RING TRANSFORMATION OF 5-ACYLPYRIMIDINES INTO 4-ACYLPYRAZOLES WITH PHENYLHYDRAZINE

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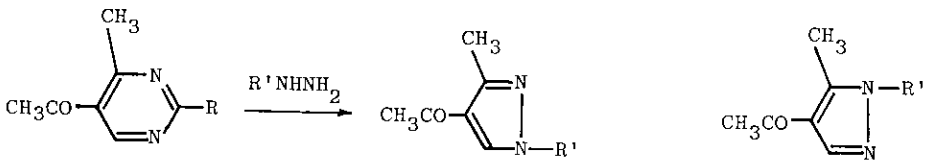
Abstract — Phenylhydrazine in alcoholic acidic medium exclusively transformed 5-benzoyl-4-methyl-2-methylthiopyrimidine into 4-acetyl-1,3-diphenylpyrazole and 5-acetyl-2-methylthio-4-phenylpyrimidine into 4-benzoyl-3-methyl-1-phenylpyrazole. The mechanism of these ring contraction reactions is proposed.

Ring contraction of pyrimidines into pyrazoles under the action of hydrazines is a well documented reaction[1]. The presence of an electron-attractive substituent, such as nitro and acyl groups, at 5-position of the pyrimidine ring facilitates this type of transformation[2,3]. We have previously shown that 2-substituted 5-acetyl-4-methylpyrimidines (1, R=SCH_3, C_6H_5, NH_2) on reaction with monosubstituted hydrazines in acidic medium were transformed to 1-substituted 4-acetyl-3-methylpyrazoles (2) without formation of their isomers, 1-substituted 4-acetyl-5-methylpyrazoles (3)[3,4]. This indicates that the primary amino group of monosubstituted hydrazines attacks either C^4 (bearing the methyl group) or carbonyl-C of 1, and the secondary amino group reacts on C^6. The structure of 1 did not allow to distinguish between these two possible mechanisms for the formation of 2.

We now report an additional study which suggests that the transformation of 5-acylpyrimidines into 4-acylpyrazoles with hydrazines proceeds *via* initial formation of the corresponding hydrazones of 5-acylpyrimidines and subsequent intramolecular attack on C^6 of the pyrimidine ring by the exocyclic NH group.

The reaction of 2-ethoxymethylene-1-phenyl-1,3-butanedione (4)[5] with s-methyliso-



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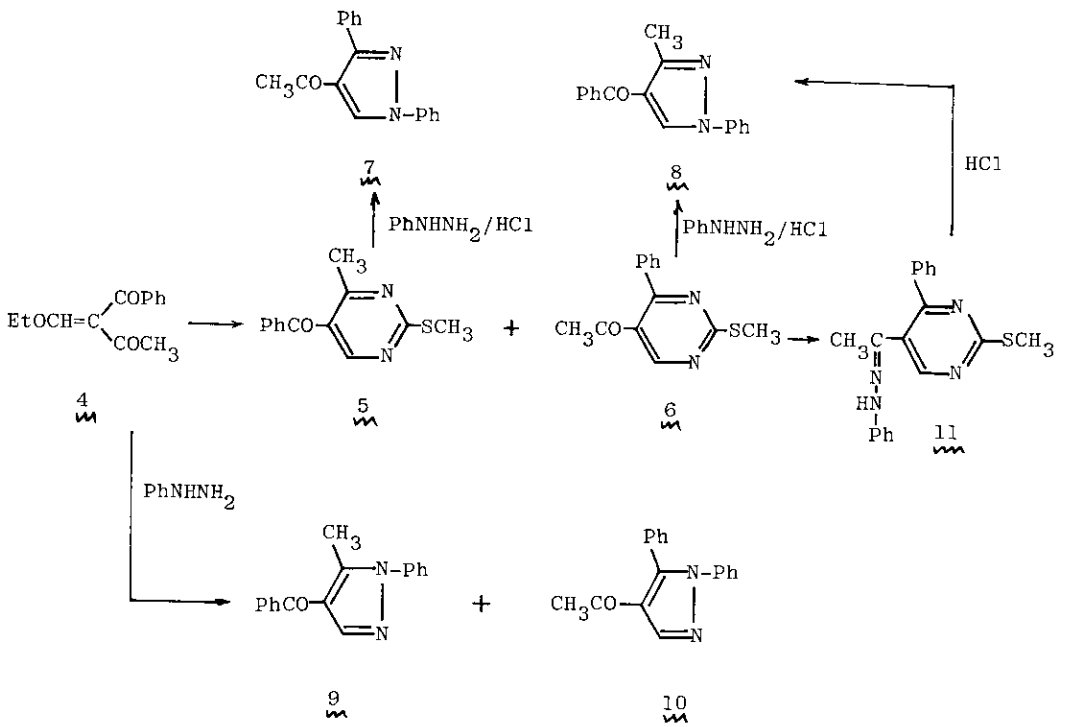
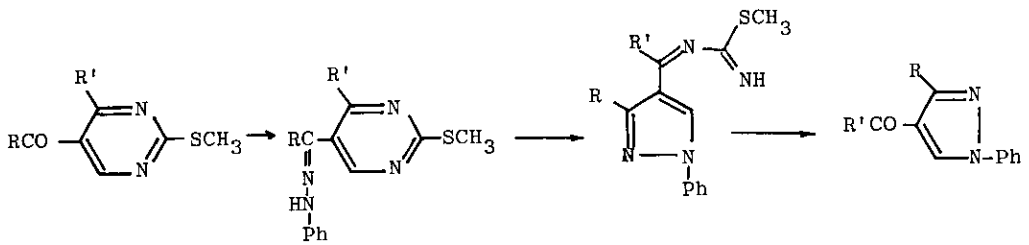
thiourea afforded two isomeric pyrimidines: 5-benzoyl-4-methyl-2-methylthiopyrimidine (5) and 5-acetyl-2-methylthio-4-phenylpyrimidine (6), which were isolated by column chromatography. When heated with phenylhydrazine in boiling methanol in the presence of hydrochloric acid, pyrimidine 5 exclusively provided 4-acetyl-1,3-diphenylpyrazole (7), while pyrimidine 6 led under the same conditions only to 4-benzoyl-3-methyl-1-phenylpyrazole (8) without formation of any other possible isomers. On the other hand, the reaction of 4 with phenylhydrazine in acidic methanol gave a mixture of 4-benzoyl-5-methyl-1-phenylpyrazole (9) and 4-acetyl-1,5-diphenylpyrazole (10), which are isomers of 8 and 7, respectively.



On the basis of the above results, we propose a mechanism for the formation of pyrazoles 7 and 8; the phenylhydrazones of 5-acylpyrimidines 5 and 6 are initially formed, and subsequent intramolecular attack on C^6 of the pyrimidine ring by the NH group of hydrazono moiety with C^6-N^1 bond fission gives pyrazole ring compounds which are hydrolyzed to 4-acylpyrazoles.



In fact, we confirmed that the phenylhydrazone 11 prepared from 6 and phenylhydrazine under mild conditions was transformed exclusively into 8 on heating in methanol in the presence of hydrochloric acid.

The results reported here demonstrate that the ring contraction mechanism of 5-acylpyrimidines into 4-acylpyrazoles is different from that of the usual transformation of pyrimidines into pyrazoles, which proceeds through attack of the substituted hydrazines to C^4 and C^6 of the pyrimidine ring.

EXPERIMENTAL

Melting points were determined using a Köfler bench apparatus and are uncorrected. ^{1}H-Nmr spectra were recorded on a Hitachi-Perkin Elmer 60 MHz spectrometer or a Varian 390 90 MHz spectrometer using tetramethylsilane as internal standard. Mass spectra were taken on a Ribermag R10-10 apparatus using a direct inlet system. Infrared spectra were obtained on a Perkin-Elmer model 1710 spectrophotometer.

5-Benzoyl-4-methyl-2-methylthiopyrimidine (5) and 5-Acetyl-2-methylthio-4-phenylpyrimidine (6).

A mixture of 2-ethoxymethylene-1-phenyl-1,3-butanedione (4) (13 g, 0.06 mol) and S-methylisothiourea hydroiodide (13 g, 0.064 mol) in an ethanolic sodium ethoxide

solution (1.4 g of Na in 180 ml of anhydrous ethanol) was stirred at room temperature for 1 h and then refluxed for 1 h. After removal of the solvent, water was added to the residue and the mixture was extracted with ethyl acetate. The extract was washed with water, dried (Na_2SO_4) and concentrated to dryness to yield a crystalline solid which was purified by silica gel column chromatography with chloroform. The eluate gave after evaporation of the solvent 10.3 g of a mixture of 5 and 6. Further purification by chromatography (silica gel/chloroform) and subsequent crystallization from hexane allowed to separate 3.05 g (21%) of 5 and 0.6 g (4%) of 6.

— 5, mp 72°. ^{1}H-Nmr (DMSO-d_6): δ =2.40 (s, 3H, CH_3), 2.55 (s, 3H, SCH_3), 7.5-8.0 (m, 5H, Ph), 8.55 (s, 1H, H-6). Ms m/z: 244 (100, M^+), 198 (16), 105 (32), 77 (72). Ir (KBr): ν = 1656 (C=O) cm^{-1}. Anal. Calcd for $C_{13}H_{12}N_2OS$: C, 63.95; H, 4.95; N, 11.46; S, 13.12. Found: C, 63.92; H, 4.96; N, 11.43; S, 13.10.

— 6, mp 74°. ^{1}H-Nmr (DMSO-d_6): δ = 2.30 (s, 3H, CH_3), 2.65 (s, 3H, SCH_3), 7.55 (s, 5H, Ph), 8.90 (s, 1H, H-6). Ms m/z: 244 (100, M^+), 199 (32), 198 (10), 155 (16), 77 (32), 43 (71). Ir (KBr): ν = 1684 (C=O) cm^{-1}. Anal. Calcd for $C_{13}H_{12}N_2OS$: C, 63.95; H, 4.95; N, 11.46; S, 13.12. Found: C, 63.94; H, 4.93; N, 11.43; S, 13.20.

The structural distinction between 5 and 6 was based on the comparison of their spectral data, notably the presence of a benzoyl fragment (m/z 105) for 5 and an acetyl fragment (m/z 43) for 6 in the mass spectra, the relative schift of H-6 in the ^{1}H-nmr spectra and the respective value of C=O vibration frequence in the ir spectra.

4-Acetyl-1,3-diphenylpyrazole (7).

A mixture of 5 (1.08 g, 4 mmol), phenylhydrazine (1.69 g, 15 mmol), conc. hydrochloric acid (20 ml) and water (28 ml) in methanol (120 ml) was refluxed for 24 h. After removal of the solvent, water was added to the residue and the resulting mixture was extracted with ethyl acetate. The extract was dried (Na_2SO_4) and concentrated to yield a crystalline solid which showed on tlc a spot with Rf 0.22 (silica gel/chloroform). Purification by column chromatography (silica gel/chloroform) afforded 0.26 g (22%) of 7, mp 108°. ^{1}H-Nmr (DMSO-d_6): δ = 2.50 (s, 3H, CH_3), 7.3-8.1 (m, 10H, Ph), 9.30 (s, 1H, H-5). Ms m/z: 262 (41, M^+), 247 (78), 185 (30), 77 (100), 51 (60), 43 (37). Ir (KBr): ν = 1665 (C=O) cm^{-1}. Anal. Calcd for $C_{17}H_{14}N_2O$: C, 77.84; H, 5.38; N, 10.68. Found: C, 77.85; H, 5.37; N, 10.65.

4-Benzoyl-3-methyl-1-phenylpyrazole (8).

A mixture of 6 (1.22 g, 5 mmol), phenylhydrazine (2.76 g, 7 mmol) and conc. hydrochloric acid (15 ml) in ethanol (100 ml) was treated in the same procedure as described for the preparation of 7 from 5. The crude product, which showed on tlc a spot with Rf 0.18 (silica gel/chloroform), was purified by column chromatography (silica gel/chloroform) and crystallization from hexane gave 1.04 g (83%) of 8, mp 84°. ^{1}H-Nmr (DMSO-d_6): δ = 2.50 (s, 3H, CH_3), 7.2-8.0 (m, 10H, Ph), 8.75 (s, 1H, H-5). Ms m/z: 262 (16, M^+), 185 (27), 105 (68), 77 (100), 51 (44). Ir (KBr): ν = 1641 (C=O) cm^{-1}. Anal. Calcd for $C_{17}H_{14}N_2O$: C, 77.84; H, 5.38; N, 10.68. Found: C, 77.78; H, 5.36; N, 10.66.

The comparison of the spectral data (^{1}H-nmr, ms and ir) between 7 and 8 allowed their structural distinction.

4-Benzoyl-5-methyl-1-phenylpyrazole (9) and 4-Acetyl-1,5-diphenylpyrazole (10).

A mixture of 4 (2.18 g, 10 mmol) and phenylhydrazine (1.3 g, 12 mmol) in methanol (120 ml) containing conc. hydrochloric acid (3 drops) was stirred at room temperature for 18 h. The reaction mixture was treated in the same procedure as described above to yield a crystalline solid whose ^{1}H-nmr spectrum showed the presence of two compounds 9 and 10. Purification by chromatography on silica gel column with chloroform and benzene afforded successively 1.52 g (54%) of 9 and 0.14 g (5.3%) of 10.

— 9, mp 83°, Rf: 0.35 (silica gel/chloroform). ^{1}H-Nmr (DMSO-d_6): δ = 2.50 (s, 3H, CH_3), 7.3-7.6 (m, 8H, Ph), 7.6-7.8 (m, 2H, H-2 and H-6 of benzoyl), 7.80 (s, 1H, H-3). Ms m/z: 262 (70, M^+), 185 (58), 158 (8), 105 (10), 77 (100), 51 (37). Ir (KBr): ν = 1632 (C=O) cm^{-1}. Anal. Calcd for $C_{17}H_{14}N_2O$: C, 77.84; H, 5.38; N, 10.68. Found: C, 77.80; H, 5.40; N, 10.65.

— 10, mp 108°, Rf: 0.30 (silica gel/chloroform). ^{1}H-Nmr (DMSO-d_6): δ = 2.25 (s, 3H, CH_3), 7.2-7.7 (m, 10H, Ph), 8.35 (s, 1H, H-3). Ms m/z: 262 (38, M^+), 247 (100), 77 (65), 51 (28), 43 (20). Ir (KBr): ν = 1655 (C=O) cm^{-1}. Anal. Calcd for $C_{17}H_{14}N_2O$: C, 77.84; H, 5.38; N, 10.68. Found: C, 77.76; H, 5.35; N, 10.60.

5-Acetyl-2-methylthio-4-phenylpyrimidine phenylhydrazone (11).

A mixture of 6 (1.22 g, 5 mmol) and phenylhydrazine (2.16 g, 20 mmol) in ethanol (100 ml) containing conc. hydrochloric acid (2 drops) was stirred at room tempera-

ture for 18 h. After removal of the solvent in vacuo, water was added to the residue and the resulting mixture was extracted with ethyl acetate. The extract was worked up to yield a crystalline solid. Purification by column chromatography (silica gel/chloroform) gave 1.0 g (60%) of 11, mp 90°, Rf: 0.18 (silica gel/chloroform). ^{1}H-Nmr (DMSO-d_6): δ = 1.80 (s, 3H, CH_3), 2.60 (s, 3H, SCH_3), 7.0-7.6 (m, 10H, Ph), 8.70 (s, 1H, H-6), 9.25 (s, 1H exch. NH). Ms m/z: 334 (100, M^+), 287 (10), 91 (75), 77 (40). Anal. Calcd for $C_{19}H_{18}N_4S$: C, 68.24; H, 5.42; N, 16.75; S, 9.59. Found: C, 68.18; H, 5.45; N, 16.71; S, 9.71.

Transformation of 11 into 8.

A solution of 11 (0.7 g, 2 mmol), conc. hydrochloric acid (2 ml) and water (8 ml) in methanol (40 ml) was refluxed for 5 h. The reaction mixture was treated in the same manner as described for the preparation of 7. The crude product (0.5 g, 95%), whose ^{1}H-nmr spectrum was identical with that of 8 previously obtained from 6, was purified by column chromatography (silica gel/chloroform) to yield an analytical sample, mp 84°.

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