Microwave-assisted generation and reactivity of aza- and diazafulvenium methides: heterocycles via pericyclic reactions

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A B S T R A C T

Azafulvenium methides and diazafulvenium methides have been generated under microwave irradiation from 2,2-dioxo-1H,3H-pyrrolo[1,2-c]thiazoles and 2,2-dioxo-1H,3H-pyrazolo[1,5-c]thiazoles, respectively. Pericyclic reactions of these 1,7-dipole intermediates, namely, sigmatropic [1,8]H shifts, 1,7-electrocyclization or [8p+2p] cycloaddition led to the synthesis of a range of pyrrole and pyrazole derivatives. The first evidence for the azafulvenium methides by intermolecular trapping via [8p+2p] cycloaddition is reported.

The study of pericyclic reactions of extended dipoles, such as azafulvenium methides 2 and diazafulvenium methides 4, is one of our current research interests (Scheme 1).1,2 It has been previously demonstrated that azafulvenium methides can be generated from 2,2-dioxo-1H,3H-pyrrolo[1,2-c]thiazoles under Flash Vacuum Pyrolysis1,3 or in some cases via sealed tube thermolysis.2,3 These dipoles participate in pericyclic reactions, namely, sigmatropic [1,8]H shifts and 1,7-electrocyclization, giving N-vinyl- or C-vinylpyrroles. The SO2 extrusion of 2,2-dioxo-1H,3H-pyrazolo[1,5-c]thiazoles occurs more readily than from the analogous pyrrolo sulfones and can be carried out in refluxing 1,2,4-trichlorobenzene.2,3 1-Methyl- and 7,7-dimethyl-diazafulvenium methides undergo intramolecular sigmatropic [1,8]H shifts giving vinylnpyrazoles. Diazulfulvenium methides unsubstituted at C-7 participate in [8p+2p] cycloadditions giving pyrazolo[1,5-a]pyridine derivatives resulting from the addition across the 1,7-position. However, generation of azafulvenium methides in the presence of dipolarophiles did not lead to the synthesis of [8p+2p] cycloadducts.1,3

The synthetic utility of the use of microwave irradiation in organic synthesis has increased considerably in recent years.4 This nonconventional energy source is able to reduce chemical reaction times, increase yields and in some cases can lead to a different outcome when compared to conventional heating. In this context we decide to evaluate the potential of microwave irradiation to generate aza- and diazafulvenium methides. In this Letter, we report that aza- and diazafulvenium methides can in fact be generated under microwave irradiation and we describe their reactivity including the first evidence for the azafulvenium methides by intermolecular trapping via [8p+2p] cycloaddition.

Starting from 3-methyl-2,2-dioxo-1H,3H-pyrrolo[1,2-c]thiazoles 5a or 5b the reaction carried out in 1,2,4-trichlorobenzene afforded the corresponding N-vinylpyrroles 7 (Scheme 2). The synthesis of these heterocycles results from the SO2 extrusion of sulfones 5 giving azafulvenium methides 6 followed by a sigmatropic [1,8]H shift. Azafulvenium methide 9

could also be generated from 3-phenyl-2,2-dioxo-1H,3H-pyrrolo-[1,2-c]thiazole 8 under microwave irradiation. In this case, the 1,7-dipole undergoes electrocyclization to give 10, which is converted into C-vinylpyrrole 11 in 63% yield. Pyrroles 7 and 11 have been previously prepared via sealed tube thermolysis of the starting sulfone in sulfolane, which required a reaction time of 1.5–2 h. These conditions allow the synthesis of pyrroles 7 and 11 in good yield but 7a could only be obtained in 8% yield. Pyrrole 7a was also obtained in low yield (11%) under flash vacuum pyrolysis conditions. Thus, the microwave-assisted reaction of sulfone 5a allows a more efficient synthesis of N-vinylpyrrole 7a, which is obtained in 59% yield.

Particularly interesting was the observation for the first time of [8π+2π] cycloadditions of azafulvenium methides (Scheme 3). In fact, the generation of azafulvenium methide 6a in the presence of diethyl diazene-1,2-dicarboxylate allowed the synthesis of the corresponding [8π+2π] cycloadduct 12a in 39% yield, together with the formation of N-vinylpyrrole 7a in 24% yield. The reaction of sulfone 5a in the presence of N-phenylmaleimide gave 5,6,7,8-tetrahydroindolizine derivative 13a in 39% yield. Attempts to promote the [8π+2π] cycloaddition of 6a with bis(trimethylsilyl)acetylene and with N-benzyldienebenzenesulfonamide led only to the isolation of N-vinylpyrrole 7a. However, the generation of azafulvenium methide 6a under microwave irradiation in the presence of DMAD afforded a mixture of 3,5-dimethylindolizine-1,2,6,7-tetracarboxylate 14a and dihydroindolizine-1,2,6,7-tetraoxocarbocycles (15a and 16) in 17% overall yield and also N-vinylpyrrole 7a in 16% yield. Azafulvenium methide 6b, generated from 3-methyl-2,2-dioxo-1H,3H-pyrrolo[1,2-c]thiazole 5b, reacted with diethyl diazene-1,2-dicarboxylate and N-phenylmaleimide giving 4,6-dimethyl-1,2,3,4-tetrahydro-pyrrolo[1,2-d][1,2,4]triazine-2,3,7,8-tetracarboxylate 12b (6%) and hexahydro-pyrrolo[3,4-f]indolizine 13b (30%), respectively. In both cases, N-vinylpyrrole 7b was the major product. The 1,7-dipole 6b did not react with bis(trimethylsilyl)acetylene, DMAD nor with N-benzyldienebenzenesulfonamide and only N-vinylpyrrole 7b could be obtained from these attempted reactions.

Azafulvenium methide 6c, generated from 2,2-dioxo-1H,3H-pyrrolo[1,2-c]thiazole 5c unsubstituted at C-3, cannot undergo the sigmatropic [1,8]H shift observed for the 1-methylazafulvenium methides (6a and 6b). Therefore, in this case there is no competitive formation of N-vinylpyroles and only 1,7-dipolar cycloadducts are obtained from the microwave-assisted reaction of sulfone 5c in the presence of dipolarophiles (Scheme 4). The reaction of 6c with diethyl diazene-1,2-dicarboxylate gave 1H,4H-pyrrolo[1,2-d][1,2,4]triazine 17 in 31% yield and from the reaction with N-phenylmaleimide the hexahydro-pyrrolo[3,4-f]indolizine 18 was obtained in 62% yield. Microwave irradiation of sulfone 5c for 20 min in the presence of N-benzyldienebenzenesulfonamide gave the 1,2,3,4-tetrahydro-5H-pyrrolo[1,2-c]pyrimidine-5,6-dicarboxylate 20 in 31% yield and the aromatized derivative 19 in 31% yield. On the other hand, the microwave irradiation for a longer period (40 min) allowed the synthesis of dimethyl 7-methyl-3-phenyl-5H-pyrrolo[1,2-c]pyrimidine-5,6-dicar-
boxylate 19 is collected in Table 1. The assignment was supported by two-dimensional HMOC and HMBC spectra (400 MHz). In the HMBC spectrum the proton with the chemical shift 8.03 ppm (H-4) shows coupling constants with C-4a and C-3 with lower intensity. Correlation of H-4 with C-8 is also observed. On the other hand, the proton at 9.54 ppm (H-1) shows coupling constants with C-4 and C-3 with higher intensity.

Attempts to carry out cycloaddition reactions of 6c with DMAD were not successful. However, azafulvenium methide 6c reacts with the electron-rich dipolarophile bis(trimethylsilyl)acetylene giving dimethyl 3-methyl-6,7-bis(trimethylsilyl)-5,8-dihydroindolizine-1,2-dicarboxylate 14b (8%) and dimethyl 3-methyl-6,7-bis(trimethylsilyl)-5,8-dihydroindolizine-1,2-dicarboxylate 15b (15%). Although in low yields the formation of these products proves that the cycloaddition of azafulvenium methide 6c is not limited to the reaction with electron-deficient dipolarophiles. This is a reactivity pattern also observed for the diazafulvenium methide 4,5-dicarboxylate, unsubstituted at C-1 and C-7.2b

The study was extended to the reactivity of diazafulvenium methide 22 generated from 2,2-dioxo-1H,3H-pyrazolo[1,5-c]-[1,3]thiazole 21 under microwave irradiation in the presence of dipolarophiles (Table 2). We have previously reported that diazafulvenium methide 22 participates in [8π+2π] cycloaddition with a range of electron-deficient dipolarophiles giving pyrazolo[1,5-a]pyridine derivatives (e.g., compounds 23–31).2c It has also been reported that the SO2 extrusion of 2,2-dioxo-1H,3H-pyrazolo[1,5-c]thiazoles occurs more readily than from the analogous pyrrolo sulfones and can be carried out in refluxing 1,2,4-trichlorobenzene.2,3 This observation was corroborated in this study since the generation of the diazafulvenium methide 22 under microwaves required lower temperature (230 °C) than the one required to form the azafulvenium methide derivatives (260 °C).

Diazafulvenium methide 22 reacts with DMAD to give a mixture of dihydro[pyrrolo[1,5-a]pyridines (23 and 24) in 81% overall yield. On the other hand, the [8π+2π] cycloaddition with methyl propiolate affords regioisomers 26 (23%) and 27 (28%) together

Table 1

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<th>(^{13}\text{C} (\text{ppm}))</th>
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<tr>
<td>C-16</td>
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</tr>
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<tr>
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<tr>
<td>C-7</td>
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<td>124.73</td>
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<td>C-8</td>
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<tr>
<td>C-15</td>
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Scheme 4.
with the formation of N-vinylpyrazole 25 (19%) resulting from the sigmatropic [1,8]H shift of diazafulvenium methide 22. The 1,7-dipolar cycloaddition of 1,2-diazafulvenium methide 22 with N-phenylmaleimide gave two diastereoisomeric products, cycloaducts 28 (67%) and 29 (14%), resulting from an endo cycloaddition with the involvement of the two possible configurations of azafulvenium methide 22. The lower stability of the configuration having the inward methyl group explains the formation of heterocycle 29 in a lower yield. This is a selectivity similar to the one observed previously carrying out the conventional solution thermolysis of 22.  The 1,7-dipole 22 can also be trapped by [8π+2π] cycloaddition with N-benzyldienebenzenesulfonamide giving tetrahydropyrazolo[1,5-c]pyrimidine-2,3-dicarboxylate 30 in 33% yield. The microwave-assisted reaction of sulfone 21 with diethyl diazene-1,2-dicarboxylate gives pyrazolo[1,5-d][1,2,4]triazine 31 in high yield (94%). However, diazafulvenium methide 22 could not be trapped with bis[trimethylsilyl]acetylene and only N-vinylpyrazole 25 was isolated.

In conclusion, we report the microwave-assisted generation of azafulvenium methides and diazafulvenium methides from 2,2-dioxo-1H,3H-pyrrolo[1,2-c]thiazoles and 2,2-dioxo-1H,3H-pyrazolo[1,5-c]thiazoles, respectively. Under these conditions and in the absence of dipolarophilesazafulvenium methides undergo sigmatropic [1,8]H shifts or 1,7-electrocyclization giving N-vinyl- or C-vinylpyroles. On the other hand, in the presence of dipolarophiles the [8π+2π] cycloaddition of diazafulvenium methides was observed for the first time leading to the synthesis of a range of pyrrole-annulated systems. Diazafulvenium methide generated from dimethyl 3-methyl-2,2-dioxo-1H,3H-pyrazolo[1,5-c][1,3]-thiazole-6,7-dicarboxylate under microwaves in the presence of dipolarophiles also participate in [8π+2π] cycloadditions. This is an interesting and useful synthetic strategy to prepare functionalized pyrazole-annulated systems since the reaction time has been reduced from 3 to 4 h in conventional heating to 10 min.

Acknowledgements

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Supplementary data

References and notes


2. (a) Pinho e Melo, T. M. V. D.; Soares, M. I. L.; Rocha Gonsalves, A. M. d’A. *Tetrahedron Lett.* **2006**, *47*, 791–794; (b) Pinho e Melo, T. M. V. D.; Soares, M. I. L.; Nunes, C. M.; Paixão, J. A.; Matos Beja, A.; Ramos Silva, M. J. *Org. Chem.* **2007**, *72*, 4406–4415; (c) General procedure for [8+2] cycloadditions of diazafulvenium methide 22 under conventional heating. A suspension of 2,2-dioxo-1H,3H-pyrazolo[1,5-c][1,3]thiazole-6,7-dicarboxylate 21 (0.87 mmol) and dipolarophile (1.74 mmol) in 1,2,4-trichlorobenzene (2.5 mL) was heated at reflux under dry nitrogen for 3–4 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.


5. General procedure for [8+2x2] cycloadditions of diazafulvenium methides. A suspension of 2,2-dioxo-1H-ppyrazolo[1,2-c][1,3]thiazole-6,7-dicarboxylate (0.5 mmol) and dipolarophile (2–4 equiv) in 1,2,4-trichlorobenzene (1 mL) was irradiated in the microwave reactor (CEM Focused Synthesis System, Discover S-Class) with the temperature set to 260 °C for the time indicated in each case. 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.

6. 2,3-Diethyl 7,8-dimethyl 4-methyl-1H-4H-pyrrolo[1,2-d][1,2,4]triazine-3,7,8-tricarboxylate 12a. Yellowish oil. IR (film) 1735, 1696, 1400, 1215 cm⁻¹. ¹H NMR (CDCl₃, 300 MHz): 1.26–1.35 (6H, m), 1.62–1.73 (3H, m), 3.82 (3H, s), 3.84 (3H, s), 4.17–4.27 (4H, m), 5.28–5.41 (1H, m), 6.28 (1H, br s), 6.54 (1H, br s), 7.16 (1H, s); ¹³C NMR (CDCl₃, 75.5 MHz): 14.3, 14.4, 14.5, 51.5, 51.7, 62.2, 62.8, 63.1, 63.7, 110.5, 116.6, 123.2, 130.0, 154.9, 163.6, 163.8; MS (EI) 397 (M⁺, 21%), 365 (100), 251 (45), 221 (24), 196 (26), 177 (40) and 135 (47) (20). HRMS (EI) m/z 397.1488 (C₁₇H₂₃N₃O₈ [M⁺], 397.1485).


8. Dimethyl 4,6-dimethyl-1,3-dioxo-2-phenyl-2,3,3a,4,9,9a-hexahydro-1H-pyrrolo[3,4-f]indolizine-7,8-dicarboxylate 13b. Brown foam. IR (KBr) 1707, 1393, 1187 cm⁻¹. ¹H NMR (CDCl₃, 300 MHz): 1.49 (3H, d, J = 7.2 Hz), 2.35 (3H, s), 3.11 (1H, dd, J = 8.6 and 16.6 Hz), 3.38 (1H, dd, J = 1.1 and 9.3 Hz), 3.51–3.60 (1H, m), 3.94–3.99 (1H, m), 5.01 (1H, dq, J = 1.0 and 7.2 Hz), 6.71–7.04 (2H, m, Ar-H), 7.34–7.42 (3H, m, Ar-H); ¹³C NMR (CDCl₃, 75.5 MHz): 10.0, 20.4, 22.3, 36.9, 46.0, 47.7, 51.4, 51.5, 112.2, 112.8, 126.2, 128.8, 129.1, 129.3, 131.2, 132.7, 164.6, 165.7, 176.1, 177.2; m/z (EI) 410 (M⁺, 20%), 378 (100), 292 (36) and 216 (40). HRMS (EI) m/z 410.1474 (C₂₂H₂₂N₂O₆ [M⁺], 410.1478).

9. Dimethyl 6-methyl-1,3-dioxo-2-phenyl-2,3,3a,4,9,9a-hexahydro-1H-pyrrolo[3,4-f]indolizine-7,8-dicarboxylate 18. Yellowish foam. IR (KBr) 1712, 1393, 1187 cm⁻¹. ¹H NMR (CDCl₃, 300 MHz): 2.34 (3H, s), 2.95–3.02 (1H, m), 3.51–3.52 (2H, m), 3.80 (6H, s), 3.81–3.94 (2H, m), 4.56–4.60 (1H, m), 6.96–7.00 (2H, m, Ar-H), 7.37–7.40 (3H, m, Ar-H); ¹³C NMR (CDCl₃, 75.5 MHz): 10.2, 23.1, 38.3, 40.2, 41.3, 51.5, 111.9, 112.7, 126.3, 128.9, 129.2, 130.5, 131.2, 133.2, 164.5, 165.6, 176.0, 176.8; m/z (EI) 396 (M⁺, 22%), 364 (100), 278 (28), 217 (24) and 131 (11). HRMS (EI) m/z 396.1324 (C₂₁H₂₀N₂O₆ [M⁺], 396.1321).