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OXIDATIVE 1,1’-COUPLING OF HIGHLY ALKYLATED 2-METHOXYCARBONYLAZULENES

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Dedicated to Professor Isao Kuwajima on the occasion of his 77th birthday

Abstract – The oxidation of highly alkylated methyl azulene-2-carboxylates **1b** – **1d** and a dimethyl azulene-1,2-dicarboxylate **1a** with TEMPO (2,2,6,6-tetramethyl-piperidine-1-oxyl) in the presence of $Et_2O{\cdot}BF_3$ ((diethyloxonio)trifluoroborate) in benzene at 5 °C leads in moderate yield to the corresponding 1,1’-biazulene-carboxylates **2a** – **2d** (Table 1).

INTRODUCTION

As for arene couplings,[1] there are principally two procedures which can be applied for the synthesis of 1,1’-biazulenes, i.e. the classical Ullmann coupling[2] or its modern transition metal variants (see, e.g.[3]) as well as oxidative coupling reactions (see, e.g.[4-6]). The exposure to air of guaiazulene, when absorbed on silica gel, is already sufficient to form 3,3’-biguaiazulene (5,5'-diisopropyl-3,3',8,8'-tetramethyl-1,1'-biazulene) as main product beside higher oxidation products,[7] and benzo[*a*]azulene with MnO_2-C (C = activated carbon) as catalyst[8] as well as azuleno[1,2-*b*]thiophene with *N*-iodosuccinimide (NIS) as oxidant[9] are converted to the corresponding biazulenes in good yields. In general, higher alkylated azulenes combine readily in their radical cation state to the corresponding biazulenium forms, which by loss of two protons yield biazulenes.[10] With the exception of ethyl 2-aminoazulene-1-carboxylate,[10,11] which indeed carries a strong π-donor group next to the carboxy group, it seems that the oxidative coupling of azulenes with electron-acceptor substituents at the 5-membered ring such as alkoxycarbonyl groups at C(2) or C(1) and C(2) has not been tried.[12-14] The AM1 calculated structure of such kind of 1,1’-biazulene-2,2’-dicarboxylate is displayed in Figure 1. Most interesting is the fact that the energetically relaxed structure of it possesses almost perpendicularly oriented azulene halves with MeO of the ester groups in *syn*-orientation and outward position. The distance of their O-atoms amounts to 426 pm, i.e., a distance for possibly further interactions. In the following, we describe our experiment to synthesize the envisaged 1,1’-biazulene-2,2’-dicarboxylates.

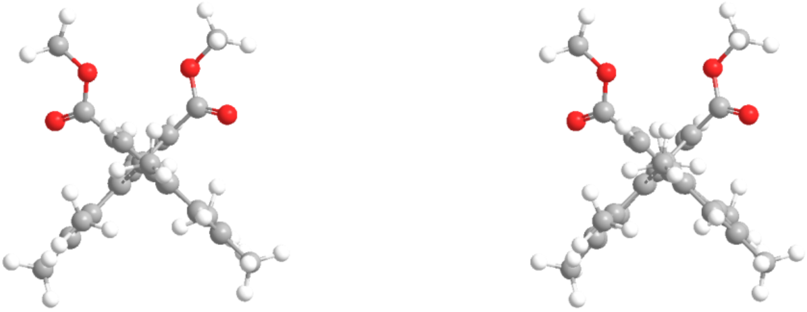


Figure 1. Stereoscopic view of the AM1 calculated structure of dimethyl 4,4',6,6',8,8'-hexamethyl-[1,1'-biazulene]-2,2'-dicarboxylate (**2c**; $\Delta H_f° = –22.87$ Kcal·mol^{-1}; Θ(C(8a)–C(1)–C(1‘)–C(8’a)) = 88.7°)

RESULTS AND DISCUSSION

We investigated the oxidative coupling of three methyl azulene-2-carboxylates **1b** – **1d** and dimethyl azulene-1,2-dicarboxylate **1a** (Figure 2). Azulene-1,2-dicarboxylates are by-products of Hafner’s heptalene synthesis starting with azulenes and dimethyl acetylenedicarboxylate.[17,18] Treatment of the azulene-1,2-dicarboxylates with phosphoric acid (see[19,20]) leads to selective demethoxycarbonylation at C(1).[21] We had **1a** and the corresponding dimethyl dicarboxylates for **1b** – **1d** from our former work on the thermal reaction of azulenes and dimethyl acetylenedicarboxylate at hand.[23,24]

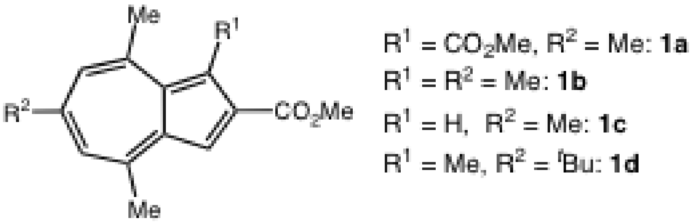
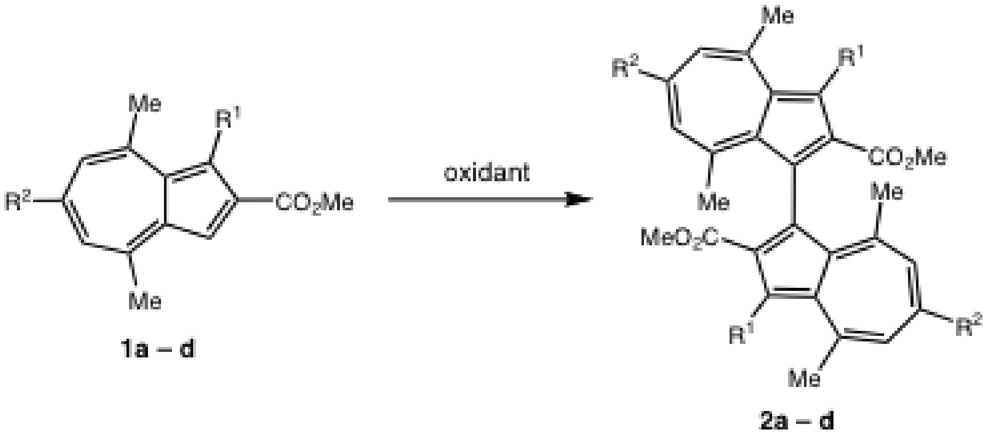


Figure 2. Dimethyl azulene-1,2-dicarboxylate **1a** and methyl azulene-2-carboxylates **1b** – **1d** for oxidative 1,1’-coupling

We chose **1a** as model substrate for our screening experiments of its oxidative 1,1’-didehydrodimerization (Scheme 2). As a result, we found that typical oxidants for inter- and intramolecular benzene coupling reactions such as CoF_3, $Th(OC(O)CF_3)_3$, RuO_2, VOX_3 (X = F, Cl), $PhI(OAc)_2/Et_2O·BF_3$ or $PhI(OC(O)CF_3)_2/Et_2O·BF_3$, and DDQ in diverse solvents gave no didehydro-dimer **2a** at all.



Scheme 1. Oxidative 1,1'-didehydrodimerization of **1a** – **1d**

Finally, we checked the oxidant system $PhI(OAc)_2/Et_2O \cdot BF_3$ again, but this time in the presence of 1 eq. of $FeCl_3$ in benzene at 5 °C and, indeed, for the first time, we found 15% of **2a** in the reaction mixture. A further experiment showed that the catalytic system worked also without $PhI(OAc)_2$, thus resulting in the formation of **2a** in an almost equal yield of 12%. On the other hand, $FeCl_3$ alone, also when adsorbed on silica gel, did not lead to the formation of **2a** in benzene. In view of the fact that $Et_2O \cdot BF_3$ seemed to play the role of an enhancer for the 1,1'-coupling reaction **1a** → **2a** with oxidants such as $FeCl_3$, we looked for another organic oxidant and selected 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO).[25] Again, we observed that TEMPO alone in benzene does not cause the 1,1'-coupling of **1a**. However, in the presence of $Et_2O \cdot BF_3$, we found 12% of **2a**. Following experiments with TEMPO and varying amounts of $Et_2O \cdot BF_3$ led with all azulenecarboxylates **1a** – **1d** to the corresponding biazulenes **2a** – **2d**. The experimental results are listed in Table 1.[26,27]

All 4 dimers could be obtained in crystalline form. But none of the crystals of **2a** – **2d** were suitable for an X-ray crystal structure analysis. The elemental analysis indicated that three of the crystallized dimers contained water, which could not be removed by drying in vacuo, in a molar ratio of 1 : 1 (**2a**, **2d**) or 0.5 : 1 (**2c**). Nevertheless, the MS spectra of all 4 dimers showed the correct molecular mass as well as the expected ^1H- and the related ^{13}C-NMR spectra.

Most interesting is the observation that $Et_2O \cdot BF_3$ is a necessary co-catalyst (enhancer) for the oxidants TEMPO or $FeCl_3$. We suppose that in the loosely coordinating solvent benzene $Et_2O \cdot BF_3$ transfers BF_3 to the oxyl O-atom of TEMPO and that it is this species, which snatches an electron from the azulene π-skeleton, thus leading to 1-((trifluoroboryl)oxy)-2,2,6,6-tetramethylpiperidine anion and the corresponding azulenium ion, which then dimerizes. As a result, biazulenes **2** are formed, accompanied by 2 eq. HF and 2 eq. 1-((difluoroboryl)oxy)-2,2,6,6-tetramethylpiperidine. Obviously, $FeCl_3$ and $Et_2O \cdot BF_3$ in benzene co-operates in a similar manner, thus leading to $FeCl_2^+$ as crucial oxidant for the azulene-2-carboxylates **1**.

Table 1. Oxidative 1,1'-coupling of alkylated methoxycarbonylazulenes[a)]

Substrate	Oxidant[b)]	Product	Yield (%)[c)]
1a	$FeCl_3/Et_2O{\cdot}BF_3$	**2a**	12
	$FeCl_3$		0
	TEMPO/ $Et_2O{\cdot}BF_3$		12
	TEMPO/2 eq. $Et_2O{\cdot}BF_3$[d)]		37
1b	TEMPO/2 eq. $Et_2O{\cdot}BF_3$	**2b**	23
1c	TEMPO/2 eq. $Et_2O{\cdot}BF_3$	**2c**	18
	$FeCl_3/Et_2O{\cdot}BF_3$		24
1d	TEMPO/2 eq. $Et_2O{\cdot}BF_3$	**2d**	21

[a)] See Figure 2 and Scheme 1.
[b)] Benzene at 5 °C.
[c)] Yield of pure material.
[d)] More than 2 eq. of $Et_2O{\cdot}BF_3$ led to decomposition.

EXPERRIMENTAL

General: See.[28,29]

Oxidative 1,1'-coupling of the methyl azulenecarboxylates 1a – 1d. – TEMPO (0.312 g, 2.0 mmol) was dissolved in benzene (5 mL). The solution was cooled to 5 °C, and the respective azulenecarboxylate **1** (1.0 mmol), dissolved in benzene (5 mL), was added under stirring and an N_2 atmosphere. Then, $Et_2O{\cdot}BF_3$ (0.284 g, 2.0 mmol) was put in drop by drop. After 1 h stirring at 5 °C, the cooling bath was removed and stirring was continued for 3 h. The reaction was quenched by addition of a saturated aqueous Na_2CO_3 solution (15 mL). The phases were separated and the water phase extracted 3 times with AcOEt (3 x 15 mL). The combined organic phases were washed with water (2 x 10 mL) and dried ($MgSO_4$). The crude product, left after evaporation, was further dried in vacuo (0.06 Torr, 1 h) in order to remove non-reacted TEMPO together with its respective amine. Non-reacted azulenecarboxylates and other by-products were removed by flash chromatography (Et_2O/AcOEt) on silica gel. Yields of the pure didehydro-dimers **2** are listed in Table 1.

Experiments with the other oxidants were performed in the same manner.

Data of tetramethyl 4,4',6,6',8,8'-hexamethyl-[1,1'-biazulene]-2,2',3,3'-tetracarboxylate (2a): mp 207.1–208.0 °C (Et_2O/AcOEt). R_f (hexane/AcOEt 1:1) 0.46. IR ($CHCl_3$): 1720s (C=O). ^{1}H-NMR (300 MHz, $CDCl_3$): 7.11 (s, H–C(5,5')); 6.96 (s, H–C(7,7')); 3.92 (s, CH_3OOC–C(3,3')); 3.44 (s, CH_3OOC–C(2,2')); 2.90 (s, CH_3–C(4,4')); 2.56 (s, CH_3–C(6,6')); 2.15 (s, CH_3–C(8,8')). ^{1}H-NOE ($CDCl_3$): 2.15 ↔

6.96; 2.56 ↔ 6.96 + 7.11; 2.90 ↔ 3.92 + 7.11. ^{13}C-NMR (75 MHz, $CDCl_3$): 170.04, 166.37 (O=*C*–C(2,2’,3,3’)); 152.89, 150.11, 149.65, 136.33, 134.90, 132.66, 126.88, 121.27 (C(1,1’,3a,3’a – 8a,8’a)); 52.20, 51.39 ($\mathit{C}H_3OOC$–C(2,2’,3,3’)); 28.45, 28.07, 27.22 ($\mathit{C}H_3$–C(4,4’,6,6’,8’,8’)). EI-MS (570.64): 571 (M^+, 100), 539 ($[M - CH_3O]^+$, 74). The elemental analysis indicated the presence of one H_2O in the crystals of **2a** ($C_{34}H_{34}O_8$ + H_2O), 588.65): Anal. Calcd for $C_{34}H_{34}O_6$: C 69.37, H 6.16. Found: C 69.29, H 6.34.

Data of dimethyl 3,3',4,4',6,6',8,8'-octamethyl-[1,1'-biazulene]-2,2'-dicarboxylate (2b): mp 205.3–206.2 °C (Et_2O/hexane). R_f (hexane/AcOEt 4:1) 0.22. IR ($CHCl_3$): 1714s (C=O). ^{1}H-NMR (300 MHz, $CDCl_3$): 7.77 (s, 2H, H–C(5,5’)); 6.64 (s, 2H, H–(7,7’)); 3.41 (s, CH_3COO–C(2,2’)); 3.02 (s, 6H, CH_3–C(3)); 2.87 (s, 6H, CH_3–C(4,4’)); 2.44 (s, 6H, CH_3–C(6)); 2.03 (s, 6H, CH_3–C(8,8’)). ^{13}C-NMR (75 MHz, $CDCl_3$): 169.00 (O=C–C(2,2’); 51.21 ($\mathit{C}H_3OOC$–C(2,2’)); 28.99, 28.20, 27.62, 17.56 ($\mathit{C}H_3$–C(3,3’,4,4’,6,6’,8,8’)). EI-MS (482.62): 482 (M^+, 100). Anal. Calcd for $C_{32}H_{34}O_4$: C 79.64, H 7.10. Found C 79.51, H 7.48.

Data of dimethyl 4,4',6,6',8,8'-hexamethyl-[1,1'-biazulene]-2,2'-dicarboxylate (2c): mp 227.0–227.5 °C (AcOEt/hexane). R_f (hexane/Et_2O 1:1) 0.31. IR ($CHCl_3$): 1715s. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.90 (H–C(3,3’)); 6.97 (s, H–C(5,5’)); 6.79 (s, H–(7,7’)); 3.58 (s, CH_3COO–C(2,2’)); 2.91 (s, CH_3–C(4,4’)); 2.53 (s, CH_3–C(6,6’)); 2.03 (s, CH_3–C(8,8’)). ^{1}H-NOE ($CDCl_3$): 7.90 ↔ 2.91, 3.58; 2.91 ↔ 7.90, 6.97; 2.53 ↔ 6.79; 2.03 ↔ 6.79. ^{13}C-NMR (75 MHz, $CDCl_3$): 166.40 (C=O, C(2,2’)); 130.67, 127.57, 117.66 (C(3,3’,5,5’,7,7’)): 51.20 ($\mathit{C}H_3OOC$–C(2,2’)); 28.74, 27.24, 25.67 (CH_3–C(4,4’,6,6’,8,8’)). CI-MS (454.57): 455 (M^+), 423 ($[M - CH_3OH]^+$, 61). The elemental analysis indicated the presence of 0.5 H_2O in the crystals of **2a** ($C_{60}H_{60}O_8$ + H_2O), 927.15): Anal. Calcd for $C_{60}H_{60}O_8$: C 77.73, H 6.74. Found: C 77.80, H 6.38.

Data of dimethyl 6,6'-di(*tert*-butyl)-3,3',4,4',8,8'-hexamethyl-[1,1'-biazulene]-2,2-dicarboxylate (2d): mp 120.0–122.0 °C (AcOEt/hexane). R_f (hexane/AcOEt 1:1) 0.23. IR ($CHCl_3$): 1712s. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.00 (s, H–C(5,5’)); 6.86 (s, H–C(7,7’)); 3.42 (s, CH_3OOC–C(2,2’)); 3.06 (s, CH_3–C(4,4’)); 2.86 (s, CH_3–C(3,3’)); 2.09 (s, CH_3–C(8)); 1.38 (s, $(CH_3)_3$–C(6,6’)). ^{1}H-NOE ($CDCl_3$): 2.86 ↔ 3.06, 3.42; 7.00 ↔ 3.06, 1.38; 6.86 ↔ 2.09, 1.38. ^{13}C-NMR (75 MHz, $CDCl_3$): 169.09 (C=O, C(2,2’)); 125.54, 125.33 (C(5,5’,7,7’)); 51.19 ($\mathit{C}H_3OOC$–C(2,2’)); 38.20 ($(CH_3)_3\mathit{C}$–C(6,6’)); 29.55, 28.27, 27.60 (CH_3–C(3,3’,4,4’,8,8’)); 17.48 ($(\mathit{C}H_3)_3C$–C(6,6’)). EI-MS (566.86): 566 (M^+, 100). The elemental analysis indicated the presence of one H_2O in the crystals of **2d** ($C_{38}H_{46}O_8$ + H_2O), 584.88): Anal. Calcd for $C_{36}H_{46}O_8$: C 78.04, H 8.27. Found: C 78.32, H 8.53.

ACKNOWLEDGEMENT

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