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REACTIONS OF DIAZOMETHANE WITH SULFONYL-ACTIVATED DOUBLE BONDS

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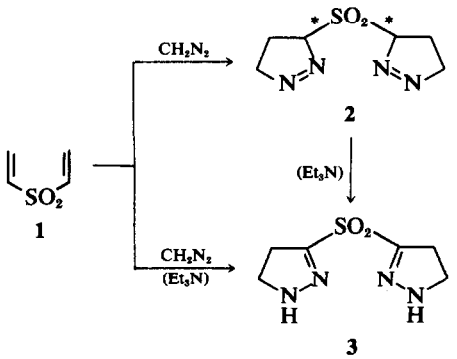
Abstract—The cyclo-addition reaction of diazomethane with α,β-unsaturated sulfones is described. Divinyl sulfone and phenyl vinyl sulfone give 1- or 2-pyrazolines depending on the reaction conditions. *cis*- and *trans*-1,2-Bis(methylsulfonyl)ethene form pyrazolines, which on reaction with either triethylamine or excess of diazomethane lead to substituted pyrazoles.

The addition of diazomethane to double bonds activated by electron-withdrawing substituents such as carbonyl, nitro and nitrile is a well-documented route to substituted pyrazolines.[1] However, the addition of diazomethane to α,β-unsaturated sulfones is scarcely mentioned. Parham *et al.*[2] reported the formation of two types of pyrazolines from α,β-unsaturated sulfones and diazomethane *viz* a normal addition product in which the C atom of the diazomethane is attached to the β-C of the vinyl sulfone and an abnormal product with the diazocarbon attached to the α-C of the unsaturated system. It is generally accepted[1] that the initial reaction products of diazomethane with activated double bonds are 1-pyrazolines, which however, may undergo a facile prototropic rearrangement to the corresponding 2-pyrazolines during crystallization, by gently warming or by a trace of acid or base.[1a] Backer *et al.*[3] reported that treatment of thiophene-1,1-dioxides with excess of diazomethane gave rise to addition of diazomethane to only one double bond of the thiophene-1,1-dioxides.

We investigated the reaction of divinyl sulfone (1)—an open chain analogue of the thiophene-1,1-dioxides—with diazomethane under similar conditions and we found that instead of one, both double bonds of **1** reacted smoothly.

Treatment of divinyl sulfone (1) with a basefree ethereal solution of diazomethane gave the 1-pyrazoline **2** as a mixture of the *meso* and *dl* form in yields up to 90%. In the presence of a trace of triethylamine the 2-pyrazoline **3** was obtained in 76% yield. Heating of **2** in acetonitrile in the presence of a little of triethylamine gave a quantitative rearrangement to **3** (Scheme 1).



SCHEME 1

The structure of **3** was established by a correct elemental analysis, a NH absorption at 3340 cm^{-1} in the IR spectrum and an A_2B_2 pattern for the protons at C_4 and C_5 in the NMR spectrum. The structure of **2** (*meso* + *dl*) was evident from the elemental analysis, the NMR spectrum which showed four multiplets in the intensity ratio of 1:1:4:4 and the absence of a NH IR absorption. Careful crystallization of the reaction product **2** gave one of the isomers (either *meso* or *dl*) as a pure substance. Its NMR showed three multiplets in the intensity ratio of 1:2:2. Heating of this pure isomer gave a quantitative tautomerization to bis-2-pyrazoline **3**.

Parham *et al.*[2] studied the addition of diazomethane to sulfones of the type $R^1—SO_2—CH=CHR^2$. With R^2 being aryl, they found normal as well as abnormal addition products. With R^2 being H or alkyl, only normal addition took place. The position of the double bond with respect to the substituent in the isolated 2-pyrazolines was not established.[2] Since we were able to isolate a 1-pyrazoline from the (normal) addition reaction of diazomethane to **1** and since we could adjudge the position of the double bond in the corresponding 2-pyrazoline **3**, we decided to reinvestigate one of Parham's sulfones. We found that the addition of diazomethane

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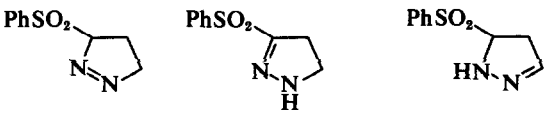
to phenyl vinyl sulfone produced a 4-pyrazoline (4). However, when the reaction was carried out in the presence of a trace of base, we isolated just as Parham *et al.*[2] did, a 2-pyrazoline (5), erroneously denoted as 4 by these authors.



4 5 6

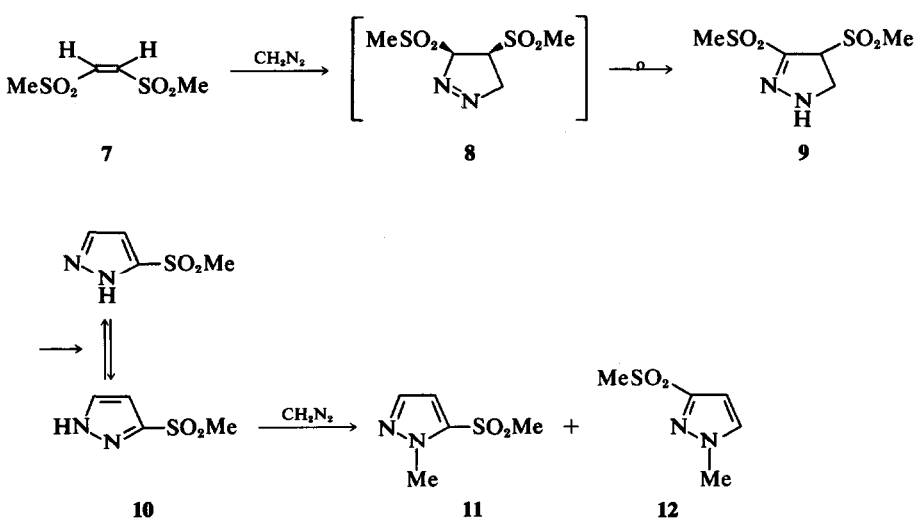
Having studied so far the addition of diazomethane to a double bond linked with one sulfonyl group (phenyl vinyl sulfone) and a sulfone connected with two double bonds (divinyl sulfone, 1) the series was completed by investigating the behaviour of a double bond flanked by two sulfonyl functions, e.g. *cis*-1,2-bis (methylsulfonyl)-ethene (7)* (Scheme 2).

*When this work was carried out Meek and Fowler published their results on the reaction of diazomethane with *cis*-1,2-bis(*p*-tolylsulfonyl) ethene (compare 7). When the reaction was stopped as soon as the starting alkene was dissolved 3-*p*-tolylsulfonylpyrazole (compare 10) was isolated in 17% yield. Leaving overnight *cis*-1,2-bis(*p*-tolylsulfonyl) ethene with excess of diazomethane resulted in a mixture from which 1-methyl-3(5)-*p*-tolylsulfonylpyrazole (compare 11 and 12) could be isolated in 57% yield. Product formation is rationalized by Meek and Fowler assuming sulfinate elimination from the intermediate 1-pyrazoline (compare 8). (J. S. Meek and J. S. Fowler, *J. Org. Chem.* 33, 985 (1968)).

†A good NMR spectrum of 9 could not be obtained; 9 was only sparingly soluble in chloroform and carbon tetrachloride, reacted with acetone and decomposed in polar solvents like dimethyl sulfoxide, water and trifluoroacetic acid.

The reaction of 7 with excess of diazomethane afforded two isomeric 1-methyl-methylsulfonylpyrazoles (m.p. 66·5–67·5°, 67% and m.p. 77–78°, 18%). The NMR spectra of these isomers differed only slightly (Experimental). The chemical shifts and coupling constants were compared with the literature data[4] for the isomer identification of pyrazoles. On basis hereof the compound with m.p. 66·5–67·5° was shown to be 1-methyl-5-methylsulfonylpyrazole (11) and the isomer with m.p. 77–78° to be 1-methyl-3-methylsulfonylpyrazole (12)—see Scheme 2. In order to gain more insight in the reaction of 7 with excess of diazomethane, it was treated with one equivalent of diazomethane. The added diazomethane solution was decolorized immediately and the adduct 9 precipitated nearly quantitatively and analytically pure. The IR† of 9 showed a NH absorption at 3370 cm^{-1} and was identical to the IR spectrum of the product obtained by treatment of *trans*-1,2-bis(methylsulfonyl) ethene (13) with one equivalent of diazomethane. The reaction of 7 with one equivalent of diazomethane and one equivalent of triethylamine gave pyrazole 10 in 94% yield. The NMR spectrum of 10 showed two doublets for the ring protons, characteristic for 3-substituted pyrazoles.

The reaction sequence depicted in Scheme 2 is a likely explanation for the product formation from 7 in the presence of excess of diazomethane. The alternative that sulfinic acid elimination from 8 takes place prior to the prototropic shift must be discarded because of the great ease by which the tautomerization to the 2-pyrazoline 9 takes place. Further evidence for the proposed mechanism is the nearly equal ratios of the quantities of 11 and 12 formed by the reaction of *cis*-1,2-bis(methylsulfonyl) ethene (7), *trans*-1,2-bis(methylsulfonyl)-



7 8 9

10 11 12

SCHEME 2

ethene (13) and 3-methylsulfonylpyrazole (10) with diazomethane under identical conditions. As a third possibility can be envisaged N-methylation of the 2-pyrazoline 9 with subsequent elimination of sulfinic acid. In that case one would expect only 1-methyl-3-methylsulfonylpyrazole (12). However, pyrazole 12 was isolated in a much lower yield than its isomer 11.

In strong contrast to the stability of pyrazoline 9 are unsuccessful attempts described recently by Witiak and Sinha[5] to isolate or detect intermediate 1- or 2-pyrazolines in the reaction of *cis*- and *trans*-β-chloroacrylates with diazomethane.

EXPERIMENTAL

M.ps are uncorrected. Microanalyses were performed by the analytical department of our laboratory under supervision of Mr. W. M. Hazenberg. NMR spectra were determined on a Varian A-60 spectrometer, using TMS as internal standard. IR spectra were taken on an Unicam SP 200.

Di(1-pyrazolin-3-yl)sulfone (2). To a soln of 820 mg (6·9 mmole) of 1 in 50 ml ether was added at 0° 24 ml 1 M CH_2N_2 in ether. Immediate decolorization of the first part of the CH_2N_2 soln and formation of a white ppt indicated a fast reaction. After 18 hr at 0°, 2 was filtered off and washed with ether, yield, 800 mg (58%). Two crystallizations from CH_2Cl_2-ether-pentane gave 600 mg of an equimolar mixture of both diastereomers 2. NMR ($CDCl_3$): δ 6·44 (m, 1 H on C_3), δ 5·93 (m, 1 H on C_3), δ 4·80 (m, 4 H on C_5) and δ 2·13 (m, 4 H on C_4); IR: no NH absorption. (Found: C, 35·69; H, 5·00; N, 27·72; S, 15·87. Calc. for $C_6H_{10}N_4O_2S$: C, 35·63; H, 4·98; N, 27·71; S, 15·85%). After 4 crystallizations one diastereomer 2 was obtained pure; NMR ($CDCl_3$): δ 5·93 (m, 1 H on C_3), δ 4·80 (m, 2 H on C_5) and δ 2·13 (m, 2 H on C_4); IR: no NH absorption, m.p. 99–104° (dec). (Found: C, 35·43; H, 4·99; N, 27·79; S, 15·83%). Analytically pure 2 (one diastereomer) heated for 15 min in MeCN in the presence of Et_3N gave a complete rearrangement to 3 as was evident from the NMR spectrum.

Di(2-pyrazolin-3-yl)sulfone (3). To a soln of 1773 mg (15·0 mmole) of 1 in 150 ml ether was added at 0° 60 ml 1 M CH_2N_2 in ether and 200 mg NaOH. After 18 hr at −5° the mixture was filtered giving 2300 mg (76%) of 3. Two crystallizations from CH_2Cl_2-ether-pentane afforded analytically pure product, m.p. 101·5–103·5° (dec). (Found: C, 35·78; H, 5·14; N, 27·58; S, 15·88. Calc. for $C_6H_{10}N_4O_2S$: C, 35·63; H, 4·98; N, 27·71; S, 15·85%); NMR ($CDCl_3$); δ 6·48 (s, 0·8 H, NH) and δ 3·40 (A_2B_2 pattern, 2 H on C_4 and 2 H on C_5); IR: 3330 cm^{-1} (NH).

3-Phenylsulfonyl-1-pyrazoline (4). To 840 mg (5 mmole) phenyl vinyl sulfone[2] in 20 ml dry ether was added at 0° 35 ml 0·4 M ethereal CH_2N_2. After 48 hr at −20° 790 mg (75%) of 4 was filtered off. Two crystallizations from CH_2Cl_2-ether-pentane afforded analytically pure 4, m.p. 79–82° (dec). (Found: C, 51·15; H, 4·90; N, 13·06; S, 15·20. Calc. for $C_9H_{10}N_2O_2S$: C, 51·41; H, 4·79; N, 13·35; S, 15·25%); NMR ($CDCl_3$): δ 7·75 (m, 5 H), δ 5·75 (m, 1 H on C_3), δ 4·57 (m, 2 H on C_5) and δ 2·05 (m, 2 H on C_4); IR: no NH absorption.

3-Phenylsulfonyl-2-pyrazoline (5). To 840 mg (5 mmole) phenyl vinyl sulfone[2] in 20 ml dry ether was added at 0° 20 ml 0·4 M ethereal CH_2N_2 and 30 mg Et_3N. After 48 hr at −20° 885 mg (85%) of 5 was isolated by filtration. After 3 crystallizations from EtOH-pentane 5 was obtained analytically pure, m.p. 95·5–97°. (Found: C, 51·44; H, 4·90; N, 13·04; S, 15·24. Calc. for $C_9H_{10}N_2O_2S$: C, 51·41; H, 4·79; N, 13·33; S, 15·25%); NMR ($CDCl_3$): δ 7·75 (m, 5 H), δ 6·30 (broad s, NH) and δ 3·30 (A_2B_2 pattern, 4 H); IR: 3380 cm^{-1} (NH).

Conversion of 4 *into* 5. 420 mg of 4 and 3 mg of Et_3N in 50 ml ether were kept at 5° for 48 hr. After cooling to −20° filtration of the mixture gave 320 mg of 5 identified by IR (NH absorption at 3380 cm^{-1}) and m.p. (94–97°).

1-Methyl-5-methylsulfonylpyrazole (11) and *1-methyl-3-methylsulfonylpyrazole* (12). To 920 mg (5 mmole) of 7 in 10 ml CH_2Cl_2 and 30 ml dioxane was added 100 ml 0·5 M ethereal CH_2N_2. After standing for 1 week at 5° the CH_2N_2 had disappeared. Solvents were removed under diminished pressure. The resulting oil was chromatographed over Al_2O_3 (activity II–III, neutral, benzene-ether), yield, 540 mg (67%) of 11, and 147 mg (18%) of 12. Pyrazole 11 was obtained analytically pure by 2 crystallizations from ether, m.p. 66·5–67·5° (Found: C, 37·93; H, 5·08; N, 17·44; S, 20·13. Calc. for $C_5H_8N_2O_2S$: C, 37·48; H, 5·03; N, 17·49; S, 20·02%); NMR ($CDCl_3$): δ 7·51 (d, 1 H, J 2 c/s), δ 6·85 d, 1 H, J 2 c/s), δ 4·16 (s, 3 H, N–Me) and δ 3·17 (s, 3 H, SO_2-Me); IR: no NH absorption. Compound 12 was also obtained analytically pure by 2 crystallizations from ether, m.p. 77–78°. (Found: C, 37·34; H, 4·86; N, 17·57; S, 20·22%); NMR ($CDCl_3$): δ 7·48 (d, 1 H, J 2·5 c/s), δ 6·75 (d, 1 H, J 2·5 c/s), δ 4·00 (s, 3 H, N-Me) and δ 3·17 (s, 3 H, SO_2-Me); IR: no NH absorption.

3,4-Di(methylsulfonyl)-2-pyrazoline (9). To 736 mg (4 mmole) of 7 in 20 ml CH_2Cl_2 and 20 ml ether was added at 0° 8 ml 0·5 M CH_2N_2 in ether. After cooling to −20° 810 mg (90%) of 9 could be filtered off. Washing with CH_2Cl_2, ether and pentane gave analytically pure 9, m.p. 130–133° (dec). (Found: C, 26·50; H, 4·45; N, 12·27; S, 28·06. Calc. for $C_5H_{10}N_2O_4S_2$: C, 26·54; H, 4·45; N, 12·38; S, 28·35%). The IR showed a NH absorption (3370 cm^{-1}). An attempt to obtain 9 analytically pure by crystallization from acetone (5x) failed since 9 reacted with acetone. The elemental analysis of the new product (m.p. 131·5–135°, dec), was in agreement with a structure of a compound formed by condensation of 2 mole of 9 with 1 mole of acetone. (Found: C, 32·15; H, 4·98; N, 11·29; S, 25·52. Calc. for $C_{13}H_{24}N_4O_8S_4$: C, 31·70; H, 4·91; N, 11·37; S, 26·04%); IR: no NH absorption.

3-Methylsulfonylpyrazole (10). To 920 mg (5 mmole) of 7 in 10 ml dioxane was added at 0° 10 ml 0·5 M CH_2N_2 in ether and 600 mg Et_3N. After standing for 48 hr at 5° the solvents were evaporated under diminished pressure. The resulting oil was chromatographed (silica gel, EtOAc) giving 685 mg (94%) of 10. Two crystallizations from EtOH gave analytically pure product, m.p. 99–103°. Found: C, 32·84; H, 4·15; N, 19·36; S, 22·08. Calc. for $C_4H_6N_2O_2S$: C, 32·86; H, 4·14; N, 19·17; S, 21·94%); NMR ($CDCl_3$): δ 7·90 (d, 1 H, J 2·5 c/s), δ 6·83 (d, 1 H, J 2·5 c/s) and δ 3·15 (s, 3 H); IR 3340 cm^{-1} (NH).

The reaction of *cis*- resp. *trans*-1,2-bis(methylsulfonyl)-ethene and 10 with CH_2N_2 under identical conditions. To 92 mg of 7 in 5 ml CH_2Cl_2 was added at 0° 15 ml of 0·45 M CH_2N_2 in ether. After standing for 1 week at 5° volatile components were removed on a vacuum evaporator, giving a nearly colourless oil. The NMR spectrum showed 11 and 12 to be present in the ratio of 3·4 : 1, and in addition some minor impurities. The same procedure was applied to 13. The ratio of 11 and 12 was found to be

4·7:1. When 5 mg of 10 in CH_2Cl_2 was treated with 15 ml 0·45 M CH_2N_2 the ratio of 11 and 12 amounted to 4·5:1.

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