Acetylation and Cyclization Reactions of Some Imidazole Derivatives Containing 1,3-Dicarbonyl System

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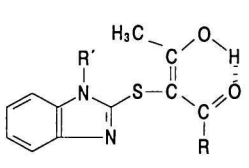
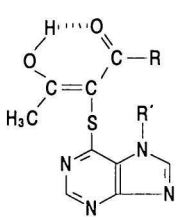
Reactions of benzimidazole as well as purine derivatives containing 1,3-pentanedione or ethyl 3-oxobutyrate moiety in their molecules with acetic anhydride were studied. *N*-Acetylation products and products of cyclization — imidazolothiazoles — were isolated and characterized by spectral methods. Under the reaction conditions used, no *O*-acetylation was observed.

It is known that 1-acetylimidazole as well as many of its ring-substituted derivatives may be obtained by dissolving the corresponding imidazole in excess acetic anhydride and evaporating the mixture *in vacuo* [1]. On the other hand, preparation of the enol acetates by the reaction of enol form of 1,3-dicarbonyl compounds with acetic anhydride requires much more drastic reaction conditions and the use of an acid catalyst or rather isopropenyl acetate in the presence of *p*-toluenesulfonic acid as an acetylating agent is used for this purpose [2]. This method also requires higher temperatures and longer reaction time. 1-Acylimidazoles are suitable substrates for nucleophilic attack [3]. With appropriate nucleophiles, under suitable reaction conditions, an intramolecular cyclization can occur giving rise to the interesting condensed heterocyclic compounds. In this respect, we have studied acetylation and cyclization reactions of some condensed imidazole derivatives containing 1,3-dicarbonyl grouping attached to the heterocycle through a sulfur atom.

Alkylation of 2-mercaptobenzimidazole with 3-chloro-2,4-pentanedione or ethyl 2-chloro-3-oxobutyrate gave corresponding 3-(2-benzimidazolylthio)-2,4-pentanedione (*I*) and ethyl 2-(2-benzimidazolylthio)-3-oxobutyrate (*II*), respectively. Analogically, starting from 6-mercaptopurine, 3-(6-purinylthio)-2,4-pentanedione (*III*) and ethyl 2-(6-purinylthio)-3-oxobutyrate (*IV*) were prepared. The absence of signal for H-2 proton of these β-diketones and β-keto esters in the ^{1}H NMR spectra as well as the ^{13}C NMR spectral data indicate the structure of corresponding enol form.

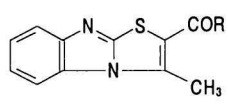
Reaction of compounds *I*—*IV* with acetic anhydride at 25 °C gave corresponding *N*-acetylated products *V*—*VIII* only. No *O*-acetylation was observed. Likewise as in the case of starting compounds *I*—*IV*, the structure of enol forms was assigned to these compounds on the basis of NMR spectral data. At higher temperature, reaction of *I* with acetic anhydride resulted in the formation of cyclic product *IX*. On the other hand, heating of *II* with acetic anhydride afforded dark brown reaction mixture which on TLC revealed the presence of acetyl derivative *VI*, product of cyclization *X* and two other, unidentified products (based on the mass spectral data probably polymers). Heating of *III* or *IV* with acetic anhydride resulted in the very fast browning of the reaction mixture. After chromatographical separation, product of acetylation *VII* (22 %) and very low yield (12 %) of the cyclization product *XI* were obtained. Preparation of the cyclization product *XII* starting from *IV* was unsuccessful. When *I* in ethanol in the presence of concentrated hydrochloric acid was heated under reflux for 4—5 h, cyclization product *IX* was obtained almost quantitatively while cyclization of *II* to *X* required the presence of concentrated sulfuric acid, much longer heating under reflux and purification of product by preparative TLC affording only low yield (24 %) of *X*.



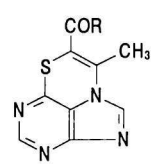


	R	R′
I	CH_3	H
II	OEt	H
V	CH_3	Ac
VI	OEt	Ac

	R	R′
III	CH_3	H
IV	OEt	H
VII	CH_3	Ac
VIII	OEt	Ac



IX R = CH_3
X R = OEt



XI R = CH_3
XII R = OEt

EXPERIMENTAL

Melting points were determined on a Kofler hot-stage and are uncorrected. Electron-impact mass spectra (70 eV) were recorded on a spectrometer JMS-100D (Jeol) at an emission current of 300 μA, applying direct sample-introduction technique. ^{1}H and ^{13}C NMR spectra were measured on a spectrometer AM-300 (Bruker) operating at 300.13 MHz or 75.46 MHz working frequencies with TMS as an internal standard. Elemental analyses were performed on a Perkin—Elmer 240 analyzer. The purity and identity of the prepared compounds were routinely checked by TLC on Silufol UV_{254} plates (Kavalier, Czech Republic). Preparative TLC was carried out using Merck Kieselgel 60 F_{254} plates (20 cm × 20 cm, 2 mm). In both cases, a mixture of chloroform—methanol (φ_r = 19 : 1) was used as an eluent.

3-(2-Benzimidazolylthio)-2,4-pentanedione (*I*)

To a stirred solution of sodium ethoxide (0.02 mol) in ethanol (75 cm^3), 2-mercaptobenzimidazole (0.02 mol) was added. After 15 min, 3-chloro-2,4-pentanedione (0.02 mol) was added dropwise and the reaction mixture was stirred for 30 min. Resulting suspension was poured into ice water (400 cm^3), the solid was filtered and recrystallized from methanol giving *I* (yield = 91 %), m.p. = 195 °C. For $C_{12}H_{12}N_2O_2S$ (M_r = 248.32) w_i(calc.): 58.04 % C, 4.88 % H, 11.28 % N; w_i(found): 58.11 % C, 4.90 % H, 11.25 % N. Mass spectrum, *m/z* (I_r/%): 248 (77, M$^+$), 205 (81), 163 (92), 43 (100). ^{1}H NMR spectrum (DMSO-d_6), δ: 17.35 (s, 1H, hydrogen-bonded proton of OH group), 7.22—7.53 (m, 4H, H_{arom}), 2.44 (s, 6H, 2 × CH_3). ^{13}C NMR spectrum (DMSO-d_6), δ: 197.8 (C=O), 150.1 (C-2), 121.7 (C-5 and C-6), 99.2 (C-3′), 24.6 (CH_3). Due to a great symmetry of the molecule as well as the fast rotation around the S—C bond, the signals of C-4 and C-7 atoms were registered at δ = 114.3 as a broad line and the signals of C-8 and C-9 atoms were missing in the spectrum.

Note: The above given procedure is general for the preparation of compounds *I—IV*. ^{1}H and ^{13}C NMR spectra are representative. The numbering of individual atoms reflects the rules for numbering of corresponding heterocycles. Positions of 1,3-dicarbonyl grouping are primed.

Compound *II*: M.p. = 156—157 °C. For $C_{13}H_{14}N_2O_3S$ (M_r = 278.35) w_i(calc.): 56.09 % C, 5.08 % H, 10.07 % N; w_i(found): 56.02 % C, 5.10 % H, 10.11 % N. Mass spectrum, *m/z* (I_r/%): 278 (86, M$^+$), 235 (71), 190 (75), 163 (92), 43 (100).

Compound *III*: M.p. = 171—172 °C. For $C_{10}H_{10}N_4O_2S$ (M_r = 250.24) w_i(calc.): 47.99 % C, 4.04 % H, 22.39 % N; w_i(found): 48.03 % C, 4.06 % H, 22.35 % N. Mass spectrum, *m/z* (I_r/%): 292 (38, M$^+$ − 1 + CH_3CO)*, 250 (46, M$^+$), 207 (84), 166 (57), 165 (54), 100 (49), 85 (42), 43 (100).

Compound *IV*: M.p. = 107—108 °C. For $C_{11}H_{12}N_4O_3S$ (M_r = 280.27) w_i(calc.): 47.14 % C, 4.32 % H, 20.00 % N; w_i(found): 47.17 % C, 4.35 % H, 20.04 % N. Mass spectrum, *m/z* (I_r/%): 322 (11, M$^+$ − 1 + CH_3CO)*, 280 (18, M$^+$), 248 (36), 207 (43), 134 (92), 43 (100). ^{1}H NMR spectrum ($CDCl_3$), δ: 13.97 (s, 1H, hydrogen-bonded proton of OH group), 8.75 (s, 1H, H-2), 8.30 (s, 1H, H-8), 5.93 (bs, 1H, NH), 4.23 (q, 2H, CH_2), 2.34 (s, 3H, CH_3), 1.18 (t, 3H, CH_3 of ethyl). ^{13}C NMR spectrum ($CDCl_3$), δ: 184.4 (C-3′), 172.7 (C-1′), 160.8 (C-6), 151.5 (C-2), 149.7 (C-4), 141.6 (C-8), 129.8 (C-5), 87.8 (C-2′), 61.5 (CH_2), 21.0 (CH_3), 14.0 (CH_3 of ethyl).

3-(1-Acetyl-2-benzimidazolylthio)-2,4-pentanedione (*V*)

A mixture of *I* (0.01 mol) and acetic anhydride (50 cm^3) was stirred at 25 °C for 5 h and then poured onto crushed ice (300 cm^3). After standing for 2 h with occasional stirring, the solid product was filtered off, dried *in vacuo* over KOH and recrystallized from EtOAc—hexane affording *V* (yield = 84 %), m.p. = 157—158 °C. For $C_{14}H_{14}N_2O_3S$ (M_r = 290.36) w_i(calc.): 57.91 % C, 4.87 % H, 9.65 % N; w_i(found): 57.86 % C, 4.90 % H, 9.67 % N. Mass spectrum, *m/z* (I_r/%): 290 (32, M$^+$), 247 (10), 230 (41), 205 (58), 163 (49), 43 (100).

Compounds *VI—VIII* were prepared by the same method. Reaction time (1—6 h) was monitored by TLC. The NMR data of *V—VIII* were essentially the same as for starting compounds *I—IV* excepting the signals of acetamido group observed at δ = 168.5 (C=O), 25.5 (CH_3), 3.00 (s, 3H, CH_3).

Compound *VI*: M.p. = 74—75 °C. For $C_{15}H_{16}N_2O_4S$ (M_r = 320.39) w_i(calc.): 56.23 % C, 5.04 % H, 8.75 % N; w_i(found): 56.27 % C, 5.06 % H, 8.78 % N. Mass spectrum, *m/z* (I_r/%): 320 (12, M$^+$), 277 (10), 260 (32), 235 (10), 163 (39), 43 (100).

Compound *VII*: M.p. = 126—127 °C. For $C_{12}H_{12}N_4O_3S$ (M_r = 292.28) w_i(calc.): 49.31 % C, 4.17 % H, 19.17 % N; w_i(found): 49.30 % C, 4.19 % H, 19.20 % N. Mass spectrum, *m/z* (I_r/%): 292 (13, M$^+$), 249 (14), 207 (36), 165 (30), 43 (100).

Compound *VIII*: M.p. = 101—102 °C. For $C_{13}H_{14}N_4O_4S$ (M_r = 322.31) w_i(calc.): 48.44 % C, 4.39 % H, 17.39 % N; w_i(found): 48.49 % C, 4.41 % H, 17.42 % N. Mass spectrum, *m/z* (I_r/%): 322 (8, M$^+$), 280 (13), 247 (19), 166 (24), 165 (26), 43 (100).

*Intramolecular migration of acetyl group or acetylation by the ketene molecule [4].

2-Acetyl-3-methylbenzo[*d*]imidazo[2,1-*b*]thiazole (*IX*)

Method A: A mixture of *I* (0.01 mol) and acetic anhydride (50 cm^3) was heated under reflux for 3 h. After cooling to room temperature, it was poured onto crushed ice (500 cm^3) and the separated product was filtered off, dried and recrystallized from hot ethanol giving yellowish needles of *IX* (yield = 88 %), m.p. = 164—165 °C. For $C_{12}H_{10}N_2OS$ (M_r = 230.30) w_i(calc.): 62.58 % C, 4.39 % H, 12.17 % N; w_i(found): 62.56 % C, 4.40 % H, 12.16 % N. Mass spectrum, *m/z* (I_r/%): 230 (100, M^+), 215 (73), 188 (11), 187 (13), 143 (49), 102 (22). ^{1}H NMR spectrum ($CDCl_3$), δ: 7.28—7.85 (m, 4H, H_{arom}), 3.12 (s, 3H, CH_3), 2.56 (s, 3H, CH_3CO). ^{13}C NMR spectrum ($CDCl_3$), δ: 190.6 (C=O), 154.3 (C-9a), 148.7 (C-4a), 137.3 (C-3), 130.2 (C-8a), 124.7 (C-6), 121.6 (C-7), 121.3 (C-2), 119.5 (C-5), 111.6 (C-8), 20.9 (CH_3 of acetyl), 14.0 (CH_3).

Method B: A mixture of *I* (5 mmol), ethanol (25 cm^3), and concentrated HCl (1.2 cm^3) was heated under reflux for 5 h. The solvent was evaporated under diminished pressure, water (25 cm^3) was added and the pH was adjusted to 9 using 5 % aqueous Na_2CO_3 solution. Separated solid was filtered off, washed with water, dried and recrystallized from ethanol affording *IX* (yield = 93 %).

2-Ethoxycarbonyl-3-methylbenzo[*d*]imidazo[2,1-*b*]thiazole (*X*)

Method A: A mixture of *II* (0.01 mol) and acetic anhydride (50 cm^3) was heated under reflux for 1 h, cooled to room temperature and poured onto crushed ice (500 cm^3). The separated dark oil was extracted with $CHCl_3$ and after usual work-up, the mixture of products was separated by the preparative TLC giving *X* (yield = 24 %, R_f = 0.7), m.p. = 125—126 °C. For $C_{13}H_{12}N_2O_2S$ (M_r = 260.33) w_i(calc.): 59.97 % C, 4.66 % H, 10.76 % N; w_i(found): 59.93 % C, 4.68 % H, 10.79 % N. Mass spectrum, *m/z* (I_r/%): 260 (100, M^+), 231 (82), 215 (12), 187 (10), 143 (56), 102 (32). ^{1}H NMR spectrum ($CDCl_3$), δ: 7.25—7.83 (m, 4H, H_{arom}), 3.38 (q, 2H, CH_2), 3.12 (s, 3H, CH_3), 1.42 (t, 3H, CH_3). ^{13}C NMR spectrum ($CDCl_3$), δ: 162.0 (C=O), 155.1 (C-9a), 148.8 (C-4a), 138.7 (C-3), 130.3 (C-8a), 124.4 (C-6), 121.4 (C-7), 121.3 (C-2), 119.4 (C-5), 111.3 (C-8), 61.7 (CH_2), 14.3 (CH_3), 13.4 (CH_3 of ethyl).

Method B: A mixture of *II* (5 mmol), ethanol (50 cm^3), concentrated HCl (1 cm^3), and concentrated H_2SO_4 (1 cm^3) was heated under reflux for 48 h. After cooling, the acids were neutralized with 5 % aqueous Na_2CO_3 solution, ethanol was evaporated and the product was extracted with $CHCl_3$. Preparative TLC afforded *X* (yield = 24 %).

2-Acetyl-3-methyl-4*H*-1,4-thiazino[6,5,4-*d*,*e*]purine (*XI*)

Starting from *III* using the above given method *A* (acetic anhydride, reflux for 1 h) followed by preparative TLC, *XI* (yield = 12 %) was obtained, m.p. = 92—93 °C. For $C_{10}H_8N_4OS$ (M_r = 232.28) w_i(calc.): 51.70 % C, 3.48 % H, 24.13 % N; w_i(found): 51.73 % C, 3.49 % H, 24.10 % N. Mass spectrum, *m/z* (I_r/%): 232 (100, M^+), 217 (78), 189 (21), 165 (12), 43 (24). ^{1}H NMR spectrum ($CDCl_3$), δ: 8.76 (s, 1H, H-2), 8.33 (s, 1H, H-8), 3.07 (s, 3H, CH_3), 2.59 (s, 3H, CH_3CO). ^{13}C NMR spectrum ($CDCl_3$), δ: 190.1 (C=O), 158.9, 151.3, 149.8, 141.8 (C-6, C-2, C-4, C-8, C-5 of the purine ring), 136.5, 122.2 (C-3 and C-2 of the thiazine ring), 20.7 (CH_3CO), 14.3 (CH_3).

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REFERENCES

1. Reddy, G. S., Mandell, L., and Goldstein, J. H., *J. Chem. Soc. 1963*, 1414.
2. Filler, R. and Naqvi, S. M., *Tetrahedron 19*, 979 (1963).
3. Theobald, R. S., in *Rodd's Chemistry of Carbon Compounds*, Vol. *IV*^{c}. (Ansell, M. F., Editor.) P. 141. Elsevier, New York, 1986.
4. Kováčik, V., Petráková, E., Mihálov, V., Tvaroška, I., and Heerma, W., *Biomed. Mass Spectrom. 12*, 49 (1985).

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