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

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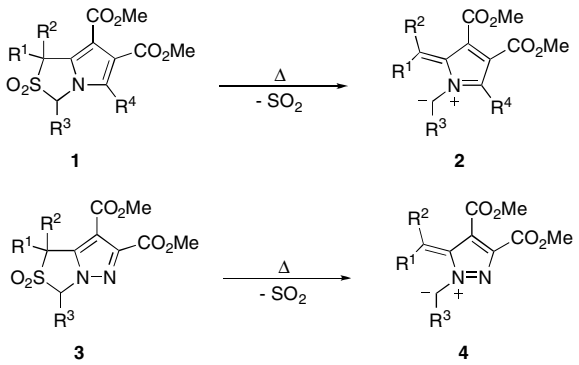
ABSTRACT

Azafulvenium methides and diazafulvenium methides have been generated under microwave irradiation from 2,2-dioxo-1*H*,3*H*-pyrrolo[1,2-*c*]thiazoles and 2,2-dioxo-1*H*,3*H*-pyrazolo[1,5-*c*]thiazoles, respectively. Pericyclic reactions of these 1,7-dipole intermediates, namely, sigmatropic [1,8]H shifts, 1,7-electrocyclization or [8π+2π] cycloaddition led to the synthesis of a range of pyrrole and pyrazole derivatives. The first evidence for the azafulvenium methides by intermolecular trapping via [8π+2π] 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-1*H*,3*H*-pyrrolo[1,2-*c*]thiazoles under Flash Vacuum Pyrolysis[1,3] or in some cases via sealed tube thermolysis.[1] These dipoles participate in pericyclic reactions, namely, sigmatropic [1,8]H shifts and 1,7-electrocyclization, giving *N*-vinyl- or *C*-vinylpyrroles. The SO_2 extrusion of 2,2-dioxo-1*H*,3*H*-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 vinylpyrazoles. Diazafulvenium methides unsubstituted at C-7 participate in [8π+2π] 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 [8π+2π] cycloadducts.[1a,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 [8π+2π] cycloaddition.

Starting from 3-methyl-2,2-dioxo-1*H*,3*H*-pyrrolo[1,2-*c*]thiazoles **5a** or **5b** the reaction carried out in 1,2,4-trichlorobenzene under microwave irradiation afforded the corresponding *N*-vinylpyrroles **7** (Scheme 2). The synthesis of these heterocyles results from the SO_2 extrusion of sulfones **5** giving azafulvenium methides **6** followed by a sigmatropic [1,8]H shift. Azafulvenium methide **9**



Scheme 1.

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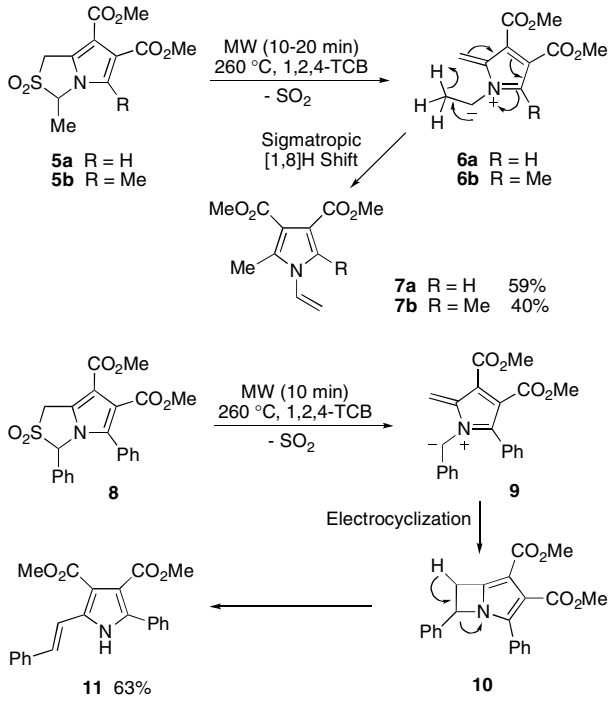
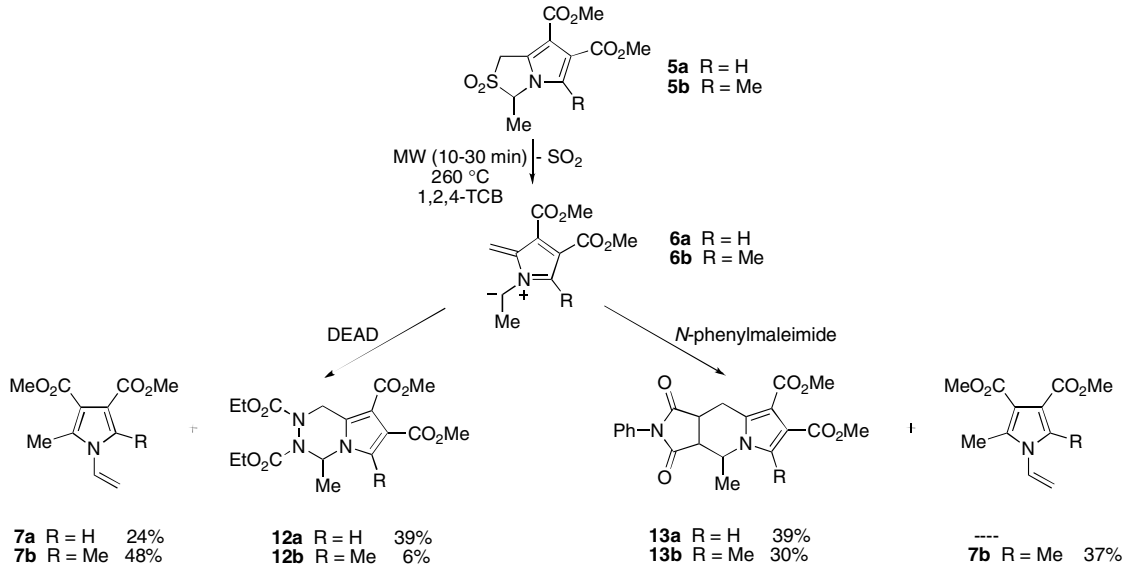


Scheme 2.

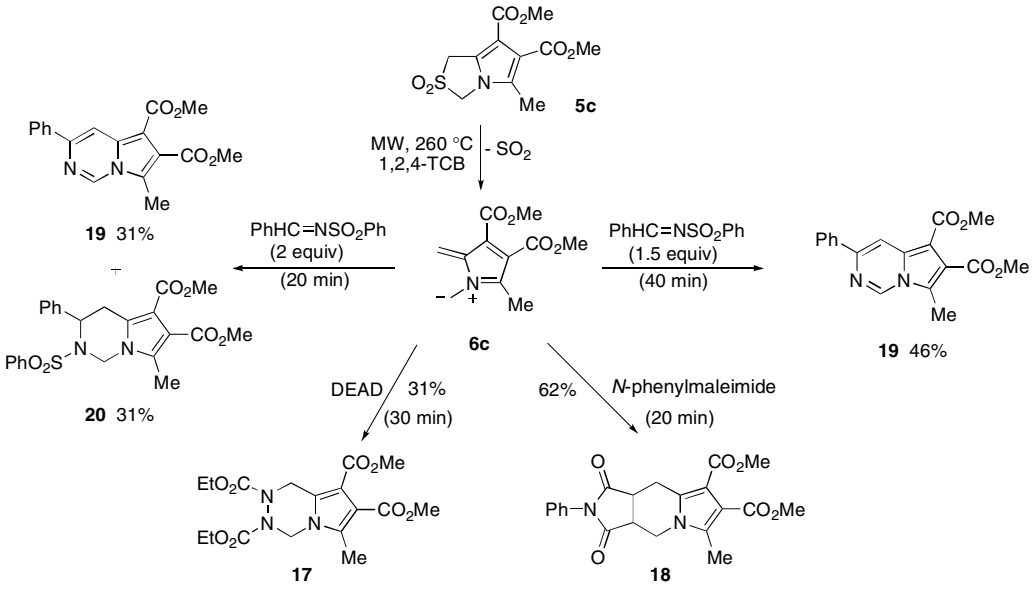
could also be generated from 3-phenyl-2,2-dioxo-1*H*,3*H*-pyrrolo-[1,2-*c*]thiazole **8** under microwave irradiation. In this case, the 1,7-dipole undergoes electrocyclization to give **10**, which is converted into *C*-vinylpyrrole **11** in 63% yield. Pyrroles **7** and **11** have been previously 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 **7b** 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).[5] 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**[6] 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*-benzylidenebenzenesulfonamide[7] 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-tetracarboxylates (**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-1*H*,3*H*-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**[8] (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*-benzylidenebenzenesulfonamide and only *N*-vinylpyrrole **7b** could be obtained from these attempted reactions.

Azafulvenium methide **6c**, generated from 2,2-dioxo-1*H*,3*H*-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*-vinylpyrroles 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 1*H*,4*H*-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**[9] was obtained in 62% yield. Microwave irradiation of sulfone **5c** for 20 min in the presence of *N*-benzylidenebenzenesulfonamide gave the 1,2,3,4-tetrahydro-5*H*-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-5*H*-pyrrolo[1,2-*c*]pyrimidine-5,6-dicarboxylate **19** in 46% yield as the only product. ^{1}H NMR and ^{13}C NMR data of dimethyl 7-methyl-3-phenylpyrrolo[1,2-*c*]pyrimidine-5,6-dicar-

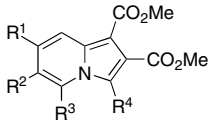


Scheme 3.

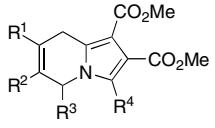


Scheme 4.

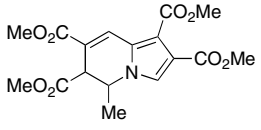
boxylate **19** is collected in Table 1. The assignment was supported by two-dimensional HMQC and HMBC spectra (400 MHz). In the HMBC spectrum the proton with the chemical shift 8.03 ppm (H-4) shows ^{2}J coupling constants with C-4a and C-3 with lower intensity. Correlation of H-4 with C-8 is also observed. On the other hand, the proton at 9.54 ppm (H-1) shows ^{3}J coupling constants with C-4 and C-3 with higher intensity.



14a $R^1 = R^2 = CO_2Me$; $R^3 = Me$; $R^4 = H$
14b $R^1 = R^2 = SiMe_3$; $R^3 = H$; $R^4 = Me$



15a $R^1 = R^2 = CO_2Me$; $R^3 = Me$; $R^4 = H$
15b $R^1 = R^2 = SiMe_3$; $R^3 = H$; $R^4 = Me$



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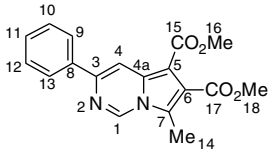
Attempts to carry out cycloaddition reactions of **6c** with DMAD were not successful. However, azafulvenium methide **6c** reacts with the electron-rich dipolarophile bis(trimethylsilyl)acetylene giving dimethyl 3-methyl-6,7-bis(trimethylsilyl)indolizine-1,2-dicarboxylate **14b** (8%) and dimethyl 3-methyl-6,7-bis(trimethylsilyl)-5,8-dihydroindolizine-1,2-dicarboxylate **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]

Table 1
^{1}H NMR and ^{13}C NMR data for pyrrolo[1,2-*c*]pyrimidine **19**

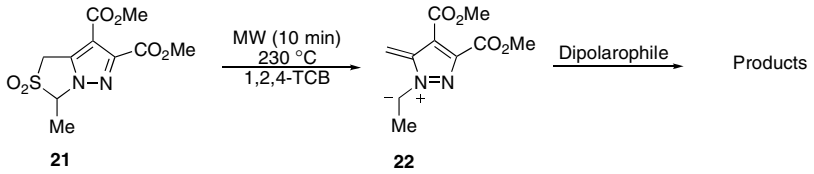


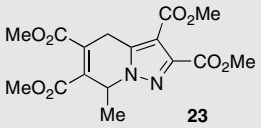
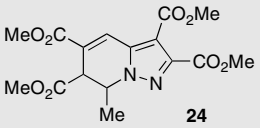
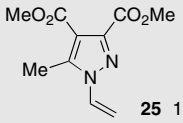
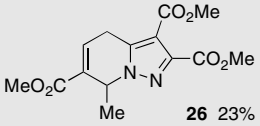
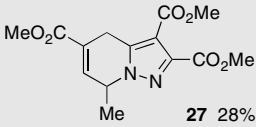
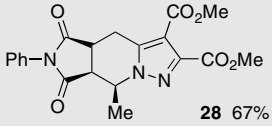
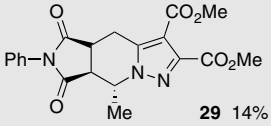
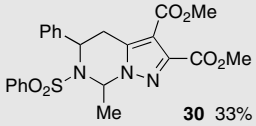
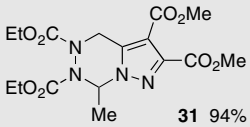
C	^{1}H (ppm)	^{13}C (ppm)
C-14	2.62	9.92
C-16	3.95	51.91
C-18	3.97	52.68
C-4	8.03	111.35
C-6	—	121.66
C-7	—	124.73
C-4a	—	127.38
C-8	—	132.82
C-3	—	141.90
C-1	9.54	145.95
C-17	—	163.32
C-15	—	165.80

The study was extended to the reactivity of diazafulvenium methide **22** generated from 2,2-dioxo-1*H*,3*H*-pyrazolo[1,5-*c*]-[1,3]thiazole **21**[2] 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 SO_2 extrusion of 2,2-dioxo-1*H*,3*H*-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 dihydropyrazolo[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 2
Generation and [8π+2π] cycloaddition of diazafulvenium methide **22**



Dipolarophile	Products		
DMAD	 **23**	 **24**	**23**:**24** (42:58) 81%
Methyl propiolate	 **25** 19%	 **26** 23%	 **27** 28%
N-Phenylmaleimide	 **28** 67%	 **29** 14%	
N-Benzylidenebenzenesulfonamide	 **30** 33%		
DEAD	 **31** 94%		

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, cycloadducts **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**.[2b] The 1,7-dipole **22** can also be trapped by [8π+2π] cycloaddition with *N*-benzylidenebenzenesulfonamide 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-1*H*,3*H*-pyrrolo[1,2-*c*]thiazoles and 2,2-dioxo-1*H*,3*H*-pyrazolo-[1,5-*c*]thiazoles, respectively. Under these conditions and in the absence of dipolarophiles azafulvenium methides undergo sigmatropic [1,8]H shifts or 1,7-electrocyclization giving *N*-vinyl- or *C*-vinylpyrroles. On the other hand, in the presence of dipolarophiles the [8π+2π] cycloaddition of azafulvenium 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-1*H*,3*H*-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

NMR data for compound dimethyl 7-methyl-3-phenylpyrrolo-[1,2-c]pyrimidine-5,6-dicarboxylate **19**. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.06.013.

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5. *General procedure for [8π+2π] cycloadditions of azafulvenium methides.* A suspension of 2,2-dioxo-1*H*-pyrrolo[1,2-*c*]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-2,3,7,8-tetracarboxylate* **12a**. Yellowish oil. IR (film) 1735, 1696, 1400, 1215 cm^{-1}. ^1H NMR ($CDCl_3$, 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); ^{13}C NMR ($CDCl_3$, 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, 154.5, 154.9, 163.6, 163.8; MS (EI) 397 (M^+, 21%), 365 (100), 251 (45), 221 (24), 209 (23), 196 (26), 177 (40),164 (35) and 147 (20). HRMS (EI) *m*/*z* 397.1488 ($C_{17}H_{23}N_3O_8$ [M^+], 397.1485).
7. Vishwakarma, L. C.; Stringer, O. D.; Davis, F. A. *Org. Synth.* **1993**, *Coll.Vol. VIII*, 546–550.
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 ($CDCl_3$, 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), 7.01–7.04 (2H, m, Ar-H), 7.34–7.42 (3H, m, Ar-H); ^{13}C NMR ($CDCl_3$, 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 ($C_{22}H_{22}N_2O_6$ [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, 1390, 1212 cm^{-1}. ^1H NMR ($CDCl_3$, 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); ^{13}C NMR ($CDCl_3$, 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, 130.9, 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 ($C_{21}H_{20}N_2O_6$ [M^+], 396.1321).