New chemistry of diazafulvenium methides: one way to pyrazoles

Teresa M. V. D. Pinho e Melo,* Maria I. L. Soares and António M. d’A. Rocha Gonsalves

Departamento de Química, Universidade de Coimbra, 3004-535 Coimbra, Portugal

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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 $[8\pi + 2\pi]$ 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-$1H$-pyrazoles.

The study of pericyclic reactions of extended dipoles (with more than $4\pi$ 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 $4\pi$ 1,3-dipoles or as $8\pi$ 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 occurs more easily than from the analogous pyrrolo sulfone. The authors reported that the

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* Corresponding author. Tel.: +351 239 854475; fax: +351 239 826068; e-mail: tmelo@ci.uc.pt

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1,2-diazafulvenium methide 4 did not react with \( \text{N-phenylmaleimide} \) or \( \text{dimethyl acetylenedicarboxylate} \) but could be intercepted in \( 8\pi + 2\pi \) 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 \( 8\pi \) 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 \([1,8]\text{H shifts}\) and 1,7-electrocyclisations, allowed the synthesis of \( \text{N-vinyl- and C-vinylpyrroles} \), which, under flash vacuum pyrolysis conditions, are converted into heterocycles where another ring system is annulated to pyrrole.\(^3\)

1,2-Diazafulvenium methides’ chemistry has also attracted our attention and our preliminary results are described in this letter. We prepared the \( 4\text{H-} \text{pyrazolo[1,5-c][1,3]thiazole-5,5-dioxide} \) 3 and observed that it undergoes \( \text{SO}_2 \) extrusion in the solution to give 1,2-diazafulvenium methide 4, which could be trapped by reacting with \( \text{bis(trimethylsilyl)acetylene} \), confirming the result reported by Storr and co-workers.\(^1\) In our hands, dimethyl 5,6-bis(trimethylsilyl)-4,7-dihydro-

pyrazolo[1,5-\( \alpha \)]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 \( \text{N-phenylmaleimide} \) giving the corresponding cycloadduct 5 in 87\% yield (Scheme 1). This result contradicts the reported experimental observation although the reactivity of this 1,7-dipole 4 towards \( [8\pi + 2\pi] \) 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\( \text{H-pyrazole} \) 14 selectively. When the FVP was carried out at 700 °C the same 5-methyl-1-vinyl-1\( \text{H-pyrazole} \) 14 was obtained, together
with 1-vinyl-1H-pyrazole 15. The FVP of 5-methyl-1-vinyl-1H-pyrazole 14 led only to sublimation of this compound and to the formation of a small percentage of 3-methyl-1-vinyl-1H-pyrazole derivative 15 (Scheme 3).

The mechanism of conversion of pyrazolo[1,5-c][1,3]thiazole-2,2-dioxides into 1-vinyl-1H-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 byazafulvenium methides 2a,f-k and 2m.4 However, 5-methyl-1-vinyl-1H-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-1H-pyrazole 14 was recovered almost unchanged on FVP whereas the N-vinylpyrroles are converted into 5-oxo-5H-pyrrolizines.

3-Methyl-pyrazolo[1,5-c][1,3]thiazole-2,2-dioxide 12 also undergoes SO₂ extrusion in the solution to give 13, which can be intercepted in 8π+2π cycloadditions with N-phenylmaleimide and dimethyl acetylenedicarb-oxide 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-1H-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 SO₂ extrusion of pyrazolo[1,5-c][1,3]thiazole-2,2-dioxides occurs more easily than from the analogous pyrrole 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 antitherapeutics.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-1H-pyrazoles.
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References and notes


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-4H-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) 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; δH (CDCl₃, 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); δC (CDCl₃, 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 C₁₉H₁₇N₃O₆: 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-1H,3H-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; δH (CDCl₃, 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); δC (CDCl₃, 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 C₁₀H₁₂N₂O₄: C, 53.57; H, 5.39; N, 12.49. Found: C, 53.75; H, 5.28; N, 12.39.