## PHOSPHORUS OXYCHLORIDE IN ORGANIC SYNTHESIS. PART 2.<sup>1</sup> SYNTHESIS OF CINNAMIC ACID ARYLAMIDES

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Translated from Khimiko-Farmatsevticheskii Zhurnal, Vol. 35, No. 2, pp. 37 – 38, February, 2001.

Original article submitted April 3, 2000.

The study of new pathways in the synthesis of cinnamic acid derivatives is of interest from the standpoint of the targeted search for new biologically active compounds. Previously [1], we reported on the use of phosphorus oxychloride in the synthesis of cinnamic acids substituted at the aromatic fragment. Below we describe a simple method for the synthesis of cinnamic acid arylamides possessing pronounced antioxidant, antihypoxant, bile-expelling, and fungicidal properties [2-5].

Traditional pathways for the synthesis of acid arylamides (including those of cinnamic acid) represent multistage processes. Typically, the following principal stages are involved [6, 7]: (i) synthesis of cinnamic acid; (ii) obtaining halogen-containing acid anhydride; (iii) condensation of the halogen-containing anhydride with amines. In the case of cinnamic acid arylamides, all these process stages are rather laborious, while usually providing a low yield of the target products.

Kira and Gadalla [8] described the reaction of condensation of DMF with dimethylacetamide in the presence of POCl<sub>3</sub>, which leads to the formation of the corresponding  $\beta$ -dimethylacrylamides. However, acetanilides were never used in these transformations because it was believed that stabilization of a carbocation (I) formed under the action of POCl<sub>3</sub> would proceed with the formation of an imido ester (II) as a result of proton detachment from the amide group. It was therefore implied that deprotonation of the methyl group with the formation of enamine (III) is unlikely.



<sup>&</sup>lt;sup>1</sup> For part 1, see [1].

However, we suggested that enamines (III) would nevertheless appear to interact as nucleophiles with carbocation (IV) formed from the aromatic aldehyde under the action of  $POCl_3$  [1], which would eventually lead to cinnamic acid acetanilides:

$$Ar - CH \cdot Cl - H_2C - C - O - POCl_2$$
  

$$O - POCl_2 + H_2C - C - O - POCl_2$$
  

$$IV = HN - Ar$$
  

$$IV = HII$$
  

$$Ar - CH = CH - C = O + O(POCl_2)_2 + HCl$$
  

$$NHAr$$
  

$$V - XVI$$

Indeed, heating a mixture of equimolar amounts of an aromatic aldehyde and acetanilide in an excess of  $POCl_3$  for 60-90 min led to a high yield of the corresponding cinnamamides. Table 1 presents comparative data on the yields of the target compounds synthesized by the proposed method (B) and by the known pathways (A). For method B, the yield is calculated for acetanilide and for method A, for

**TABLE 1.** Yields of Cinnamic Acid Arylamides (V – XVI)

Compound	nl	$\mathbf{p}^2$	D <sup>3</sup>	Yield, %		
	К	ĸ	K	Method A	Method B	
V	Н	Н	Н	63.2	71.0	
VI	Н	Н	$OC(O)C_2H_5$	63.7	79.0	
VII	OCH <sub>3</sub>	Н	Н	63.2	70.0	
VIII	OCH <sub>3</sub>	Н	$OC(O)CH_3$	63.5	75.2	
IX	$\mathrm{OCH}_3$	Н	$OC(O)C_2H_5$	63.6	75.0	
Х	OCH <sub>3</sub>	OCH <sub>3</sub>	$OC(O)CH_3$	55.5	76.4	
XI	OCH <sub>3</sub>	OCH <sub>3</sub>	Н	55.4	71.0	
XII	OCH <sub>3</sub>	OCH <sub>3</sub>	$OC(O)C_2H_5$	55.4	76.0	
XIII	Br	Н	Н	55.6	79.0	
XIV	Br	Н	$OC(O)C_2H_5$	55.6	73.0	
XV	$NO_2$	Н	Н	62.4	81.0	
XVI	$NO_2$	Н	$OC(O)C_2H_5$	63.5	83.0	

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Compound		Empirical formula	Spectral characteristics					
	M.p., °C		UV: $\lambda_{max}$ , nm —	IR: $v_{max}$ , cm <sup>-1</sup>				
				C=O	C=C	N–H	E-HC=CH	
V	149 - 150	C <sub>15</sub> H <sub>13</sub> NO	296, 222	1680	1630	1525, 1260	975	
VI	172 - 174	C <sub>18</sub> H <sub>17</sub> NO <sub>3</sub>	330, 220	1680	1634	1530, 1260	975	
VII	127 - 128	C <sub>16</sub> H <sub>15</sub> NO <sub>2</sub>	276	1680	1630	1530, 1270	970	
VIII	184 - 185	C <sub>18</sub> H <sub>17</sub> NO <sub>4</sub>	325, 230	1680	1630	1530, 1265	970	
IX	156 - 157	C19H19NO4	328, 230	1680	1640	1520, 1260	970	
Х	163 - 165	C19H19NO5	330, 213	1680	1630	1525, 1265	975	
XI	96 - 98	C <sub>17</sub> H <sub>17</sub> NO <sub>3</sub>	327, 234	1680	1635	1520, 1260	970	
XII	187 - 188	$C_{20}H_{21}NO_5$	336, 230	1680	1630	1525, 1265	975	
XIII	187 - 188	C15H12BrNO	310, 220	1685	1630	1530, 1270	970	
XIV	115 - 116	C <sub>18</sub> H <sub>16</sub> BrNO <sub>3</sub>	300, 222	1685	1625	1525, 1260	970	
XV	228 - 229	$C_{15}H_{12}N_2O_3$	329, 259	1690	1625	1530, 1265	975	
XVI	224 - 225	$C_{18}H_{16}N_{2}O_{5} \\$	327, 270	1690	1625	1530, 1270	970	

TABLE 2. Physicochemical Characteristics of Cinnamic Acid Arylamides (V - XVI)

the initial aromatic aldehyde. Some physicochemical characteristics of the synthesized compounds are summarized in Table 2.

Thus, the new method proposed for the synthesis of cinnamic acid arylamides offers a number of significant advantages over the traditional pathways: the target products are obtained in a single-stage process, the time of synthesis is markedly shorter, while the product yields increase from 55 - 63% to 70 - 80%.

## **EXPERIMENTAL PART**

**Method A.** Cinnamic acid arylamides are obtained by a patented method as described in [6]. A mixture of 3 ml of freshly distilled acetic acid, 0.01 mole of the corresponding aromatic aldehyde, and 1.5 g of anhydrous sodium acetate was boiled for 8 - 16 h. Upon cooling, the reaction mixture was poured into 50 - 100 ml of an ice – water mixture acidified with hydrochloric acid. The precipitate was separated by filtration, washed with water until neutral reaction, and dried. Finally, the product was recrystallized from water, aqueous ethanol, or anhydrous ethanol.

To a toluene solution of the obtained acid was added an excess amount of thionyl chloride and the mixture was heated on a water bath for 30-60 min. To the resulting solution of cinnamic acid chloroanhydride was added a solution

of the corresponding amine in the same solvent. The precipitating cinnamamides were separated by filtration, washed with a small amount of ethanol and then with water, dried, and recrystallized from ethanol or 2-propanol.

**Method B.** To a solution of acetanilide (0.01 mole) in 6-10 ml of POCl<sub>3</sub> was added aromatic aldehyde (0.01 mole) and the mixture was heated for 60-90 min at  $80-90^{\circ}\text{C}$ . Upon cooling, the reaction mixture was poured into 50-100 ml of an ice – water mixture. The precipitate was separated by filtration, washed with water until neutral reaction, dried, and recrystallized as above.

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