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[3+2]- Versus [4+2]-cycloaddition reactions of 3-methylsulfanyl-2-arylazo-3-(pyrrolidin-1-yl)acrylonitriles with *N*-substituted maleimides involving pyrrolidine-derived azomethine ylides

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Abstract—3-Methylsulfanyl-2-arylazo-3-(pyrrolidin-1-yl)acrylonitriles do not enter into [4+2]-cycloaddition reactions with maleimides to form the expected pyrrolo-pyridazines. Instead the formation of novel pyrrolo-pyridazines of type **4** takes place via a formal [3+2]-cycloaddition of initially formed pyrrolidine-derived azomethine ylides **7**. The mechanism leading to the final product is discussed.

[4+2]-Cycloaddition reactions of 1,2-diazadienes represent an efficient method to prepare pyridazines.[1–4] In turn, 1,2-diazadienes can be synthesized either by base catalyzed dehydrohalogenation of α-halomethyl-hydrazones[1–5] or by oxidation of hydrazones.[6–8] 1,2-Diazadienes are rather reactive and unstable compounds, and therefore, besides their main reaction course, side reactions may take place leading to a mixture of compounds.[4] We have found that the alkylation reaction of 2-arylhydrazono-3-(pyrrolidin-1-yl)-3-thioketopropionitriles occurs on the sulfur atom of the thioamide group to form rather stable 3-methylsulfanyl-2-arylazo-3-(pyrrolidin-1-yl)acrylonitriles. We envisaged that these compounds would undergo a [4+2]-cycloaddition reaction with maleimides to afford pyrrolo-pyridazines of type **4** which would be of interest in medicinal chemistry, as interesting biological properties were recently found in a series of fused pyridazines.[3] However, when 1,2-diazadienes **1a**–**d** were heated at reflux with five equivalents of maleimides **2a**,**b** in benzene for 5–10 h solid products were found in good yields (55–80%) but these were not the expected product **4** (see Scheme 1).

The IR, mass, ^{1}H and ^{13}C NMR spectra of the products are in good accordance with the structures of the tricyclic pyrrolizines **5** and **6**. The IR spectra of all the compounds exhibited an absorption band corresponding to a cyano group at 2200 cm^{-1}. Compounds **5** and **6** were isolated as inseparable mixtures of double bond isomers (Scheme 2). Indeed, double signals were present in the NMR spectra. Typical resonances included two doublets at 4.7–5.10 ppm corresponding to the 3a proton ($^{3}J_{3a-8b} = 8.5–8.8$ Hz) and two doublet of doublets ($^{3}J_{8b-3a} = 8.5–8.8$ Hz; $^{3}J_{8b-8a} = 10.0–10.3$ Hz) for the 8b proton. The number of protons in the pyrrolidine fragment has changed from eight to seven and one of them is shifted 0.6–0.8 ppm downfield in comparison with N–CH_2 signals in the starting compound. We assigned the all-*cis*-H structure by analogy with similar tricyclic compounds reported by Viehe et al.[9,10] which have coupling constants in the same range.

Keywords: Cycloaddition; Diazadienes; Azomethine ylides; Maleimides; Pyrrolizidines.
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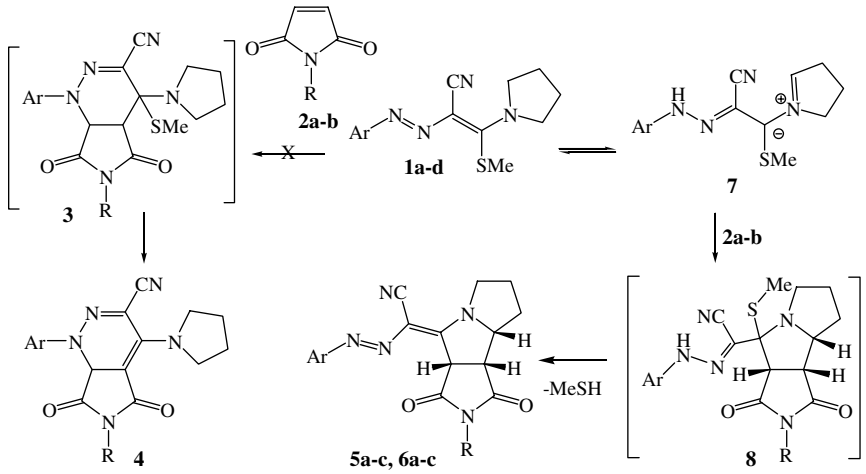
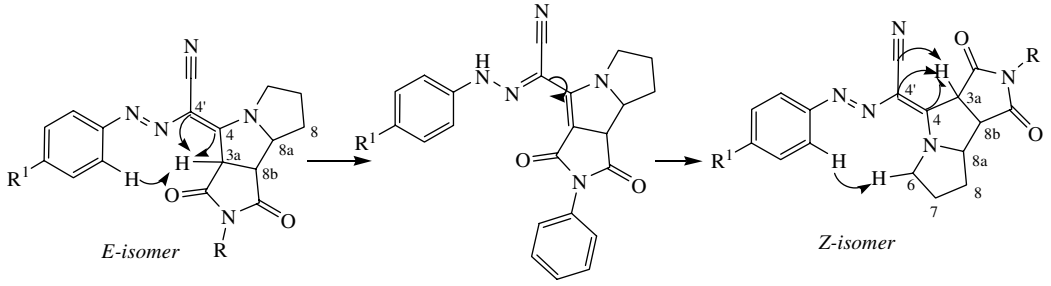


1a Ar = 4-$NO_2C_6H_4$; **1b** Ar = Ph; **1c** Ar = 4-MeC_6H_4; **1d** Ar = 4-$MeOC_6H_4$
2a R = Ph ; **2b** R =Me
5a R = Me, Ar = 4-$NO_2C_6H_4$; **5b** R = Me, Ar = Ph; **5c** R = Me, Ar = 4-$MeOC_6H_4$
6a R = Ph, Ar = 4-$NO_2C_6H_4$; **6b** R = Ph, Ar = 4-MeC_6H_4; **6c** R = Ph, Ar = 4-$MeOC_6H_4$

Scheme 1.



Scheme 2. Selected NOESY and COSY correlations observed in **5** and **6**.

The assignment of the signals in the ^{13}C NMR spectrum were made on the basis of DEPT, 2D COSY, HSQC, HMBC, and H–H NOESY experiments (Scheme 2). In **6b**, the presence of interactions of an aromatic proton with the 3a proton in the *E*-isomer and the aromatic proton with the proton at position 6 in the *Z*-isomer were found in the H–H NOESY spectra. The interaction of C4 and C4′ with the 3a proton was confirmed by 2D COSY experiments. The signal due to C4′ were apparent in the 102.8 (*E*-isomer) and 103.9 ppm (*Z*-isomer) as two doublets with coupling constants $^3J = 1.3$ and 0.6 Hz,[11] and the signal for C4 occurred at 158.9 (*E*-isomer) and 154.3 ppm (*Z*-isomer) with H3a of $^2J = 6.4$ and 3.4 Hz.

All our attempts to separate the *Z*- and *E*-isomers failed. We propose that these isomers exist in equilibrium and transform into each other via rotation around the C4–C4′ double bond, facilitated by a reversible shift of H-3a to the azo group to form the hydrazono function. Indeed, measurement of the ^1H NMR spectrum at a higher temperature showed that the proton signals approach each other with increasing temperature. The coalescence of the H-3a signals was achieved at about 120 °C.

We suggest the following mechanism for the interaction of compounds **1** with maleimides **2**. We propose that the course of the reaction involves the formation of an azomethine ylide **7** followed by [3+2]-cycloaddition to the double bond of the maleimide to afford **8** and then the final compound after loss of MeSH. The proton shift required to form **7** is aided by the push-pull electronic character present in compound **1**.

It should be noted that Viehe[9,10] reported the generation of pyrrolidine-derived azomethine ylides containing a methylthio group at the negatively charged atom by reaction of a thioamidinium salt with a strong base at low temperature. The same author showed that the generation of an azomethine ylide is possible via acid catalyzed elimination of methylthiol from a trifluoromethyl thioaminal by heating at reflux in toluene. However, the conditions for the generation of azomethine ylides used in our method are very different. No catalyst is required, and the generation of the azomethine ylides takes place by heating thioimidate **1** in benzene at reflux.

Thus, the thioimidates of arylazoacrylonitriles are shown to be good synthons for the generation of azomethine ylides under mild conditions. The heterocycles **5** and **6** synthesized in this work are the first examples of 4-methylene pyrrolizidines.

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11. All new compounds reported here gave analytical and spectral data consistent with the assigned structures. For **5a** yield 50%: EIMS *m*/*z* 380 (M^+, 51). Anal. Calcd for $C_{18}H_{16}N_6O_4$: C, 56.84; H, 4.24; N, 22.09. Found: C, 56.72; H, 4.19; N, 21.97. For **5b** yield 53%: EIMS *m*/*z* 335 (M^+, 25). Anal. Calcd for $C_{18}H_{17}N_5O_2$: C, 64.47; H, 5.11; N, 20.88. Found: C, 64.26; H, 5.05; N, 20.96. For **5c** yield 69%: IR (KBr) υ_{max} cm^{-1}: 1705, 2195, 2965. ^1H NMR (400 MHz, DMSO-d_6) δ_H, ppm: 1.27–1.52 (m, 1H, C8-H_2), 1.95–2.11 (m, 1H, C8-H_2), 2.12–2.32 (m, 2H, C7-H_2), 2.89 and 2.91 (s, 3H, NCH_3), 3.62–3.93 (m, 3H, C8b-H and C6-H_2), 3.82 (s, 3H, OMe), 4.43–4.58 (m, 1H, C8a-H_2), 4.74 and 5.10 (d and d, 1H, C3a-H, $J = 8.8$ Hz), 7.92 and 7.70 (AA′BB′, 4H, Ar, $J = 8.8$ Hz); ^{13}C NMR (DMSO-d_6, 100 MHz) δ_c, ppm: 174.6 (CO), 174.5 (CO), 172.8 (CO), 172.0 (CO), 159.4 (Ar-C), 159.2 (Ar-C), 158.2 (C-4), 153.4 (C-4), 147.0 (Ar-C), 146.7 (Ar-C), 123.1 (Ar-CH), 122.7 (Ar-CH), 114.4 (Ar-CH), 114.0 (Ar-CH), 114.8 (CN), 115.1 (CN), 103.4 (C-4′), 102.4 (C-4′), 69.8 (CH-8a), 69.3 (CH-8a), 56.8 (CH-3a), 56.7 (CH-3a), 55.3 (OCH_3), 48.9 (CH_2-6), 46.1 (CH_2-6), 40.5 (CH-8b), 40.3 (CH-8b), 26.9 (CH_2-7), 26.7 (CH_2-7), 26.6 (CH_2-8), 26.4 (CH_2-8), 25.2 (NCH_3), 25.15 (NCH_3). EIMS *m*/*z* 365 (M^+, 27). Anal. Calcd for $C_{19}H_{19}N_5O_3$: C, 62.46; H, 5.24; N, 19.17. Found: C, 62.39; H, 5.32; N, 19.09. For **6a** yield 63%: EIMS *m*/*z* 442 (M^+, 95). Anal. Calcd for $C_{23}H_{18}N_6O_4$: C, 62.44; H, 4.10; N, 18.99. Found: C, 62.36; H, 4.00; N, 18.76. For **6b** yield 50%: IR (KBr) υ_{max} cm^{-1}: 1715, 2195, 2950. ^1H NMR (400 MHz, DMSO-d_6) δ_H, ppm: 1.46–1.60 (m, 1H, C8-H_2), 1.96–2.06 (m, 1H, C8-H_2), 2.13–2.28 (m, 2H, C7-H_2), 2.32 and 2.33 (s, 3H, Me), 3.90 and 3.93 (dd, 1H, C8b-H, $J^1 = 8.7$, $J^2 = 10.3$), 3.72–3.87 (m, 2H, C6-H_2), 4.56–4.66 (m, 1H, C8a-H_2), 4.93 and 5.29 (d and d, 1H, C3a-H, $J = 8.7$ Hz), 7.27 and 7.62 (2H, AA′BB′, Ar, $J = 8.4$), 7.21 and 7.51 (2H, AA′BB′, Ar, $J = 8.1$), 7.30–7.36 (m, 2H, Ar), 7.42–7.55 (m, 3H, Ar); ^{13}C NMR (DMSO-d_6, 100 MHz) δ_c, ppm: 173.9 (m, CO), 173.8 (m, CO), 171.14 (dd, CO, $J = 7.4$ Hz, $J = 4,3$ Hz), 171.9 (dd, CO, $J = 7.5$ Hz, $J = 4.1$ Hz), 158.9 (d, C-4, $J = 6.4$ Hz), 154.3 (ddd, C-4, $J = 3.4$ Hz, $J = 1.7$ Hz, $J = 1.7$ Hz), 150.9 (Ar-C), 150.6 (Ar-C), 137.9 (ddd, Ar-C, $J = 6.5$ Hz, $J = 7.7$ Hz, $J = 6.5$ Hz), 137.46 (dddd, Ar-C, $J = 8.9$ Hz, $J = 6.8$ Hz, $J = 5.2$ Hz, $J = 4.1$ Hz), 132.5 (ddd, Ar′-C, $J = 9.3$ Hz, $J = 7.7$ Hz, $J = 1.5$ Hz), 132.2 (dd, Ar′-C, $J = 10.1$ Hz, $J = 9.2$ Hz), 129.7 (d, Ar-CH, $J = 158.1$ Hz), 129.4 (d, Ar-CH, $J = 158.0$ Hz), 128.8 (d, Ar′-CH, $J = 157.3$ Hz), 128.8 (d, Ar′-CH, $J = 157.1$ Hz), 128.7 (d, Ar′-CH, $J = 158.0$ Hz), 128.6 (d, Ar′-CH, $J = 158.3$ Hz), 127.5 (d, Ar′-CH, $J = 163.6$ Hz), 127.3 (d, Ar′-CH, $J = 163.1$ Hz), 121.6 (dd, Ar-CH, $J = 161.0$ Hz, $J = 5.4$ Hz), 121.2 (dd, Ar-CH, $J = 161.0$ Hz, $J = 5.1$ Hz), 114.8 (CN), 115.2 (CN), 103.9 (d, C-4′, $J = 1.2$ Hz), 102.8 (d, C-4′, $J = 0.6$ Hz), 70.3 (d, CH-8a, $J = 150.7$ Hz), 69.8 (d, CH-8a, $J = 150.1$ Hz), 57.1 (dd, CH-3a, $J = 147.1$ Hz, $J = 2.1$ Hz), 56.9 (dd, CH-3a, $J = 148.6$ Hz, $J = 2.1$ Hz), 49.2 (t, CH_2-6, $J = 147.5$ Hz), 46.4 (t, CH_2-6, $J = 146.3$ Hz), 40.3 (m, CH-8b), 40.6 (m, CH-8b), 26.8 (m, CH_2-7), 26.9 (m, CH_2-7), 26.5 (m, CH_2-8), 26.7 (m, CH_2-8), 20.8 (dt, CH_3, $J = 126.6$ Hz, $J = 4.4$ Hz), 20.7 (dt, CH_3, $J = 126.4$ Hz, $J = 4.3$ Hz). EIMS *m*/*z* 411 (M^+, 21). Anal. Calcd for $C_{24}H_{21}N_5O_2$: C, 70.06; H, 5.14; N, 17.02. Found: C, 69.91; H, 5.05; N, 16.84. For **6c** yield 55%: EIMS *m*/*z* 427 (M^+, 27). Anal. Calcd for $C_{24}H_{21}N_5O_3$: C, 67.44; H, 4.95; N, 16.38. Found: C, 67.29; H, 4.81; N, 16.15.