9th International Electronic Conference on Synthetic Organic Chemistry. ECSOC-9
1-30 November 2005. http://www.usc.es/congresos/ecsoc/9/ECSOC9.HTM & http://www.mdpi.net/ecsoc/

A Facile Route to Phenylselanyl substituted Pyrano[3,2-c]chromenes.

[D003]

Pavol Kois[1], Hafez M. El Shaaer[2], and Margita Lacova*[1]

[1] Department of Organic Chemistry, Faculty of Natural Sciences, Comenius University, SK-842 15 Bratislava, Slovakia
[2] Department of Chemistry, Faculty of Education, Ain Shams University, Cairo - Roxy - Egypt

Authors to whom correspondence should be addressed:
lacova@fns.uniba.sk; Tel. (+421) 2 60296-338 ; Fax (+421) 2 60296-690;
kois@fns.uniba.sk Tel. (+421) 2 60296-341

Abstract: The synthesis of a new family of phenylselanyl substituted pyrano[3,2-c] chromenes is presented. The cyclocondensation reaction of 3-formylchromones **1** with phenylselanylacetic acid **2** in acetic anhydride under mild conditions gave the novel 3-(phenylselanyl)-2-oxo-2*H*,5*H*-pyrano[3,2-c]chromen-5-yl acetates $\mathbf{P_1}$ in 80% yield. Further treatment of acetates $\mathbf{P_1}$ with ethanolic or aqueous medium led to the corresponding 5-ethyloxy-3-(phenylselanyl)-2-oxo-2*H*,5*H*-pyrano[3,2-c]chromen $\mathbf{P_3}$ and 3-(phenylselanyl)-2*H*,5*H*-pyrano[3,2-c]chromen-5-ol $\mathbf{P_4}$, respectively. We found the reaction of phenylselanylacetic acid with arylcarbaldehydes in acetanhydride at room temperature yielded the corresponding 2-(phenylselanyl)cinnamoyl acid $\mathbf{P_5}$. This reaction at elevated temperature, under reflux or in the solventless mixture at 180°C led only to the diphenyl-diselane $\mathbf{P_6}$ and a pitch polymer.

Keywords: Benzopyranes, 2-Oxopyrones, Aldol-, Nucleophilic- and Cyclization reactions

Introduction

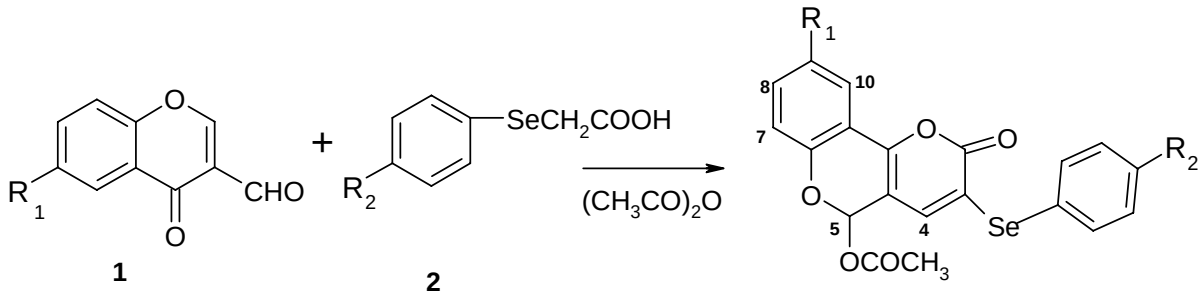
Although selenium was obtained for the first time by Berzelius in 1817, its chemistry in contrast to the chemistry of O- and S-containing organic molecules is less developed. In recent years, interest in the chemistry of Se-containing compounds has increased remarkably due to their chemical properties and biological activities. Organic Se compounds mostly resemble those of their S analogues, but in some cases remarkable differences are observed, e.g. they appear to be less stable than their S analogues, they are oxidation- and photo-sensitive, very toxic and very often bad smelling. Therefore, new approaches to organic Se compounds by using more stable and less toxic starting materials are an attractive goal.

The aim of this study was aldol synthesis with thermolabile **phenylselanylacetic acids**, which are not convenient components for condensation reaction at higher temperature[1,2,3]. In the form of ammonium salts phenylselanylacetic acids have interesting pharmacological properties as inhibitors of thrombocyte agregation, hypocoagulative activity and moderate antihemolytic activity[4]. The most popular reaction for the formation of carbon-carbon bonds is still the aldol addition. Unfortunately, we know aldol reactions of phenylselanylacetic acid only with two aldehydes - benzaldehyde and heptanal and final products of these reactions are aldols[5,6].

The second component of our study is 4-oxo-4*H*-1-benzopyran-3-carboxaldehyde **1** (**3-formyl-chromone**). Derivatives of 3-formylchromone are available by Vilsmeier-Haack reaction[7], they are attractive intermediates for preparation of many different heterocycles[8,9,10] and many of them have significant biological activity, exceptionally antiallergic and antimycobacterial activities[11,12]. This paper is a continuation of our previous works in synthesis[12,13], kinetics[14], photochemical[15] and theoretical properties[16,17] of chromone derivatives. In this paper a new cyclization reaction of phenylselanylacetic acids and 3-formylchromones is described.

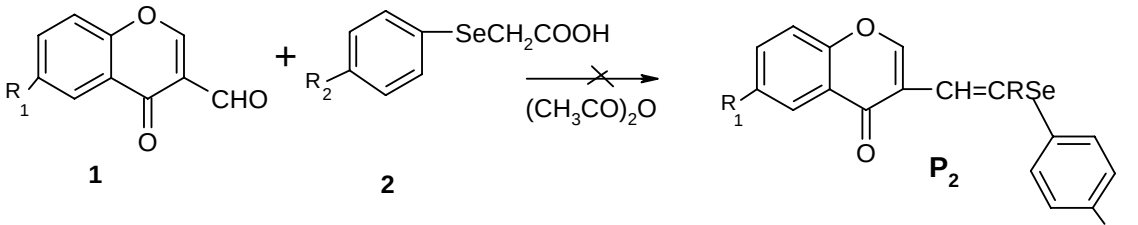
Results and Discussion

The novel products 3-(phenylselanyl)-2-oxo-2*H*,5*H*-pyrano[3,2-c] chromen-5-yl acetates $\mathbf{P_1}$ were prepared as a result of atypical reaction of 3-formylchromones **1** and 4-R-phenylselanylacetic acids **2**. Acetates $\mathbf{P_1}$ were obtained by heating of equimolar mixture of both reactants in acetic anhydride using CH_3COOK as catalyst. Optimized conditions for this reaction are 60-80 ^{o}C for 2-3 h, but for thermolabile Se-component is acceptable also the overnight reaction at room temperature. In the course of condensation reaction the 4-oxo-4*H*-benzopyrane ring is transformed into 2-oxo-2*H*-benzopyrane-ring (**Scheme 1**.).



a R_1 =H R_2 = H
b R_1 =CH_3, R_2 = H
c R_1 =Cl R_2 = H
d R_1 =Cl R_2 = Br

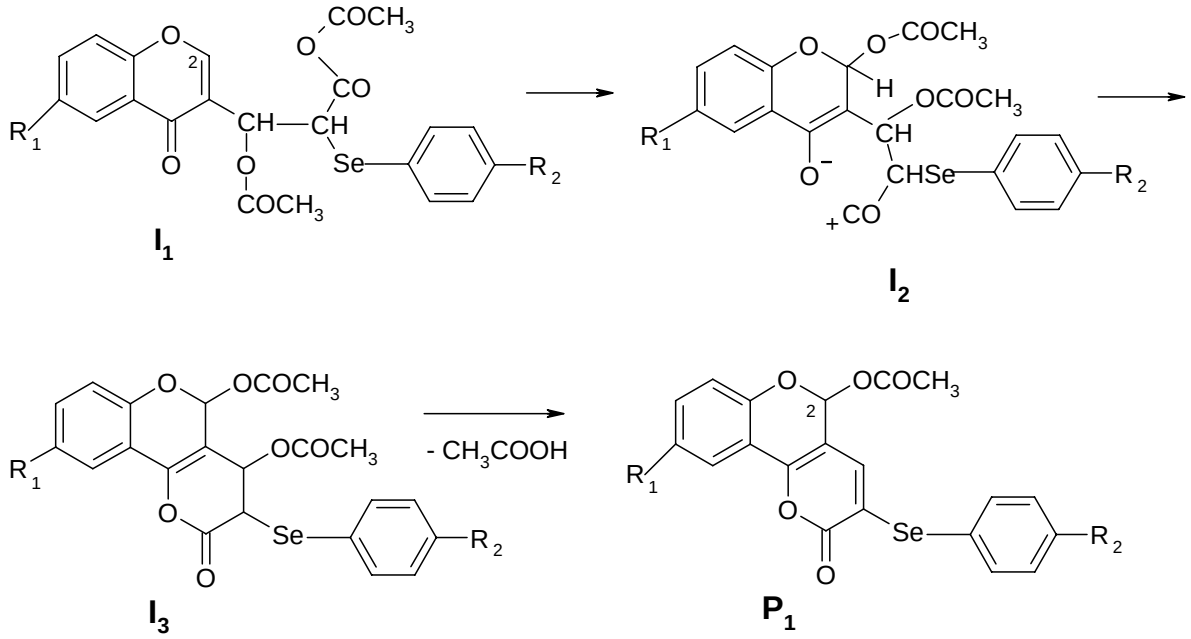
Our experimental results showed that in the course of this reaction the usual aldol condensation products $\mathbf{P_2}$ were not obtained (**Scheme 2**.).



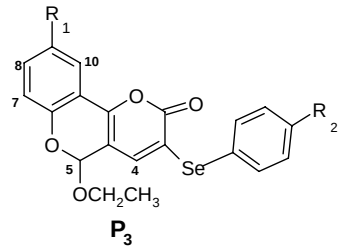
R = H , COOH; R_1= H, NO_2; R_2 = H, Br

The proposed mechanism for the formation of 3-(phenylselenyl)-2-oxo-2*H*,5*H*-pyrano[3,2-c] chromen-5-yl acetates $\mathbf{P_1}$ is in **Scheme 3**. The assumed route preferes an acylation of both components in the begining of the reaction. The acylated intermediates $\mathbf{I_1}$ - $\mathbf{I_3}$ are more reactive than nonacylated components and they can change the course of reaction, forming the new pyrone cycle. The addition of $^{-}OCOCH_3$ group on the electron deficient site-2 of pyrone cycle has a stabilising effect. We did not assume the opening of pyrone ring in the course of reaction because the opening of γ-pyrone cycle is accompanied by color change into orange or red color of reaction mixture[8,12,14] and we did not observe color changes of the reaction mixture.

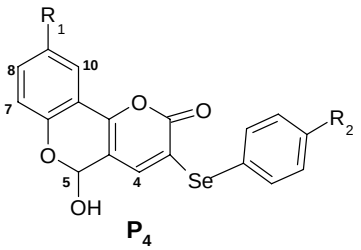
Scheme 3.



We found that the acetyloxy group of the final product **P$_1$** in the presence of acid catalyst, in our case p-toluenesulfonic acid, undergoes to nucleophilic substitution. Heating and stirring of pyrano[3,2-c] chromen-5-yl acetates **P$_1$** in ethanol with catalytic amount of p-toluenesulfonic acid for 2 h yielded ethyloxy derivative **P$_3$.** Realizing this reaction in water or in dioxan-water mixture at 60–70 ^{o}C the product **P$_4$** was formed. Structure of new isolated compounds was confirmed by elemental analysis and ^{1}H-NMR spectra. Products **P$_1$**, **P$_3$**, **P$_4$** are very intensive fluorescencent compounds.



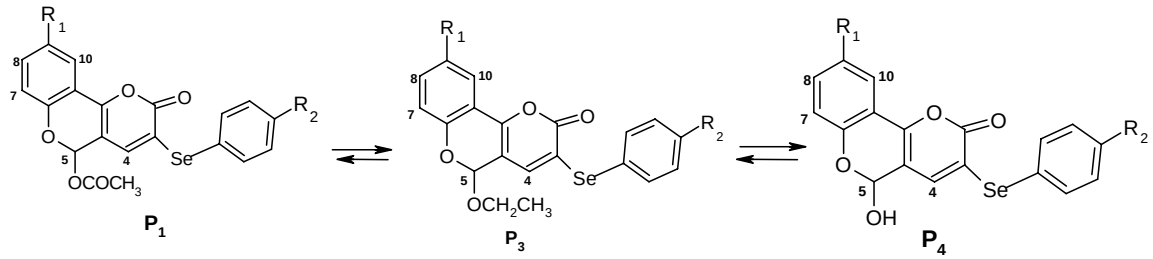
P$_3$



P$_4$

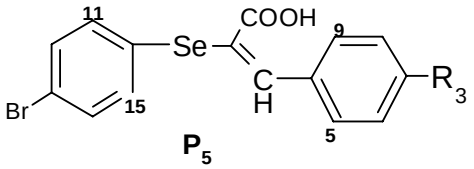
P$_3$: **a** R_1 =Cl, R_2 = H**;**
b R_1 =Cl, R_2 = Br

P$_4$: R_1 =CH_3, R_2 = H

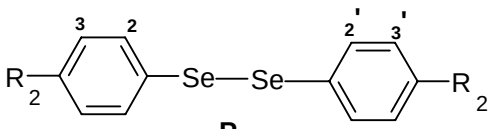


P$_1$ **P$_3$** **P$_4$**

We found, that the phenylselanylacetic acid in condensation reaction with other carbonyl compounds produced normal aldol-condensation products or diphenyldiselane as a product of decomposition. After stirring and heating the mixture of phenylselanylacetic acid, arylcarbaldehyde and triethylamine in acetanhydride at 40 ^{o}C for 4 h the 2-phenylselanylcinamoyl acid **P$_5$** was prepared**.** Refluxing the mixture or using Perkin modification of aldol reaction at 180 ^{o}C without solvent resulted only in polymeric products from which we were able to isolate product **P$_6$**.



P5



P6

P5: **a** R_3 =H; **b** $R_3 = NO_2$ **P6:** R_2 = H, Br

Experimental part

Melting points (uncorrected) of the synthesized compounds were determined on the Kofler block. The microanalyses (Carlo Erba Instrumentazione 1106) were in satisfactory agreement with the calculated values (the results for C, H, and N showed an agreement within ± 0.40%). ^{1}H-NMR spectra were measured at 300MHz, ^{13}C-NMR spectra at 75MHz on a Varian Gemini 2000 NMR spectrometer. Chemical shifts are given in δ-scale, coupling constants in Hz, TMS was used as an internal standard.

The 3-formylchromones **1** were prepared by Vilsmeier double formylation of appropriate 2-hydroxyacetophenones[7]. The preparation of R-phenylselanylacetic acid was carried out by modification of publidhed procedures[2,3]. The reactions were monitored by TLC in the ethylacetate-isohexane mixture.

General procedure for the P_1

A mixture of 3-formylchromones **1** (20 mmol) and R_2-phenylselanylacetic acid **2** (20 mmol) in 10 ml of acetic anhydride with 15 mg of CH_3COOK resulted in a yellow precipitated product after stirring for 2 h at 60-70°C. The mixture was cooled to room temperature, product was separated, washed 3-times with cold diethylether and crystallised from dioxane.

9-Chloro-3-(phenylselanyl)-2-oxo-2*H*,5*H*-pyrano[3,2-c]chromen-5-yl acetate **P_1a**.

$C_{20}H_{13}ClO_5Se$, MW= 447.7; Melting point 266-268 °C.

1-HNMR (CDCl3),δppm: 1.97(s,3H,CH3),6.73(s,1H,H-5);6.99(d,1H,H-7,J=8.5Hz); 7.06(s,1H,H-4); 7.32(dd,1H,H-8,J=8.6Hz, J=2.8Hz); 7.43-7,53(m,3H,H-phenyl); 7.65-7.70 (m,2H,h-phenyl), 7.82(d,1H,H-10,J=2.8Hz).

9-Chloro-3-(4-bromo-phenylselenyl)-2-oxo-2*H*,5*H*-pyrano[3,2-c]chromen-5-yl acetate **P_1b**

$C_{20}H_{12}BrClO_5Se$, MW= 526.6; Melting point 285-287 °C,

1-HNMR (DMSO-6d),δppm: 2.13(s,3H,CH3),6.32(s,0.5H,H-5); 6.35(s,0.5H,H-5); 7.33-7,56(m,4H,H-phenyl); 7.78(d,1H,H-7, J=9Hz); 7.89(dd,1H,H-8, J=9Hz, J=2.8Hz); 8.00(d,1H,H-10, J=2.8Hz); 8.69(s,1H,H-4);

9-Chloro-5-ethyloxy-3-(phenylselanyl)-2-oxo-2*H*,5*H*-pyrano[3,2-c]chromen ***P_3***

A solution of 9-chloro-3-phenylselanyl-2-oxo-2*H*,5*H*-pyrano[3,2-c]chromen-5-yl acetate (200mg) and 15mg of p-toluenesulfonic acid in ethanol (20ml) was stirred at 60 °C for 3 h. Then the mixture was cooled, the solid product was separated and crystallized from ethanol.

$C_{20}H_{15}ClO_4Se$, MW= 433.7; Melting point 133-135 °C

1-HNMR (CDCl3),δppm:1.12(t,3H,CH3), 3.63(q,1H,CH2), 3.85(q,1H,CH2),5.79(s,1H,H-5); 6.69(s,1H,H-4); 6.93(d,1H,H-7,J=8.6Hz); 7.28(dd,1H,H-8 ,J=8.6Hz, J=2.6Hz); 7.42-7.51(m,3H,H-phenyl); 7.67-7,70(m,2H,H-phenyl); 7.79(d,1H,H-10,J=2.6Hz).

9-Methyl-3-(phenylselanyl)-2*H*,5*H*-pyrano[3,2-c]chromen-5-ol ***P_4***

Method a.

A mixture of 6-methyl-3-formylchromone (20 mmol) and phenylselanylacetic acid (20 mmol) in 30 ml of toluene with 50 mg of CH_3COOK was stirred and at 60 °C for 8 h. The mixture was then cooled, the solid product was separated, washed with cold diethylether and then crystallised from dioxane.

Method b

Product ***P*** *1* (200 mg) and 15mg of p-toluenesulfonic acid was heated in water (50 ml) at 70 °C for 30 min. Reaction mixture was cooled , the solid product was separated and crystallised from dioxane.
$C_{19}H_{14}O_4Se$, MW= 385.2; Melting point 257-259 °C,
1-HNMR (CDCl3),δppm: 2.39(s,3H,CH3), 6.24(s,1H,H-5); 6.45(s,1H,H-4);6.55(d,1H,H-7,J=7.8Hz); 7.13(dd,1H,H-8 J=7.8Hz, J=1.6Hz); 7.33-7.56(m,5H,H-phenyl);7.58(d,1H,H-10,J=1.6Hz).

2-(4-Bromophenylselanyl)cinnamoyl acid ***P*** *5*

A mixture of benzaldehyde (20 mmol) and 4-bromophenylselanylacetic acid (20 mmol) in 20 ml of acetic anhydride with 30 mg of CH_3COOK was stirred at 30-40 °C for 8 h. Reaction mixture was cooled , the solid product was separated, washed with ethanol and crystallised from dioxane.
$C_{15}H_{11}BrO_2Se$ MW= 382.1, Melting point 166-168 °C,
1H-NMR(DMSO-d6)(ppm) 8.22(s,1H,H-6); 7.65-7.69(m,2H,H-1,5);7.40-7.45(m,6H,H-2-4,8-10); 7.24-7.29(m,2H,H-7,11); 13.03(s-broad,1H,OH).

Products ***P*** *6*

Diphenyldiselenid $C_{12}H_{10}Se_2$ MW= 311.9; Melting point 62-63 °C.
^{1}H-NMR($CDCl_3$)(ppm) 7.21-7.29(m, 6H, H- 3-5,3‘-5‘), 7.57- 7.62(m,4H,H-2,2‘6,6‘)
(4,4‘-Dibromdiphenyl)diselenid $C_{12}H_8Br_2Se_2$ MW= 417.7; Melting point 111-113°C
1H-NMR($CDCl_3$)(ppm): 7.39(dd, 4H, H-3-5,3‘-5‘ J=8.6Hz,J=2.0Hz), 7.43(m,4H,H-2,2',6,6').

Acknowledgements: This work was supported by Science and Technology Assistance Agency under the contract No. APVT-20-031904 and Grant No. 1/0071/03 and 1/1374/04 of the Slovak Grant Agency.

References

1. *Organic Selenium Compounds: Their Chemistry and Biology.* Wiley, New York, **1973**
2. Morgan,G.T., Porritt,W.H., *J.Chem.Soc.* **1925,** 127, 1759.
3. Martynov ,A.V., Mirskova,A.N., Kalikhman,I.D., Voronkov,M.,G.; *J.Org.Chem.* 24, **1988**, 454.
4. Nefedova,T.V.,Kubatiev,A.A., Martynov,A.V., Guseva,S.A., Kazimirovskya,V.B., *Pharm.Chem.J.* 21, **1987,** 648 .
5. Reich,H.,J., at al, *J.Amer.Chem.Soc.* 101, **1979,** 6638.
6. Lucchetti,J., Krief,A., *Tetrahedron Lett.* **1978,** 2693.
7. Nohara, A.; Ishiguto, T.; Sanno, Y., *Tetrahedron* **1974**, *13*, 1183.
8. Sabitha,G., *Aldrichimica Acta* **1996**, *29*, 15.
9. Ghosh, Ch., K.; Bandyopadhyay Ch., *J. Chem. Soc. Perkin Trans. 1*, **1983**, 1989.
10. Eicher, T., Hauptmann, S.: The Chemistry of Heterocycles, Georg Thieme Verlag Stuttgart, New York (**1995**).
11. Edwards, A.M., Howell, J.B.L.:*Clinical and Experimental Allergy 30*, **2000,**756.
12. EL-Shaaer, H.M., Foltinova, P., Lacova, M., Chovancova, J., Stankovicova, H., *Il Farmaco* **1998**, *53, 224.*
13. Lacova,M., Gasparova, R.., Loos D., Liptay,T., Pronayova,N.: Molecules **2000,** 5, 167.
14. Stankovicova,H.; Lacova,M., Gaplovsky, A.; Chovancova, J.; Pronayova,N., *Tetrahedron*, **2001**, *57*, 3455 -3464.
15. Gaplovsky, A.; Donovalova, J.; Lacova, M.; Mracnova, R.; El-Shaaer,H.,M.,: *Journal of Photochemistry and Photobiology, A: Chemistry* **2000**, *136*, 61.
16. El-Shaaer, H.,M., Perjessy, A., Zahradnik, P., Lacova,M., Sustekova,Z.: *Monatshefte fur Chemie* **1993,** 124, 539.
17. Stankovicova, H., Fabian W.M.F., Lacova, M.; *Molecules*, **1996**, 1, 223.
14. Nohara, A.; Ishiguto, T.; Sanno, Y., *Tetrahedron* **1974**, *13*, 1183.