Chemistry of Heterocyclic Compounds, Vol. 43, No. 6, 2007

MICHAEL CONDENSATION OF 3-ARYLIDENE-3H-PYRROL-2-ONES AND 3-ARYLIDENE-3H-FURAN-2-ONES WITH CYCLOHEXANONE

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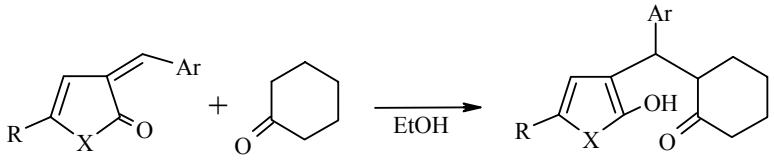
The Michael condensation in the series of 5-aryl-3-arylidene-3H-pyrrol-2-ones and 5-aryl-3-arylidene-3H-furan-2-ones, containing an activated C=C bond, with cyclohexanone was investigated. It was shown that the condensation products were 1,5-dicarbonyl compounds containing a heterocyclic fragment. The enolization of one of the oxo groups, leading to the formation of hydroxypyrrole or hydroxyfuran structures, was demonstrated by the spectral data.

Keywords: N-aryl-5-aryl-3-arylidene-3H-pyrrol-2-ones, N-unsubstituted 5-aryl-3-arylidene-3H-pyrrol-2-ones, 5-aryl-3-arylidene-3H-furan-2-ones, cyclohexanone, acceptor, condensation.

It is possible to obtain acyclic and semi- and bicyclic ketones with symmetrical and unsymmetrical structures by the Michael reaction. This condensation is of great value since it makes it possible to increase the length of a carbon chain and to introduce various substituents into the structure of the investigated compounds in a single stage.

Transformations based on Michael condensation with heterocyclic compounds as addends were examined in the series of 5-pyrazolones [1], pyrones [2], and 5-R-3H-furan-2-ones [3]. However, there are no data on the use of unsaturated five-membered heterocycles as acceptors in the Michael reaction.

The structures of 3-arylidene-3H-furan-2-ones and 3-arylidene-3H-pyrrol-2-ones contain an activated double bond. As demonstrated earlier [4], the C=C and C=O bonds are fixed in the *S-cis*-configuration, which makes it possible to use them as acceptors in Michael condensation. We introduced cyclohexanone as addend.



1a,b–3a,b **4a,b–6a,b**

1-6 R = C_6H_4Me; **1**, **4** X = N–Ph, **a** Ar = Ph, **b** Ar = C_6H_4OMe-*p*; **2**, **5** X = N–H, **a** Ar = Ph, **b** Ar = $C_6H_4NMe_2$-*p*; **3**, **6** X = O, **a** Ar = $C_6H_4NO_2$-*m*, **b** Ar = C_6H_4OH-*p*

The Michael condensation in the series of 3-arylidene-3H-pyrrol-2-ones **1**, **2** was realized at 60-65°C under the conditions of base catalysis (piperidine) with ethanol as solvent. N-Phenyl-3-(aryl-2-cyclohexanonylmethyl)-2-hydroxy-5-(4-methylphenyl)pyrroles **4a**,**b** and 3-(aryl-2-cyclohexanonylmethyl)-2-hydroxy-5-(4-methylphenyl)pyrroles **5a**,**b** were isolated with yields of up to 70% (Table 1).

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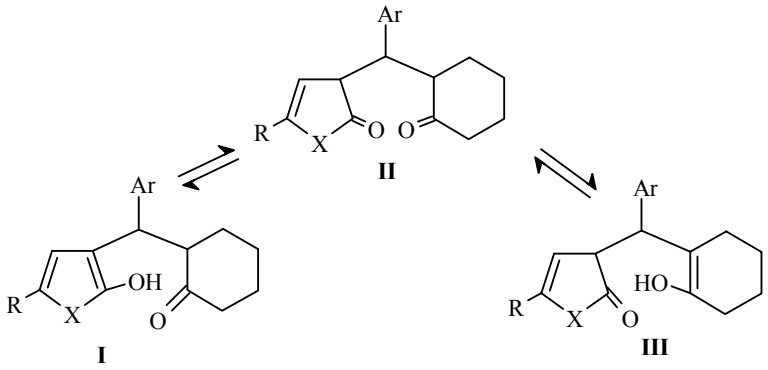
The absence of an absorption band characteristic of the carbonyl group of β,γ-unsaturated lactams in the IR spectra of compounds **4** and **5** and the presence of a broad absorption band for a bonded hydroxyl group provide grounds to suppose that the isolated compounds **4** and **5** exist in the enolic form. Both the carbonyl group of the heterocyclic fragment and the C=O group of the cyclohexanone fragment can undergo enolization, making the existence of the following isomers possible.



In the region of 1610-1608 cm^{-1} there is an absorption band characteristic of a C=C bond conjugated with the aromatic substituent, in the region of 3352-3188 cm^{-1} there is a broad absorption band for the hydroxyl group, and in the region of 1700 cm^{-1} there is a strong absorption band for the carbonyl of the cyclohexanone fragment.

The ^1H NMR spectra provide further evidence for the structure of compounds **4a**,**b** and **5a**,**b**. The spectra contain a singlet for the vinyl proton of the pyrrole ring at 5.90-6.16 (1H) and a series of signals for the protons of the cyclohexanone ring in the upfield region at 1.05-2.10 ppm (8H). The methine protons appear in the upfield region and differ in form. Thus, the exocyclic proton adjacent to the aryl substituent is observed at 3.00-3.06 cm^{-1} (1H, d), and the tertiary proton of the cyclohexanone ring is observed at 3.20-3.30 ppm (1H, m). In the downfield region there is a broad signal for the proton of the hydroxyl group at 5.00-5.06 ppm. The protons of the aromatic substituents are at 7.35-7.75 ppm (Table 2).

TABLE 1. The Physicochemical Characteristics of the Synthesized Compounds

Compound	Empirical formula	Found, % / Calculated, %			mp, °C	n_D^{20}	Yield, %
		C	H	N			
4a	$C_{30}H_{29}NO_2$	82.86 / 82.73	6.82 / 6.71	3.31 / 3.22	—	1.6095	70
4b	$C_{31}H_{31}NO_3$	80.06 / 79.97	6.41 / 6.71	3.23 / 3.01	—	1.6140	63
5a	$C_{24}H_{25}NO_2$	79.74 / 80.19	6.53 / 7.01	3.42 / 3.90	—	1.6030	65
5b	$C_{26}H_{30}N_2O_2$	78.13 / 77.58	6.08 / 7.51	6.53 / 6.96	—	1.6100	65
6a	$C_{24}H_{23}NO_5$	70.98 / 71.10	5.60 / 5.71	3.56 / 3.45	146-148	—	60
6b	$C_{24}H_{24}O_4$	70.98 / 76.57	5.60 / 6.43	—	125-126	—	68

TABLE 2. The ^{1}H NMR Spectra of the Synthesized Compounds

Compound	Chemical shifts, δ, ppm (*J*, Hz)
4a	6.10 (1H, s, H-4); 3.06 (1H, d, *J* = 2.00, H-2 Ar); 3.30 (1H, m, H-2); 1.05-2.10 (8H, m, 4CH_2); 2.33 (3H, s, CH_3); 7.35-7.65 (14H, m, C_6H_5); 5.02 (1H, br. s, OH)
4b	6.15 (1H, s, H-4); 3.05 (1H, d, *J* = 2.20, H-2 Ar); 3.25 (1H, m, H-2); 1.05-2.00 (8H, m, 4CH_2); 2.33 (3H, s, CH_3); 3.80 (3H, s, OCH_3); 7.35-7.75 (13H, m, C_6H_5); 5.00 (1H, br. s, OH)
5a	5.95 (1H, s, H-4); 3.00 (1H, d, *J* = 2.50, H-2 Ar); 3.30 (1H, m, H-2); 1.10-2.10 (8H, m, 4CH_2); 2.35 (3H, s, CH_3); 7.35-7.75 (9H, m, C_6H_5); 5.06 (1H, br. s, OH); 5.00 (1H, br. s, NH)
5b	5.90 (1H, s, H-4); 3.00 (1H, d, *J* = 2.50, H-2 Ar); 3.20 (1H, m, H-2); 1.10-2.10 (8H, m, 4-CH_2); 2.35-2.85 (9H, s, CH_3); 7.35-7.75 (8H, m, C_6H_5); 5.02 (1H, br. s, OH); 5.00 (1H, br. s, NH)
6a	6.10 (1H, s, H-4); 3.05 (1H, d, *J* = 2.00, H-2 Ar); 3.23 (1H, m, H-2); 1.05-2.10 (8H, m, 4CH_2); 2.33 (3H, s, CH_3); 7.35-7.55 (8H, m, C_6H_5); 5.00 (1H, br. s, OH)
6b	6.12 (1H, s, H-4); 3.08 (1H, d, *J* = 2.10, H-2 Ar); 3.25 (1H, m, H-2); 1.15-2.20 (8H, m, 4CH_2); 2.35 (3H, s, CH_3); 7.30-7.50 (8H, m, C_6H_5); 5.00 (1H, br. s, OH)

The enolization of compounds **4** and **5** can be explained by the fact that the cyclohexanone ring is in the *chair* conformation and the two carbonyl groups are close. As a result compounds **4** and **5** are stabilized in the enolic form.

In order to explain the obtained experimental data and define the possible tautomeric forms of the products from the given reaction we calculated the standard heats of formation ($\Delta H_{f\,298}$) of compounds **4-6** and their keto-enol tautomers, the formation of which is possible during the condensation, by the quantum-chemical MO LCAO SCF method in the PM3 approximation using MOPAC software.

Analysis of the thermodynamic characteristics makes it possible to conclude that compounds **4** are thermodynamically most stable in the form of tautomer **I**. The greater ability of the carbonyl group of the heterocycle to undergo enolization compared with the carbonyl group of the cyclohexanone fragment of tautomer **II** is explained by the formation of more stable aromatic structures and agrees with the data from the IR and ^{1}H NMR spectra (Table 3).

For the 3-arylidene-3H-furan-2-ones **3** the reaction was carried out under conditions analogous with the condensation in the series of N-containing analogs. The 3-(aryl-2-cyclohexanonoylmethyl)-2-hydroxy-5-(4-methylphenyl)furans **6a**,**b** were isolated with yields of up to 74% (Table 1).

The IR spectra of compounds **6a**,**b** contain a band characteristic of a C=C bond conjugated with the aromatic substituent in the region of 1610-1605 cm^{-1}, a broad absorption band for the hydroxyl group in the region of 3350-3186 cm^{-1}, and a strong absorption band for the carbonyl group of the cyclohexanone fragment in the region of 1698 cm^{-1}.

The data from the ^{1}H NMR spectra are most informative as regards evidence for the structure of compounds **6**. The spectra contain a singlet for the vinyl proton of the furan ring at 6.10-6.12 (1H) and a series of signals for the protons of the cyclohexanone ring in the upfield region at 1.05-2.20 ppm. The methyl protons appear in the upfield region and differ in form. Thus, the proton adjacent to the aryl substituent is observed at 3.05-3.08 (1H, d), and the proton of the cyclohexanone ring is observed at 3.23-3.25 ppm (1H, m). In the downfield region there is a broad signal for the proton of the hydroxyl group at 5.00 ppm. The protons of the aromatic substituents are observed at 7.30-7.55 ppm (Table 2).

The one-electron densities at the lowest unoccupied molecular orbital (LUMO) of the exocyclic sp^2-hybridized carbon atom were calculated for the initial arylidene-3H-pyrrol-2-ones **1** and **2** and 3H-furan-2-ones **3** by the PM3 method using MOPAC software: **1a** 0.2335, **1b** 0.2168, **2a** 0.2090, **2b** 0.2100, **3a** 0.1736, **3b** 0.2209.

TABLE 3. The Standard Heats of Formation of Compounds **4a**-**6a** and their Isomers **I-III**

Compound	ΔH_{f298}, kJ/mol		
	I	**II**	**III**
4a	-8.23	30.97	59.06
5a	-133.42	-110.78	-87.94
6a	-283.85	-261.15	-248.53

In this case it can be supposed on the basis of the obtained results that 3-benzylidene-5-(4-methylphenyl)-1-phenyl-3H-pyrrol-2-one (**1a**) has the highest activity (maximum localization of the LUMO, corresponding to the highest value for the one-electron density, the highest index) during participation in Michael condensation as acceptor.

The nitro group reduces the value of the one-electron density in the LUMO to the greatest degree (the electron density has maximum delocalization), and for this reason 5-(4-methylphenyl)-3-(3-nitrobenzylidene)-3H-furan-2-one (**3a**) is the least active. Thus, the better yield of compound **4a** (Table 1) can be explained by the effect of the substituent in the aromatic fragment.

Thus, it was shown for the first time on the basis of the experimental and calculated data that 3-arylidene-3H-pyrrol-2-ones and 3-arylidene-3H-furan-2-ones are highly reactive compounds, exhibit high polarity in the π bond, and are capable of reacting with such addends as cyclohexanone under the conditions of Michael condensation.

EXPERIMENTAL

The IR spectra were recorded on an IKS-29 instrument. The ^{1}H NMR spectra were recorded on a Varian FT-80A instrument (80 MHz) in $CDCl_3$ with TMS as internal standard.

The 5-aryl-3-arylidene-3H-furan-2-ones were obtained by the procedure described in [5], and the N-H(Ar)-3-arylidene-3H-pyrrol-2-ones were obtained by the procedure in [6].

N-Phenyl-3-(2-cyclohexanonylphenylmethyl)-2-hydroxy-5-(4-methylphenyl)pyrrole (4a), N-Phenyl-3-[2-cyclohexanonyl(4-methoxyphenyl)methyl]-2-hydroxy-5-(4-methylphenyl)pyrrole (4b), 3-(2-Cyclohexanonylphenylmethyl)-2-hydroxy-5-(4-methylphenyl)pyrrole (5a), and 3-[2-Cyclohexanonyl(4-dimethylaminophenyl)methyl]-2-hydroxy-5-(4-methylphenyl)pyrrole (5b). In a three-necked flask with a stirrer, a dropping funnel, and a reflux condenser we placed a solution of the corresponding 3-arylidene-3H-pyrrol-2-one **1a**,**b** or **2a**,**b** (0.01 mol) in ethanol and cyclohexanone (0.01 mol) with piperidine as catalyst. The reaction mixture was heated on a water bath for 2 h. The mixture was washed with water and purified on a chromatographic column with hexane as eluent.

3-(Aryl-2-cyclohexanonylmethyl)-2-hydroxy-5-(4-methylphenyl)furans 6a,b. The compounds were obtained by a similar method from the corresponding 3-arylidene-3H-furan-2-one **3a**,**b** (0.01 mol) of, cyclohexanone (0.01 mol), and catalytic amounts of piperidine. After treatment with water the precipitated crystals were filtered off and recrystallized from ethanol.

The work was carried out with the financial support of a grant from the President of the Russian Federation for state support for young scientists MK-2952.2007.3 and RFFI 05-03-32196.

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