# SYNTHESIS OF POLYFLUORINATED CHROMONES AND FLAVONES

CHEMISTRY

1965

SovietRxiv

## Abstract

## Full Text

UDC 547.814

CHEMISTRY

Corresponding Member of the Academy of Sciences of the USSR N. N. Vorozhtsov, Jr., V. A. Barkhash,
A. T. Prudchenko, T. I. Khomenko

# SYNTHESIS OF POLYFLUORINATED CHROMONES AND FLAVONES

As is known, the interaction of benzoyl chloride with sodium acetoacetic ester leads to the formation of benzoylacetoacetic ester, from which benzoylacetic ester can readily be obtained ($^1$).

In studying the properties of derivatives of pentafluorobenzoic acid, we investigated the interaction of its acid chloride ($^2$) with sodium and also magnesium ethoxyacetoacetic esters in benzene. In all cases, instead of the expected $\beta,\beta'$-diketo ester, 2-methyl-3-carbethoxy-5,6,7,8-tetrafluorochromone (I) was isolated:

$$C_6F_5COCl \xrightarrow[Mg(OC_2H_5)]{CH_3COCH_2COOC_2H_5} [\text{ intermediate }]$$

(I)

$$(I) \xleftarrow[20^\circ]{C_6H_5CH_2NH_2} \text{N-benzylamide derivative}$$

$$(I) \xrightarrow[(CH_2COOH)]{NH_2OH} \text{oxime derivative}$$

The structure of I was confirmed by analytical data, chemical transformations, and spectra. On interaction of I with hydroxylamine hydrochloride in acetic acid, oxime I was obtained, and in the reaction with benzylamine in benzene the N-benzylamide of 2-methyl-5,6,7,8-tetrafluorochromone-3-carboxylic acid was formed (cf. ($^3$)). I does not form an oxonium salt with HCl (as do 3-acetylchromones ($^4$)) and does not add bromine, apparently owing to steric hindrance.

In the IR spectrum of I the following characteristic frequencies are present: 1740 (C=O in esters), 1660 (C=O in chromones), 1010 (C–F), 1500 and 1520 (fluorinated aromatic ring), 1090 and 1120 (C–O–C in cyclic ethers), 2880, 2910, 2945, and 2990 ($CH_2$ and $CH_3$), 1610 cm$^{-1}$ (C=C conjugated with C=O). The UV spectrum of I has all the features characteristic of chromones ($^5$), differing

Fig. 1. UV spectra I-III in ethanol

Figure 1: Fig. 1. UV spectra I-III in ethanol

Fig. 2. NMR spectrum of 2-methyl-3-carboethoxy-5,6,7,8-tetrafluorochromone (I). Peaks 1, 2, 3—explanation in the text, peak 4—(CH3)4Si

Figure 2: Fig. 2. NMR spectrum of 2-methyl-3-carboethoxy-5,6,7,8-tetrafluorochromone (I). Peaks 1, 2, 3—explanation in the text, peak 4—(CH3)4Si

from isomeric coumarins (Fig. 1): strong absorption in the region 240–250 m$\mu$ (lg $\epsilon > 3.8$), one minimum and one maximum at 296 m$\mu$ (lg $\epsilon$ 3.65). In the NMR spectrum of I (internal standard tetramethylsilane) there are three peaks with an area ratio of $3:3:2$ (Fig. 2). Peak 1 is a triplet with $\delta_1$ 1.6 ppm; peak 3 is a quartet with $\delta_3$ 4.6 ppm. The structure of these peaks and the magnitude of their chemical shifts indicate that they belong to the $-CH_2CH_3$ group of the ester-

ester (6). Peak 2 ($\delta_2$ 2.8 ppm) belongs to a single $CH_3$ group at a double bond (7). In the $F^{19}$ NMR spectrum of I there are four bands. On the basis of these data we assign to I the structure of 2-methyl-3-carboethoxy-5,6,7,8-tetrafluorochromone.

The formation of I is apparently explained by cyclization of the intermediately formed pentafluorobenzoylacetoacetic ester with elimination of *o*-fluorine; moreover, in the case of $C_2H_5OMg$-acetoacetic ester the cyclization proceeds under very mild conditions and chromone I is formed in a yield of 84.2%. Earlier, in the reaction of hexafluorobenzene with Na-acetoacetic ester, 2-methyl-3-carboethoxy-4,5,6,7-tetrafluorocoumarone was obtained as a result of cyclization with elimination of *o*-fluorine (8). The easier and smoother course of cyclization in our case is evidently explained by the activating influence of the carbonyl group on the *o*-fluorine atom.

**Fig. 1.** UV spectra *I—III* in ethanol

**Fig. 2.** NMR spectrum of 2-methyl-3-carboethoxy-5,6,7,8-tetrafluorochromone (I). Peaks 1, 2, 3—explanation in the text, peak 4—$(CH_3)_4$Si

Analogously, in the condensation of pentafluorobenzoyl chloride with $C_2H_5OMg$-benzoylacetic and $C_2H_5OMg$-pentafluorobenzoylacetic esters (for the synthesis of pentafluorobenzoylacetic ester see (9)) polyfluorinated flavones were obtained in yields of 75–90%:

$$\text{pentafluorobenzoyl chloride} \xrightarrow[\text{Mg(OC}_2\text{H}_5)_2]{\text{RCOCH}_2\text{COOC}_2\text{H}_5} \text{tetrafluoroflavone derivative}$$

$$\text{II},\ R = C_6H_5; \quad \text{III},\ R = C_6F_5.$$

Thus, the condensation of enolates of $\beta$-keto esters with acid chlorides of polyfluoroaromatic acids can be used for the synthesis of polyfluoro derivatives of $\gamma$-benzopyrone.

## Experimental Part

IR spectra were recorded on a UR-10 instrument in the neat state and in KBr pellets. UV spectra were recorded on an SDF-2 instrument; solvent—ethanol, molar concentration $10^{-4}$, layer thickness 0.5 cm. NMR spectra were recorded on a JNM-3 instrument at a frequency of 40 MHz.*

* The authors express their gratitude to A. K. Petrov for recording the NMR spectra.

**2-Methyl-3-carbethoxy-5,6,7,8-tetrafluorochromone (I).** Into a three-necked flask equipped with a stirrer, dropping funnel, and reflux condenser with a calcium chloride tube are placed 0.84 g (0.035 g-mol) of magnesium turnings, 1.1 ml of absolute ethyl alcohol, and 0.1 ml of $CCl_4$. As soon as a vigorous reaction begins, a mixture of 3 ml of alcohol and 15 ml of absolute benzene is added. After all the magnesium has dissolved, 4.14 g (0.032 g-mol) of acetoacetic ester is added dropwise, the mixture is stirred for 1 h at room temperature, and then a solution of 6.85 g (0.03 g-mol) of pentafluorobenzoic acid chloranhydride in 15 ml of benzene is added. The reaction mixture is stirred for 1 h at room temperature and for 15 min at 50°. It is cooled with ice, 1.7 ml of conc. $H_2SO_4$ in 20 ml of water is poured in, the benzene layer is separated, and the aqueous layer is extracted with ether. The extracts are dried over $MgSO_4$; after removal of the solvent and the remaining acetoacetic ester, 6.77 g (84.2%) of I is obtained, m.p. 91-91.5° (from petroleum ether).

Found, %: C 51.56, 51.24; H 2.73, 2.86; F 24.83, 24.53; $OC_2H_5$ 15.05, 14.76
$C_{13}H_8F_4O_4$. Calculated, %: C 51.36; H 2.65; F 25.00; $OC_2H_5$ 14.80

To a solution of 0.2 g of I in 2 ml of $CH_3COOH$ are added 0.05 g of hydroxylamine hydrochloride, and the mixture is heated on a water bath until the precipitate dissolves. The dark oil formed after removal of the acetic acid gradually crystallizes. Oxime of I, m.p. 122-124° (from aqueous alcohol).

Found, %: N 4.32, 4.47; F 23.10, 23.20
$C_{13}H_9F_4NO_4$. Calculated, %: N 4.39; F 23.82%

**N-Benzylamide of 2-methyl-5,6,7,8-tetrafluorochromone-3-carboxylic acid.** To 0.5 g of I, dissolved in 3 ml of benzene, are added 0.35 g of freshly distilled benzylamine. The mixture is allowed to stand at room temperature for 24 h, the solvent is distilled off, and the separated oil is heated with water. The precipitate is washed with hot water and dried. Yellow crystals with m.p. 131-136° (from alcohol).

Found, %: C 58.91, 58.82; H 2.85, 2.86; F 20.95, 20.72; N 4.20, 3.92.
$C_{18}H_{11}F_4NO_3$. Calculated, %: C 59.10; H 3.01; F 20.80; N 3.84.

**3-Carbethoxy-5,6,7,8-tetrafluoroflavone (II).** $C_2H_5OMg$-benzoylacetic ester is prepared from 0.98 g Mg, 4.8 ml of absolute alcohol in 17.5 ml of benzene, and 7.02 g of benzoylacetic ester, as described above for $C_2H_5OMg$-acetoacetic ester. To the resulting solution are added 7.04 g of pentafluorobenzoic acid chloranhydride in 17.5 ml of benzene. The reaction and work-up are carried out as in the preceding experiment. II is obtained in an amount of 10.25 g (91.5%), m.p. 123–124.5° (from petroleum ether).

Found, %: C 59.12, 58.89; H 2.75, 2.77; F 20.85, 21.06; $OC_2H_5$ 12.21, 12.38. $C_{18}H_{10}F_4O_4$. Calculated, %: C 59.02; H 2.75; F 20.75; $OC_2H_5$ 12.29.

$\lambda$max (in alcohol) 250 and 292 $\mu$ (lg $\epsilon$ 4.3 and 4.15). Mol. wt. found 366, 370, calculated 366. IR spectrum (in KBr): 1035 s (C–F), 1125 s (C–O–C in cyclic ethers), 1510 s (polyfluorinated aromatic ring), 1670 s (C=O in flavones), 1760 s (C=O in esters), 2910 w, 2945 w, 2990 m ($CH_2$ and $CH_3$).

**3-Carbethoxy-2′,3′,4′,5′,6′,5,6,7,8-nonafluoroflavone (III).** $C_2H_5OMg$-pentafluorobenzoylacetic ester is prepared, as usual, from 0.53 g Mg, 2.6 ml of absolute alcohol in 9.5 ml of absolute benzene, and 5.75 g of ethyl 2,3,4,5,6-pentafluorobenzoylacetate. To this solution are added 3.8 g of pentafluorobenzoic acid chloranhydride in 10 ml of benzene. The proce-

the conduct of the synthesis and the work-up—as in the preparation of I. III is obtained in an amount of 3.27 g (75.3%). M.p. 100–103° (from petroleum ether).

Found, %: C 47.38, 47.66; H 1.31, 1.26; F 37.29, 37.12; $OC_2H_5$ 10.29, 10.38. $C_{18}H_5F_9O_4$. Calculated, %: C 47.38; H 1.10; F 37.48; $OC_2H_5$ 9.89.

$\lambda_{max}$ (in alcohol) 246 and 289 m$\mu$ (lg $\varepsilon$ 4.18 and 3.66). IR spectrum (in KBr): 1005 s, 1145 s, 1515 s, 1700 s, 1740 s, 2915 w, 2945 w, and 2990 m cm$^{-1}$—assignment of bands as in II.

Novosibirsk Institute of Organic Chemistry
Siberian Branch of the Academy of Sciences of the USSR

Received
9 IV 1965

## CITED LITERATURE

1. *Synthesis of Organic Preparations*, **2**, 584, 1949.
2. A. K. Barbour, M. W. Buxton et al., *J. Chem. Soc.*, 1961, 808.
3. W. Baker, V. S. Butt, *J. Chem. Soc.*, 1949, 2142.
4. G. Wittig, *Ann.*, **446**, 157 (1925).

5. B. K. Ganguly, P. Bagchi, *J. Org. Chem.*, **21**, 1415 (1956).

6. N. Bhacca, L. Johnson, J. Shoolery, *NMR Spectra Catalog*, No. 295, Varian Associate, 1962.

7. J. Pople, W. Schneider, G. Bernstein, *High-Resolution Nuclear Magnetic Resonance Spectra*, IL, 1962, p. 334.

8. G. G. Yakobson, T. D. Petrova, L. I. Kain, T. I. Savchenko, A. K. Petrova, N. V. Porokhovnikov, *DAN*, **158**, 926 (1964).

9. N. N. Vorozhtsov, V. A. Barkhash, A. T. Prudchenko, G. S. Shchegoleva, *Izv. AN SSSR*, in press.

*Note: Figure translations are in progress. See original paper for figures.*

*Source: Math-Net.Ru and CyberLeninka. Machine translation. Verify with the original.*