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INTERACTION OF 3-ACETOACETYL-2H-CHROMEN-2-ONE WITH AZANUCLEOPHILIC REAGENTS

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The reactions of 3-acetoacetylchromen-2-one with mono- and binucleophilic reagents, under the action of microwave irradiation have been studied. It was shown that depending on the nucleophilicity of the reactant new heterocyclic systems were formed involving the oxo group of the substituent in position 3 of the heterofragment, its opening, or recyclization.

Keywords: 3-acetoacetylchromen-2-one, nucleophilic reactions, microwave irradiation.

Up to the present time a whole series of preparations based on chromen-2-one possessing a wide spectrum of biological action, is used in medical practice. Their use as antioxidants [1] and antimicrobial, antiviral, and antitumor preparations [2] is known. Such medicinal preparations, as for example, Dicoumarin and Neodicoumarin, containing a 2H-chromen-2-one fragment, are known anticoagulants, and possess antitumor and antiHIV activity [3].

Unlike their unsubstituted analogs, reactions of 3-acetoacetyl-4,7-dihydroxychromen-2-ones, with such nucleophiles as hydroxylamine, *o*-phenylenediamine, 2,4-dinitrophenylhydrazine, have been studied in detail, and proceed without opening of the lactone ring with the participation of the 1,3-dioxo fragment of the aliphatic portion of the molecule [4]. A route is thereby opened to the formation of new heterosystems of the benzodiazepine, isoxazole, and pyrazole type.

Considering the high chemical potential of 3-acetoacetylchromen-2-ones, the presence of carbonyl groups of different character (ketonic and lactone), and a heterocycle free to recyclize, it seemed important to fill the information gap concerning their reactivity with mono- and binucleophilic reagents.

We have shown that in formamide, acting as a reactant and solvent, 3-acetoacetyl-2H-chromen-2-one (**1**), through enolization of the acetyl carbonyl undergoes hemiketalization to a new type of linear system, 10a-hydroxy-2-methyl-4H,10aH-pyrano[2,3-*b*]chromen-4-one (**2**).

Such behavior of substrate **1** in relation to formamide is explained by the stability of the resulting hemiketal, which in its turn determines the high degree of delocalization of electron density involving the condensed benzene ring [5]. It is also necessary to take into consideration the insufficient nucleophilicity of formamide, which does not create adequate conditions for the recyclization of the heterofragment.

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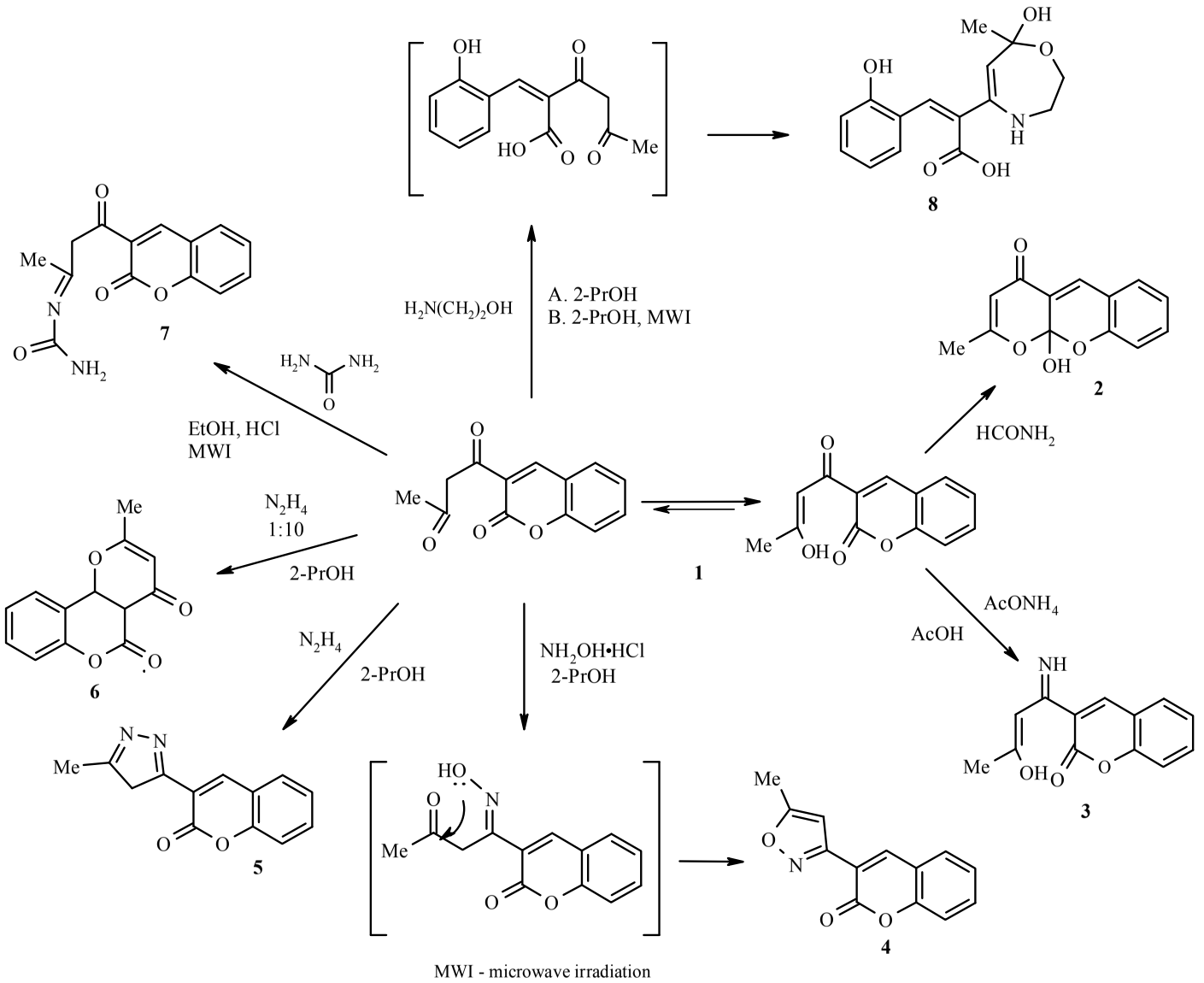
H2N(CH2)2OH
A. 2-PrOH
B. 2-PrOH, MWI
EtOH, HCl
MWI
N2H4
1:10
2-PrOH
N2H4
2-PrOH
NH2OH•HCl
2-PrOH
HCONH2
AcONH4
AcOH
1
2
3
4
5
6
7
8
MWI - microwave irradiation

Interaction of chromen-2-one **1** with ammonium acetate leads to nucleophilic attack at the carbon atom of the carbonyl group in position 1 of the substituent and the formation of 3-(3-hydroxybut-2-enimidoyl)-2H-chromen-2-one (**3**). The isolation of imine **3** confirms the tendency of 3-substituted coumarins to retain the 2H-chromen-2-one fragment in reactions with weak mononucleophilic reagents [6].

It was shown that reaction with the binucleophilic reagents, hydroxylamine and hydrazine, has a general character and proceeds with the participation of the carbonyl groups in positions 1 and 3 of the aliphatic portion of the molecule with the formation of new heterocyclic systems, *viz.* 3-(5-methylisoxazol-3-yl)- (**4**) and 3-(5-methyl-4H-pyrazol-3-yl)-2H-chromen-2-ones (**5**).

On carrying out the reaction of compound **1** in an excess of hydrazine hydrate (1:10) the competing direction at the multiple bond of the heterofragment is brought about and its O-heterocyclization occurs into 2-methyl-4a,10b-dihydro-4H,5H-pyrano[3,2-*c*]chromene-4,5-dione (**6**).

Interaction of substrate **1** with urea in 2-propanol solution gave no positive results. However under the action of microwave irradiation, attack of the reactant, as in the conversions considered above, was directed towards the most reactive carbonyl group, as a result of which 1-[4-oxo-4-(2-oxo-2H-chromen-3-yl)butan-2-ylidene]urea (**7**) was formed.

The distinctive special feature of the reaction with ethanolamine, displaying the properties of a primary amine, both on heating in 2-propanol solution and on microwave action, was the recyclization of the lactone fragment with the formation of 2-(7-hydroxy-7-methyl-2,3,4,7-tetrahydro-1,4-oxazepin-5-yl)-3-(2-hydroxyphenyl)acrylic acid (**8**).

The physicochemical characteristics of the obtained compounds are given in Table 1.

TABLE 1. Data of Elemental Analysis and IR Spectroscopy of Compounds **2-8**

Compound	Empirical formula	Found, % / Calculated, %			IR spectrum, ν, cm^{-1}
		C	H	N	
2	$C_{13}H_{10}O_4$	67.77 / 67.82	4.56 / 4.38	—	3647 (OH), 1681 (C=C–C=O)
3	$C_{13}H_{11}NO_3$	67.92 / 68.11	4.53 / 4.84	5.99 / 6.11	3378 (C=NH), 3200-2500 (OH), 1726 (C=C–CO–OR), 1662 (C=NH)
4	$C_{13}H_9NO_3$	68.54 / 68.72	3.65 / 3.99	6.05 / 6.16	1721 (C=C–CO–OR), 1664 (C=N)
5	$C_{13}H_{10}N_2O_2$	69.38 / 69.02	4.72 / 4.46	11.97 / 12.38	1722 (C=C–C=O), 1686, 1672 (C=N), 3038, 1020 (CH_2), 2974, 2852, 1425, 1377 (CH_3)
6	$C_{13}H_{10}O_4$	67.54 / 67.82	3.97 / 4.38	—	1720 (C=O lact.), 2924, 3044, 1456,1385 (CH_3), 1645 (C=C–C=O)
7	$C_{14}H_{12}N_2O_4$	61.54 / 61.76	4.52 / 4.44	9.86 / 10.29	1699 (C=O lact.), 2926, 3061, 1454, 1379 (CH_3), 1691, 1586 (O=C–NH_2), 3500 (O=C–NH_2), 3757 (OH)
8	$C_{15}H_{17}NO_5$	61.39 / 61.85	5.89 / 5.88	4.92 / 4.81	1647 (C=C–C=O), 2938, 3061, 1456, 1383 (CH_3), 3520-3389 (OH), 3430 (NH)

EXPERIMENTAL

A MW2717 microwave emitter (700 W) was used. The IR spectra were recorded on a FSM 1201 Fourier spectrometer in hexachlorobutadiene (in the ranges 4000-1800 and 1500-1300) and in nujol (1800-1500 and 1400-1300 cm^{-1}) in KBr cuvettes. The ^1H NMR spectra were obtained on a Varian 400 spectrometer at 25°C in $CDCl_3$ (compounds **7** and **8**), on a Bruker MSL-400 (400 MHz) spectrometer in $CDCl_3$ (compounds **3** and **4**) and in DMSO-d_6 (compounds **1** and **2**). Internal standard was TMS. A check on the progress of reactions and the homogeneity of the obtained compounds was effected by TLC on Silufol UV-254 plates, eluent was hexane–ether–acetone, 3:1:1, hexane–ethyl acetate–acetone, 2:2:1, the developer was iodine vapor.

3-Acetoacetyl-2H-chromen-2-one (1) was obtained by condensing 4-hydroxy-6-methyl-2H-pyran-2-one with salicylic aldehyde by the known procedure of [7]. ^1H NMR spectrum, δ, ppm: 2.27 (3H, s, CH_3); 6.89-7.61 (5H, m, H Ar + CH); 6.66 (1H, s, CH); 15.80 (1H, s, OH).

10a-Hydroxy-2-methyl-4H,10aH-pyrano[2,3-*b*]chromen-4-one (2). 2H-Chromen-2-one **1** (1 g, 4.3 mmol) was dissolved with heating and constant stirring in formamide (40 ml). The reaction mixture was heated for 5 h, then poured into water (50 ml). The precipitated light-yellow crystals were filtered off, washed with water, and compound **2** (0.35 g, 35%) was obtained with mp 144-145°C. ^1H NMR spectrum, δ, ppm: 2.28 (3H, s, CH_3); 3.65 (1H, s, OH); 6.68 (1H, s, CH); 6.92-7.65 (5H, m, H Ar + CH).

3-(3-Hydroxybut-2-enimidoyl)-2H-chromen-2-one (3) was obtained by an analogous procedure using glacial acetic acid (15 ml), substrate **1** (1 g, 4.3 mmol), and ammonium acetate (0.67 g, 8.7 mmol). Reaction time was 12 h. Yield of compound **3** was 0.56 g (57%); mp 149-150°C. ^1H NMR spectrum, δ, ppm: 2.27 (3H, s, CH_3); 6.97 (1H, s, CH); 7.05-8.32 (5H, m, H Ar + CH); 11.71 (1H, s, NH); 15.82 (1H, s, OH).

3-(5-Methylisoxazol-3-yl)-2H-chromen-2-one (4) was obtained by an analogous procedure using 2-propanol (25 ml), substrate **1** (1 g, 4.3 mmol), and hydroxylamine hydrochloride (0.6 g, 8.6 mmol). Reaction time was 4 h. Yield of compound **4** was 0.62 g (63%); mp 196-197°C. ^1H NMR spectrum, δ, ppm: 2.28 (3H, s, CH_3); 6.83 (1H, s, CH); 7.12-8.50 (5H, m, H Ar + CH).

3-(5-Methyl-4H-pyrazol-3-yl)-2H-chromen-2-one (5) was obtained by an analogous procedure during 5 h using 2-propanol (50 ml), trioxo compound **1** (1 g, 4.3 mmol), and hydrazine hydrate (0.45 ml, 8.6 mmol). Yield of compound **5** was 0.46 g (47%); mp 179-180°C. ^1H NMR spectrum, δ, ppm: 2.27 (3H, s, CH_3); 4.25 (2H, s, CH_2); 7.05-8.43 (5H, m, H Ar + CH).

2-Methyl-4a,10b-dihydro-4H,5H-pyrano[3,2-*c*]chromene-4,5-dione (6) was obtained by an analogous procedure during 7 h using 2-propanol (50 ml), trioxo compound **1** (1 g, 4.3 mmol), and hydrazine hydrate (5 ml, ~100 mmol). Yield of compound **6** was 0.81 g (82%); mp 242-243°C. ^1H NMR spectrum, δ, ppm, (*J*, Hz): 2.27 (3H, s, CH_3); 3.87 and 4.74 (2H, two d, J = 20.0, H-4a,10b); 4.63 (1H, s, CH); 6.89-7.43 (4H, m, H Ar).

1-[4-Oxo-4-(2-oxo-2H-chromen-3-yl)butan-2-ylidene]urea (7). Ethanol (3 ml) and HCl (*d* 1.19 g/ml) (1 ml) were added to substrate **1** (2 g, 8.7 mmol) and urea (0.78 g, 13 mmol). The reaction mixture was subjected to microwave irradiation of power 700 W for 24 min. The yellow crystals formed were washed with water and compound **7** (1.70 g, 72%) was obtained; mp 120-121°C. ^1H NMR spectrum, δ, ppm: 2.27 (3H, s, CH_3); 3.37 (2H, s, CH_2); 6.85-7,71 (5H, m, H Ar + CH); 11.10 (2H, br. s, NH_2).

2-(7-Hydroxy-7-methyl-2,3,4,7-tetrahydro-1,4-oxazepin-5-yl)-3-(2-hydroxyphenyl)acrylic Acid (8). A. Ethanolamine (0.66 g, 10.8 mmol) was added to a solution of trioxo compound **1** (1 g, 4.3 mmol) in 2-propanol (30 ml). The mixture was heated for 18 h, the solvent evaporated, and water (50 ml) added. The precipitated crystals were filtered off, washed with water, and compound **8** (0.95 g, 75%) was obtained; mp 188-189°C. ^1H NMR spectrum, δ, ppm: 1.38-2.64 (4H, m, CH_2); 2.27 (3H, s, CH_3); 6.25 (1H, s, CH); 6.35-7.71 (5H, m, H Ar + CH); 11.78-11.84 (2H, br. s, OH).

B. By a procedure analogous to the preparation of compound **7** using ethanolamine (0.66 g, 1.08 mmol) with 2-propanol (3 ml) as solvent. The duration of microwave action was 21 min. The resulting mixture was poured into water. The precipitated crystals were filtered off, washed with water, and compound **8** (1.01 g, 80%) was obtained.

REFERENCES

1. P. I. Yagodinets, O. V. Skripskaya, N. G. Prodanchuk, I. N. Chernyuk, and V. G. Sinchenko, *Khim.-farm. Zh.*, **26**, No. 5, 59 (1992).
2. K. Lakin, T. Smirnova, and G. Vishnyakova, *Khim.-farm. Zh.*, **23**, 1212 (1989).
3. Y. U. Al-Soud, I. A. Al-Masoudi, and B. Saeed, *Khim. Geterotsikl. Soedin.*, 669 (2006). [*Chem. Heterocycl. Comp.*, **42**, 583 (2006)].
4. I. Manolov, C. Maichle-Moessmer, and N. Danchev, *Eur. J. Med. Chem.*, **41**, 882 (2006).
5. M. Perel'son, A. Tutkevich, and Yu. Sheinker, *Teor. Eksp. Khim.*, **2**, 575 (1966).
6. M. Lacan, M. Cacic, and V. Cizmar, *Bull. Soc. Chim. Belg.*, **46**, 531 (1981).
7. J. Riboulleau, C. Deschamps-Vallet, and D. Molho, *Bull. Soc. Chim. France*, 3138 (1970).