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1,3-DIPOLAR CYCLOADDITION OF DIAZOMETHANE TO 5-METHOXYFURAN-2(5H)-ONES

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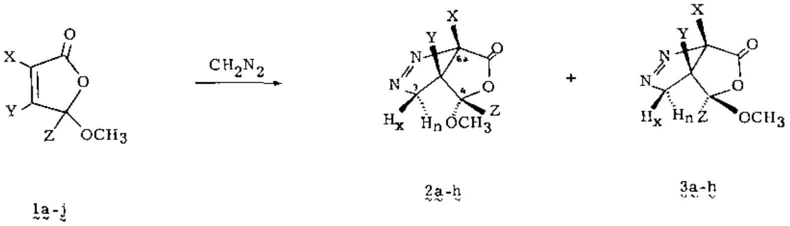
Abstract - Cycloaddition of diazomethane to 5-methoxyfuran-2(5H)-ones (**1**) occurs in a practically regiospecific manner to give the expected adducts. The cycloadducts are mixtures of the furopyrazoline derivatives **2** and **3** epimeric at C-4, with the exception of those of **1f** and **1h** that afford only one detectable adduct (**2f** and **2h**) in each case. The regio- and stereochemistry of the adducts follows from the ^{1}H-NMR data. The regiochemistry of the cycloaddition is also corroborated by chemical correlations. Pyrolysis of the epimeric mixtures **2a**/**3a**, **2b**/**3b** and **2d**/**3d** affords the 4-methyl substituted furanones **1c**, **1i** and **1j** in good yields.

Earlier parts of this series have examined several aspects of the chemistry and synthetic potential of 3-formylacrylic acid derivatives. Thus, the Diels-Alder reaction of cyclic pseudoesters of 3-formylacrylic acids [5-alkoxyfuran-2(5H)-ones] has already been reported[2-5]. We extend now these studies to 1,3-dipolar cycloaddition reactions with 5-methoxyfuran-2(5H)-ones which could provide a convenient route for the synthesis of new fused heterocyclic systems.



It is the purpose of the present work to study the cycloaddition of diazomethane to furanones of type **1**. The reaction is explored with differently substituted derivatives **1a**-**j** in order to obtain information on the influence of the substituents X and Y upon the reactivity and regioselectivity of the reaction. Moreover, the selectivity of the cycloaddition to the diastereotopic faces of the methoxyfuranones **1** is also considered. Finally, several transformations effected on the adducts not only confirm the regiochemistry of cycloadditions but also can be used with preparative purposes.

Results and discussion

Treatment of furanones **1a-h** with excess of ethereal diazomethane afforded the expected cycloadducts **2** and / or **3** in essentially quantitative yield, with the exception of **1c** which, after 45 days, gave only a partial conversion. In contrast, furanones **1i, j** after 60 days in the presence of the 1, 3-dipole were recovered unchanged and no trace of cycloaddition product could be detected.

Table 1. Cycloaddition of diazomethane to 5-methoxyfuran-2(5H)-ones **1**.

Substrate	X	Y	Z	Time[a] (days)	Product[b] **2**	**3**	Isolation[c]
1a	H	H	H	0.5	30	70	A
1b	CH_3	H	H	20	60	40	A
1c	H	CH_3	H	45[d]	50	50	B
1d	H	H	CH_3	15	89	8[e]	B
1e	Br	H	H	3	65	35	C
1f	H	Br	H	10	100	0	-
1g	Cl	H	H	7	70	30	C
1h	H	Cl	H	15	100	0	-
1i	CH_3	CH_3	H	-[f]	-	-	-
1j	H	CH_3	CH_3	-[f]	-	-	-

[a] Time required for a total conversion. [b] Relative product distribution (%) (^{1}H-NMR). [c] A: Column chromatography on silica gel (benzene-ethyl acetate 2 : 1); B: Column chromatography on silica gel (benzene-ethyl acetate 4 : 1); C: Different solubility in benzene. [d] Only a partial conversion (ca. 50%) is attained in 45 days. [e] The presence of a regioisomer to the extent of 3% was also detected (^{1}H-NMR). [f] No reaction after 60 days.

The results of these reactions are summarized in Table 1. The reaction was practically regiospecific and led to the adducts **2** and/or **3**, epimeric at C-4, in which the C atom of the dipole became attached to the electron defficient 4-position of the furanone **1**. The cycloaddition of the diazoalkane occurred in the expected direction, in accord with the early von Auwers rule[6] and with the previously reported[7,8] behaviour of related lactones.

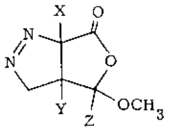
The presence of methyl substituents at the 3- or 4-position decreases the reactivity compared with the unsubstituted case, the effect being larger for the 4-substituted derivative. Comparable results have previously been reported for acrylic acid derivatives[9,10]. A similar effect was observed for the 3- and 4-halo derivatives, although the reaction with halofuranones **1e-h** proceeds at a rate somewhat faster than the formation of the cycloadducts from the respective methylfuranones **1b, c**.

A simple semiquantitative FMO aproach[11] has been performed in order to rationalize the experimental results. The observed regioselectivities of the 1, 3-dipolar cycloaddition of diazomethane to the furanones **1a-h** are in good agreement with those predicted from the FMO approach. Thus, the stabilization energy (ΔE) calculated for the approach of the dipole and dipolarophile leading to regioisomers of the type A is, in each case, greater than that for the alternative orientation B (Table 2). The FMO approach also allows to explain the electronic effects of the substituents on the reactivity of the different furanones. From the inspection of Table 2, a direct relationship between the stabilization energy differences ($\Delta\Delta E$) and the experimental results (Table 1) is deduced. The disagreements observed for the 3- and 4-substituted furanones, that show a decreased reactivity compared with the theoretical values and with the unsubstituted case, disclose the importance of steric factors of the substituents, not considered in the FMO method.

The cycloaddition to the parent furanone **1a** occurs preferentially from the side opposite to the OCH_3 group, sterically less hindered. However, the results summarized in Table 1 suggest that both steric and electronic effects of the substituents play a significant role and their influence on the stereoselectivity of the reaction is difficult to rationalize.

Table 2. Stabilization energies (kcal/mol) of cycloaddition of diazomethane to furanones **1**

Furanone	ΔE_A	ΔE_B	$\Delta E_A - \Delta E_B$
1a	45.43	41.41	4.02
1b	44.17	40.47	3.70
1c	43.75	39.96	3.79
1d	45.08	40.90	4.18
1g	50.71	44.69	6.03
1h	44.62	43.79	0.83
1i	39.27	38.40	0.87
1j	43.37	39.47	3.90



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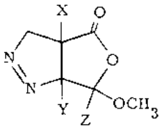


B

The structure of the adducts was established on the basis of their spectral data. Thus, the presence of bands approximately at 1780 (C=O) and 1550 (N=N) and the absence of bands over 3000 cm^{-1} (N-H) in the IR spectra of **2** and **3** are indicative of the existence of γ-lactone and Δ^1-pyrazoline moieties. The regioisomeric assignments could be made from a detailed study of their ^1H-NMR spectra. Additional confirmation of the regiochemistry was obtained from the results of chemical transformations discussed below.

Although the assignment of stereochemistry in pentacycles is often difficult, the cycloadducts **2** and **3** show a relatively rigid fused system in which a correlation is possible. Thus, the stereochemistry was assigned from the ^1H-NMR data on the basis of the following observations (Table 3):

(i) Compounds in which Y = Z = H display coupling constants $J_{Y,Z}$ = 6.5 - 6.8 Hz for a cis arrangement of these protons (endo MeO group, **2**). In contrast, for a trans relationship of the protons (exo MeO groups, **3**) vicinal coupling constants $J_{Y,Z}$ = 1.6 - 2.0 Hz are observed.

(ii) The H-3_x and H-6a protons are considerably deshielded by the anisotropy effect of an exo MeO group. Moreover, an endo MeO group causes a large deshielding on the H-3_n proton.

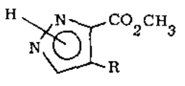
(iii) The signals of endo groups at C-4 *are shielded by the anisotropy effect of the* N = N double bond. Thus, the resonances of the protons and substituents are shifted to higher field. In fact, a comparison of the values for the C-4 epimers is consistent with the above assigments.

Table 3. ^{1}H-NMR chemical shifts and coupling constants of adducts **2** and **3**

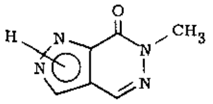
Adduct	H-3_x	H-3_n	X	Y	Z	OMe	$^J{}_{Y,Z}$	$^J{}_{Y,X}$	$^J{}_{Y,3_x}$	$^J{}_{Y,3_n}$	$^J{}^*_{X,3_x}$	$^J{}^*_{X,3_n}$	$^J{}_{3_x,3_n}$
2a	3.64	4.77	4.86	2.17	4.54	2.87	6.8	9.2	8.8	2,0	-2.3	-2,4	-18.1
3a	4.02	3.98	5.09	2.01	4.21	3.03	1.8	9.2	8.0	5.9	-1.8	-2.2	-18.9
2b	3.94	5.05	(1.36)$^{+}$	2.10	4.76	3.03	6.6	-	8.0	1.8	-	-	-18.2
3b	4.23	4.09	(1.51)$^{+}$	1.89	4.29	3.10	1.6	-	9.5	4.2	-	-	-18.9
2c	4.15	5.04	4.87	(0.53)$^{+}$	4.54	2.90	-	-	-	-	-2.3	-1.7	-18.4
3c	4.25	4.03	5.01	(0.66)$^{+}$	4.49	3.09	-	-	-	-	-0.8	-2.2	-18.6
2d	3.85	5.10	5.17	2.29	(1.02)$^{+}$	2.76	-	9.7	8.3	2.5	-1.9	-2.2	-18.0
3d	4.18	4.32	5.43	2.38	(0.90)$^{+}$	2.95	-	8.9	10.1	4.4	-1.4	-2.3	-18.9
2e	3.78	4.82	-	2.36	4.39	2.81	6.7	-	7.7	1.5	-	-	-18.9
3e	4.10	4.02	-	2.49	4.19	3.04	2.0	-	9.1	3.1	-	-	-18.8
2f	4.94	5.49	5.59	-	5.75	3.56	-	-	-	-	-1.0	-1.7	-19.7
2g	3.89	4.86	-	2.39	4.56	2.50	6.5	-	7.4	1.5	-	-	-18.8
3g	4.18	4.04	-	2.38	4.20	2.70	1.8	-	8.8	3.5	-	-	-18.2
2h	4.36	4.89	5.28	-	4.80	2.92	-	-	-	-	-0.9	-0.6	-19.8

* Azahomoallylic coupling constants[12,13]; $^{+}$Me signals.

Further confirmation of the regiochemistry of the above cycloadditions was obtained from the results of chemical correlations. Thus, treatment of the halogenated pyrazolines **2e-h** and **3e, g** with methanolic potassium hydroxide resulted in HCl or HBr elimination and subsequent ring opening to give in all cases methyl 4-formyl-3(5)-pyrazolecarboxylate **4**, and a small amount of its corresponding dimethyl acetal **5**, identical with authentic samples prepared by an independent route[14].



4, R = CHO
5, R = CH(OCH$_3$)$_2$



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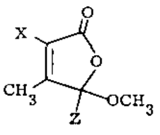

1c, X = Z = H
i, X = CH$_3$; Z = H
j, X = H; Y = CH$_3$

Furthermore, the reaction of the halogenated cycloadducts **2e-h** and **3e-g** with 2 mol equiv. of methylhydrazine, by dehydrohalogenation followed by condensation, afforded the pyrazolopyridazinone **6**, identical with a sample prepared by a different route[15]. Finally, the thermal decomposition of the cycloadducts was also studied. Pyrolysis of the epimeric mixtures **2a**/**3a**, **2b**/**3b**, and 2d/3d, by heating at 130° C in chlorobenzene, gave the respective 4-methyl substituted furanones **1c**, **i**, **j** in good yields, in accord with previous results reported for 2(5*H*)-furanones[8]. It should be noted that cyclopropane derivatives were practically not formed in our case. Therefore this reaction provides a convenient method for introducing an alkyl group at the 4-position of the alkoxyfuranones.

EXPERIMENTAL

Mps are uncorrected. IR spectra were recorded on a Perkin-Elmer, model 257 grating spectrometer, $\tilde{\nu}$ values in cm^{-1}. ^{1}H-NMR spectra on a Varian XL-100/15 spectrometer, in benzene-d_6 solutions (unless otherwise stated) using TMS (δ = 0 ppm) as internal reference. Analysis of the spectra were carried out using a LAOCOON III program running on a Nicolet 1180 computer. Mass spectra were recorded on Hewlett-Packard 5985 GC-M5 System or Hitachi Perkin-Elmer RMU-6 MG spectrometers. 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 eigenvalues and eigenvectors (energies and coefficients) of FMO of furanones have been obtained from a CNDO/2 program running on a IBM 360/65 computer, using standard bond lengths and dihedral angles. The corresponding values for diazomethane and β values have been taken from Houk[11].

Cycloaddition of diazomethane to 5-methoxyfuran-2(5*H*)-ones (**1**). General procedure

To a solution of the furanone **1** (10 mmol) in diethyl ether (20 ml) was added a solution of diazomethane (20 ml, containing 0.6 mmol/ml). The reaction was kept at -10° C during the period indicated in Table 1. For prolongated reaction times additional portions of diazomethane solution were periodically added. The solvent was removed and the residue was analyzed by ^{1}H-NMR and purified as indicated in Table 1.

2a.- Mp 64-56° C (from ethyl acetate-petroleum ether). (Found: C, 46.17; H, 5.09; N, 18.19. Calcd. for $C_6H_8O_3N_2$: C, 46.15; H, 5.12; N, 17.94). IR (nujol): 1780 (C=O); 1555 (N=N). MS, *m/z*: 127 (M-29)$^+$, 111, 97, 69, 68, 41 (100).

3a.- Mp 55-56° C (from ethyl acetate-petroleum ether). (Found: C, 45.90; H, 5.36; N, 17.69. Calcd. for $C_6H_8O_3N_2$: C, 46.15; H, 5.12; N, 17.94). IR (nujol): 1790-1770 (C=O); 1565 (N=N). MS, *m/z*: 127 (M-29)$^+$, 111, 97, 69, 68, 41 (100).

2b.- Mp 31-32° C (from chloroform-petroleum ether). (Found: 49.13; H, 5.74; N, 16.39. Calcd. for $C_7H_{10}O_3N_2$: C, 49.41; H, 5.88; N, 16.47). IR (nujol): 1790-1760 (C=O); 1550 (N=N). MS, *m/z*: 114 (M-56)$^+$, 111, 95, 83 (100), 55.

3b.- Mp 80-81° C (from chloroform-petroleum ether). (Found: C, 49.12; H, 5.90; N, 16.32. Calcd. for $C_7H_{10}O_3N_2$: C, 49.41; H, 5.88; N, 16.47). IR (nujol): 1780 (C=O); 1560 (N=N). MS, *m/z*: 114 (M-56)$^+$, 111, 98, 83, 55 (100).

2c.- Mp 84-85° C (from ethyl acetate-petroleum ether). (Found: C, 49.07; H, 5.97; N, 16.28. Calcd. for $C_7H_{10}O_3N_2$: C, 49.41; H, 5.88; N, 16.47). IR (nujol): 1790 (C=O); 1555 (N=N). MS, *m/z*: 170 (M$^+$), 113, 111, 97, 95, 83, 82, 55 (100).

3c.- Mp 74-75° C (from ethyl acetate-petroleum ether). (Found: C, 49.47; H, 5.98; N, 16.40. Calcd. for $C_7H_{10}O_3N_2$: C, 49.41; H, 5.88; N, 16.47). IR (nujol): 1770 (C=O); 1560 (N=N). MS, *m/z*: 170 (M$^+$), 113, 111, 97, 95, 83, 82 (100), 55.

2d.- Mp 56-57° C (from ethyl acetate-petroleum ether). (Found: C, 49.54; H, 6.03; N, 16.72. Calcd. for $C_7H_{10}O_3N_2$: C, 49.41; H, 5.88; N, 16.47). IR (nujol): 1780 (C=O); 1550 (N=N). MS, *m/z*: 170 (M$^+$), 142, 127, 111, 99, 97, 83, 68 (100), 43 (100).

From the crude reaction mixture of the cycloaddition of diazomethane to furanone **1d**, by column chromatography, were isolated the epimer **3d** (8%) and the regioisomeric 3a,6a-dihydro-6-methoxy-6-methylfuro [3,4-*d*] pyrazol-4(3*H*)-one. IR (film): 1785 (C=O); 1560 (N=N). ^{1}H-NMR:

4.65 (m, 1H, C-3; $J_{3,3'}$ = -18.0, $J_{3,3a}$ = 2.0, $J_{3,6a}$ = -2.1); 4.40 (m, 1H, C-6a; $J_{6a,3a}$ = 7.6, $J_{6a,3'}$ = -2.5); 3.72 (m, 1H, C-3'; $J_{3',3a}$ = 9.3); 2.94 (s, 3H, OCH_3); 2.40 (m, 1H, C-3a); 1.54 (s, 3H, CH_3). MS, *m/z*: 170 (M^+), 142, 127, 111, 97, 83, 69, 55, 43 (100).

Halogenated adducts decompose spontaneously at room temperature and were only characterized by ^{1}H-NMR (Table 3).

Dehydrohalogenation of the cycloadducts **2e-h** and **3e, g**

To a solution of the adduct (5 mmol) in methanol (10 ml) was added methanolic potassium hydroxide (5 ml). The precipitated potassium halide was filtered off and the solvent removed in vacuo. The residue was analyzed by ^{1}H-NMR and contains as main component methyl 4-formyl-3(5)-pyrazolecarboxylate (**4**) together with a minor amount of its dimethyl acetal **5**[14]. The crude product was chromatographed on silica gel (ethyl acetate-petroleum ether 1:1) to afford the pyrazole **4** in 63% yield.

Reaction of the cycloadducts **2e-h** and **3e, g** with methylhydrazine

To a solution of the halogenated adduct (20 mmol) in methanol (30 ml) was added methylhydrazine (44 mmol) and the mixture heated under reflux for 15 min. After addition of acetic acid (10 ml) the mixture was heated for 2 h and the solvent removed under reduced pressure. The residue was washed with water to afford, after sublimation, 6-methylpyrazolo [3, 4-*d*]pyridazin-7(6*H*)-one(**6**) in 40% yield, identical with an authentic sample[15]. Mp 246° C. IR (nujol): 3110 (NH); 1665, 1600 (C=O amide). ^{1}H-NMR (DMSO-d_6): 8.43, 8.30 (2s, 1H, 1H, C-3 and C-4); 3.73 (s, 3H, NCH_3). MS, *m/z*: 150 (M^+), 122, 95, 94, 52.

Thermal decomposition of the cycloadducts **2a, b, d** and **3a, b, d**

A solution of the isomeric mixture of adducts **2** and **3** (10 mmol) in chlorobenzene (30 ml) was heated under reflux for 48 h. The solvent was removed in vacuo and the residue distilled to afford the corresponding methylfuranone: 4-methyl-5-methoxyfuran-2(5*H*)-one (**1c**)[16] in 70% yield from **1a**; 3,4-dimethyl-5-methoxyfuran-2(5*H*)-one (**1i**) in 85% yield from **1b** [(Found: C, 59.11; H, 6.97. Calcd. for $C_7H_{10}O_3$: C, 59.15; H, 6.90). IR (film): 1770 (C=O); 1690 (C=C). ^{1}H-NMR (Cl_3CD): 5.52 (br s, 1H, C-5); 3.53 (s, 3H, OCH_3); 1.96, 1.82 (2 br s, 3H, 3H, CH_3). MS, *m/z*: 142 (M^+), 141, 114, 111, 83, 67, 55 (100)]; 4,5-dimethyl-5-methoxyfuran-2-one (**1j**)[17] in 75% yield from **1d**.

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