Synthesis of Arylsulfonyl Substituted Pyrroles

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The cycloaddition reaction of symmetrically and unsymmetrically substituted munchnones with arylsulfonyl alkynes has been studied. The reaction affords pyrrole derivatives whose structures were assigned on the basis of spectroscopic data. The distribution of regioisomers observed in the case of unsymmetrically substituted munchnones is discussed.

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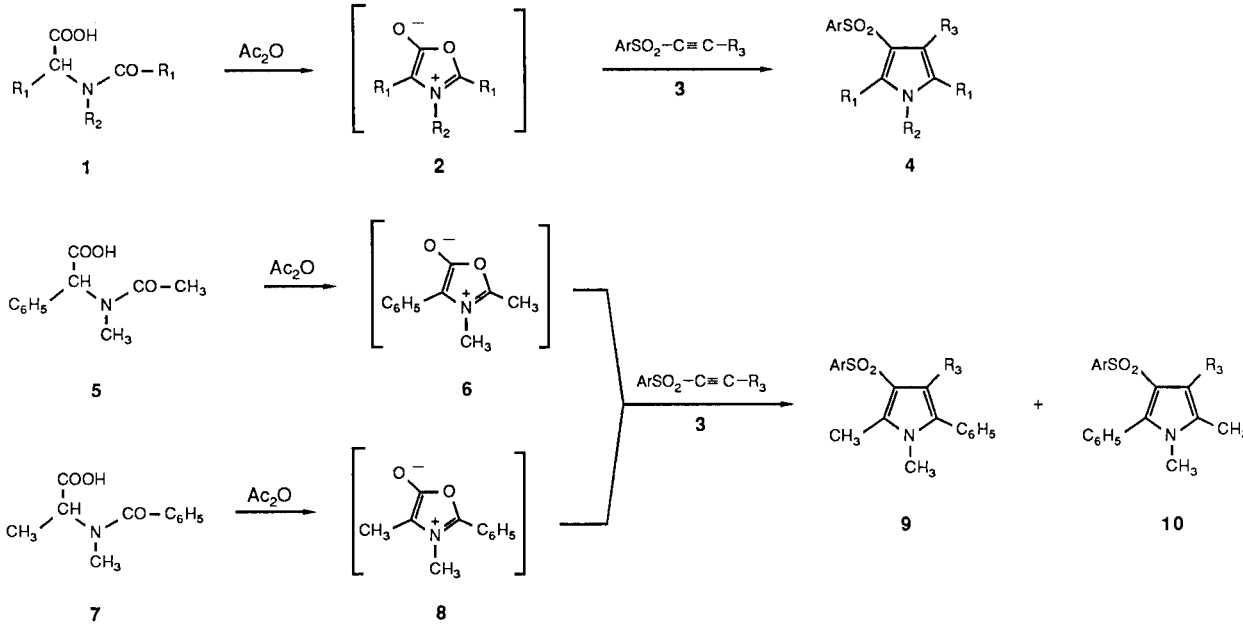
As part of our research program devoted to the behaviour of phenylsulfonyl substituted olefinic [1] and acetylenic [2] dipolarophiles towards 1,3-dipoles we report the results on the reaction between alkynyl sulfones and mesoionic oxazolium 5-oxides. Such compounds commonly titled - munchnones [3] - behave as a masked 1,3-dipole, azomethine-ylide type. Apart from synthetic utility associated with the preparation of unknown phenylsulfonyl substituted pyrroles, there is considerable interest in the problem of regioselectivity of the mesoionic cycloadditions.

Results.

The reactions were performed in toluene solution at 80° starting from alkynyl sulfones **3** and α-acetyl-α-amino acid **1,5,7** in the presence of acetic anhydride which promoted their transformation into the corresponding mesoionic derivatives **2,6,8**. No attempt was made to isolate the intermediate munchnones owing to their known [4] high reactivity.

The reaction progress was monitored by the carbon dioxide evolution and was complete in 6-8 hours. Work-up

Scheme I



1a,2a $R_1 = C_6H_5$, $R_2 = CH_3$
1b,2b $R_1 = H$, $R_2 = C_6H_5$
3a Ar = C_6H_5, $R_3 = H$
3b Ar = C_6H_5, $R_3 = CH_3$
3c Ar = (4) CH_3-C_6H_4, $R_3 = C_6H_5$

4a Ar, $R_1 = C_6H_5$, $R_2 = CH_3$, $R_3 = H$
4b Ar, $R_1 = C_6H_5$, $R_2 = CH_3$, $R_3 = CH_3$
4c Ar = (4) CH_3-C_6H_4, R_1, $R_3 = C_6H_5$, $R_2 = CH_3$,
4d Ar, $R_2 = C_6H_5$, R_1, $R_3 = H$
4e Ar, $R_2 = C_6H_5$, $R_1 = H$, $R_3 = CH_3$
4f Ar = (4) CH_3-C_6H_4, $R_1 = H$, R_2, $R_3 = C_6H_5$
9a,10a Ar = C_6H_5, $R_3 = H$
9b,10b Ar = C_6H_5, $R_3 = CH_3$
9c,10c Ar = (4) CH_3-C_6H_4, $R_3 = C_6H_5$

Table I

Reaction of Munchnones **2**, **6** and **8** with Alkynes **3**

Dipole	Dipolarophile	Time (hours)	Cycloadducts	Overall Yield (%)	Regioisomeric [a] Ratio 9:10
	3a	6	**4a**	72	—
2a	**3b**	7	**4b**	63	—
	3c	8	**4c**	55	—
	3a	8	**4d**	61	—
2b	**3b**	8	**4e**	62	—
	3c	8	**4f**	68	—
	3a	6	**9a**	62	100:0
6	**3b**	2	**9b**	67	100:0
	3c	8	**9c**	72	100:0
	3a	4	**9a** + **10a**	86	25:75
8	**3b**	3	**9b** + **10b**	92	10:90
	3c	4	**9c** + **10c**	83	12:88

[a] The ratio was determined by nmr and hplc analysis of the crude product mixture.

Table II

Physical, Spectral and Analytical Data of Pyrroles **4**, **9** and **10**

Compound	MP °C (Isopropyl Alcohol)	^{1}H NMR, (Deuteriochloroform) [a,b]
4a	141-143	3.30 (s, 3H, N-CH_3), 6.80 (s, 1H, H4)
4b	194-195	2.25 (s, 3H, C4-CH_3), 3.10 (s, 3H, N-CH_3)
4c	220-222	2.30 (s, 3H, CH_3-C_6H_4), 3.20 (s, 3H, N-CH_3)
4d	155-156	6.55 (m, 1H, H4), 6.95 (m, 1H, H5), 7.60 (m, 1H, H2)
4e	130-133	2.30 (s, 3H, C4-CH_3), 7.80 (d, 1H, H5), 8.20 (d, 1H, H2)
4f	142-145	2.25 (s, 3H, CH_3-C_6H_4), 6.90 (d, 1H, H5), 7.70 (d, 1H, H2)
9a	140-142	2.50 (s, 3H, C2-CH_3), 3.45 (s, 3H, N-CH_3), 6.50 (s, 1H, H4)
9b	153-155	2.10 (s, 3H, C2-CH_3), 2.60 (s, 3H, C4-CH_3), 3.30 (s, 3H, N-CH_3)
9c	212-213	2.30 (s, 3H, CH_3-C_6H_4), 2.70 (s, 3H, C2-CH_3), 3.40 (s, 3H, N-CH_3)
10a	133-135	2.20 (d, 3H, C5-CH_3, J = 1.17 Hz), 3.20 (s, 3H, N-CH_3), 6.40 (q, 1H, H4)
10b	107-108	2.20 (s, 3H, C4-CH_3), 2.30 (s, 3H, C5-CH_3), 3.20 (s, 3H, N-CH_3)
10c	123-125	2.00 (s, 3H, CH_3-C_6H_4), 2.30 (s, 3H, C5-CH_3), 3.20 (s, 3H, N-CH_3)

[a] In the nmr data the phenylsulfonyl group is conventionally assumed at C_3. [b] For sake of simplicity the chemical shifts of aromatic hydrogens have not been reported.

procedure usually involved the evaporation of solvent under reduced pressure and purification of the product by crystallization; only in the case of a mixture of regioisomeric pyrroles where they separated by fractioned crystallization. Reaction times, yields and regioisomeric ratio are reported in Table I.

Munchnones **2a,b**, symmetrically substituted in 2,4 position, do not give problem of regioselectivity and the structure of pyrroles **4** was assigned on the basis of analytical and spectroscopic data (Tables II, III). However unsymmetrically substituted munchnones **6,8** can lead to a mixture of the regioisomeric pyrroles **9,10** whose relative

structure has been determined by suitable spectroscopic studies. In **9a** C2-CH_3 (δ 2.50) and H4 (δ 6.50) appear as singlets while in **10a** C5-CH_3 (δ 2.20) and H4 (δ 6.40) are respectively a doublet and a quartet with J = 1.2 Hz.

Table III

Analytical Values

Compound	Molecular Formula	Analysis (%) Calcd. (Found) C	H	N
4a	$C_{23}H_{19}NO_2S$	73.98 (73.77)	5.13 (5.15)	3.78 (3.68)
4b	$C_{24}H_{21}NO_2S$	74.40 (74.34)	5.46 (5.20)	3.62 (3.68)
4c	$C_{30}H_{25}NO_2S$	77.73 (77.62)	5.44 (5.46)	3.02 (2.98)
4d	$C_{16}H_{13}NO_2S$	67.84 (67.75)	4.63 (4.58)	4.95 (4.82)
4e	$C_{17}H_{15}NO_2S$	67.67 (67.77)	5.08 (5.04)	4.71 (4.67)
4f	$C_{23}H_{19}NO_2S$	73.98 (73.85)	5.13 (5.09)	3.75 (3.65)
9a	$C_{18}H_{17}NO_2S$	69.44 (69.32)	5.50 (5.44)	4.50 (4.41)
9b	$C_{19}H_{19}NO_2S$	70.14 (70.24)	5.89 (5.85)	4.31 (4.20)
9c	$C_{25}H_{23}NO_2S$	74.79 (74.62)	5.78 (5.86)	3.49 (3.44)
10a	$C_{18}H_{17}NO_2S$	69.44 (69.33)	5.50 (5.40)	4.50 (4.45)
10b	$C_{19}H_{19}NO_2S$	70.14 (70.20)	5.89 (5.82)	4.31 (4.18)
10c	$C_{25}H_{23}NO_2S$	74.79 (74.70)	5.78 (5.66)	3.49 (3.45)

The ^{1}H nmr spectra of compounds **9b** and **10b**, beyond the aromatic protons resonances, consist in three methyl singlets. The lowest field ones (δ 3.30 for compound **9b** and δ 3.20 for compound **10b**) are easily assignable to *N*-methyls by chemicals shift considerations, while the other two couples are not.

Two different nmr experiments have been run on both compounds to clarify the assignments and remove any ambiguity regarding the structure of regioisomers **9b** and **10b**.

The first one was a 2-D homonuclear chemical shift correlation (COSY) [5] to check scalar couplings; compound **9b** displays only a weak long-range coupling between the *N*-methyl and the singlet at δ 2.10 (Fig. 1A), while compound **10b** shows a further stronger coupling between the two methyl signals at δ 2.20 and δ 2.30 (Fig. 1B). Looking at the resolution enhanced 1-D spectra of both compounds, only this latter coupling constant can be detected (0.7 Hz) while the other two between the *N*-methyl and the adjacent C2- or C5-methyl cannot (<0.2 Hz).

The second experiment was a homonuclear 2-D NOE (NOESY) [6] which gave evidence of direct (through space) couplings, *i.e.* spatial proximity of protons. It is well known that during the NOESY experiments also coherent transfer of magnetization may occur. This might lead to erroneous conclusions, that is deduce NOE effects where only scalar couplings are operating. To prevent this possibility, specially for the analysis of compounds **10b**, we used a pulse sequence utilizing systematically incremented values of the "mixing time" [6]. Figures 1C and 1D show the spectra obtained from compounds **9b** and **10b** respectively. While the first does not show any appreciable NOE effect, the latter displays a rather strong cross-peak between the singlets at δ 2.20 and δ 2.30 thus indicating a mutual dipole-dipole relaxation of C4- and C5-methyl which are close to each other. No NOE effect is detectable between the *N*-methyl and the C5- or C2-methyl, even in different experimental conditions (in different values of the starting "mixing time"), this only indicating that cross-relaxation mechanism between the *N*-methyl and the adjacent C5- or C2-methyls does not operate both in compounds **9b** and **10b**. Both COSY and NOESY experiments gave consonant results and allowed us to assign compounds **9b** and **10b** the indicated structures and resonances.

On the basis of the spectroscopic considerations drawn for **9/10 (a-b)** together with the regiochemical propensity observed in munchnones cycloaddition also **9c** and **10c** are consistent with the reported structures.

Discussion.

The reaction between **3** and munchnones is a typical [3 + 2] cycloaddition and gives an unstable, primary bicyclic adduct which loses carbon dioxide leading to the phenylsulfonyl substituted pyrroles **4,9,10**. As shown in Table I the reaction with phenylsulfonylalkynes **3** gives only one regioisomer with munchnone **6** whereas it leads to a mixture of regioisomeric pyrroles **9** and **10** with the reversed munchnone **8**. The exclusive or prevailing orientation in the dipole/dipolarophile approach is that which leads to bond formation between the C4 of mesoionic system and the β-carbon of the sulfone. The experimental observation that replacement of 4-phenyl group in **6** with a methyl substituent in **8** gives the same preferred orientation can be attributed to the postulated [3] higher negative charge density located on C4, together with steric and electronic factors [7].

For munchnones **6,8** it is possible to estimate on the basis of the values determined for the simpler molecule, [8] the HOMO/LUMO orbitals energy and coefficients. Although quantitative values are not available for alkynylsulfones **3**, it is plausible according to the data calculated for the alkenylsulfones [1], that the strong electron withdrawing effect of sulfonyl group lowers the orbital energy

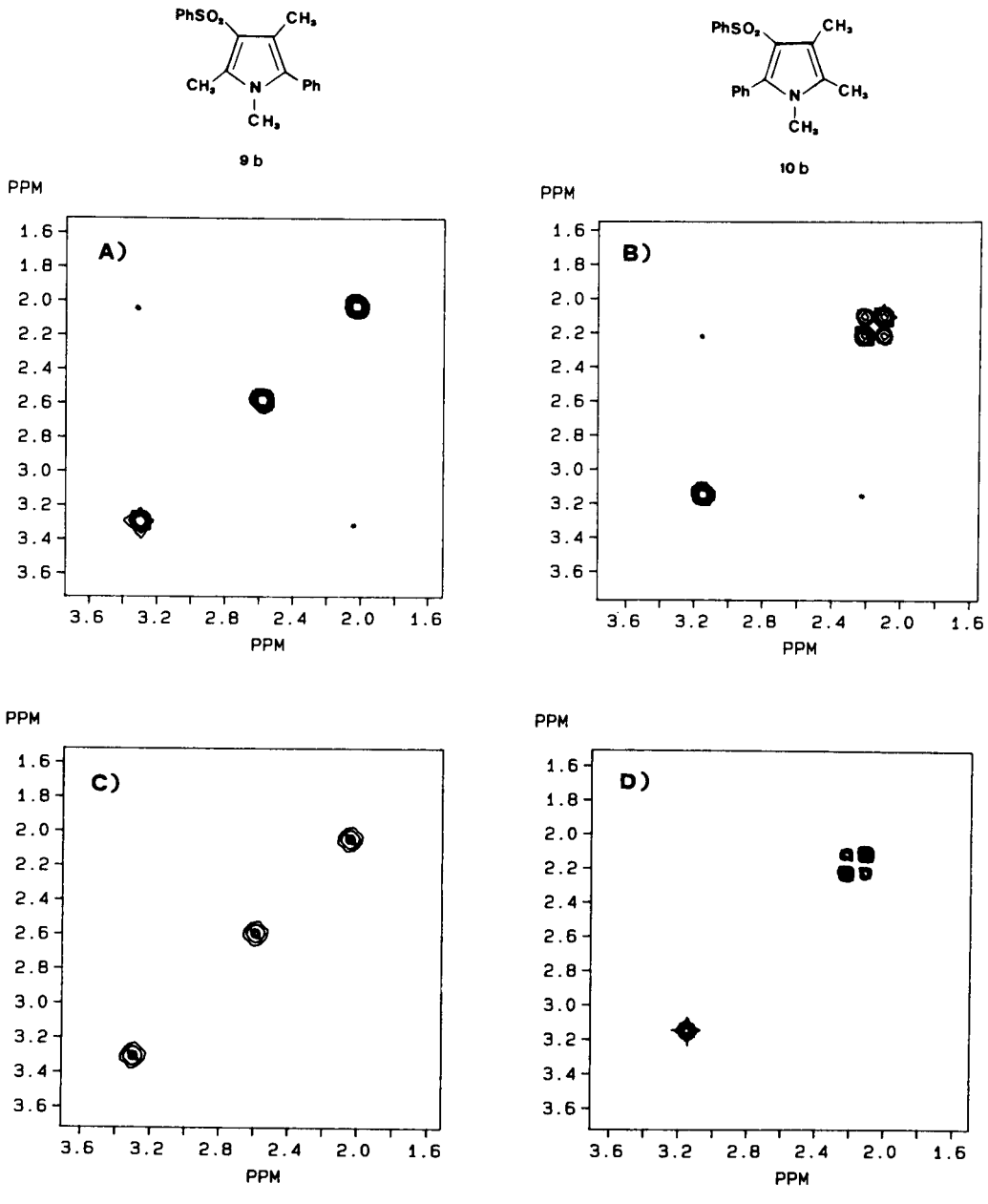


Figure 1. 200 MHz COSY and NOESY spectra of compounds **9b** and **10b**. Only the aliphatic regions are represented as absolute value contour plots; A) COSY spectrum of compound **9b**; B) COSY spectrum of compound **10b**; C) NOESY spectrum of compound **9b**; D) NOESY spectrum of compound **10b**. See experimental for details.

and determines a large HOMO coefficient at the β-carbon. Consequently the HOMO-dipole (orbital energy *ca* -7.8 eV)/LUMO-dipolarophile (orbital energy *ca* 0.0 eV) may be the controlling interaction [9], since this is much closer in energy respect to the opposite one (LUMO-dipole -0.9 eV/HOMO-dipolarophile -13 eV). The different degree of regioselectivity observed with munchnones **6** (complete regioselectivity) in regard to its reversed **8** (mixture of regioisomers) may be explained as a consequence of the marked effect of the substituent, bonded to mesoionic system, on the magnitude of C2 and C4 coefficients.

In the first case the overall effect of the two substituents gives to a reduction of C2 coefficient with an increase of HOMO polarisation; conversely in **8** a leveling effect on C2 and C4 coefficients decreases the regioselectivity.

EXPERIMENTAL

All melting points were measured with a Büchi apparatus and are un-

corrected. The nmr spectra were recorded on a Varian EM-390 and a Bruker WP 80-SY instruments; chemical shifts are expressed in parts per million relative to tetramethylsilane. The 1- and 2-D ^1H nmr spectra of compounds **9b** and **10b** were run on a Varian XL-200 spectrometer operating at 200.057 MHz. The 1-D ^1H nmr spectra were run in 0.04 *M* deuteriochloroform solutions. The 90° pulses were applied (5 μsec); a spectral width of 1400 Hz and an acquisition time of 4 sec were used leading to a digital resolution of 0.25 Hz/point. Both COSY and NOESY experiments were run on properly degassed 0.04 deuteriochloroform solutions. A spectral window of 1400 Hz and an acquisition time of 0.366 s were chosen leading to a digital resolution of 1.95 Hz/point. A relaxation delay of 2 s was added and 4 (COSY) or 32 (NOESY) scans accumulated for the 256 traces. The pseudo-echo Gaussian shaping function available in the XL-200 software was applied in both dimensions. For the NOESY experiments, different starting values of the "mixing time" (τm) were tried: 0.3, 0.5 and 1.0 s. A pulse sequence utilizing systematically incremented τm followed by a symmetrization with respect to the main diagonal after full matrix transformation was applied in order to suppress coherent transfer effects [6].

Products **1a** [12], **1b** [13], **3a** [14], **3b** [15], **3c** [16], **5** [3] and **7** [17] were prepared according to literature methods.

Cycloaddition Reaction. General Procedure.

Acetic anhydride (11 mmoles) was added to a mixture of **1**, **5** or **7** (10 mmoles) and **3** (10 mmoles) in toluene (100 ml). The mixture was heated at 80° under a dry nitrogen stream. The solvent was evaporated and the residue was recrystallized from isopropyl alcohol to give the products listed in Table II.

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