Chemical Reactivity and Nucleophilic Ring Closure Reactions of 3-Formylchromone

H. M. EL-SHAAER

Department of Chemistry, Faculty of Education, Ain-Shams University, Roxy, Cairo, Egypt

Received 29 May 1995

The interaction between 3-formylchromone and primary amines such as sulfadiazine and thiosemicarbazide followed by nucleophilic ring closure has been studied. Structure of the products has been established on the basis of elemental analysis, IR, ^{1}H NMR, and mass spectra. The investigation indicates that the course of these reactions is governed by the medium and the reaction conditions.

Chromones are usually readily ring-opened *via* nucleophilic attack at the position 2 [1, 2]. The presence of a 3-(aryliminomethyl) group in the chromone ring alters the reactivity of the chromone system towards nucleophiles, and in certain cases facilitates nucleophilic ring addition rather than ring fission [3]. In continuation to our interest in the chemistry of formylchromone ring system [4—6], owing to its considerable biological activities [7], we report here on the behaviour of 3-formylchromone towards the action of a variety of nucleophilic reagents.

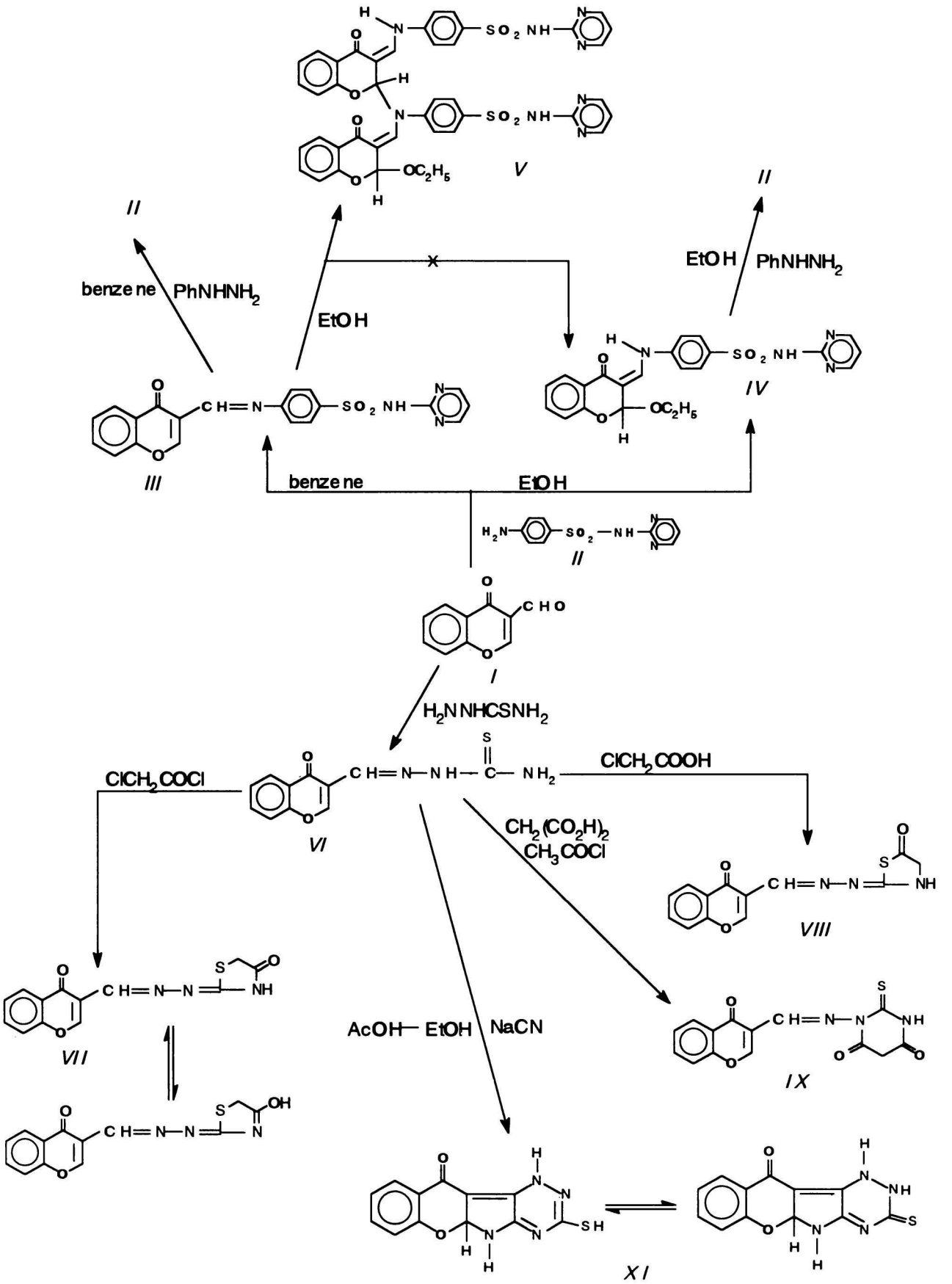
Thus, the reaction between equimolar quantities of 3-formylchromone *I* and sulfadiazine *II* in dry benzene and 4-toluenesulfonic acid as catalyst gave anil *III* (Scheme 1). The structure of *III* was established from IR spectra, which revealed the presence of a strong band of pyrone CO at $\tilde{\nu}$ = 1673 cm^{-1} and of exocyclic C=N at 1615 cm^{-1}. ^{1}H NMR spectra of *III* showed signals attributed to aromatic protons at δ = 6.86—8.51 and NH proton at δ = 11.54 (Table 1).

Refluxing of anil *III* in absolute ethanol gave 1,4-adduct *V*. IR spectra of *V* indicated the presence of C=N, CO, and NH groups, while ^{1}H NMR spectrum of *V* revealed signals at δ = 1.09, 3.73 of ethoxy group, 5.97 of H-2 proton, and supported the presence of H-2 on a pyranone system and not on a pyrone system; it also showed three signals for NH protons. The fine structure of *V* was confirmed using mass spectroscopy, which showed fragmentation pattern of the molecular ion at m/z = 859.60. The formation of compound *V* is assumed to proceed *via* nucleophilic attack of ethanol on the parent moiety *III* to give *IV* as intermediate followed by another nucleophilic attack of *IV* on the parent moiety *III* to give *V*.

The interaction between equimolar quantities of 3-formylchromone *I* and sulfadiazine *II* in absolute ethanol gave 1,4-adduct *IV*. The structure of adduct *IV* was confirmed from IR spectra which indicated the presence of exocyclic C=C, CO, and NH groups. ^{1}H NMR spectrum of *IV* indicated the presence of ethoxy group which has the triplet and quartet signals at respective δ = 1.14 and 3.73, and the presence of H-2 hydrogen atom of pyranone which has a singlet signal at δ = 5.97. Also, the structure of *IV* was supported by the presence of two singlet signals for NH protons at δ = 11.74 and 11.89. In addition, the fine structure of *IV* was also established from mass spectroscopy, which revealed the molecular ion at m/z = 452.01.

The treatment of *III* and/or *IV* with phenylhydrazine was also studied. Thus, interaction between compounds *III* and/or *IV* with phenylhydrazine in dry benzene and/or absolute ethanol gave the same product *II*. Structure of *II* was deduced from IR spectra, melting point and mixed melting point being 255 °C.

Some nucleophilic ring closure reactions of thiosemicarbazone *VI* with bifunctional halogen and oxygen compounds have been reported [8]. Thus, acylation of thiosemicarbazone *VI* with chloroacetyl chloride in the presence of acetic acid and fused NaOAc [9] afforded thiazolidin-4-one derivative *VII*, while alkylation of *VI* using monochloroacetic acid under the same conditions [10] furnished the isomeric structure, thiazolidin-3-one derivative *VIII*. The structures of isomers *VII* and *VIII* were established from IR spectra which indicated that the stretching frequency of pyrone CO of isomer *VII* ($\tilde{\nu}$ = 1650 cm^{-1}) is relatively lower than that of *VIII* ($\tilde{\nu}$ = 1672 cm^{-1}) due to the extension of conjugated system of the enol form of isomer *VII*. The enol form of isomer *VII* was supported by the presence of enolic OH group at $\tilde{\nu}$ = 3290 cm^{-1}. The structural difference between isomers *VII* and *VIII* was supported by the ^{1}H NMR spectra which indicated singlet signals due to CH_2, =CH at δ = 1.75—2.48 and 4.02, on the other hand, two signals at δ = 8.22—8.38 and 8.62—8.81 of CH=N and H-2 of pyrone. These signals appeared as multiplets due to


V
II
benzene
PhNHNH2
EtOH
X
EtOH
PhNHNH2
II
IV
III
benzene
EtOH
II
I
H2NNHCSNH2
ClCH2COCl
VI
ClCH2COOH
CH2(CO2H)2
CH3COCl
VIII
VII
AcOH—EtOH
NaCN
IX
XI

Scheme 1

Table 1. Spectral Data of the Prepared Compounds

Compound	IR, $\tilde{\nu}$/cm^{-1}				^{1}H NMR, δ
	ν(C=O) Pyrone	ν(C=O)*	ν(C=N) ν(C=C)	ν(NH) ν(OH)	
III	1673	–	1615	3105—3180	6.86—8.28 (m, 11H, H-5 diazine, H_{arom}, —CH=N), 8.51 (d, 2H, J = 4.58 Hz, H-4, H-6 diazine), 11.54 (br s, 1H, NH)
IV	1665	–	1620	3040—3100	1.14 (t, 3H, CH_3), 3.73 (q, 2H, CH_2), 5.97 (s, 1H, H-2 chromanone), 7.06—7.61 (m, 6H, H-5 diazine, H_{arom}, —CH=N), 7.82—8.23 (m, 4H, H_{arom}), 8.53 (d, 2H, J = 4.88 Hz, H-4, H-6 diazine), 11.74, 11.89 (each s, 1H, NH)
V	1660	–	1580, 1600 1615	3040—3120	1.09 (t, 3H, CH_3), 3.73 (q, 2H, CH_2), 5.97 (br s, 2H, H-2 chromanone), 6.55—6.65 (m, 2H, H-5 diazine), 6.95—8.23 (m, 18H, H_{arom}, —CH=N), 8.48, 8.54 (each d, 2H, J = 2.14 Hz, H-4, H-6 diazine), 11.50 (br s, 1H, NH), 11.73, 11.88 (each s, 1H, NH)
VII	1650	1730	1610, 1620	3090, 3150, 3290	2.16, 2.48 (each s, 2H, CH_2), 4.02 (s, 1H, =CH), 6.60 (br s, 1H, H-6 chromone), 7.11—7.13 (m, 1H, H-8 chromone), 7.30—7.66 (m, 1H, H-7 chromone), 7.68—7.80 (m, 1H, H-5 chromone), 8.22—8.38 (m, 1H, —CH=N), 8.61—8.71 (m, 1H, H-2 chromone)
VIII	1672	1732	1620, 1635	3070	1.75 (s, 2H, CH_2), 4.02 (s, 1H, =CH), 6.59—7.57 (m, 3H, H- 6, H-7, H-8 chromone), 7.70—7.91 (m, 1H, H-5 chromone), 8.27—8.36 (m, 1H, —CH=N), 8.62—8.81 (m, 1H, H-2 chromone), 9.17 (s, 1H, NH)
IX	1620	–	1650	3020—3680	2.16 (m, 2H, CH_2), 6.70—8.01 (m, 4H, H_{arom}), 8.20 (s, 1H, —CH=N), 9.37 (s, 1H, H-2 chromone), 11.27, 11.77 (each s, 1H, NH), 12.51 (br s, 1H, OH_{enol})
XI	1648	–	1623 1610	3160, 3255, 3440	7.52—8.21 (m, 5H, H_{arom}), 9.17 (s, 1H, NH), 11.54 (br s, 1H, NH)

*CO of thiazolidinone.

finding of molecular distribution.

One of the most important studies was that of the reactivity of thiosemicarbazone towards bifunctional oxygen compounds. Thus thiosemicarbazone *VI* reacted with malonic acid in the presence of acetyl chloride [11] to give 2,3-dihydro-2-thioxo-4,6-(1*H*,5*H*)pyrimidinedione derivative *IX*. Molecular structure of *IX* was deduced from elemental analysis and spectral data. IR spectra of *IX* indicated the presence of a broad band at $\tilde{\nu}$= 1620—1650 cm^{-1} of the C=N and CO groups of pyrone and pyrimidinedione and a broad band at 3020—3680 cm^{-1} for NH and enolic OH groups. The ^{1}H NMR spectrum of *IX* indicated the presence of methylene group at δ = 2.16, two singlet signals at δ = 8.20 and 9.37 of CH=N and H-2 of pyrone, as well as the presence of signals at δ = 11.27, 11.77, and 12.51 of NH and enolic OH groups, which supported the postulated structure.

One of the aims of the present study was to synthesize some new heterocyclic system *via* the addition reaction to polyactive centre of thiosemicarbazone *VI*. Thus addition of NaCN to compound *VI* in the presence of AcOH—EtOH led to the direct formation of 3-mercapto-1*H*,5*H*-[1,2,4]triazino[5′,6′:5,4]pyrrolo[2,3-*b*]-chroman-12-one *XI*. The formation of compound *XI* may be rationalized as 1,2-addition of HCN to the CH=N group of thiosemicarbazone *VI* followed by 1,2-addition of NH_2 group on the CN group to give the intermediate *X* which can cyclize *via* 1,4-addition of NH_2 group to the pyrone ring leading to *XI*. The IR spectra of *XI* indicated the presence of C=N, CO, and NH groups. The ^{1}H NMR spectra of *XI* showed signals at δ = 7.52—8.21, 9.17, and 11.54 for aromatic and NH protons. The structure of compound *XI* was also supported by mass spectroscopic fragmentation analysis which indicated the molecular ion at m/z = 271.75.

EXPERIMENTAL

Melting points were determined in open glass capillaries and are uncorrected. IR spectra in KBr were recorded on a Perkin—Elmer 550 spectrophotometer, ^{1}H NMR spectra of compounds *III*—*V*, *IX*, *XI* (DMSO-d_6) on Tesla BS 487A (80 MHz) and of compounds *VII*, *VIII* ($CDCl_3$) on Bruker (200 MHz) spectrometers using TMS as internal standard. Mass spectra were taken on Hewlett—Packard Model MS 5988 (70 eV, direct inlet recording). 3-Formylchromone *I* was prepared according to the method reported by *Nohara et al.* [12] and thiosemicarbazone *VI* according to Ref. [8]. Analytical data are given in Table 2.

Table 2. Physical Data of the New Synthesized Compounds

Compound	Formula M_r	w_i(calc.)/% w_i(found)/%				Yield	M.p.	Solvent
		C	H	N	S	%	°C	
III	$C_{20}H_{14}N_4SO_4$	59.11	3.47	13.79	7.89	80	238—240	Benzene
	406.42	58.80	3.60	13.21	7.41			
IV	$C_{22}H_{20}N_4SO_5$	58.40	4.46	12.38	7.09	81	268—269	Ethanol
	452.49	58.86	4.55	12.30	6.89			
V	$C_{42}H_{34}N_8S_2O_9$	58.73	3.99	13.05	7.47	60	233—234	Ethyl acetate
	858.91	58.10	4.15	12.55	7.01			
VII	$C_{13}H_9N_3SO_3$	54.35	3.16	14.63	11.16	95	223—225	Diluted AcOH
	287.30	54.24	3.11	14.60	11.01			
VIII	$C_{13}H_9N_3SO_3$	54.35	3.16	14.63	11.16	57	255	AcOH
	287.30	54.67	3.28	14.52	10.95			
IX	$C_{14}H_9N_3SO_4$	53.33	2.88	13.33	10.17	60	above	AcOH
	315.31	53.94	2.90	13.01	9.76		275	
XI	$C_{12}H_8N_4SO_2$	52.93	2.96	20.58	11.78	50	227	AcOH
	272.29	52.23	2.67	20.10	11.25			

3-Aryliminomethylchromone Derivative *III*

A mixture of 3-formylchromone *I* (0.01 mol), sulfadiazine *II* (0.01 mol), and catalytic amount (about 5 mg) of 4-toluenesulfonic acid in dry benzene (30 cm^3) was heated under reflux for 2 h, cooled and the solid that separated was filtered off and crystallized from the appropriate solvent.

3-Arylaminomethylene-2-ethoxychromone Derivative *IV*

To a solution of 3-formylchromone *I* (0.01 mol) in the least amount of absolute ethanol, sulfadiazine *II* (0.01 mol) in the least amount of absolute ethanol was added, the mixture was heated under reflux for 2 h, cooled and the resultant solid was crystallized.

Formation of 1,4-Adduct *V*

A suspension of compound *III* (0.005 mol) in absolute ethanol (20 cm^3) was refluxed for 2 h. The solid that separated upon cooling was crystallized from the proper solvent.

Thiazolidin-4-one Derivative *VII*

A mixture of *VI* (0.006 mol), chloroacetyl chloride (0.6 cm^3), and fused sodium acetate (2 g) in glacial acetic acid (20 cm^3) was refluxed for 3 h, cooled, then poured into cold water. The solid thus obtained was filtered and recrystallized.

Thiazolidin-3-one Derivative *VIII*

A mixture of *VI* (0.006 mol), monochloroacetic acid (0.016 mol), and fused sodium acetate (2 g) in glacial acetic acid (20 cm^3) was heated under reflux for 8 h, cooled and poured into cold water. The separated solid was crystallized from the proper solvent.

2,3-Dihydro-2-thioxo-4,6-(1*H*,5*H*)pyrimidinedione Derivative *IX*

A mixture of *VI* (0.004 mol) and malonic acid (0.004 mol) in acetyl chloride (1.5 cm^3) was refluxed for 6 h on a steam bath. The mixture was poured into crushed ice and the resultant solid was crystallized.

3-Mercapto-1*H*,5*H*-[1,2,4]triazino[5′,6′:5,4]-pyrrolo[2,3-*b*]chroman-12-one (*XI*)

A mixture of *VI* (0.008 mol) and sodium cyanide (0.008 mol) in the mixture AcOH—EtOH (φ_r = 1:1, 20 cm^3) was heated under reflux for 6 h. The mixture was filtered hot and the filtrate after cooling gave yellow crystalline product, and then recrystallized from the appropriate solvent.

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