Molecules **1996**, *1*, 223 – 235

Synthesis and Theoretical Study of Mannich Type Reaction Products of 3-Formylchromones with Triazoles and Amides and Nucleophilic Formation of 2,3-Disubstituted-4-Chromanones

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Received: 17 October 1996 / Accepted: 7 February 1997 / Published: 21 February 1997

Abstract

The semiempirical PM3 method has been used to study possible reaction paths of the condensation of 3-formylchromones with amides and triazoles. Optimal geometries of intermediates **7**, products **8** and all other putative reaction intermediates were obtained. Pertinent transition states, **TS I** for the dehydratation to carbocation **13**, and **TS II** for amidoalkylation, were located. The semiempirical PM3 method was also used for the calculation of the heats of formation and optimal structures of 4-chromanones **10** and 4-chromones **11**. Several compounds of these types have been prepared. Their structures were proved by elemental analysis and ^{1}H-NMR spectra.

Keywords: PM3 calculations, geometry optimization, 4-oxo-4*H*-[1]-benzopyran-3-carboxaldehydes, reaction path, molecular modelling

Introduction

The synthetic and pharmaceutical importance of chromones and chromanones prompted us to synthesize and to study theoretically *N*-[1-(1, 2, 4-triazolyl)-3-chromonylmethyl]amides or *N*-[1-(1, 2, 3-benzotriazolyl)-3-chromonylmethyl]amides, respectively, and 2,3-disubstituted-4-chromanones. Chromones possessing a formyl group in the 3-position are useful synthones for the synthesis of a wide variety of heterocycles [1]. The synthetic significance and pharmaceutical activity of the O-C = C-C = O moiety as the main structural feature of 3-formylchromone derivatives have led to a great interest in these compounds.

For instance, chromone-3-carboxaldehydes are very interesting from a synthetic and theoretical point of view because these compounds contain three electron-deficient positions (C-2, C-4 and the carbon atom of the formyl group) where nucleophilic attack is possible. A well known feature of chromone derivative reactions is the facile ring-opening via nucleophilic attack at the 2-position [2]. How-

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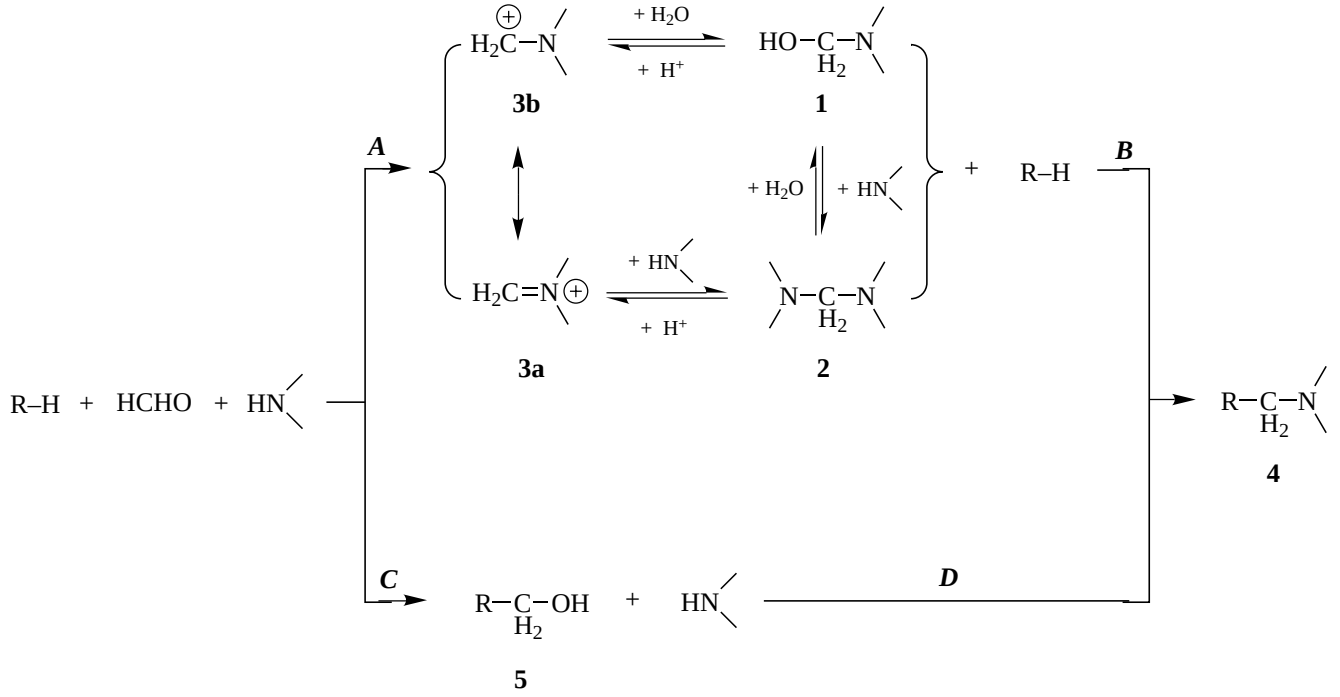
† *Presented at the Joint 12th Symposium on the Chemistry of Heterocyclic Compounds (SCHHC) and the 6th Blue Danube Symposium on Heterocyclic Chemistry (BDSHC), Brno, Czech Republic, September 1–4, 1996.*



Scheme 1. *Reaction path of Mannich reaction.*

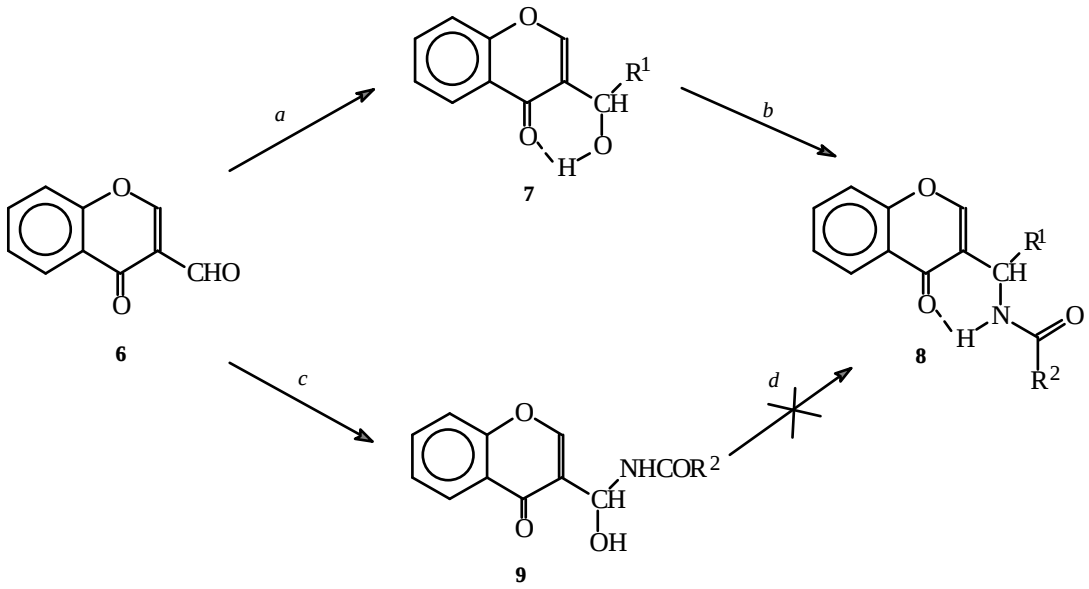
ever, not every interaction of position C-2 with nucleophiles leads to γ-pyrone ring-opening. The presence of certain substituents at position 3, especially those which are in conjugation with the C2-C3 double bond, change the reactivity of chromone system towards nucleophiles leading to a preference for nucleophilic addition [3] to the double bond. We recently reported similar behaviour of 3-formylchromone with aromatic amino acids in alcoholic reaction medium [4]. Our recent investigations were focused on spectral and theoretical (AM1) [5,6], synthetic [4,7,8] and biological [4,8] studies of 3-formylchromones derivatives. We now report the synthesis, as well as the results of semiempirical PM3 calculations of several types of chromanone and chromone derivatives.

It is known that the amide group is an important constituent of many biologically significant compounds and amidoalkylation has found versatile application in organic synthesis as a valuable alternative to, or extension of, the Mannich reaction [9–11]. The reaction path of the Mannich reaction (Scheme 1) has been well investigated [12]. The reaction consist of the condensation of a substrate (R-H) possessing at least one active hydrogen with formaldehyde (or other aldehydes [13]) and a primary or secondary amine (or amide [9]). The condensation occurs in two steps: first, the amine reacts with formaldehyde to give condensation product **1**-**2**-**3** (step A), which then attacks the substrate R-H (step B). The reaction does not normally follow the other possible route (steps C and D); however, some successful reaction between hydroxymethyl derivatives **5** and alkylamines to give Mannich base **4** can take place. If the nucleophilicity of the carbanion derived from the labile hydrogen compound is greater than that of amine, formation of a hydroxymethyl derivative **5** would be favoured over formation of derivative **1**.

Results and discussion

Recent work in our laboratory has proved that the Mannich type reaction is a very suitable method for the preparation of chromone derivatives containing various amide moieties **8** [14]. Our investigations led to a novel extension of the utilisation of 3-formylchromones **6** in Mannich type reaction with two base components, 1*H*-1,2,4-triazole or 1*H*-1,2,3-benzotriazole, respectively, and with amides as H-active components (Scheme 2). We found the reaction is general at least for 4-oxo-4*H*-[1]benzopyran-3-carboxaldehydes and primary amides because there were used aliphatic, aromatic and heterocyclic amides. We were able to isolate Mannich type reaction intermediates **7**. The products **8** of the Mannich reaction as well as these compounds could be stored in capped vials for months without any decomposition.

We have shown that *N*-[1-(1,2,4-triazolyl)-3-(6-R-chromonyl)methyl]amides **8** and *N*-[1-(1,2,3-benzotriazolyl)-3-(6-R-chromonyl)methyl]amides **8** readily react with nucleophiles under mild conditions (Scheme 3) to form chromane derivatives of enamide type **10** as stable products in 50–75% yields [14]. The formation of 2,3-disubstituted-4-chromanones **10** can be explained via attack of nucleophile at the 2-position of the chromone ring of **8** followed by a double bond shift and elimination of 1*H*-1,2,4-triazole or 1*H*-1,2,3-benzotriazole as the final step



Scheme 2. *Synthesis of chromone derivatives* ***7–9***.
Synthesized compounds:
for ***7*** R^1 *= 1-(1,2,4-triazolyl)-, 1-(1,2,3-benzotriazolyl)-; for* ***8*** R^1 *= 1-(1,2,4-triazolyl)-,* R^2 *= Ph, 3-Py;*
R^1 *= 1-(1,2,3-benzotriazolyl)-,* R^2 *= Me, Ph; for* ***9*** R^2 *= Me, Ph, 3-Py*
Reagents and conditions:
*(*a*)* R^1*H, dry touene, reflux 3-8 h; (*b*)* R^2CONH_2*, dry toluene, reflux 15-23 h; (c)* R^2CONH_2*,* p*-TsOH, dry toluene, reflux 30 min; (*d*) A:* R^1*H, dry toluene, reflux 20 h; B:* R^1*H,* p*-TsOH, dry toluene, reflux 20 h; C:* R^1*H, AcOH, dry toluene, reflux 20 h.*

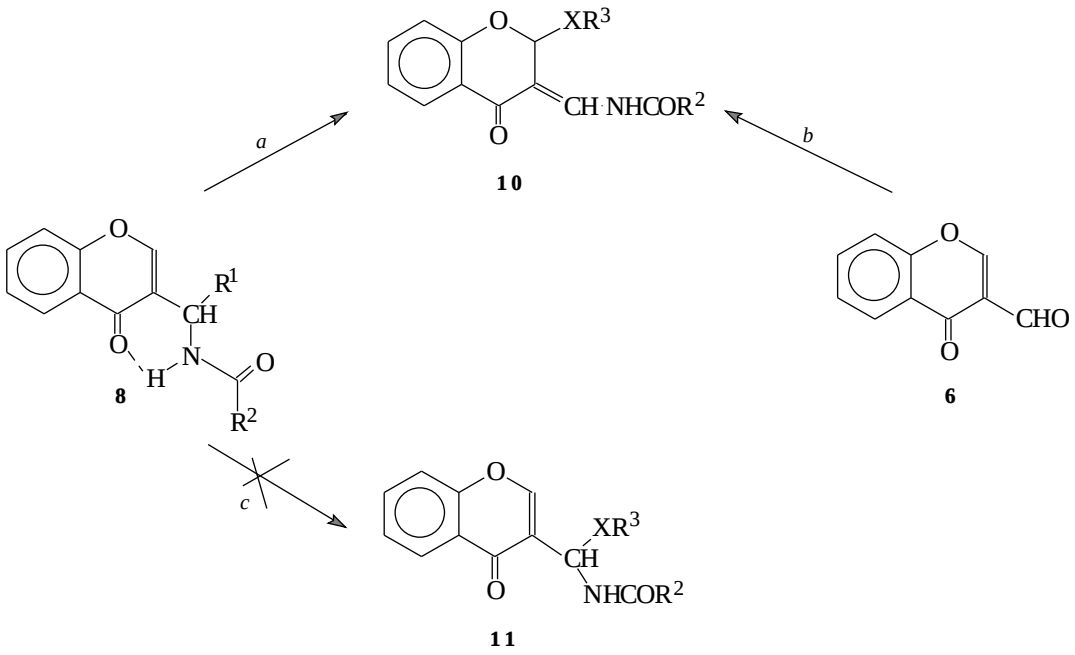
of the reaction (Fig. 1). ^{1}H-NMR spectra of prepared derivatives **10** (R^3 = Ar, R; X = O, S, NH) showed two singlet signals for the H-2 proton at about δ 5.8–7 ppm [14]. This finding prompted us to study the possible optimal geometries of compounds **10** by the semiempirical PM3 method. We chose simple systems for calculation (R^2 = H, Me, Ph; R^3 = H, Me, Et; X = O, S, NH).

Synthetic study of possible reaction routes

We investigated both possible reaction paths which could lead to the requested products **8**, but only one of them was successful (Scheme2). Reaction path *a*+*b*: Hydroxy-derivatives **7** were prepared by reaction of 3-formylchromones **6** with 1*H*-1,2,4-triazole or 1*H*-1,2,3-benzotriazole, respectively, in 75–76% yields (*a*). Products are stable in a solid state. Their isolation from the reaction mixture is very easy, because they are insoluble in hot toluene. Derivatives **7** undergo a reaction with amides (*b*) to form *N*-[1-(1,2,4-triazolyl)-3-chromonylmethyl]-amides or *N*-[1-(1,2,3-benzotriazolyl)-3-chromonyl-methyl]-amides, respectively, **8** in good yields. The succesful preparation of compounds **7**, **8** required special attention to the purification of every component of the reaction mixture. The reaction is unsuccesful in the presence of even a trace of water. We prepared some derivatives **8**, which were substituted at position 6 of the benzopyranone ring [14] (substituent at position 6 = CH_3, Cl, Br, NO_2; R^1 = 1-(1,2,4-triazolyl)-, 1-(1,2,3-benzotriazolyl)-; R^2 = CH_3, Ph, 3-Py, 4-Py).

Reaction path *c*+*d*: 3-Formylchromones undergo reaction with amides in the presence of 4-toluenesulfonic acid in dry toluene to form 3-(*N*-acylamino-1-hydroxymethyl)chromones **9** in 75–80% yields. The reaction is very fast, the products precipitate from the boiling reaction mixture after 7–9 minutes. The prepared products **9** can be stored in capped vials for months without any decomposition. The preparation of compounds **8** from 3-(*N*-acylamino-1-hydroxymethyl)chromones **9** by reaction with 1*H*-1,2,4-triazole was unsuccessful. Derivatives **8** did not form under the conditions examined (Scheme 2, path *d*: *A–C*). We isolated only starting materials **9** and 1*H*-1,2,4-triazole in all cases. We could not use basic reaction conditions because 3-formylchromones and their derivatives undergo ring-opening reactions at the C-2 position in basic reaction media [2].

In another part of our study, the behaviour of Mannich type reaction products **8** in nucleophilic reaction media was investigated. We prepared 2,3-disubstituted-chroman-4-ones **10** by two different ways - reaction paths *a*,*b* (Scheme 3). Reaction path *a*: *N*-[1-(1,2,4-Triazolyl)-3-chromonylmethyl]amides **8** or *N*-[1-(1,2,3-benzotriazolyl)-3-chromonylmethyl]amides **8**, respectively, undergoes nucleophilic substitution with nucleophile R^3XH (may be also



Scheme 3. *Reactions of derivatives* ***8*** *with nucleophiles. Synthesized compound:* ***10*** $R^2 = Ph$, $R^3 = Et$, $X = O$ *Reagents and conditions:* (a) *ethanol, reflux 3 h;* (b) *ethanol,* p-*TsOH, reflux 4 h;* (c) *ethanol, reflux 6 h*

the solvent with nucleophilic properties) to form compounds **10** in 60–70% yields. According to Katritzky's works [13] describing reactions of derivatives **8** (derived from aliphatic and aromatic aldehydes), compounds **8** undergo nucleophilic substitution reaction at the benzotriazolate moiety bearing carbon atom (**11** in Scheme 3). In contrast, as shown in our previous investigation [14] chromone derivatives **11** can not be gained according to reaction path *c* (Scheme 3).

In case of chromone derivatives **8** nucleophilic attack preferentially occurs at position 2 of the chromone ring (Fig. 1) rather than direct nucleophilic substitution of benzotriazolate moiety or triazolate, respectively, by nucleophilic reagent.

Reaction path *b*: The same derivative **10** (R^3 = Et, X = O) may be prepared by another way by reaction of 4-oxo-4*H*-[1]-benzopyran-3-carboxaldehyde with amides in the presence of catalytic amounts of 4-toluenesulfonic acid in ethanol, but in lower yield as from compounds **8**.

Semiempirical PM3 calculations and molecular modelling

We used semiempirical PM3 molecular orbital calculations to (I) corroborate the proposed mechanism (Scheme 4) of the Mannich amidoalkylation; (ii) to obtain information about conformational properties of the Mannich products **8**; and (iii) to investigate the reactivity of chromone derivatives **8** towards nucleophiles.

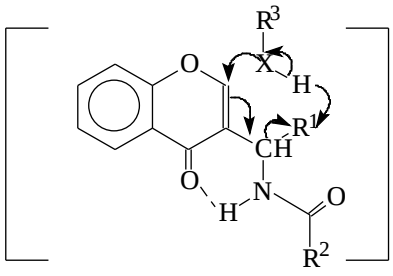


Fig. 1.

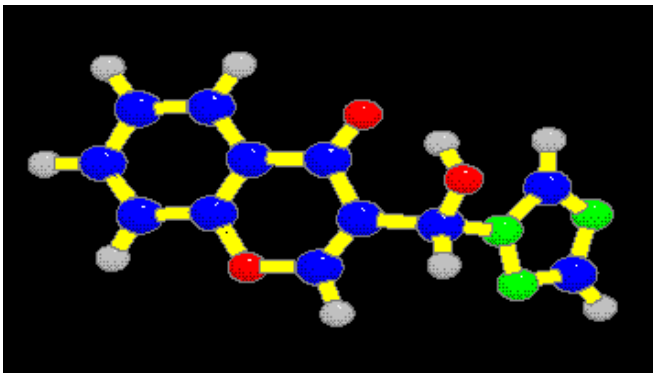
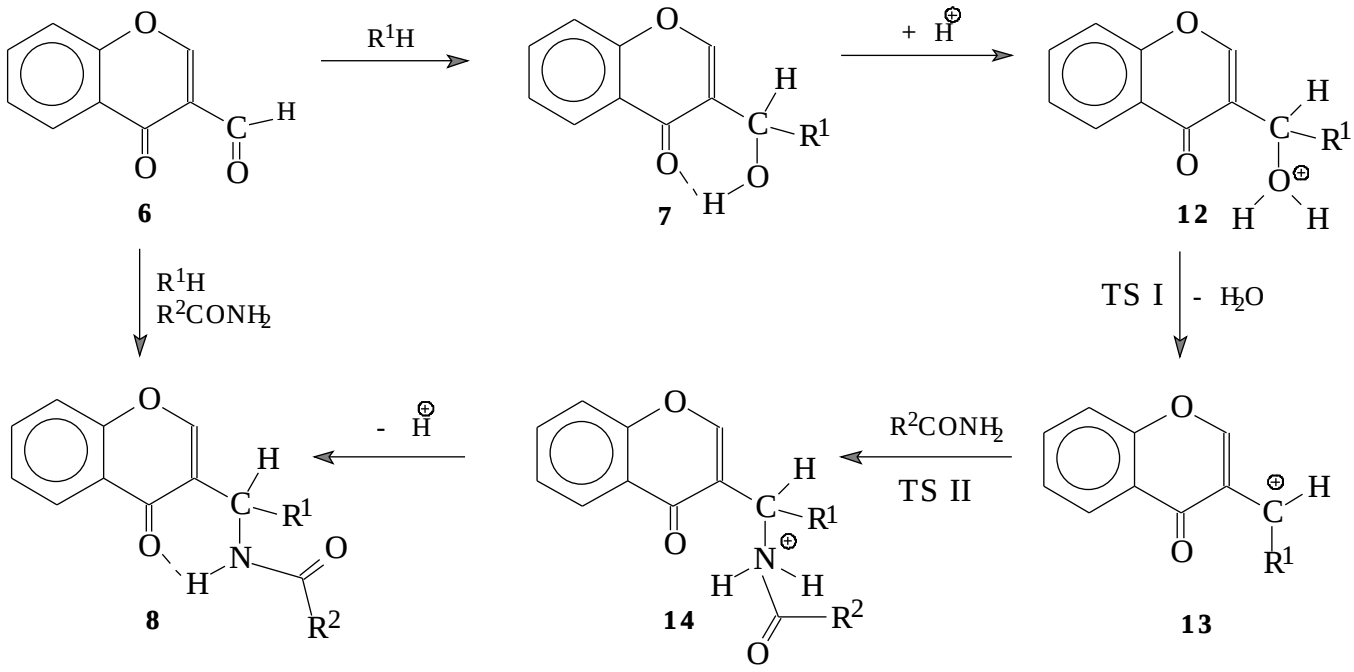


Fig. 2. *3D-structure of* ***7****.*



Scheme 4. *Proposed and calculated reaction path of Mannich type reaction of 3-formylchromone.*
R^1 = 1-(1,2,4-triazolyl)-, 1-(1,2,3-triazolyl)-, 1-(1,2,3-benzotriazolyl)-; R^2 = H, CH_3, Ph, 3-Py, 4-Py

Mechanism of the Mannich type amidoalkylation. The reaction path of the Mannich reaction was studied theoretically (MNDO [15], AM1 [16]), but not the reaction paths of amidoalkylation.

We have calculated the reaction path of the condensation reaction of unsubstituted 3-formylchromone with several amides (R^2 = H, CH_3, Ph, 3-Py, 4-Py) and triazoles or benzotriazole, respectively, according to the proposed reaction path represented in Scheme 4. We have supposed that the reaction proceeds through the carbocation **13**, which can be formed from intermediate **7** after protonation (structure **12**) and dehydratation, because of the weak acidic conditions (e.g. benzotriazole itself serving as an acid). Attack of the amide to carbocation **13** to form intermediate **14** is the following step of the reaction path. Deprotonation of intermediate **14** is the last step of the path which leads to the *N*-[1-(1, 2, 4-triazolyl)-3-chromonylmethyl]amides or *N*-[1-(1, 2, 3-benzotriazolyl)-3-chromonylmethyl]amides **8**, respectively.

We calculated optimal geometries and heats of formation of all intermediates and products. In addition, two transition states (**TS I** for dehydratation of intermediate **12** and **TS II** for formation of intermediate **14**) were located. The results of these calculations are collected in Tables 1 and

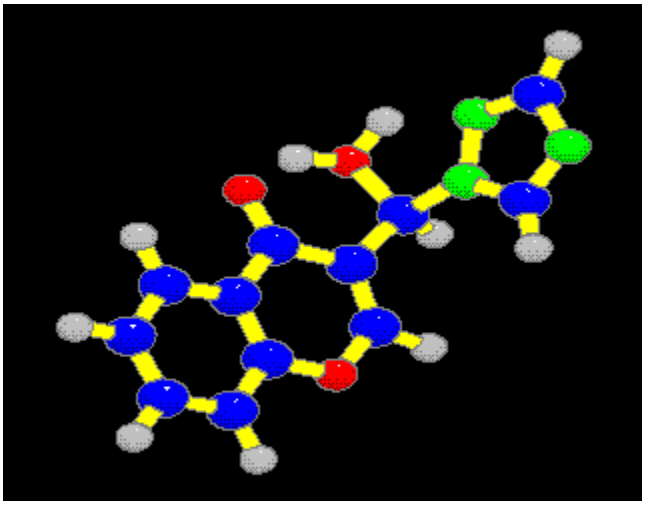


Fig. 3. *3D-structure of* ***12****.*

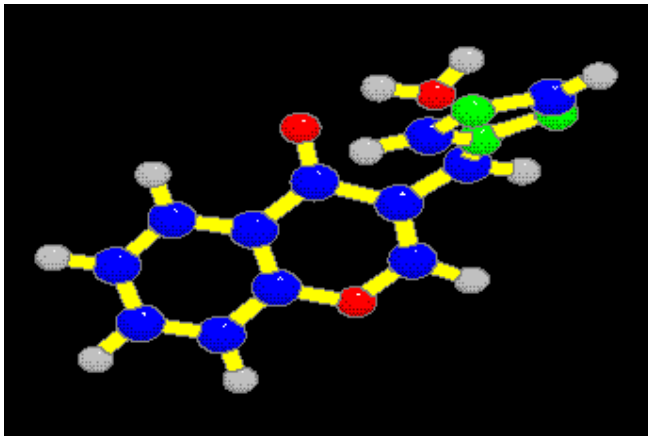
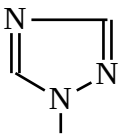
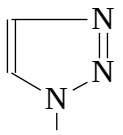
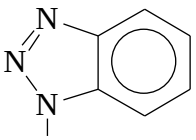


Fig. 4. *3D-structure of* ***TS I****.*

Table 1. *Data for intermediates* ***7***, ***12***, ***13*** *and transition state* ***TS I***

R^1	ΔH_f/kcal **7**	ΔH_f/kcal **12**	ΔH_f/kcal **TS I**	bond length[a] **TS I**	energy barrier[b] **12**→**TS I**	$\tilde{\nu}$* of **TS I** cm^{-1}	ΔH_f/kcal **13**
	-18.77	169.65	172.43	1.909	2.78	155.5	218.85
	-2.95	185.61	186.45	1.764	0.84	200.4	234.68
	15.36	195.76	197.67	1.720	1.91	190.2	241.00

(a) the length of the breaking bond [$C_9 - O_{H_2O}$] in Å.
(b) activation barrier in kcal·mol^{-1}
***** *imaginary frequency*

2. The optimised structures of all compounds **7** showed the presence of an intramolecular hydrogen bond between the γ-pyrone carbonyl group and the hydroxy group. Optimised geometries for all reaction intermediates and transition states are represented in Figs. 2–8 (for all figures R^1 = 1-(1,2,4-triazolyl)-; R^2 = Ph).

The reaction barriers for dehydratation (**12** → **TS I**, see Table 1) decrease in the following order: R^1: 1-(1,2,4-triazolyl) → 1-(1,2,3-benzotriazolyl) → 1-(1,2,3-triazolyl). The second step, addition of the amides to carbocation **13** (**13** → **TS II**, Table 2) appears to be rate determining. Here, for 1*H*-1,2,3-triazole or benzotriazole, respectively, among aliphatic amides formamide derivatives have lower activation energies than acetamide derivatives, for 1*H*-1,2,4-triazole this ordering is reversed. In the case of aromatic and heterocyclic amides the following order is discernible: for R^1 = 1-(1,2,3-triazolyl)-: R^2 - Ph > 3-Py > 4-Py; for R^1 = 1-(1,2,4-triazolyl)-: R^2 - Ph > 4-Py > 3-Py.

Conformational properties of compounds ***8***. Each one of the Mannich products **8** can exist as two isomers (*trans* and *cis* arrangement of -CO-NH- bond, Fig. 9). The com-

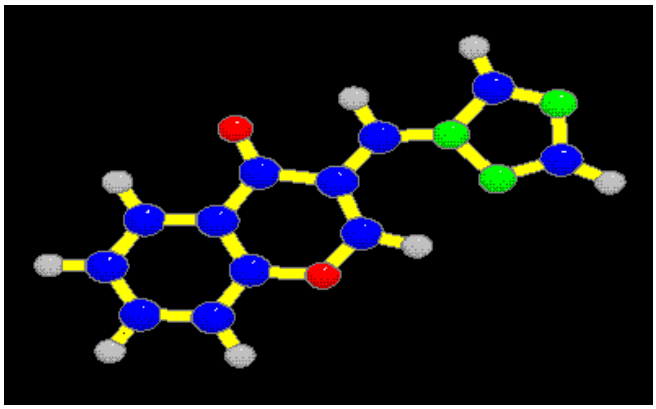


Fig. 5. *3D-structure of* ***13***.

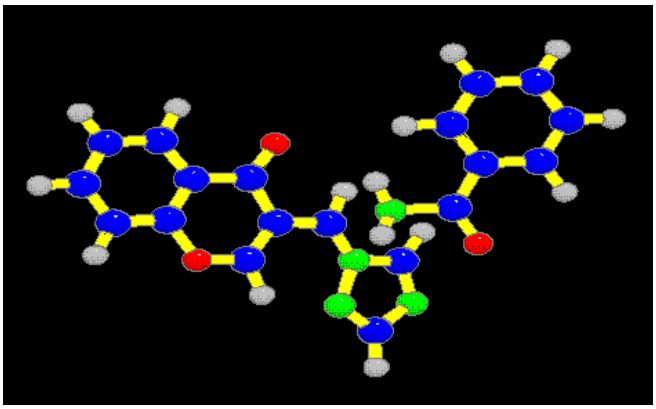
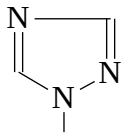
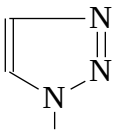
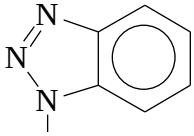


Fig. 6. *3D-structure of* ***TS II***.

Table 2. *Data for intermediate* ***14*** *and transition state* ***TS II***

R^1	R^2	ΔH_f/kcal **TS II**	bond length[a] **TS II**	energy barrier[b] **13** → **TS II**	$\tilde{\nu}$* of **TS II** cm^{-1}	ΔH_f/kcal **14**
	H	194.92	2.325	13.46	251.8	180.54
	CH_3	185.82	2.235	13.30	334.3	164.61
	Ph	211.23	2.256	.77	294.9	199.49
	3-Py	228.27	2.233	13.78	317.5	206.22
	4-Py	224.60	2.203	.31	345.6	215.90
	H	209.60	2.339	12.31	254.9	196.47
	CH_3	202.09	2.361	13.74	242.6	179.06
	Ph	234.12	2.288	10.38	310.2	210.03
	3-Py	243.66	2.263	13.34	292.8	220.43
	4-Py	244.62	2.253	13.50	298.0	222.02
	H	215.49	2.251	11.88	290.8	201.81
	CH_3	207.10	2.214	12.43	339.0	198.84

(a) the length of the forming bond [C_9-N_{amide}] in Å
(b) reaction barrier in kcal·mol^{-1}
** imaginary frequency*

puted heat of formation differences between both isomers were in the range 0.02–3.54 kcal·mol^{-1} (Table 3). For almost all cases, with only exception of unsubstituted acetamide-1-(1,2,3,-triazolyl)-derivative, the *trans*- are predicted to be more stable than *cis*-isomers. The optimised structures of all compounds **8** showed the presence of hydrogen bonds between γ-pyrone carbonyl group and amide NH group.

Reactivity of compounds ***8*** *towards nucleophiles.* As we have already mentioned in the synthetic part of our report, nucleophilic attack preferentially occurs at position 2 of the chromone ring of compounds **8** (Fig. 1) rather than direct nucleophilic substitution of the benzotriazolate moiety or the triazolate moiety by the nucleophilic reagent.

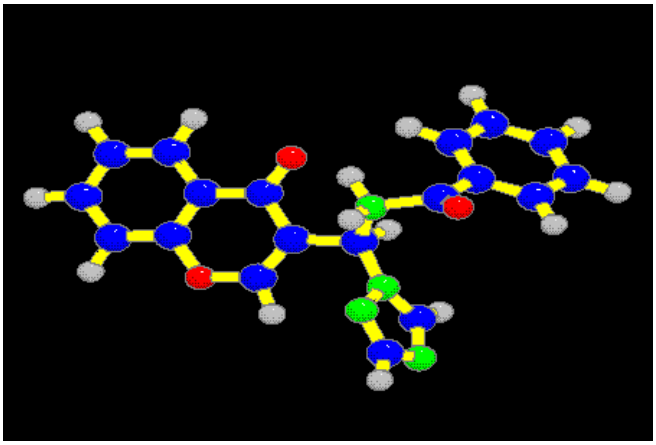


Fig. 7. *3D-structure of* ***14****.*

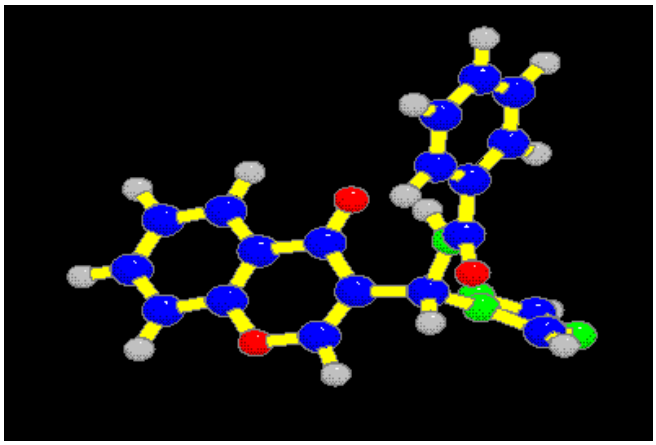
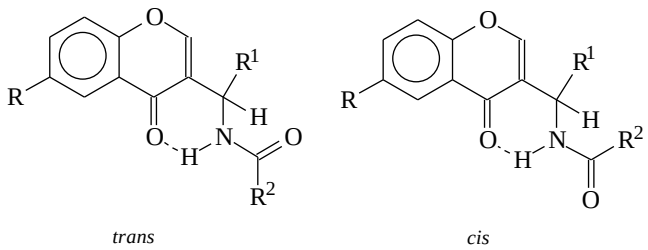


Fig. 8. *3D-structure of* ***8****.*

Table 3. *Heats of formation for isomers of compounds* ***8****.*

	ΔH_f /kcal		$\Delta\Delta H_f^*$	ΔH_f /kcal		$\Delta\Delta H_f^*$	ΔH_f /kcal		$\Delta\Delta H_f^*$	ΔH_f /kcal		$\Delta\Delta H_f^*$
	trans	cis	trans–cis	trans	cis	trans–cis	trans	cis	trans–cis	trans	cis	trans–cis
$R^2\backslash R$		H			CH_3			Cl			NO_2	
					1–(1,2,4–triazolyl)-							
H	–3.53	–3.18	*–0.35*	–12.95	–12.60	*–0.35*	–9.40	–9.03	*–0.37*	–10.15	–9.64	*–0.51*
CH_3	–12.24	–12.21	*–0.03*	–21.68	–21.66	*–0.02*	–18.05	–17.96	*–0.09*	–18.57	–18.20	*–0.37*
Ph	22.68	–	–	13.28	–	–	16.79	–	–	15.93	16.70	*–0.77*
3–Py	29.96	–	–	20.54	–	–	24.12	–	–	23.46	26.13	*–2.67*
4–Py	30.47	–	–	21.04	–	–	24.63	–	–	23.99	26.78	*–2.79*
					1–(1,2,3–triazolyl)-							
H	12.12	12.79	*–0.67*	2.69	3.37	*–0.68*	6.26	6.93	*–0.67*	5.51	6.30	*–0.79*
CH_3	3.66	3.61	*0.05*	–5.77	–5.73	*–0.04*	–2.16	–2.15	*–0.01*	–2.71	–1.64	*–1.07*
Ph	38.25	–	–	29.06	–	–	32.39	–	–	31.56	34.11	*–2.60*
3–Py	45.53	–	–	36.11	–	–	39.70	–	–	38.99	42.53	*–3.54*
4–Py	46.13	–	–	36.71	–	–	40.31	–	–	39.68	42.44	*–2.76*
					1–(1,2,3–benzotriazolyl)–							
H	29.16	30.78	*–1.62*	19.77	21.38	*–1.61*	23.27	24.91	*–1.64*	22.39	24.16	*–1.77*
CH_3	20.36	22.28	*–1.92*	10.97	12.87	*–1.90*	14.45	16.41	*–1.96*	13.52	15.66	*–2.06*

To investigate this problem of different reactivity of carbons at positions 2 and 9 of the benzopyranone ring of Mannich type reaction products **8** towards nucleophiles, the PM3 charge densities (point charges, see Table 4) on these atoms as well as the molecular electrostatic potential (MEP) on the van der Waals surface were used as reactivity indices. The above mentioned preference for nucleophilic attack at C-2 is clearly visible on the MEP distribution on the van der Waals surface of the compound **8** (Fig. 10; R^1 = 1-(1,2,4-triazolyl)-; R^2 = Ph), where the carbon C-2 (point charge = 0.1326) appears to be more electrophilic centre than C-9 (point charge = 0.0701). For



R = H, CH_3, Cl, NO_2
R^1 = 1-(1,2,4-triazolyl)-, 1-(1,2,3-triazolyl)-, 1-(1,2,3-benzotriazolyl)-
R^2 = H, CH_3, Ph, 3-Py, 4-Py

Fig. 9. *Calculated substituted isomers of compounds* ***8****.*

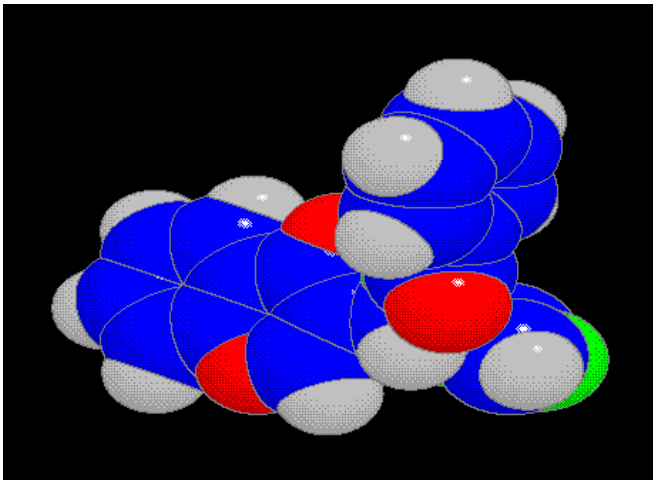


Fig. 10a. *3D-structure of the van der Waals surface of* ***8*** *(R^1 = 1-(1,2,4-triazolyl)-; R^2 = Ph).*

Table 4. *Point charges on C-2 and C-9 of derivatives* ***8****.*

R	H		CH_3		Cl		NO_2	
	trans	cis	trans	cis	trans	cis	trans	cis
	q (C-2)		q (C-2)		q (C-2)		q (C-2)	
	q (C-9)		q (C-9)		q (C-9)		q (C-9)	
R^2	*Δq (C2-C9)*		*Δq (C2-C9)*		*Δq (C2-C9)*		*Δq (C2-C9)*	
				1-(1,2,4-triazolyl)-				
H	0.1330	0.1467	0.1334	0.1471	0.1326	0.1467	0.1263	0.1416
	0.0704	0.0648	0.0707	0.0649	0.0701	0.0650	0.0678	0.0642
	0.0626	*0.0819*	*0.0627*	*0.0822*	*0.0625*	*0.0817*	*0.0585*	*0.0774*
CH_3	0.1487	0.1469	0.1491	0.1474	0.1484	0.1469	0.1420	0.1413
	0.0841	0.0590	0.0843	0.0592	0.0837	0.0590	0.0813	0.0582
	0.0646	0.0879	0.0648	0.0882	0.0647	0.0879	0.0607	0.0832
Ph	0.1316	-	0.1320	-	0.1313	-	0.1246	0.1285
	0.0715	-	0.0717	-	0.0712	-	0.0688	0.0630
	0.0601	-	*0.0603*	-	*0.0601*	-	*0.0558*	*0.0655*
3-Py	0.1347	-	0.1352	-	0.1344	-	0.1279	0.1300
	0.0730	-	0.0732	-	0.0727	-	0.0703	0.0685
	0.0617	-	*0.0620*	-	*0.0617*	-	*0.0576*	*0.0615*
4-Py	0.1358	-	0.1366	-	0.1356	-	0.1292	0.1170
	0.0729	-	0.0732	-	0.0726	-	0.0703	0.0810
	0.0629	-	*0.0634*	-	*0.0630*	-	*0.0589*	*0.0360*
				1-(1,2,3-triazolyl)-				
H	0.1349	0.1471	0.1358	0.1474	0.1351	0.1472	0.1289	0.1424
	0.0732	0.0661	0.0738	0.0662	0.0733	0.0663	0.0709	0.0655
	0.0617	*0.0810*	*0.0620*	*0.0812*	*0.0618*	*0.0809*	*0.0580*	*0.0769*
CH_3	0.1487	0.1468	0.1492	0.1428	0.1486	0.1466	0.1422	0.1359
	0.0871	0.0618	0.0874	0.0741	0.0869	0.0618	0.0843	0.0800
	0.0616	*0.0850*	*0.0618*	*0.0687*	*0.0617*	*0.0848*	*0.0579*	*0.0559*
Ph	0.1362	-	0.1488	-	0.1360	-	0.1302	0.1452
	0.0741	-	0.0867	-	0.0737	-	0.0712	0.0704
	0.0621	-	*0.0621*	-	*0.0623*	-	*0.0590*	*0.0748*
3-Py	0.1385	-	0.1389	-	0.1382	-	0.1324	0.1201
	0.0757	-	0.0759	-	0.0753	-	0.0730	0.0847
	0.0628	-	*0.0630*	-	*0.0629*	-	*0.0594*	*0.0354*
4-Py	0.1387	-	0.1392	-	0.1385	-	0.1327	0.1321
	0.0760	-	0.0762	-	0.0757	-	0.0733	0.0713
	0.0627	-	*0.0630*	-	*0.0628*	-	*0.0594*	*0.0608*
				1-(1,2,3-benzotriazolyl)-				
H	0.1317	0.1232	0.1323	0.1237	0.1313	0.1226	0.1242	0.1148
	0.0832	0.1086	0.0834	0.1088	0.0828	0.1081	0.0798	0.1050
	0.0485	*0.0146*	*0.0489*	*0.0149*	*0.0485*	*0.0145*	*0.0444*	*0.0098*
CH_3	0.1315	0.1281	0.1320	0.1287	0.1311	0.1276	0.1240	0.1203
	0.0835	0.0885	0.0837	0.0888	0.0830	0.0882	0.0799	0.0856
	0.0480	*0.0396*	*0.0483*	*0.0399*	*0.0481*	*0.0394*	*0.0441*	*0.0347*

Table 5. *Heats of formation for compounds* ***10, 11****.*

				O-nucleophiles					
R^3X		OH			OMe			OEt	
R^2	**10a**	**10b**	**11**	**10a**	**10b**	**11**	**10a**	**10b**	**11**
H	-114.58	-113.33	-110.65	-107.71	-104.43	-102.07	-115.35	-114.16	-106.59
Me	-123.66	-122.20	-119.43	-118.03	-115.02	-110.83	-122.92	-118.86	-115.36
Ph	-88.65	-87.39	-84.56	-81.83	-78.75	-75.90	-89.54	-84.09	-81.67
				S-nucleophiles					
R^3X		SH			SMe			SEt	
R^2	**10a**	**10b**	**11**	**10a**	**10b**	**11**	**10a**	**10b**	**11**
H	-54.62	-51.24	-55.18	-59.57	-56.10	-58.56	-63.71	-60.31	-61.69
Me	-63.74	-60.27	-64.01	-66.70	-65.91	-67.45	-70.16	-69.14	-70.57
Ph	-28.76	-25.73	-29.04	-33.68	-30.58	-32.28	-37.82	-33.78	-35.83
				N-nucleophiles					
R^3X		NH_2			NHMe			NHEt	
R^2	**10a**	**10b**	**11**	**10a**	**10b**	**11**	**10a**	**10b**	**11**
H	-65.30	-62.75	-62.06	-66.10	-63.57	-63.69	-73.83	-71.49	-69.98
Me	-74.28	-71.59	-70.79	-75.82	-70.98	-72.40	-81.66	-77.26	-78.84
Ph	-40.94	-36.85	-35.80	-39.59	-39.53	-37.39	-48.55	-44.35	-44.16

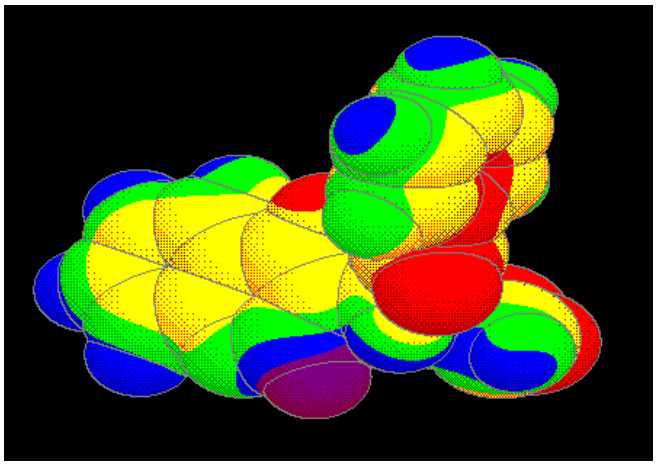


Fig. 10b. *3D-structure and MEP on the van der Waals surface of* ***8*** *(R^1 = 1-(1,2,4-triazolyl)-; R^2 = Ph).*

all cases the highest differences between point charges on C-2 and C-9 are in 6-methylderivatives and the lowest difference in 6-nitroderivatives (Table 4). The exceptions from these results are the benzamide-1-(1,2,3-triazole)-derivatives (the highest difference is in chloroderivative for *trans*-isomers) and the acetamide-1-(1,2,3-triazole)-derivatives (the highest difference is in unsubstituted derivative for *cis*-isomers).

N-[1-(1, 2, 4-Triazolyl)- and *N*-[1-(1, 2, 3-benzotriazolyl)-3-(6-R-chromonyl)methyl]amides **8** readily react with nucleophiles under mild conditions to form chromane derivatives of enamide type **10**. ^{1}H-NMR spectra display two singlet signals for proton H-2 proton at about δ 5.8–7 ppm [14]. PM3 semiempirical computations indicate the existence of two isomers for 3-acylaminomethylene-2-substituted-chroman-4-ones **10** (**10a** and **10b**, Fig. 11). For all cases the isomers **10a** are predicted to be more stable than the isomer **10b** (Table 5), although the computed energy differences between these isomers are only 1–3 kcal. The greater stability of **10a** can be explained by the presence

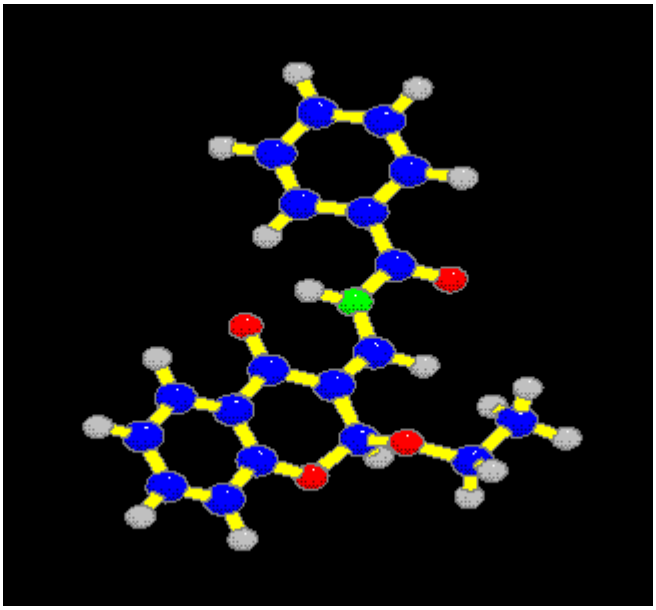


Fig. 11a. *Structure of* ***10a*** $R^2 = Ph$; $R^3 = Et$; $X = O$.

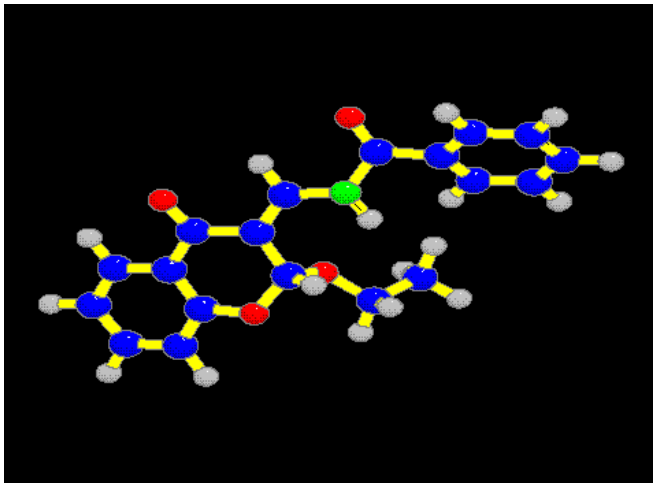


Fig. 11b. *Structure of* ***10b*** $R^2 = Ph$; $R^3 = Et$; $X = O$.

of an intramolecular hydrogen bond between the amide NH group and the γ-pyrone carbonyl group. For X = O, NH in almost all cases of isomers **10b** a hydrogen bond between amide NH group and heteroatom X was present. No such H-bond was found for X = S.

Finally, energies of chromone derivatives **11**, isomers of **10**, were also calculated. According to the results obtained (Table 5) chromone derivatives **11** are less stable than their chromanone isomers **10** by 3–9 kcal mol^{-1}. Only for *S*-nucleophiles do both isomers have similar energies.

Experimental section

General details

The melting points were determined on a Kofler hot stage and are uncorrected. ^{1}H-NMR spectra were measured on a Spectrometer BS-487 (80 MHz, Tesla) in deuteriochloroform or hexadeuteriodimethyl sulfoxide with tetramethylsilane as internal standard. The IR spectra were measured on a Specord 75 IR (Zeiss, Jena) apparatus using a suspension in paraffin oil. The reaction course was monitored by thin-layer chromatography in ethyl acetate-isohexane.

*3-[1-(1, 2, 4-Triazolyl)hydroxymethyl]-4-oxo-4*H*-[1]-benzopyrane and 3-[1-(1, 2, 3-benzotriazolyl)-hydroxymethyl]-4-oxo-4*H*-[1]-benzopyrane* ***7***

3-Formylchromone (2 mmol) and 1*H*-1,2,4-triazole or 1*H*-1,2,3-benzotriazole (2 mmol) were refluxed in dry toluene (5 ml) for 8 hours. The solid product was filtered off, stirred with diethylether at room temperature for 1 hour and dried. Toluene from the filtrate was removed at 60 °C/30 mm Hg. The residue was treated with diethylether and filtered off. Both filtered products were identical.

IR (paraffin oil) 3120—2890 (OH_{bonded}), 1645 (C = O, pyrone), 1620 (C = C), 1125 (C-*O*-C).

7a (R^1 = 1-(1,2,4-triazolyl)-) - Yield 75%, light yellow crystals. mp 147.5—149 °C

Anal. Calcd for $C_{12}H_9N_3O_3$, M_w = 243.22: C, 59.26; H, 3.73; N, 17.28. Found: C, 58.95; H, 3.57; N, 16.98.

7b (R^1 = 1-(1,2,3-benzotriazolyl)-) - Yield 76%, light yellow crystals. mp 105—107 °C

Anal. Calcd for $C_{16}H_{11}N_3O_3$, M_w = 293.28: C, 65.53; H, 3.78; N, 14.33. Found: C, 65.36; H, 3.77; N, 14.15.

N-*[1-(1, 2, 4-Triazolyl)-3-chromonylmethyl]amides and* N-*[1-(1, 2, 3-benzotriazolyl)-3-chromonylmethyl]-amides* ***8***

3-Formylchromone (2 mmol), primary amide (2 mmol) and 1*H*-1,2,4-triazole or 1*H*-1,2,3- benzotriazole (2 mmol) were refluxed in dry toluene (10 ml) for 27—50 hours. The solid product was filtered off, stirred with diethylether at room temperature for 1 hour and dried. Toluene was removed from the filtrate at 60 °C/30 mm Hg The residue was treated with diethylether and filtered off. Both filtered products were identical.

8a (R^1 = 1-(1,2,4-triazolyl)-; R^2 = Ph) - Yield 80%, white crystals, crystallised from chloroform. mp 158—160 °C; after two crystallisations mp 177—179 °C.

^{1}H NMR (80 MHz; DMSO) 7.48—7.99 m, 10H (Ar-H), 8.10 d, 1H, J = 7.9 Hz (H-9), 8.60 s, 1H (*H*-triazole), 8.81 s, 1H (H-2), 9.69 d, 1H, J = 7.9 Hz (NH). ^{1}H NMR (80 MHz; $CDCl_3$) 7.38—7.96 m, 10H (Ar-H), 8.25 d, 1H, J = 8.79 Hz (H-9), 8.36 s, 1H (*H*-triazole), 8.52 s, 1H (H-2), 9.44 d, 1H, J = 8.79 Hz (NH).

Anal. Calcd for $C_{19}H_{14}N_4O_3$, M_w = 346.35: C, 65.89; H, 4.07; N, 16.18. Found: C, 65.85; H, 4.06; N, 16.08.

8b (R^1 = 1-(1,2,4-triazolyl)-; R^2 = 3-Py) - Yield 85%, white crystals. mp 197—199.5 °C.

^{1}H NMR (80 MHz; DMSO) 7.46—8.05 m, 5H (Ar-H), 7.80 d, 1H, ^{4}J = 1.70 Hz (*H*-4 pyridine), 8.05 s, 1H (*H*-triazole), 8.22 d, 1H, J = 7.08 Hz (H-9), 8.61 s, 1H (H-2), 8.76 dd, 1H, ^{3}J = 2.19 Hz, ^{4}J = 1.70 Hz (*H*-5 pyridine), 8.85 s, 1H (*H*-2 pyridine), 9.08 d, 1H, ^{3}J = 2.19 Hz (*H*-6 pyridine), 9.91 d, 1H, J = 7.08 Hz (NH).

Anal. Calcd for $C_{18}H_{13}N_5O_3$, M_w = 347.33: C, 62.23; H, 3.77; N, 20.16. Found: C, 61.81; H, 3.73; N, 19.93.

8c (R^1 = 1-(1,2,3-benzotriazolyl)-; R^2 = Me) - Yield 70%, white crystals. mp 183—186 °C.

^{1}H NMR (80 MHz; DMSO) 2.01 s, 3H (CH_3), 7.35—8.13 m, 9H (Ar-H, H-9), 8.81 s, 1H (H-2), 9.72 d, 1H, J = 9 Hz (NH).

Anal. Calcd for $C_{18}H_{14}N_4O_3$, M_w = 322.30: C, 63.35; H, 4.38; N, 17.38. Found: C, 63.08; H, 4.18; N, 17.17.

8d (R^1 = 1-(1,2,3-benzotriazolyl)-; R^2 = Ph) — Yield 70%, white crystals. mp 212—214 °C.

^{1}H NMR (80 MHz; DMSO) 7.44—8.04 m, 13H (Ar-H), 8.20 d, 1H, J = 8.54 Hz (H-9), 8.81 s, 1H (H-2), 10.11 d, 1H, J = 8.54 Hz (NH).

Anal. Calcd for $C_{23}H_{16}N_4O_3$, M_w = 396.40: C, 69.69; H, 4.14; N, 14.13. Found: C, 69.46; H, 4.07; N, 14.12.

*3-(*N*-Acylamino-1-hydroxymethyl)chromones* ***9***

A solution of 3-formylchromone (2 mmol), amide (2 mmol) and 4-toluenesulfonic acid (0.03 mmol) in dry toluene (8 ml) was refluxed for 30 minutes. The precipitate was collected, washed with diethylether, and dried.

9a (R^2 = Ph, R^3 = Me) - Yield 75%, white crystals. mp 192—195 °C.

^{1}H NMR (80 MHz; DMSO) 1.84 s, 3H (CH_3), 6.45 t, 1H (H-9), 7.51—7.77 m, 4H (Ar-H), 8.09 d, 1H, J = 7.81 Hz (OH), 8.34 s, 1H (H-2), 8.36 d, 1H, J = 6.83 Hz (NH).

Anal. Calcd for $C_{12}H_{11}NO_4$, M_w = 233.22: C, 61.80; H, 4.75; N, 6.01. Found: C, 61.75; H, 4.70; N, 5.95.

9b (R^2 = Ph, R^3 = Ph) - Yield 78%, white crystals. mp 245—248 °C.

^{1}H NMR (80 MHz; DMSO) 7.47 t, 1H (H-9), 7.53—7.97 m, 9H (Ar-H), 8.14 d, 1H, J = 7.57 Hz (OH), 8.53 s, 1H (H-2), 8.96 d, 1H, J = 6.84 Hz (NH).

Anal. Calcd for $C_{17}H_{13}NO_4$, M_w = 295.29: C, 69.15; H, 4.44; N, 4.74. Found: C, 69.11; H, 4.42; N, 4.74.

9c (R^2 = Ph, R^3 = 3-Py) - Yield 80%, white crystals. mp 234—236 °C.

^{1}H NMR (80 MHz; DMSO) 7.46 t, 1H (H-9), 7.45—7.79 m, 4H (Ar-H), 8.08 d, 1H, ^{4}J = 1.70 Hz (*H*-4 pyridine), 8.27 d, 1H, J = 5.86 Hz (OH), 8.57 s, 1H (H-2), 8.74 dd, 1H, ^{3}J = 2.19 Hz, ^{4}J = 1.70 Hz (*H*-5 pyridine), 9.06 s, 1H (*H*-2 pyridine), 9.10 d, 1H, ^{3}J = 2.19 Hz (*H*-6 pyridine), 9.20 d, 1H, J = 6.59 Hz (NH).

Anal. Calcd for $C_{16}H_{12}N_2O_4$, M_w = 296.28: C, 64.86; H, 4.08; N, 9.45. Found: C, 64.61; H, 4.04; N, 9.42.

3-Benzylaminomethylene-2-ethoxychroman-4-one ***10***

Method A. Compound **8** (R^1 = 1-(1,2,4-triazolyl)- or 1-(1,2,3-triazolyl)-; R^2 = Ph) (2 mmol) was refluxed in ethanol for 3 hours. The solid product was filtered off, washed with cold water, dried and crystallised from ethanol. Yield 70%

Method B. A solution of benzamide (2 mmol), 3-formylchromone (2 mmol) and 4-toluenesulfonic acid (0.03 mmol) in 8 ml ethanol was refluxed for 4 hours. The ethanol was removed from the reaction mixture and the solid product was cystallised from ethanol. Yield 60%. White crystals, mp 257—257 °C

^{1}H NMR (80 MHz; $CDCl_3$) 1.25 t, 3H (CH_3), 3.67, 3.76 2q, 2H (CH_2), 6.19 s, 0.5H (H-2), 6.31 s, 0.5H (H-2), 7.27—8.11 m, 9H (Ar-H), 8.21 d, J = 9.28 Hz (H-9), 8.85 d, J = 9.28 Hz (NH).

Anal. Calcd for $C_{19}H_{17}NO_4$, M_w = 323.35: C, 70.58; H, 5.30; N, 4.33. Found: C, 70.39; H, 5.15; N, 4.26.

Semiempirical PM3 calculations and molecular modelling

All calculations were done by the VAMP program package[17] using the PM3 hamiltonian [18,19]. This semiempirical method was chosen because it has turned out to be superior to AM1 [20] in compounds containing adjacent nitrogen atoms [21].

Geometries were completely optimised (keyword PRECISE) without any restrictions using the eigenvector following routine [22]. Transition states were approximately located by reaction path calculations, refined by gradient norm minimisation and fully characterised by force constant calculations.

All 3D-graphics and MEP were done by the MGP program package [23]. MEP on the van der Waals surface was calculated using so called “point charge approximation”. This approximation was shown to give satisfactory results [23]. Intervals for distribution of MEP on van der Waals surface are following: (—1.5; —1.0) cyclamen, (—1.0; —0.5) red, (—0.5; 0) yellow, (0; 0.5) green, (0.5; 1.0) blue, (1.0; 1.5) violet. For 3D-graphics the colours of the atoms are as follows: carbons - blue, hydrogens - white, oxygens - red and nitrogens - green.

Acknowledgement. Financial support for this research was granted by the Academic programme CEEPUS, network SK-20 and the Slovak Grant Agency (Grant no 1/2178/95) and is gratefully acknowledged. The authors’ thanks also go to Dr D. Loos for the molecular modelling.

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Notes

Heats of formation of starting compounds (in kcal)

A: triazoles
1*H*-1,2,4-triazole = 51.83; 1*H*-1,2,3-triazole = 67.91; 1*H*-1,2,3-benzotriazole = 85.45

B: amides
formamide = -37.39; acetamide = -46.33; benzamide = -11.39; nicotinamide = -4.36; isonicotinamide = -3.56

C: aldehydes
unsubstituted = -63.56; 6-methyl = -72.97; 6-chloro = -69.52; 6-nitro = -70.40

D: nucleophiles
oxygen water = -53.43; methanol = -51.88; ethanol = -56.85
sulfur hydrogen sulfide = -0.91; methanethiol = -5.53; ethanethiol = -8.72
nitrogen ammonia = -3.07; methylamine = -5.18; ethylamine = -11.15