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Synthesis of 3-Alkoxymethylcoumarin from 3-Cyanochromene via a Novel Intermediate 2-Phenylimino-3-alkoxymethylchromene

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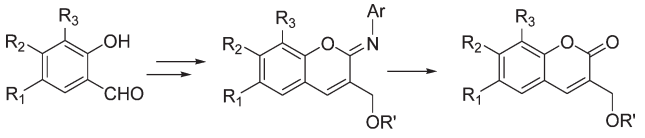

In this paper a concise, efficient, and environmentally benign method for the synthesis of 3-alkoxymethylcoumarin is described. From the reaction of 3-cyanochromene with an alkoxide and arylamine in THF, (*Z*)-2-phenylimino-3-alkoxymethylchromene was obtained as a novel intermediate via an isomerization of the double bond, a 1,2-addition of alkoxide, a Michael-type addition of aniline, an another isomerization of double bond and an elimination of ammonia. Subsequently, the intermediate was converted into the desired coumarin by treatment with 15% HCl in THF in good yield.

Coumarins, which are chemical derivatives of benzo-2-pyrones or chromen-2-ones, are widely distributed in various species of plants.[1,2] In addition, diverse approaches have been used to synthesize numerous artificial coumarins. Both naturally occurring and synthetic coumarins have attracted intensive attention from chemists due to their broad spectral properties and potential for biological activities. For example, the bioactivity of coumarins includes steroid sulfatase inhibitory activity,[3] lipid-lowering activity,[4] anticarcinogenic activity,[5] fungicidal activity,[6] acaricidal activity,[7] potential anticonvulsant and analgesic activities,[8] as well as other activities.[9] The major synthetic methods for the preparation of coumarins include the Pechmann reaction and its modifications,[10] the Knoevenagel condensation,[11] the Wittig reaction,[12] the Claisen rearrangement,[13] the Vilsmeier−Haack and Suzuki cross-coupling reactions,[14] Pd-catalyzed site-selective cross-coupling reactions,[15] as well as other reactions. Despite the large number of syntheses reported, the synthesis of 3-alkoxymethylcoumarins has gained little attention. Up to the present, only two methods which were reported included the chloromethylation of coumarin, followed by the reaction with alcohol[16a] and the reaction of coumarin with an chloromethyl ether.[16b] However, only a few target compounds were synthesized in these reported methods. Other drawbacks include the tedious reaction condition, long reaction time, and low overall yield. The recent increased interest is due to the potential anticancer activity exhibited by some coumarin-3-*N*-arylsulfonamides[17] and coumarin-3-carboxamides.[18] Thus, development of a concise, unique, and efficient synthesis for 3-alkoxymethylcoumarins is requisite and significant from both chemical and biological viewpoints. Herein, we disclose

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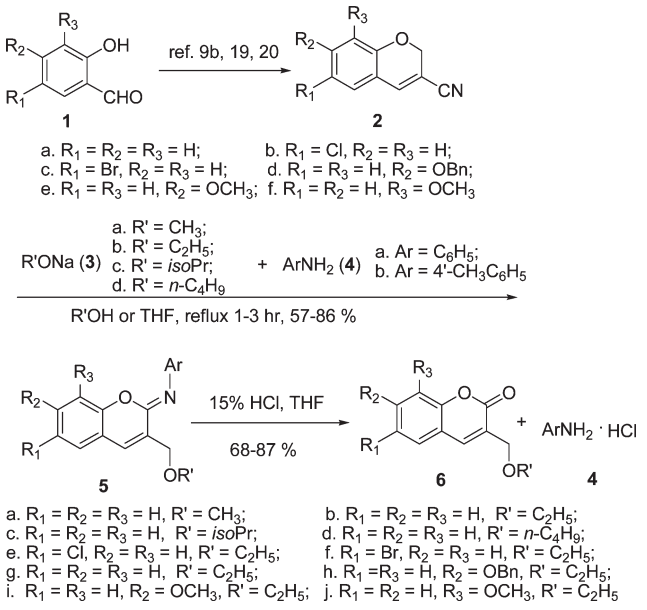
SCHEME 1. Synthesis of 3-Alkoxymethylcoumarin via a Novel Intermediate



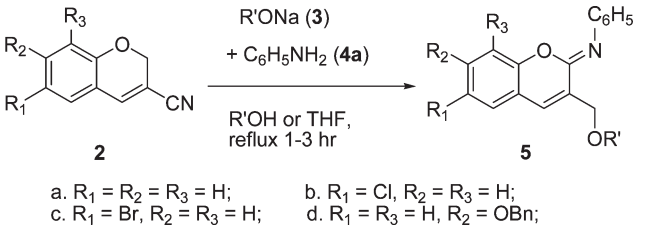
a complete new method for the synthesis of 3-alkoxymethylcoumarins via a novel intermediate.

Our synthetic strategy involves the reaction of 3-cyanochromene with an alkoxide and aniline in either THF or alcohol to yield various 2-phenylimino-3-alkoxymethyl-2*H*-chromenes as intermediates. The resultant intermediates were treated, respectively, with 15% HCl in THF to yield the title compounds (Scheme 1).

3-Cyanochromenes **2a**−**f**, which were prepared according to previous reports,[9b,19,20] were reacted with sodium alkoxide **3a**−**d** and arylamine **4a**,**b** to generate 2(*Z*)-phenylimino-3-alkoxymethylchromenes **5a**−**j** stereospecifically. In order to optimize the yield of **5**, compounds **2a**−**d** were studied in a model reaction using sodium alkoxide **3** and aniline (**4a**) in either refluxing THF or anhydrous alcohol. The results are summarized in Table 1. From the results, THF was found to be a better solvent than anhydrous alcohol. The alkoxide was also varied, and it was found that the reactivities followed the trend *n*-butoxide > isopropoxide > ethoxide > methoxide.

The proposed reaction mechanism for the generation of compound **5** is shown below (Scheme 2). 3-Cyanochromene (**2**) initially undergoes alkoxide-mediated isomerization to form I, which is subsequently converted to II by attack of the alkoxide on the cyano group. The α,γ-unsaturated functionality of II then undergoes a Michael addition by the soft base to afford the enamine in chromane III. With the existing alkoxide in solution, the π-bond of intermediate III migrates to form IV, which has both enamine and hemiaminal functionality. Due to the formation of a hydrogen bond between enamine hydrogen and the hemiaminal nitrogen, the lone-pair electrons of nitrogen on enamine functional group moves and pushes π electrons into the chromene ring to eliminate ammonia to generate V. Through the sequential

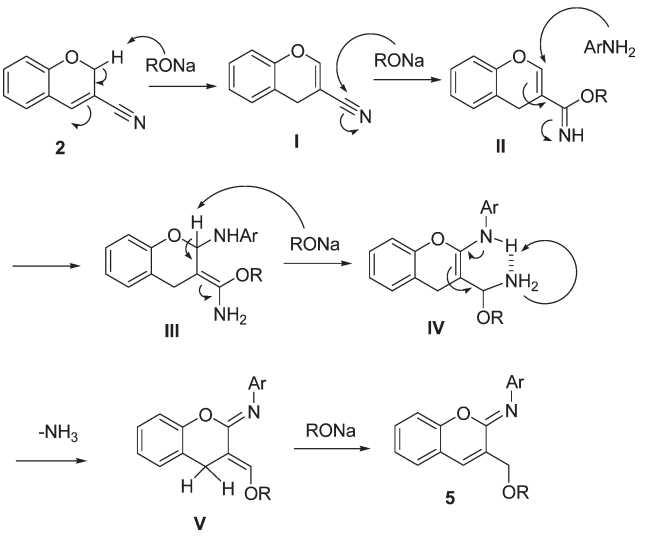
TABLE 1. Results of the Reaction of Compounds 2a−d with a Sodium Alkoxide 3 and Aniline (4a) in Refluxing Alcohol or THF[a]



entry	compd	R′ONa/solvent[b]	reaction time (h)[c]	product (% yield)[d]
1	**2a**	MeONa/MeOH	3	**5a** (48)
2	**2a**	MeONa/THF	3	**5a** (65)
3	**2b**	EtONa/EtOH	2	**5b** (62)
4	**2b**	EtONa/THF	2	**5b** (79)
5	**2c**	*i*-PrONa/*i*-PrOH	1	**5c** (68)
6	**2c**	*i*-PrONa/THF	1	**5c** (82)
7	**2d**	*n*-BuONa/*n*-BuOH	1	**5d** (73)
8	**2d**	*n*-BuONa/THF	1	**5d** (86)

[a]Reaction conditions: **2** (5.0 mmol), **3** (10 mmol), and **4a** (7.5 mmol) dissolved in ROH (30 mL) or THF (30 mL) was heated to reflux. [b]THF is dried from sodium and benzophenone; alcohols are dried from anhydrous calcium oxide. [c]Reaction time is determined by checking the formation of product and almost consumption of starting material by TLC. [d]Percent yield is determined by isolating the product from column chromatography.

SCHEME 2. Proposed Reaction Mechanism of the Formation of Compound 5 from 2



steps described above, the oxygen of the chroman ring and the *N*-aryl group in the structure V located on the same side is established. In order to clarify if the NH_2 or OR group is participating in the hydrogen bonding to the HNC_6H_5 in IV, the heats of formation of both rotomers were calculated by PM3. The conformation of IV which a hydrogen bond between the NH_2 and HNC_6H_5 showed a length of 1.870 Å with heat of formation of $H_f = -7.04157$ kcal/mol. The other conformation in which the hydrogen bond is between the OR and HNC_6H_5 showed a length of 1.911 Å with heat of formation of $H_f = -5.98868$ kcal/mol. The energy-minimized structures of compounds IV and IV′ are shown in

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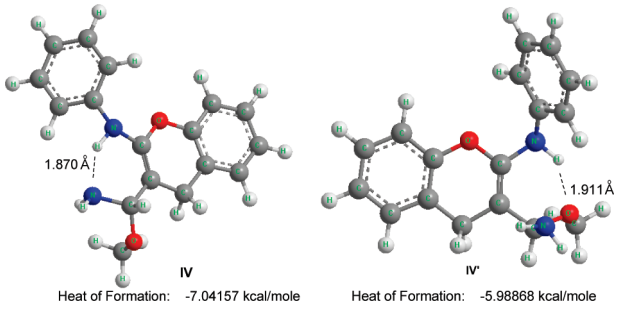

FIGURE 1. Conformation of energy-minimized compounds IV and IV′.

TABLE 2. Selected Bond Length (Å) and Bond Angles (deg) of Compound 5g

bond length		bond angle	
atom−atom	length	atom	angle
O(1)−C(1)	1.374(2)	C(1)−O(1)−C(9)	121.46(14)
O(1)−C(9)	1.382(2)	C(10)−O(2)−C(11)	112.26(16)
O(2)−C(10)	1.408(2)	C(1)−N(1)−C(13)	121.06(16)
O(2)−C(11)	1.417(2)	N(1)−C(1)−O(1)	120.01(17)
N(1)−C(1)	1.266(3)	N(1)−C(1)−C(2)	121.57(17)
N(1)−C(13)	1.424(2)	O(1)−C(1)−C(2)	118.42(16)
C(1)−C(2)	1.458(3)	C(3)−C(2)−C(1)	119.94(18)
C(2)−C(3)	1.332(3)	C(3)−C(2)−C(10)	124.27(18)
C(3)−C(4)	1.444(3)	C(1)−C(2)−C(10)	115.79(16)

Figure 1. The results of the PM3 calculation are consistent with the proposed mechanism requiring the conformation shown in compound IV. In the final step of the mechanism, the double bond of intermediate V undergoes an alkoxide-mediated isomerization to provide conjugation with the benzene ring, thereby forming stable product **5**.

Since the *N*-phenyl group is on the same side of chromene as the oxygen, **5** is obtained stereospecifically in the *Z*-configuration. For the structural determination of compounds **5a**−**j**, the data of the ^{1}H NMR, ^{13}C NMR, EI-MS, and HRMS or elemental analyses were acquired and corroborate the proposed structures. The structure of 3-ethoxymethyl-2(*Z*)-(4-methylphenyl)imino-2*H*-chromene (**5g**) which was crystallized from dichloromethane and *n*-hexane was further confirmed by X-ray crystallography. The final structural model was refined by full-matrix, least-squares procedures to give an R_1 value of 0.041 and an R_w of 0.122. The molecules in the yellow prismatic crystal (0.8 × 0.7 × 0.5 mm) crystallized in space group $P2_1/m$ with lattice parameters a = 9.856(2) Å, b = 7.395(2) Å, c = 11.096(2) Å, β = 101.07(2)°, V = 793.7(3) Å^3, and Z = 2. The data were collected on a Rigaku AFC7S diffractometer with graphite-monochronated Mo Kα (0.71073 Å) radiation. The selected data of bond lengths (Å) and bond angles (deg) of **5g** are depicted in Table 2, respectively.

The crystal structure of **5g** contains a chroman ring with an *N*-aryl and an ethoxymethyl group. The crystallographic plane where the chroman ring and the ethoxymethyl group lie cuts the perpendicular *N*-aryl group in half. The double bond of C(1)=N(1) is in the *Z*-configuration. The ORTEP diagram of **5g** is shown in Figure 2.[21]

(21) The CIF file has been deposited at the Cambridge Crystallographic Centre (CCDC), UK, and received the CCDC no. 680478.

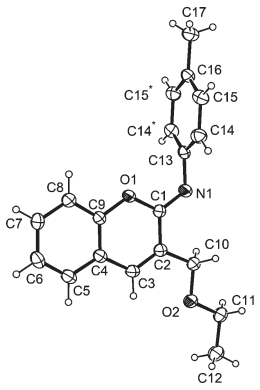

FIGURE 2. Molecular plot of 3-ethoxymethyl-2-(4-methylphenyl)-imino-2*H*-chromene (**5g**).

In conclusion, we have established a novel reaction for the formation of 3-alkoxymethyl-2(*Z*)-(4-aryl)imino-2*H*-chromene **5a**−**j** from 3-cyanochromene (**2**), an alkoxide **3**, and arylamine **4** through multiple mechanistic steps including isomerization of the double bond, a 1,2-addition of alkoxide, a Michael-type addition of arylamine, another isomerization of the double bond, and an elimination of ammonia. We initially converted compound **5** into a series of 3-alkoxymethylcoumarins **6a**−**j** by treating **5a**−**j** with 15% HCl in THF resulting in yields of 68−87%. All prepared coumarins have satisfactory spectral data such as ^{1}H NMR, ^{13}C NMR, EI-MS, and HRMS or elemental analysis. In conclusion, we have established a novel route for the synthesis of 3-alkoxymethyl-2(*Z*)-(4-aryl)imino-2*H*-chromene **5a**−**j** independent of previous studies. Furthermore **5** can be smoothly used in the synthesis of 3-alkoxymethylcoumarins **6a**−**j**. In addition, arylamine, which is a known environmental pollutant, can be recovered, thereby providing an environmentally friendly synthetic route.

Experimental Section

General Procedure for the Preparation of Substituted 3-Alkoxymethyl-2-phenyliminochromenes 5a−j. Under the protection of dried argon, to a solution of 3-cyano-2*H*-chromene **2a**−**f** (5.0 mmol) in anhydrous THF (30 mL) were added sodium alkoxide (10.0 mmol) **3a**−**d** and arylamine **4a**,**b** (7.5 mmol). The reaction mixture was stirred and heated at reflux for 1−3 h until TLC analysis showed the consumption of the starting material. The resultant reaction mixture was concentrated in vacuo to remove the solvent. The residue was purified by silica gel column chromatography (ethyl acetate/*n*-hexane = 1:20) to give **5a**−**j**. The physical and spectral data of selected **5a** and **5b** are illustrated as follows.

3-Methoxymethyl-2(*Z*)-phenylimino-2*H*-chromene (5a). Compound **5a** (0.86 g, 65%) was obtained as yellow crystals: mp 64−65 °C; R_f = 0.51 (ethyl acetate/*n*-hexane = 1: 6); IR (KBr) ν 2936, 2869, 1644, 1585, 1487, 1451, 1403, 1225, 1180, 1115, 1058, 761, 705 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.53 (s, 3H), 4.45 (d, 2H, J = 1.6 Hz), 7.00 (d, 1H, J = 8.0 Hz), 7.06−7.12 (m, 2H), 7.18−7.21 (m, 2H), 7.25 (td, 1H, J = 7.2, 1.6 Hz), 7.29 (dd, 1H, J = 7.6, 1.6 Hz), 7.32−7.36 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 59.0, 69.6, 115.3, 119.8, 122.9, 123.6, 123.7, 127.1, 128.5, 128.9, 129.6, 129.7, 146.0, 147.7, 152.2; MS (EI) 265 (M^+, 10), 250 (100), 235 (27). Anal. Calcd for $C_{17}H_{15}NO_2$: C, 76.96; H, 5.70; N, 5.28. Found: C, 76.93; H, 5.68; N, 5.22.

3-Ethoxymethyl-2(*Z*)-phenylimino-2*H*-chromene (5b). Compound **5b** (1.10 g, 79%) was obtained as yellow crystals: mp

71−72 °C; R_f = 0.56 (ethyl acetate/*n*-hexane = 1:6); IR (KBr) ν 2978, 2861, 1640, 1583, 1486, 1449, 1386, 1227, 1182, 1116, 1064, 758, 703 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.37 (t, 3H, J = 6.8 Hz), 3.74 (q, 2H, J = 6.8 Hz), 4.53 (d, 2H, J = 2.0 Hz), 7.04 (d, 1H, J = 8.0 Hz), 7.11−7.16 (m, 2H), 7.21−7.24 (2H, m), 7.29 (1H, td, J = 8.0, 1.2 Hz), 7.34−7.41 (m, 3H), 7.42 (t, 1H, J = 1.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.6, 67.1, 67.8, 115.7, 120.2, 123.2, 123.9, 124.0, 127.5, 128.9, 129.6, 129.9, 130.0, 146.4, 148.2, 152.6; MS (EI) 279 (M^+, 0.3), 250 (100), 236 (49), 235 (58), 233 (47). Anal. Calcd for $C_{18}H_{17}NO_2$: C, 77.40; H, 6.13; N, 5.01. Found: C, 77.46; H, 6.21; N, 4.82.

General Procedure for the Preparation of 3-Alkoxymethylcoumarins 6a−j. 3-Alkoxymethyl-2-phenyliminochromene **5a−j** (1.0 mmol) dissolved in THF (10 mL) was stirred and cooled in an ice bath. To the cooled solution was added 15% HCl (20 mL) in drops. The reaction mixture was continually stirred at room temperature for 1 h. To the resultant mixture was added saturated NaCl solution (50 mL) and the mixture extracted with dichloromethane (50 mL × 3). The organic extracts were combined and washed with $NaHCO_3$ (50 mL × 3), dried with anhydrous $MgSO_4$, and filtered. The filtrate was concentrated in vacuo to remove the solvent to give a crude crystal. The resultant crystal was recrystallized from ethyl acetate and *n*-hexane to yield pure coumarin (**6a−j**). The physical and spectral data of selected **6a** and **6b** are illustrated as follows.

3-Methoxymethylcoumarin (6a). Compound **6a** (0.13 g, 68%) was obtained as colorless crystals: mp 72−73 °C (lit.[16a] mp 126 °C, lit.[16b] mp 70 °C); R_f = 0.33 (ethyl acetate/*n*-hexane = 1:5); IR (KBr) ν 2957, 2919, 1713, 1603, 1454, 1394, 1168, 1115, 1043, 1010, 925, 780, 630 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.52 (s, 3H), 4.41 (d, 2H, J = 1.6 Hz), 7.28 (td, 1H, J = 7.6, 0.8 Hz), 7.34 (d, 1H, J = 8.4 Hz), 7.48−7.53 (m, 2H), 7.78 (t, 1H, J = 1.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 59.1, 69.0, 116.5, 119.2, 124.5, 126.0, 127.7, 131.1, 138.2, 153.1, 160.4; MS (EI) 190 (M^+, 2), 175 (68), 160 (100), 103 (41). Anal. Calcd for $C_{11}H_{10}O_3$: C, 69.46; H, 5.30. Found: C, 69.21; H, 5.42.

3-Ethoxymethylcoumarin (6b). Compound **6b** (0.15 g, 73%) was obtained as colorless crystals: mp 95−96 °C; R_f = 0.38 (ethyl acetate/*n*-hexane = 1: 5); IR (KBr) ν 2970, 2924, 2863, 2341, 1717, 1605, 1574, 1447, 1384, 1283, 1172, 1116, 1061, 919, 756, 630 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.31 (t, 3H, J = 7.0 Hz), 3.68 (q, 2H, J = 7.0 Hz), 4.46 (d, 2H, J = 1.6 Hz), 7.28 (td, 1H, J = 7.6, 1.2 Hz), 7.34 (d, 1H, J = 8.0 Hz), 7.48−7.52 (m, 2H), 7.81 (t, 1H, J = 1.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.2, 66.9, 66.9, 116.5, 119.2, 124.4, 126.4, 127.7, 131.0, 138.1, 153.1, 160.5; MS (EI) 175 ($[M - (C_2H_5)]^+$, 53), 160 (100), 132 (51), 131 (42). Anal. Calcd for $C_{12}H_{12}O_3$: C, 70.57; H, 5.92. Found: C, 70.60; H, 5.95.

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Supporting Information Available: General experimental methods; characterization data for **4a−f**, **5c−j**, and **6c−j**; copies of ^1H and ^{13}C NMR spectra; and crystallographic information files (CIFs) of **5g** are available. This material is available free of charge via the Internet at http://pubs.acs.org.