DIRECT SYNTHESIS OF 2-SUBSTITUTED 5-FORMYLPYRIMIDINES AND RING TRANSFORMATION OF THEIR PHENYLHYDRAZONES INTO 4-FORMYL-1-PHENYLPYRAZOLE

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Abstract —— Triformylmethane (1) reacted with benzamidine, guanidine and S-methylisothiourea to give 2-substituted 5-formylpyrimidines (**2a-c**), whose phenylhydrazones (**3a-c**) readily underwent ring transformation into 4-formyl-1-phenylpyrazole (**4**) on heating in acidic methanol.

Some amidinohydrazone derivatives exhibit good antitumor activities.[1] In continuation of our studies on amidinohydrazones of 4-acylpyrazoles and 5-acylpyrimidines,[2-5] we previously reported that the reaction of triacetylmethane with amidine derivatives did not lead to the expected 5-acyl-4,6-dimethylpyrimidines, but, due to the great susceptibility of triacetylmethane to hydrolysis, to different condensation products depending on the nucleophiles used. We observed, in contrast with triacetylmethane, that triformylmethane reacted with some amidine analogues to afford the expected 5-formylpyrimidines. We now wish to describe this direct synthesis of 2-substituted 5-formylpyrimidines and the ring transformation of their phenylhydrazones into 4-formyl-1-phenylpyrazole.

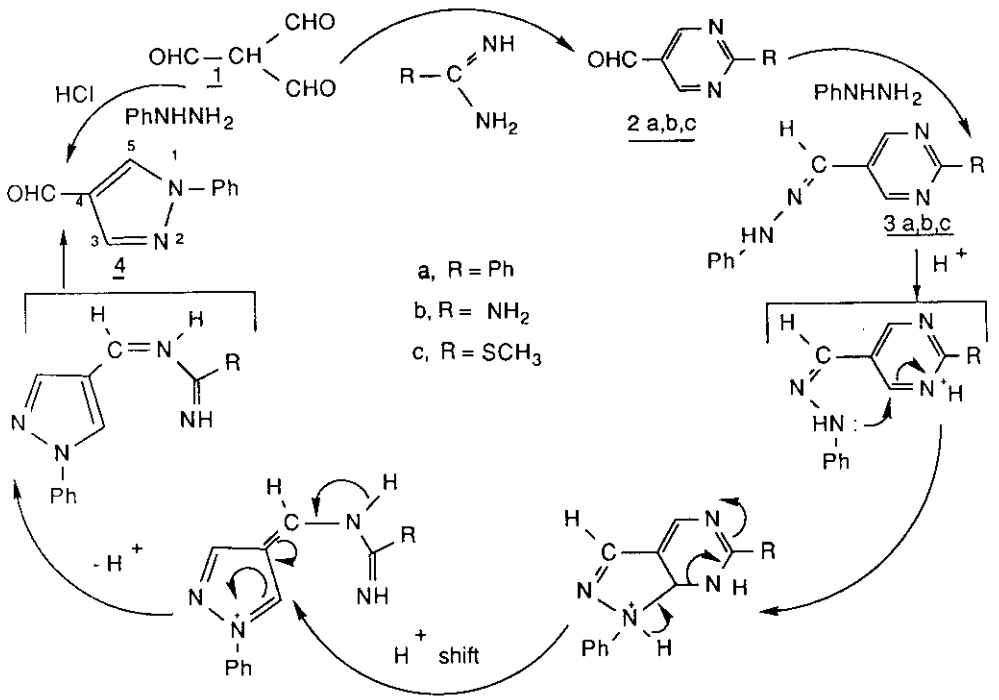
Treatment of triformylmethane (1) with an equimolecular amount of benzamidine, guanidine or S-methyl-isothiourea in boiling anhydrous ethanol for 20 h gave 2-substituted 5-formylpyrimidines (**2a-c**). The structural elucidation of these pyrimidines was based on elemental analysis and spectral data. Especially, in the ^{1}H-nmr spectra of **2a-c**, the signals due to the formyl proton (δ 9.63-10.25 ppm, s, 1H) as well as the signal assignable to C4 and C6 protons (δ 8.56-9.15 ppm, s, 2H) are quite characteristic. The ir spectra of **2a-c** showed absorption band at 1678-1705 cm^{-1} attributed to C=O stretching vibration.

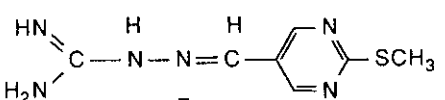
Similar reaction of 1 with formamidine and acetamidine did not afford the expected pyrimidine derivatives. Heating 1 with thiourea in anhydrous ethanol in the presence of sodium ethoxide or hydrochloric acid, resulted in the formation of degradation products. The fact that thiourea, which is usually a good agent for the formation of pyrimidines, did not lead to the expected pyrimidine, either in alkaline or acidic media, is very likely due to the ring instability of the type of

pyrimidine to which it should have led.[6]

Pyrimidines (2a-c) were readily converted to the corresponding phenylhydrazones (3a-c) by the usual method. When heated with hydrochloric acid in methanol, these phenylhydrazones underwent ring transformation into 4-formyl-1-phenylpyrazole (4)[7] which was directly obtained by reaction of 1 with phenylhydrazine in acidic methanol at room temperature. The mechanism of this ring contraction involves ring opening of the pyrimidine nucleus by nucleophilic attack of NH group of the phenylhydrazono moiety on 4- (or 6-) position of the pyrimidine ring. Previously, we reported analogous ring transformation of 5-acylpyrimidines into pyrazole derivatives by the action of some hydrazines without (always) isolating the hydrazone intermediates.[2-4,8] However, our attempts to directly transform pyrimidine (2c) into 4 by the reaction with an excess of phenylhydrazine in boiling acidic methanol was unsuccessful.

It is worth noting that 5-formyl-2-methylthiopyrimidine amidinohydrazone (5), prepared by conden-





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sation of 2c with aminoguanidine in acidic methanol, did not undergo ring transformation into pyrazole derivative on heating in methanol in the presence of hydrochloric acid. We recovered in this case the starting hydrazone. Such difference of reactivity between amidinohydrazones and phenylhydrazones of 5-acylpyrimidines have already been pointed out.[4]

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.

2-Substituted 5-Formylpyrimidines (2a-c).

To an ethanolic sodium ethoxide solution (50 mg of sodium in 25 ml of anhydrous ethanol) were added benzamidine hydrochloride (0.38 g, 2.4 mmol) and 1[9] (0.2 g, 2.0 mmol). The mixture was stirred at room temperature for 1 h, and then refluxed for 20 h. After evaporation of the solvent, the residue was treated with water (20 ml). The mixture was made acidic (pH 1) by addition of hydrochloric acid, and extracted with ethyl acetate. The extract was washed with water, dried ($MgSO_4$) and concentrated to yield **2a** which was cristallised in cyclohexane. In the same manner by using guanidine hydrochloride or S-methylisothiourea hydroiodide in place of benzamidine hydrochloride, pyrimidine **2b** or **2c** was obtained (in the case of **2b**, after removal of the solvent from the reaction mixture, water was added to the residue and the resultant solution was made acidic by addition of hydrochloric acid and then neutralized with sodium hydrogencarbonate before extraction with ethyl acetate).

— **2a**, yield 0.22 g (60%), mp 131-132° (cyclohexane). ^{1}H-Nmr (DMSO-d_6): δ 7.2-7.6 (m, 3H, Ph), 8.1-8.5 (m, 2H, Ph), 9.15 (s, 2H, C4- and C6-H), 10.25 (s, 1H, CHO). Ms m/z: 184 (75, M^+), 155 (13), 104 (36), 103 (100), 77 (20), 76 (25). Ir (KBr): ν 1705 (C=O) cm^{-1}. Anal. Calcd for $C_{11}H_8N_2O$: C, 71.73; H, 4.38; N, 15.21. Found: C, 71.65; H, 4.56; N, 15.45.

— **2b**, yield 0.12 g (49%), mp 208-210° (benzene/ethanol). ^{1}H-Nmr (DMSO-d_6): δ 7.53 (br s, 2H, NH_2), 8.56 (s, 2H, C4- and C6-H), 9.63 (s, 1H, CHO). Ms m/z: 123 (100, M^+), 122 (88), 95 (25), 94 (38), 68 (38), 66 (39), 53 (48). Ir (KBr): ν 3287, 3181 (NH_2), 1678 (C=O) cm^{-1}. Anal. Calcd for $C_5H_5N_3O$: C, 48.78; H, 4.09; N, 34.13. Found: C, 48.85; H, 3.83; N, 34.44.

— **2c**, yield 0.1 g (33%), mp 83-84° (cyclohexane) (lit.[10] mp 84°).

Phenylhydrazones of 2-Substituted 4-Formylpyrimidines (3a-c).

A mixture of **2a**, **b** or **c** (1.0 mmol), phenylhydrazine (0.22 g, 2.0 mmol) and 2 drops of conc. hydrochloric acid in methanol (15 ml) was stirred at room temperature for 18 h. After evaporation of the solvent, the residue was treated with water (20 ml). The mixture was made acidic (in the case of **3b**, the resultant acidic solution was neutralized with sodium hydrogencarbonate) and extracted with ethyl acetate. The organic layer was washed with water, dried ($MgSO_4$) and concentrated to yield **3a**, **b** or **c**. The crude products, collected by filtration, washed with methanol and dried, were practically pure without further purification.

— **3a**, yield 0.24 g (88%), mp 225-226°. ^{1}H-Nmr (DMSO-d_6): 6.7-7.4 (m, 5H, Ph), 7.4-7.7 (m, 3H, Ph), 7.87 (s, 1H, -CH=), 8.2-8.5 (m, 2H, Ph), 9.07 (s, 2H, C4- and C6-H), 10.67 (s, 1H, NH). Ms m/z: 274 (14, M^+), 128 (9), 103 (50), 92 (71), 77 (64), 65 (100). Anal. Calcd for $C_{17}H_{14}N_4$: C, 74.43; H, 5.14; N, 20.46. Found: C, 74.56; H, 5.02; N, 20.19.

— **3b**, yield 0.11 g (51%), mp 240-242°. ^{1}H-Nmr (DMSO-d_6): 6.4-7.3 (m, 5H, Ph), 6.70 (s, 2H, NH_2), 7.67 (s, 1H, -CH=), 8.47 (s, 2H, C4- and C6-H), 10.00 (s, 1H, NH). Ms m/z: 213 (100, M^+), 172 (9), 96 (38), 92 (68), 83 (18), 77 (23), 65 (57). Anal. Calcd for $C_{11}H_{11}N_5$: C, 61.96; H, 5.20; N, 32.84. Found: C, 61.77; H, 5.03; N, 33.13.

— **3c**, yield 0.15 (61.5%), mp 189-190°. ^{1}H-Nmr (DMSO-d_6): 2.47 (s, 3H, CH_3), 6.5-7.2 (m, 5H, Ph), 7.57 (s, 1H, -CH=), 8.63 (s, 2H, C4- and C6-H), 10.5-10.8 (br, 1H, NH). Ms m/z: 244 (100, M^+), 124 (4), 96 (5), 92 (21), 77 (13), 65 (30). Anal. Calcd for $C_{12}H_{12}N_4S$: C, 58.99; H, 4.95; N, 22.93; S, 13.12. Found: C, 58.53; H, 4.89; N, 23.42; S, 13.06.

4-Formyl-1-phenylpyrazole (4).

A mixture of **1** (0.1 g, 1.0 mmol), phenylhydrazine (0.13 g, 1.2 mmol) and conc. hydrochloric acid (0.2 ml) in methanol (15 ml) was stirred at room temperature for 24 h. After removal of the solvent, the residue was treated with water (20 ml) and the mixture was extracted with ethyl acetate. The extract was washed with water, dried ($MgSO_4$) and evaporated to yield a crystalline solid. Recrystallization from cyclohexane gave **4** (0.11 g, 64%), mp 84-85° (lit.[7] mp 85°).

Transformation of 3a-c into 4.

A mixture of **3a**, **b** or **c** (0.5 mmol) and conc. hydrochloric acid (0.5 ml) in methanol (20 ml) was refluxed for 20 h. After removal of the solvent, the residue was treated in the same manner as described above to yield **4**, mp 85°, yields 43 mg (50%) from **3a**, 71 mg (83%) from **3b** and 61 mg (71%) from **3c**. The ^{1}H-Nmr spectra of the products were identical with that of **4** prepared from **1** and phenylhydrazine.

5-Formyl-2-methylthiopyrimidine Amidinohydrazone (5).

A mixture of 2c (0.46 g, 3 mmol), aminoguanidine hydrogencarbonate (0.5 g, 3.6 mmol) and conc. hydrochloric acid (1 ml) in methanol (20 ml) was stirred at room temperature for 5 h. After evaporation of the solvent under reduced pressure, a crystalline solid was collected by filtration, washed with ethanol and dried to yield 5 (0.63 g, 85%) which was practically pure, mp 263-264°. Recrystallization from ethanol gave an analytical sample. ^{1}H-Nmr (DMSO-d_6): δ 2.54 (s, 3H, CH_3), 7.85 (br s, 4H, exch.), 8.12 (s, 1H, -CH=), 9.04 (s, 2H, C4- and C6-H), 12.5 (br s, 1H, exch.). Ms m/z: 210 (80, M^+), 209 (78), 195 (7), 167 (14), 121 (13), 111 (9), 96 (68), 59 (21), 43 (100). Anal. Calcd for $C_7H_{10}N_6S$ HCl: C, 34.08; H, 4.49; N, 34.06; S, 12.99; Cl, 14.37. Found: C, 33.91; H, 4.68; N, 33.74; S, 12.48; Cl, 14.07.

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REFERENCES

1. a) E. Minich, "Antineoplastic and Immunosuppressive Agents. Part II", ed. by A.C. Sartorelli and D.G. Johns, Springer-Verlag, Berlin, Heidelberg, 1975, Chap. 71 and references cited therein. b) C.W. Porter, C.V. Dave, and E. Mihich, "Polyamine in Biology and Medicine", ed. by D.R. Morris and L.J. Marton, Mared Dekker, Inc, 1981, p. 407.
2. G. Menichi, J. Naciri, B. Kokel, and M. Hubert-Habart, Heterocycles, 1984, 22, 2013.
3. G. Menichi, M. Boutar, B. Kokel, K. Takagi, and M. Hubert-Habart, J. Heterocycl. Chem., 1986, 23, 275.
4. A. Bajnati, B. Kokel, and M. Hubert-Habart, Bull. Soc. Chim. France, 1987, 318.
5. A. Bajnati and M. Hubert-Habart, Bull. Soc. Chim. France, 1988, 540.
6. D.J. Brown, P.W. Ford, and M.N. Paddon-Row, J. Chem. Soc. (C), 1968, 1452.
7. Synthesis of 4 by oxidation of 4-chloromethyl-1-phenylpyrazole and the formylation of 1-phenylpyrazole has been reported, I. L. Finar and G. H. Lord, J. Chem. Soc., 1957, 3314, and references cited therein.
8. a) A. Bajnati, M. Hubert-Habart, K. Takagi, and H. Terada, Heterocycles, 1989, 29, 1583.
9. Z. Arnold, Coll. Czech. Chem. Commun., 1961, 26, 3051.
10. Pyrimidine (2c) has been prepared from 5-bromo-2-methylthiopyrimidine-4-carboxylic acid, J. Arukwe and K. Undheim, Acta Chem. Scand., 1986, B40, 588.

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