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

Alexander N. Andin, Vladimir A. Kaminskii, Sergey V. Dubovitskii*

Far Eastern State University, Vladivostok 690950, Russia

Abstract

The respective adduct 3 has been prepared by condensation of dimedone 1 with 1,1-diacetyl-2-benzoylethylene 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-benzoylethylene 2 to give hexahydroquinoline 8.

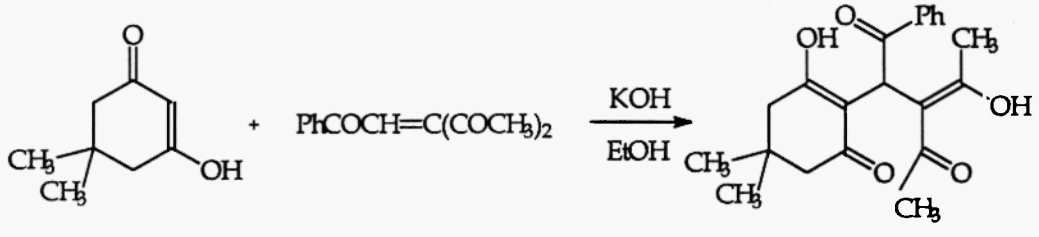
Introduction

It has been shown in the last reports that dimedone 1 and disubstituted ethylenes such as 1,2-dibenzoylethylene 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-dibenzoylethylene 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-benzoylethylene 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-benzoylethylene 2 was carried out in ethanol in the presence of alkali to give 3. The formation of a pentaketone is confirmed with



1 2 3

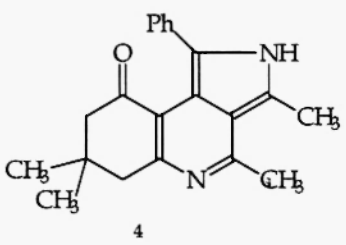
data of IR and ^{1}H NMR spectra.

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.

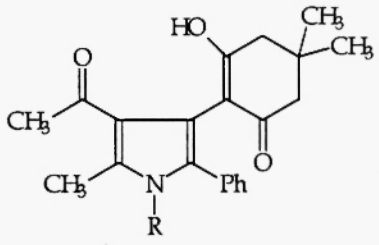
Pyrroles 5 a,b were prepared by interaction of 3 with primary amines, namely methylamine and p-toluidine in ethanol. Pentaketone 3 behaves as 1,4-dicarbonyl compound. Moreover, the dimedone fragment doesn't react.

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.

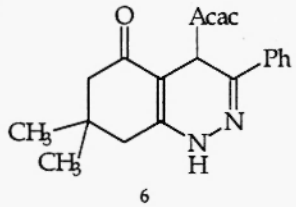
Using enamine of dimedone 7 we condensed it with 1,1-diacetyl-2-benzoylethylene 2 to give hexahydroquinoline 8. An analogous reaction with 1,2-dibenzoylethylene has already been observed (5).



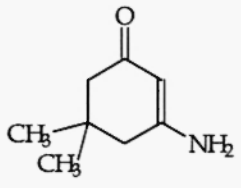
4



5 a,b

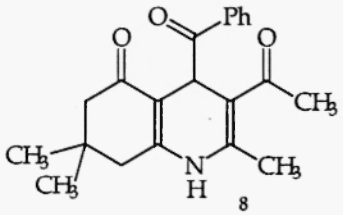


6



7

5 a R=CH_3; b R= 4-$CH_3C_6H_4$



8

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).

^{1}H 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-benzoylethylene 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. ^{1}H 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): $[M+2 - PhCOCH]^+$ 240; $[PhCO]^+$ 105. Found, % : C 71.0; H 6.5. $C_{21}H_{24}O_5$. Calcd., % : C 70.8; H 6.8.

2,3,6,6-Tetramethyl-8-oxo-9-phenyl-5,6,7,8-tetrahydropyrrolo[3,4-c] quinoiine (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. ^{1}H 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. $C_{21}H_{22}N_2O$. 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. ^{1}H NMR spectrum ($CDCl_3$): 7.32-7.36 (m, 3H, H_{arom}), 7.16- 7.21 (m, 2H, H_{arom}), 3.38 (s, 3H, CH_3-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. $C_{22}H_{25}NO_3$. 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. ^{1}H 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. $C_{28}H_{29}NO_3$. 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 (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, $2CH_3$), 1.94- 2.24 (m, 2H, CH_2), 1.02 (s, 3H, CH_3), 0.88 (s, 3H, CH_3). $[M - acac]^+$ 253. Found, %: C 71.4; H 6.8; N 8.2. $C_{21}H_{24}N_2O_3$. 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-benzoylethylene 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). $[M - PhCO]^+$ 232. Found, % : C 74.5; H 7.1; N 4.3. $C_{21}H_{23}NO_3$. Calcd., % : C 74.8; H 6.9; N 4.2.

Acknowledgements

The research described in this publication was made possible in part by Award No. REC-003 of the U.S. Civilian Research & Development Foundation for the Independent State of the Former Soviet Union (CRDF) and by Award No. 98-03-32891 of Russian Foundation for Basic Research (RFBR).

References

(1) S.V. Dubovitskii and V.A. Kaminskii, Zh. Org. Khim. 33, 1118 (1997).

(2) A.N. Andin, V.A. Kaminskii and S.V. Dubovitskii, Khim. Geterotsikl. Soedin. 11, 1497 (1999).

(3) A.N. Andin, V.A. Kaminskii and S.V. Dubovitskii, Khim. Geterotsikl. Soedin., in press.

(4) E.A. Bisenieks, M.F. Bundule, Ya.R. Uldrikis, G.Ya. Dubur, A.F. Mishnev and Ya.Ya. Bleidelis, Khim. Geterotsikl. Soedin. 1 , 107 (1987).

(5) Y. Tamura, T. Sakaguchi, T. Kawasaki and Y. Kita, Heterocycles. 2, 645 (1974).

Received on January 8, 2001