Pharmaceutical Chemistry Journal *Vol. 33, No. 9, 1999*

DRUG SYNTHESIS METHODS AND MANUFACTURING TECHNOLOGY

INTERACTION OF PYRYLIUM SALTS WITH C-NUCLEOPHILES. PART 1.

É. T. Oganesyan,[1] A. V. Pyshchev,[1] and L. I. Butenko[1]

Translated from Khimiko-Farmatsevticheskii Zhurnal, Vol. 33, No. 9, pp. 21 – 23, September, 1999.

Original article submitted February 12, 1998.

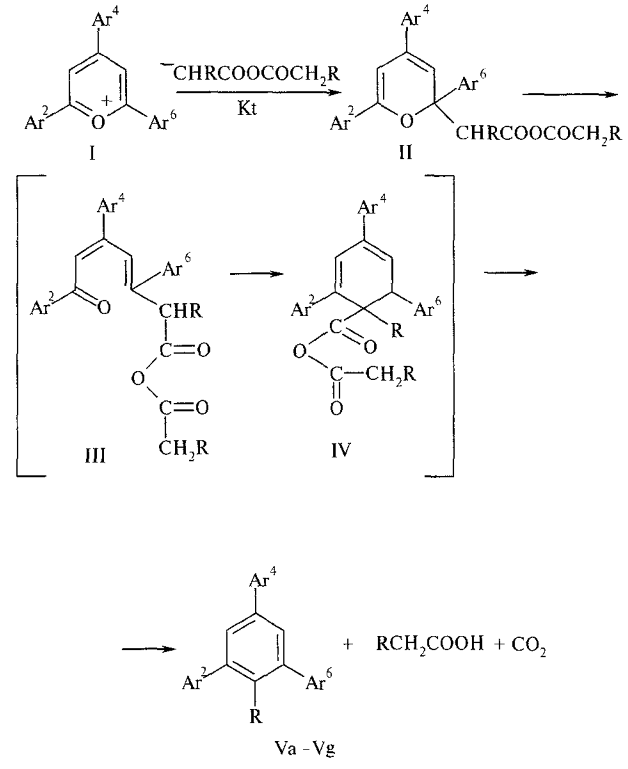
Reactions between 2,4,6-triaryl-substituted pyrylium salts and aliphatic acid anhydrides have been extensively studied [1 – 8]. In these reactions, the anhydrides $(RCH_2CO)_2O$ act as CH-acids.

The interaction of pyrylium salts with CH-acids usually requires using strong bases. However, the presence of such bases may give rise to competitive reactions with the formation of various side products, depending on the nucleophilic properties of the particular base employed.

We suggested that a methylene-reactive component may be initiated by the same weak bases that are used in the Perkin condensation reactions. In accordance with this, boiling 2,4,6-triphenylpyrylium perchlorate (I) with acetic anhydride in the presence of sodium acetate led to the formation of 1,3,5-triphenylbenzene (Va) [9].

We have established that the reactions of pyrylium salts with the anhydrides of acetic, propionic, and butyric acids in the presence of the corresponding sodium carboxylates led to the formation of triarylbenzenes (Va – Vf) with a yield of 30 – 50 % (Table 1, method A). Simultaneously, the same conclusion was drawn by Zimmerman and Fischer [6, 7]. All these data allow us to suggest the following scheme explaining the transformation of pyrylium salts into benzene derivatives.

It was found that the reaction mixtures contain, besides triarylbenzenes V, products (IX) distinguished by higher solubility in organic solvents. The IR spectra of these products displayed, in contrast to the spectra of benzenes V, three additional absorption bands in the region of 1767 – 1620 cm^{-1} and one more band at 3000 – 3300 cm^{-1}. Two bands observed in the 1650 – 1767 cm^{-1} interval disappeared after passing the product through a column filled with Al_2O_3.



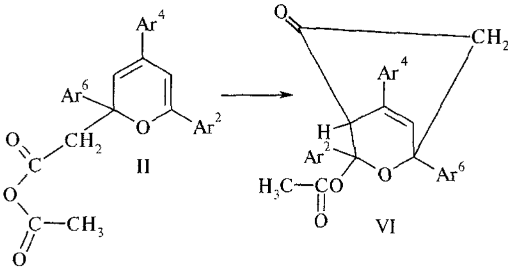
R = H, Me, ET;
Ar = phenyl, *p*-bromophenyl, *p*-methoxyphenyl, *p*-chlorophenyl;
Kt = RCH_2COONa or Bu_3N.

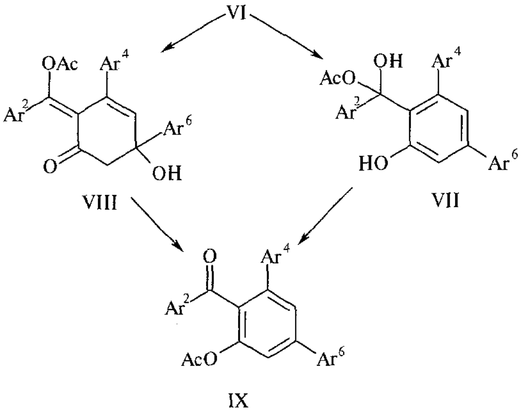
The formation of product IX can be explained assuming that the system features intramolecular acylation of the C(5) carbon atom of pyrane II with the formation of adduct VI.

Subsequent transformations of the intermediate compound VI may proceed, depending on the site of C–O–C chain breakage, in two directions (via structures VII and VIII). however, both pathways lead to the same product IX

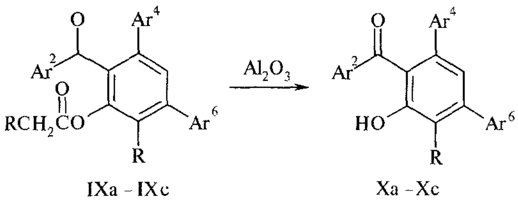
---

[1] Pyatigorsk State Pharmaceutical Academy, Pyatigorsk, Russia.





Using butyric anhydride (instead of acetic anhydride) leads to compound IXb. Chromatography on Al_2O_3 leads to deacylation:



IX, X: R = H (a, c), Et (b).

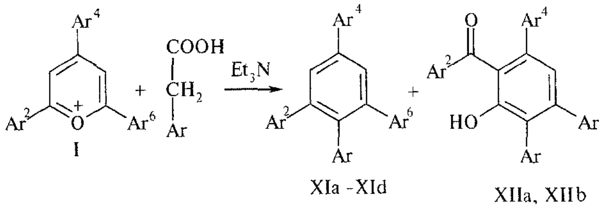
The interaction of 2,4,6-triphenylpyrylium perchlorate (I) with acetic anhydride at room temperature in the presence of tributylamine (method B) led to the same products Va and Xa, but their ratio in the reaction mixture was markedly different from that in the case of method A: 33% (Va) : 34% (Xa) = 1 : 1 (in boiling anhydride, method A) versus 20% (Va) : 40% (Xa) = 1 : 2 (room temperature, method B).

Arylacetic acids, including phenylacetic acid, are widely used in the Perkin condensation reactions [10, 11]. The activity of the acid component depends on the nature of substituents at the α-carbon atom and increases in the following sequence: hydrogen = alkyl < aryl. This suggests that arylacetic acids may be used instead of their anhydrides. To verify this conclusion, we have studied the interaction of 2,4,6-triaryl-substituted pyrylium salts with phenylacetic acids in acetic anhydride in the presence of triethylamine (method C).

As expected, the reaction yielded products of two types – benzenes (XIa – XId) and phenols (XIIa, XIIb) with a yield of 40 – 60 and 30 – 45%, respectively.

TABLE 1. Some Physicochemical Characteristics of the Synthesized Compounds

Compound	Name	Empirical formula	M.p., °C	IR spectrum, cm^{-1}			Method	Yield, %
				$\nu_{O\text{-}H}$	$\nu_{C=O}$	$\nu_{C=C\ arom}$		
Và	1,3,5-Triphenylbenzene	$C_{24}H_{18}$	172	–	–	1580 – 1567	A (B)	33 (20)
Vb	2,4,6-Triphenyltoluene	$C_{25}H_{20}$	138	–	–	1600 – 1560	A	46
Vc	1,3,5-Triphenylethylbenzene	$C_{26}H_{22}$	120	–	–	1593 – 1560	A	47
Vd	1-Phenyl-3,5-di(*p*-bromophenyl)benzene	$C_{24}H_{16}Br_2$	182	–	–	1580 – 1556	A	49
Ve	1,3-Diphenyl-5-(*p*-methoxyphenyl)benzene	$C_{25}H_{20}O$	135	–	–	1595 – 1563	A	49
Vf	1,3-Diphenyl-5-(*p*-chlorophenyl)benzene	$C_{24}H_{17}Cl$	143	–	–	1590 – 1560	A	33
Xa	2-Benzoyl-3,5-diphenylphenol	$C_{25}H_{18}O_2$	106	3170 – 3500	1620	1593 – 1540	A (B)	34 (40)
Xb	2-Benzoyl-3,5-diphenyl-6-ethylphenol	$C_{27}H_{22}O_2$	106	3100 – 3450	1620	1590 – 1513	A	16
Xc	2-(*p*-Methylbenzoyl)-3-(*p*-methoxyphenyl)-5-(*p*-methylphenyl)phenol	$C_{28}H_{24}O_3$	80	3200 – 3400	1617	1593 – 1500	A	39
XIa	1,2,4,6-Tetraphenylbenzene	$C_{30}H_{22}$	217	–	–	1600 – 1553	C	50
XIb	1-Naphthyl-2,4,6-triphenylbenzene	$C_{34}H_{24}$	233	–	–	1593 – 1533	B	38
XIc	1-(*p*-Nitrophenyl)-2,4,6-triphenylphenol	$C_{30}H_{21}NO_2$	209	–	–	1600 – 11530	B	60
XId	1-(*p*-Methoxyphenyl)-2,4,6-triphenylbenzene	$C_{31}H_{24}O$	178	–	–	1590 – 1534	B	82
XIIa	2-Benzoyl-2,4,6-triphenylphenol	$C_{31}H_{22}O_2$	165	3200 – 3500	1630	1593 – 1500	B	45
XIIb	2-Benzoyl-3,5-diphenyl-6-(α-naphthyl)phenol	$C_{35}H_{24}O_2$	166	3170 – 345C	1620	1596 – 1500	B	32
XIIIa	1-Phenoxy-2,4,6-triphenylbenzene	$C_{30}H_{22}O$	148	–	–	1600 – 1580	D	66
XIIIb	1-Phenoxy-2,4-diphenyl-4-(*p*-methoxyphenyl)benzene	$C_{31}H_{24}O_2$	111	–	–	1593 – 1560	D	53
XIIIc	1-Phenoxy-2,4-diphenyl-4-(*m*-methoxyphenyl)benzene	$C_{31}H_{24}O_2$	116	–	–	1607 – 1597	D	51

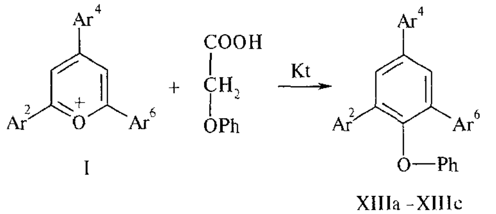


Ar = C_6H_6, α = naphthyl, *p*-nitrophenyl, *p*-methoxyphenyl.

To continue our investigation of the reactivity of pyrylium salts and to search for new methods of synthesis of various functional benzene derivatives, it was of interest to study the interaction of trisubstituted pyrylium salts with weak CH-acids such as phenoxyacetic acid. If the conversion mechanism described above is possible in this system, the final reaction products must contain various nonsymmetric diphenyl esters – substances that are very difficult to obtain by different methods.

Preliminarily we have studied the condensation of 2,4,6-triphenylpyrylium perchlorate with phenoxyacetic anhydride at 160°C in the presence of sodium phenoxyacetate. As a result, we obtained 1-phenoxy-2,4,6-triphenylbenzene (XIIIa). However, since the synthesis of phenoxyacetic anhydride presents certain difficulties, we decided to simplify the method of diphenyl ester synthesis by reacting pyrylium salts directly with phenoxyacetic acid in acetic anhydride medium (method D). The activity of phenoxyacetic acids has proved to be higher as compared to the activity of acetic anhydride, and the main reaction products were diphenyl esters (XIIIa – XIIIc). Moreover, the yield of ester XIIIa was the same as in the case of phenoxyacetic anhydride, which is indicative of a rapid acid ↔ anhydride exchange in the prekinetic reaction stage.

The formation of esters XIII is illustrated by the scheme



Kt = $PhOCH_2COONa$.

We have used the above relationships in the development of new preparative methods for the synthesis of polyaryl-substituted benzenes [9].

EXPERIMENTAL PART

The IR spectra of the synthesized compounds were measured on a Specord IR-71 spectrophotometer (Germany) using samples prepared as nujol mulls. The ^1H NMR spectra were recorded on a Tesla BS-587A 80-MHz spectrometer using deuterated chloroform as the solvent and HMDS as the internal standard.

The course of reactions was monitored by TLS in a thin layer of Al_2O_3 eluted in a chloroform – benzene system with various ratios of the components.

The data of elemental analyses agreed with empirical formulas. The yields and some physicochemical characteristics of the synthesized compounds are listed in Table 1.

Synthesis of compounds Va – Vf and Xa – Xc (method A). Reactions of pyrylium salts with aliphatic acid anhydrides are conducted according to the general procedure.

A mixture of an acid anhydride (0.02 – 0.015 mole) and a sodium salt of the corresponding acid (0.001 mole) is heated to boiling. To this mixture is added in one portion 0.001 mole of pyrylium perchlorate (I) and the mixture is boiled for 30 min and cooled. The product is extracted with 10 – 15 ml of diethyl ether. Finally, ether is evaporated and the residue is washed with 2 ml ethanol to obtain substituted benzenes Va – Vf.

The ethanol mother liquor is treated with water to precipitate benzophenones IX. Compounds IX are passed through a column filled with Al_2O_3 (eluent, benzene) to obtain phenols Xa – Xc.

Synthesis of compounds Va and Xa (method B). A flask is charged with 2 ml (0.02 mole) of acetic anhydride, 0.4 g (0.001 mole) of 2,4,6-triphenylpyrylium perchlorate, and 0.2 ml (0.001 mole) of tributylamine and the mixture is allowed to stand at room temperature until complete dissolution of the deposit (about 1 month). The products are extracted from the reaction mixture with 10 – 15 ml of diethyl ether. The ether extract is separated, ether is evaporated, and the residue is treated with 2 – 3 ml of ethanol. Filtration of the mixture yields 0.06 g (20%) of 1,3,5-triphenylbenzene (Va). The ethanol mother liquor is treated with water to precipitate 1-acetoxy-2-benzoyl-3,5-diphenylbenzene (IXa); yield, 40%; m.p., 59°C. Compound IXa is deacylated by passing through a column filled with Al_2O_3 to obtain 2-benzoyl-3,5-diphenylphenol (Xa); m.p., 106°C.

Synthesis of compounds XIa – XId and XIIa – XIIb (method C). Reactions of pyrylium salts with phenylacetic acids are conducted according to the general procedure.

A mixture of a substituted phenylacetic acid (1 mmole) and acetic anhydride (20 mmole) is heated to boiling. To this mixture is added 1 mmole of triethylamine and the mixture is heated to boiling again. Then 1 mmole of pyrylium perchlorate is added in one portion and the mixture is boiled for 30 min and cooled. The precipitated crystals of compound XI are separated by filtration. The filtrate is treated with water to precipitate compounds XII.

Synthesis of compounds XIIIa – XIIIc (method D). A mixture of acetic anhydride (20 mmole) and phenoxyacetic acid sodium salt (1 mmole) is heated to boiling. To this mixture is added 1 mmole of phenoxyacetic acid and the mixture is heated to boiling again. Then 1 mmole of pyrylium perchlorate is added in one portion and the mixture is boiled for 30 min, cooled, and extracted with 10 – 15 ml of diethyl ether. The ether layer is separated and the solvent is evaporated. The residue is washed with 2 ml of ethanol to obtain phenoxy-substituted benzenes XIIa – XIIc (see Table 1).

REFERENCES

1. G. N. Dorofeenko, E. I. Sadekova, and E. V. Kuznetsova, *Preparative Chemistry of Pyrylium Salts* [in Russian], Izdat. Rostov. Univ., Rostov (1972).
2. J. Balaban, G. Fischer, An. Dinculescu, et al., *Pyrylium Salts, Syntheses, Reactions and Physical Properties*, Acad. Press, New York, London (1982).
3. A. K. Sheinkman, *Khim. Geterotsikl. Soedin.*, No. 1, 3 – 18 (1974).
4. V. F. Lipnitskii and O. P. Shvaika, *Khim. Geterotsikl. Soedin.*, No. 12, 1685 – 1689 (1988).
5. T. Zimmerman and G. W. Fischer, *A Method for the Synthesis of Thiobenzophenones*, DDR Patent no. 259 398 (1988).
6. T. Zimmerman and G. W. Fischer, *Arylbenzene und Thiobenzophenone aus 2,4,6-Triarylthiopyrylium Salzen und Essigsaureanhydrid*, Hauptjahrestad (1988), pp. 16 – 18.
7. T. Zimmerman and G. W. Fischer, *Arylbenzene aus 2,4,6-Triarylpyrylium Salzen und Carbonsaureanhydraiden*, Chemiedozententag, Leipzyg (1988), pp. 23 – 25.
8. T. Zimmerman and G. W. Fischer, *J. Prakt. Chem.*, No. 2, 292 – 305 (1989).
9. A. I. Pyshchev, É. T. Oganesyan, L. I. Butenko, et al., USSR Inventor's Certificate no. 1 553 528; *Byull. Izobret.*, No. 12 (1990).
10. D. Johnson, *Organic Reactions* [Russian translation], Inostr. Literatura, Moscow (1948).
11. C. Buehler and D. Pearson, *Survey of Organic Synthesis*, Wiley, New York (1970).