PREPARATION OF 2,4-IMIDAZOLIDINEDIONES (HYDANTOINS) FROM α-KETO HEMITHIOACETAL AND UREAS

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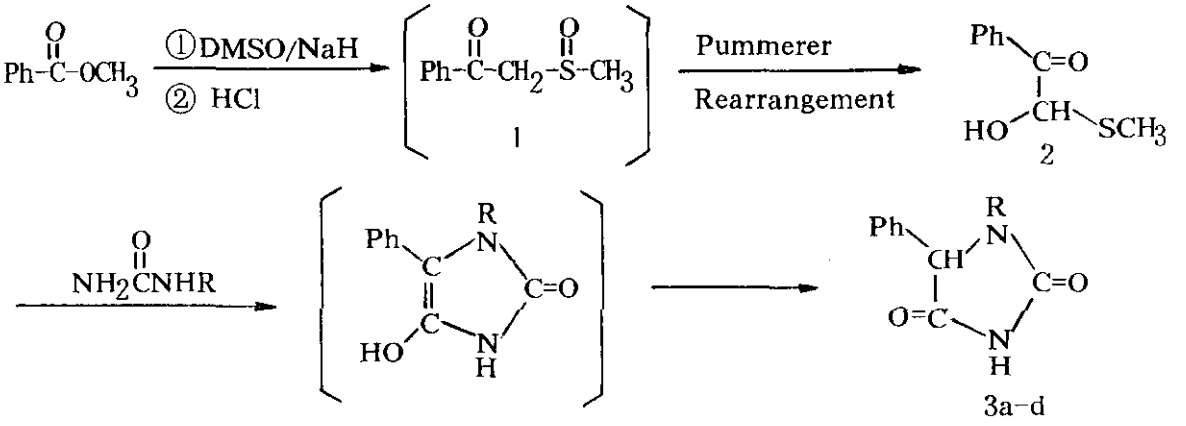
Abstract - 5-Phenyl-2,4-imidazolidinedione (**3a**) and 1-aryl-5-phenyl-2,4-imidazolidinediones (**3b-d**) have been synthesized from α-keto hemithioacetal and urea or arylureas.

Although thioacetals have been enough studied and applied in organic synthesis, [1] hemithioacetals have seldom been investigated. In our investigation of hemithioacetals, we discovered that α-keto hemithioacetals are quite stable and they have two electrophilic sites which can react with a difunctional group to form a heterocyclic ring. Here, we wish to report a reaction of α-benzoylhemithioacetal (**2**) and ureas to form 2, 4-imidazolidinediones (hydantoins) (**3a-d**), which are used in medicine because of a variety of bioactive activities.[2-3]

α-Benzoylhemithioacetal (**2**) can be simply prepared by the reaction of methyl benzoate and DMSO in the presence of sodium hydride, followed by acidification to pH≈1 to give β-keto sulfoxide (**1**), which further rearranged to α–benzoyl-hemithioacetal (**2**) by Pummerer rearrangement. [4-5] Compound (**2**) can react with urea and arylureas in slightly acidic medium to give 65-75% yield of 2, 4-imidazolidinediones (**3a-d**). The synthetic route is shown as follows.



3a: R=H; 3b: R=Ph; 3c: R=*p*-$CH_3C_6H_4$; 3d: R=*p*-$C_2H_5OC_6H_4$

The structures of **3a-d** are confirmed by their ir, ^{1}H nmr, ms spectra and elemental analyses. Their ir spectra show two absorption bands of the carbonyl group(C=O) at 1800-1700 cm^{-1}. [6-7] Mass spectral studies agree with their molecular weight, *viz.*, M^+ of **3a-d** at 176(41), 252(84), 266(97), 296(89). The localization of substituents in the 2,4-imidazolidinedione (hydantoin) ring is based on the ^{1}H nmr data and the acidity of NH.The N_3-H of hydantoins show weak acidity, however, the N_1-H of hydantoins show no measurable acidity. [2,9] On the other hand, the N_3-H signals appear at more down field than N_1-H in the ^{1}H nmr, because of there are two carbonyl groups adjacent to N_3-H. [8] The ^{1}H nmr spectrum of **3a** shows two single peaks at the 11.0 and 8.4 ppm of which the former corresponds to N_3-H (-CONHCO-), the latter to N_1-H(-CONH-). The C_5-H peak appears at 5.2 ppm and the multiple peak(7.3-7.6 ppm) can be attributed to the protons of benzene ring. [8] The ^{1}H nmr spectrum of **3b** shows only one peak for NH at 11.3 ppm, which corresponds to N_3-H. The N_1-H peak (8.4 ppm) disappears because of phenyl-substituted the hydrogen of N_1-atom. The C_5-H and the protons of benzene ring peaks appear at 5.9 and 7.0-7.5 ppm, respectively. [6-7] Furthermore, compound **3b** can be dissolved in 5% sodium hydroxide, it means the presence of acidic proton, *viz.*, N_3-H. So the strcture of **3b** is 1,5-diphenyl-2,4-imidazolidinedione. The ^{1}H nmr spectra of **3c-d** are similar to **3b** and can be dissolved in 5% sodium hydroxide, so we can conclude that **3c-d** are 1-aryl-5-phenyl-2,4-imidazolidinediones.

EXPERIMENTAL

Melting points were determined with an Electrothermal Eng. Ltd. Digital Melting Point apparatus and are uncorrected. The elemental analyses for C. H. N were performed by a Carlo Erba 1106 elemental analyser. The infrared spectra were recorded on a Mattson Alpha-Centauri FT-IR spectrophotometer, the ^{1}H nmr spectra were recorded on a Broker 300 spectrometer in DMSO-d_6 or $CDCl_3$ using TMS as an internal standard. The mass spectra were determined with a VG-ZAB-HS mass spectrometer.

Preparation of α-benzoylhemithioacetal (2)

A dry 500 ml three-necked flask was fitted with a mechanical stirrer, a pressure-equalizing addition funnel and a mineral oil bubble trap which served to close the system to the atmosphere. 80% Sodium hydride (5.4 g, 0.18 mol) and dry DMSO (240 ml) were placed in the flask in a nitrogen atmosphere and the mixture was stirred with heating at 60-65°C for 2-2.5 h until sodium hydride had dissolved and no bubble produced. After cooling the mixture to 15 °C, methyl benzoate (20 ml, 0.16 mol) was added dropwise and the mixture was allowed to react for 1-1.5 h at room temperature. Then the mixture was dissolved in 400 ml of cold water, the aqueous solution was extracted with ether for three times, then acidified to pH=1 by addition of concentrated hydrochloric acid, and allowed to stand

at room temperature for 48 h, the white precipitate was formed. Then, filtered, the precipitate was washed with water and dried to give α-benzoylhemithioacetal (**2**) (23.3 g, 80%), mp 100-101°C (recrystallized from anhydrous ethanol) (cf lit., [4] 104-106°C).

Preparation of 5-phenyl-2,4-imidazolidinedione (3a) and 1-aryl-5-phenyl-2,4-imidazolidinediones (3b-d); General procedure:

α-Benzoylhemithioacetal (**2**) (3 mmol) and urea or arylurea (4 mmol) were dissolved in EtOH/H_2O (1:1) (15 ml), and acetic acid (1 ml) were added into 50 ml three-necked flask. The mixture was refluxed for 8 h and cooled. A precipitate was filtered and recrystallized from 95% ethanol to give compounds (**3a-d**).

5-Phenyl-2,4-imidazolidinedione (3a):

3a was obtained in 74% yield, mp 180-181°C (cf lit., [10] 183-185°C).

1,5-Diphenyl-2,4-imidazolidinedione (3b)

3b was obtained in 69% yield, mp 208-210 °C(cf lit., [11] 205-206°C).

5-Phenyl-1-*p*-tolyl-2,4-imidazolidinedione (3c):

3c was obtained in 65% yield, mp 192-194°C. Ir (KBr) : ν 3400, 3200, 1780, 1720, 1520, 1400 cm^{-1}. ^1H Nmr(DMSO-d_6/TMS) : δ 11.3 (s, 1H, -CONHCO-), 7.0-7.5 (m, 9H, C_6H_4 and C_6H_5), 5.8 (s, 1H, -COCH-), 2.2 (s, 3H, CH_3) ppm. Ms: m/z (rel. int. %) 266(M^+, 97), 237(2), 195(40), 194(86), 152(3.4), 132(12), 119(23), 91(71), 65(31), 51(9). Anal. Calcd for $C_{16}H_{14}N_2O_2$: C, 72.18; H, 5.26; N,10.53. Found: C, 72.12; H, 5.23; N, 10.53.

1-*p*-Ethoxyphenyl-5-phenyl-2, 4-imidazolidinedione (3d):

3d was obtained in 71% yield, mp 130-131°C. Ir (KBr): ν 3450, 3200, 1780, 1720, 1520, 1410 cm^{-1}. ^1H Nmr(DMSO-d_6/TMS): δ 11.3(s, 1H, -CONHCO-), 7.0-7.5(m, 9H, C_6H_4 and C_6H_5), 5.9 (s, 1H, -COCH-), 4.1 (q, J=6.90 Hz, 2H, CH_2), 1.3 (t, J=6.90 Hz, 3H, CH_3) ppm. Ms: m/z (rel. int. %) 296(M^+, 89), 268(20), 225(12), 197(56), 196(100), 167(18), 141(16), 115(5), 89(5). Anal. Calcd for $C_{17}H_{16}N_2O_3$: C, 68.92; H, 5.41; N, 9.46. Found: C, 68.85; H, 5.41; N, 9.42.

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