1,3-DIPOLAR CYCLOADDITION OF DIAZOMETHANE TO DIFFERENTLY SUBSTITUTED 2-METHYLPYRIDAZIN-3(2*H*)-ONES

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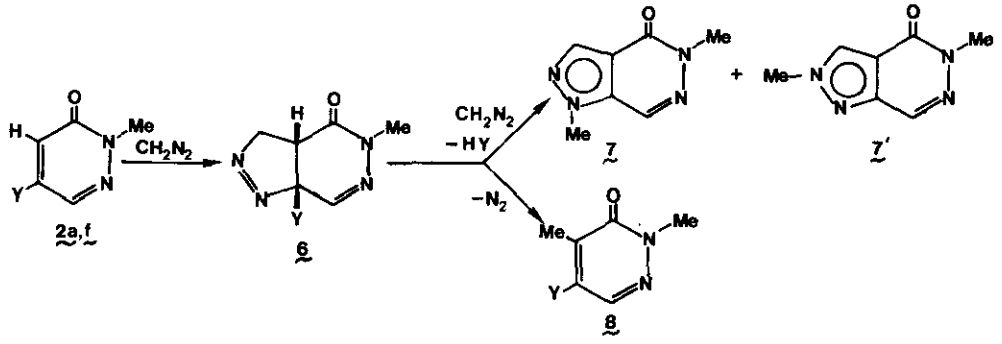
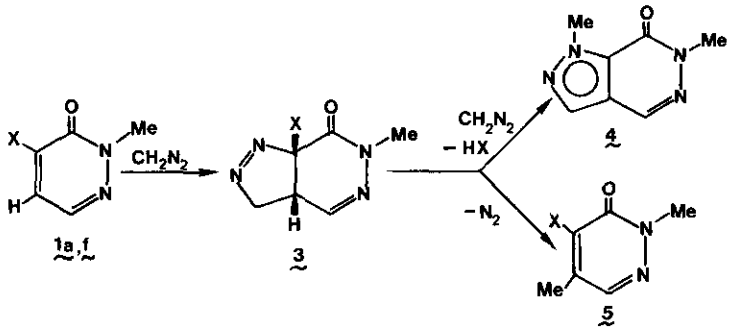
Abstract - Cycloaddition of diazomethane to 4- or 5-substituted 2-methylpyridazin-3(2*H*)-ones **1, 2** occurs in a practically regiospecific manner to give the expected adducts, which are not stable enough to be isolated and under the reaction conditions are transformed into *N*,*N*'-dimethylpyrazolopyridazinones and/or 2,4 (or 2,5)-dimethylpyridazin-3(2*H*)-ones, depending on the nature and position of the substituents. The regiochemistry of the cycloaddition and the reactivity of pyridazin-3(2*H*)-ones **1, 2** have been accounted for theoretically by the FMO approach.

The 1,3-dipolar cycloaddition reaction is a valuable method for the synthesis of heterocyclic systems and has been extensively studied.[1] However, very little is known about cycloadditions with heteroaromatic dipolarophiles. Some of the scarcely reported examples include the addition of diazoalkanes to 2-methyl-6-phenylpyridazin-3(2*H*)-one,[2] pyridones,[3] and recently, to heterocyclic systems with two fused rings.[4]
In a previous communication[5] we have also reported the preliminary results of 1,3-dipolar cycloadditions of diazomethane to simple pyridazin-3(2*H*)-ones. The present work extends this study to the reaction of diazomethane with a variety of 4- and 5-substituted 2-methylpyridazin-3(2*H*)-ones and reports new results concerning the influence of the nature and position of the substituents on the reactivity of pyridazinones and on the regiochemistry of the cycloaddition.
The reaction enables the synthesis of pyrazolo[3,4-*d*]pyridazinones,[5] potentially useful as pharmacological agents, and is also shown to be a convenient method for the introduction of methyl groups at the 4- or 5-position of the 2-methylpyridazin-3(2*H*)-ones.

RESULTS AND DISCUSSION

The cycloadditions of diazomethane to 2-methylpyridazin-3(2*H*)-ones **1** and **2** were performed in a methanol-ether solution at -5°C by using a large excess of the dipole. The results of the cycloadditions of diazomethane to compounds **1a-f** and **2a-f** are summarized in Table 1, and the reaction pathways are illustrated in the following schemes.





	a	b	c	d	e	f
X,Y	Cl	SEt	SOEt	SO_2Et	CN	CO_2Me

An estimate of the reactivity of the pyridazinones has been achieved from the percentage of conversion attained in parallel reactions. In all cases, we have found that the 5-substituted pyridazinones **2** react faster than the corresponding 4-substituted isomers **1** do.

In most cases, the initial adducts **3** and **6** were not stable enough to be isolated or detected, therefore the regiochemistry of the cycloadditions was deduced from the structure of the products originated under the conditions of the reaction or during the work-up to isolate the individual compounds.

The cycloadducts readily undergo further transformations by different ways depending on the pattern of substitution. Thus, adducts **3a**, **3c**, **6a** and **6b** undergo HX or HY elimination under the reaction conditions leading to *N*-methylpyrazolopyridazinones, that are further methylated by diazomethane to yield the *N*,*N*'-dimethylpyrazolopyridazinones **4** or **7** (and **7'**). In contrast, adducts **3e**, **3f**, **6e** and **6f** undergo nitrogen elimination to yield the corresponding 2-methylpyridazin-3(2*H*)-ones **5** or **8**.[6,7] Finally, compounds **6c** and **6d** suffer simultaneously both transformations.

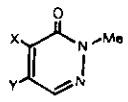
An unequivocal proof of the formation of the primary cycloadducts **3** or **6** was only obtained in the case of the bicyclic compound **3d**, originated from 2-methyl-4-ethylsulphonylpyridazin-3(2*H*)-one (**1d**), which could be isolated from the reaction medium by filtration, as a colorless solid, and it was unequivocally characterized. This adduct, by standing for 15 days at room temperature in chloroform solution, was transformed into a 1:1 mixture of 2,5-dimethyl-4-ethylsulphonylpyridazin-3(2*H*)-one (**5d**) and the starting pyridazinone **1d**, originated by nitrogen elimination and by cycloreversion reaction, respectively.

Thus, the 4-substituted pyridazinones **1a-f**, regardless of the nature of the substituent, reacted with diazomethane in a regiospecific manner to give only adducts of type **3**, in which the carbon of the dipole became attached to the 5-position of the pyridazinone ring. Whereas, the 5-substituted pyridazinones **2a-f** solely yield adducts of type **6**, with a reverse orientation, in which the terminal nitrogen of diazomethane is attached to the 5-position of the pyridazinone ring.

The analysis of experimental results shows an important influence of the substituents on the reactivity of the pyridazinones and on the regiochemistry of the cycloaddition, that could be rationalized applying the FMO theory.[8]

In order to evaluate the stabilization energies arising from frontier orbital overlap in the approximation of the reactants, we have only considered the electronic interaction term of the Klopman and Salem equations.[9,10] The fact that diazomethane cycloadditions belong to type I in the Sustmann classification[11] allows an additional simplification of the equation, therefore we have only employed the term corresponding

Table 1. Cycloaddition of diazomethane to 2-methylpyridazin-3(2*H*)-ones

 N°	X	Y	Time (Conversion)[a]	Adduct[b]	Products (ratio)[c]
1a	Cl	H	15 days (3)	**3a**	**4**
2a	H	Cl	15 days (27)	**6a**	**7** (30), **7'** (70)
1b	SEt	H	60 days (0)	--[d]	-
2b	H	SEt	60 days (5)	**6b**	**7**
1c	SOEt	H	24 h (9)	**3c**	**4**
2c	H	SOEt	24 h (100)	**6c**	**7** (25), **7'** (50), **8c** (25)
1d	SO_2Et	H	6 h (100)	**3d**[e]	**3d**
2d	H	SO_2Et	10 min (100)	**6d**	**7** (10), **7'** (25), **8d** (65)
1e	CN	H	60 min (100)	**3e**	**5e**
2e	H	CN	30 min (100)	**6e**	**8e**
1f	CO_2Me	H	90 min (100)	**3f**[f]	**3f** (30), **5f** (70)
2f	H	CO_2Me	60 min (100)	**6f**	**8f**

[a] % of cycloaddition products determined by ^{1}H-nmr; [b] Primary adducts not isolated, unless otherwise stated; [c] Relative ratio determined by ^{1}H-nmr; [d] Starting material was recovered unchanged and no traces of cycloaddition products were observed; [e] Primary adduct isolated and fully characterized; [f] Primary adduct characterized by ^{1}H-nmr.

to the main interaction ($HOMO_{diazomethane}$-$LUMO_{pyridazinone}$).

The values calculated for the stabilization energies of approximations A (ΔE_A) and B (ΔE_B) in the cycloaddition of diazomethane to 4- or 5-substituted pyridazin-3(2*H*)-ones **1a-f** and **2a-f** to give adducts **3** and **6** respectively are summarized in Table 2.

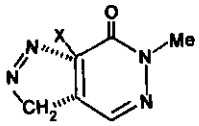
From a comparison between theoretical and experimental results it is possible to establish a rough qualitative relationship between the calculated stabilization energy (ΔE) (Table 2) and the experimental reactivity data. However the 2-methylpyridazin-3(2*H*)-one (**9**) experimentally is more reactive than could be predicted from theoretical calculation, this fact could be fitted to the lack of steric effect, present in other substituted pyridazinones.

On the other hand, a direct relationship between the differences in the stabilization energies ($\Delta\Delta E$) for the two possible approximations and the experimental results (Table 1) could be derived. Therefore, the 4-substituted 2-methylpyridazin-3(2*H*)-ones **1**, where $\Delta E_A > \Delta E_B$, lead regiospecifically to adducts of type **3**; on the contrary, the 5-substituted 2-methylpyridazin-3(2*H*)-ones **2**, in which $\Delta E_B > \Delta E_A$, exclusively afford cycloadducts **6**, with the opposite regiochemistry. The 2-methylpyridazin-3(2*H*)-one (**9**), where the difference of stabilization energy $\Delta\Delta E$ is between 0 and 1 kcal/mol, gives both adducts.

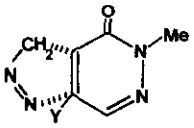
In conclusion, the reaction of diazomethane with the pyridazinones of the types **1** and **2** can be modelized

Table 2. Stabilization energies (kcal/mol) in cycloadditions of diazomethane to substituted 2-methylpyridazin-3(2*H*)-ones **1,2**

N°	X	Y	ΔE_A [a]	ΔE_B [a]	$\Delta\Delta E$ [b]
9	H	H	37.06	36.62	0.44
1a	Cl	H	37.82	35.86	1.96
2a	H	Cl	37.74	38.74	-1.00
1b	SEt	H	35.60	33.67	1.93
2b	H	SEt	34.91	35.90	-0.99
1c	SOEt	H	35.72	32.74	2.98
2c	H	SOEt	33.53	35.58	-2.05
1d	SO_2Et	H	41.00	39.08	1.92
2d	H	SO_2Et	39.22	40.49	-1.27
1e	CN	H	39.89	38.18	1.71
2e	H	CN	39.36	39.89	-0.53
1f	CO_2Me	H	38.44	36.38	2.06
2f	H	CO_2Me	37.45	38.58	-1.13



A



B

[a] Approximations A and B lead to adducts of type **3** and **6**, respectively; [b] $\Delta\Delta E = \Delta E_A - \Delta E_B$.

through the FMO theory, only considering the electronic interaction between $HOMO_{diazomethane}$-$LUMO_{pyridazinone}$. The reactivity of pyridazinones and the regiochemistry of the cycloaddition can be predicted from molecular computations, but paying attention to the steric factors that are not considered in this approach.

EXPERIMENTAL

Mps are uncorrected. Ir spectra were recorded on a Perkin Elmer, model 257 grating spectrophotometer, values in cm^{-1}. ^1H-nmr spectra on a Varian model EM-390 spectrometer, in $CDCl_3$ solutions (unless otherwise stated) using TMS ($\delta \approx 0$ ppm) as internal reference. Mass spectra were recorded on a Hitachi Perkin-Elmer model RMU-6MG spectrometer. Silica gel Merck 60 (70-230 mesh) and DC-Alufolien 60 F_{254} were used for column chromatography and analytical tlc, respectively. The *eigenvalues and eigenvectors* (energies and coefficients) of FMO of pyridazinones have been obtained from a CNDO/2 program running on a IBM 360/65 computer, starting from standard bond lengths and dihedral angles. The HOMO and LUMO eigenvalues and eigenvectors for diazomethane and resonance overlap integrals (β) values have been taken from Houk.[8] The starting 2-methylpyridazin-3(2*H*)-ones have been prepared according to literature.[12,13,14,15]

Cycloaddition of diazomethane to 2-methylpyridazin-3(2*H*)-ones 1,2. General procedure

To a solution of the 2-methylpyridazin-3(2*H*)-one **1** or **2** (1 mmol) in methanol (5-10 ml) cooled at -15°C,

was added an ethereal solution of diazomethane (10 ml, containing 0.6 mmol/ml). The reaction was kept at -15°C during the period indicated in Table 1. For prolongated reaction times (more than 1 week) additional portions of diazomethane solution were periodically added. The solvent was removed and the residue was analyzed by ^{1}H-nmr (Table 1).

Cycloaddition to 1a.- The crude product is composed of the starting pyridazinone **1a** (97%) and the pyrazolopyridazinone **4**[5] (3%).

Cycloaddition to 2a.- The crude product is composed of the starting pyridazinone **2a** (70%) and a mixture of the pyrazolopyridazinones **7** and **7'**[16] (8% and 20%, respectively).

Cycloaddition to 1b.- Starting material was recovered unchanged and no traces of cycloaddition product were observed.

Cycloaddition to 2b.- The reaction product is composed of the starting material **2b** (90%) and the pyrazolopyridazinone **7** (5%).

Cycloaddition to 1c.- The crude product is composed of the starting pyridazinone **1c** (90%) and the pyrazolopyridazinone **4** (9%).

Cycloaddition to 2c.- The crude product was chromatographed on silica gel (toluene-acetone 8:2) to yield the pyridazinone **8c** (20%) and the pyrazolopyridazinones **7** and **7'** (18% and 45%, respectively).

5-Ethylsulphinyl-2,4-dimethylpyridazin-3(2*H*)-one (8c).- Mp 129-130°C (from cyclohexane). (Found: C, 47.82; H, 5.92; N, 14.25; S, 15.84. Calcd. for $C_8H_{12}N_2O_2S$: C, 47.98; H, 6.04; N, 13.99; S, 16.01). Ir (nujol): 1640 ($CONCH_3$); 1130 (S=O). ^{1}H-nmr: 8.11 (s, 1H, H-6); 3.85 (s, 3H, NCH_3); 3.22 (c, 2H, $SOCH_2CH_3$, J = 8.2 Hz); 2.58 (s, 3H, C-CH_3); 1.40 (t, 3H, $SOCH_2CH_3$). MS, *m/z*: 200 (M^+), 185, 172, 142 (100), 124.

Cycloaddition to 1d.- The crude product was recrystallized from toluene-cyclohexane (1:2) to give adduct **3d** (90%).

7a-Ethylsulphonyl-6-methyl-3*H*-3a,7a-dihydropyrazolo [3,4-*d*]pyridazin-7(6*H*)-one (3d).- Mp 51-59°C (decomp). (Found: C, 39.45; H, 5.16; N, 22.67; S, 13.40. Calcd. for $C_8H_{12}N_4O_3S$: C, 39.34; H, 4.95; N, 22.94; S, 13.13). Ir (nujol): 1640 ($CONCH_3$); 1320, 1140 (SO_2). ^{1}H-nmr: 6.95 (d, 1H, H-4, $J_{3a,4}$ = 3.3 Hz); 5.35 (dd, 1H, H-3, $J_{3,3a}$ = 9.9; J_{gem} = 19.8 Hz); 4.83 (dd, 1H, H-3', $J_{3',3a}$ = 6.6 Hz); 3.98 (m, 2H, $SO_2CH_2CH_3$); 3.65 (m, 1H, H-3a); 3.40 (s, 3H, NCH_3); 1.45 (t, 3H, $SO_2CH_2CH_3$, J = 8.0 Hz). MS, *m/z*: 216 (M^+ -28), 202, 187, 174, 138, 124 (100), 110.

The adduct **3d**, was allowed to stand for 15 days at room temperature in chloroform solution to yield a mixture of the starting pyridazinone **1d** (45%) and 4-ethylsulphonyl-2,5-dimethylpyridazin-3(2*H*)-one (**5d**) (45%) [^{1}H-nmr: 7.60 (s, 1H, H-6); 3.75 (s, 3H, NCH_3); 3.55 (c, 2H, $SO_2CH_2CH_3$, J = 8.0 Hz); 2.61 (s, 3H, C-CH_3); 1.25 (t, 3H, $SO_2CH_2CH_3$)].

Cycloaddition to 2d.- The crude product was chromatographed on silica gel (toluene-acetone 8:2) yielding the pyridazinone **8d** (60%) and the pyrazolopyridazinones **7** and **7'** (8% and 19%, respectively).

5-Ethylsulphonyl-2,4-dimethylpyridazin-3(2*H*)-one (8d).- Mp 133-134°C (from cyclohexane). (Found: C, 44.69; H, 5.95; N, 12.68; S, 14.74. Calcd. for $C_8H_{12}N_2O_3S$: C, 44.44; H, 5.60; N, 12.96; S, 14.80). Ir (nujol): 1650 ($CONCH_3$); 1460, 1310, 1140 (SO_2). ^{1}H-nmr: 8.05 (s, 1H, H-6); 3.80 (s, 3H, NCH_3); 3.01 (c, 2H, $SO_2CH_2CH_3$, J = 8.0 Hz); 2.55 (s, 3H, C-CH_3); 1.30 (t, 3H, $SO_2CH_2CH_3$). MS, *m/z*: 216 (M^+), 202, 187, 152, 138, 124 (100).

Cycloaddition to 1e.- The crude product was recrystallized from cyclohexane to yield the pyridazinone **5e** (95%).

4-Cyano-2,5-dimethylpyridazin-3(2*H*)-one (5e).- Mp 136-137°C. (Found: C, 56.25; H, 4.83; N, 28.52. Calcd. for $C_7H_7N_3O$: C, 56.36; H, 4.73; N, 28.18). Ir (nujol): 2250 (CN); 1660 ($CONCH_3$). ^{1}H-nmr: 7.72 (s, 1H, H-6); 3.80 (s, 3H, NCH_3); 2.41 (s, 3H, C-CH_3). MS, *m/z*: 149 (M^+), 134, 121, 93, 78 (100).

Cycloaddition to 2e.- The crude product was recrystallized from cyclohexane to yield the pyridazinone **8e** (96%).

5-Cyano-2,4-dimethylpyridazin-3(2*H*)-one (8e).- Mp 85-86°C. (Found: C, 56.17; H, 4.51; N, 27.94.

Calcd. for $C_7H_7N_3O$: C, 56.36; H, 4.73; N, 28.18). Ir (nujol): 2220 (CN); 1650 ($CONCH_3$). ^{1}H-nmr: 7.75 (s, 1H, H-6); 3.81 (s, 3H, NCH_3); 2.45 (s, 3H, C-CH_3). MS, *m/z*: 149 (M^+), 134, 121, 93, 78 (100).

Cycloaddition to 1f.- The crude product, after 90 min, is composed of the primary adduct **3f** (30%) [^{1}H-nmr (DMSO-d_6): 7.15 (d, 1H, H-4, $J_{3a,4}$ = 3.3 Hz); 4.95 (m, 2H, H-3 and H-3'); 3.7 (2s, 6H, NCH_3 and CO_2CH_3)] and the transformation product **5f** (70%). When the reaction mixture was allowed to stand for 24 h, the crude product was recrystallized from cyclohexane to yield the pyridazinone **5f** (90%).

2,5-Dimethyl-4-methoxycarbonylpyridazin-3(2*H*)-one (5f).- Mp 81°C. (Found: C, 52.61; H, 5.35; N, 15.30. Calcd. for $C_8H_{10}N_2O_3$: C, 52.74; H, 5.49; N, 15.38). Ir (nujol): 1730 (CO_2CH_3); 1650 ($CONCH_3$). ^{1}H-nmr (DMSO-d_6): 7.85 (s, 1H, H-6); 3.81 (s, 3H, NCH_3); 3.55 (s, 3H, CO_2CH_3); 2.10 (s, 3H, C-CH_3). MS, *m/z*: 182 (M^+), 167, 152, 139, 124 (100).

Cycloaddition to 2f.- The crude product was recrystallized from cyclohexane to give pyridazinone **8f** (95%).

2,4-Dimethyl-5-methoxycarbonylpyridazin-(2*H*)-one (8f).- Mp 102-103°C. (Found: C, 52.55; H, 5.40; N, 15.28. Calcd. for $C_8H_{10}N_2O_3$: C, 52.74; H, 5.49; N, 15.38). Ir (nujol): 1720 (CO_2CH_3); 1670 ($CONCH_3$). ^{1}H-nmr: 8.00 (s, 1H, H-6); 3.91 (s, 3H, NCH_3); 3.75 (s, 3H, CO_2CH_3; 2.45 (s, 3H, C-CH_3). MS, *m/z*: 182 (M^+), 167, 152 (100).

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