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Reactivity of azafulvenium methides derived from pyrrolo-[1,2-*c*]thiazole-2,2-dioxides: synthesis of functionalised pyrroles

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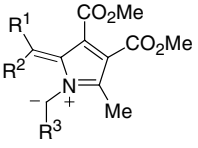
Abstract—Extrusion of sulfur dioxide from pyrrolo[1,2-*c*]thiazole-2,2-dioxides led to the synthesis of functionalised pyrroles via the generation of 1-azafulvenium methides. Sealed tube reaction conditions allowed the synthesis of *N*- and *C*-vinylpyrroles whereas from FVP methyl 1,3-dimethyl-5-oxo-5*H*-pyrrolizine-2-carboxylate and 4-oxo-1,4-dihydro-1-aza-benzo[*f*]azulene-3-carboxylates were obtained. These last compounds could also be obtained from the FVP of the *N*- and *C*-vinylpyrroles.

It has been reported the generation of 1-azafulvenium methides (**1**–**4**) by the thermal extrusion of sulfur dioxide from pyrrolo[1,2-*c*]thiazole-2,2-dioxides.[1] These extended dipolar systems **1**–**3** undergo sigmatropic [1,8]H shifts giving vinylpyrroles and the acyl derivatives **4** electrocyclise to give pyrrolo[1,2-*c*]-[1,3]oxazines. Having access to a broad range of pyrrolo[1,2-*c*]thiazoles[2] we decided to explore the generation of new azafulvenium methides in order to get further knowledge on the reactivity of these transient 8π 1,7-dipoles.



1 $R^1 = R^2 = H$; $R^3 = CH_3$
2 $R^1 = H$; $R^2 = CH_3$; $R^3 = H$
3 $R^1 = R^2 = CH_3$; $R^3 = H$
4 $R^1 = H$; $R^2 = COR$; $R^3 = H$

As a first objective we decided to prepare 3,5-diphenyl-1*H*-pyrrolo[1,2-*c*]thiazole-2,2-dioxide **6a** from **5a**[2d] by oxidation with MCPBA and promote its thermolysis (Scheme 1). We found that the extrusion of SO_2 from pyrrolo[1,2-*c*]thiazole-2,2-dioxide **6a** could be carried out in a sealed tube leading to styryl-1*H*-pyrrole **9a**. The best result was obtained by heating at 220 °C for 1.5 h a solution of **6a** in sulfolane giving **9a** in 80% yield (Table 1).

A similar result was obtained starting from 5-methyl-3-phenyl-1*H*-pyrrolo[1,2-*c*]thiazole-2,2-dioxide **6b** and the corresponding styryl-1*H*-pyrrole **9b**[3] could be obtained in 54% yield (Scheme 1 and Table 1). Storr and co-workers[1b] have described attempts of thermal extrusion of SO_2 from **6b** although no products of this reaction were reported.

The formation of styryl-1*H*-pyrroles **9** can be explained considering the generation of azafulvenium methides **7** followed by an 1,7-electrocyclic reaction giving **8**, which rearrange to the final products. Attempts were made to trap **7a** by promoting the sealed tube thermolysis in the presence of DMAD and also in the presence of bis(trimethylsilyl)acetylene although no evidence was obtained for the formation of adducts and the only product was styryl-1*H*-pyrrole **9a**. Nevertheless, the synthesis of pyrroles **9** is a strong evidence of the generation of the new azafulvenium methides **7**.

Encouraged by the preceding results we decided to look more carefully into the generation of azafulvenium

Keywords: 1-Azafulvenium methides; *N*- and *C*-Vinylpyrroles; 1,3-Dimethyl-5-oxo-5*H*-pyrrolizine-2-carboxylate; 1-Aza-benzo[*f*]azulene-3-carboxylate.
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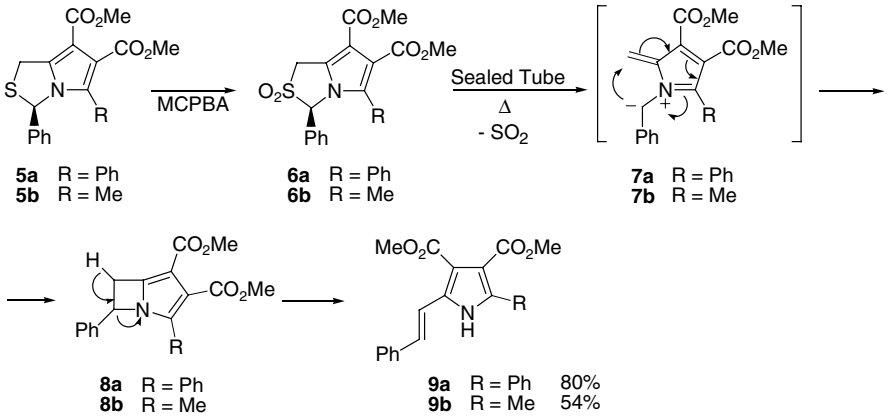


Scheme 1.

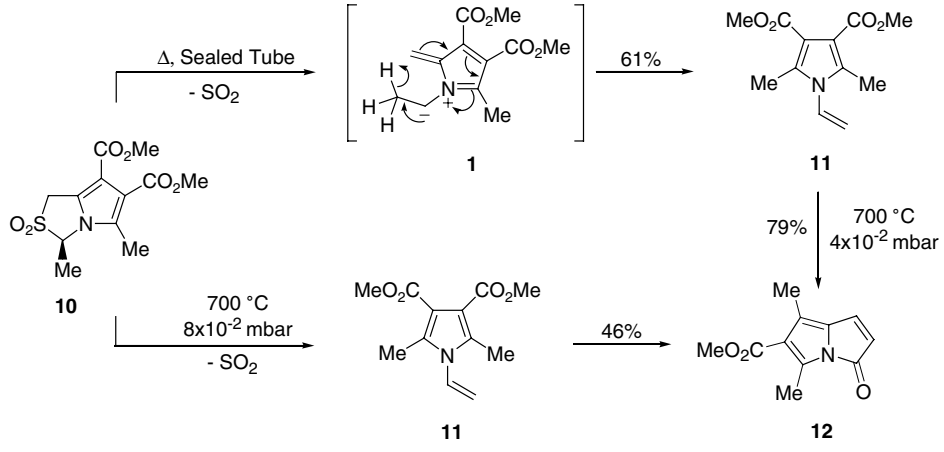
Table 1. Sealed tube reactions using sulfolane as solvent

Starting compound	Reaction conditions	Product
6a	215 °C, 3 h	**9a**, 5%
6a	190–195 °C, 3 h	**9a**, 20%
6a	220 °C, 1.5 h	**9a**, 80%
6b	185–195 °C, 3 h	**9b**, 8%
6b	240 °C, 3 h	**9b**, 31%
6b	220 °C, 1.5 h	**9b**, 54%
11	260 °C, 3 h	**11,** 17%
11	215 °C, 3 h	**11**, 8%
11	260 °C, 2 h	**11**, 61%

methide **1**. It has been reported that on FVP (700 °C/ 1.3×10^{-3} mbar) sulfone **10** leads to vinylpyrrole **11** via an allowed, suprafacial [1,8]H shift in the 8π 1,7-dipolar system **1**.[1] We found that the same vinylpyrrole (**11**) could be obtained in 61% yield carrying out the reaction in a sealed tube allowing us to conclude that sulfone **10** extrudes SO_2 without the need of FVP conditions (Scheme 2 and Table 1).

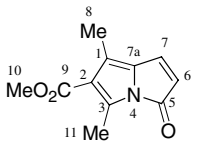
The flash vacuum pyrolysis of sulfone **10** was also studied. Interestingly our FVP conditions (700 °C/ 8×10^{-2} mbar) led to a different outcome than the previously reported result.[1] One product was obtained in 46% yield, which was identified as being methyl 1,3-dimethyl-5-oxo-5*H*-pyrrolizine-2-carboxylate **12**[4] (Scheme 2).

^{1}H and ^{13}C NMR data of pyrrolizinone **12** is collected in Table 2.[5] The ^{13}C NMR spectra with broad band proton decoupling and with proton off-resonance decoupling ($^1J_{CH}$) of compound **12** allowed the assignment of signals corresponding to the carbons double bond with chemical shifts of 119.0 (C-6) and 135.9 (C-7) ppm. This assignment was also supported by a two-dimensional HMQC spectrum (750 MHz). The fully coupled ^{13}C NMR spectrum of compound **12** was also recorded leading to the assignment of signals corresponding to the carbonyl carbons: at 164.3 ppm one quartet is observed (C-9, $^3J = 3.8$ Hz) and the carbonyl carbon C-5 is observed at 165.6 ppm as a double doublet ($^2J = 7.7$ Hz and $^3J = 12.1$ Hz). The fully coupled ^{13}C NMR spectrum with selective proton irradiation at $\delta = 7.12$ ppm (the chemical shift of H-7) was recorded. This converted the signal at 165.6 (C-5) into a doublet with coupling constant of $^2J = 7.7$ Hz thus proving that H-7 was coupled with C-5. On the other hand, the signal at 135.9 ppm shown as a double doublet ($^2J = 3.3$ Hz and $^1J = 175.3$ Hz) in the fully coupled ^{13}C NMR spectrum becomes a doublet ($^2J = 3.3$ Hz) on irradia-



Scheme 2.

Table 2. ^{1}H NMR and ^{13}C NMR (with proton off-resonance decoupling) data for methyl 1,3-dimethyl-5-oxo-5*H*-pyrrolizine-2-carboxylate **12**



C	^{1}H NMR	^{13}C NMR
C-8	2.11 (3H, s)	10.9 (q, $J = 129.2$ Hz)
C-11	2.57 (3H, s)	11.2 (q, $J = 130.7$ Hz)
C-10	3.73 (3H, s)	49.9 (q, $J = 147.4$ Hz)
C-2	—	117.1 (s)
C-6	5.58 (1H, d, $J = 6.0$ Hz)	119.0 (d, $J = 181.9$ Hz)
C-1	—	123.7 (s)
C-7a	—	131.4 (s)
C-7	7.12 (1H, $J = 6.0$ Hz)	135.9 (d, $J = 174.7$ Hz)
C-3	—	141.3 (s)
C-9	—	164.3 (s)
C-5	—	165.6 (s)

tion at $\delta = 7.12$ ppm, which confirms the assignment of the carbon C-7. In the HMBC spectrum of compound **12**, H-7 show connectivity with C-6, C-5, C-7a and H-6 show connectivity with C-7, C-5, C-7a (Fig. 1). The signals for H-11 show connectivity with C-2, C-1, C-7a, C-3, C-9 whereas H-8 correlates with C-2, C-1, C-7a, C-7, C-3, C-9. On the other hand, the protons of the methyl ester group show connectivity with C-2. This NMR study allowed us to establish unambiguously the structure of methyl 1,3-dimethyl-5-oxo-5*H*-pyrrolizine-2-carboxylate **12**. It is noteworthy that this compound has an intense orange colour typical of pyrrolizinone derivatives.[5b]

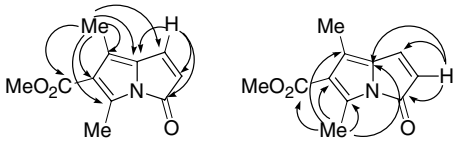


Figure 1. Main connectivity observed in the HMBC spectrum (750 MHz) of compound **12**.

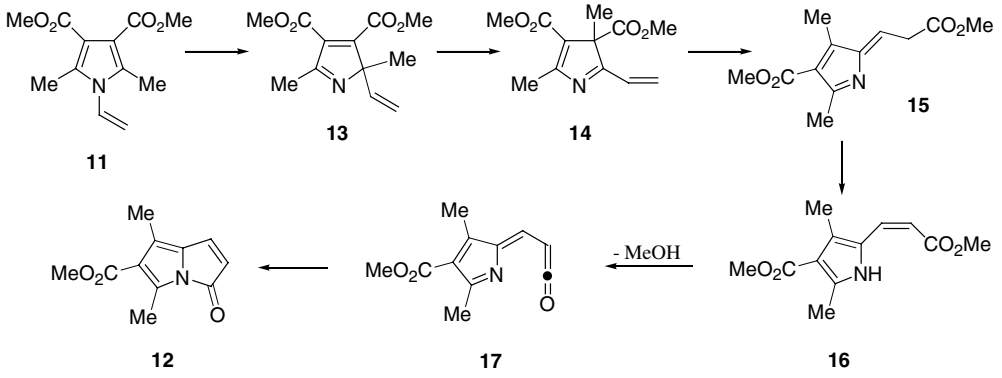
When the FVP of **10** was carried out at 700 °C/4×10^{-2} mbar a mixture of **12** (44%) and **11** (27%) was obtained. This suggested that the lower pressure reduces the period of time that the substance to be pyrolysed remains in the hot zone not allowing the complete conversion of **10** into compound **12**. The result of the sulfone **10** FVP (700 °C/1.3×10^{-3} mbar) described by Storr and co-workers[1] is also in agreement with this observation. Thus, vinylpyrrole **11** must in fact be an intermediate in the formation of methyl 1,3-dimethyl-5-oxo-5*H*-pyrrolizine-2-carboxylate **12** from sulfone **10**.

In order to corroborate this mechanistic interpretation we performed the FVP of dimethyl 2,5-dimethyl-1-vinyl-1*H*-pyrrole-3,4-dicarboxylate **11** (Scheme 2). In fact, the flash vacuum pyrolysis carried out at 700 °C/4×10^{-2} mbar led to the efficient synthesis of compound **12** (79%).

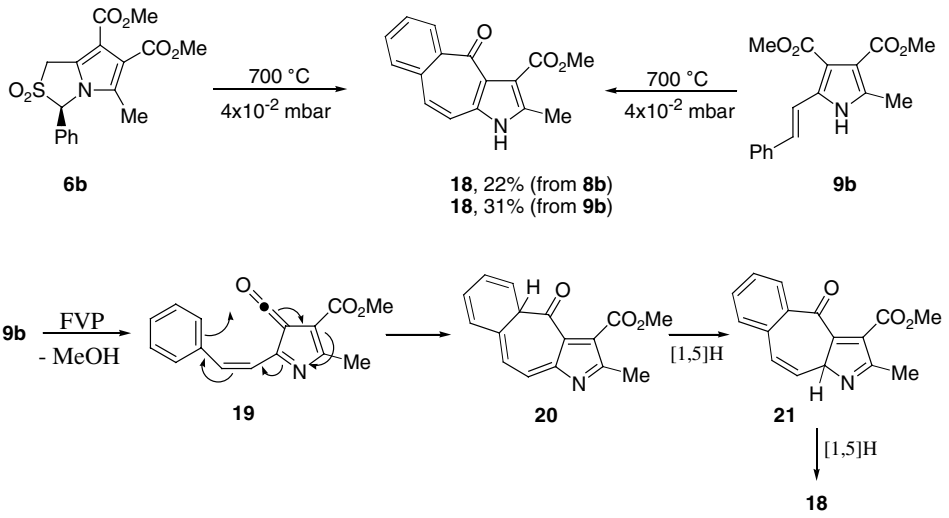
The formation of methyl 1,3-dimethyl-5-oxo-5*H*-pyrrolizine-2-carboxylate **12** from *N*-vinylpyrroles **11** can be rationalised as outlined in Scheme 3. It is known that 2-substituted 3-(pyrrol-2-yl)propionate methyl esters undergo concerted elimination of methanol on FVP to give pyrrol-2-ylideneketene intermediates, which give pyrrolizinones by electrocyclisation.[5b,6] Thus methyl 3-(4-methoxycarbonyl-3,5-dimethylpyrrol-2-yl)propionate methyl **16** must be an intermediate in the synthesis of **12**. In our case we envisage that pyrrole **16** is formed from **11** through a sequence of sigmatropic shifts.

The FVP of compound **11** was also performed using milder reaction conditions (400 °C and 550 °C/4×10^{-2} mbar) in attempting to intercept intermediates of the synthesis of **12**. However, only sublimation of *N*-vinylpyrroles **11** occurred.

5-Methyl-3-phenyl-1*H*-pyrrolo[1,2-*c*]thiazole-2,2-dioxide **6b** is converted into methyl 2-methyl-4-oxo-1,4-dihydro-1-aza-benzo[*f*]azulene-3-carboxylate **18**[7] on flash vacuum pyrolysis (Scheme 4). Under these reaction conditions styryl-1*H*-pyrrole **9b** is formed and converted into a pyrrole fused to a benzocyclohepten-5-one ring system. This was confirmed by promoting the FVP of styryl-1*H*-pyrrole **9b**, which also gave compound **18** (31%).



Scheme 3.



Scheme 4.

The most likely mechanism for the formation of **18** is shown in Scheme 4. It has been reported that methyl pyrrole-2-carboxylate undergoes elimination of methanol to produce pyrrol-2-ylketene under FVP conditions.[8] In a similar manner styryl-1*H*-pyrrole **9b** generates pyrrol-3-ylketene **19** on eliminating methanol. Electrocyclisation of **19** followed by two sigmatropic H-shifts gives compound **18**.

Compound **6a** and **9a** showed similar chemical behaviour when compared with **6b** and **9b**, respectively, and the corresponding 4-oxo-1,4-dihydro-1-aza-benzo[*f*]azulene-3-carboxylate could be obtained on FVP although in low yield.

In conclusion, we have shown that 1-azafulvenium methides, generated by the thermal extrusion of sulfur dioxide from pyrrolo[1,2-*c*]thiazole-2,2-dioxides, are valuable intermediates for the synthesis of heterocylic compounds. Sealed tube reaction conditions allow the synthesis of *N*-(**11**) and *C*-vinylpyrroles (**9**) whereas FVP conditions lead to heterocycles where another ring system is annulated to pyrrole namely 1,3-dimethyl-5-oxo-5*H*-pyrrolizine-2-carboxylate (**12**) and 2-methyl-4-oxo-1,4-dihydro-1-aza-benzo[*f*]azulene-3-carboxylate (**13**). The efficient synthesis of 1,3-dimethyl-5-oxo-5*H*-pyrrolizine-2-carboxylate (**12**) was also achieved via FVP of *N*-vinylpyrrole **11** and the styryl-1*H*-pyrroles **9** FVP gave 4-oxo-1,4-dihydro-1-aza-benzo[*f*]azulene-3-carboxylates.

Acknowledgements

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3. Dimethyl 2-methyl-5-styryl-1H-pyrrole-3,4-dicarboxylate **9b**. 3-Methyl-5-phenyl-1*H*-pyrrolo[1,2-*c*]thiazole-2,2-dioxide **6b** (0.34 g, 0.93 mmol) was dissolved in sulfolane (2 mL) in a glass pyrolysis tube, which was cooled in liquid nitrogen, evacuated, sealed and heated at 220 °C for 1.5 h. After cooling to room temperature the tube was opened, the reaction mixture diluted with dichloromethane and washed with water. Purification by flash chromatography [SiO_2, ethyl-acetate–hexane (1:2) then ethyl-acetate–hexane (1:1)] gave **9b** as a solid (54%). Mp 151.9–153.6.0 °C (from ethyl ether). δ_H ($CDCl_3$, 300 MHz) 2.40 (3H, s, Me), 3.80 (3H, s, CO_2Me), 3.85 (3H, s, CO_2Me), 6.77 (1H, d, $J = 16.8$ Hz), 7.32 (1H, d, $J = 16.8$ Hz), 7.19–7.38 (5H, m, Ar–H); δ_C ($CDCl_3$, 75.5 MHz) 12.6, 51.5, 51.8, 113.0, 114.2, 116.3, 126.4, 127.8, 127.9, 128.6, 132.3, 135.7, 136.5, 165.7, 165.9; *m*/*z* (EI) 299 (M^+, 100%), 267 (53), 236 (39), 209 (25), 180 (51). Anal. Calcd for $C_{17}H_{17}NO_3$: C, 68.22; H, 5.72; N, 4.68. Found: C, 68.60; H, 6.07; N, 4.79%.
4. Methyl 1,3-dimethyl-5-oxo-5*H*-pyrrolizine-2-carboxylate **12**. Pyrolysis of 3,5-dimethyl-1*H*-pyrrolo[1,2-*c*]thiazole-2,2-dioxide **10** (0.20 g, 0.67 mmol) at 700 °C/8×10^{-2} mbar onto a surface cooled at −196 °C over a period of 2 h 20 min gave a yellowish pyrolysate. (The rate of volatilisation of the starting material was controlled by the use of a Kugelrohr oven, which heated the sample at 200 °C.) After cooling to room temperature the pyrolysate was

removed from the cold finger with dichloromethane. The solvent was removed in vacuo and the residue purified by flash chromatography [SiO_2, ethyl-acetate–hexane (1:1)] to give **12** as an orange solid (46%). Mp 116.0–118.0 °C (from ethyl ether–hexane). ν (KBr) 1614, 1695 and 1729 cm^{-1}; δ_H ($CDCl_3$, 500 MHz) 2.11 (3H, s, H-8), 2.57 (3H, s, H-11), 3.73 (3H, s, H-10), 5.58 (1H, d, $J = 6.0$ Hz, H-6), 7.12 (1H, d, $J = 6$ Hz, H-7); δ_C ($CDCl_3$, 125.7 MHz, off-resonance decoupling) 10.9 (q, $J = 129.2$ Hz, C-8), 11.2 (q, $J = 130.7$ Hz, C-11), 49.9 (q, $J = 147.4$ Hz, C-10), 117.1 (s, C-2), 119.0 (d, $J = 181.9$ Hz, C-6), 123.7 (s, C-1), 131.4 (s, C-7a), 135.9 (d, $J = 174.7$ Hz, C-7), 141.3 (s, C-3), 164.3 (s, C-9), 165.6 (s, C-5); m/z (EI) 205 (M^+, 100%), 190 (24), 174 (69), 162 (16), 145 (45) and 117 (16).

5. NMR data in agreement with the NMR spectra reported for other pyrrolizinones in: (a) McNab, H. *J. Chem. Soc., Perkin Trans. 1* **1987**, 657–659; (b) Campbell, S. E.; Comer, M. C.; Derbyshire, P. A.; Despinoy, X. L. M.; McNab, H.; Morrison, R.; Sommerville, C. C.; Thornley, C. *J. Chem. Soc., Perkin Trans. 1* **1997**, 2195–2202.
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7. Methyl 2-methyl-4-oxo-1,4-dihydro-1-aza-benzo[*f*]azulene-3-carboxylate **18** obtained as a yellow solid. Mp 261.0–263.0 °C (from ethyl ether–hexane). δ_H 2.77 (3H, s, Me), 3.95 (3H, s, CO_2Me), 7.36 (1H, d, $J = 12.0$ Hz), 7.75–7.76 (1H, m, Ar–H), 7.77–7.80 (1H, m, Ar–H), 7.84 (1H, dd, $J = 1.4$ and 7.8 Hz, Ar–H), 8.27 (1H, d, $J = 12.0$ Hz), 9.96 (1H, dd, $J = 1.5$ and 8.0 Hz, Ar–H); m/z (EI) 267 (M^+, 100%), 252 (11), 236 (64), 178 (12), 152 (37) and 76 (16). Anal. Calcd for $C_{16}H_{13}NO_3$: C, 71.90; H, 4.90; N, 5.24. Found: C, 72.27; H, 5.52; N, 5.28.
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