1,3-DIPOLAR CYCLOADDITIONS OF AN AZIRIDINE VIA AZOMETHINE YLIDE TO 2-METHYLPYRIDAZIN-3(2*H*)-ONES

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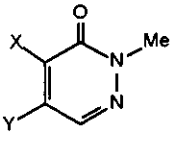
Abstract- The 1,3-dipolar cycloaddition of the azomethine ylide generated by thermal ring opening of dimethyl *trans*-1-(*p*-methoxyphenyl)aziridine-2,3-dicarboxylate (**1**) to 2-methylpyridazin-3(2*H*)-one (**3**) and its cyano (**4**) and ethylsulphonyl (**5**,**6**) derivatives have been carried out. The azomethine ylide (**2**) undergoes addition to the 4,5 C=C double bond of 2-methylpyridazinones (**3**-**6**) to afford pyrrolo[3,4-*d*]pyridazin-1(2*H*)-one derivatives.

A few years ago, we have reported 1,3-dipolar cycloadditions of diazomethane to pyridazinone (**3**) and to its 4- and 5-substituted derivatives as a synthetic route to new pyrazolo[3,4-*d*]pyridazinones.[2] Our results showed the behaviour of pyridazinones as dipolarophiles, and the influence of the nature and position of the substituents on the reactivity of the pyridazinones towards diazomethane and on the regioselectivity of the cycloaddition. The above synthetic strategy has also been used with several dipoles for the obtention of isoxazolo[4,5-*d*]pyridazin-4-ones[3] and other heterocyclic systems with two fused rings.[4]

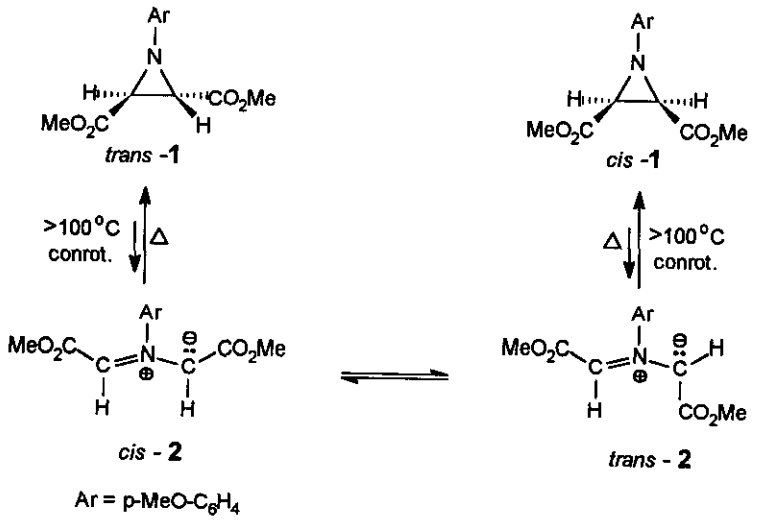
Our interest in 1,3-dipolar cycloadditions to pyridazinones to provide a convenient entry to novel fused heterocyclic systems, led us to study the addition of azomethine ylides to pyridazinone (**3**) and its cyano (**4**) and ethylsulphonyl (**5**,**6**) derivatives as a synthetic route to pyrrolo[3,4-*d*]pyridazinones.



	3	4	5	6
X	H	CN	$EtSO_2$	H
Y	H	H	H	$EtSO_2$

Among the different methods developed for the generation of azomethine ylides[5] we selected the thermal conrotatory ring-opening of aziridines.[6] According to Huisgen[6a] the thermal equilibration at temperatures above 100 °C of aziridines *trans*-(**1**) and *cis*-(**1**) takes place *via* the azomethine ylides *cis*-(**2**) and *trans*-(**2**) originated by conrotatory ring-opening, as shown in the Scheme I. However, in the presence of a highly active dipolarophile, such as dimethyl acetylenedicarboxylate, the azomethine ylide *cis*-(**2**) is trapped to give

exclusively the *cis*-adduct and the equilibration *cis*-(**2**) ⇄ *trans*-(**2**) is suppressed. If the dipolarophilic activity of the multiple bond system is reduced, *cis*-(**2**) isomerizes in part to *trans*-(**2**) and mixtures of *cis*- and *trans*-adducts are obtained.[6c,6f] With poor dipolarophiles, such as phenanthrene, the sequence *trans*-(**1**) → *cis*-(**2**) → *trans*-(**2**) leads exclusively to the *trans*-adduct.[6g]



Scheme I

RESULTS AND DISCUSSION

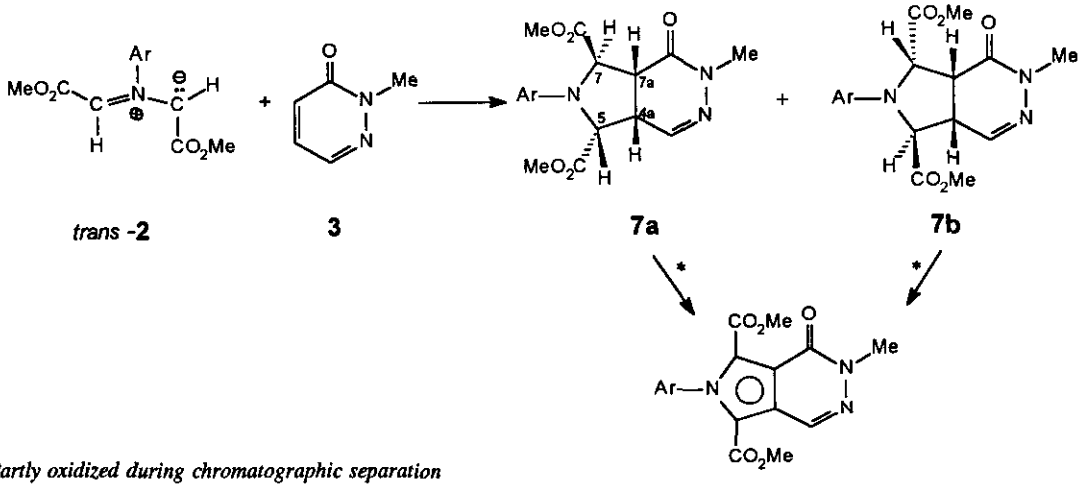
The cycloaddition of azomethine ylides generated from aziridine (**1**) does not present regiochemical problems. However, the pyridazinone ring contains a C=C bond and a C=N bond, which in principle could add to the azomethine ylide. The C=C bond, directly attached to an electron withdrawing group, was expected to be more reactive than the C=N bond. In fact, the addition of azomethine ylide (**2**) to 2-methylpyridazin-3(2*H*)-ones (**3-6**) occurs exclusively across the 4,5 C=C bond to give 6*H*-pyrrolo[3,4-*d*]pyridazin-1(2*H*)-one derivatives.

The reactions of aziridine *trans*-(**1**) to 2-methylpyridazin-3(2*H*)-one (**3**) and its derivatives substituted at 4- or 5-position (**4-6**) have been performed under nitrogen, for prolonged periods in refluxing chlorobenzene, using a three fold excess of dipolarophile. The results of the reactions summarized in Table I indicate that high conversions are obtained under these conditions.

2-Methylpyridazin-3(2*H*)-one (**3**) reacted with aziridine (**1**) giving two stereoisomeric adducts (**7a** and **7b**) in a 1:1 ratio. These adducts were isolated by flash column chromatography. After chromatography, a third product (**8**) was isolated, which results from aromatization of the initial adducts (**7a** and **7b**).

Table I. 1,3-Dipolar cycloadditions of azomethine ylide (2) to pyridazinones (**3-6**).

Piridazinone	X	Y	Time (h)	Conversion (%)	Products (Ratio %)
3	H	H	120	99	**7a** + **7b** (50) (50)
4	CN	H	48	70	**9** + **12a** + **12b** + **8** (50) (20) (20) (10)
5	$EtSO_2$	H	72	95	**12a** + **12b** + **8** (40) (40) (20)
6	H	$EtSO_2$	36	95	**12a** + **12b** + **8** (30) (50) (20)



Scheme II

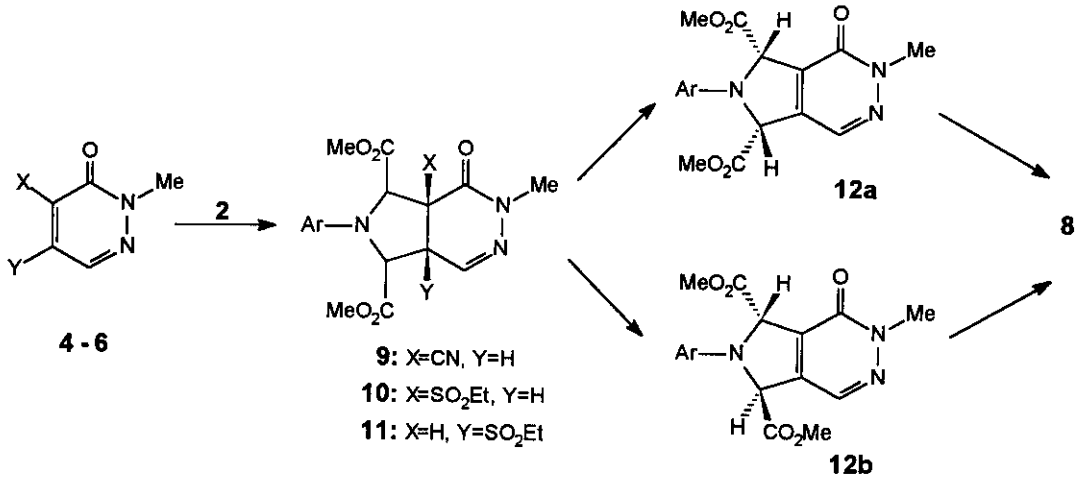
The structure of adducts (**7a** and **7b**) was determined on the basis of their ^1H nmr spectra (Table II). Thus, the disappearance of the signals corresponding to the olefinic protons of the pyridazinone ring and the presence of signals assigned to H-4a and H-7a, coupled respectively with H-5 and H-7 protons of the pyrrole ring, confirmed that the addition took place at the 4,5 double bond of pyridazinone. The *cis* junction between both rings was corroborated from the magnitude of the coupling constant $J_{4a,7a}$=9.8 Hz. The stereochemical relationship between the methoxycarbonyl groups in the adducts (**7a** and **7b**) could be directly deduced from the magnitude of the coupling constants between H-4a and H-5, and H-7 and H-7a (Table II). The *trans* arrangement of the methoxycarbonyl groups in both adducts, was justified by the isomerization process of the

cis-(**2**) to *trans*-(**2**) azomethine ylides, because the pyridazinone (**3**) is not active enough to trap the *cis* isomer and to suppress the equilibration process.

Table II. ^{1}H Nmr data of pyrrolo[3,4-*d*]pyridazinones

Compound		Chemical shift					Coupling Constants			
N°	X	H-4	H-4a	H-5	H-7	H-7a	$J_{4,4a}$	$J_{4a,5}$	$J_{4a,7a}$	$J_{7,7a}$
7a	H	7.11	3.85	4.77	5.34	3.20	4.3	9.6	9.8	1.1
7b	H	7.06	3.39	4.75	4.87	3.84	1.2	2.1	9.8	9.5
9	CN	7.10	3.84	4.80	5.15	-	1.9	3.4	-	-
12a	-	8.05	-	5.46	5.46	-	-	-	-	-
12b	-	7.95	-	5.70	5.70	-	-	-	-	-

The cycloadditions of azomethine ylide (**2**) to the substituted pyridazinones (**4-6**) proceeded at a rate faster than that of the unsubstituted pyridazinone (**3**). The reaction of cyanopyridazinone (**4**) with **2** produced a mixture of adduct (**9**), compounds (**12a** and **12b**) and the fully aromatic compound (**8**) in a 5:2:2:1 ratio. The reaction of ethylsulphonylpyridazinones (**5** and **6**) afforded a mixture of compounds (**12a**, **12b** and **8**) in a 2:2:1 and 3:5:2 ratio, respectively, although in both cases the primary adducts (**10** and **11**) could not be detected.



Scheme III

A *trans* stereochemistry of H-5 and H-4a in adduct (**9**) could be assigned on the basis of the magnitude of the coupling $J_{4a,5}$. However, the stereochemistry of the substituents on C-7 and C-7a could not be established on

a similar basis because of the absence of a proton at 7a position.

We have assigned the *cis* and *trans* arrangement of the methoxycarbonyl groups in compounds (**12a** and **12b**), respectively, by comparison with the Huisgen data for the cycloaddition of azomethine ylide *cis*-(**2**) and *trans*-(**2**) to dimethyl acetylenedicarboxylate.[6a] Thus, in the *cis* compound (**12a**) the signal of H-5 and H-7 appears at higher field (5.46 ppm) than that of the *trans* isomer (**12b**) (5.70 ppm).

Compounds (**12a** and **12b**) could be originated by HX or HY elimination from the primary *cis*- or *trans*-adducts (**9-11**). The formation of *cis* adducts in this case may be explained by the increased reactivity of the substituted pyridazinones (**4-6**) as dipolarophiles that allows the partial cycloaddition to the azomethine ylide *cis*-(**2**).[7]

The above results show the influence of the substituents on the reactivity of the pyridazinones towards azomethine ylide (**2**). The reactivity of the pyridazinones increases with the presence of electron withdrawing substituents at 4- or 5-positions. Among the pyridazinones studied, the 5-ethylsulfonyl derivative (**6**) proved to be most reactive, followed by those with ethylsulphonyl (**5**) and cyano groups (**4**) at 4-position, the unsubstituted pyridazinone (**3**) being the less reactive as dipolarophile. In summary, the dipolarophilic activity of pyridazinones towards 1,3-dipole (**2**) parallels that observed towards diazomethane,[2c] although the cycloadditions require somewhat more severe conditions.

EXPERIMENTAL

Melting points are uncorrected and were determined with a Kofler hot-stage apparatus. Microanalyses were performed with a Perkin-Elmer analyzer model 240 C and with a Heraeus analyzer model CHN-O-Rapid. Ir spectra were recorded on Perkin-Elmer models 681 and Infracord 137 E grating spectrophotometer, ν values in cm^{-1}. ^1H Nmr spectra were determined on a Varian EM-390 or on a Bruker AM-200 spectrometer, ^{13}C nmr were determined on a Bruker AM-200, in $CDCl_3$ solutions (unless otherwise stated). Chemical shifts are reported in ppm (δ) downfield from TMS. Mass spectra were determined on either a Hitachi-Perkin-Elmer spectrometer model RMU-6MG or a VG-12-250. Silica gel Merck 60 (70-230 mesh), 60 (230-400 mesh) and DC-Alufolien 60 F_{254} were used for conventional, flash column chromatography and analytical t.l.c., respectively. The starting aziridine (**1**)[8] and pyridazinones (**3-6**)[9] have been prepared according to literature.

Cycloaddition of dimethyl *trans*-1-(p-methoxyphenyl)aziridine-2,3-dicarboxylate to 2-methylpyridazin-3(2H)-ones. General procedure.

To a solution of the pyridazin-3(2*H*)-one (**3-6**) (3 mmol) in chlorobenzene (15 ml) was added a solution of aziridine *trans*-(**1**) (256 mg, 1 mmol) in chlorobenzene (5 ml). The reaction mixture was refluxed under nitrogen during the period indicated for each case in Table I. The solvent was removed under reduced pressure and the residue was analyzed by ^1H nmr. The crude product was purified by chromatography on silica gel

(petroleum ether-acetone 7:3).

Cycloaddition to 3. Reaction time 120 h. The crude residue contained the unreacted pyridazinone (**3**) and a 1:1 mixture of adducts (**7a** and **7b**). This mixture was chromatographed affording the two stereoisomeric adducts (**7a**) (39%, 146 mg), (**7b**) (34%, 126 mg) and the pyrrolopyridazinone (**8**) (8%, 29 mg).

2-Methyl-*t*-5,*c*-7-dimethoxycarbonyl-6-(*p*-methoxyphenyl)-6*H*-*r*-4a,5,7,*c*-7a-tetrahydropyrrolo[3,4-*d*]pyridazin-1(2*H*)-one (7a). Mp 189-190 °C (petroleum ether-acetone 7:3). Anal. Calcd for $C_{18}H_{21}N_3O_6$: C, 57.60; H, 5.60; N, 11.20. Found: C, 57.69; H, 5.60; N, 11.29. Ir (nujol): 1750, 1730, 1675. ^{1}H Nmr: 7.11 (d, 1H, H-4, $J_{4,4a}$=4.3 Hz); 6.64 (AB syst., 4H arom., J=9.07 Hz); 5.34 (d, 1H, H-7, $J_{7,7a}$=1.1 Hz); 4.77 (d, 1H, H-5, $J_{4a,5}$=9.6 Hz); 3.85 (dt, 1H, H-4a, $J_{4a,7a}$=9.8 Hz, $J_{4,4a}$=4.3 Hz); 3.76 and 3.74 (2s, 6H, $CO_2C\underline{H}_3$ in C-5 and C-7); 3.61 (s, 3H, $OC\underline{H}_3$); 3.35 (s, 3H, $NC\underline{H}_3$); 3.20 (dd, 1H, H-7a, $J_{4a,7a}$=9.8 Hz, $J_{7,7a}$=1.1 Hz). ^{13}C Nmr: 173.1, 171.7 ($\underline{C}O_2CH_3$); 161.6 (C=O); 152.8 (arom.); 138.7, 138.4 (arom., C-4); 115.1, 114.0 (arom.); 65.6, 63.7 (C-5, C-7); 55.6, 52.5, 52.3 (OCH_3); 43.6, 40.1 (C-4a, C-7a); 37.2 (NCH_3). Ms, m/z: 375 (M^+), 343, 316 (100), 284, 256, 206, 205.

2-Methyl-*c*-5,*t*-7-dimethoxycarbonyl-6-(*p*-methoxyphenyl)-6*H*-*r*-4a,5,7,*c*-7a-tetrahydropyrrolo[3,4-*d*]pyridazin-1(2*H*)-one (7b). Mp 179 °C (petroleum ether-acetone 7:3). Anal. Calcd for $C_{18}H_{21}N_3O_6$: C, 57.60; H, 5.60; N, 11.20. Found: C, 57.69; H, 5.41; N, 11.19. Ir (nujol): 1740, 1720, 1670. ^{1}H Nmr: 7.06 (d, 1H, H-4, $J_{4,4a}$=1.2 Hz); 6.65 (AB syst., 4H arom., J=9.58 Hz); 4.87 (d, 1H, H-7, $J_{7,7a}$=9.5 Hz); 4.75 (d, 1H, H-5, $J_{4a,5}$=2.1 Hz); 3.84 (dd, 1H, H-7a, $J_{4a,7a}$=9.8 Hz, $J_{7,7a}$=9.5 Hz); 3.73 (s, 6H, $CO_2C\underline{H}_3$ in C-5 and C-7); 3.62 (s, 3H, $OC\underline{H}_3$); 3.39 (dt, 1H, H-4a, $J_{4a,7a}$=9.8 Hz, $J_{4a,5}$=2.1 Hz, $J_{4,4a}$=1.2 Hz); 3.34 (s, 3H, $NC\underline{H}_3$). ^{13}C Nmr: 172.3, 170.9 ($\underline{C}O_2CH_3$); 161.3 (C=O); 153.2 (arom.); 142.3, 138.2 (arom., C-4); 115.1, 114.7 (arom.); 65.7, 65.0 (C-5, C-7); 55.5, 52.7, 52.3 (OCH_3); 43.0, 42.7 (C-4a, C-7a); 36.8 (NCH_3). Ms, m/z: 375 (M^+), 316 (100), 256, 206.

2-Methyl-5,7-dimethoxycarbonyl-6-(*p*-methoxyphenyl)-6*H*-pyrrolo[3,4-*d*]pyridazin-1(2*H*)-one (8). Mp 196 °C (cyclohexane). Anal. Calcd for $C_{18}H_{17}N_3O_6$: C, 58.22; H, 4.58; N, 11.32. Found: C, 58.33; H, 4.58; N, 11.33. Ir (nujol): 1750, 1730, 1670. ^{1}H Nmr: 8.50 (s, 1H, H-4); 7.1 (AB syst., 4H arom., J=9.1 Hz); 3.82 (s, 3H, $OC\underline{H}_3$); 3.76 (s, 3H, $NC\underline{H}_3$); 3.72 (s, 6H, $CO_2C\underline{H}_3$ in C-5 and C-7). Ms, m/z: 371 (M^+, 100), 343, 298, 279, 254.

Cycloaddition to 4. Reaction time 48 h. The crude residue contained the unreacted pyridazinone (**4**) and compounds (**9**, **12a**, **12b** and **8**) in 5:2:2:1 ratio. The crude product was chromatographed to afford: the adduct

(**9**) (32%, 128 mg), (**12a**) (12%, 46 mg), (**12b**) (13%, 48 mg) and the pyrrolopyridazinone (**8**) (11%,41 mg).

7a-Cyano-2-methyl-5,7-dimethoxycarbonyl-6-(*p*-methoxyphenyl)-6*H*-4a,5,7,7a-tetrahydropyrrolo[3,4-*d*]piridazin-1(2*H*)-one (9). Mp 179-180 °C (petroleum ether-acetone 7:3). Anal. Calcd for $C_{19}H_{20}N_4O_6$: C, 57.00; H, 5.00; N, 14.00. Found: C, 57.13; H, 5.09; N, 13.88. Ir (nujol): 2225, 1750, 1690. ^{1}H Nmr: 7.10 (d, 1H, H-4, $J_{4,4a}$=1.9 Hz); 6.73 (AB syst., 4H arom., J=9.03 Hz); 5.15 (s, 1H, H-7); 4.80 (d, 1H, H-5, $J_{4a,5}$=3.4 Hz); 3.84 (m, 1H, H-4a); 3.76 and 3.75 (2s, 6H, $CO_2C\underline{H}_3$ in C-5 and C-7); 3.61 (s, 3H, $OC\underline{H}_3$); 3.37 (s, 3H, $NC\underline{H}_3$). Ms, m/z: 400 (M^+), 371, 341 (100), 314, 270, 206.

2-Methyl-*cis*-5,7-dimethoxycarbonyl-6-(*p*-methoxyphenyl)-6*H*-5,7-dihydropyrrolo[3,4-*d*]piridazin-1(2*H*)-one (12a). Mp 92-93 °C (cyclohexane). Anal. Calcd for $C_{18}H_{19}N_3O_6$: C, 57.90; H, 5.09; N, 11.26. Found: C, 57.93; H, 5.17; N, 11.21. Ir (nujol): 1750, 1730, 1670. ^{1}H Nmr: 8.05 (s, 1H, H-4); 6.78 (AB syst., 4H arom., J=9.16 Hz); 5.46 (s, 2H, H-5 and H-7); 3.83 (s, 6H, $CO_2C\underline{H}_3$ in C-5 and C-7); 3.80 (s, 3H, $OC\underline{H}_3$); 3.76 (s, 3H, $NC\underline{H}_3$). Ms, m/z: 373 (M^+), 371, 343, 314 (100), 270.

2-Methyl-*trans*-5,7-dimethoxycarbonyl-6-(*p*-methoxyphenyl)-6*H*-5,7-dihydropyrrolo[3,4-*d*]piridazin-1(2*H*)-one (12b). Mp 215-216 °C (cyclohexane). Anal. Calcd for $C_{18}H_{19}N_3O_6$: C, 57.90; H, 5.09; N, 11.26. Found: C, 57.97; H, 4.99; N, 11.16. Ir (nujol): 1750, 1740, 1670. ^{1}H Nmr: 7.95 (s, 1H, H-4); 6.98 (AB syst., 4H arom., J=9.07 Hz); 5.70 (s, 2H, H-5 and H-7); 3.76 (s, 3H, $OC\underline{H}_3$); 3.68 (s, 6H, $CO_2C\underline{H}_3$ in C-5 and C-7); 3.67 (s, 3H, $NC\underline{H}_3$). Ms, m/z: 373 (M^+), 314 (100), 270.

Cycloaddition to 5. Reaction time 72 h. The crude residue contained the unreacted pyridazinone (**5**) and compounds (**12a**, **12b** and **8**) in a 2:2:1 ratio. The crude product was chromatographed to afford: the compounds (**12a**, 30%, 112 mg), (**12b**, 26%, 97 mg) and (**8**, 15%, 55 mg).

Cycloaddition to 6. Reaction time 36 h. The crude residue contained the unreacted pyridazinone (**6**) and compounds (**12a**, **12b** and **8**) in a 5:3:2 ratio. After chromatogrphy the compounds (**12a**, **12b** and **8**) were isolated in 38% (141mg), 23% (85 mg), and 12% (44 mg) yield respectively.

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