetramethylazulene in moderate yields [2a][2]).

We were interested in a plain synthesis of 4,6,8-trisubstituted methyl azulene-2-carboxylates and checked the reaction of sodium (methoxycarbonyl)cyclopentadienide (**1**), which is easily accessible by the reaction of dimethyl carbonate and sodium cyclopentadienide in THF at 70° [5], with 2,4,6-trimethylpyrylium tetrafluoroborate (**2a**). In THF, we obtained only mixtures of the corresponding 1- and 2-carboxylates **3a** and **4a** (*Scheme 1*; *cf.* also [6]).

However, when the reaction was run in boiling MeOH, only the 2-carboxylate **4a** was formed in 47% yield. It was deposited as a microcrystalline powder directly from the boiling solution. It was pure and showed no traces of the 1-carboxylate **3a**. The examples in *Scheme 2* show that the described procedure can generally be applied to the synthesis of 4,6,8-trisubstituted azulene-2-carboxylates.

We assume that, in the protic solvent MeOH, **1** reacts in its 6-methoxyfulvene 6-oxide form, *i.e.*, it should attack the corresponding pyrylium salts with its C(3,4)-atoms, favoring the formation of the 2-carboxylates.

The azulene-2-carboxylates can be reduced in one step to the corresponding 2-methylazulenes with sodium dihydridobis(2-methoxyethoxy)aluminate in the presence of $AlCl_3$ in toluene (*cf. Exper. Part*).

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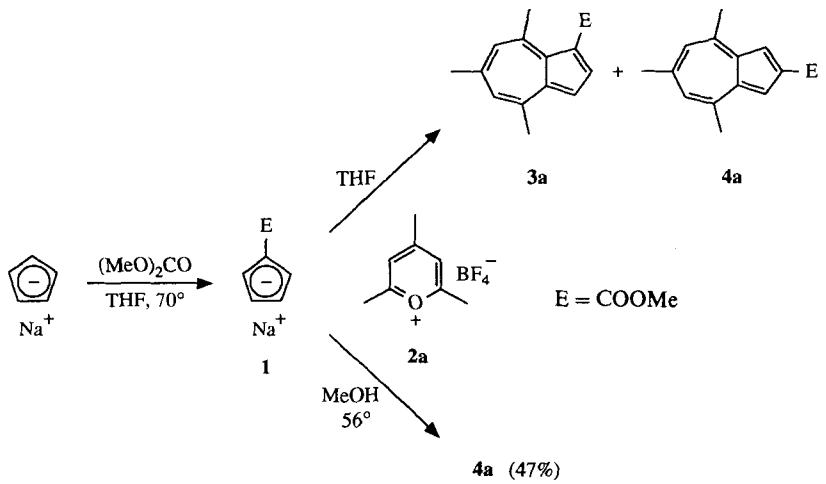
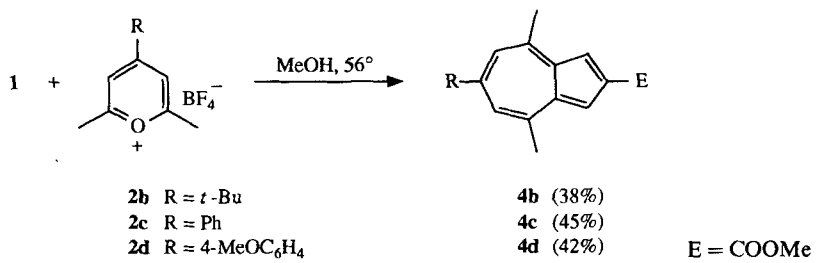
[2]) Our own experience showed us that the corresponding pyrylium tetrafluoroborate always yields mixtures of 1,4,6,8- and 2,4,6,8-tetramethylazulene.

Scheme 1



Scheme 2



We thank Prof. *M. Hesse* and his coworkers for mass spectra, Prof. *W. von Philipsborn* and his coworkers for NMR support and ^{1}H-NOE measurements, and *H. Frohofer* for elemental analysis. The financial support of this work by the *Schweizerischer Nationalfonds zur Förderung der wissenschaftlichen Forschung* is gratefully acknowledged.

Experimental Part

General. See [7] [8]. All reactions were performed under N_2. Et_2O and hexane were distilled before use. Cyclopentadiene (from dicyclopentadiene, *Fluka, pract.*) was freshly distilled over a *Vigreux* column before use. NaH (60–65% dispersion in oil, *Fluka*) was washed with hexane before use. THF (*Fluka, puriss. p.a.*), MeOH (*Merck*, z. A.), dimethyl carbonate (*Fluka, purum*), and 2,6-dimethyl-4-pyrone (*Fluka, purum*) were used without further purification.

1. Formation of the Methyl Azulene-2-carboxylates. 1.1. *Methyl 4,6,8-Trimethylazulene-2-carboxylate* (**4a**). NaH (4.5 g, 0.19 mol) was suspended in THF (190 ml). The suspension was cooled to 0°, and cyclopentadiene (39 ml, 0.38 mol) was added dropwise. The mixture turned red. After all cyclopentadiene had been added, stirring was continued for 1 h at 0° and then the soln. warmed up to r.t. At that point, $(MeO)_2CO$ (50 ml, 0.58 mol) was added dropwise under stirring. After 10 min at r.t., the soln. was heated during 4 h under reflux. The solvent was removed *in vacuo* and the ocker-colored residue suspended in MeOH (250 ml). *2,4,6-Trimethylpyrylium tetrafluoroborate* (**2a**; 21.5 g, 0.11 mol) [9] was added with stirring. The mixture turned at once blue. It was heated under reflux during 12 h. The blue microcrystalline precipitate was filtered, washed with H_2O (2 × 200 ml) and cooled MeOH (2 × 100

ml) to yield pure **4a** (12.1 g, 47% with respect to **2a**). M.p. 175.3–176.7° (Et_2O). R_f (hexane/Et_2O 1:1): 0.52. UV (hexane): λ_{max} 368.0 (3.77), 351.4 (3.72), 339.2 (3.66, sh), 301.7 (4.70), 291.5 (4.70), 249.5 (4.43), 218.4 (4.09); λ_{min} 360.7 (3.54), 310.2 (3.43), 297.5 (4.64), 266.8 (3.83), 227.1 (4.02). IR ($CHCl_3$): 3021*w*, 2926*w*, 1700*s*, 1540*m*, 1506*m*, 1435*m*, 1324*m*, 1249*m*, 1130*s*. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.76 (*s*, H–C(1,3)); 7.05 (*s*, H–C(5,7)); 3.95 (*s*, COOMe); 2.86 (*s*, Me–C(4,8)); 2.61 (*s*, Me–C(6)). ^{13}C-NMR (75 MHz, $CDCl_3$): 168.51 (*C*OOMe); 151.95 (C(6)); 151.88 (C(4,8)); 137.70 (C(3a,8a)); 135.22 (C(2)); 129.92 (C(5,7)); 118.99 (C(1,3)); 53.48 (COO*Me*); 30.84 (*Me*–C(6)); 26.94 (*Me*–C(4,8)). EI-MS: 227 (100, $M^{+\cdot}$), 196 (27, $[M - OCH_3]^+$). Anal. calc. for $C_{15}H_{16}O_2$ (227.27): C 79.27, H 7.10; found: C 79.02, H 7.03.

1.2. *Methyl 6-(*tert*-Butyl)-4,8-dimethylazulene-2-carboxylate* (**4b**). 1.2.1. *4-(*tert*-Butyl)-2,6-dimethylpyrylium Tetrafluoroborate* (**2b**). It was prepared in analogy to [10] from 2,6-dimethyl-4-pyrone and *t*-BuMgCl/Et_2O (crystallized from MeOH/EtOH as long white needles in a yield of 35%). M.p. 200.1–200.9° (MeOH/EtOH). ^{1}H-NMR (300 MHz, (D_6)acetone): 8.27 (*s*, H–C(3,5)); 3.02 (*s*, Me–C(2,6)); 1.49 (*s*, *t*-Bu).

1.2.2. *Formation of* **4b**. The ester was prepared in analogy to **4a** starting with NaH (1.2 g, 50 mmol), THF (50 ml), cyclopentadiene (10.3 ml, 100 mmol), $(MeO)_2CO$ (13.2 ml, 153 mmol), **2b** (4.78 g, 29 mmol), and MeOH (65 ml). The ester **4b** (3.0 g; 38% with respect to **2b**) was obtained as a blue microcrystalline powder. M.p. 160.5–162.1° (hexane/AcOEt). R_f (hexane/Et_2O 1:1): 0.61. UV (hexane): λ_{max} 366.2 (3.86), 349.5 (3.80), 296.0 (4.80), 285.8 (4.81), 244.5 (4.53), 213.2 (4.16); λ_{min} 358.5 (3.65), 339.2 (3.77), 320.8 (3.69), 291.3 (4.77), 258.7 (4.27), 221.0 (4.13). IR (KBr): 2996*w*, 2961*w*, 1710*s*, 1575*m*, 1323*m*, 1221*s*. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.76 (*s*, H–C(1,3)); 7.33 (*s*, H–C(5,7)); 3.96 (*s*, COOMe); 2.93 (*s*, Me–C(4,8)); 1.46 (*s*, *t*-Bu). ^{13}C-NMR (75 MHz, $CDCl_3$): 167.17 (*C*OOMe); 162.15 (C(6)); 149.69 (C(4,8)); 135.97 (C(3a,8a)); 133.86 (C(2)); 124.74 (C(5,7)); 116.65 (C(1,3)); 51.57 (COO*Me*); 38.94 (Me_3C); 31.84 (Me_3C); 25.71 (*Me*–C(4,8)). MS: 270 (100, $M^{+\cdot}$), 255 (11, $[M - CH_3]^+$), 239 (9, $[M - OCH_3]^+$). Anal. calc. for $C_{18}H_{22}O_2$ (270.37): C 79.97, H 7.20; found: C 79.76, H 7.15.

1.3. *Methyl 4,8-Dimethyl-6-phenylazulene-2-carboxylate* (**4c**). 1.3.1. *2,6-Dimethyl-4-phenylpyrylium Tetrafluoroborate* (**2c**). It was prepared from 2,6-dimethyl-4-pyrone and PhMgBr/Et_2O (crystallized from MeOH/EtOH as red-brown platelets and needles in a yield of 73%). M.p. 201.9–202.4° (MeOH/EtOH). ^{1}H-NMR (300 MHz, (D_6)acetone): 8.61 (*s*, H–C(3,5)); 8.33 (*d* (f.s.), ^3J = 7.2, H–C(2,6) of Ph); 7.88 (*t* (f.s.), ^3J = 7.2, H–C(4) of Ph); 7.77 (*t* (f.s.), ^3J = 7.2, H–C(3,5) of Ph); 3.08 (*s*, Me–C(2,6)).

1.3.2. *Formation of* **4c**. The ester was prepared in analogy to **4a** starting with NaH (1.2 g, 50 mmol), THF (50 ml), cyclopentadiene (10.3 ml, 100 mmol), $(MeO)_2CO$ (13.2 ml, 153 mmol), **2c** (5.37 g, 29 mmol), and MeOH (65 ml). The ester **4c** (3.80 g; 45% with respect to **2c**) was obtained as a blue-greenish microcrystalline powder. M.p. 165.3–167.5° (hexane/AcOEt). R_f (hexane/Et_2O 1:1): 0.49 UV (hexane): λ_{max} 377.4 (4.02), 346.0 (3.74, sh), 333.5 (3.66), 304.1 (4.75), 295.7 (4.69, sh), 248.5 (4.26), 212.9 (3.93); λ_{min} 338.2 (3.63), 320.8 (3.63), 262.0 (3.56), 224.6 (3.83). IR (KBr): 3022*w*, 2971*w*, 1714*s*, 1577*m*, 1452*m*, 1329*m*, 1230*s*. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.86 (*s*, H–C(1,3)); 7.63 (*dd*, ^3J = 6.8, ^4J = 1.3, H–C(2,6) of Ph); 7.52–7.43 (*m*, H–C(3,4,5) of Ph); 7.37 (*s*, H–C(5,7)); 3.98 (*s*, COOMe); 2.97 (*s*, Me–C(4,8)). ^{13}C-NMR (75 MHz, $CDCl_3$): 165.07 *C*OOMe); 150.14 (C(4,8)); 145.27 (C(6)); 136.11 (C(3a,8a)); 134.32 (C(2)); 134.03 (C(1) of Ph); 128.64 (2 arom. C); 128.54 (2 arom. C); 128.16 (C(4) of Ph); 127.31 (C(5,7)); 177.44 (C(1,3)); 51.93 (COO*Me*); 25.39 (*Me*–C(4,8)). MS: 290 (100, $M^{+\cdot}$), 259 (49, $[M - OCH_3]^+$). Anal. calc. for $C_{20}H_{18}O_2$ (290.36): C 82.74, H 6.25; found: C 82.73, H 6.21.

1.4. *Methyl 6-(4-Methoxyphenyl)-4,8-dimethylazulene-2-carboxylate* (**4d**). 1.4.1. *4-(4-Methoxyphenyl)-2,6-dimethylpyrylium Tetrafluoroborate* (**2d**). It was prepared from 2,6-dimethyl-4-pyrone and (4-$MeOC_6H_4$)MgBr/Et_2O (crystallized from MeOH/EtOH as a microcrystalline yellowish powder). M.p. 203.8–204.6° (MeOH/EtOH). ^{1}H-NMR (300 MHz, (D_6)acetone): 8.56 (*s*, H–C(3,5)); 8.45 (*d* (f.s.), ^3J = 9.0, H–C(2,6) of 4-$MeOC_6H_4$); 7.33 (*t* (f.s.), ^3J = 9.0, H–C(3,5) of 4-$MeOC_6H_4$); 4.04 (*s*, CH_3O); 2.96 (*s*, Me–C(2,6)).

1.4.2. *Formation of* **4d**. The ester was prepared in analogy to **4a** starting with NaH (1.2 g, 50 mmol), THF (50 ml), cyclopentadiene (10.3 ml, 100 mmol), $(MeO)_2CO$ (13.2. ml, 153 mmol), **2a** (5.37 g, 29 mmol), and MeOH (65 ml). The ester **4d** (3.90 g; 42% with respect to **2d**) was obtained as a microcrystalline greenish powder. M.p. 169.8–172.5° (hexane/AcOEt). R_f (hexane/Et_2O 1:1): 0.45. UV (hexane): λ_{max} 381.1 (4.32), 320.5 (4.78), 308.7 (4.71), 292.5 (4.61), 243.0 (4.50, sh), 233.4 (4.52); λ_{min} 356.1 (4.12), 312.8 (4.69), 297.0 (4.60), 263.9 (4.26). IR (KBr): 3042*w*, 2976*w*, 1718*s*, 1576*m*, 1516*m*, 1441*m*, 1326*m*, 1298*m*, 1264*m*, 1223*s*. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.83 (*s*, H–C(1,3)); 7.58 (*d*, ^3J = 8.5, H–C(2,6) of 4-$MeOC_6H_4$); 7.35 (*s*, H–C(5,7)); 7.02 (*d*, ^3J = 8.8, H–C(3,5) of 4-$MeOC_6H_4$); 3.98 (*s*, COOMe); 3.88 (*s*, MeO); 2.96 (*s*, Me–C(4,8)). ^{13}C-NMR (75 MHz, $CDCl_3$): 165.83 (*C*OOMe); 151.71 (C(6)); 150.13 (C(4,8)); 137.68 (C(4) of 4-$MeOC_6H_4$); 135.94 (C(3a,8a)); 133.67 (C(2)); 129.94 (C(2,6) of 4-$MeOC_6H_4$); 127.52 (C(1) of 4-$MeOC_6H_4$); 127.09 (C(5,7)); 117.46 (C(1,3)); 114.25 (C(3,5) of 4-$MeOC_6H_4$); 55.46 (MeO); 51.75 (COO*Me*); 25.52 (*Me*–C(4,8)). MS: 320 (100, M^+), 289 (31, $[M - OCH_3]^+$). Anal. calc. for $C_{21}H_{20}O_3$ (320.39): C 78.72, H 6.29; found: C 78.62, H 6.29.

2. Reduction of **4a**. $AlCl_3$ (0.53 g, 4.0 mmol; *Fluka, puriss.*) was added to toluene (10 ml). After cooling to 0°, sodium dihydridobis(2-methoxyethoxy)aluminate in toluene (4.6 ml, 16 mmol; *Fluka, pract.* 70% in toluene) was added and the mixture stirred for 1 h at 0°. After this time, a soln. of **4a** (0.86 g, 4 mmol) in toluene (20 ml) was added dropwise. The temp. went up to 28–30°, and the color of the mixture changed from blue to red-blue. TLC showed that most of **4a** had reacted to 2-(hydroxymethyl)-4,6,8-trimethylazulene, and only traces of 2,4,6,8-tetramethylazulene were recognizable. Stirring was continued at r.t. for 20 h. After this time, only 2,4,6,8-tetramethylazulene was detectable by TLC. An aq. soln. of NaOH (20 ml, 20%) was added and the colorless precipitate removed by filtration. The filtrate was extracted with Et_2O, and the combined org. layers, after washing with H_2O, were dried ($MgSO_4$). Evaporation of the solvent yielded pure 2,4,6,8-tetramethylazulene (0.65 g, 90%; *cf.* [10]). M.p. 99.8–101.1° (EtOH). R_f (hexane/Et_2O 1:1): 0.71. UV (hexane): λ_{max} 351.8 (3.74), 313.3 (3.82), 293.6 (4.76), 285.2 (4.71), 245.6 (4.45); λ_{min} 342.7 (3.60), 311.8 (3.78), 287.3 (4.73), 258.5 (3.63), 220.9 (4.23). IR (KBr): 3005*w*, 2923*w*, 1578*m*, 1501*m*, 1447*m*, 1375*w*, 1333*m*, 1312*w*, 1088*w*, 1027*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.12 (*s*, H–C(1,3)); 7.02 (*s*, H–C(5,7)); 2.82 (*s*, Me–C(4,8)); 2.61, 2.59 (2*s*, Me–C(2,6)).

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