PREPARATION OF 3,4,5-TRISUBSTITUTED PYRAZOLES FROM 2,2-DIOXOKETENE-S,S-ACETALS[1]

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2,2-Dioxoketene-S,S-acetals (5-7) react with hydrazine to give 5-methylthiopyrazoles (8-10) rather than diazafulvenes (A). Nucleophilic displacement of the 5-methylthio (or the derived 5-methylsulfonyl) substituent in these pyrazoles was not possible.

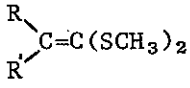
The utilization of 2-keto- and 2-cyanoketene-S,S-acetals as β-dicarbonyl synthons in reactions with bifunctional nucleophiles for the preparation of heterocycles has received considerable recent attention. For example, 2-aroylketene-S,S-acetals (1,2) react with guanidine, cyanoacetamide and hydrazine to give pyrimidines,[3-5] pyridones[6] and pyrazoles[7] respectively. 2-Cyano-3,3-bis(methylthio)acrylonitrile (3) also gives pyrimidines with guanidine,[8] and 2-cyano-3,3-bis(methylthio)acrylic acid esters (4) have been shown to react with hydrazine to give 4-cyano-5-methylthio-3-pyrazolones[9] and with isoquinolium N-imine to give a pyrazolo(2,3-a)isoquinoline.[10]

It was of interest to us to examine the reaction of 2,2-dioxoketene-S,S-acetals (5-7) with hydrazine to see whether cyclization would involve the 1,3-dicarbonyl functionality (to give diazafulvenes, A) or displacement of one of the methylthio groupings and cyclization to pyrazoles (e.g., 8-10), whose ortho-situated methylthio and carbonyl substituents would make them intriguing potential intermediates for further transformations.

In all cases examined, the products formed upon reaction of 2,2-dioxoketene-S,S-acetals (5-7) with hydrazines were

pyrazoles; no evidence for the formation of diazafulvenes (A) could be found. Condensation of phenylhydrazine with the diacetyl derivative 6 gave 1-phenyl-3-methyl-4-acetyl-5-methylthiopyrazole (10) as the sole reaction product.[11]

We were disappointed to find that these 3,4,5-trisubstituted pyrazoles failed to react with guanidine to give pyrazolo-pyrimidines. Compounds 8 and 9 were oxidized with peracetic acid to the corresponding methylsulfonyl derivatives 11 and 12, but once again, no cyclization to pyrazolopyrimidines took place, even upon fusion with guanidine. Thus, even under apparently optimum conditions (intramolecular cyclization with displacement of a superb leaving group[12]), nucleophilic substitution on the pyrazole nucleus was not possible.



1, R = ArCO, R' = H

2, R = CN, R' = H

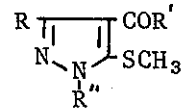
3, R = R' = CN

4, R = CN, R' = COOR

5, R = CH_3CO, R' = $COOC_2H_5$

6, R = R' = CH_3CO

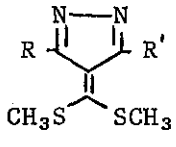
7, R = C_6H_5CO, R' = $COOC_2H_5$



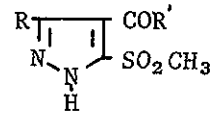
8, R = CH_3, R' = OC_2H_5, R'' = H

9, R = C_6H_5, R' = OC_2H_5, R'' = H

10, R = R' = CH_3, R'' = C_6H_5



A



11, R = CH_3, R' = OC_2H_5

12, R = C_6H_5, R' = OC_2H_5

EXPERIMENTAL SECTION

3-Methyl-4-carbethoxy-5-methylthiopyrazole (8): A mixture of 1.5 g (0.0064 mol) of ethyl 3,3-bis(methylthio)-2-acetylacrylate[13] and 0.32 g (0.0064 mol) of 99% hydrazine hydrate was boiled vigorously in 25 ml of ethanol for 12 hr. Methyl mercaptan was evolved (Hood!). Removal of the solvent under reduced pressure gave 1.1 g (83%) of 8; mp (from benzene) 127-129° (lit.[14] mp 128-129°). Nmr ($DCCl_3$) δ 1.35 (3,t,CH_3), 2.45 (3,s,CH_3), 2.50 (3,s,CH_3), 4.35 (2,q,CH_2), 10.83 (1,s,NH).

Anal. Calcd for $C_8H_{12}N_2O_2S$: C, 47.98; H, 6.04; N, 13.99; S, 16.01. Found: C, 48.10; H, 6.11; N, 14.00; S, 15.87.

3-Phenyl-4-carbethoxy-5-methylthiopyrazole (9): This compound was prepared in 97% yield from ethyl 3,3-bis(methylthio)-2-benzoylacrylate[15] (0.6 g, 0.002 mol) as described above for the preparation of 8; yield 0.51 g, mp (from cyclohexane: benzene, 3:1) 124-126°. Nmr ($DCCl_3$) δ 1.23 (3,t,CH_3), 2.5 (3,s,CH_3), 4.25 (2,q,CH_2), 7.45 (5,m,ArH), 10.4 (1,s,NH).

Anal. Calcd for $C_{13}H_{14}N_2O_2S$: C, 59.52; H, 5.38; N, 10.68; S, 12.22. Found: C, 59.65; H, 5.52; N, 10.65; S, 12.19.

1-Phenyl-3-methyl-4-acetyl-5-methylthiopyrazole (10): This compound was prepared in 81% yield from 1,1-bis(methylthio)-2,2-diacetylethylene[15] (0.10 g, 0.0005 mol) and phenylhydrazine (0.052 g, 0.0005 mol) as described above; yield 0.10 g, mp (from cyclohexane: benzene, 1:2) 148-149°. Nmr ($DCCl_3$) δ 2.50 (6,s,CH_3), 2.57 (3,s,CH_3), 7.50 (5,m, ArH).

Anal. Calcd for $C_{13}H_{14}N_2OS$: C, 63.38; H, 5.73; N, 11.37; S, 13.02. Found: C, 63.35; H, 5.71; N, 11.47; S, 13.00.

3-Methyl-4-carbethoxy-5-methylsulfonylpyrazole (11): A solution of 0.5 g (0.0025 mol) of 3-methyl-4-carbethoxy-5-

methylthiopyrazole and 0.283 g (0.0025 mol) of 30% hydrogen peroxide in 10 ml of glacial acetic acid was boiled vigorously for 2 hr. The reaction mixture was concentrated to half its volume under reduced pressure and added to 50 ml of water. The white precipitate which formed was collected by filtration and recrystallized from cyclohexane:benzene (3:1) to give 0.26 g (45%) of 11, mp 140-142°. Nmr ($DCCl_3$) δ 1.35 (3,t,CH_3), 2.57 (3,s,CH_3), 3.35 (3,s,CH_3), 4.35 (2,q,CH_2), 12.2 (1,s, broad, NH).

Anal. Calcd for $C_8H_{12}N_2O_4S$: C, 41.37; H, 5.81; N, 12.06; S, 13.81. Found: C, 41.13; H, 5.33; N, 12.08; S, 13.75.

3-Phenyl-4-carbethoxy-5-methylsulfonylpyrazole (12): A solution of 0.20 g (0.00076 mol) of 3-phenyl-4-carbethoxy-5-methylthiopyrazole and 0.090 g (0.0008 mol) of 30% hydrogen peroxide in 10 ml of glacial acetic acid was boiled vigorously for 2 hr, concentrated to one-third its volume, and added to 50 ml of ethanol. The white precipitate which formed was collected by filtration and recrystallized from aqueous ethanol (3:1) to give 0.18 g (80%), mp 117-119°. Nmr ($DCCl_3$) δ 1.10 (3,t,CH_3), 3.2 (3,s,CH_3), 4.15 (2,q,CH_2), 7.37 (5,m,ArH), 11.25 (1,s,broad, NH).

Anal. Calcd for $C_{13}H_{14}N_2O_4S$: C, 53.05; H, 4.79; N, 9.52; S, 10.89. Found: C, 52.59; H, 4.72; N, 9.44; S, 10.72.

REFERENCES AND NOTES

1. This work was supported in part by a grant (CA-12876) to Princeton University from the National Cancer Institute, National Institutes of Health, Public Health Service.

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