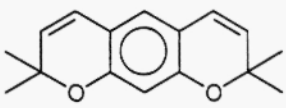
ON THE SYNTHESIS OF BENZODIPYRANS

Tibor Eszenyi, Tibor Tímár*, Péter Sebők, Jozsef Jekő
Department of Chemical Research, ICN Hungary Co. Ltd., Tiszavasvári, Hungary, H-4440

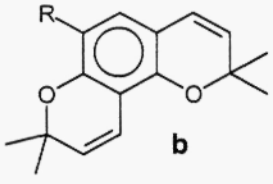
Abstract: The reaction of 2,2-dimethyl-7-hydroxy-4-chromanone and 3-methylbut-2-enoic acid in zinc chloride/phosphorus oxychloride and aluminum chloride/phosphorus oxychloride leads to the formation of a series of benzodipyran derivatives. The structures of intermediates as well as the final regioisomer products were determined by ^{1}H-NMR and MS methods.

Introduction

Benzodipyrans are well known heterocyclic compounds and widely distributed in plant Kingdom (1). They also have considerable biological importance, *e.g.* benzodipyran derivatives (**a**,**b**) have been reported to show insect antijuvenile hormone activity (2-5).



a



b

R: H, CH_3O

There are some, relatively low yielding procedures for the synthesis of compounds above and their possible precursors (4, 6-9). Thus, the reaction of phloroglucinol and 3-methylbut-2-enoic acid in polyphosphoric acid at 100 °C gives both linear and angular dihydropyranochromanones (6). Under these conditions the angular isomer can be rearranged to the linear product.

There is also a report (7) on the condensation reaction from phenols and α,β-unsaturated carboxylic acids using different kind of polyphosphoric acids being able to produce several products, including benzodipyran derivatives.

The photo-Fries rearrangement of a series of aryl esters of α,β-unsaturated carboxylic acids has recently been reported (8). The transformation of 7-(3-methyl-2-butenoyloxy)-2,2-dimethyl-4-chromanone (**2**) into the corresponding 7-hydroxy-6-(3-methyl-2-butenoyloxy))-2,2-dimethyl-4-chromanone (**4**) has been accomplished this way in 9% yield. The cyclisation of latter compound led to the quantitative formation of 2,2,8,8-tetramethyl-2,3,7,8-tetrahydro-4*H*,6*H*-benzo[1,2-b:5,4-b']dipyran-4,6-dione (**7**).

Enolate from 2,4-diacetylresorcinol generated by deprotonation using lithium diisopropylamide (9) undergoes condensation with two equivalents of acetone to give bis-β-ketol which can be cyclised (MeOH/HCl) into dipyran-4,6-dione (7).

During our optimisation studies (applying different molar ratio between starting resorcinol and 3-methylbut-2-enoic acid) for the large scale synthesis of 2,2-dimethyl-7-hydroxy-4-chromanone (**1**) and related compounds (10-12) we observed the formation of several side-products. We conceived, that 2,2-dimethyl-7-hydroxy-4-chromanone already formed could compete with the unreacted resorcinol for 3-methylbut-2-enoic acid and benzodipyrans could also exist among these side-products. Consequently, we decided to investigate the reaction of 2,2-dimethyl-7-hydroxy-4-chromanone (**1**) and 3-methylbut-2-enoic acid (Scheme).

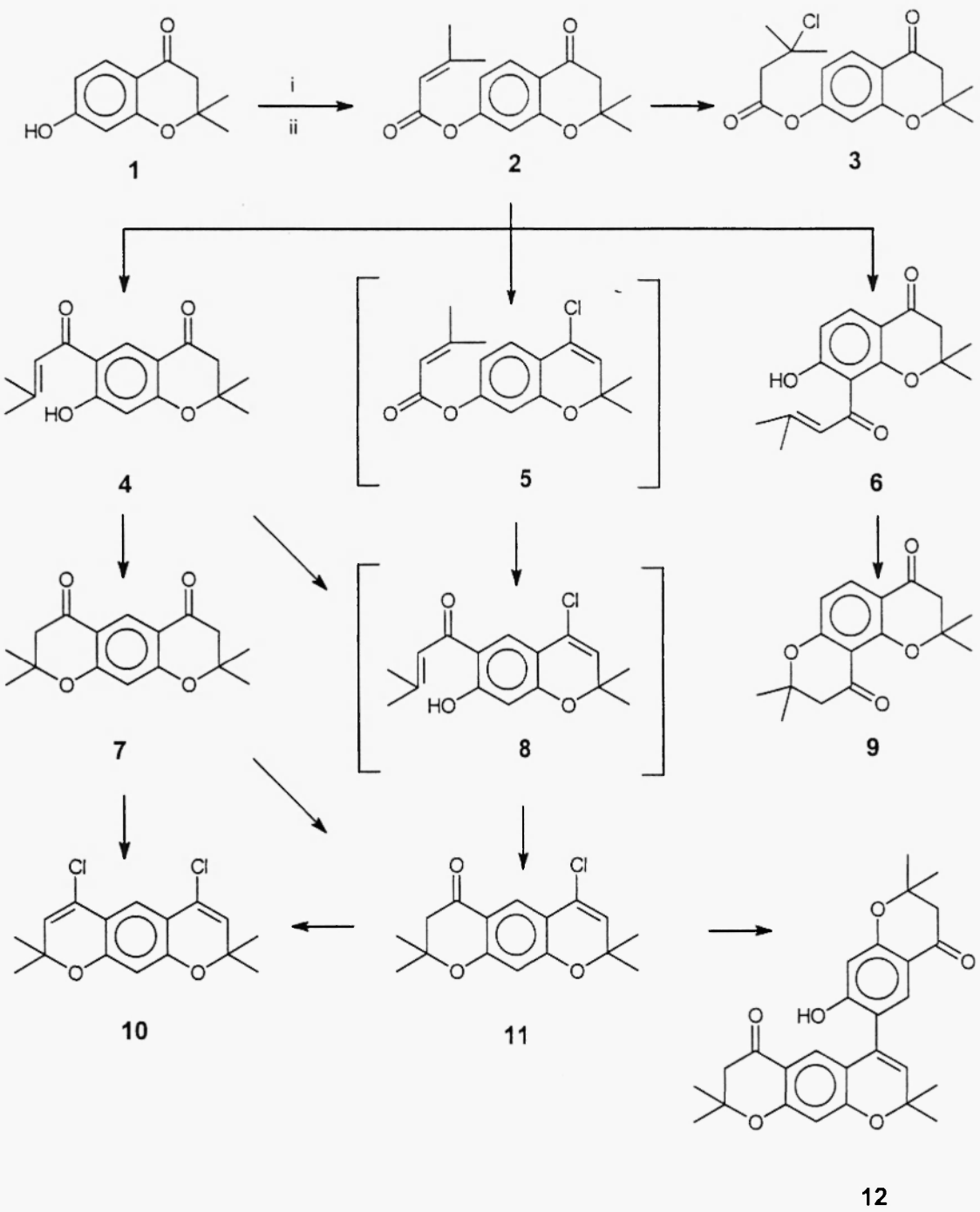
Results and Discussion

2,2-Dimethyl-7-hydroxy-4-chromanone (**1**) and 3-methylbut-2-enoic acid were reacted in zinc chloride/phosphorus oxychloride and aluminum chloride/phosphorus oxychloride at 25 and 60 °C. TLC and GC monitoring of the progress of reactions showed a very complex mixture of products. After the consumption of the starting material, the reaction mixture was worked up (Experimantal) and by the use of repeated column chromatography each component of the reaction mixture was separated and purified. The structures of products formed were determined by ^{1}H-NMR, MS methods and elemental analyses. Based on these information we were able to establish the reaction route that can be seen on Scheme.

The reaction of 2,2-dimethyl-7-hydroxy-**4**-chromanone (**1**) and 3-methylbut-2-enoic acid in zinc chloride/phosphorus oxychloride completed at 25 °C in 80 hours and at 60 °C in 8 hours, that means ten-fold increase in reaction time comparing to the reaction of resorcinol using similar reaction conditions (10). In the course of the reaction 7-(3-methyl-2-butenoyloxy)-2,2-dimethyl-4-chromanone (**2**) was formed, which then transformed partly *via* hydrochloric acid addition to the saturated ester (**3**) and partly by ortho / ortho'-Fries rearrangement to the unsaturated ketones **4** and **6**, respectively. Fries rearrangement of **2** took place regioselectively, as the ratio of **4** and **6** was 10 : 1. These ketones were then cyclised to the corresponding dipyran-diones (**4** to **7** and **6** to **9**). As the reaction proceeded further, the formation of chloro-dipyran (**11**) and dichloro-dipyran (**10**) derivatives was observed. When applying prolonged reaction time the Friedel-Crafts alkylation of the unreacted **1** by **11** afforded the small amount of dipyrano-4-chromanone derivative (**12**).

The reaction of 2,2-dimethyl-7-hydroxy-4-chromanone (**1**) and 3-methylbut-2-enoic acid in aluminum chloride/phosphorus oxychloride showed basically similar reaction sequence. The formation of esters (**2** and **3**), the ortho / ortho'-Fries-rearrangement of **2** to the unsaturated ketones (**4** and **6**) as well as the cyclisation of the latter compounds to the corresponding dipyran-diones (**7** and **9**) took place.

Scheme



i: 3-methylbut-2-enoic acid/$ZnCl_2$-$POCl_3$

ii: 3-methylbut-2-enoic acid/$AlCl_3$-$POCl_3$

However, in this case the formation of compounds **5** and **8** was observed. The reaction sequences from **2** *via* **5** to **8** and **4** to **8** as well as **7** to **11** were confirmed by GC measurements. Figures 1 and 2 show the temperature dependence of the reaction of 2,2-dimethyl-**7**-hydroxy-4-chromanone and 3-methylbut-2-enoic acid in zinc chloride/phosphorus oxychloride.

In conclusion, benzodipyran-diones (**7** and **9**) can be prepared by the reaction of 2.2-dimethyl-7-hydroxy-4-chromanone and 3-methylbut-2-enoic acid. At the same time we were able to detect and isolate different novel intermediates (**3**, **5**, **6**, **8**). The possibility of a novel synthesis of new benzodipyran derivatives (**10**, **11** and **12**) was also demonstrated.

Figure 1 GC monitoring of the reaction of **1** and 3-methylbut-2-enoic acid/$ZnCl_2$-$POCl_3$ at 25 °C

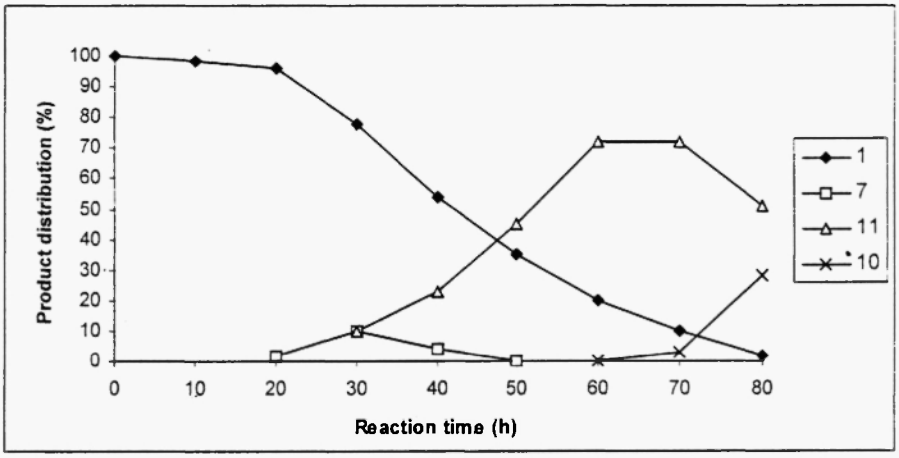


Figure 2 GC monitoring of the reaction of **1** and 3-methylbut-2-enoic acid/$ZnCl_2$-$POCl_3$ at 60 °C

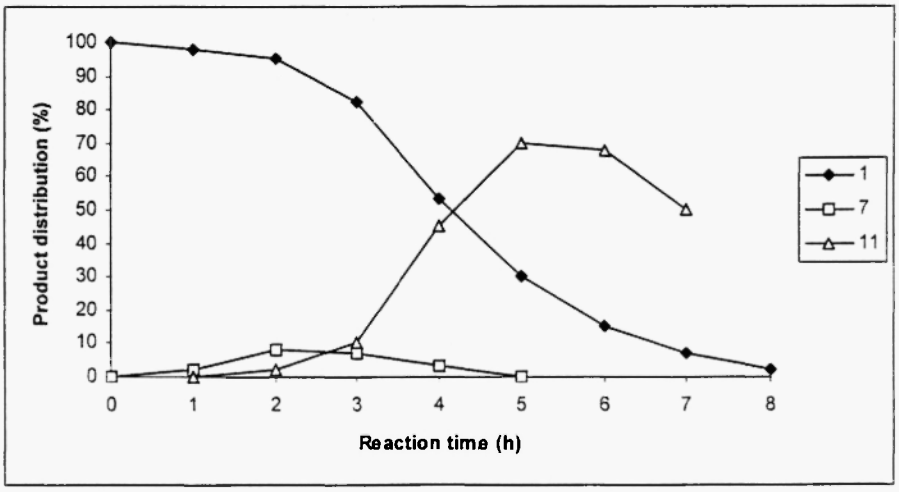


Table Physical and Spectral Data of Compounds (**2-12**) Formed

Compound	mp (°C)	^{1}H-NMR ($CDCl_3$/TMS) δ, *J* (Hz)	HR-MS or Elemental analysis
2	105-106[a]	1.45 (s, 6H), 2.01 (d, *J*=1, 3H), 2.24 (d, *J*=1, 3H), 2.70 (s, 2H), 5.98 (m, 1H), 6.80 (m, 2H), 7.89 (d, *J*=8, 1H)	calcd/found for $C_{16}H_{18}O_4$: C:70.05/70.40 H: 6.61/7.01
3	oil	1.45 (s, 6H), 1.80 (s, 6H), 2.72 (s, 2H), 3.07 (s, 2H), 6.70 (m, 2H), 7.87 (d, *J*=10, 1H)	310.0972 (^{35}Cl, calcd.) 310.0974 (measured)
4	90-92[b]	1.47 (s, 6H), 2.07 (d, *J*=1, 3H), 2.22-(d, *J*=1, 3H), 2.72 (s, 2H), 6.42 (s, 1H), 6.92 (m, 1H), 8.43 (s, 1H), 13.50 (s,1H)	274.1205 (calcd.) 274.1225 (measured)
5	oil	1.45 (s, 6H), 2.05 (d, *J*=1, 3H), 2.20 (d, *J*=1, 3H), 6.00 (m, 1H), 6.33 (s, 1H), 6.80 (m, 2H), 7.85 (d, *J*=8, 1H)	calcd/found for $C_{16}H_{17}ClO_3$: C:65.64/65.85 H: 5.85/6.01,Cl:12.11/12.35
6	oil	1.50 (s, 6H), 2.02 (d, *J*=1, 3H), 2.21 (d, *J*=1, 3H), 2.71 (s, 2H), 6.60 (d, *J*=8, 1H), 6.95 (m, 1H), 7.95 (d, *J*=8, 1H), 14.00 (s, 1H)	calcd/found for $C_{16}H_{18}O_4$: C:70.05/70.33 H: 6.61/6.91
7	185-187[c]	1.48 (s, 12H), 2.61 (s, 4H), 6.30 (s, 1H), 8.35 (s, 1H)	calcd/found for $C_{16}H_{18}O_4$: C:70.05/70.22 H: 6.61/6.89
8	oil	1.47 (s, 6H), 2.08 (d, *J*=1, 3H), 2.21 (d, *J*=1, 3H), 5.70 (s, 1H), 6.40 (s, 1H), 6.71 (m, 1H), 7.85 (s, 1H), 13.45 (s,1H)	292.0866 (^{35}Cl, calcd.) 292.0886 (measured)
9	oil	1.46 (s, 6H), 1.60 (s, 6H), 2.67 (s, 2H), 2.77 (s, 2H), 6.65 (d, *J*=8, 1H), 7.91 (d, *J*=8, 1H)	calcd/found for $C_{16}H_{18}O_4$: C:70.05/70.19 H: 6.61/6.89
10	oil	1.45 (s, 12H), 5.65 (s, 2H), 6.28 (s,1H), 7.50 (s, 1H)	calcd/found for $C_{16}H_{16}Cl_2O_2$: C:61.75/61.70 H: 5.18/5.29,Cl:22.78/22.90
11	oil	1.47 (s, 6H), 1.51 (s, 6H), 2.65 (s, 2H), 5.71 (s, 1H), 6.35 (s, 1H), 7.95 (s, 1H)	calcd/found for $C_{16}H_{17}ClO_3$: C:65.64/65.90 H: 5.85/5.99,Cl:12.11/12.30
12	259-260	1.42 (s, 6H), 1.48 (s, 6H), 1.52 (s, 6H), 2.65 (s, 2H), 2.70 (s, 2H), 5.65 (s, 1H), 6.30 (s, 1H), 6.48 (s, 1H), 7.12 (s, 1H), 7.58 (s, 1H), 9.45 (s, 1H)	calcd/found for $C_{27}H_{28}O_6$: C:72.30/72.46 H: 6.29/6.50

[a] lit. mp. 94-95 °C (8) [b] lit. mp. 88-89 °C (8) [c] lit. mp. 179-180 °C (8)

Experimental

Melting points were determined with a Koffler hot-stage apparatus and are uncorrected. Analytical thin-layer chromatography was performed on precoated aluminium-backed 0.2 mm silica gel plates. Column chromatography was carried out with Kieselgel 60 silica gel. GC measurements were performed on a Hewlett-Packard 5890 instrument. ^{1}H NMR spectra were determined for solutions in deuteriochloroform with TMS internal reference on a Varian Gemini-200 instrument. Ms data were obtained on a VG 7035 spectrometer in EI mode. Microanalyses were performed by Microlaboratory, L. Kossuth University, Debrecen, Hungary. Solvents were used either as purchased or dried and purified by standard methods.

Typical procedure

To a stirred mixture of phosphorus oxychloride (20 ml, 218 mmol) and 3-methylbut-2-enoic acid (1.1 g, 11 mmol), fused zinc chloride (2.04 g, 15 mmol) or aluminum chloride (2.00 g, 15 mmol) and 2,2-dimethyl-7-hydroxy-4-chromanone (1.92 g, 10 mmol) were added at room temperature and the reaction mixtures were stirred at 25 or 60 °C. The progress of reaction was monitored by TLC (benzene/ether: 8/1) and GC. When the starting material disappeared the mixture was poured onto crushed ice (200 g), extracted with diethyl ether (3x30 ml), organic layer was washed acid free and dried over sodium sulfate. The diethyl ether was removed in vacuum. Using repeated column chromatography each component of the reaction mixture was separated and purified. For physical and spectral data see Table.

Acknowledgement

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