

The Synthesis of 3-Acetyl-2-(4,4-dimethyl-2,6-dioxocyclohexyl)-1-phenylpentanedione-1,4 and its Reactions with N-Nucleophiles

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Abstract

The respective adduct **3** has been prepared by condensation of dimedone **1** with 1,1-diacetyl-2-benzoyl-ethylene **2**. Its reactions with primary amines give the pyrroles **5a,b**, reaction with ammonium acetate gives the derivative of pyrrolo[3,4-c]quinoline **4**. The derivative of pyridazine **6** has been prepared by reaction with hydrazine hydrate. The enamine of dimedone **7** reacts with 1,1-diacetyl-2-benzoyl-ethylene **2** to give hexahydroquinoline **8**.

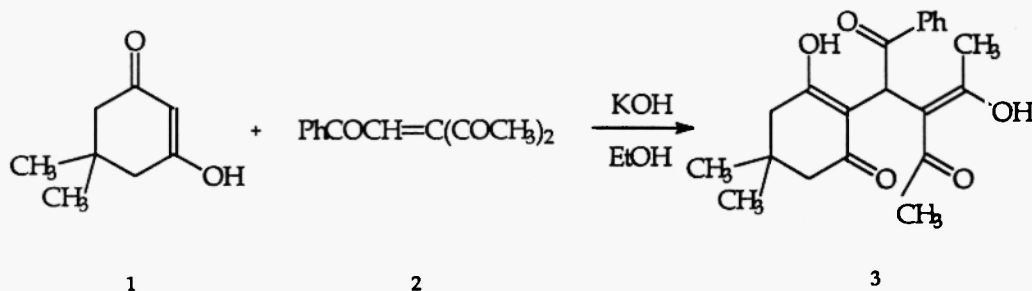
Introduction

It has been shown in the last reports that dimedone **1** and disubstituted ethylenes such as 1,2-dibenzoyl-ethylene and β -benzoylacrylic acid gave the respective adducts under Michael reaction conditions (1,2). The reactions of these adducts with different N-nucleophiles have also been observed (1-3). Michael addition product of dimedone **1** and 1,2-dibenzoyl-ethylene gives the derivatives of pyrrole with ammonia and primary amines (2), whereas the adduct of dimedone **1** and β -benzoylacrylic acid gives the derivatives of quinoline with the same nucleophiles (3) and pyrrolo[4,3,2-d,e]quinoline with ammonia (1).

In the present report we spread the above-mentioned scheme of Michael reaction to the trisubstituted ethylene, 1,1-diacetyl-2-benzoyl-ethylene **2**. The condensations with dimedone **1** and its enamine **7** have been carried out, the reactions of adduct **3** with ammonium acetate, methylamine, p-toluidine and hydrazine hydrate have been observed.

Results and discussion

The condensation of dimedone **1** with 1,1-diacetyl-2-benzoyl-ethylene **2** was carried out in ethanol in the presence of alkali to give **3**. The formation of a pentaketone is confirmed with



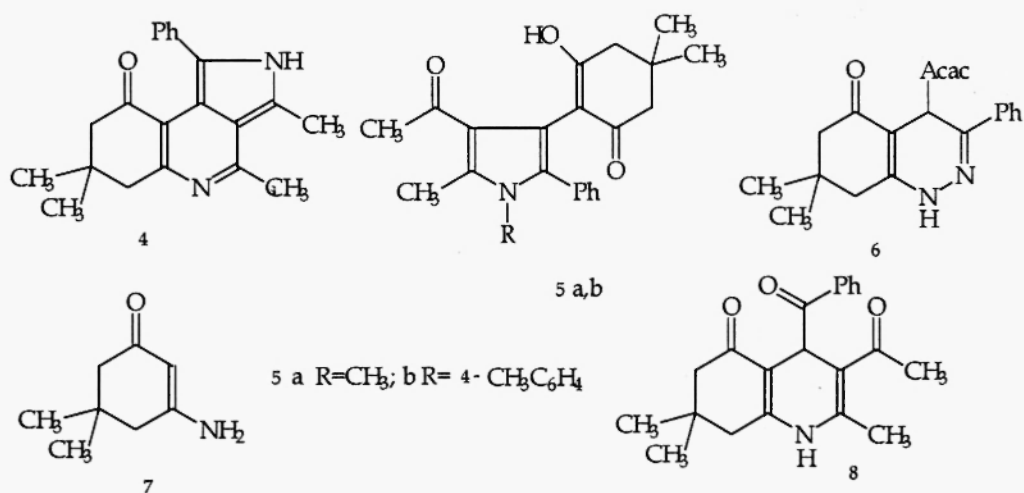
data of IR and ^1H NMR spectra.

Pyrrolo[3,4-c] quinoline **4** was prepared by reaction of the pentaketone **3** with ammonium acetate. Similar investigations have been made in (4) and following reports on the basis of products of "diketonic" condensation of the substituted glyoxals and cyclic 1,3-diketones. It has also been shown that the treatment of comparable compounds with ammonia led to pyrrolo[4,3,2-m,n] acridine.

Pyrroles **5 a,b** were prepared by interaction of **3** with primary amines, namely methylamine and p-toluidine in ethanol. Pentaketone **3** behaves as 1,4-dicarbonyl compound. Moreover, the dimedone fragment doesn't react.

In contrast, the reaction of **3** with hydrazine hydrate proceeds with participation of the dimedone fragment, and the acetylacetonyl substituent is free of transformation. The treatment of adduct **3** with hydrazine hydrate led to pyridazine **6**.

Using enamine of dimedone **7** we condensed it with 1,1-diacetyl-2-benzoyl ethylene **2** to give hexahydroquinoline **8**. An analogous reaction with 1,2-dibenzoyl ethylene has already been observed (5).



Conclusion

In accordance with the proposed structures, pentaketone **3** proved to be an interesting starting material for the synthesis of different heterocyclic systems such as pyrrolo[3,4-c] quinolines, pyrroles or pyridazines.

The use of dimedone enamine **7** led to the formation of 1,4-dihydropyridine ring.

Experimental

IR spectra were recorded using a Perkin Elmer Spectrum BX spectrophotometer. Mass spectra were determined on a chromatomass-spectrometric system HP 5972 MSD/ HP (70 eV).

^1H NMR spectra were registered on a Bruker WM-250 spectrometer (250 MHz). Chemical shifts are given in ppm relative to tetramethylsilane (TMS).

3-Acetyl-2-(4,4-dimethyl-2,6-dioxocyclohexyl)-1-phenylpentanedione-1,4 (3). A solution of dimedone **1** (1.56 g; 11.1 mmol), 1,1-diacetyl-2-benzoyl ethylene **2** (2.40 g; 11.1 mmol) and 1 ml 15 % aqueous KOH in 40 ml of ethanol is heated at 50°C for 1 h, neutralized with acetic acid and poured into ice. Precipitated oil crystallized with difficulty by rubbing up with ice cooling. The crystals are filtered, washed with water and dried. Yield 3.35 g (85 %). M.p. 158-161°C (after flash-chromatographic purification over Al_2O_3 (eluent: dichloromethane, then ethanol)). IR spectrum (KBr, ν , cm^{-1}): 3492, 2655, 1694, 1598. ^1H NMR spectrum (CDCl_3): 15.11 (s, 1H, OH), 7.49-7.54 (m, 2H, H_{arom}), 7.37-7.41 (m, 3H, H_{arom}), 3.77 (q, 1H, CH), 2.47 (m, 2H, CH_2), 2.31 (d, 2H, CH_2), 1.74 (s, 3H, CH_3), 1.32 (s, 3H, CH_3), 1.19 (s, 3H, CH_3), 1.17 (s, 3H, CH_3). Mass spectrum (m/z): $[\text{M}+2-\text{PhCOCH}]^+$ 240; $[\text{PhCO}]^+$ 105. Found, %: C 71.0; H 6.5. $\text{C}_{21}\text{H}_{24}\text{O}_5$. Calcd., %: C 70.8; H 6.8.

2,3,6,6-Tetramethyl-8-oxo-9-phenyl-5,6,7,8-tetrahydropyrrolo[3,4-c] quinoine (4). A solution of **3** (0.22 g; 0.6 mmol) and ammonium acetate (0.25 g; 3.2 mmol) in 3 ml of acetic acid is refluxed for 0.5 h and poured into an excess of saturated solution of sodium carbonate. Precipitated product is filtered, washed with water, and dried. Yield 0.15 g (76 %). M.p. 108-111°C. IR spectrum (CH_2Cl_2 , ν , cm^{-1}): 3415, 1671. ^1H NMR spectrum (CDCl_3): 7.15-7.35 (m, 5H, Ph), 3.05 (s, 2H, CH_2), 2.93 (s, 3H, CH_3), 2.81 (s, 3H, CH_3), 2.41 (s, 2H, CH_2), 1.08 (s, 6H, 2 CH_3). M^+ 318. Found, %: C 79.5; H 7.2; N 9.0. $\text{C}_{21}\text{H}_{22}\text{N}_2\text{O}$. Calcd., %: C 79.2; H 7.0; N 8.8.

3-Acetyl-1,2-dimethyl-4-(4,4-dimethyl-2,6-dioxocyclohexyl)-5-phenylpyrrole (5a). A solution of **3** (0.40 g; 1.1 mmol) and 2 ml of 25 % aqueous methylamine in 5 ml of ethanol is refluxed for 0.5 h, diluted with water, then neutralized with acetic acid. Precipitated crystals are filtered, washed with water and dried. Yield 0.18 g (46 %). M.p. 196-198°C (acetone-water, 1:2). IR spectrum (KBr, ν , cm^{-1}): 2645, 1645, 1571. ^1H NMR spectrum (CDCl_3): 7.32-7.36 (m, 3H, H_{arom}), 7.16-7.21 (m, 2H, H_{arom}), 3.38 (s, 3H, $\text{CH}_3\text{-N}$), 2.59 (s, 3H, CH_3), 2.31-2.41 (m, 2H, CH_2), 2.24 (s, 3H, CH_3), 2.13-2.23 (m, 2H, CH_2), 1.07 (s, 3H, CH_3), 0.72 (s, 3H, CH_3). M^+ 351. Found, %: C 74.8; H 7.3; N 4.1. $\text{C}_{22}\text{H}_{25}\text{NO}_3$. Calcd., %: C 75.2; H 7.2; N 4.0.

3-Acetyl-2-methyl-1-(4-methylphenyl)-4-(4,4-dimethyl-2,6-dioxocyclohexyl)-5-phenylpyrrole (5b). A solution of **3** (0.30g; 0.8 mmol) and p-toluidine (0.09 g; 0.8 mmol) in 5 ml of ethanol is refluxed for 0.5 h, poured into a mixture of ice and salt. Precipitated crystals are filtered, washed with water and dried. Yield 0.21 g (58 %). The product is purified on Al_2O_3 (eluent: dichloromethane- acetone, 1:1). M.p. 207-209°C. IR spectrum (KBr, ν , cm^{-1}): 2633, 1635, 1602, 1506. ^1H NMR spectrum (CDCl_3): 7.08-7.12 (m, 5H, Ph), 6.94-7.00 (m, 4H, H_{arom}), 2.35-2.45 (m, 2H, CH_2), 2.39 (s, 3H, CH_3), 2.32 (s, 3H, CH_3), 2.31 (s, 3H, CH_3), 2.17-2.26 (m, 2H, CH_2), 1.11 (s, 3H, CH_3), 0.81 (s, 3H, CH_3). M^+ 427. Found, %: C 79.0; H 6.6; N 3.5. $\text{C}_{28}\text{H}_{29}\text{NO}_3$. Calcd., %: C 78.7; H 6.8; N 3.3.

4-Acetylacetonyl-7,7-dimethyl-5-oxo-3-phenyl-1,4,5,6,7,8-hexahydrobenzo[c] pyridazine (6).

A solution of **3** (0.30 g; 0.8 mmol) and hydrazine hydrate (0.13 g; 2.6 mmol) in 3 ml of ethanol is refluxed for 1 h, diluted with cold water (3 ml). Precipitated crystals are filtered, washed with aqueous ethanol and dried. Yield 0.15 g (51%). M.p. 260–262°C (aqueous ethanol). IR spectrum (KBr, ν , cm^{-1}): 3375, 3198, 3132, 1596, 1486. ^1H NMR ($\text{DMSO}-d_6$): 11.84 (s, 1H, OH), 10.68 (s, 1H, NH), 7.66 (d, 2H, H_{arom}), 7.26–7.37 (m, 3H, H_{arom}), 4.99 (s, 1H, CH), 2.28–2.41 (m, 2H, CH_2), 2.13 (s, 6H, 2 CH_3), 1.94–2.24 (m, 2H, CH_2), 1.02 (s, 3H, CH_3), 0.88 (s, 3H, CH_3). $[\text{M} - \text{acac}]^+$ 253. Found, %: C 71.4; H 6.8; N 8.2. $\text{C}_{21}\text{H}_{24}\text{N}_2\text{O}_3$. Calcd., %: C 71.6; H 6.9; N 8.0.

3-Acetyl-4-benzoyl-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline (8). A solution of enamine **7** (0.45 g; 3.2 mmol) and 1,1-diacetyl-2-benzoyl-ethylene **2** (0.70 g; 3.2 mmol) in 10 ml of ethanol is refluxed for 1 h, poured into water, then extracted with dichloromethane. The combined organic layers are dried, the solvent is distilled, and the residue recrystallized from ethanol. Yield 0.52 g (48%). M.p. 195–196°C. IR spectrum (KBr, ν , cm^{-1}): 3277, 1670, 1654, 1633, 1593. ^1H NMR spectrum (CDCl_3): 8.20 (d, 2H, H_{arom}), 7.43–7.53 (m, 3H, H_{arom}), 6.20 (s, 1H, NH), 5.72 (s, 1H, CH), 2.36 (s, 3H, CH_3), 2.28–2.35 (m, 2H, CH_2), 2.20 (d, 2H, CH_2), 2.16 (s, 3H, CH_3), 1.08 (s, 3H, CH_3), 0.93 (s, 3H, CH_3). $[\text{M} - \text{PhCO}]^+$ 232. Found, %: C 74.5; H 7.1; N 4.3. $\text{C}_{21}\text{H}_{23}\text{NO}_3$. Calcd., %: C 74.8; H 6.9; N 4.2.

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