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REGIOSELECTIVITY IN THE 1,3-DIPOLAR CYCLOADDITION REACTION OF 3-METHYLOXAZOLIUM 5-OLATES WITH ACETYLENIC DIPOLAROPHILES

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Abstract - The cycloaddition reaction of unsymmetrically substituted munchnones with monosubstituted alkynes has been examined. The reaction affords a mixture of regioisomeric pyrroles. The observed regioselectivity is qualitatively discussed on the basis of the MO-perturbation theory.

The synthetic utility of the "munchnones", namely mesoionic oxazolium 5-olates, in the preparation of pyrroles has been widely demonstrated[1-4]. The cycloaddition reaction of such compounds, considered as masked 1,3-dipoles of azomethine ylide types, with acetylenic dipolarophiles affords pyrrole derivatives. Apart from the synthetic utility there is considerable interest in the problem of regioselectivity of these cycloaddition reactions.

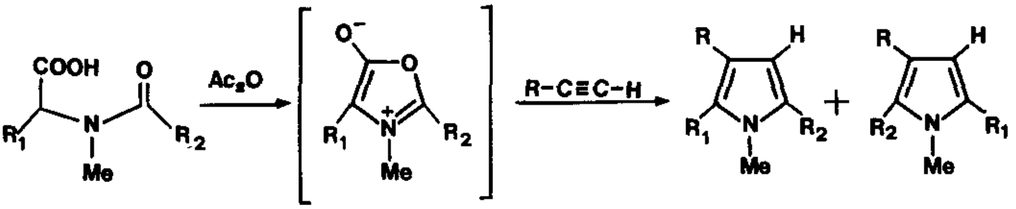
In an attempt to gain a better insight in this problem and to rationalize the inhomogeneous results reported in literature[1,4] we planned to investigate a series of cycloadditions using mono and disubstituted munchnones. As shown in Scheme 1 we considered the cycloaddition reactions between alkynes (3) and some pairs of 2-methyl- or 2-phenyl and 2-methyl-4-phenyl substituted munchnones (2) and their reversed isomers. Our aim was to verify the suggested[4] high effect of C2 or C4 substituents, in the mesoionic moiety, on the size of orbital coefficients at the same positions[5].

RESULTS

Owing to their high reactivity munchnones were prepared "in situ" starting from the corresponding N-acyl-α-amino acids (1) and acetic anhydride. The reactions were performed in toluene solution at 80° in the presence of acetylenic dipolarophiles (3). After evaporation of the solvent the mixture of regioisomeric pyrroles was separated by column chromatography on silica gel. Yields, regioisomeric ratio, analytical and spectral data of pyrroles (4) and (5) are summarized in Table I and II respectively.

The structures of the known pyrroles (4A)[6], (4B)[7], (4C)[4], (5C)[4], (4I)[1] and (5I)[1] were assigned by comparing their physical and spectral data with those reported in the literature; whereas for the unknown pyrroles (5A), (5B), (4D), (5D), (4E), (5E), (4F), (5F), (4G) and (4H) by suitable spectroscopic studies. In (5F) C2-CH_3 (δ 2.65) and H4 (δ 6.35) appears, in ^{1}H-nmr, as singlets while in (4F) C5-CH_3 (δ 2.30) and H4 (δ 6.30) are respectively a doublet (J=1.1 Hz) and a quartet. Similarly, in assigning the structure to the pyrroles (5A), (5B), (4D), (5D), (4E), (5E), (4G), (4H) we considered the value of the coupling constant J_3 between H4 and H5 in (4D), (4E), (4G), (4H) and J_4 between H2 and H4 in (5A), (5B), (5D), (5E). Typical values of J_3 (H4-H5) and J_4 (H2-H4) in a pyrrole are comprised respectively between 2.4-3.1 Hz and 1.4-1.8 Hz[8]. ^{1}H-Nmr spectra of compounds (4D), (4E), (4G), (4H) show two doublets for H4 and H5 with J_3=2.8-3.1 Hz, while spectra of (5A), (5B), (5D), (5E) present two doublets for H2 and H4 with J_4=1.9-2.0 Hz. Particular compounds (5B) and (5E) also show a J_4=0.9 Hz between C5-CH_3 and H4.

SCHEME 1



1 2 3 4 5

1a,2a: R_1=Ph, R_2=H
1b,2b: R_1=H, R_2=Ph
1c,2c: R_1=Me, R_2=H
1d,2d: R_1=H, R_2=Me
1e,2e: R_1=Ph, R_2=Me
1f,2f: R_1=Me, R_2=Ph

3a: R=COOEt
3b: R=COPh
3c: R=Ph

4A,5A: R=COOEt, R_1=Ph, R_2=H
4B,5B: R=COOEt, R_1=Me, R_2=H
4C,5C: R=COOEt, R_1=Ph, R_2=Me
4D,5D: R=COPh, R_1=Ph, R_2=H
4E,5E: R=COPh, R_1=Me, R_2=H
4F,5F: R=COPh, R_1=Ph, R_2=Me
4G: R=Ph, R_1=Ph, R_2=H
4H: R=Ph, R_1=Me, R_2=H
4I,5I: R=Ph, R_1=Ph, R_2=Me

TABLE I. OVERALL YIELD AND REGIOISOMERIC RATIO OF PYRROLES (4), (5).

REAGENTS	PRODUCTS	OVERALL YIELDS (%)	REGIOISOMERIC RATIO 4/5*
1a + 3a	4A + 5A	77	75/25
1b + 3a	4A + 5A	30	86/14
1a + 3b	4D + 5D	80	75/25
1b + 3b	4D	58	100/0
1a + 3c	4G	34	100/0
1b + 3c	==	==	==
1c + 3a	4B + 5B	51	84/16
1d + 3a	4B + 5B	24	75/25
1c + 3b	4E + 5E	85	80/20
1d + 3b	4E	11	100/0
1c + 3c	4H	4	100/0
1d + 3c	==	==	==
1e + 3a	4C + 5C	87	38/62
1f + 3a	4C + 5C	99	57/43
1e + 3b	4F + 5F	29	2/98
1f + 3b	4F + 5F	83	82/18
1e + 3c	4I + 5I	50	98/2
1f + 3c	4I + 5I	44	1/99

*The ratio was determined by nmr analysis of the crude products mixture.

TABLE II. ANALYTICAL AND SPECTRAL DATA OF PYRROLES (4), (5)

COMPOUND	M.P. (°C) B.P. (mm Hg) [Lit.]	CRYST. SOLV.	^{1}H-NMR ($CDCl_3$) (ppm); *J*(Hz)	ELEMENTAL ANALYSIS FOUND (REQUIRED)		
				C	H	N
4A	47 [49-50]	pentane	1.1(t,3H,COOCH$_2$C$\underline{H}_3$); 3.4(s,3H,N-CH$_3$); 4.1(q,2H,COOC$\underline{H}_2$CH$_3$); 6.6(q,2H,H4+H5,J$_3$H4-H5=2.9); 7.4(s,5H,aromatics).			
5A	148(0.5)		1.2(t,3H,COOCH$_2$C$\underline{H}_3$); 3.5(s,3H,N-CH$_3$); 4.2(q,2H,COOC$\underline{H}_2$CH$_3$); 6.5(d,1H,H2,J$_4$H2-H4=1.9); 7.1-7.3(m,6H,H4+aromatics).	73.29 (73.34)	6.48 (6.59)	6.10 (6.11)
4B	98(0.3) [136(9)]		1.3(t,3H,COOCH$_2$C$\underline{H}_3$); 2.5(s,3H,C2-CH$_3$); 3.6(s,3H,N-CH$_3$); 4.2(q,2H,COOC$\underline{H}_2$CH$_3$); 6.4(q,2H,H4+H5,J$_3$H4-H5=3.1).			
5B	56	pentane	1.3(t,3H,COOCH$_2$C$\underline{H}_3$); 2.2(d,3H,C5-CH$_3$,J$_4$CH$_3$-H4=0.9); 3.5 (s,3H,N-CH$_3$); 4.3(q,2H,COOC$\underline{H}_2$CH$_3$); 6.1(m,1H,H4); 7.2(d, 1H,H2,J$_4$H2-H4=2).	64.41 (64.65)	7.62 (7.84)	8.27 (8.38)
4C	62 [64-66]	diisopropyl ether	1.1(t,3H,COOCH$_2$C$\underline{H}_3$); 2.2(d,3H,C5-CH$_3$,J$_4$CH$_3$-H4=1); 3.3 (s,3H,N-CH$_3$); 4.1(q,2H,COOC$\underline{H}_2$CH$_3$); 6.4(q,1H,H4); 7.2-7.6 (m,5H,aromatics).			
5C	83 [83-85]	diisopropyl ether	1.3(t,3H,COOCH$_2$C$\underline{H}_3$); 2.6(s,3H,C2-CH$_3$); 3.5(s,3H,N-CH$_3$); 4.3(q,2H,COOC$\underline{H}_2$CH$_3$); 6.5(s,1H,H4); 7.3-7.5(m,5H,aromatics).			
4D	113	diisopropyl ether	3.5(s,3H,N-CH$_3$); 6.6(q,2H,H4+H5,J$_3$H4-H5=2.9); 7.2-7.8 (m,10H,aromatics).	82.62 (82.73)	5.83 (5.79)	5.48 (5.36)

5D	77-79	diisopropyl ether	3.7(s,3H,N-CH_3); 6.7(d,1H,H2,J_4H2-H4=2.0); 7.2(d,1H,H_4); 7.3-7.8(m,10H,aromatics).	82.59 (82.73)	5.67 (5.79)	5.22 (5.36)
4E	71-73	diisopropyl ether	2.5(s,3H,C2-CH_3); 3.5(s,3H,N-CH_3); 6.3(q,2H,H4+H5,J_3H4-H5=3.1); 7.3-7.9(m,5H,aromatics).	78.18 (78.36)	6.61 (6.58)	7.12 (7.03)
5E	150(0.5)		2.2(d,3H,C5-CH_3,J_4CH_3-H4=0.9); 3.5(s,3H,N-CH_3); 6.4(m,1H,H4); 7.1(d,1H,H2,J_4H2-H4=2.1); 7.3-7.9(m,5H,aromatics).	78.22 (78.36)	6.55 (6.58)	7.10 (7.03)
4F	81	diisopropyl ether	2.3(d,3H,C5-CH_3,J_4CH_3-H4=1.1); 3.4(s,3H,N-CH_3); 6.3(q,1H,H4); 7.2-7.6(m,10H,aromatics).	82.73 (82.88)	6.24 (6.22)	4.93 (5.09)
5F	113	diisopropyl ether	2.6(s,3H,C2-CH_3); 3.6(s,3H,N-CH_3); 6.3(s,1H,H4); 7.3-7.9 (m,10H,aromatics).	82.67 (82.88)	6.28 (6.22)	4.98 (5.09)
4G	96-97	diisopropyl ether	3.5(s,3H,N-CH_3); 6.4(d,1H,H4,J_3H4-H5=2.8); 6.7(d,1H,H5); 7.1-7.4(m,10H,aromatics).	87.71 (87.51)	6.28 (6.48)	5.95 (6.00)
4H	78(0.3)		2.3(s,3H,C2-CH_3); 3.7(s,3H,N-CH_3); 6.3(d,1H,H5,J_3H4-H5=2.8); 6.6(d,1H,H4); 7.2-7.5(m,5H,aromatics).	84.02 (84.17)	7.68 (7.65)	8.07 (8.18)
4I	140 [145-146]	diisopropyl ether	2.3(d,3H,C5-CH_3,J_4CH_3-H4=1.2); 3.4(s,3H,N-CH_3); 6.2(q,1H,H4); 6.9-7.6(m,10H,aromatics).			
5I	158-160 [160-162]	diisopropyl ether	2.4(s,3H,C2-CH_3); 3.5(s,3H,N-CH_3); 6.3(s,1H,H4); 6.9-7.6 (m,10H,aromatics).			

DISCUSSION

The reaction of (1) with acetylenic dipolarophiles (3) involves a typical 1,3-dipolar cycloaddition to give an unstable primary bicyclic adduct that loses carbon dioxide and gains aromaticity. As shown in Table I the reaction of monosubstituted munchnones (2a-d) with alkynes (3) affords a mixture of regioisomeric pyrroles where the prevailing or exclusive isomers are always the ones with two adjacent hydrogens in despite of the nature and position of the substituent in mesoionic system. The reaction with disubstituted munchnones (2e-f) leads to a mixture of *regioisomeric pyrroles with the major* isomer derived from the dipole/dipolarophile approach in which the bond is always formed between the C4 of mesoionic system and the β carbon of the alkyne.

The prediction of regioselectivity in a cycloaddition reaction, according to a simple FMO theory, requires the values of energies and coefficients of the frontier orbitals. For a qualitative discussion, suitable to explain our experimental results, we used the values calculated by Padwa[4] for the parent munchnone (R_1, R_2=H in Scheme 1). We took in account the effect promoted by the substituents bonded to C2 and/or C4 of mesoionic system, on the energy levels and size of their frontier orbitals. Comparing the energy values of munchnones with those of acetylenic dipolarophiles[9] the HOMO-dipole (orbital energy ca -7.8 eV)/LUMO-dipolarophile (orbital energy ca 0 eV) is the controlling interaction[10], since these two levels are much closer in energy compared than the other combination (LUMO-dipole -0.9 eV/HOMO-dipolarophile ca -10.5 eV). The observed regioselectivity resulted from the preferential combination between the atoms with larger orbital coefficients.

On the basis of the experimental results the following conclusions can be drawn. In monosubstituted munchnones (2a-d) the presence of a substituent at C2 or C4 has a marked effect on the HOMO polarization leading to a modification of C2/C4 orbital coefficients and justifying the different degree of regioselectivity observed. In the case of disubstituted munchnones the overall effect of the two substituents gives to a reduction of C2 coefficient for (2e) and to an increase for (2f) making the process respectively more or less selective. The observed regioselectivity is markedly dependent on the presence of substituents and on the position to which they are bonded in mesoionic system.

Benzoylacetylene (3b) presents a higher selectivity than ethyl propiolate (3a) in the reaction with the same munchnones and this reflects the more distinct difference in LUMO polarization for (3b).

As outlined in Table I the behaviour of phenylacetylene (3c) is quite different from those of ethyl propiolate (3a) and benzoylacetylene (3b). The reactions of (1) with (3c) are slower, (give lower yields) or in some cases (munchnones 2b,d) do not occur, and with compounds (1e,f) the regiochemistry is the opposite to that obtained with (3a) and (3b). Such different behaviour can be explained by considering phenylacetylene as an electron-rich dipolarophile, with a larger LUMO coefficient on C α. Moreover it agrees with the Gotthardt[11] conclusions on the reaction of mesoionic 1,3-dithiolanes with phenylacetylene.

EXPERIMENTAL

Melting points, measured on a Buchi apparatus, are uncorrected.

The ^{1}H-nmr spectra were recorded on a Bruker WP 80-SY spectrometer, using TMS as an internal standard. Compounds (1b)[13], (1d)[14], (1e)[1], (1f)[12], (3b)[15] were prepared by following the reported methods; N-formyl-N-methyl-C-phenyl-D,L-glycine (1a) and N-formyl-N-methyl-D,L-alanine (1c) were prepared by formylation respectively of N-methyl-C-phenyl-D,L-glycine[1] and N-methyl-D,L-alanine[12] according to the following procedure:

acetic anhydride (50 mmoles) was added dropwise to a mixture of the amino acid (10 mmoles) and 20 ml of 99% formic acid at a rate to maintain the temperature of the reaction mixture between 5-15°C. After the addition was complete, the mixture was stirred at room temperature for 12 h; 10 ml of ice-water was introduced and the mixture was concentrated at reduced pressure.

(1a) was recrystallized from water/ethanol=4/1 [yield: 72%; mp 148-149°C; ^{1}H-nmr ($CDCl_3$): δ 2.8(s,3H,N-CH_3), 6.2(s,1H,-CH-N), 7.3(s,5H,aromatics), 8.2(s,1H,-CHO), 8.4(s,1H,-COOH)].

(1c) was distilled at reduced pressure [yield: 84%; bp 149-150°C/0.5 mm Hg; ^{1}H-nmr ($CDCl_3$): δ 1.5(d,3H,CH_3-C), 2.9(s,3H,N-CH_3), 4.3(q,1H,-CH-N), 8.2(s,1H,-CHO), 10.3(s,1H,-COOH)].

Cycloaddition Reactions - General Procedure

Acetic anhydride (12 mmoles) was added to a mixture of (1) (10 mmoles) and (3) (10 mmoles) in toluene (30 ml). The mixture was heated at 80°C under a dry nitrogen stream for 4-8 h. The solvent was evaporated and the residue was chromatographed on silica gel. Elution with toluene/ethyl acetate (90/10 to 50/50) gave the products (4) and (5).

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