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A facile and efficient synthesis of substituted 2-oxo-2H-chromen-7-yl phenylcarbamates from differently substituted 7-hydroxycoumarin

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ABSTRACT

The study was aimed to synthesize substituted 2-oxo-2H-chromen-7-yl phenylcarbamates from differently substituted 7-hydroxycoumarin by three different methods. In Ist method, substituted 2-oxo-2H-chromen-7-ylphenylcarbamate derivatives were synthesised in two steps by reacting benzoyl chloride with differently substituted 7-hydroxycoumarin in the presence of NaOH followed by reaction of an intermediate with sodium azide. In 2nd and 3rd methods, substituted 2-oxo-2H-chromen-7-ylphenylcarbamates were synthesized in a single step by reacting differently substituted 7-hydroxycoumarin with phenyl isocyanate or phenylcarbamic chloride, respectively. Due to lower yields (30-40% for Ist and 50-60% for 3rd method), longer reaction time (8-10 hours for Ist and 1 hour for 3rd method), hygroscopic and lacrimating reagents (benzoyl chloride and phenyl carbamic chloride), the Ist and 3rd methods were inconvenient as compared to 2nd method with higher yield (85-95%) and shorter reaction duration (15 min). Therefore, one pot synthesis of substituted 2-oxo-2H-chromen-7-ylphenylcarbamates may be conveniently achieved by reacting phenylisocyanate with differently substituted 7-hydroxycoumarin in the presence of triethylamine and petroleum ether.

KEYWORDS

Phenylcarbamate;
7-hydroxycoumarin;
Phenyisocyanate;
Phenylcarbamic chloride;
Benzoyl chloride.

INTRODUCTION

Carbamate is an important moiety which has been conventionally used as a insecticide to control insect pests throughout the world such as metolcarb, methomyl, thiodicarb, carbofuran, carbosulfhan and aldicarb[1,2]. The carbamate insecticides inhibit acetylcholinesterase (AChE), a key enzyme in the nervous system, by covalently carbamylating the serine residue within active site gorge. In addition carbamate is also an integral part of clinically employed AChE inhibitor i.e., rivastigmine for the management of Alzheimer's disease[3]. Various research groups have synthesised carbamate derivatives by incorporating different chemical moieties to produce potent AChE inhibitors including phenyl ring[4], benzopyrano[4,3-b] pyrroles[5], 1,2-phenylalkyl-substituted piperidines[6], phthalimide alkyloxyphenyl[7], N-propargylaminoindan and N-propargylphenethylamine[8]. A number of studies have demonstrated that natural as well as chemically synthesized carbamate analogues exhibited wide range of pharmacological properties such as anti- bacterial[8,9], anti-malarial[10], anticonvulsant[11] and antifungal[12].

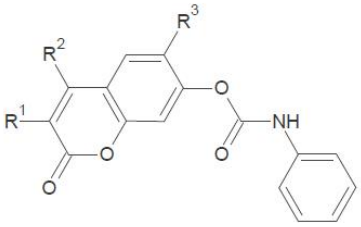
Coumarins are naturally occurring phytochemicals

in many plants species with a wide range of biologically activities such as anti-inflammatory, anti-tumour, hepatoprotective, antiviral, antifungal, antimicrobial, anti-oxidant, anti-diabetic and anti-amnestic[13-19]. Based on these, it is proposed that addition of carbamate moiety to coumarin nucleus may produce carbamate derivatives with significant pharmacological activities. Although many different carbamate derivatives have been synthesized during the last decade, very little attention has been paid for the synthesis of carbamate derivative of different substituted 7-hydroxycoumarin. In this article, we describe three methods for the synthesis of substituted 2-oxo-2H-chromen-7-yl phenylcarbamate from different substituted 7-hydroxycoumarin using benzoyl chloride and sodium azide; phenyl isocyanate and phenylcarbamic chloride and compare the best method with respect to yield, reaction time and suitability of reagents.

RESULTS AND DISCUSSION

In the present study, the differently substituted 2-oxo-2H-chromen-7-yl phenylcarbamates were synthesized by using three different methods. In the first method, benzoylation of different substituted 7-hydroxy coumarin (1a-1e) with benzoyl chloride (2) in the presence of cold 5% NaOH solution provided substituted 2-oxo-2H-chromen-7-ylbenzoate[20] (3a-3e) that in turn was treated with H_2SO_4 and NaN_3 to afford substituted-2-oxo-2H-chromen-7-ylphenylcarbamate[21] (4a-4e), respectively (Figures 1 and 2). The yield of the target compound was 30-40% (TABLE 1) in the two step reaction of first method with the total reaction time of around 10 hours. In addition, benzoyl chloride used in this method is hygroscopic, highly lacrimating agent and is inconvenient to handle in laboratory. In the second method, the refluxing of differently substituted 7-hydroxycoumarin (1a-1e) with phenyl isocyanide (2') in the presence of petroleum-ether and triethylamine (2 or 3 drops) provided substituted 2-oxo-2H-chromen-7-ylphenylcarbamates[22] (4a-4e) (Figures 3 and 4). The yield of the target compound was 85-95 % in the single step reaction in second method with the total reaction time of around 15 minutes. In the third method, the condensation of differently substituted 7-hydroxycoumarin (1a-1e) with phenyl carbamic chloride (3') in the presence of dichloromethane and NaOH yielded substituted-2-oxo-2H-chromen-7-ylphenylcarbamate[23] (4a-4e) (Figures 5 and 6). The yield of the target compound was 50-60 % in the single step reaction in third method with the total reaction time of around 1 hour. The phenyl carbamic chloride employed in the third method is lacrimating and hygroscopic agent.

TABLE 1 : Showing % yield of substituted 2-oxo-2H-chromen-7-ylphenylcarbamate (4a-4e) during different three methods



compound	R^1	R^2	R^3
4a	H	H	H
4b	H	H	MeO
4c	H	CH_3	H
4d	Cl	CH_3	H
4e	H	CF_3	H

Compound	% yield (I^{st} method)	% yield (2^{nd} method)	% yield (3^{rd} method)
4a	36	87	53
4b	30	85	50
4c	35	89	53
4d	37	90	57
4e	40	95	60

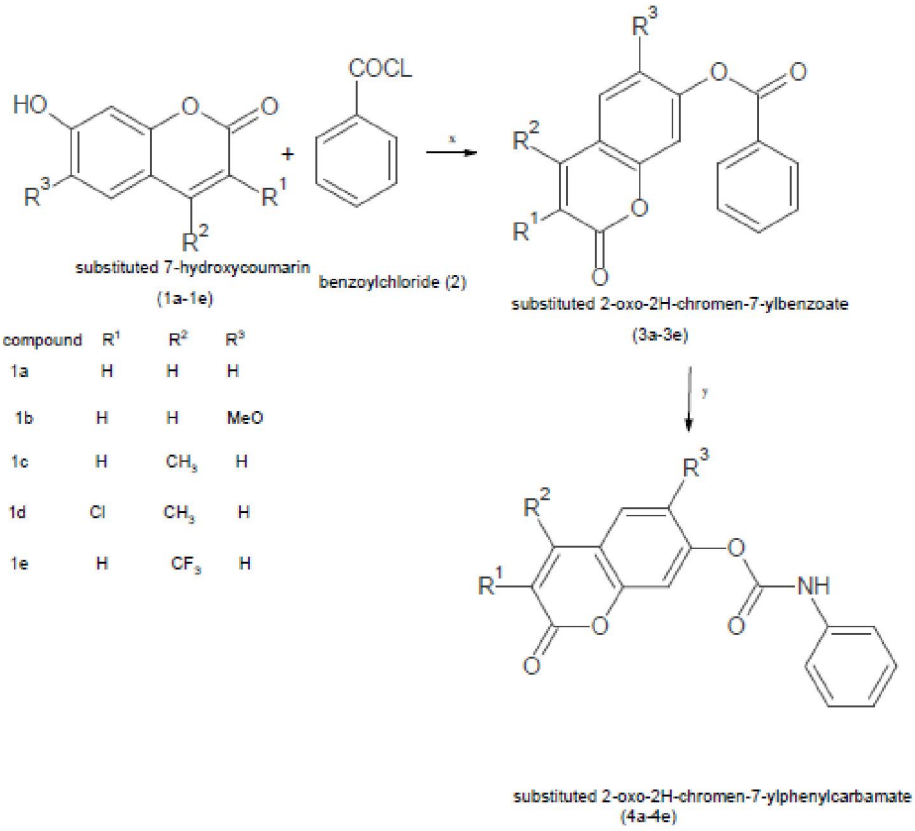
CONCLUSION

Based on the results of the study, it is concluded that substituted 2 oxo-2H-chromen-yl phenyl carbamate may be synthesized in a high yield, in a single step with shorter reaction time by reacting substituted 7-hydroxycoumarin with phenyl isocyanate in the presence of triethyl amine and petroleum ether.

EXPERIMENTAL

All the reagents and the solvents used were of analytical grade. Melting points were recorded on Gallen–Kamp apparatus and were uncorrected. IR spectra were recorded on a Perkin Elmer spectrum RX IFT-IR system. H^1 NMR spectra were recorded on Bruker Advance II 400 MHz spectrometer in DMSO with TMS as an internal standard. The chemical shifts were recorded in parts per million (ppm), coupling constants (J values) in Hertz, multiplicities as singlet (s), doublet (d), triplet (t), quadruplet (q) and multiplet (m). Mass spectra (MS) signals were given in m/z. Elemental analy-

sis (EA) was measured on an Elementar Analysensysteme GmbH. All the reactions were monitored using TLC. The carbamate derivatives of substituted 7-hydroxycoumarin *i.e*, substituted 2-oxo-2H-chromen-7-ylphenylcarbamate were synthesised by three methods.



compound	R^1	R^2	R^3
1a	H	H	H
1b	H	H	MeO
1c	H	CH_3	H
1d	Cl	CH_3	H
1e	H	CF_3	H

Reagents and conditions : (x) 40 ml cold 5% NaOH solution with stirring at room temperature for 8 hours; (y) NaN_3 and H_2SO_4 with stirring at room temperature for 6 hours

Figure 1 : Schematic diagram describing the steps for the synthesis of substituted 2-oxo-2H-chromen-7-ylphenylcarbamate by 1st method

General procedure of I[st] method

(a) Step 1

Substituted 7-hydroxycoumarin (1a-1e) (0.05 mol) and benzoyl chloride (2) (0.05 mol) were added in 40 ml of 5% cold NaOH solution. The mixture was stirred at room temperature for 8 hours until the odour of benzoyl chloride was disappeared (TLC monitoring, EtOAc/toluene 70:30). The solid product was filtered and washed with cold water to obtain white solid that in turn was recrystallized from 50% aqueous ethanol solution to get substituted 2-oxo-2H-chromen-7-yl benzoate (3a-3e) respectively.

(b) Step 2

1 mmol solution of substituted 2-oxo-2H-chromen-7-yl benzoate (3a-3e) in H_2SO_4 (3 ml) was stirred at room temperature for 10 minutes followed by addition of sodium azide (0.13g, 2 mmol). The mixture was stirred at room temperature for 2 hours (TLC monitoring, EtOAc/toluene 60:40) and then, poured into ice water (100 ml). The white solid was collected and recrystallized from 10% aqueous ethanolic solution to afford substituted 2-oxo-2H-chromen-7-ylphenylcarbamate (4a-4e) respectively.

General procedure of 2[nd] method

The dissolved mixture of 0.01 mole of different substituted 7-hydroxycoumarin (1a-1e) and 0.01 mole of phenyl isocyanate (2') in 20 ml of petroleum ether with 2-3 drops of triethylamine was refluxed for 15-20 minutes. Thereafter, the reaction mixture was allowed to stand for crystallisation followed by filtration and recrystallisation to get the target compound (4a-4e) *i.e.*, substituted 2-oxo-2H-chromen-7-ylphenylcarbamate.

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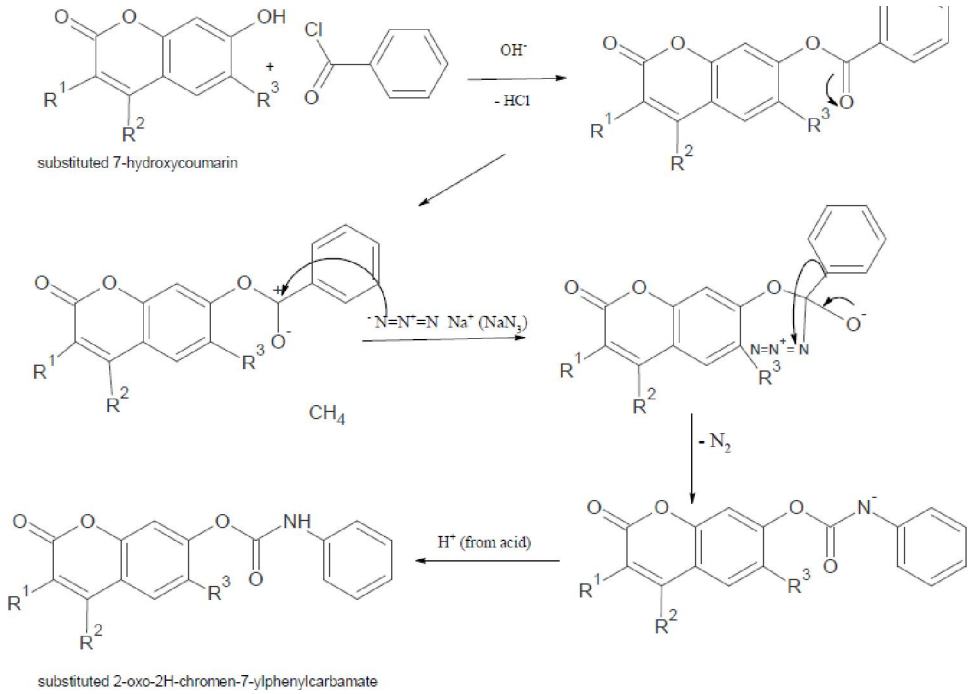
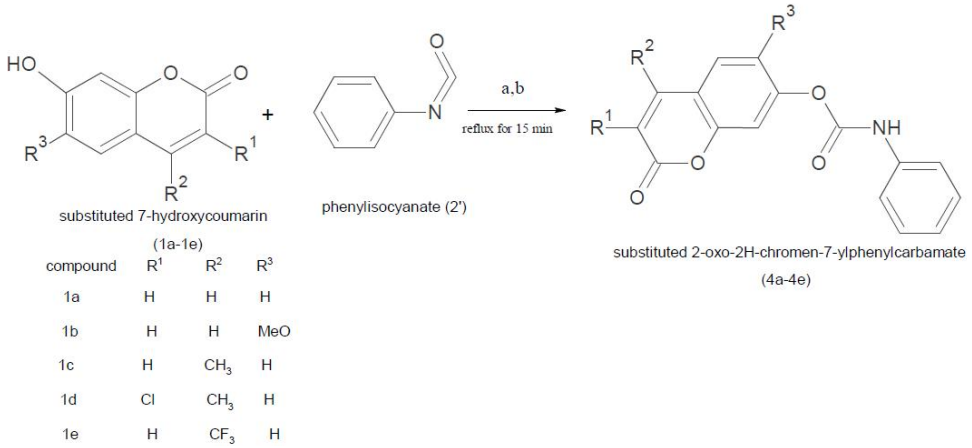


Figure 2 : Possible mechanism of reaction of synthesis of substituted 2-oxo-2H-chromen-7-ylphenylcarbamate by reaction of benzoyl chloride with substituted 7-hydroxycoumarin in step I followed by reaction of an intermediate with sodium azide in step II (I[st] method)



compound	R^1	R^2	R^3
1a	H	H	H
1b	H	H	MeO
1c	H	CH_3	H
1d	Cl	CH_3	H
1e	H	CF_3	H

Reagents: (a) petroleum ether (b) triethylamine

Figure 3 : Schematic diagram describing synthesis of substituted 2-oxo-2H-chromen-7-ylphenylcarbamate using phenylisocyanate in the presence of triethylamine and petroleum ether by 2[nd] method

General procedure of 3[rd] method

Substituted 7-hydroxycoumarin (1.05g, 3.36 mmol) (1a-1e) and phenylcarbamic chloride (0.63g, 6.72 mmol) (3') were dissolved in dichloromethane (50 ml) in an ice bath and then 20% NaOH aqueous solution (2 ml) was added to the solution for 5 min. at 0-5° C. After stirring the mixture for 20 minutes in an ice bath, 5% brine (50 ml) was added and the mixture was again stirred for 40 minutes at room temperature. The organic layer was isolated and washed with water twice and dried over anhydrous sodium sulphate. The solvent was evaporated *in vacuo* to obtain solid product substituted 2-oxo-2H-chromen-7-ylphenylcarbamate (4a-4e) respectively.

The synthesized compounds (4a-4e) were characterized by H^1-NMR, IR, and mass spectroscopy in addition to its melting point and elemental analysis as given below.

2-oxo-2H-chromen-7-ylphenylcarbamate (4a)

White solid, mp 160-162°C ; IR (Nujol) υ 3157,

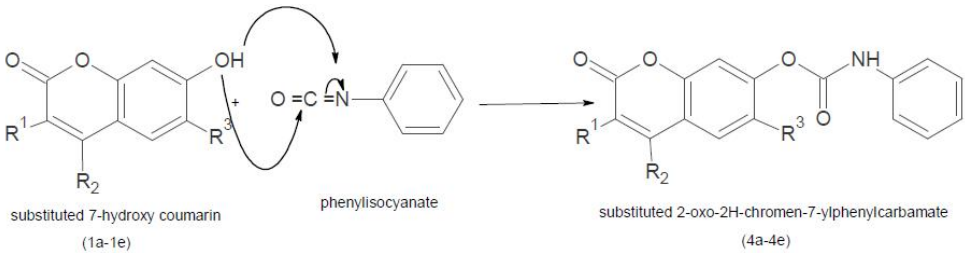
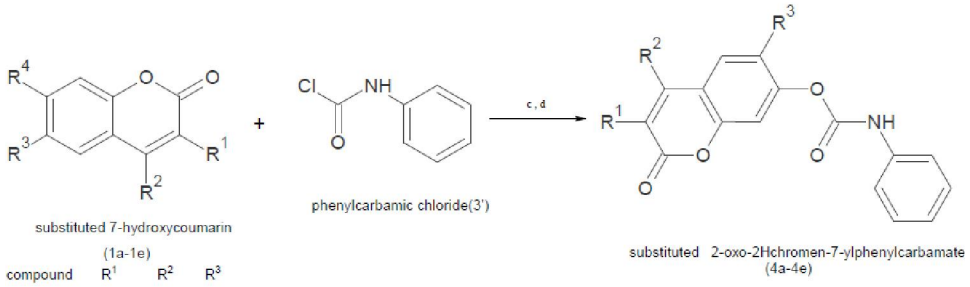


Figure 4 : Possible mechanism of reaction of synthesis of substituted 2-oxo-2H-chromen-7-ylphenylcarbamate by reaction of phenyl isocyante with substituted 7-hydroxycoumarin in single step reaction (2nd method)



compound	R^1	R^2	R^3
1a	H	H	H
1b	H	H	MeO
1c	H	CH_3	H
1d	Cl	CH_3	H
1e	H	CF_3	H

Reagents : (c) dichloromethane (d) sodium hydroxide

Figure 5 : Schematic diagram describing synthesis of substituted 2-oxo-2H-chromen-7-ylphenylcarbamate using phenylcarbamic chloride in the presence of dichloromethane and NaOH

2970, 1799, 1681, 1603, 1273, 1239,1213 cm^{-1}; H^1 NMR (DMSO, 400 MHz) δ 6.12-6.13 (d, 1H, aromatic H, J = 8.12Hz), 6.58-6.59 (d, 1H, aromatic H, J=7.94Hz), 6.75-6.76 (m, 1H aromatic H, J=8.41Hz), 7.36-7.37 (d, 1H, aromatic H, J= 2.15 Hz), 7.47-7.49 (m, 2H, aromatic H, J= 8.35Hz), 7.54-7.56 (m, 2H, aromatic H, J= 8.36Hz), 7.61-7.62 (d, 1H, aromatic H, J= 7.98 Hz), 7.92-7.93 (d, 1H,aromatic H, J= 8.10 Hz), 10.06 (s, 1H, NH); MS : m/z 282 $(M+H)^+$; Analytical calculation for $C_{16}H_{11}NO_4$: C 68.32, H 3.94, N 4.98, O 22.75.

6-methoxy- 2-oxo-2H-chromen-7-yl phenylcarbamate (4b)

White solid, mp 172-174°C; IR (Nujol) υ 3156, 2970, 1792, 1678, 1272, 1238, 1214, 1030 cm^{-1}; H^1 NMR (DMSO, 400 MHz) δ 3.83 (s, 3H, OCH3), 6.12-6.13 (d, 1H, aromatic H, J= 8.12 Hz), 6.68 (s, 1H aromatic H), 6.79-6.81 (m, 1H, aromatic H, J= 8.42 Hz), 7.33 (s, 1H, aromatic H), 7.45-7.46 (m, 2H, aromatic H, J= 8.36Hz), 7.58-7.59 (m, 2H, aromatic H, J= 8.37 Hz), 7.94-7.96 (d, 1H, aromatic H, J= 8.14 Hz), 10.12 (s, 1H, NH) ; MS : m/z 312 $(M+H)^+$; Analytical calculation for $C_{17}H_{13}NO_5$: C 65.59, H 4.21, N 4.50, O 25.70.

4-methyl- 2-oxo-2H-chromen-7-yl phenylcarbamate (4c)

White solid, mp 165-166°C; IR (Nujol) υ 3157, 2971, 1799, 1680, 1602, 1274, 1212 cm^{-1}; H^1 NMR (DMSO, 400 MHz) δ 2.39 (s, 3H, methyl H), 6.03 (s, 1H, aromatic H), 6.70-6.71 (d, 1H aromatic H, J=8.12 Hz), 6.78-6.80 (m, 1H, aromatic H, J= 8.42Hz), 7.35-7.36 (d, 1H, aromatic H, J= 2.16Hz), 7.42-7.43 (m, 2H, aromatic H, J= 8.32Hz), 7.56-7.58 (m, 2H, aromatic H, J= 8.33Hz), 7.95-7.98 (d, 1H, aromatic H, J= 8.13Hz), 10.16 (s, 1H, NH) ; MS : m/z 296 $(M+H)^+$; Analytical calculation for $C_{17}H_{13}NO_4$: C 69.15, H 4.44, N 4.74, O 21.67.

3-chloro-4-methyl- 2-oxo-2H-chromen-7-yl phenylcarbamate (4d)

White solid, mp 168-169°C; IR (Nujol) υ 3157, 2972, 1773, 1683, 1603, 1273, 1238, 1213, 847 cm^{-1}; H^1 NMR (DMSO, 400 MHz) δ 2.38 (s, 3H, methyl H), 6.65-6.66 (d, 1H aromatic H, J=8.05Hz), 6.75-

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6.78 (m, 1H aromatic H, J=8.40Hz), 7.31-7..32 (d, 1H, aromatic H, J= 2.13 Hz), 7.39-7.41 (m, 2H, aromatic H, J= 8.36Hz), 7.54-7.56 (m, 2H, aromatic H, J= 8.37Hz), 7.86-7.87 (d, 1H, aromatic H, J= 8.12Hz), 10.08 (s, 1H, NH); MS : m/z 330 $(M+H)^+$; Analytical calculation for $C_{17}H_{12}NO_4Cl$: C 61.92, H 3.67, N 4.25, O 19.41, Cl 10.75.

4-(trifluoromethyl)- 2-oxo-2H-chromen-7-yl phenylcarbamate (4e)

White solid, mp 178-180°C; IR (Nujol) υ 3157, 2970, 1775, 1681, 1605, 1272, 1237, 1213 cm^{-1}; H^1 NMR (DMSO, 400 MHz) δ 6.34 (s, 1H aromatic H), 6.78-6.80 (d, 1H, aromatic H, J= 8.03Hz), 6.84-6.85 (m, 1H, aromatic H, J= 8.48Hz), 7.32-7.33 (d, 1H, aromatic H, J= 2.28Hz), 7.44-7.45 (m, 2H, aromatic H, J= 8.40Hz), 7.59-7.60 (m, 2H, aromatic H, J= 8.41Hz), 7.96-7.97 (d, 1H, aromatic H, J= 7.98Hz), 10.02 (s, 1H, NH); MS : m/z 350 $(M+H)^+$; Analytical calculation for $C_{17}H_{10}F_3NO_4$: C 58.46, H 2.89, N 4.01, O 18.32, F 16.32.

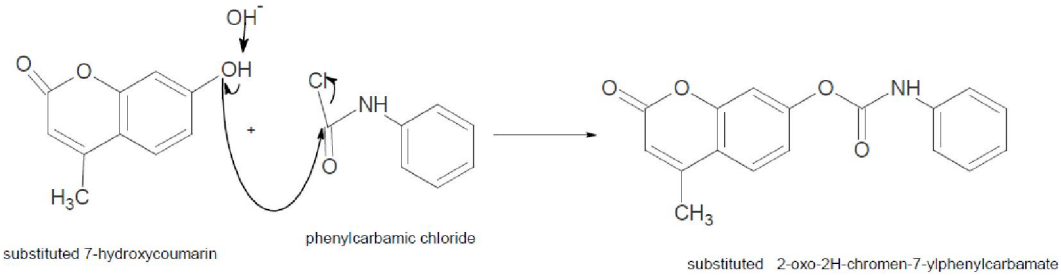

Figure 6 : Possible mechanism of reaction of synthesis of substituted 2-oxo-2H-chromen-7-ylphenylcarbamate by reaction of phenyl carbamic chloride with substituted 7-hydroxycoumarin in single step reaction (3rd method)

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