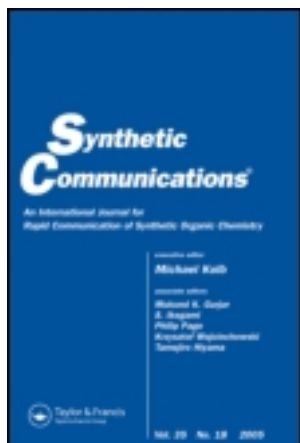


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## USE OF POLYPHOSPHORIC ACID IN THE HYDROLYSIS OF CHROMONE ESTERS

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### ABSTRACT

Hydrolysis of esters was achieved in fairly high yield (59–98%) using polyphosphoric acid (PPA). The reagent was particularly useful for the hydrolysis of chromone side chain esters without ring opening.

7-Methoxy-4-oxo-4H,1-benzopyran-2-carboxylic acid (**1b**) possesses many important biological properties, including antimicrobial,<sup>1</sup> antiviral,<sup>2,3</sup> and aldose reductase inhibiting activities.<sup>4</sup> Its salt was also formulated into a transdermal preparation for melanin.<sup>5</sup> Some of its salts with organic bases have vitamin P activity and have been used in the treatment of circulatory disorders.<sup>6</sup>

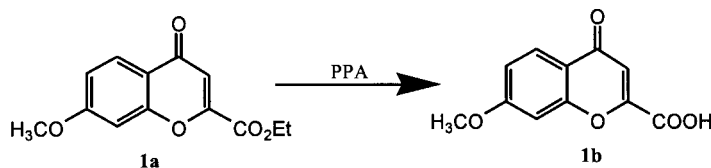
Derivatives of chromone-2-carboxylic acids are mostly obtained through hydrolysis of the corresponding methyl or ethyl esters under either acidic or basic condition with the chromone ring intact. Acids used include concentrated hydrochloric acid in acetic acid<sup>7</sup> or 48% hydrobromic acid in acetic acid,<sup>8</sup> or a mixture of aqueous dioxan and hydrochloric acid.<sup>9</sup> Bases used include sodium hydroxide,<sup>10–12</sup> sodium carbonate<sup>13</sup> or

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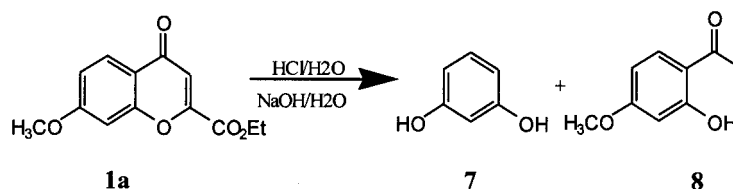
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sodium bicarbonate,<sup>14</sup> even aqueous triethylamine<sup>15</sup> in a solvent which is inert to the reaction condition, for example, methanol,<sup>13,15</sup> ethanol<sup>10,12,14</sup> and acetone.<sup>11</sup>

During our research, we intended to introduce a benzimidazole group to the 6-position of chromone using 2-ethoxycarbonyl-4-oxo-4H, 1-benzopyran-6-carboxylic acid as the starting material in PPA. We only got a product with a free acid group attached to the 2-position of chromone instead of the desired ethyl ester group on the position. The fact was that the ethyl chromone-2-carboxylate was hydrolyzed by PPA leaving the labile chromone ring intact. Then we successfully applied this procedure to the hydrolysis of (**1a**) to (**1b**) (Scheme 1). Compared with this new procedures, the authors treated (**1a**) with aqueous hydrochloric acid, sodium hydroxide, or sodium carbonate, only ring-opening products (**7**) and (**8**) (Scheme 2) were recovered.



*Scheme 1.* Hydrolysis of chromone ester (**1a**) with PPA.



*Scheme 2.* Hydrolysis of **1a** with aqueous strong acid or base.

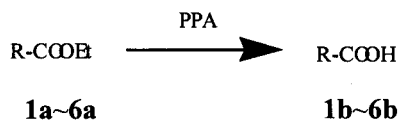
PPA is a reagent with a tendency to combine with water. In organic synthesis, PPA has been used in dehydration and cyclization of aryl or arylalkyl acid. Scholl and Meyer<sup>16</sup> first effected ring closures with it and soon after Koebner and Robinson<sup>17</sup> realize its usefulness in cyclodehydration. In some reaction, PPA was more effective than concentrated sulfuric acid, hydrochloric acid and even liquid hydrogen fluoride. Since PPA is a medium-strong acid without oxidizing properties, fission,<sup>18</sup> rearrangement,<sup>19</sup> isomerization,<sup>20,21</sup> ether cleavage<sup>22</sup> and transformation of nitriles

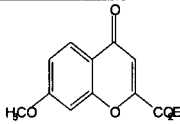
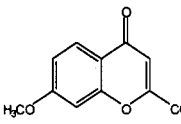
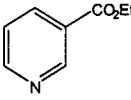
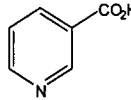
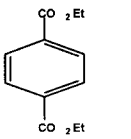
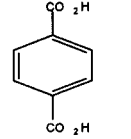
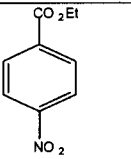
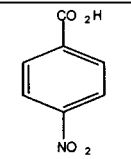
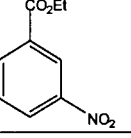
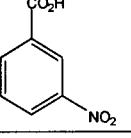
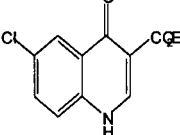
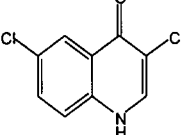


HYDROLYSIS OF CHROMONE ESTERS

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Table 1. Hydrolysis of Esters in PPA



	Esters (a)	Acids (b)	T(°C) & t(h)	yield	m.p.	
					found .....	lit.& ref.
1			150 3.5	86	274- 276	270 <sup>24</sup>
2			155 4.5	98	232- 233	236.6 <sup>25</sup>
3			154 4.2	96	398- 401	402 <sup>26</sup>
4			154 4.5	72	239- 241	241.5 <sup>27</sup>
5			152 4	87	140- 142	139~ 142 <sup>28</sup>
6			148 5	* 59.4	231- 234	236 <sup>29</sup>

\* 29.8% Decarboxylated product was obtained.

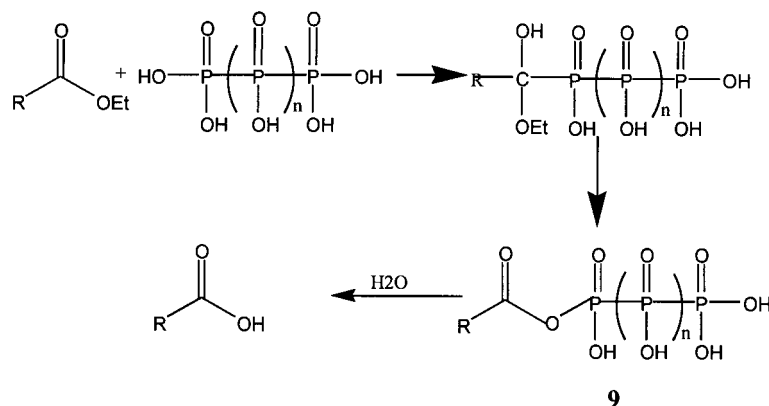


to amides. However, to date, its use in the hydrolysis of esters to the corresponding acids has not been evaluated.

In our research, we found that some esters also gave the corresponding acids in good yield (59–98%) when heated in PPA for several hours (Table 1). All products were verified by IR, <sup>1</sup>H-NMR. This reaction system was particularly useful for chromone ester hydrolysis where the starting material is very sensitive to strong acids and bases and oxidizing agents.

In our studies, we found that ethyl 2-furancarboxylate in PPA become dark above 80°C and L-phenylalanine methyl ester underwent polymerization. Some compounds with hydroxyl or/and mercapto group formed phosphoric esters.<sup>23</sup>

The mechanism of hydrolysis of esters by PPA may involve nucleophilic attack of the hydroxyl group of PPA on the carbonyl group of esters produces carbonyl polyphosphates (9) which release carboxylic acids when mixed with water (Scheme 3).



**Scheme 3.** The postulated mechanism of hydrolysis of esters by PPA.

### GENERAL PROCEDURES

Esters (1 part) were mixed with a sufficient quantity of PPA (10–20 parts) to give a paste. The mixture was heated to about 145–160°C for 3.5–5 h, permitted to cool to about 100°C, and poured into a large volume of rapidly stirred cold water in a thin stream and neutralized with sodium hydroxide or sodium carbonate at low temperature. The precipitate was collected by filtration and washed with water for several times.



The filtrate was extracted with ethyl acetate. The products were recrystallized from alcohol or chloroform.

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