Transformation of 4-Oxo-4*H*-[1]-benzopyran-3-carboxaldehydes into Pyrazolo[3,4-*b*]pyridines

Henrieta Stankovičová* and Anton Gáplovský

Institute of Chemistry, Faculty of Natural Sciences, Comenius University, Mlynská dolina CH-2, 842 15 Bratislava, Slovak Republic, stankovh@fns.uniba.sk

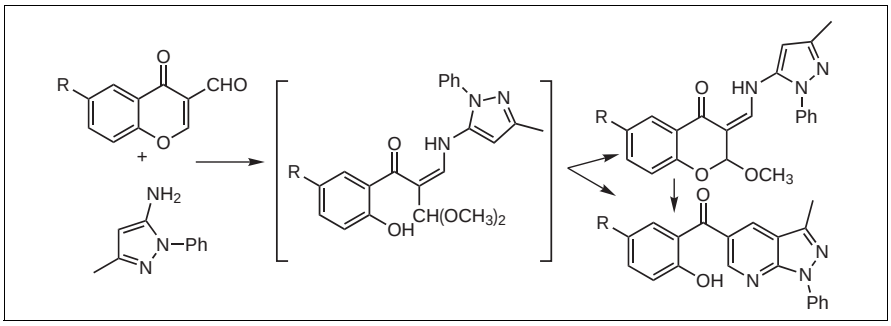
Margita Lácová and Jarmila Chovancová

Department of Organic Chemistry, Faculty of Natural Sciences, Comenius University, Mlynská dolina CH-2, 842 15 Bratislava, Slovak Republic

Agnieszka Puchała

Institute of Chemistry, Swietokrzyska University, Checinska 5, 25-020 Kielce, Poland

Received July 22, 2005



Reaction of 6-methyl-4-oxo-4*H*-[1]-benzopyran-3-carboxaldehyde **1** with 5-amino-3-methyl-1-phenylpyrazole **2** in alcoholic reaction media in the presence of 4-toluenesulfonic acid as catalyst afforded 5-(2-hydroxy-5-methylbenzoyl)-3-methyl-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine **3** and 2-methoxy-6-methyl-3-(3-methyl-1-phenylpyrazol-5-ylaminomethylene)chroman-4-one **7**. We explain the mechanism of formation of both products on the basis of kinetic study of individual reaction steps.

J. Heterocyclic Chem., **43**, 843 (2006).

Introduction.

Important role of 6-substituted-4-oxo-4*H*-[1]-benzopyran-3-carboxaldehydes (3-formylchromones) **1** as versatile synthons in heterocyclic chemistry is well known [1,2]. Although a lot of heterocycles have been prepared from **1**, the exact route of their formation is not always clear. Formation of products is usually preceded by formation of one or two intermediates, making the kinetics of these reactions complicated. Aldehydes **1** contain three potential sites for attack of nucleophile *viz*. C-2, CHO, C-4, the last one having obviously the least electrophilicity compared to that at the two other centers. It is very difficult to pintpoint whether an initial step of the reaction is C-2 or CHO attack of the nucleophile because of "chemical symmetry" of these reaction centers. Unfortunately none of the published methods for the preparation of 3-formylchromones is suitable for incorporation of the specific labeling [3-12].

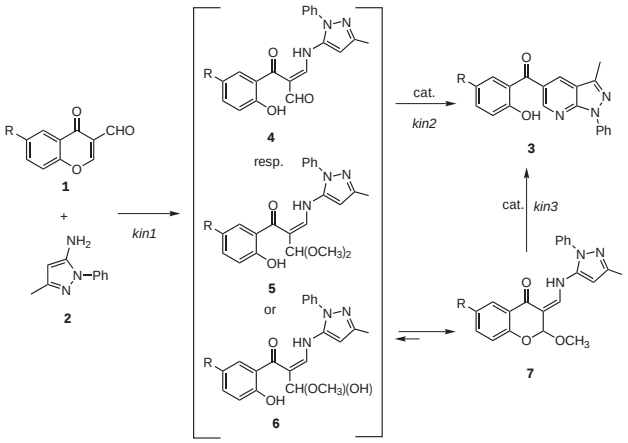
Recently in our previous study we described the acid catalyzed reaction of aldehydes **1** with weak *N*-nucleophiles [13]. We now report a kinetic investigation of reaction between 6-methyl-4-oxo-4*H*-[1]-benzopyran-3-carboxaldehyde **1** (R = CH_3) with 5-amino-3-methyl-1-phenylpyrazole **2**. 5-Aminopyrazoles are useful reactive agents for synthesis of pyrazolo[3,4-*b*]pyridines under highly acidic annelation conditions. An electrophilic attack at the C-4 position of pyrazole ring takes place in the presence of suitable reaction counterpart [14]. The aim of this study was to contribute to clarification of exact reaction mechanism of reaction of **1** with amines. The choice of suitable nucleophile was not random. Primary enamines as ambident nucleophiles can form upon condensation with **1** a new ring system. The mechanisms of these reactions are partially clarified, the probable reaction courses were proposed [15,16].

Results and Discussion.

Reaction of 6-methyl-4-oxo-4*H*-[1]-benzopyran-3-carboxaldehyde **1** with 5-amino-3-methyl-1-phenylpyrazole **2** afforded 5-(2-hydroxy-5-methylbenzoyl)-3-methyl-1-phenyl-*1H*-pyrazolo[3,4-*b*]pyridine **3** (Scheme I). The

reaction was carried out by refluxing equimolar amounts of aldehyde **1** and pyrazole **2** in alcohol in the presence of 4-toluenesulfonic acid as catalyst. The product is isolated in good yield (85%) as stable crystalline product and easily purified by recrystallization from alcohol. Alcohols as solvents were found most suitable for synthesis. Dioxane, toluene or chloroform as solvents can also be used but the reaction is slower and the yields of product are lower with lower purity.

Scheme I



Unlike 5-amino-3-methyl-1-phenylpyrazole, 5-amino-3-methyl-1*H*-pyrazole reacts with 3-formylchromones in ethanol affording 6-(2-hydroxybenzoyl)pyrazolo[1,5-*a*]-pyrimidines. No pyrazolo[3,4-*b*]pyridines were isolated in that case [17]. Introduction of a substituent on the N-1 atom of pyrazole ring prevents formation of tautomers and changes its reactivity towards 3-formylchromone. Pyrazolo[3,4-*b*]pyridines were also obtained when reaction of **1** with **2** was carried out in glacial acetic acid, but with lower yield (46%) [15].

Reactivity of aldehyde **1** (R = CH_3) and pyrazole **2** as well as the number of reaction steps is dependent on reaction conditions. On the basis of kinetic experiments and results of synthesis we suggested for formation of 5-(2-hydroxy-5-methylbenzoyl)-3-methyl-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine **3** a mechanism depicted in Scheme I.

The study of reaction kinetics was performed in three different solvents: dioxane, methanol and 2-propanol in the presence of 4-toluenesulfonic acid as catalyst or without catalyst. UV-VIS absorption spectra were used for monitoring the kinetics of above process. All of the components of the reaction mixture had different absorption bands and intensities (Figure 1). Fluorescence spectroscopy was used with benefit for unambiguous identification of reaction mixture components (Figure 2).

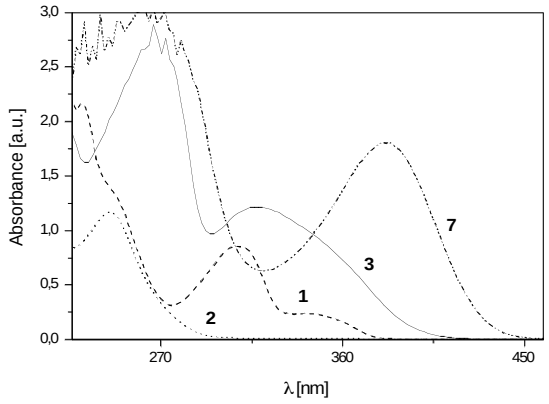


Figure 1. UV-VIS spectra of compounds in methanol.

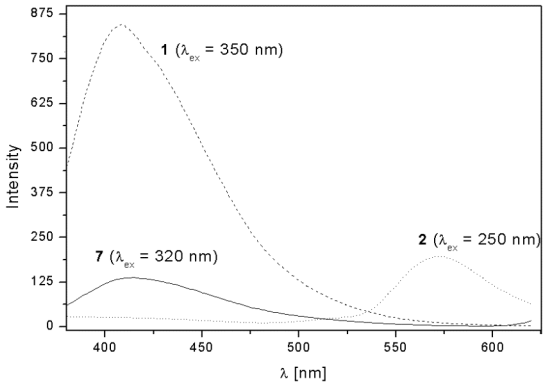


Figure 2a. Fluorescence emission spectra of compounds in dioxane.

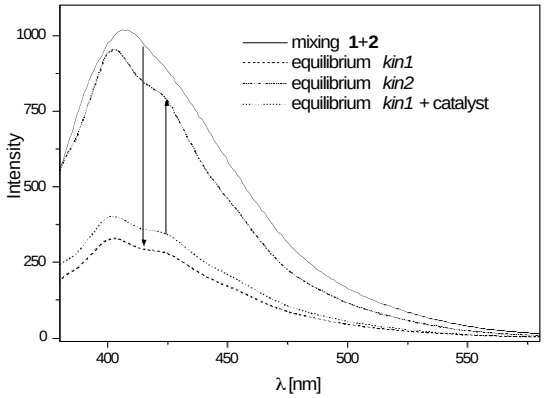


Figure 2b. Fluorescence emission spectra of reaction mixtures in dioxane (λ_{ex} = 350 nm).

The first step of the reaction is a nucleophilic attack to the 2-position of the chromone system followed by

benzopyrone ring opening. The isolation of intermediate **4** from reaction mixture was not successful. ^{1}H NMR spectroscopy was used to prove its formation. Spectra were recorded immediately after mixing equimolar amounts of starting compounds **1** and **2** in suitable solvent, they revealed a signal at δ 5.58 due to phenolic OH group, dublet at δ 7.62 for CH group and signal at δ 9.76 for aldehydic group. Formation of intermediate is expressed in UV-VIS spectra as an appearance of absorption band at λ = 340 nm (Figure 3). Increase of absorbance at 340 nm was observed predominantly in reaction mixtures without catalyst in protic solvents. Intermediate **5**, respectively **6** is formed relatively fast in methanol. Its formation is observable in UV-VIS spectra few seconds after mixing starting materials.

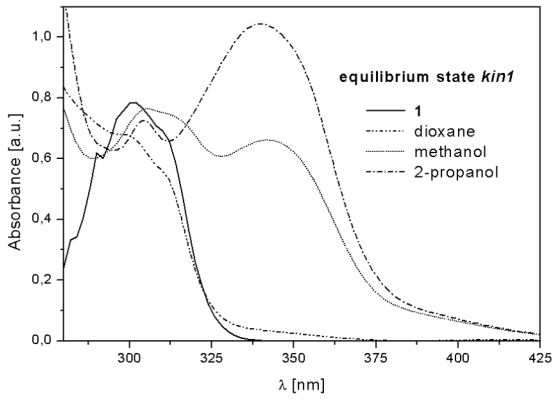


Figure 3. UV-VIS spectra of equilibrium states *kin1* in various solvents and of aldehyde.

Insignificant increase of absorbance (at 340 nm corresponding to absorbance of **4**) was observed when reaction was carried out without catalyst in dioxane. Loss of the aldehyde **1** (R = CH_3) is clearly visible in the area of its absorption maxima at λ = 308 nm. Reactivity of intermediate **4** is dependent on reaction conditions. It does not react further to the product **3** without 4-toluene-sulfonic acid. Addition of catalyst leads directly to pyrazolo[3,4-*b*]pyridine **3** (Figure 4).

Unlike in dioxane, the intermediate of reaction *kin1* (**5**, resp. **6**) in alcoholic reaction media reacts further without catalyst to 2-alkoxy-6-methyl-3-(3-methyl-1-phenyl-pyrazol-5-ylaminomethylene)chroman-4-one **7**. Its formation is discernible in absorption spectra as an appearance of new absorption band at λ = 400 nm. Evidence of its presence in reaction mixture was confirmed by fluorescence emission spectra. As it is shown on Figure 5a, the rate of formation of **5**, resp. **6** is higher than the rate of subsequent reaction, formation of **7** from **5**, resp. **6**. Concentration of chroman-4-one **7** is relatively low and approximately after 1200 s moderately decreases. Pyrazolo[3,4-*b*]pyridine **3** is formed from compound **7** by rate comparable with that of formation of **7** from **5**, resp. **6**. Absorption spectra of **7** are overlapping with spectra of intermediates **5**, resp. **6** and partially with spectra of starting aldehyde (Figure 5b).

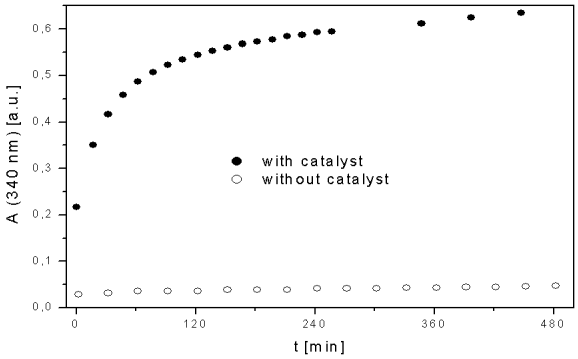


Figure 4. Time change of absorbance due to formation of **3** in dioxane.

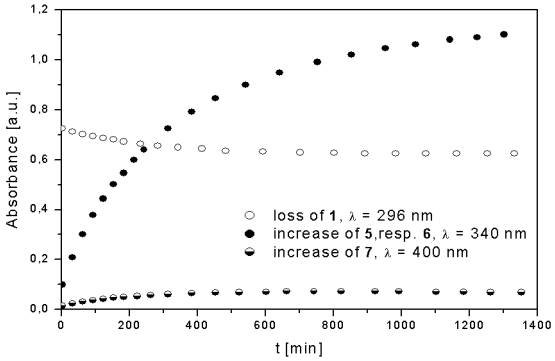


Figure 5a. Time change of absorbance during reaction *kin1* in 2-propanol at 40 °.

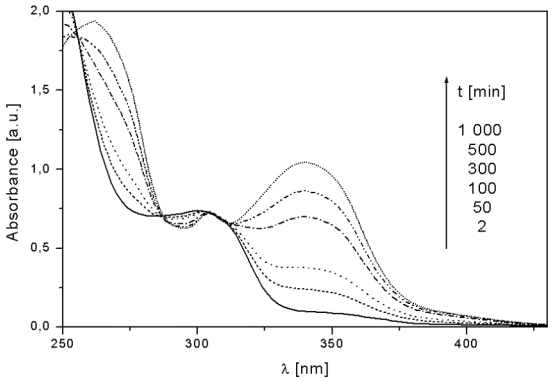


Figure 5b. Change of UV-VIS spectra during reaction *kin1* in 2-propanol.

Presence of 4-toluenesulfonic acid in reaction mixture significantly influences the reactivity of intermediates **4**-**6** in all reaction media (Figures 4, 6 and 7). It was found that fast increase of concentration of intermediate **5**, resp. **6** occurs when the reaction was carried out in 2-propanol (Figure 6). This concentration decreases approximately after 100 minutes. Similarly, decrease of absorbance at λ 400 nm (compound **7**) was observed, its concentration is significantly lower than in case of uncatalyzed reaction. The findings for methanol are similar (Figure 7). The concentration of **7** is very low in the presence of catalyst and does not change during reaction. Concentration of chroman-4-one **7** increases in the case of catalyzed reaction. The results show clearly that 4-toluenesulfonic acid catalyses transformation of **7** to pyrazolo[3,4-*b*]-pyridine **3**.

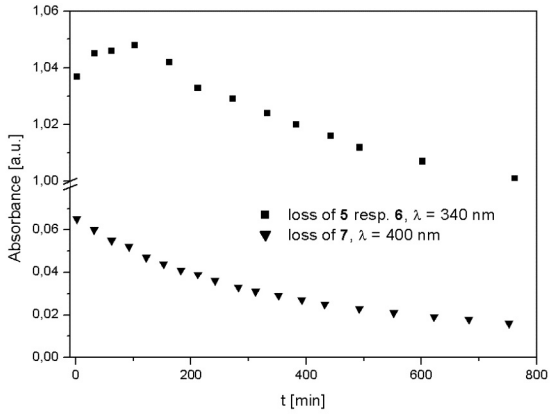


Figure 6. Time change of absorbance during reaction *kin2* in 2-propanol at 40 °.

2-Methoxy-6-methyl-3-(3-methyl-1-phenylpyrazol-5-ylaminomethylene)chroman-4-one **7** was isolated from reaction mixture at low temperature (-15º) and we performed kinetic measurements of its transformation to 5-(2-hydroxy-5-methylbenzoyl)-3-methyl-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine (**3**). The results show unambigously that **3** is formed from **7** (Figure 8). We have not found so clear evidence for direct transformation of intermediates **5**, resp. **6** to compound **3**. We suppose that like in dioxane product **3** is also formed directly from **5**, resp. **6** by a competitive process to the formation of chroman-4-one **7**. A direct proof is missing because we were not able to isolate intermediates **5**, resp. **6** from reaction mixtures. The different reactivity of intermediates in protic and aprotic solvents indicates various intermediate

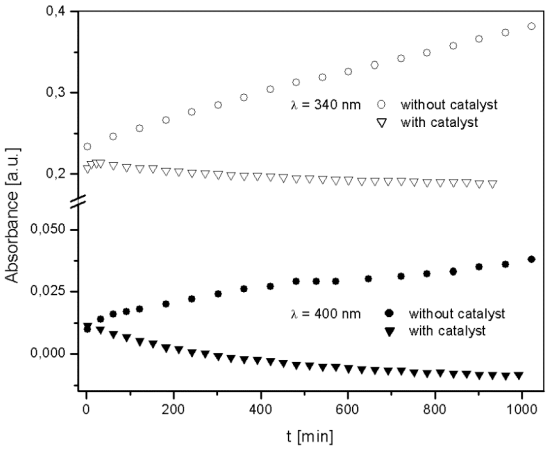


Figure 7. Time change od absorbance during reaction **1** with **2** in methanol (20 º).

structures. NMR spectra recorded immediately after mixing **1** (R = NO_2) and **2** in CD_3OD revealed a signal at δ 5.41 ppm due to methoxyacetal CH group (the signal ppm for acetal derived from aldehyde is at δ 5.56) and a signal for phenolic OH group at δ 8.21 ppm, signal for CHO group was not found. The same spectra were recorded when pyrazole **2** was added to the mixture of **1** and catalyst in CD_3OD (*i.e.* acetal) at room temperature. The structure of intermediate corresponds to structure formed after nucleophilic attack to the pyrone C-2 position and subsequent ring opening. Compound **7** is formed also by uncatalyzed reaction from acetal **5**, resp. hemiacetal **6**. Similar reactivity was found also for other substrates [18]. The reason for this ring closure can be a formation of a stable hydrogen bond [18,19] or ketoamine hydrogen bond [20]. Formation of 2-hydroxy analogue of **7** was not proved when the reaction was carried out in the presence of catalyst in dioxane. The acid catalyzed annelation of **4** to pyrazolo[3,4-*b*]pyridine was the only one observed process in dioxane.

EXPERIMENTAL

General.

Melting points (uncorrected) were measured on a Kofler hot stage. The NMR spectra were recorded in $CDCl_3$ on Varian Gemini 2000 spectrometer. UV-VIS spectra were recorded on Hewlett-Packard 'Diode Array 8254' spectrometer. Fluorescence spectra were taken in dioxane on a Hitachi F2000 spectrometer (S_1, S_2 = 10 nm). Elemental analyses were performed on a Carlo Erba Strumentacione 1106 apparatus.

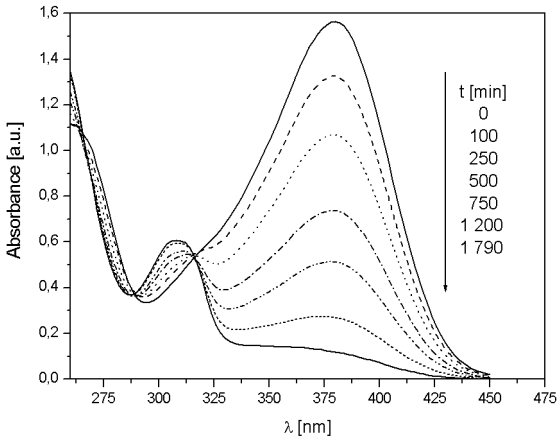


Figure 8a. Change of UV-VIS spectra during reaction *kin3* in methanol (t = 40 °; c_{cat} = 5x10^{-4} mol.dm^{-3}).

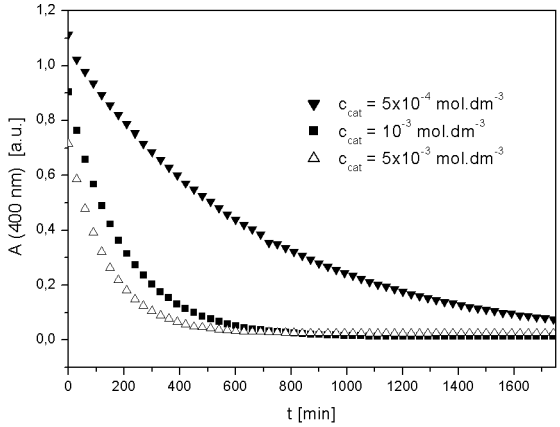


Figure 8b. Absorbance at λ = 400 nm probing the loss of **7** as a function of time in methanol, illustrating the dependence of reaction rate on catalyst concentration.

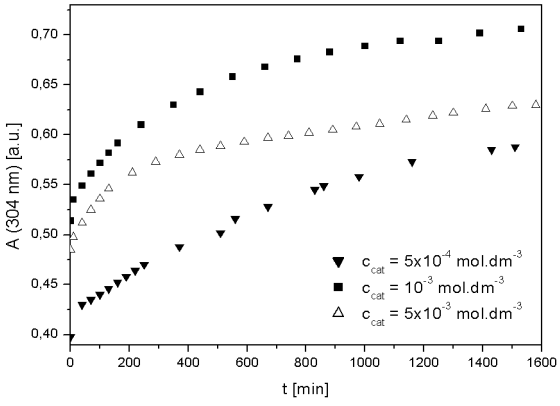


Figure 8c. Absorbance at λ = 340 nm probing the increase of **3** as a function of time in methanol, illustrating the dependence of reaction rate on catalyst concentration.

Synthesis.

Commercial chemicals (solvents, 4-toluenesulfonic acid) were used after purification (if their purity was < 99%). 6-Methyl-4-oxo-4*H*-[1]-benzopyran-3-carboxaldehyde **1** [4] and 5-amino-3-methyl-1-phenylpyrazole **2** [21] were prepared according to literature procedures.

5-(2-Hydroxy-5-methylbenzoyl)-3-methyl-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine (**3**).

A solution of 5-amino-3-methyl-1-phenylpyrazole (199 mg, 1.148 mmol) in 4 mL of ethanol was added to a stirred solution of 6-methyl-4-oxo-4*H*-[1]-benzopyran-3-carboxaldehyde (216 mg, 1.148 mmol) and 4-toluenesulfonic acid (5 mg, 0.029 mmol) in 4 mL of ethanol, and the mixture was refluxed for 45 minutes. After cooling, the yellow precipitate was collected by filtration, washed with ethanol, dried and recrystallized from ethanol. Yield 85%, mp 145-146°; ^{1}H NMR (300 MHz): 2.27 (s, 3H, $(CH_3)_{benzene}$), 2.72 (s, 3H, $(CH_3)_{pyrazole}$), 7.04 (d, 1H, $H_{o\text{-}OH}$, J = 7.7Hz), 7.34 (tt, 1H, H_{phenyl}, J = 7.6Hz, J = 1.1Hz), 7.38 (dd, 1H, $H_{p\text{-}CO}$, J = 7.7Hz, J = 0.8Hz), 7.39 (d, 1H, $H_{o\text{-}CO}$, J = 0.8Hz), 7.55 (t, 2H, H_{phenyl}, J = 7.6Hz, J = 1.1Hz), 8.26 (dd, 2H, H_{phenyl}, J = 7.6Hz, J = 1.1Hz,), 8.47 (d, 1H, $H_{pyr\text{-}\chi}$, J = 1.9Hz), 8.94 (d, 1H, $H_{pyr\text{-}\alpha}$, J = 1.9Hz), 11.67 (s, 1H, OH).

Anal. Calcd. for $C_{21}H_{17}N_3O_2$: C, 73.45; H, 4.99; N, 12.24. Found: C, 73.26; H, 4.85; N 12.32%.

2-Methoxy-6-methyl-3-(3-methyl-1-phenylpyrazol-5-ylamino-methylene)chroman-4-one (**7**).

A solution of 5-amino-3-methyl-1-phenylpyrazole (199 mg, 1.148 mmol) and 6-methyl-4-oxo-4*H*-[1]-benzopyran-3-carboxaldehyde (216 mg, 1.148 mmol) in 6 mL of methanol was stirred at –5 ° for 20 minutes. A precipitate was formed. A crystal of 4-toluenesulfonic acid was added to the reaction mixture at 0 °. The previously formed precipitate was dissolved and a new light yellow precipitate was formed in course of 10 minutes. The product was collected by filtration, washed with methanol at 0-5 ° and dried. Yield 40%, mp 154-156 °, ^{1}H NMR (300 MHz): 2.37 (s, 3H, $(CH_3)_{chromane}$), 2.50 (s, 3H, $(CH_3)_{pyrazole}$), 3.48 (s, 3H, OCH_3), 6.25 (s, 1H, H-2), 7.32 (d, 1H, H-8, J = 7.2Hz), 7.40-7.48 (m, 3H, H_{phenyl}), 7.52 (dd, 1H, H-7, J = 7,2Hz, J = 1.5Hz), 7.65-7.68 (m, 2H, H_{phenyl}), 8.08 (d, 1H, H-5, J = 1.5Hz), 8.68 (s, 1H, H-9), 8.99 (s, 1H, $H_{pyrazole}$), 11.69 (s, 1H, NH).

Anal. Calcd for $C_{22}H_{21}N_3O_3$: C, 70.38; H, 5.64; N, 11.19. Found: C, 70.35; H, 5.55; N 11.05%.

Kinetics.

All measurements were performed in a 1-cm thick absorption cell at 40 or 20 °. The kinetics of reactions was monitored *via* UV-VIS spectrophotometry using a Hewlett-Packard 'Diode Array 8254' spectrometer. Kinetic experiments were measured until the limiting equilibrium concentration was reached.

Kin1: A solution of 6-methyl-4-oxo-4*H*-[1]-benzopyran-3-carboxaldehyde **1** (4 mL, c = 2x10^{-4} mol.dm^{-3}) and a solution of 5-amino-3-methyl-1-phenylpyrazole **2** (4 mL, c = 2x10^{-4} mol.dm^{-3}) in appropriate solvents were separately heated to 40 or 20 ° and mixed.

Kin2: A solution of 6-methyl-4-oxo-4*H*-[1]-benzopyran-3-carboxaldehyde **1** (4 mL, c = 2x10^{-4} mol.dm^{-3}) and a solution of 5-amino-3-methyl-1-phenylpyrazole **2** (4 mL, c = 2x10^{-4} mol.dm^{-3}) in appropriate solvents were mixed and the mixture

was heated at 40 or 20° for 24 hours. A solution of 4-toluenesulfonic acid (0.2 ml, c = $3x10^{-2}$ mol.dm^{-3}) in appropriate solvent was added to the mixture.

Kin3: A solution of 2-methoxy-6-methyl-3-(3-methyl-1-phenylpyrazol-5-ylaminomethylene)chroman-4-one **7** (3 mL, c = 10^{-4} mol.dm^{-3}) was heated to 40° and then mixed with solution of 4-toluenesulfonic acid.

Acknowledgement.

We are grateful to the Slovak Grant Agency (Grant No 1/0089/03) for support of this research.

REFERENCES

[1] C. K. Ghosh, *J. Heterocyclic Chem.*, **20**, 1437 (1983).

[2] G. Sabitha, *Aldrichimica Acta*, **29**, 15 (1996).

[3] A. Nohara, T. Umetani, Y. Sanno, *Tetrahedron Lett.*, **14**, 1995 (1973).

[4] A. Nohara, T. Umetani, Y. Sanno, *Tetrahedron*, **30**, 3553 (1974).

[5] F. Eiden, H. Haverland, *Arch. Pharm*., **300**, 806 (1967).

[6] G. A. Reynolds, J. A. van Allan, *J. Heterocyclic Chem.*, **6**, 375 (1969).

[7] H. Harnisch, *Liebigs Ann. Chem.*, **765**, 8 (1972).

[8] S. Klutchko, M. P. Cohen, J. Shavel Jr., M. von Strandtmann, *J. Heterocyclic Chem.*, **11**, 183 (1974).

[9] G. J. P. Becket, G.P.Ellis, *Tetrahedron Lett.*, **17**, 719 (1976).

[10] D. Kaminsky, U. S. Patent 3,912,760 (1975); *Chem. Abstr*,. **84**, 30891t (1976).

[11] G. J. P. Becket, G. P. Ellis, M. I. U. Trindade, *J. Chem. Res. (S)*, 1978, 47.

[12] S. Klutchko, D. Kaminsky, M. von Strandtmann, U. S. Patent 4,098,799 (1978); *Chem. Abstr*., **90**, 22813c (1979).

[13] Stankovičová, M. Lácová, A. Gáplovský, J. Chovancová, N. Prónayová, *Tetrahedron*, **57**, 3455 (2001).

[14] B. M. Lynch, M. A. Khan, H. C. Teo, F. Pendrotti, *Can. J. Chem*., **66**, 420 (1988).

[15] G. Haas, J. L. Stanton, A. von Sprecher, P. Wenk, *J. Heterocyclic Chem.*, **18**, 607 (1981).

[16] D. Heber, *Arch. Pharm.*, **316**, 55 (1983).

[17] J. Quiroga, D. Mejía, B. Insuasty, R. Abonía, M. Nogueras, A. Sánchez, J. Cobo, J. N. Low, *J. Heterocyclic Chem.*, **39**, 51 (2002).

[18] H. Stankovičová, *Ph.D. Thesis*, Comenius University Bratislava (1998).

[19] H. Stankovičová, W. M. F. Fabian, M. Lácová, *Molecules*, **1**, 223 (1996).

[20] G. O. Dudek, *J. Am. Chem. Soc*., **85**, 694 (1963).

[21] A. Ganesan, C. H. Heathcock, *J. Org. Chem*., **58**, 6155 (1993).