JOC The Journal of Organic Chemistry

Article

pubs.acs.org/joc

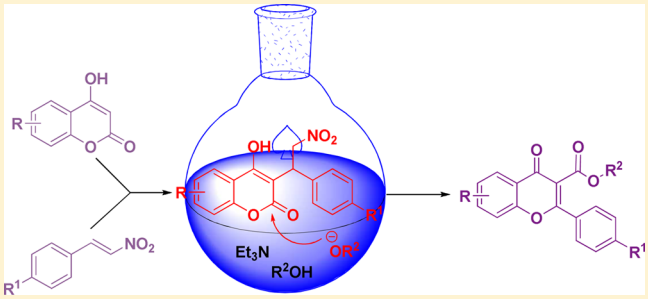
Alcohol Mediated Synthesis of 4-Oxo-2-aryl-4*H*-chromene-3-carboxylate Derivatives from 4-Hydroxycoumarins

Manoj R. Zanwar, Mustafa J. Raihan, Sachin D. Gawande, Veerababurao Kavala, Donala Janreddy, Chun-Wei Kuo, Ram Ambre, and Ching-Fa Yao*

Department of Chemistry, National Taiwan Normal University, 88, Sec. 4, Tingchow Road, Taipei, Taiwan 116, R.O.C.

Supporting Information

ABSTRACT: The unusual alcohol mediated formation of 4-oxo-2-aryl-4*H*-chromene-3-carboxylate (flavone-3-carboxylate) derivatives from 4-hydroxycoumarins and *β*-nitroalkenes in an alcoholic medium is described. The transformation occurs via the *in situ* formation of a Michael adduct, followed by the alkoxide ion mediated rearrangement of the intermediate. The effect of the different alcohol and nonalcohol media on the reaction was investigated.



INTRODUCTION

Flavones are an important class of oxygen heterocycles and are useful intermediates in the fields of medicinal, pharmaceutical, and synthetic chemistry (Figure 1).[1−4] Several natural products that contain this heterocyclic framework have antiviral, anticancer, anti-inflammatory, and antioxidant properties.[1] Among the members of the flavone family, 4-oxo-4*H*-chromene-3-carboxylate derivatives are very interesting scaffolds, since they can act as both a Michael acceptor and a 1,3-diketone, due to the presence of an ester functionality at C-3.[2−4] However, concerning the polysubstituted counterparts, the chemistry of 2-alkyl substituted derivatives have been explored much more extensively than the 2-aryl derivatives.[3,4] This may be due to the absence of a convenient protocol for preparing 2-aryl derivatives. In fact, all of the reported methodologies for the synthesis of these esters consist of a multistep process or involve the use of complex mixtures of reagents.[1−4] As a result, a demand exists for a more straightforward and cost-effective procedure for the synthesis of 4*H*-chromen-4-one moieties.

In addition to controlling the efficacy of a reaction, the medium used also has a significant role in determining the reaction pathway.[5] The polarity of the solvent used in a reaction is a major determinant of the fate of the reaction. The reaction pathway is determined by the stability of a particular transition state that is produced in a specific medium. Thus, the effect of the medium on a chemical transformation is a very important issue in the field of chemistry.[5]

Our long-term goal is directed at exploring the utility of (*E*)-(2-nitrovinyl)benzenes in organic synthesis.[6] In a continuation of our research dealing with nitro olefins, we wish to report, herein, on the unprecedented alcohol mediated synthesis of 4-oxo-2-aryl-4*H*-chromene-3-carboxylates from 4-hydroxycoumarins and *β*-nitroalkenes.

RESULTS AND DISCUSSION

In a recent publication, we reported on the synthesis of a series of oximes, hydroxyiminodihydrofuroquinolinone derivatives, from 4-hydroxy-1-methyl quinolin- 2(1*H*)-one and (*E*)-(2-nitrovinyl)benzenes, using methanol as the solvent, in the presence of a catalytic amount of diisopropylethylamine.[6a] We proposed that the conversion occurred via the formation of a Michael adduct. The Michael adduct underwent base mediated C−O bond formation to produce an oxime. However, when we examined the reactions of 4-hydroxycoumarin (**a**, Scheme 1) and (*E*)-(2-nitrovinyl)benzenes (**2**) under the same conditions, the reaction was sluggish. From these two experimental outcomes, it appeared that the nitrogen heterocycle, 4-hydroxy-1-methylquinolin-2(1*H*)-one, itself acts as a base and, because of this, the basicity of the medium appears to be an important factor in the formation of an oxime derivative. Taking cues from these observations, we used 2 equiv of diisopropylethylamine to synthesize an oxime derivative (**2a′**, Scheme 1), from 4-hydroxycoumarin (**a**) and (*E*)-(2-nitrovinyl)benzenes derivatives (**2**). At room temperature, only the corresponding Michael adduct was observed. At this point, with the desired oxime in mind, we carried out the reaction at 70 °C. However, the desired oxime was not formed, but the result was more exciting and interesting than our expectation. ^{1}H and ^{13}C NMR, IR, mass, and single crystal X-ray analysis data (Figure 2 and Supporting Information) revealed that the product was methyl 4-oxo-2-*p*-tolyl-4*H*-chromene-3-carboxylate (**2a**), which was formed in 33% yield. The use of 4 equiv of diisopropylethylamine improved the yield to 51%. This finding presents a novel and straightforward route

Received: May 21, 2012
Published: July 18, 2012

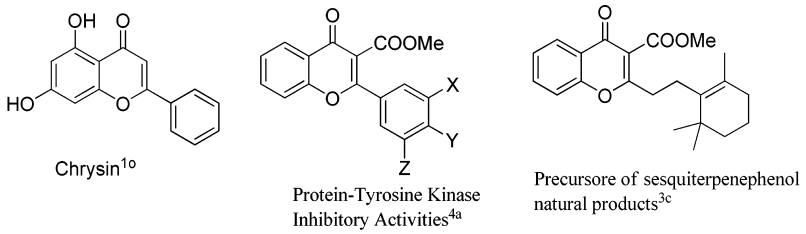
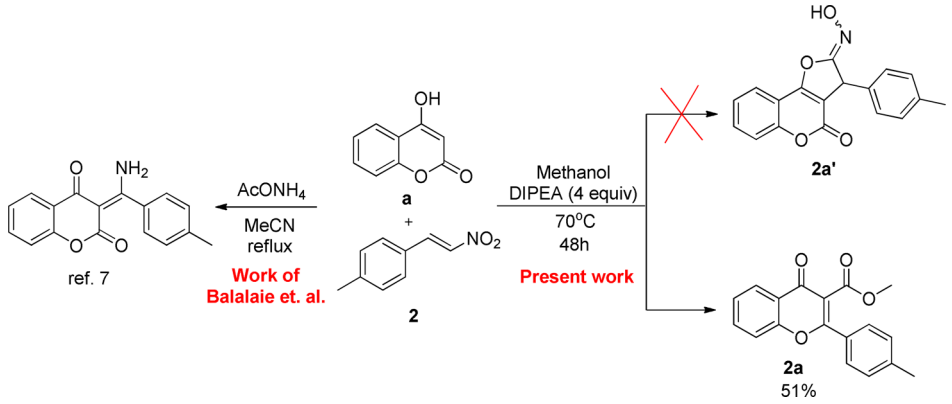


Figure 1. Biologically active 4*H*-chromen-4-one derivatives.

Scheme 1. Reaction of 4-Hydroxycoumarin and (*E*)-1-Methyl-4-(2-nitrovinyl)benzene



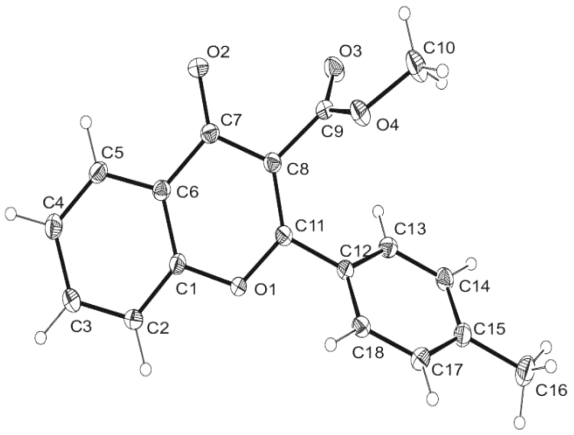


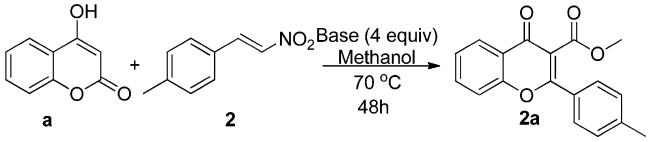
Figure 2. X-ray crystal structure of **2a** (ORTEP diagram).

for the preparation of a relatively unexplored member of the flavone family.

In this context, recently, Balalaie and co-workers disclosed that the treatment of 4-hydroxycoumarin with (*E*)-(2-nitrovinyl)benzenes in acetonitrile, in the presence of ammonium acetate, resulted in the formation of the (3*E*)-3-[amino(aryl)methylidene]chromane-2,4-dione derivative (Scheme 1).[7] However, in our case, when methanol was used as the solvent instead of acetonitrile, a flavone derivative was produced as the major product. Hence, these results explain the effect of the media in chemical transformations in a more comprehensive fashion.

This exciting experimental outcome prompted us to determine the optimal conditions for the conversion. To pursue this goal, we first ran the reaction using different bases (Table 1). No product was obtained with diethylamine (entry 3), piperidine (entry 7) and amberlyst A-25, a basic ion-exchange resin (entry 8). However, the use of ammonium acetate (entry 4), DABCO (entry 5), $NaHCO_3$ (entry 6), and

Table 1. Effect of Different Bases



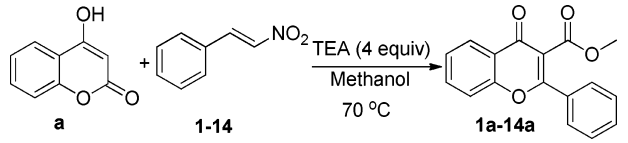
Entry	Base	Yield[a,b]
1	DIPEA	51
2	Pyridine	55
3[c]	Diethyl Amine	—
4[d]	Ammonium Acetate	—
5[d]	DABCO	—
6[d]	$NaHCO_3$	—
7[c]	Piperidine	—
8[c]	Amberlyst A-25 Basic	—
9	TEA	68
10	KF	46
11[d]	DBU	—
12	*N*, *N*′-Dimethylcyclohexylamine	53

[a]All reactions were performed on a 2 mmol scale. [b]Yield refers to the isolated yield of the purified compound. [c]No product was observed. [d]An inseparable mixture was formed.

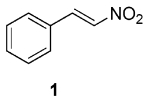
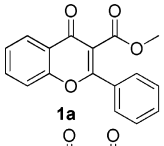
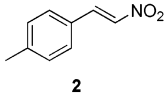
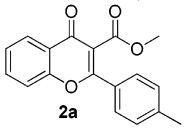
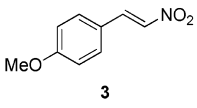
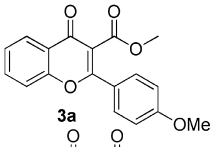
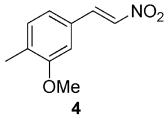
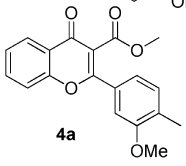
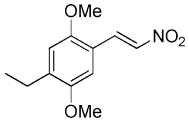
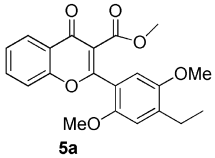
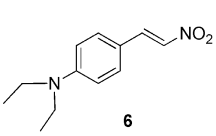
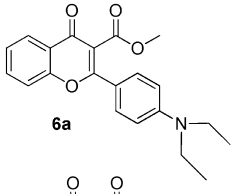
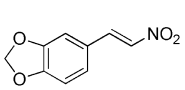
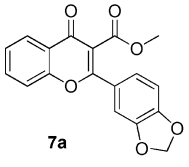
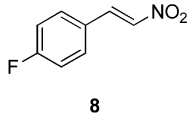
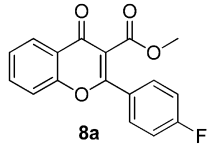
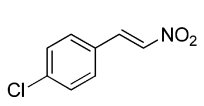
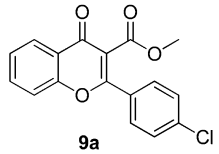
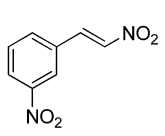
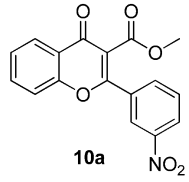
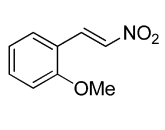
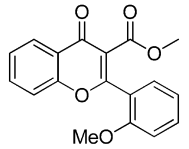
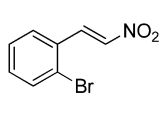
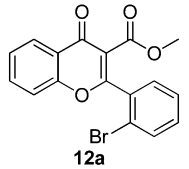
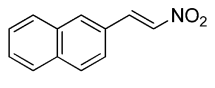
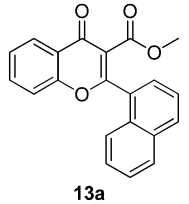
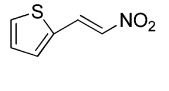
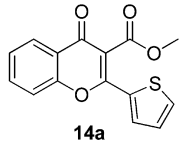
DBU (entry 11) resulted in the formation of an inseparable mixture. On the other hand, bases such as DIPEA (entry 1), pyridine (entry 2), TEA (entry 9), KF (entry 10), and *N*,*N*-dimethyl cyclohexyl amine (entry 12) were found to be more effective. Among them, TEA was found to be superior to the other bases used. When the reaction was carried out at room temperature, only the Michael adduct was formed and no evidence of the desired product was observed. However, at 70 °C the desired product (**2a**) was obtained in good yield and the yield was not improved when the reaction was conducted at higher temperatures. Hence, the substrate scope was explored by carrying out the reaction at 70 °C with TEA as the base.

dx.doi.org/10.1021/jo301044y | *J. Org. Chem.* 2012, 77, 6495−6504

Table 2. Reaction of 4-Hydroxycoumarin with Different Nitroalkene Derivatives



a 1-14 1a-14a

Entry	Nitroalkenes	Product	Time (h)	Yield (%)[a,b]
1	 1	 1a	49	72 (76)
2	 2	 2a	50	68 (75)
3	 3	 3a	54	66 (74)
4	 4	 4a	48	64 (73)
5	 5	 5a	45	63 (72)
6	 6	 6a	46	66 (77)
7	 7	 7a	50	62 (71)
8	 8	 8a	48	53 (59)
9	 9	 9a	60	51 (54)
10	 10	 10a	57	21 (33)
11	 11	 11a	32	80 (86)
12	 12	 12a	48	85 (97)
13	 13	 13a	48	81 (86)
14	 14	 14a	56	27 (33)

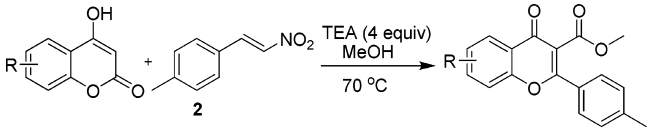
[a]Yields refer to isolated and purified compounds. Parentheses indicate the yield calculated by ^{1}H NMR spectroscopy of the crude reaction mixture using CH_2Br_2 as an internal standard. [b]All reactions were performed on a 2 mmol scale.

The scope of the methodology was examined, first, by treating 4-hydroxycoumarin with a series of *β*-nitroalkene derivatives. To accomplish this, we used several *o*-, *m*-, *p*- as well as unsubstituted (*E*)-(2-nitrovinyl)benzenes, containing both electron-donating and -withdrawing groups (Table 2). We also tested a variety of 4-hydroxycoumarin derivatives (Scheme 2) and alcohols (Table 3) to elaborate the chemistry further.

In the case of 4-hydroxycoumarin, the yields of the desired products were found to be dependent on the electronic nature of the substituents on the phenyl moiety of (*E*)-(2-nitrovinyl)-benzene (Table 2). With the unsubstituted (*E*)-(2-nitrovinyl)-benzene the expected product was obtained in 72% yield (entry 1). The desired products were obtained in moderate to good yields when electron-donating groups were present on the phenyl ring (entries 2−7). However, the introduction of an electron-withdrawing group (such as a nitro group) resulted in a lower product yield (entry 10). Halide substituted (*E*)-(2-nitrovinyl)benzenes (entries 8 and 9) also produced lower

dx.doi.org/10.1021/jo301044y | J. Org. Chem. 2012, 77, 6495−6504

Scheme 2. Reaction of Substituted 4-Hydroxycoumarin and (*E*)-1-Methyl-4-(2-nitrovinyl) Benzene



	R	time (h)	Yield (%)[a,b]
1b	5-Cl	59	48 (53)
1c	5-CH_3	50	65 (72)
1d	6-NO_2	57	26 (35)
1e	6-$N(CH_3)_2$	38	84 (89)

[a]Yields refer to isolated and purified compound. Parentheses indicate the yield calculated by ^{1}H NMR spectroscopy of the crude reaction mixture using CH_2Br_2 as the internal standard. [b]All reactions were performed on a 2 mmol scale.

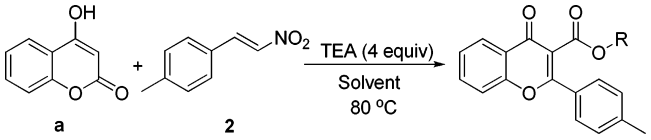
product yields than the (*E*)-(2-nitrovinyl)benzenes with methoxy, methyl, ethyl, and amine functionalities; presumably, the electron-withdrawing inductive effect of the halide functionality makes the phenyl ring electron deficient. The effect of steric factors on product yields was quite interesting. When more sterically hindered (*E*)-(2-nitrovinyl)benzenes were used, the yields were improved. The presence of an *o*-substituent resulted in good to excellent yields of the desired products (entries 11 and 12). (*E*)-(2-Nitrovinyl)benzenes, derived from 2-napthaldehyde, produced the expected product in good yield (entry 13). However, a low product yield was obtained in the case of (*E*)-2-(2-nitrovinyl)thiophene (entry 14). With other heterocyclic nitroalkenes, such as pyridine, pyrrole, indole, and furan, we did not observe the desired product and an inseparable mixture of products were obtained in all the cases.

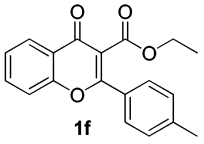
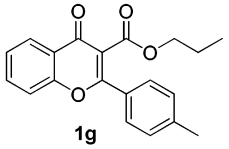
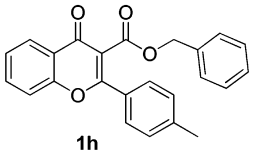
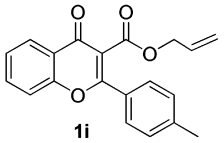
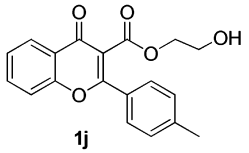
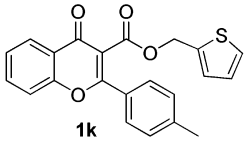
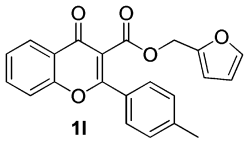
Next, to explore the diversity of our protocol further, we treated halo (**1b**, Scheme 2) and methyl (**1c**, Scheme 2) substituted 4-hydroxycoumarin derivatives with (*E*)-1-methyl-4-(2-nitrovinyl)benzene. Presumably, due to the electron-donating inductive effect of the methyl functionality, the latter produced a higher product yield (**1c**) than the former (**1b**). The presence of a strong electron-withdrawing group, such as 4-hydroxy-6-nitro-2*H*-chromen-2-one, the desired product (**1d**) was obtained in poor yield. However, with 6-(dimethylamino)-4-hydroxy-2*H*-chromen-2-one, the expected flavone derivative (**1e**) was obtained in good yield.

After studying the different reactions of (*E*)-(2-nitrovinyl)-benzenes and 4-hydroxycoumarins, we focused our attention on determining the effect of the medium used in the reaction (Table 3). To pursue this goal, the reaction of (*E*)-1-methyl-4-(2-nitrovinyl)benzene and 4-hydroxycoumarin were performed in different alcoholic media. We observed that the presence of an sp^2 carbon α to the C−O bond resulted in a higher yield of the flavone derivative than bulkier sp^3 counterparts. Hence, benzyl alcohol (entry 3, Table 3) and allylic alcohol (entry 4) were more productive than ethanol (entry 1), *n*-propyl alcohol (entry 2), and ethylene glycol (entry 5). The low yields of the desired products with thiophene methanol (entry 6) and furfuryl alcohol (entry 7) are probably due to the instability of the sulfur and oxygen heterocycles at the high temperature used.

To further explore the effect of the medium, we used methylamine and ethylmercaptan as solvents (Scheme 3). In

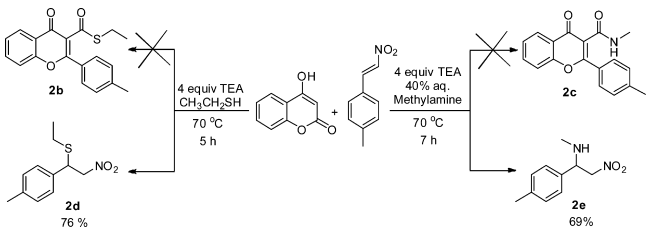
Table 3. Reaction in Different Alcoholic Medium



Entry	Solvent	Product	Time (h)	Yield (%)[a,b]
1	Ethanol	 **1f**	65	34 (37)
2	n-Propyl alcohol	 **1g**	72	34 (38)
3	Benzyl alchohol	 **1h**	51	68 (75)
4	Allyl alcohol	 **1i**	48	58 (65)
5	Ethylene Glycol	 **1j**	72	32 (35)
6	Thiophene Methanol	 **1k**	72	24 (33)
7	Furfuryl Alcohol	 **1l**	72	29 (44)

[a]Yields refer to isolated and purified compounds. Parentheses indicate the yield calculated by ^{1}H NMR spectroscopy of the crude reaction mixture using CH_2Br_2 as the internal standard. [b]All reactions were performed on a 2 mmol scale.

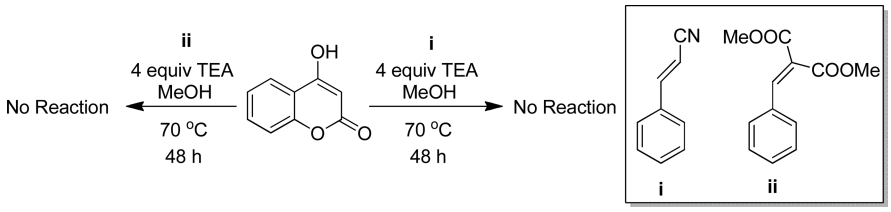
Scheme 3. Reaction in Nonalcoholic Medium



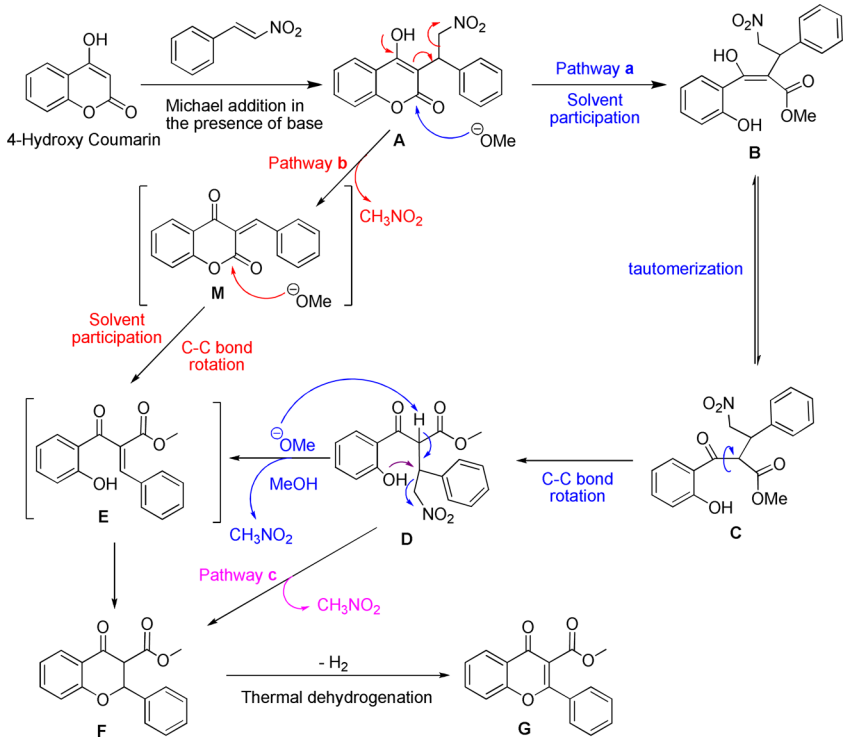
these cases, no expected product (**2b** and **2c**) was obtained. However, compounds **2d** and **2e** were formed as the primary

dx.doi.org/10.1021/jo301044y | J. Org. Chem. 2012, 77, 6495−6504

Scheme 4. Use of Different Michael Acceptors



Scheme 5. Plausible Mechanism for the Formation of Methyl 4-Oxo-2-phenyl-4*H*-chromene-3-carboxylate Derivatives



amine and the thio nucleophiles underwent a faster Michael addition with (*E*)-(2-nitrovinyl)benzene than the *C*-nucleophile, 4-hydroxycoumarin, in the presence of a base. However, with less activated nitrogen containing nucleophiles, such as aniline and *N*-methylaniline, a complex mixture of products was obtained.

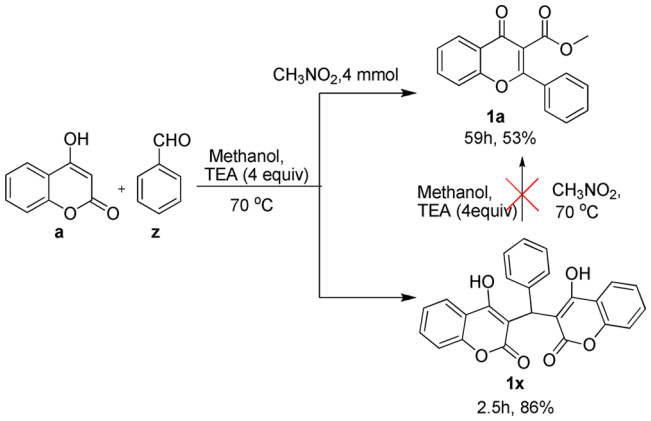
To study the efficacy of other Michael acceptors in this transformation, we used cinnamylnitrile (**i**, Scheme 4) and cinnamyl gemdicarboxylate (**ii**). However, no Michael adduct was formed and only the starting materials were recovered.

The phenomenon could be explained by considering the role of the methoxide ion in the reaction, which is formed from the solvent methanol in the presence of a base (Scheme 5). The initially formed Michael adduct (**A**) either is attacked by a methoxide ion to form intermediate **B** via C−O bond cleavage (Pathway **a**, Scheme 5) or undergoes elimination of nitromethane, resulting in the formation of intermediate **M** (Pathway **b**). Intermediate **B** (Pathway **a**) undergoes tautomerism and C−C bond rotation to form intermediate **D**. The base mediated elimination of nitromethane from intermediate **D** results in the formation of **E**. The intermediate **E** could also be formed from intermediate **M** via the participation of the solvent. **E** then undergoes cyclization via an intramolecular Michael addition of the phenolic OH to form **F**. The thermal dehydrogenation of **F** results in the formation of the product, **G**. The driving force behind this thermal dehydrogenation is the extensive conjugation, which is achieved by the product, due to the formation of multiple bonds. Presumably, the presence of an electron-withdrawing ester group drives the intermediate, **F**, toward this dehydrogenation. The possible alternative route (Pathway **c**) for this conversion would involve the S_N2 type attack of the phenolic OH at the benzylic carbon which, upon elimination of nitromethane, would produce intermediate **F**. However, it is likely an S_N2 attack would be controlled by steric factors.

The proposed mechanism of the reaction (Scheme 5) indicates that the elimination of nitromethane in an intermediate step leads to the formation of the final product and, hence, the likely active reactants are 4-hydroxycoumarin and benzaldehyde. Based on this assumption, we examined the reaction of 4-hydroxycoumarin and benzaldehyde in the presence triethylamine (Scheme 6). However, 3,3′-(phenylmethylene) bis(4-hydroxy-2*H*-chromen-2-one) (**1x**) was produced as the sole product. This result can be explained by considering the formation of intermediate **M** (Scheme 5) from 4-hydroxycoumarin and benzaldehyde. The attack of the second molecule of 4-hydroxycoumarin at intermediate **M** results in the formation of **1x**. On the other hand, the desired product (**1a**) was obtained along with traces of an inseparable mixture of byproducts, when the same reaction was carried out

dx.doi.org/10.1021/jo301044y | *J. Org. Chem.* 2012, 77, 6495−6504

Scheme 6. Reactions in the Presence and Absence of Nitromethane



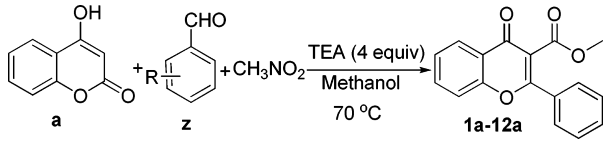
in the presence of nitromethane. The probable explanation for this outcome is that the nitromethane attacks intermediate **M** faster than the second molecule of 4-hydroxycoumarin to form the Michael adduct **A**, which was observed during the reaction. This provides convincing evidence to support that the elimination of nitromethane actually occurred after cleavage of the C−O bond (Pathway **a**, Scheme 5). This finding rules out the possibility that pathway **b** is operative. To confirm this, we examined the reaction between 4-hydroxycoumarin and (*E*)-(2-nitrovinyl)benzene in a 2:1 ratio. No biscoumarin product (**1x**) was detected. Moreover, to determine whether the reaction occurs via the intermediate formation of **1x**, we carried out a reaction between biscoumarin (**1x**) and nitromethane in the presence of TEA in methanol at 70 °C. However, the desired product (**1a**) was not produced, even after 48 h, and the starting material was recovered.

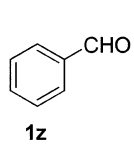
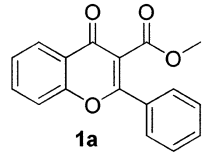
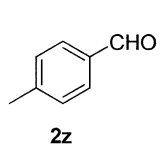
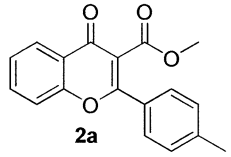
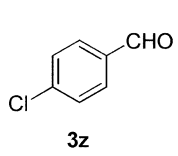
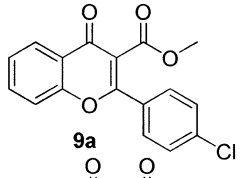
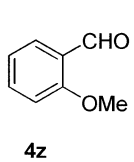
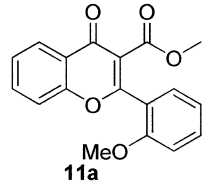
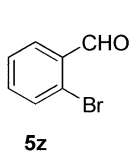
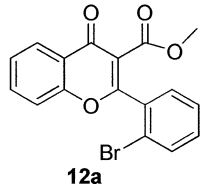
Besides elaborating the reaction mechanism, this experiment revealed the possibility that our desired flavone could be synthesized via a three component reaction (Table 4). Hence, we focused our attention toward the possibility of such a multicomponent protocol. This goal was pursued by the treatment of 4-hydroxycoumarin and nitromethane with different aldehydes in the presence of TEA in methanol. In all the cases, the products were obtained in moderate yields (entries 1, 2, 4, and 5); however, the expected flavone was obtained in poor yield in the case of 4-chlorobenzaldehyde (entry 3).

In this context, to determine whether the medium participates in this step via the *in situ* generation of alkoxide ions, we isolated the Michael adduct and carried out the reaction in methanol in the presence and absence of a base (Scheme 7). The reaction clearly proceeded more efficiently in the presence of a base than in the absence of base. Hence, in the presence of base the alcohol produces alkoxide ions *in situ*. The alkoxide ion plays a key role in the formation of the final product from the Michael adducts.

We next carried out a reaction between 4-hydroxycoumarin and (*E*)-1-methyl-4-(2-nitrovinyl)benzene at room temperature in the presence of sodium methoxide to determine whether the direct use of sodium methoxide would enhance the efficiency of the reaction (Scheme 8). Only the Michael adduct was detected in the reaction mixture, and no expected product was produced in 48 h. However, the desired product was formed on heating, but the yield was low. Although, this experiment did not result in an increase in the yield of the desired product, it explains the

Table 4. Multicomponent Protocol for the Synthesis of Flavone Derivatives



Entry	Aldehyde	Product	Time (h)	Yield (%)[a,b]
1	 1z	 1a	59	58
2	 2z	 2a	58	57
3	 3z	 9a	65	38
4	 4z	 11a	44	68
5	 5z	 12a	56	63

[a]Yields refer to isolated and purified compounds. [b]The reaction was performed on a 2 mmol scale.

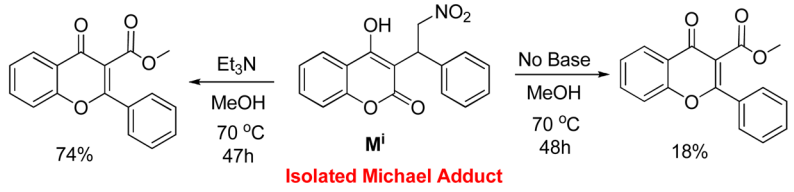
role of temperature and base in a more comprehensive manner. The former is required to excite the methoxide ion to participate in a nucleophilic attack at the carbonyl carbon of the Michael adduct, and the latter mediates the formation of a Michael adduct by the abstraction of an alcoholic proton of the 4-hydroxycoumarins as well generating a methoxide ion *in situ*.

CONCLUSIONS

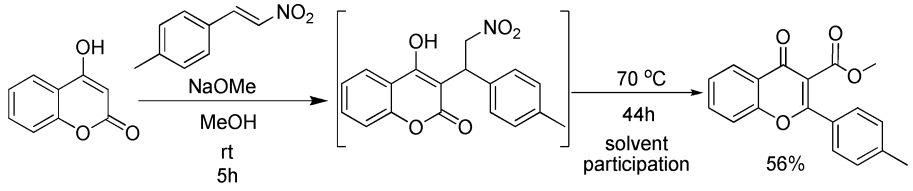
In conclusion, we demonstrate, here, a simple and cost-effective method for the synthesis of a wide variety of 4-oxo-2-aryl-4*H*-chromene-3-carboxylate derivatives. The method, which permits the synthesis of many new 4-oxo-2-aryl-4*H*-chromene-3-carboxylate derivatives, overcomes many of the previous limitations and provides a route to producing these moieties for use in the fields of medicinal and synthetic chemistry. The reaction occurs through the *in situ* generation of a Michael adduct, followed by the C−O bond cleavage of the coumarin moiety of the Michael adduct via participation by the alcoholic medium. The most plausible pathway for the

dx.doi.org/10.1021/jo301044y | *J. Org. Chem.* 2012, 77, 6495−6504

Scheme 7. Role of Base in the Formation of Flavone Derivatives from a Michael Adduct



Scheme 8. Reaction in the Presence of Methoxide Ion



conversion was explored by examining a wide variety of reaction conditions.

EXPERIMENTAL SECTION

General Information. All chemicals were purchased from various sources and were used directly without further purification. Analytical thin-layer chromatography was performed using silica gel 60F glass plates, and silica gel 60 (230−400 mesh) was used in flash chromatographic separations. NMR spectra were recorded in $CDCl_3$ with tetramethylsilane and Chloroform as the internal standards for ^1H NMR (400 MHz) and $CDCl_3$ solvent as the internal standard for ^{13}C NMR (100 MHz). Coupling constants were expressed in hertz. HRMS spectra were recorded using FAB-TOF, ESI, or EI^+ mode. Melting points were recorded using an electrothermal capillary melting point apparatus and are uncorrected.

General Procedure for Preparation of 4-Oxo-2-aryl-4*H*-chromene-3-carboxylate Derivatives (Tables 2 and 3). To a stirred solution of 4-hydroxycoumarin (0.32 g, 2 mmol) and (*E*)-1-methyl-4-(2-nitrovinyl)benzene (0.65 g, 4 mmol) in alcohol (6 mL) was added triethylamine (1.10 mL, 4 equiv). The reaction mixture was heated at 70−80 °C, and the progress of the reaction was monitored by TLC. After completion of the reaction, the solvent was evaporated in vacuum. The resulting residue was further purified by flash column chromatography (ethyl acetate/hexane) on silica gel.

General Procedure for the One-Pot Preparation of 4-Oxo-2-aryl-4*H*-chromene-3-carboxylate Derivatives via a Three Component Reaction (Table 4). To a stirred solution of 4-hydroxycoumarin (0.32 g, 2 mmol), benzaldehyde (0.42 g, 4 mmol), and nitromethane (0.42 mL, 8 mmol) in alcohol (6 mL) was added triethylamine (1.10 mL, 4 equiv). The reaction mixture was heated at 70 °C, and the progress of the reaction was monitored by TLC. After completion of the reaction, the solvent was evaporated in vacuum. The resulting residue was further purified by flash column chromatography (ethyl acetate/hexane) on silica gel.

Procedure for Preparation of 3,3′-(Phenylmethylene)bis(4-hydroxy-2*H*-chromen- 2-one) (Scheme 6). To a stirred solution of 4-hydroxycoumarin (0.32 g, 2 mmol) and benzaldehyde (0.42 g, 4 mmol) in alcohol (6 mL) was added triethylamine (1.10 mL, 4 equiv). The reaction mixture was heated at 70 °C, and the progress of the reaction was monitored by TLC. After the completion of the reaction, the solvent was evaporated in vacuum. The resulting residue was further purified by flash column chromatography (ethyl acetate/hexane) on silica gel.

SPECTRAL DATA

Methyl 4-Oxo-2-phenyl-4*H*-chromene-3-carboxylate (1a). Compound **1a** was eluted with 15% EtOAc/Hex as an off-white solid (407 mg, 72%); m.p.: 100−102 °C; FT-IR (KBr) ν/cm^{-1} 1736, 1643, 1569, 1466, 1384, 1092, 760; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.27 (d, J = 8.0 Hz, 1H), 7.76−7.70 (m, 3H), 7.57−7.50 (m, 4H), 7.45 (t, J = 7.6 Hz, 1H), 3.80 (s, 3H) ; ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.2, 165.8, 163.3, 156.0, 134.5, 132.2, 131.9, 129, 128.2, 126.4, 125.9, 123.4, 118.3, 118.3, 52.9; LRMS (FAB) (m/z) (relative intensity) 281 (M^+ + 1, 88), 273 (9); HRMS (FAB) calcd for $C_{17}H_{13}O_4$ (M + H)$^+$: 281.0814, found 281.0810.

Methyl 4-Oxo-2-*p*-tolyl-4*H*-chromene-3-carboxylate (2a). Compound **2a** was eluted with 15% EtOAc/Hex as a brown solid (402 mg, 68%); mp: 126−128 °C; FT-IR (KBr) ν/cm^{-1} 1737, 1644, 1619, 1564, 1466, 1383, 1091, 762; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.24 (dd, J = 8.0, 1.5 Hz, 1H), 7.72−7.68 (m, 1H), 7.63 (d, J = 8.2 Hz, 2H), 7.51 (d, J = 8.3 Hz, 1H), 7.45−7.41 (m, 1H), 7.30 (d, J = 8.0 Hz, 2H), 3.81 (s, 3H), 2.43 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.2, 166.0, 163.4, 156.0, 142.6, 134.4, 129.8, 129.3, 128.1, 126.3, 125.8, 123.3, 118.2, 117.9, 52.9, 21.8; LRMS (EI) (m/z) (relative intensity) 294 (M^+, 100), 279 (30), 276 (20); HRMS (EI) calcd for $C_{18}H_{14}O_4$ (M^+): 294.0892, found 294.0893.

Methyl 2-(4-Methoxyphenyl)-4-oxo-4*H*-chromene-3-carboxylate (3a). Compound **3a** was eluted with 15% EtOAc/Hex as a brown solid (411 mg, 66%); mp: 103−105 °C; FT-IR (KBr) ν/cm^{-1} 1735, 1638, 1606, 1560, 1466, 1382, 1091, 760; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.23 (dd, J = 7.9, 1.6 Hz, 1H), 7.71−7.66 (m, 3H), 7.50 (d, J = 8.4 Hz, 1H), 7.43−7.39 (m, 1H), 7.01−6.97 (m, 2H), 3.87 (s, 3H), 3.81 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.2, 166.2, 163.0, 162.5, 155.9, 134.3, 130.0, 126.2, 125.7, 124.2, 123.2, 118.1, 117.3, 114.5, 55.7, 52.9; LRMS (FAB) (m/z) (relative intensity) 311 (M^+ + 1, 100), 289 (28), 279 (75), 273 (6); HRMS (FAB) calcd for $C_{18}H_{15}O_5$ (M + H)$^+$: 311.0919, found 311.0919.

Methyl 2-(3-Methoxy-4-methylphenyl)-4-oxo-4*H*-chromene-3-carboxylate (4a). Compound **4a** was eluted with 20% EtOAc/Hex as a brown solid (415 mg, 64%); mp: 106−108 °C; FT-IR (KBr) ν/cm^{-1} 1733, 1638, 1517, 1466, 1379, 1091, 760; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.25 (dd, J = 7.9, 1.6 Hz, 1H), 7.73−7.69 (m, 1H), 7.53 (d, J = 8.4 Hz, 1H), 7.46−7.42 (m, 1H), 7.38 (dd, J = 8.4, 2.2 Hz, 1H), 7.27 (d, J = 2.1 Hz, 1H), 6.96 (d, J = 8.5 Hz, 1H), 3.96 (s, 3H), 3.94 (s, 3H), 3.83 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.2, 166.3, 162.9, 156.0, 152.2, 149.3, 134.4, 126.3, 125.8, 124.4, 123.3, 122.0, 118.2, 117.6, 111.2, 111.0, 56.3, 56.3, 53.0; LRMS (FAB) (m/z) (relative intensity) 324 (M^+, 13), 309 (100), 307 (20), 289 (12), 281 (6), 279 (5); HRMS (FAB) calcd for $C_{19}H_{16}O_5$ (M^+): 324.0998, found 324.0994.

Methyl 2-(4-Ethyl-2,5-dimethoxyphenyl)-4-oxo-4*H*-chromene-3-carboxylate (5a). Compound **5a** was eluted with 20% EtOAc/Hex as an off-white solid (463 mg, 63%); mp: 156−158 °C; FT-IR (KBr) ν/cm^{-1} 1739, 1647, 1506, 1466, 1376, 1086, 760; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.26 (dd, J = 8.0, 1.6 Hz, 1H), 7.70−7.65 (m, 1H), 7.48−7.40 (m, 2H), 7.01 (s, 1H), 6.81 (s, 1H), 3.83 (s, 3H), 3.78 (s, 3H), 3.75 (s, 3H), 2.69 (q, J = 7.5 Hz, 2H), 1.23 (t, J = 7.5 Hz, 3H) ; ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.9, 165.5, 163.4, 156.2, 151.5, 151.3, 138.2, 134.2, 126.4, 125.7, 123.8, 119.3,

dx.doi.org/10.1021/jo301044y | J. Org. Chem. 2012, 77, 6495−6504

118.9, 118.2, 113.1, 111.9, 77.5, 77.2, 76.9, 24.0, 14.1; LRMS (FAB) (m/z) (relative intensity) 369 (M^+ + 1, 100), 368 (M^+, 67), 337 (87), 322 (7), 307 (10); HRMS (FAB) calcd for $C_{21}H_{21}O_6$ $(M+H)^+$: 369.1338, found 369.1335.

Methyl 2-(4-(Diethylamino)phenyl)-4-oxo-4*H*-chromene-3-carboxylate (6a). Compound **6a** was eluted with 20% EtOAc/Hex as a green solid (466 mg, 66%); mp: 147−149 °C; FT-IR (KBr) ν/cm^{-1} 1735, 1654, 1601, 1560, 1474, 1376, 1086; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.22 (d, J = 7.9 Hz, 1H), 7.67−7.61 (m, 3H), 7.48 (d, J = 8.4 Hz, 1H), 7.38 (t, J = 7.5 Hz, 1H), 6.68 (d, J = 9.1 Hz, 2H), 3.87 (s, 3H), 3.42 (q, J = 7.0 Hz, 4H), 1.21 (t, J = 7.0 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.1, 166.9, 163.4, 155.7, 150.3, 133.7, 129.8, 126.0, 125.1, 123.2, 117.8, 117.2, 115.0, 110.9, 52.7, 44.5, 12.5; LRMS (FAB) (m/z) (relative intensity) 352 (M^+ + 1, 100), 351 (M^+, 82), 320 (66), 307 (45); HRMS (FAB) calcd for $C_{21}H_{22}O_4N$ $(M + H)^+$: 352.1549, found 352.1552.

Methyl 2-(Benzo[*d*][1,3]dioxol-5-yl)-4-oxo-4*H*-chromene-3-carboxylate (7a). Compound **7a** was eluted with 15% EtOAc/Hex as a red solid (406 mg, 62%); mp: 161−163 °C; FT-IR (KBr) ν/cm^{-1} 1730, 1641, 1448, 1383, 1082, 760; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.22 (dd, J = 8.0, 1.5 Hz, 1H), 7.71−7.67 (m, 1H), 7.49 (d, J = 8.2 Hz, 1H), 7.43−7.39 (m, 1H), 7.27 (dd, J = 8.2, 1.8 Hz, 1H), 7.19 (d, J = 1.7 Hz, 1H), 6.89 (d, J = 8.2 Hz, 1H), 6.06 (s, 2H), 3.82 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.1, 166.0, 162.6, 155.9, 150.8, 148.4, 134.4, 126.2, 125.8, 125.7, 123.5, 123.2, 118.1, 117.6, 108.8, 108.2, 102.2, 53.0; LRMS (FAB) (m/z) (relative intensity) 325 (M^+ + 1, 100), 324 (M^+, 37), 293 (70), 289 (12); HRMS (FAB) calcd for $C_{18}H_{13}O_6$ $(M + H)^+$: 325.0712, found 325.0719.

Methyl 2-(4-Fluorophenyl)-4-oxo-4*H*-chromene-3-carboxylate (8a). Compound **8a** was eluted with 20% EtOAc/Hex as a brown solid (320 mg, 53%); mp: 111−113 °C; FT-IR (KBr) ν/cm^{-1} 1737, 1647, 1621, 1605, 1570, 1466, 1383, 1092, 761; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.25 (dd, J = 7.9, 1.5 Hz, 1H), 7.77−7.69 (m, 3H), 7.51 (d, J = 8.3 Hz, 1H), 7.46−7.42 (m, 1H), 7.22−7.17 (m, 2H), 3.81 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.0, 164.8 (J = 252.0 Hz), 165.7, 162.2, 156.0, 134.6, 130.5 (J = 9.0 Hz), 128.3 (J = 4.0 Hz), 126.3, 126.0, 123.3, 118.3, 118.2, 116.3 (J = 22.0 Hz), 53.0 ; LRMS (FAB) (m/z) (relative intensity) 299 (M^+ + 1, 100), 273 (4); HRMS (FAB) calcd for $C_{17}H_{12}O_4F$ $(M + H)^+$: 299.0720, found 299.072.

Methyl 2-(4-Chlorophenyl)-4-oxo-4*H*-chromene-3-carboxylate (9a). Compound **9a** was eluted with 15% EtOAc/Hex as a white solid (320 mg, 51%); mp: 134−136 °C; FT-IR (KBr) ν/cm^{-1} 1735, 1647, 1618, 1560, 1466, 1380, 1088, 759; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.25 (dd, J = 7.9, 1.4 Hz, 1H), 7.75−7.67 (m, 3H), 7.53−7.43 (m, 4H), 3.81 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.0, 165.6, 162.0, 156.0, 138.3, 134.7, 130.6, 129.6, 129.4, 126.4, 126.0, 123.3, 118.4, 118.2, 53.1; LRMS (FAB) (m/z) (relative intensity) 315 (M^+ + 1, 100), 307 (26), 285 (19), 283 (55); HRMS (FAB) calcd for $C_{17}H_{12}O_4$ Cl $(M + H)^+$: 315.0424, found 315.0423.

Methyl 2-(3-Nitrophenyl)-4-oxo-4*H*-chromene-3-carboxylate (10a). Compound **10a** was eluted with 20% EtOAc/Hex as a yellow solid (140 mg, 21%); mp: 170−172 °C; FT-IR (KBr) ν/cm^{-1} 1735, 1648, 1534, 1466, 1380, 1094, 761; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.64−8.63 (m, 1H), 8.42−8.39 (m, 1H), 8.26 (dd, J = 7.9, 1.3 Hz, 1H), 8.06 (d, J = 7.4 Hz, 1H), 7.78−7.70 (m, 2H), 7.56 (d, J = 8.4 Hz, 1H), 7.48 (t, J = 7.6 Hz, 1H), 3.85 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.8, 165.2, 160.3, 155.9, 148.6, 135.0, 133.9, 133.7, 130.3, 126.4, 126.4, 126.3, 123.4, 123.3, 119.2, 118.3, 53.3; LRMS (FAB) (m/z) (relative intensity) 326 (M^+ + 1, 100), 310 (8), 294 (46), 289 (17), 278 (6); HRMS (FAB) calcd for $C_{17}H_{12}O_6N$ $(M + H)^+$: 326.0665, found 326.0664.

Methyl 2-(2-Methoxyphenyl)-4-oxo-4*H*-chromene-3-carboxylate (11a). Compound **11a** was eluted with 15% EtOAc/Hex as a brown solid (498 mg, 80%); mp: 130−132 °C; FT-IR (KBr) ν/cm^{-1} 1740, 1647,1618, 1466, 1382, 1088, 759; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.26 (dd, J = 8.0, 1.5 Hz, 1H), 7.70−7.66 (m, 1H), 7.54−7.40 (m, 4H), 7.09−7.05 (m, 1H), 6.98 (d, J = 8.4 Hz, 1H), 3.82 (s, 3H), 3.71 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.9, 165.2, 163.6, 157.1, 156.2, 134.2, 132.9, 130.2, 126.4, 125.7, 123.8, 121.8, 120.8, 119.4, 118.3, 111.4, 55.7, 52.3; LRMS (FAB) (m/z) (relative intensity) 311 (M^+ + 1, 95), 307 (12), 280 (19), 279 (100); HRMS (FAB) calcd for $C_{18}H_{15}O_5$ $(M + H)^+$: 311.0919, found 311.0923.

Methyl 2-(2-Bromophenyl)-4-oxo-4*H*-chromene-3-carboxylate (12a). Compound **12a** was eluted with 15% EtOAc/Hex as a white solid (614 mg, 85%); mp: 103−105 °C; FT-IR (KBr) ν/cm^{-1} 1736, 1648, 1462, 1384, 1096, 760; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.29−8.28 (m, 1H), 7.74−7.70 (m, 2H), 7.49−7.37 (m, 5H), 3.65 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.7, 164.4, 164.4, 156.0, 134.7, 133.6, 133.4, 132.3, 130.6, 127.5, 126.4, 126.1, 123.8, 122.3, 119.6, 118.4, 52.7; LRMS (FAB) (m/z) (relative intensity) 359 (M^+ + 1, 100), 327 (46), 307 (58); HRMS (FAB) calcd for $C_{17}H_{12}O_4Br$ $(M + H)^+$: 358.9919, found 358.9926.

Methyl 2-(Naphthalen-1-yl)-4-oxo-4*H*-chromene-3-carboxylate (13a). Compound **13a** was eluted with 20% EtOAc/Hex as a yellow solid (537 mg, 81%); mp: 184−186 °C; FT-IR (KBr) ν/cm^{-1} 1736, 1648, 1458; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.34 (dd, J = 8.0, 1.6 Hz, 1H), 8.02 (d, J = 8.3 Hz, 1H), 7.95−7.93 (m, 1H), 7.88−7.85 (m, 1H), 7.75−7.68 (m, 2H), 7.57−7.46 (m, 5H), 3.53 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.7, 164.9, 164.8, 156.0, 134.5, 133.5, 131.6, 130.6, 129.6, 128.6, 127.8, 127.5, 126.7, 126.3, 125.9, 124.8, 124.8, 123.6, 120.7, 118.2, 52.5; LRMS (FAB) (m/z) (relative intensity) 331 (M^+ + 1, 100), 307 (16), 300 (18); HRMS (FAB) calcd for $C_{21}H_{15}O_4$ $(M + H)^+$: 331.0970, found 331.0976.

Methyl 4-Oxo-2-(thiophen-2-yl)-4*H*-chromene-3-carboxylate (14a). Compound **14a** was eluted with 15% EtOAc/Hex as a brown solid (157 mg, 27%); mp: 99−101 °C; FT-IR (KBr) ν/cm^{-1} 1735, 1637,1569, 1466, 1387, 1091, 759; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.21 (dd, J = 7.6, 1.6 Hz, 1H), 7.72−7.68 (m, 1H), 7.66−7.65 (m, 2H), 7.51 (d, J = 8.4 Hz, 1H), 7.44−7.40 (m, 1H), 7.18−7.16 (m, 1H), 3.96 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.1, 165.8, 156.3, 155.7, 134.6, 133.4, 131.8, 131.0, 128.6, 126.2, 125.9, 123.2, 118.1, 116.0, 53.3; LRMS (FAB) (m/z) (relative intensity) 287 (M^+ + 1, 100), 271 (9); HRMS (FAB) calcd for $C_{15}H_{11}O_4S$ $(M + H)^+$: 287.0378, found 287.0382.

Methyl 5-Chloro-4-oxo-2-*p*-tolyl-4*H*-chromene-3-carboxylate (1b). Compound **1b** was eluted with 20% EtOAc/Hex as a yellow solid (313 mg, 48%); mp: 160−162 °C; FT-IR (KBr) ν/cm^{-1} 1738, 1644, 1557, 1436, 1368, 1090; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.20 (d, J = 2.3 Hz, 1H), 7.76−7.61 (m, 3H), 7.48 (d, J = 8.8 Hz, 1H), 7.31 (d, J = 8.0 Hz, 2H), 3.81 (s, 3H), 2.44 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.0, 165.7, 163.7, 154.3, 142.9, 134.7, 131.8, 129.8, 128.9, 128.1, 125.6, 124.3, 120.0, 117.8, 53.0, 21.8; LRMS (FAB) (m/z) (relative intensity) 329 (M^+ + 1, 100), 307 (27); HRMS (FAB) calcd for $C_{18}H_{14}O_4Cl$ $(M + H)^+$: 329.0581, found 329.0581.

Methyl 5-Methyl-4-oxo-2-*p*-tolyl-4*H*-chromene-3-carboxylate (1c). Compound **1c** was eluted with 20% EtOAc/Hex as a pink solid (401 mg, 65%); mp: 129−131 °C; FT-IR (KBr) ν/cm^{-1} 1738, 1645, 1486, 1368, 1091; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.02 (d, J = 0.9 Hz, 1H), 7.62 (d, J = 8.2 Hz, 2H), 7.50 (dd, J = 8.5, 2.1 Hz, 1H), 7.40 (d, J = 8.5 Hz, 1H), 7.29 (d, J = 8.1 Hz, 2H), 3.8 (s, 3H), 2.46 (s, 3H), 2.43 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.3, 166.2, 163.3, 154.3, 142.4, 135.9, 135.7, 129.7, 129.4, 128.1, 125.6, 123.0, 118.0, 117.7, 52.9, 21.7, 21.2; LRMS (EI) (m/z) (relative intensity) 308 (M^+, 74), 293 (15), 277 (100); HRMS (EI) calcd for $C_{19}H_{16}O_4$ (M^+): 308.1049, found 308.1050.

Methyl 6-Nitro-4-oxo-2-(*p*-tolyl)-4*H*-chromene-3-carboxylate (1d). Compound **1d** was eluted with 15% EtOAc/Hex as an off-white solid (178 mg, 26%); mp: 158−160 °C; FT-IR (KBr) ν/cm^{-1} 1737, 1650, 1623, 1533, 1499, 1344, 1090; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 9.10 (d, J = 2.5 Hz, 1H), 8.55−8.52 (m, 1H), 7.68 (d, J = 9.2 Hz, 1H), 7.64 (d, J = 7.8 Hz, 2H), 7.33 (d, J = 7.9 Hz, 2H), 3.82 (s, 3H), 2.45 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.7, 165.0, 164.0, 158.7, 145.3, 143.5, 130.0, 128.8, 128.3, 128.2, 123.5, 123.0, 120.1, 118.2, 53.2, 21.8; LRMS (ESI) (m/z) (relative intensity) 341 (M^+ + 1, 100), 295 (23); HRMS (ESI) calcd for $C_{18}H_{14}NO_6$ $(M + H)^+$: 340.0821, found 340.0814.

Methyl 6-(Dimethylamino)-4-oxo-2-(*p*-tolyl)-4*H*-chromene-3-carboxylate (1e). Compound **1e** was eluted with 15% EtOAc/Hex as a yellow solid (567 mg, 84%); mp: 187−189 °C; FT-IR (KBr)

dx.doi.org/10.1021/jo301044y | J. Org. Chem. 2012, 77, 6495−6504

ν/cm^{-1} 1730, 1612, 1502, 1435, 1373, 1233, 1185, 1093, 901; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.61 (d, J = 8.0 Hz, 2H), 7.40 (d, J = 9.1 Hz, 1H), 7.34 (d, J = 3.0 Hz, 1H), 7.28 (d, J = 8.0 Hz, 2H), 7.13 (dd, J = 9.2, 3.1 Hz, 1H), 3.79 (s, 3H), 3.03 (s, 6H), 2.42 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.4, 166.6, 162.7, 148.6, 148.6, 142.0, 129.8, 129.6, 128.0, 123.9, 120.1, 118.8, 116.9, 105.4, 52.8, 40.9, 21.7; LRMS (ESI) (m/z) (relative intensity) 338 (M^+ + 1, 100); HRMS (ESI) calcd for $C_{20}H_{20}NO_4$ (M + H)$^+$: 338.1392, found 338.1385.

Ethyl 4-Oxo-2-*p*-tolyl-4*H*-chromene-3-carboxylate (1f). Compound **1f** was eluted with 15% EtOAc/Hex as a white solid (210 mg, 34%); mp: 106−108 °C; FT-IR (KBr) ν/cm^{-1} 1733, 1645, 1465, 1380, 1088; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.25 (dd, J = 8.0, 1.5 Hz, 1H), 7.72−7.64 (m, 3H), 7.50 (d, J = 8.3 Hz, 1H), 7.44−7.40 (m, 1H), 7.29 (d, J = 8.0 Hz, 2H), 4.29 (q, J = 7.2 Hz, 2H), 2.43 (s, 3H), 1.20 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.2, 165.4, 163.2, 156.0, 142.4, 134.3, 129.6, 129.7, 128.2, 126.2, 125.7, 123.3, 118.2, 118.1, 62.0, 21.7, 14.0; LRMS (FAB) (m/z) (relative intensity) 309 (M^+ + 1, 100), 308 (M^+, 6), 279 (4); HRMS (FAB) calcd for $C_{19}H_{17}O_4$ (M + H)$^+$: 309.1127, found 309.1122.

Propyl 4-Oxo-2-*p*-tolyl-4*H*-chromene-3-carboxylate (1g). Compound **1g** was eluted with 15% EtOAc/Hex as a brown gummy solid (221 mg, 34%); FT-IR (KBr) ν/cm^{-1} 1732, 1645, 1619, 1465, 1379, 1088, 759; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.25 (dd, J = 8.0, 1.6 Hz, 1H), 7.72−7.64 (m, 3H), 7.51 (d, J = 8.4 Hz, 1H), 7.45−7.41 (m, 1H), 7.29 (d, J = 8.0 Hz, 2H), 4.17 (t, J = 6.6 Hz, 2H), 2.43 (s, 3H), 1.63−1.55 (m, 2H), 0.79 (t, J = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.2, 165.6, 163.3, 156.0, 142.4, 134.4, 129.7, 129.4, 128.2, 126.3, 125.8, 123.4, 118.3, 118.2, 67.7, 21.9, 21.7, 10.4; LRMS (FAB) (m/z) (relative intensity) 323 (M^+ + 1, 100), 322 (M^+, 6), 279 (5); HRMS (FAB) calcd for $C_{20}H_{19}O_4$ (M + H)$^+$: 323.1283, found 323.1281.

Benzyl 4-Oxo-2-*p*-tolyl-4*H*-chromene-3-carboxylate (1h). Compound **1h** was eluted with 4% EtOAc/Hex as a white solid (506 mg, 68%); mp: 158−160 °C; FT-IR (KBr) ν/cm^{-1} 1731, 1645, 1386, 1089; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.26 (dd, J = 7.9, 1.4 Hz, 1H), 7.72−7.67 (m, 1H), 7.56−7.49 (m, 3H), 7.43 (t, J = 7.6 Hz, 1H), 7.29−7.27 (m, 3H), 7.20−7.14 (m, 4H), 5.25 (s, 2H), 2.40 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.1, 165.2, 163.8, 156.0, 142.4, 135.3, 134.4, 129.6, 129.2, 128.9, 128.6, 128.4, 128.2, 126.3, 125.8, 123.4, 118.2, 117.9, 67.7, 21.7; LRMS (FAB) (m/z) (relative intensity) 371 (M^+ + 1, 100), 370 (M^+, 4), 307 (7); HRMS (FAB) calcd for $C_{24}H_{19}O_4$ (M + H)$^+$: 371.1283, found 371.1285.

Allyl 4-Oxo-2-*p*-tolyl-4*H*-chromene-3-carboxylate (1i). Compound **1i** was eluted with 20% EtOAc/Hex as a brown gummy solid (370 mg, 58%); FT-IR (KBr) ν/cm^{-1} 1732, 1644, 1620, 1464, 1385, 1088, 760; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.25 (dd, J = 8.0, 1.6 Hz, 1H), 7.73−7.66 (m, 1H), 7.64 (d, J = 6.5 Hz, 2H), 7.52 (d, J = 8.1 Hz, 1H), 7.46−7.42 (m, 1H), 7.29 (d, J = 8.0 Hz, 2H), 5.87−5.79 (m, 1H), 5.30−5.18 (m, 2H), 4.73−4.71 (m, 2H), 2.37 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.2, 165.2, 163.5, 156.0, 142.5, 134.4, 131.6, 129.7, 129.3, 128.3, 126.3, 125.8, 123.4, 119.2, 118.2, 118.0, 66.6, 21.8; LRMS (FAB) (m/z) (relative intensity) 321 (M^+ + 1, 100), 320 (M^+, 3), 279 (8); HRMS (FAB) calcd for $C_{20}H_{17}O_4$ (M + H)$^+$: 321.1127, found 321.1125.

2-Hydroxyethyl 4-Oxo-2-*p*-tolyl-4*H*-chromene-3-carboxylate (1j). Compound **1j** was eluted with 15% EtOAc/Hex as a brown solid (210 mg, 32%); mp: 119−121 °C; FT-IR (KBr) ν/cm^{-1} 1731, 1621, 1466, 1388, 1091, 761; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.25 (dd, J = 8.0, 1.5 Hz, 1H), 7.75−7.71 (m, 1H), 7.67 (d, J = 8.2 Hz, 2H), 7.54 (d, J = 8.4 Hz, 1H), 7.46 (t, J = 7.6 Hz, 1H), 7.32 (d, J = 8.0 Hz, 2H), 4.48 (t, J = 4.5 Hz, 2H), 3.84 (m, 2H), 3.59 (t, J = 6.3 Hz, 1H), 2.43 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.9, 165.5, 164.3, 156.1, 142.9, 134.7, 129.9, 128.9, 128.4, 126.3, 126.0, 123.2, 118.3, 117.6, 67.7, 60.7, 21.8; LRMS (FAB) (m/z) (relative intensity) 325 (M^+ + 1, 100), 289 (43), 273 (8); HRMS (FAB) calcd for $C_{19}H_{17}O_5$ (M + H)$^+$: 325.1076, found 325.1076.

(Thiophen-2-yl)methyl 4-Oxo-2-*p*-tolyl-4*H*-chromene-3-carboxylate (1k). Compound **1k** was eluted with 15% EtOAc/Hex as a brown solid (179 mg, 24%); mp: 136−138 °C; FT-IR (KBr) ν/cm^{-1} 1730, 1642, 1386, 1082; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.25 (dd, J = 8.0, 1.5 Hz, 1H), 7.71−7.67 (m, 1H), 7.52−7.48 (m, 3H), 7.43 (t, J = 7.6 Hz, 1H), 7.30 (dd, J = 5.0, 0.7 Hz, 1H), 7.14 (d, J = 8.0 Hz, 2H), 7.04 (d, J = 3.3 Hz, 1H), 6.96 (dd, J = 5.0, 3.4 Hz, 1H), 5.41 (s, 2H), 2.39 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.1, 165.0, 163.9, 156.0, 142.4, 137.0, 134.4, 129.6, 129.2, 129.0, 128.1, 127.3, 127.0, 126.3, 125.8, 123.4, 118.2, 117.6, 61.6, 21.8; LRMS (FAB) (m/z) (relative intensity) 377 (M^+ + 1, 100), 376 (M^+, 4); HRMS (FAB) calcd for $C_{22}H_{17}O_4S$ (M + H)$^+$: 377.0848, found 377.0840.

(Furan-2-yl)methyl 4-Oxo-2-*p*-tolyl-4*H*-chromene-3-carboxylate (1l). Compound **1l** was eluted with 15% EtOAc/Hex as an off-white solid (211 mg, 29%); mp: 148−150 °C; FT-IR (KBr) ν/cm^{-1} 1731, 1643, 1385, 1085; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.24 (dd, J = 8.0, 1.4 Hz, 1H), 7.71−7.67 (m, 1H), 7.54−7.48 (m, 3H), 7.43 (t, J = 7.6 Hz, 1H), 7.36 (d, J = 0.7 Hz, 1H), 7.18 (d, J = 8.0 Hz, 2H), 6.39 (d, J = 3.2 Hz, 1H), 6.35−6.34 (m, 1H), 5.24 (s, 2H), 2.41 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.1, 165.0, 163.7, 156.0, 149.0, 143.4, 142.3, 134.4, 129.6, 129.0, 128.1, 126.3, 125.8, 123.3, 118.2, 117.6, 111.5, 110.7, 59.2, 21.8; LRMS (FAB) (m/z) (relative intensity) 361 (M^+ + 1, 100), 360 (M^+, 5), 307 (3); HRMS (FAB) calcd for $C_{22}H_{17}O_5$ (M + H)$^+$: 361.1076, found 361.1074.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Crystallographic data of compound **2a** and ^{1}H and ^{13}C NMR copies of all the compounds are available in Supporting Information. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

cheyaocf@ntnu.edu.tw

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Financial support for this work by the National Science Council of the Republic of China (NSC 100-2113-M-003-008-MY3) and National Taiwan Normal University (99T3030-2, 99-D, 100-D-06) is gratefully acknowledged.

■ REFERENCES

(1) (a) Mijangos, M. V.; González-Marrero, J.; Miranda, L. D.; Vincent-Ruz, P.; Lujan-Montelongo, A.; Olivera-Díaz, D.; Bautista, E.; Ortega, A.; Campos- González, M. D. L. L.; Gamez-Montaño, R. *Org. Biomol. Chem.* **2012**, *10*, 2946−2949. (b) Gong, J.; Xie, F.; Ren, W.; Chen, H.; Hu, Y. *Org. Biomol. Chem.* **2012**, *10*, 486−489. (c) Zhao, J.; Zhao, Y.; Fu, H. *Angew. Chem., Int. Ed.* **2011**, *50*, 3769−3773. (d) Wu, C.; Liu, Y.; Zeng, H.; Liu, L.; Wang, D.; Chen, Y. *Org. Biomol. Chem.* **2011**, *9*, 253−256. (e) Gaspar, A.; Silva, T.; Yanez, M.; Vina, D.; Orallo, F.; Ortuso, F.; Uriarte, E.; Alcaro, S.; Borges, F. *J. Med. Chem.* **2011**, *54*, 5165−5173. (f) Wu, C.; Zeng, H.; Liu, L.; Wang, D.; Chen, Y. *Tetrahedron* **2011**, *67*, 1231−1237. (g) Vedachalam, S.; Wong, Q.-L.; Maji, B.; Zeng, J.; Ma, J.; Liu, X.-W. *Adv. Synth. Catal.* **2011**, *353*, 219−225. (h) Chai, G.; Qiu, Y.; Fu, C.; Ma, S. *Org. Lett.* **2011**, *13*, 5196−5199. (i) Gong, J.; Xie, F.; Chen, H.; Hu, Y. *Org. Lett.* **2010**, *12*, 3848−3851. (j) Sakamoto, M.; Yagishita, F.; Kanehero, M.; Kasashima, Y.; Mino, T.; Fujita, T. *Org. Lett.* **2010**, *12*, 4435−4437. (k) Saxin, M. F-.; Pemberton, N.; Andersson, K. D. S.; Dyrager, C.; Friberg, A.; Grotli, M.; Luthman, K. *J. Org. Chem.* **2009**, *74*, 2755−2759. (l) Mal, D.; De, S. R. *Org. Lett.* **2009**, *11*, 4398−4401. (m) Shimizu, M.; Tsurugi, H.; Satoh, T.; Miura, M. *Chem.—Asian J.* **2008**, *3*, 881−886. (n) Abe, I.; Utsumi, Y.; Oguro, S.; Morita, H.; Sano, Y.; Noguchi, H. *J. Am. Chem. Soc.* **2005**, *127*, 1362−1363. (o) Dao, T. T.; Chi, Y. S.; Kim, J.; Kim, H. P.; Kim, S.; Park, H. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 1165−1167. (p) Recanatin, M. i.; Bisi, A.; Cavalli, A.; Belluti, F.; Gobbi, S.; Rampa, A.; Valenti, P.; Palzer, M.; Palusczak, A.; Hartmann, R. W. *J. Med. Chem.* **2001**, *44*, 672−680 and references therein.

(2) (a) Cai, S.; Shen, Y.; Lu, P.; Wang, Y. *Tetrahedron Lett.* **2011**, *52*, 4164−4167. (b) Jana, R.; Trivedi, R.; Tunge, J. A. *Org. Lett.* **2009**, *11*, 3434−3436. (c) Budzisz, E.; Keppler, B. K.; Giester, G.; Wozniczka, M.; Kufelnicki, A.; Nawrot, B. *Eur. J. Inorg. Chem.* **2004**, 4412−4419. (d) Ishizuka, N.; Matsumura, K.-i.; Sakai, K.; Fujimoto, M.; Mihara, S.-I.; Yamamori, T. *J. Med. Chem.* **2002**, *45*, 2041−2055. (e) Seth, P. P.; Totah, N. I. *Org. Lett.* **1999**, *1*, 1411−1414. (f) Lee, Y.-G.; Ishimaru, K.; Iwasaki, H.; Ohkata, K.; Akiba, K.-Y. *J. Org. Chem.* **1991**, *56*, 2058−2066. (g) Cremins, P. J.; Saengchantara, S. T.; Wallace, T. W. *Tetrahedron* **1987**, *43*, 3075−3082 and references therein.

(3) (a) Budzisz, E.; Miernicka, M.; Lorenz, I.-P.; Mayer, P.; Balcerczak, E.; Krajewska, U.; Rozalski, M. *Eur. J. Med. Chem.* **2010**, *45*, 2613−2621. (b) Budzisz, E.; Malecka, M.; Nawrot, B. *Tetrahedron* **2004**, *60*, 1749−1759. (c) Crombie, B. S.; Smith, C.; Varnavas, C. Z.; Wallace, T. W. *J. Chem. Soc., Perkin Trans. 1* **2001**, 206−215. (d) Crombie, B. S.; Redhouse, A. D.; Smith, C.; Wallace, T. W. *J. Chem. Soc., Chem. Commun.* **1995**, 403−404. (e) Cremins, P. J.; Hayes, R.; Wallace, T. W. *Tetrahedron* **1993**, *49*, 3211−3220. (f) Cremins, P. J.; Hayes, R.; Wallace, T. W. *Tetrahedron* **1991**, *47*, 9431−9438. (g) Saengchantara, S. T.; Wallace, T. W. *Tetrahedron* **1990**, *46*, 3029−3036. (h) Cremins, P. J.; Wallace, T. W. *J. Chem. Soc., Chem. Commun.* **1986**, 1602−1603. (i) Chantegrel, B.; Nadi, A. I.; Gelin, S. *J. Org. Chem.* **1984**, *49*, 4419−4424. (j) Wallace, T. W. *Tetrahedron Lett.* **1984**, *25*, 4299−4302. (k) Nixon, N. S.; Scheinmann, F.; Suschitzky, J. L. *Tetrahedron Lett.* **1983**, *24*, 597−600. (l) Klutchko, S.; Shavel, J., Jr.; Strandtmann, M. V. *J. Org. Chem.* **1974**, *39*, 2436−2437 and references therein.

(4) (a) Cushman, M.; Nagarathnam, D.; Burg, D. L.; Geahlen, R. L. *J. Med. Chem.* **1991**, *34*, 798−806. (b) O. Hormi, E. O.; Moisio, M. R.; Sund, B. C. *J. Org. Chem.* **1987**, *52*, 5272−5274. (c) Costa, A. M. B. S. R. C. S.; Dean, F. M.; Jones, M. A.; Varma, R. S. *J. Chem. Soc., Perkin Trans. 1* **1985**, 799−808. (d) Chantegrel, B.; Nadi, A. I.; Gelin, S. *J. Org. Chem.* **1984**, *49*, 4419−4424. (e) Bapin, P.; Dunogues, J.; Petraud, M. *Tetrahedron* **1981**, *37*, 1131−1139. (f) Coppola, G. M.; Dodsworth, R. W. *Synthesis* **1981**, 523−524. (g) Costa, A. M. B. S. R. C. S.; Dean, F. M.; Jones, M. A.; Smith, D. A.; Varma, R. S. *J. Chem. Soc., Chem. Commun.* **1980**, 1224−1226.

(5) (a) Boess, E.; Sureshkumar, D.; Sud, A.; Wirtz, C.; Fares, C.; Klussmann, M. *J. Am. Chem. Soc.* **2011**, *133*, 8106−8109. (b) Ghandi, M.; Bozcheloei, A. H.; Nazari, S. H.; Sadeghzadeh, M. *J. Org. Chem.* **2011**, *76*, 9975−9982. (c) Liu, H.; Chen, C.; Wang, L.; Tong, X. *Org. Lett.* **2011**, *13*, 5072−5075. (d) Verma, A. K.; Rustagi, V.; Aggarwal, T.; Singh, A. P. *J. Org. Chem.* **2010**, *75*, 7691−7703. (e) Zhao, Y.; Yeung, Y.-Y. *Org. Lett.* **2010**, *12*, 2128−2131. (f) Zhang, J.; Chang, C.-W. T. *J. Org. Chem.* **2009**, *74*, 685−695. (g) Minegishi, S.; Kobayashi, S.; Mayr, H. *J. Am. Chem. Soc.* **2004**, *126*, 5174−5181 and references therein.

(6) (a) Barange, D. K.; Kavala, V.; Kuo, C.-W.; Lei, P.-M.; Yao, C.-F. *Tetrahedron* **2011**, *67*, 2870−2877. (b) Habib, P. M.; Kavala, V.; Kuo, C.-W.; Raihan, M. J.; Yao, C.-F. *Tetrahedron* **2010**, *66*, 7050−7056. (c) Barange, D. K.; Raju, B. R.; Kavala, V.; Kuo, C. -W.; Tu, Y.-C.; Yao, C.-F. *Tetrahedron* **2010**, *66*, 3754−3760. (d) Gao, S.; Tu, Z.; Kuo, C.-W.; Liu, J.-T.; Chu, C.-M.; Yao, C.-F. *Org. Biomol. Chem.* **2006**, *4*, 2851−2857. (e) Jang, Y.-J.; Yan, M.-C.; Lin, Y.-F.; Yao, C.-F. *J. Org. Chem.* **2004**, *69*, 3961−3963. (f) Jang, Y.-J.; Shih, Y.-K.; Kuo, W.-Y.; Yao, C.-F. *Chem.—Eur. J.* **2003**, *9*, 2123−2128. (g) Chu, C.-M.; Liu, J.-T.; Lin, W.-W.; Yao, C.-F. *J. Chem. Soc., Perkin Trans. 1* **1999**, 47−52. (h) Yao, C.-F.; Chu, C.-M.; Liu, J.-T. *J. Org. Chem.* **1998**, *63*, 719−722.

(7) Ghabraie, E.; Bararjanian, M.; Balalaie, S.; Rominger, F.; Bijanzadeh, H. R. *Helv. Chim. Acta* **2011**, *94*, 1440−1446.

(8) (a) Singh, P.; Kumar, P.; Chandra, R.; Katyal, A.; Kalra, R.; Dass, S. K.; Prakash, S. *Catal. Lett.* **2010**, *134*, 303−308. (b) Khurana, J. M.; Kumar, S. *Tetrahedron Lett.* **2009**, *50*, 4125−4127. (c) Heravi, M. M.; Nahavandi, F.; Sadjadi, S.; Oskooie, H. A.; Bamoharram, F. F. *Synth. Commun.* **2010**, *40*, 498−503. (d) Sangshetti, J. N.; Kokare, N. D.; Shinde, D. B. *Green Chem. Lett. Rev.* **2009**, *2*, 233−235.