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NMR spectroscopic characterization of keto–enol equilibria of 1, 3-dimethyl-5-((4, 4-dimethyl-2,6-dioxocyclohexyl)(aryl)methyl)pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione in solution phase

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Abstract: The 1:1 adducts of dimedone with 1, 3-dimethylbenzylidene barbituric gives pyrimidine derivatives that have quite different tautomeric structure in different solution. 1,3-dimethyl-5-((4,4-dimethyl-2,6-dioxocyclohexyl)(phenyl)methyl) pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione exists as keto-form in polar media like DMSO, while in low polar media like chloroform presents as dienol form.

Keywords: NMR study, Tautomerism, Enol-Keto form, Dimedone, N, N-dimethylarylidene barbituric acid.

Introduction

The presence of β-dicarbonyl groups separated by a methylene group causes the occurrence of keto–enol tautomerism. Research on β-diketones has been one of the most interesting topics in chemistry, particularly in terms of studying their keto–enol tautomerism, isomerization between the two forms, structures of both diketo- and keto-enolic forms, and the intramolecular hydrogen bonding formed by the enolic structure [1-4]. Main influencing factors on keto-enol equilibria have been determined as solvent polarity, substitution groups, and environmental motivation, e.g. pH values and UV light irradiation [5-7]. The photo-induced ketonization of β-diketones generally occurs after UV irradiation. This procedure can be done in the form of cis-enol in darkness [8]. The keto–enol tautomerism has been widely investigated by various spectroscopic and spectrometric methods such as IR, Raman, NMR, UV, electron energy-loss, and mass spectra [9-12]. Pitucha et al. experimentally and theoretically investigated the keto–enol tautomerism of substituted triazol derivatives [13].

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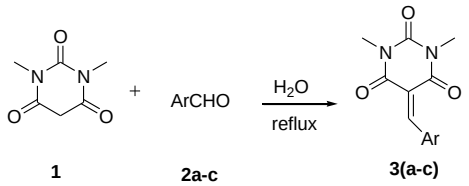
X-ray crystallographic structures of keto–enol tautomers and their H-bonding effects were studied by Glli et al. [14, 15]. Synthesis and investigation of the keto–enol tautomeric equilibrium of long-chain β-diketone compounds were also introduced by Kenar et. al. [16].

Dimedone, also known as 5, 5-dimethylcyclohexane-1, 3-dione, methone, or 5, 5-dimethyl dihydroresorcinol, belongs to the cyclic β-dicarbonyl compounds as a very important class of organic compounds. Many practical implementation of 1, 3-dicarbonyl compound is it's distinguished feature. For example, synthesis of numerous xanthene derivatives, hetero, and spiroketal compounds with their industrial and synthetic applications and as a reagent for various analytical determinations [17-20]. Like other β-diketones, dimedone can exist as an enol–keto tautomerism. However, as distinct from acyclic 1, 3-diketones, the enol form of dimedone cannot be stabilized by the intramolecular hydrogen bond. In the solid state, dimedone exists in the enolic form and these molecules pack in the crystalline'systems of infinite chains linked together by hydrogen bonds in the *y* direction [21, 22]. The ^{1}H and ^{13}C NMR spectra

of dimedone solutions indicate that, in non-polar or low-polar solvents like chloroform, this compound appears in the diketo- rather than mono-enol forms [23]. In spite of the existence of a wide variety of dimedone, its adducts with *N*, *N*-dimethyl-arylidene-barbituric acid are unknown.

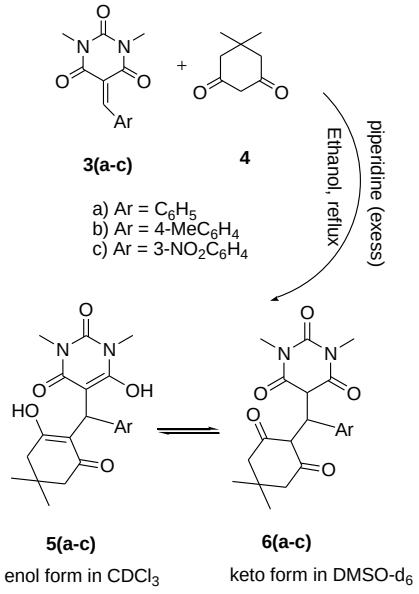
Results and discussion

N, *N*-dimethylarylidene barbituric acids **3a-c** were obtained from the reaction of aromatic aldehydes **2a-c** with *N*, *N*-dimethy barbituric acid **1** in water at reflux temperature (Scheme **1**) [17].



Scheme 1: Synthesis of *N*, *N*-dimethylarylidene barbituric acid

The reaction of *N*, *N*-dimethylarylidene barbiturics **3a-c** with two equivalent of dimedone **4** and piperidine (excess) in ethanol furnished 6-hydroxy-5-((2-hydroxy-4,4-dimethyl-6-oxocyclohex-1-enyl)(aryl)methyl)-1,3-dimethyl pyrimidine-2,4(1H,3H)-dione derivatives **5a-c** (Scheme **2**).



Scheme 2: Keto–enol equilibria of pyrimidine derivatives in solution phase

The IR spectrum of dimethylpyrimidine-dione derivatives show strong absorptions at 2300-3400 due to presence of an enol group. The ^{1}H NMR spectrum of **5c** in $CDCl_3$ (Fig. 1) contains two OH signals (a narrow singlet at 12.79 (H_c) ppm belonging to the OH on the side of the aryl substituent and a very broad one at 9.85 (H_a) ppm which disappeared in D_2O), two doublets at 7.47 and 8.02 ppm and a multiplet at 8.07-8.10 ppm for aromatic hydrogenes, a singlet at 5.58 ppm (H_b), two singlets of CH_3-N at 3.36 and 3.46 ppm, a multiplet for CH_2 at 2.17-2.56 ppm and two singlets for CH_3 at 1.26 and 1.13 ppm, which proves the dienolic structure of **5c**. No other tautomers are observed. Quite different spectral pattern is observed for these compounds in DMSO-d_6 (Fig. 2). According to ^{1}H and ^{13}C NMR, these are in keto-form **(6a-c)**. The keto-form structure of **6c** is confirmed by the presence of two CH doublets (4.52 (H_c) and 4.87 (H_a) ppm), a multiplet for CH proton (H_b) in **6c** at 3.10 ppm and elimination of OH proton.

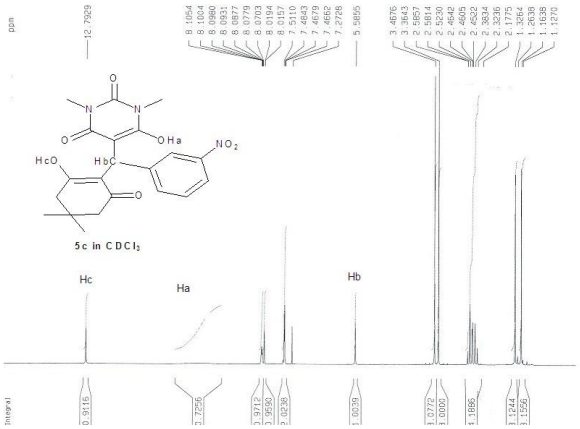


Figure 1: ^{1}H NMR spectrum of **5c** in $CDCl_3$.

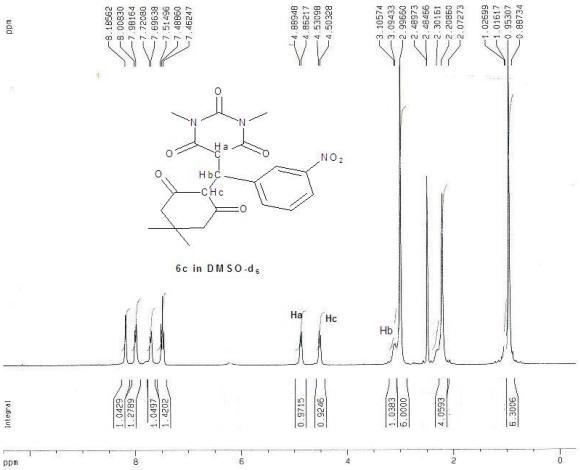
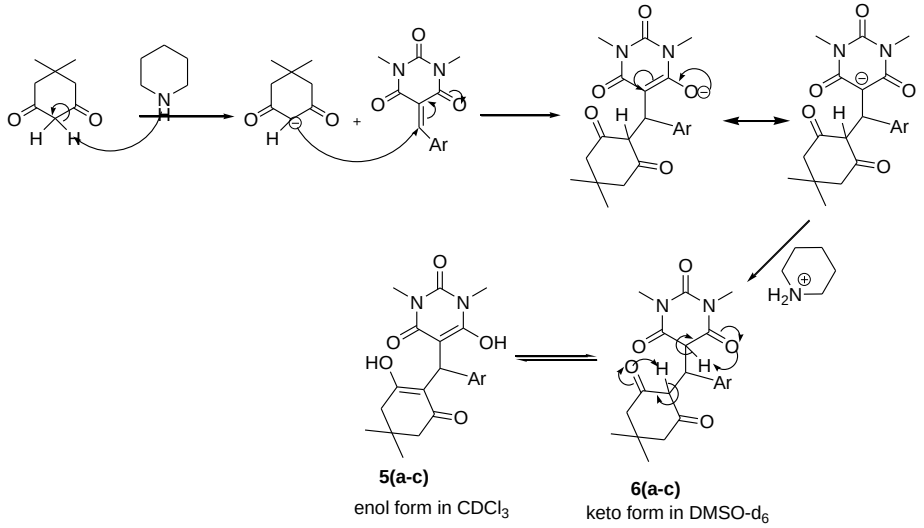


Figure 2: ^{1}H NMR spectrum of **6c** in DMSO-d_6.

^{13}C NMR spectrum of **5c** in $CDCl_3$ exhibited 21distinct resonances in agreement with the enol structure which reduce to 16 distinct resonances in DMSO-d_6 in agreement with the keto-form (**6c**) with

more symmetry. The ^{13}C NMR spectra of compounds **6a-c** do not show the ketone groups, which are expected to appear at about 190-200 ppm. Partial assignments of these resonances are given in the experimental section. A proposed mechanism for this tautomerism described in scheme **3**.



Scheme 3: Proposed mechanism for keto–enol equilibria

Conclusion

In conclusion, addition of dimedone to 1, 3-dimethylbenzylidene barbituric produce pyrimidin derivatices in good yeilds. On the basis of experimental and NMR study the keto–enol tautomerism of β-diketones in these products can be affected by solvent polarity. There is only keto–form in polar solvent shuch as DMSO-d_6, while in less polar media like chloroform exists in enol-form.

Experimental

General procedure for the synthesis of N, N-dimethylarylidene barbituric acid:

In a round-bottomed flask the selected aldehyde (6 mmol) and *N, N*-dimethyl barbituric acid (6 mmol) in water (20 ml) were heated at reflux under stirring for 5-8 h. Then the reaction mixture was cooled and filtered on Büchner funnel. The products were purified, if necessary, by washing with hot water (yield 90%).

General procedure for the preparation of 5-((aryl)(2-hydroxy-6-oxocyclohex-1-enyl)methyl)-6-hydroxy-1,3-dimethylpyrimidine-2,4(1H,3H)-dione:

Piperidine was added dropwise to a solution of *N, N*-dimethylarylidene barbituric acid (2 mmol) and dimedone (4 mmol) in absolute ethanol (15 ml) at room temperature. The reaction mixture was refluxed until the disappearance of the starting material (4-6 h), (monitored by TLC), solvent was evaporated and was diluted with H_2SO_4 (10%) (15 ml), precipitated solid product was recrystallized from water/acetone and identified by spectroscopic data.

*6-Hydroxy-5-((2-hydroxy-6-oxocyclohex-1-enyl)(phenyl)methyl)-1,3-dimethylpyrimidine-2,4(1H,3H)-dione (**5a**):*

Yield 70%. Mp 186-188 °C. IR (KBr, cm^{-1}) 2200-3383, 1700, 1631, 1616. ^1H NMR (300 MHz, $CDCl_3$) δ:ppm 1.15 (s, 3H, Me), 1.28 (s, 3H, Me), 2.30-2.54 (m, 4H, $2CH_2$), 3.36 (s, 3H, N-Me), 3.45 (s, 3H, N-Me), 5.58 (s, 1H, CH), 7.12-7.33 (m, 5H, aryl), 10.6 (broad, 1H, OH), 12.85 (s, 1H, OH). ^{13}C NMR (75 MHz, $CDCl_3$) δ: ppm 27.1, 28.9, 29.2, 29.7, 31.12, 33.6, 45.7, 47.0, 92.4, 116.4, 126.2, 126.5, 128.3, 137.2, 150.7, 162.3, 164.2, 190.6, 191.5. MS: m/z (%) = 384 (M^+, 68), 263 (8), 243 (26), 227 (100), 171 (14), 156 (22), 129 (12), 116 (19), 102 (27), 83 (13), 71 (9), 55 (14), 42 (33). Anal. Calcd for $C_{21}H_{24}N_2O_5$: C, 65.61; H, 6.29; N, 7.29. Found: C, 65.71; H, 6.32; N, 7.08.

*Keto-form (**6a**):* ^1H NMR (300 MHz, DMSO-d_6) δ:ppm 0.93 (s, 6H, 2Me), 2.17 (s, 4H, $2CH_2$), 2.96 (s, 3H, N-Me), 3.98 (s, 3H, N-Me), 3.12 (broad, 1H, CH), 4.45 (d, *J* = 9.2 Hz, 1H, CH), 4.68 (d, , *J* = 9.2 Hz, 1H, CH), 7.02-7.29 (m, 5H, aryl). ^{13}C NMR (75 MHz, DMSO-d_6) δ:ppm 27.7, 28.0, 31.4, 40.33, 43.3, 46.5, 52.1, 111.6, 125.9, 127.4, 128.6, 140.6, 152.1, 167.8, 168.4.

6-Hydroxy-5-((2-hydroxy-6-oxocyclohex-1-enyl)(p-tolyl)methyl)-1,3-dimethylpyrimidine-2,4(1H,3H)-dione ***5b****:*

Yield 68%. Mp 176-179 °C. IR (KBr, cm^{-1}) 2200-3200, 1703, 1604. ^{1}H NMR (300 MHz, $CDCl_3$) δ:ppm 1.10 (s, 3H, Me), 1.27 (s, 3H, Me), 2.32 (s, 3H, Me-aryl), 2.34-2.53 (m, 4H, $2CH_2$), 3.35 (s, 3H, N-Me), 3.44 (s, 3H, N-Me), 5.53 (s, 1H, CH), 7.01 (d, *J* = 7.7 Hz, 2H, aryl) 7.10 (d, *J* = 8.1 Hz, 2H, aryl), 10.99 (broad, 1H, OH), 12.83 (s, 1H, OH). ^{13}C NMR (75 MHz, $CDCl_3$) δ:ppm 20.9, 27.1, 28.8, 29.2, 29.9, 31.2, 33.2, 46.9, 50.7, 92.5, 116.5, 126.4, 129.0, 133.9, 135.6, 150.7, 162.3, 164.1, 190.7, 191.4. MS: m/z (%) = 398 (M^+, 6), 364 (17), 349 (12), 273 (21), 257 (18), 241 (25), 227 (100), 171 (21), 156 (30), 129 (14), 115 (49), 97 (17), 83 (29), 69 (46), 57 (30), 43 (39). Anal. Calcd for $C_{22}H_{26}N_2O_5$: C, 66.32; H, 6.58; N, 7.03. Found: C, 65.99; H, 6.58; N, 7.03.

*Keto-form (****6b****):* ^{1}H NMR (300 MHz, DMSO-d_6) δ:ppm 0.93 (s, 6H, 2Me), 2.15-2.18 (m, 4H, $2CH_2$), 2.24 (s, 3H, Me-aryl), 2.95 (s, 3H, N-Me), 3.97 (s, 3H, N-Me), 3.15 (broad, 1H, CH), 4.42 (d, *J* = 9.5 Hz, 1H, CH), 4.68 (d, *J* = 9.5 Hz, 1H, CH), 6.97 (d, *J* = 7.8 Hz, 2H, aryl) 7.15 (d, *J* = 7.8 Hz, 2H, aryl). ^{13}C NMR (75 MHz, DMSO-d_6) δ:ppm 24.3, 27.6, 28.1, 31.5, 40.32, 43.4, 46.5, 52.2, 111.7, 125.9, 126.2, 126.6, 137.2, 151.2, 166.8, 167.3.

6-Hydroxy-5-((2-hydroxy-6-oxocyclohex-1-enyl)(3-nitrophenyl)methyl)-1,3-dimethylpyrimi-dine-2,4(1H,3H)-dione ***5c****:*

Yield 59%. Mp 170-172 °C. IR (KBr, cm^{-1}) 2200-3392, 1703, 1609. ^{1}H NMR ($CDCl_3$) δ:ppm 1.13 (s, 3H, Me), 1.26 (s, 3H, Me), 2.17-2.56 (m, 4H, $2CH_2$), 3.36 (s, 3H, N-Me), 3.46 (s, 3H, N-Me), 5.58 (s, 1H, CH), 7.47 (d, *J* = 4.53 Hz, 2H, aryl), 8.02 (d, *J* = 1.12 Hz, 1H, aryl), 8.09 (m, 1H, aryl), 9.85 (broad, 1H, OH), 12.79 (s, 1H, OH). ^{13}C NMR ($CDCl_3$) δ:ppm 27.0, 28.9, 29.3, 29.9, 31.2, 33.72, 46.1, 46.9, 91.5, 115.7, 121.4, 122.4, 129.2, 132.7, 139.9, 148.5, 150.5, 162.4, 164.2, 191.4, 191.6. MS: m/z (%) = 429 (M^+, 11), 378 (11), 289 (27), 273 (60), 256 (100), 242 (15), 226 (44), 189 (19), 156 (61), 129 (29), 115 (28), 101 (37), 69 (21), 55 (43), 42 (89). Anal. Calcd for $C_{21}H_{23}N_3O_7$: C, 58.71; H, 5.40; N, 9.79. Found: C, 58.94; H, 5.41; N, 9.56.

*Keto-form (****6c****)*: ^{1}H NMR (300 MHz, DMSO-d_6) δ:ppm 0.95 (s, 6H, 2Me), 2.20 (s, 4H, $2CH_2$), 2.99 (s, 6H, 2N-Me), 3.10 (m, 1H, CH), 4.52 (d, *J* = 8.3 Hz, 1H, CH), 4.87 (d, *J* = 8.3 Hz, 1H, CH), 7.48 (t, *J* = 7.9 Hz, 1H, aryl), 7.71 (d, *J* = 7.3 Hz, 1H, aryl), 7.99 (d, *J* = 8.0 Hz, 1H, aryl), 8.11 (s, 1H, aryl), ^{13}C NMR (75 MHz, DMSO-d_6) δ:ppm 27.7, 27.9, 28.0, 31.5, 41.5, 51.3, 110.4, 121.0, 123.4, 128.9, 135.6, 143.6, 147.2, 151.9, 167.4, 168.0.

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