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New chemistry of diazafulvenium methides: one way to pyrazoles

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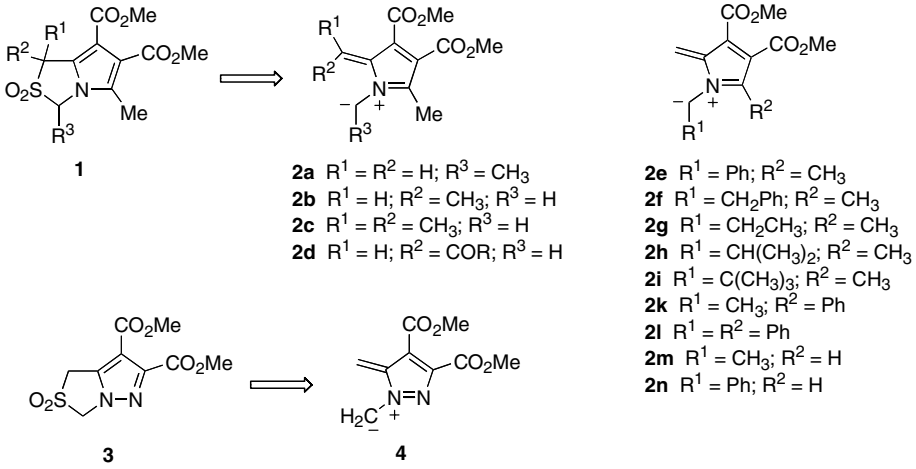
Abstract—Diazafulvenium methides generated from the solution pyrolysis of pyrazolo[1,5-*c*][1,3]thiazole-2,2-dioxides participate in [8π+2π] cycloadditions giving pyrazolo[1,5-*a*]pyridine derivatives. 1-Methyl-diazafulvenium, generated under flash vacuum pyrolysis reaction conditions, undergoes an intramolecular sigmatropic [1,8]H shift giving 1-vinyl-1*H*-pyrazoles.

The study of pericyclic reactions of extended dipoles (with more than 4π electrons) is an almost unexplored research area. However, Storr and co-workers explored the reactivity of pyrrolo[1,2-*c*]thiazole-2,2-dioxides (**1**) and pyrazolo[1,5-*c*][1,3]thiazole-2,2-dioxides (**3**) and proved that they can be considered masked aza- and diazafulvenium methides (**2** and **4**).[1] Earlier, Padwa and co-workers described unsuccessful attempts to extrude SO_2 from pyrrolo[1,2-*c*]thiazole-2,2-dioxides for the generation of an azafulvenium methide, both thermally (300 °C) and photochemically.[2] Azafulvenium methides can be considered as 'higher-order' azomethine ylides and, in principle, can act as 4π 1,3-dipoles or as 8π 1,7-dipoles.

Storr and co-workers found that the generation of 1-azafulvenium methides (**2a**–**d**) by the thermal extrusion of sulfur dioxide from pyrrolo[1,2-*c*]thiazole-2,2-dioxides **1** could be achieved under flash vacuum pyrolysis (FVP) reaction conditions. They described the first evidence for trapping of transient 1-azafulvenium methide systems in pericyclic reactions. These extended dipolar systems **2a**–**c** undergo sigmatropic [1,8]H shifts giving vinylpyrroles and the acyl derivatives **2d** electrocyclise to give pyrrolo[1,2-*c*][1,3]oxazines.[1]

It was also reported that the SO_2 extrusion of the pyrazole derivative **3**[3] occurs more easily than from the analogous pyrrolo sulfone. The authors reported that the



Keywords: Diazafulvenium methides; Vinyl-1*H*-pyrazoles; Pyrazolo[1,5-*a*]pyridines; Pyrazolo[1,5-*a*]pyrrolo[3,4-*c*]pyridine; [8π+2π] Cycloaddition; Sigmatropic shift.
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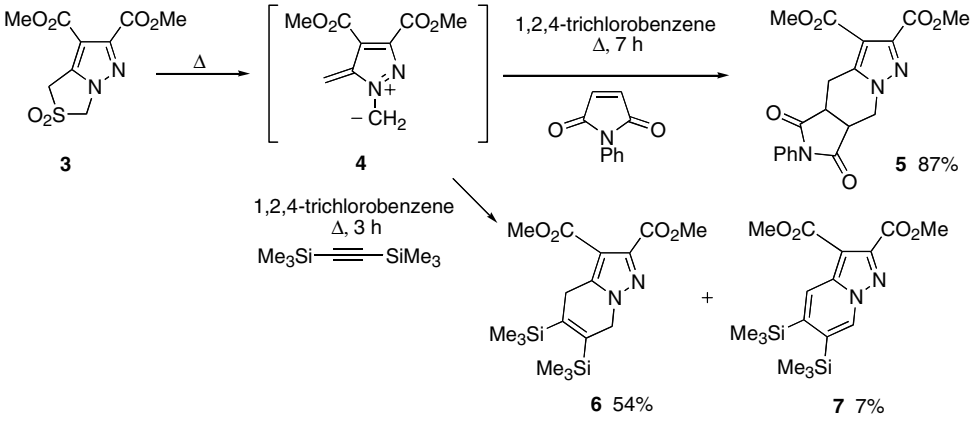
1,2-diazafulvenium methide **4** did not react with *N*-phenylmaleimide or dimethyl acetylenedicarboxylate but could be intercepted in 8π+2π cycloaddition with silylated acetylenes giving adducts resulting from the addition across the 1,7-position.[1]

We have further studied the reactivity of azafulvenium methides including the reactivity of a range of new derivatives **2e**–**n** and showed that these transient 8π 1,7-dipole systems are interesting intermediates for the synthesis of functionalised heterocyclic compounds. The intramolecular trapping of the 1,7-dipoles in pericyclic reactions, namely sigmatropic [1,8]H shifts and 1,7-electrocyclisations, allowed the synthesis of *N*-vinyl- and *C*-vinylpyrroles, which, under flash vacuum pyrolysis conditions, are converted into heterocycles where another ring system is annulated to pyrrole.[4]

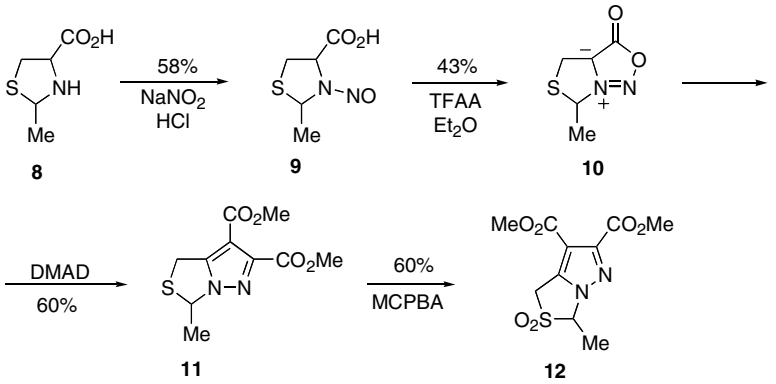
1,2-Diazafulvenium methides' chemistry has also attracted our attention and our preliminary results are described in this letter. We prepared the 4*H*-pyrazolo-[1,5-*c*][1,3]thiazole-5,5-dioxide **3**[1,3] and observed that it undergoes SO_2 extrusion in the solution to give 1,2-diazafulvenium methide **4**, which could be trapped by reacting with bis(trimethylsilyl)acetylene, confirming the result reported by Storr and co-workers.[1] In our hands, dimethyl 5,6-bis(trimethylsilyl)-4,7-dihydropyrazolo[1,5-*a*]pyridine-2,3-dicarboxylate **6** was obtained in 54% yield together with the formation of the aromatised derivative **7** in 7% yield. However, the dipolar system **4** also participates in the cycloaddition with *N*-phenylmaleimide giving the corresponding cycloadduct **5**[5] in 87% yield (Scheme 1). This result contradicts the reported experimental observation although the reactivity of this 1,7-dipole **4** towards [8π+2π] cycloaddition, characterised by the participation in the reaction with both electron-rich and electron-deficient dipolarophiles, is in agreement with the reported MO calculations for the unsubstituted diazafulvenium methide.[1]

We decided to explore the possibility of generating new diazafulvenium methides systems and study their reactivity in the absence of dipolarophiles. 3-Methyl-pyrazolo[1,5-*c*][1,3]thiazole-2,2-dioxide **12** was prepared as outlined in Scheme 2. Sydnone **10** is a stable mesoionic species, which can be isolated and undergoes 1,3-dipolar cycloaddition with DMAD to give pyrazolo[1,5-*c*]-[1,3]thiazole **11**. The oxidation of **11** with MCPBA gives sulfone **12** (Scheme 2).

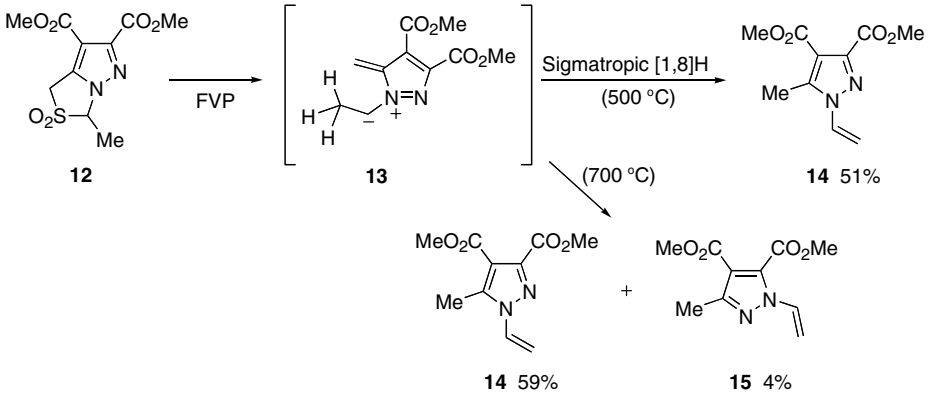
Carrying out flash vacuum pyrolysis of sulfone **12** at 500 °C, we obtained 1-vinyl-1*H*-pyrazole **14**[6] selectively. When the FVP was carried out at 700 °C the same 5-methyl-1-vinyl-1*H*-pyrazole **14** was obtained, together



Scheme 1.



Scheme 2.



Scheme 3.

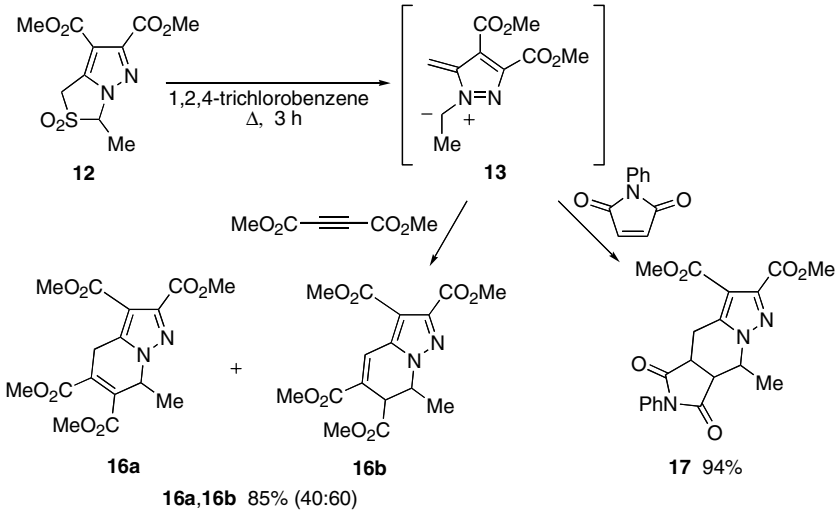
with 1-vinyl-1*H*-pyrazole **15**. The FVP of 5-methyl-1-vinyl-1*H*-pyrazole **14** led only to sublimation of this compound and to the formation of a small percentage of 3-methyl-1-vinyl-1*H*-pyrazole derivative **15** (Scheme 3).

The mechanism of conversion of pyrazolo[1,5-*c*][1,3]thiazole-2,2-dioxides into 1-vinyl-1*H*-pyrazole involves the generation of diazafulvenium methide **13** which is trapped in an allowed, suprafacial [1,8]H sigmatropic shift. This reactivity, observed for the first time for the diazafulvenium methide derivatives, is similar to the one shown by azafulvenium methides **2a**,**f**–**k** and **2m**.[4] However, 5-methyl-1-vinyl-1*H*-pyrazole **14** proved to be more stable under FVP reaction conditions than the *N*-vinylpyrroles obtained previously from azafulvenium methides. In fact, 5-methyl-1-vinyl-1*H*-pyrazole **14** was recovered almost unchanged on FVP whereas the *N*-vinylpyrroles are converted into 5-oxo-5*H*-pyrrolizines.

3-Methyl-pyrazolo[1,5-*c*][1,3]thiazole-2,2-dioxide **12** also undergoes SO_2 extrusion in the solution to give **13**, which can be intercepted in 8π+2π cycloadditions with *N*-phenylmaleimide and dimethyl acetylenedicarboxylate giving the corresponding adducts resulting from the addition across the 1,7-positions in high yields (Scheme 4). An attempt to react **13** with bis(trimethylsilyl)acetylene led only to the synthesis of 1-vinyl-1*H*-pyrazole **14** in 16% yield.

In conclusion, in this letter, we describe new diazafulvenium methides' chemistry. These intermediates can be generated via thermal sulfur dioxide extrusion of pyrazolo[1,5-*c*][1,3]thiazole-2,2-dioxides.

The SO_2 extrusion of pyrazolo[1,5-*c*][1,3]thiazole-2,2-dioxides occurs more easily than from the analogous pyrrolo sulfones and can be carried out in refluxing 1,2,4-trichlorobenzene. The diazafulvenium methides, generated this way, can be intercepted in 8π+2π cycloadditions giving adducts resulting from the addition across the 1,7-position. This type of reactions is an interesting approach to the synthesis of pyrazolo[1,5-*a*]pyridine derivatives, a class of compounds with potential interest as antiherpetics.[7] In the absence of dipolarophiles, the 1-methyl-diazafulvenium methide, generated under FVP reaction conditions, undergoes an intramolecular sigmatropic [1,8]H shift giving 1-vinyl-1*H*-pyrazoles.



Scheme 4.

Acknowledgements

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5. *Dimethyl 5,7-dioxo-6-phenyl-4a,5,6,7,7a,8-hexahydro-4H-pyrazolo[1,5-a]pyrrolo[3,4-d]pyridine-2,3-dicarboxylate* **5**. A suspension of dimethyl 5,5-dioxo-4*H*-pyrazolo[1,5-*c*]-[1,3]thiazole-2,3-dicarboxylate-2,2-dioxide **3** (0.16 g, 0.58 mmol) and *N*-phenylmaleimide (2 equiv, 0.20 g, 1.16 mmol) in 1,2,4-trichlorobenzene (1.8 mL) was heated at reflux under dry nitrogen for 7 h. After cooling to room temperature, the mixture was purified by flash chromatography [hexane] to remove 1,2,4-trichlorobenzene followed by elution with ethyl acetate–hexane (2:1), then ethyl acetate–hexane (4:1) to give **5** as a white solid (87%). Mp 144.8–146.7 °C (from diethyl ether). *ν* (KBr) 1150, 1221, 1385, 1497 and 1715 cm^{-1}; δ_H ($CDCl_3$, 300 MHz): 3.20 (1H, dd, $J = 7.2$ and 16.4 Hz), 3.58–3.70 (2H, m), 3.85 (3H, s), 3.93 (3H, s), 3.93–4.00 (1H, m), 4.31 (1H, dd, $J = 5.7$ and 13.9 Hz), 4.90 (1H, dd, $J = 2.5$ and 13.9 Hz), 7.07–7.10 (2H, m, Ar–H), 7.37–7.44 (3H, m, Ar–H); δ_C ($CDCl_3$, 75.5 MHz): 22.5, 37.1, 40.4, 46.1, 51.9, 52.6, 112.0, 126.1, 129.0, 129.2, 131.0, 141.5, 143.3, 162.0, 174.9, 176.0; *m*/*z* (EI) 383 (M^+, 28%), 351 (100), 204 (61), 176 (12), 147 (7), 119 (8) and 77 (7). Anal. Calcd for $C_{19}H_{17}N_3O_6$: C, 59.53; H, 4.47; N, 10.96. Found: C, 59.49; H, 4.64; N, 10.84.
6. *Dimethyl 5-methyl-1-vinyl-1H-pyrazole-3,4-dicarboxylate* **14**. Pyrolysis of dimethyl 3-methyl-1*H*,3*H*-pyrazolo[1,5-*c*]-[1,3]thiazole-6,7-dicarboxylate-2,2-dioxide **12** (0.21 g, 0.73 mmol) at 500 °C/2×10^{-2} mbar onto a surface cooled at −196 °C over a period of 1 h gave a colourless pyrolysate. [The rate of volatilisation of the starting material was controlled by the use of a Kugelrohr oven which heated the sample at 100–250 °C.] After cooling to room temperature the pyrolysate was removed from the cold finger with dichloromethane and the solvent was removed in vacuo. The crude product was purified by flash chromatography [ethyl acetate–hexane (1:2), then ethyl acetate–hexane (1:1)] to give **14** as a white solid (51%). Mp 46.3–48.0 °C (from diethyl ether–hexane). *ν* (KBr) 1088, 1269, 1320, 1648, 1719 and 1740 cm^{-1}; δ_H ($CDCl_3$, 300 MHz): 2.56 (3H, s), 3.85 (3H, s), 3.95 (3H, s), 5.14 (1H, dd, $J = 0.9$ and 8.8 Hz), 5.95 (1H, dd, $J = 0.9$ and 15.2 Hz), 6.99 (1H, dd, $J = 8.8$ and 15.2 Hz); δ_C ($CDCl_3$, 75.5 MHz): 10.3, 51.7, 52.5, 106.4, 112.6, 128.2, 142.9, 144.4, 162.8, 163.0; MS (EI) *m*/*z* 224 (M^+, 28%), 193 (100), 163 (27), 133 (12) and 68 (9). Anal. Calcd for $C_{10}H_{12}N_2O_4$: C, 53.57; H, 5.39; N, 12.49. Found: C, 53.75; H, 5.28; N, 12.39.
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