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The Synthesis of a Series of Phosphoryl Coumarins

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Abstract: Different hydroxy substituted coumarins were successfully phosphorylated with diisopropylphophite (DIPPH) by the Atherton-Todd reaction in 76-89% yields. Moreover, the reaction activities of different hydroxys of the coumarins in the Atherton-Todd reaction were studied.

Keywords: Phosphorylation, Atherton-Todd reaction, coumarin, phosphoryl coumarins.

It is well known that the phosphorylation and dephosphorylation of proteins play an important role in regulating complicated biochemical processes[1]. Moreover, phosphorylated biomolecules and medical molecules have many unique activities and characteristics[2]. Our group did a lot of work in the phosphorylation of amino acid and phenolic hydroxyl group by the Atherton-Todd reaction and found that it was an effective method to synthesis the phosphoric esters[3].

Coumarin derivatives possess a wide range of various biological and pharmaceutical activities[4,5], and some of them are also used as a fluorescence probe[6]. In addition, the phosphocoumarin derivatives have been used as agricultural insecticides[7-9] and phosphatase substrates[10,11]. In order to investigate the influences of the phosphoryl on the biological activities of coumarins, we synthesized a series of phosphoryl coumarins derivatives by the Atherton-Todd reaction in 76-89% yields (**Scheme 1** and **Table 1)**.

In the reaction, the diisopropylphophite (DIPPH) was used as phosphorylating agent, carbon tetrachloride as the chlorinating agent in basic organic media. When coumarin derivatives contained only one hydroxyl group, such as 7-hydroxycoumarin derivatives **1a-c**, 7-phosphoryl products **2a-c** would be obtained. For 5,7-dihydroxyl coumarined **1d** and 6,7-dihydroxyl coumarin **1e**, diphosphoryl products **2d** or **2f** would be obtained if the mole ratio of **1d** (or **1e**) with diisopropylphophite was 1:2. However, if the mole ratio of **1d** or **1e** with diisopropylphophite was equivalent, the result was different. The product **2e** was obtained from **1d**, and **2g** from **1e**. **2g** was cultivated into crystal and

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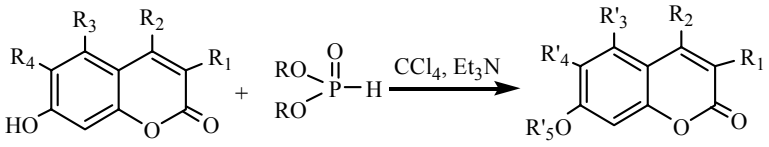
Scheme 1



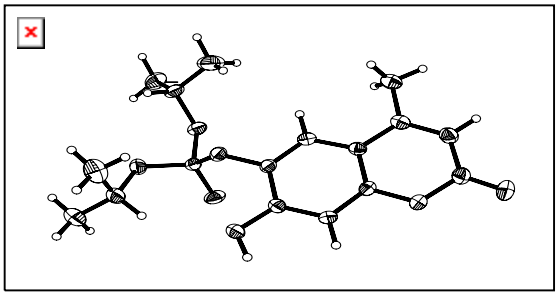
1a-e **2a-f**

Table 1 Dialkyloxyphosphoryl coumarin derivatives

Entry	R_1	R_2	R_3	R_4	R'_3	R'_4	R'_5	Yield (%)[a]
1a	H	H	H	H				
1b	H	CH_3	H	H				
1c	C_2H_5	CH_3	H	H				
1d	H	CH_3	OH	H				
1e	H	CH_3	H	OH				
2a	H	H			H	H	$P(O)(OPr^i)_2$	89
2b	H	CH_3			H	H	$P(O)(OPr^i)_2$	87
2c	C_2H_5	CH_3			H	H	$P(O)(OPr^i)_2$	85
2d	H	CH_3			$OP(O)(OPr^i)_2$	H	$P(O)(OPr^i)_2$	80
2e	H	CH_3			H	H	$P(O)(OPr^i)_2$	82
2f	H	CH_3			H	$OP(O)(OPr^i)_2$	$P(O)(OPr^i)_2$	76
2g	H	CH_3			H	$OP(O)(OPr^i)_2$	H	83

[a] All yields are isolated yields.

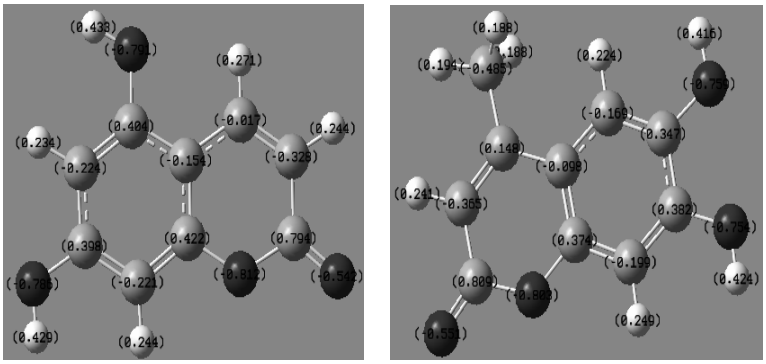
Figure 1 The crystal structure of **2g**



confirmed by X-ray crystal analysis (**Figure 1**).

After completing calculations using quantum chemistry, we find that the negative charge of the 5-hydroxy and 6-hydroxy group is greater than that of 7-hydroxy group for compound **1d** and **1e**(**Figure 2**). So the nucleophilic reactivity of 5-hydroxy and 6-hydroxy group is stronger than that of 7-hydroxy group. Therefore, if 7-hydroxy coumarin derivative contains *meta-situ* or *ortho-situ* hydroxyl group, it was impossible to obtain a single 7-phosphorylated coumarin product. However, for the *meta-situ* or *ortho-situ* hydroxyl group, only 5-phosphorylated or 6-phosphorylated coumarin product could be obtained by controlling the molar ratio.

Figure 2 The electron population of compounds **1d**, **1e** in their stable conformations (the net charges of atomsare in parenthesis)



1d **1e**

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12. General procedure for the preparation of **2a-g** To a solution of **1a-e** (1.0 mmol) in acetone (20 mL) and triethylamine (2 mL) was slowly added a solution of diisopropylphophite (1.0 or 2.0 mmol) in carbon tetrachloride (5 mL) at 0 ^{o}C. The mixture was warmed to room temperature, and stirred at rt for 12-14 hr. The solid triethylamine hydrochloride was removed by filtration, and the filtrate was evaporated. The crude product was extracted with ethyl acetate, washed with water (15 mL× 4) and dried over anhydrous magnesium sulfate. After evaporation of the ethyl acetate, the crude product was purified *via* column chromatography with hexane: ethyl acetate (3:7) to afford **2a-g**. All the analytical data (IR, NMR, and MS *etc*.) of the compounds were consistent with their structures. The spectra data of compound **2g**: White solid. mp: 166-167℃; IR (KBr): ν=1292 cm^{-1} (P=O); ^{1}H NMR (400 MHz, $CDCl_3$, δ_{ppm}): 1.37(m, 12H, CH_3), 2.36 (s, 3H, CH_3), 4.83 (m, 2H, CH), 7.27, 7.08 (s, 2H, Ar-H), 6.09 (s, 1H, C=CH); ^{31}P NMR (400MHz, $CDCl_3$, δ_{ppm}): -4.86; ES-MS (*m/z*): 356; Anal. Calcd. for $C_{16}H_{21}O_7P$: C 53.93, H 5.94, P 8.69. Found: C 54.06, H 5.92, P 8.66. Data of **2a -2f** were deposited in editorial office of CCL.

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