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Novel Synthesis of Substituted Furo[3,2-*c*]chromen-4-ones via Four-component Reaction from Substituted Nitrostyrenes, Aromatic Aldehydes, Coumarins, and Ammonium Acetate

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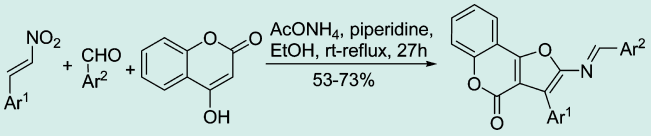
Supporting Information

ABSTRACT: An efficient and direct synthesis of 2-arylideneamino-3-aryl-4*H*-furo[3,2-*c*]chromen-4-ones has been developed via four-component reaction from substituted nitrostyrenes, aromatic aldehydes, coumarins, and ammonium acetate under very mild conditions, which involves sequentially a Michael addition, an aza-nucleophilic addition, of the imine to the double bond, an intermolecular nucleophilic addition and a dehydration reaction. The resulting biologically intriguing structures could have broad applications in related biomedical-program structures.



KEYWORDS: *furo[3,2-c]chromenes, substituted nitrostyrenes, multicomponent reactions, Michael reaction, cyclizations, heterocycles, Schiff base*

INTRODUCTION

The coumarin ring is a key structural unit for numerous natural products, synthetic pharmaceuticals, and a wide variety of biologically active compounds.[1] Many synthetical coumarin compounds with the π-conjugated lactone−(hetero)aryl motifs as the fluorescent core objects have been frequently used in molecular materials such as optical brightening agents,[3] dispersed fluorescent and laser dyes.[2] Coumarin derivatives have also been used as food additives and perfumes.[3] Recently, coumarins fused with (hetero)aryl frameworks as candidates with potential pharmaceutical activity have attracted considerable attention. Studies have revealed that a number of biologically important properties of the coumarins fused with (hetero)aryl frameworks are dependent upon structural features of the (hetero)aryl framework. Chemical modification of the (hetero)aryl framework provides a way to alter the functional groups, sizes, and stereochemistry of the coumarin derivatives, and numerous structure−activity relationships have been established by such synthetic alterations. For example, modified coumarin deriviatives have exhibited a broad range of biological activities as potent anti-HIV agents and anticancer agents.[4]

Similarly, the furan ring also is a common structural motif in many biologically active molecules and natural products, furans being widely employed as versatile building blocks in synthetic organic chemistry.[5] The important role played by these five-membered heterocycles in the field of flavors and fragrances should also be highlighted.[6] Furan derivatives on the other hand are known to have wide applications as drugs and pharmaceuticals. A combination of chromene with a furan moiety in a single molecule has also been explored for the identification of promising bioactive molecules. Among them, furochromen-4-ones (furocoumarins), tricyclic systems in which a furan ring is fused to the chromen-2-one unit, are of particular interest since they exhibit potent biological and pharmacological activity.[7]

In addition, Schiff bases are important class of compounds that show vast biological applications.[8] Also the combination of several heterocycles with Schiff base moieties has been reported.[9]

The development of efficient syntheses of these bioactive heterocycles bearing Schiff base moieties has thus attracted organic and medicinal chemists for decades. Although several general approaches are presently available, such as the classical name reaction, Paal−Knorr synthesis, the search for new methodologies proceeding more efficiently and involving readily available starting materials still remains an active area of research. During the past decade, many efficiently synthetic routes to furochromen-4-ones have been developed. Among others, relevant contributions to this field have recently emerged with the aid of transition-metal catalysts, such as CAN, rhodium, or palladium catalysts because they allow the construction of complex furochromen-4-ones from readily available chromenes with terminal alkynes under mild conditions.[10] More recently, Lin and co-workers reported that furo[3,2-*c*]coumarin derivatives were synthesized starting from highly functional phosphorus zwitterions as synthetic reagents with commercially available acid chlorides in a one-step procedure.[11] Nair and co-workers reported a novel procedure for the synthesis of furocoumarin via a three-component reaction of 4-hydroxycoumarin with aryl aldehydes and cyclohexyl isocyanide in refluxing benzene.[12] Afterward, Wu developed the reaction of aryl isocyanides and aldehydes with

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common 4-hydroxycoumarin as a starting material to furnish functionalized furo[3,2-*c*]chromen-4-ones in excellent yields under microwave irradiation.[13]

In the same way, using 4-hydroxycoumarin as a starting material, heating a mixture of 4-hydroxycoumarin, an isocyanide, and an aldehyde at high temperature (180 °C) under an argon atmosphere and solvent-free conditions also afforded furo[3,2-*c*]chromen-4-ones.[14] Additionally, Shafiee and co-workers also described an appealing strategy to directly construct furo[3,2-*c*]coumarin core via a one-pot oxidative pseudo three-component condensation of aldehydes and 4-hydroxycoumarin (2 equiv) in poly(ethyleneglycol) (PEG) as solvent using a mixture of I_2 and $K_2S_2O_8$ as an oxidative reagent.[15] It is known that multicomponent reactions as an efficient synthetic strategy have drawn considerable attention over the past decades, because complex products are formed in a one-pot reaction and diversity can be simply attained by relatively simple starting materials.[16] However there are only a few one-pot multicomponent reactions for the construction of structurally and stereochemically diverse 2-alkylamino-3-arylfuro[3,2-*c*]chromen-4-ones.[12−14] Recently, as a useful building block for the formation of carbon−carbon bond, *α,β*-nitroalkenes were employed in synthesis of many important heterocyclic compounds.[17] The Michael addition of activated methylenes to *α,β*-nitroalkenes is an efficient synthetic tool for the formation of C−C bonds, which provides easy access to synthetically important nitroalkanes.[18] The transformation of the corresponding adducts could yield a variety of useful synthetic intermediates. Recently, we reported a straightforward one-pot, multicomponent synthesis of polysubstituted piperidines using nitrostyrenes as essential building blocks with aromatic aldehydes, dialkyl malonates, and ammonium acetate.[19] However, to our knowledge, there is no direct method available for one-pot synthesis of 2-alkylamino-3-arylfuro[3,2-c]chromen- 4-ones using nitrostyrenes as a building block with commercially available 4-hydroxycoumarin. It is known that 4-hydroxy coumarins, because of their tautomeric existence, act as cyclic *β*-keto esters. The active methylene group of such cyclic *β*-keto esters could be used for the Michael addition of nitro-alkenes as Michael acceptors.[20] Hence, we envisioned the Michael addition of 4-hydroxycoumarins to *α,β*-nitroalkenes, keto−enol tautomerism, an intramolecular cyclization and aromatization in a single operation. As a part of our continuous interest directed toward the development of new methodologies using nitrostyrenes as essential building blocks for the synthesis of 2-alkylamino-3-arylfuro[3,2-*c*]chromen-4-ones, we report the results of our recent efforts devoted to efficient one-pot, multicomponent reactions from substituted nitrostyrenes **1** (Figure 1), aromatic aldehydes **2** (Figure 2), 4-hydroxycoumarin **3** (Figure 3), and ammonium acetate for the direct formation of substituted furo[3,2-*c*]chromene ring bearing Schiff base moiety.

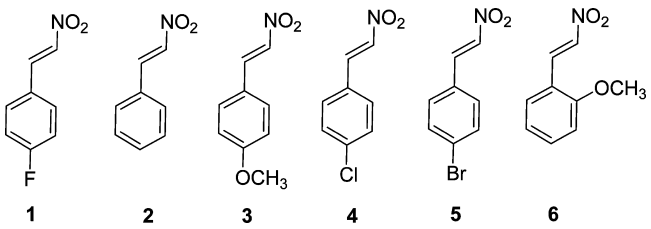

Figure 1. Diversity of substituted nitrostyrenes **1**{*1*−*6*}.

RESULTS AND DISCUSSION

Our initial test reaction was run by mixing 1-nitro-2-(*p*-fluorophenyl)ethane{*1*}, *p*-methoxybenzaldehyde{*1*}, 4-hydroxycoumarin{*1*}, and ammonium acetate together without any catalyst or promoter in methanol at room temperature for 24 h, but no reaction occurred (Table 1, entry 1). It is known that bases can promote the Michael-type reaction, but both inorganic weak base K_2CO_3 and Cs_2CO_3, strong base NaOH did not afford the desired reaction. Piperidine was also used in the same reaction to no avail even though the reaction was carried out under reflux. Reconsidering the possible mechanism of our expected one-pot reaction, we knew that the Michael addition of 4-hydroxycoumarin{*1*} to *α,β*-nitroalkenes is a key step. However, the reported studies showed the Michael addition adducts easily cyclized to form a dihydrofuran ring in the presence of an inorganic base, thus the C2-substitution failed. The experimental procedure was improved by mixing equimolecular amounts of 1-nitro-2-(*p*-fluorophenyl)ethane{*1*} and 4-hydroxycoumarin{*1*} together with the catalyst piperidine. The resultant mixture was stirred for 12 h at room temperature followed by the addition of *p*-methoxybenzaldehyde{*1*}and ammonium acetate with stirring for 12 h at room temperature. The final mixture was refluxed for 2h. This modified method gave better results to the one-pot reaction (Table 1, entry 8). Interestingly, no reaction was observed without ammonium acetate (Table 1, entry 9), suggesting it was integral to the reaction. Encouraged by these results, the reaction conditions were then screened with the aim of optimizing the yield of **4a**. It was observed that **4a** could be obtained in 46% yield when piperidine (50 mol %) and ammonium acetate (1.0 equiv.) were subjected to the reaction at room temperature for 24 h and then refluxed for 2 h (Table 1, entry 10). 1.5 Equiv. of ammonium acetate accelerated the reaction and improved the yield (Table 1, entry 11). Further increase of the amount of piperidine and ammonium acetate had no significant beneficial effect on the reaction. Extending the reflux time to 3 h resulted in a slightly higher yield (Table 1, entry 12). Triethylamine was also examined as a basic additive in the reaction, but was less effective than piperidine (Table 1, entry 14). The reaction of 1-nitro-2-(*p*-fluorophenyl)ethane {*1*}, *p*-methoxybenzaldehyde {*1*}, 4-hydroxy coumarin {*1*}, and ammonium acetate could proceed in other solvents, such as ethanol, acetonitrile and DMF (Table 1, entries 15−17). Among those tested, methanol proved to be the best. The use of ethanol is similarly effective as methanol.

A series of experiments revealed that the optimal results were obtained when the reaction of 1-nitro-2-(*p*-fluorophenyl)-ethane{*1*}(1.0 equiv) and 4-hydroxy coumarin{*1*} (1.0 equiv) together with 50 mol % piperidine was mixed, the resultant mixture was stirred for 12 h at room temperature, followed by addition of *p*-methoxybenzaldehyde{*1*}(1.0 equiv) and ammonium acetate (1.0 equiv), then stirring for 12 h at room temperature, the final mixture was refluxed for 3h, whereby the yield of **4a**{*1,1,1*} reached 62% (Table 1, entry 12).

Having established the optimal conditions for the synthesis of **4a** {*1,1,1*}, to determine the scope of the protocol, a number of commercially available aldehydes **2**{*1*−*9*} and substituted nitrostyrenes **1**{*1*−*6*} generated from aromatic aldehydes and nitromethane were condensed with 4-hydroxy-2*H*-chromen-2-one **3**{*1*}, and ammonium acetate under optimized reaction condition. The results are summarized in Table 2. Both electron-deficient and electron-rich aromatic aldehydes were

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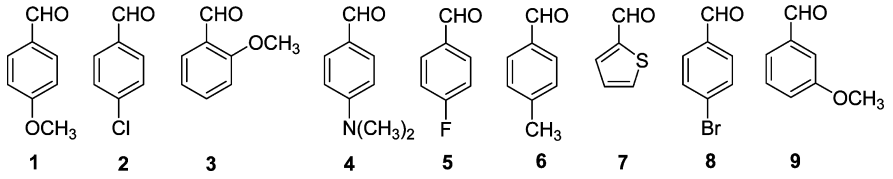


Figure 2. Diversity of aromatic aldehydes **2**{*1*−*9*}.

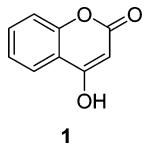
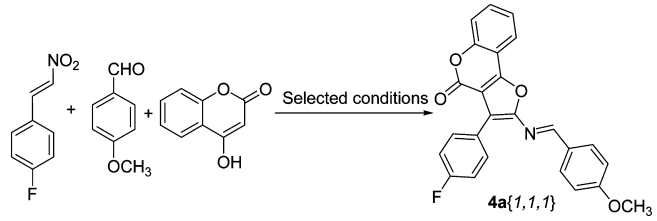


Figure 3. 4-Hydroxy-2*H*-chromen-2-one **3**{*1*}.

similarly viable affording the products in moderate to good yields. The structures of all compounds were elucidated with the aid of ^{1}H and ^{13}C NMR. The structure of compound **4r**{*6,2,1*} was determined by X-ray crystallographic analysis (Figure 4).[22]

The reaction mechanism shown in Scheme 1 is proposed. First, the Michael addition of 4-hydroxycoumarin to the substituted nitrostyrene formed 3-(1-aryl-2-nitroethyl) 4-hydroxycoumarin (Scheme 1, **A**), which is followed by base-promoting deprotonation to form a resonance-stabilized N-oxide oxime (Scheme 1, **B**). Next, intermediate arylimine nucleophilic addition to N-oxide oxime (Scheme 1, **B**) gave an intermediate N-oxide hydroxyamine (Scheme 1, **C**), following dehydration yielded 2-nitroso Schiff base (Scheme 1, **D**). Then removal of nitroso group formed a key intermediate accumulated 2-azaallene cation (Scheme 1, **E**). Finally, intramolecular nucleophilic addition in 2-azaallene cation gave dihydrofuro[3,2-*c*]chromen-4-one (Scheme 1, **F**), further aromatization afforded the title 2-alkylamino-3-aryl-4*H*-furo-[3,2-*c*]chromen-4-ones. These title compounds with an imine are stable in the reaction process and post treatment because the electron-rich furan ring stables a carbon−nitrogen double bond of the imine. We tested two-component reaction of *m*-methoxynitrostyrene and 4-hydroxycoumarin in the above same conditions. 2,3-Dihydro-2-(hydroxyimino)-3-(3-methoxyphenyl)furo [3,2-*c*]chromen- 4-one (**5**) was obtained in low yield of 45% (Scheme 2), which was mixed with ammonium acetate and p-methoxybenzaldehyde. Then the reaction was carried out again in the presence of piperidine using methanol as solvent, but no reaction occurred. Obviously, this result indicated the four-component reaction from substituted nitrostyrenes, aromatic aldehydes, coumarins, and ammonium acetate did not give dihydro-2-(hydroxyimino)-furo[3,2-*c*]chromen-4-one first, followed by the reaction with ammonium acetate and aryl aldehyde to form the desirable products.

Table 1. Optimization of Promoters, Solvents and Time in the Synthesis of 4a{*1,1,1*}[a]



entry	base (mol %)/AcONH$_4$(equiv)/solvent/*T* (°C)/time (h)	yield (%)[b] no wa
1	(-)/(1 equiv)/MeOH/rt/24 h	0
2	Na_2CO_3(20)/1 equiv/MeOH/rt/24 h	0
3	Cs_2CO_3(20)/1 equiv/MeOH/rt/24 h	0
4	NaOH(20)/1 equiv /MeOH/rt/24 h	0
5	piperidine(20)/1 equiv/MeOH/rt/24 h	0
6	piperidine(20)/1 equiv/MeOH/reflux/24 h	0
7	piperidine(20)/1 equiv/MeOH/rt−reflux/12−12 h	0
8	piperidine(20)/1 equiv/MeOH/rt−rt−reflux/12−12−2 h	35
9	piperidine(20)/0 equiv/MeOH/rt−rt−reflux/12−12−2 h	0
10	piperidine(50)/1 equiv/MeOH/rt−rt−reflux/12−12−2 h	46
11	piperidine(50)/1.5 equiv/MeOH/rt−rt−reflux/12−12−2 h	57
12	piperidine(50)/1.5 equiv/MeOH/rt−rt−reflux/12−12−3 h	62
13	piperidine(100)/1.5 equiv/MeOH/rt−rt−reflux/12−12−3 h	62
14	Et_3N(50)/1.5 equiv/MeOH/rt−rt−reflux/12−12−3 h	24
15	piperidine(50)/1.5 equiv/EtOH/rt−rt−reflux/12−12−3 h	58
16	piperidine(50)/1.5 equiv/MeCN/rt−rt−reflux/12−12−3 h	42
17	piperidine(50)/1.5 equiv/DMF/rt−rt−reflux/12−12−3 h	12

[a]Reaction condition: 1-Nitro-2-(*p*-fluorophenyl)ethene/*p*-methoxybenzaldehyde/4-hydroxycoumarin/ammonium acetate = 1/1/1/1.5 (mol). [b]Isolated yields.

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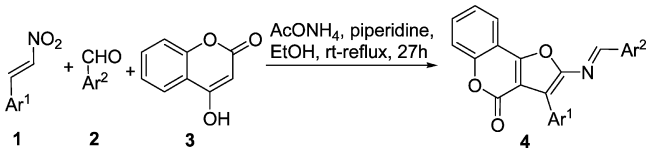
Table 2. Preparation of 2-Arylideneamino-3-aryl-4*H*-furo[3,2-*c*]chromen-4-ones[a]



entry	Ar^1	Ar^2	product	yield (%)[b]
1	*p*-FC_6H_4	*p*-$MeOC_6H_4$	**4a**{*1,1,1*}	62
2	C_6H_5	*p*-$MeOC_6H_4$	**4b**{*2,1,1*}	57
3	*p*-$MeOC_6H_4$	*p*-ClC_6H_4	**4c**{*3,2,1*}	73
4	*p*-$MeOC_6H_4$	*p*-$MeOC_6H_4$	**4d**{*3,1,1*}	72
5	*p*-$MeOC_6H_4$	*o*-$MeOC_6H_4$	**4e**{*3,3,1*}	64
6	*p*-FC_6H_4	*p*-$(CH_3)_2NC_6H_4$	**4f**{*1,4,1*}	67
7	*p*-FC_6H_4	*p*-FC_6H_4	**4g**{*1,5,1*}	56
8	*p*-FC_6H_4	*p*-MeC_6H_4	**4h**{*1,6,1*}	72
9	*p*-FC_6H_4	3-thiophenyl	**4i**{*1,7,1*}	66
10	*p*-$MeOC_6H_4$	*p*-$(CH_3)_2NC_6H_4$	**4j**{*3,4,1*}	68
11	*p*-ClC_6H_4	*p*-MeC_6H_4	**4k**{*4,6,1*}	57
12	*p*-ClC_6H_4	*p*-$MeOC_6H_4$	**4l**{*4,1,1*}	62
13	*p*-ClC_6H_4	*p*-ClC_6H_4	**4m**{*4,2,1*}	53
14	*p*-ClC_6H_4	*p*-$(CH_3)_2NC_6H_4$	**4n**{*4,4,1*}	64
15	*p*-BrC_6H_4	*p*-MeC_6H_4	**4o**{*5,6,1*}	58
16	*p*-BrC_6H_4	*p*-BrC_6H_4	**4p**{*5,8,1*}	58
17	*p*-BrC_6H_4	*p*-$MeOC_6H_4$	**4q**{*5,1,1*}	63
18	*o*-$MeOC_6H_4$	*p*-ClC_6H_4	**4r**{*6,2,1*}	52
19	*p*-BrC_6H_4	*m*-$MeOC_6H_4$	**4s**{*5,9,1*}	60

[a]Reaction condition: Substituted nitrostyrene/aromatic aldehyde/4-hydroxycoumarin/ammonium acetate = 1/1/1/1.5 (mol), 50 mol % piperidine, rt, 24 h, and reflux, 3 h, solvent = MeOH. [b]Isolated yields.

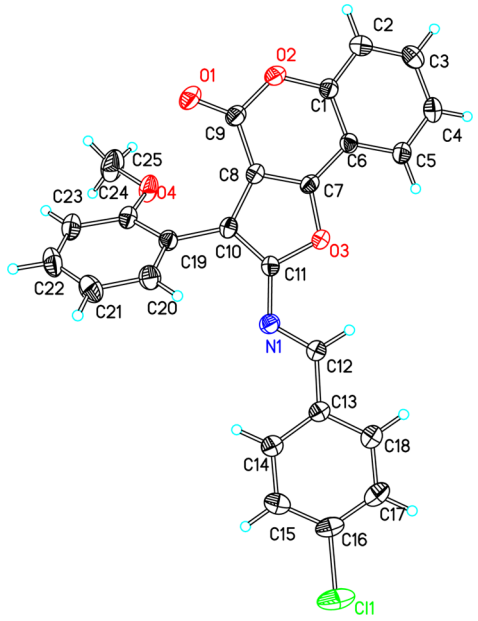


Figure 4. Molecular structure of compound **4r**{*6,2,1*}.

CONCLUSION

In summary, we have demonstrated an efficient, one-pot method for the expeditious synthesis of 2-alkylamino-3-aryl-4*H*-furo[3,2-*c*]chromen-4-ones via a one-pot, multicomponent reaction from substituted nitrostyrenes, aromatic aldehydes, 4-hydroxycoumarin, and ammonium acetate which involves sequential Michael addition, aza-nucleophilic addition of imine to the double bond, intermolecular nucleophilic addition, and dehydration reactions. This protocol, combining construction and modification of the furo[3,2-*c*]chromene skeleton, increases the structural diversity of final products from readily available starting materials. We expect that the resulting biologically intriguing structures will have broad applications in our related biomedical program.

EXPERIMENTAL PROCEDURES

General. All melting points were determined in a Yanaco melting point apparatus and are uncorrected. IR spectra were recorded in a Nicolet FT-IR 5DX spectrometer. The ^1H NMR (600 MHz) and ^{13}C NMR (150 MHz) spectra were recorded in a Bruker AV-600 spectrometer with TMS as internal reference in $CDCl_3$ solutions. The *J* values are given in hertz. Only discrete or characteristic signals for the ^1H NMR are reported. The MS spectra were obtained on a ZAB-HS mass spectrometer with 70 eV. The elemental analyses were performed in a Perkin-Elmer 240C instrument. X-ray crystallographic analysis was performed with a Smart-1000 CCD diffractometer. Flash chromatography was performed on silica gel (230−400 mesh) eluting with ethyl acetate−hexanes mixture. All reactions were monitored by thin layer chromatography (TLC). All reagents and solvents were purchased from commercial sources and purified commonly before used.

General Procedure for Preparation of 2-Arylideneamino-3-aryl-4*H*-furo[3,2-*c*]chromen-4-ones. The 4-hydroxycoumarin (324 mg, 2 mmol), appropriate 2-aryl-1-nitroethene (2 mmol) and piperidine (85 mg, 1 mmol) were dissolved in 10 mL of methanol at room temperature and the resultant mixture was stirred at room temperature for 12 h. Then, to the resultant solution appropriate aromatic aldehyde (2 mmol) and ammonium acetate (230 mg, 3 mmol) were added at room temperature. The reaction mixture was stirred at room temperature for 12 h and under reflux for 3 h, and the completion of reaction was confirmed by TLC (EtOAc/methanol 10:1). Subsequently, the precipitated product was filtered off and the solid washed with methanol and diethyl ether two times to give a product **4a**{*1,1,1*}−**4s**{*5,9,1*}. The filtrate was purified by flash chromatography (silica gel, EtOAc/CH_2Cl_2, 10/1) to give other product **4a**{*1,1,1*}−**4s**{*5,9,1*}. The merged crude product was purified ulteriorly by crystallization from hot ethanol−ethyl acetate or ethyl acetate-dichloromethane to yield pure **4a**{*1,1,1*}−**4s**{*5,9,1*}. The air-dried product showed a single spot on TLC and was pure enough for all analytical purposes.

2-(4-Methoxybenzylideneamino)-3-(4-fluorophenyl)-4*H*-furo[3,2-*c*]chromen-4-one (4a): mp 218−219 °C (MeOH/CH_2Cl_2); ^1H NMR ($CDCl_3$, 600 MHz) δ (ppm) 8.78 (s, 1H), 7.88 (d, *J* = 7.8 Hz, 1H), 7.80 (d, *J* = 8.4 Hz, 2H), 7.76 (d, *J* = 7.8 Hz, 2H), 7.46 (t, *J* = 7.8 Hz, 1H), 7.38 (t, *J* = 8.4 Hz, 3H), 7.31 (t, *J* = 7.8 Hz, 1H), 6.98 (d, *J* = 8.4 Hz, 2H), 3.82 (s, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ (ppm) 162.20 (*J* = 242 Hz), 158.76, 156.40 153.49, 152.97, 150.54, 136.73, 133.65, 131.20 (*J* = 7.8 Hz), 130.14, 129.10, 128.22, 123.48 (*J* = 3.2 Hz), 120.46, 117.74, 116.26, 113.80 (*J* = 21 Hz), 112.45, 111.23, 109.46, 54.31; IR (KBr, cm^{-1}) 2963, 2855, 1727, 1609, 1556, 1422, 1384, 1161, 1074, 804; MS (EI) (M + 1) 414.55 (78%); Anal. Calcd. for $C_{25}H_{16}FNO_4$ (%) C 72.63, H 3.90, N 3.39; Found C 72.82, H 4.06, N 3.40.

2-(4-Methoxybenzylideneamino)-3-phenyl-4*H*-furo-[3,2-*c*]chromen-4-one (4b): mp 223−225 °C (MeOH/

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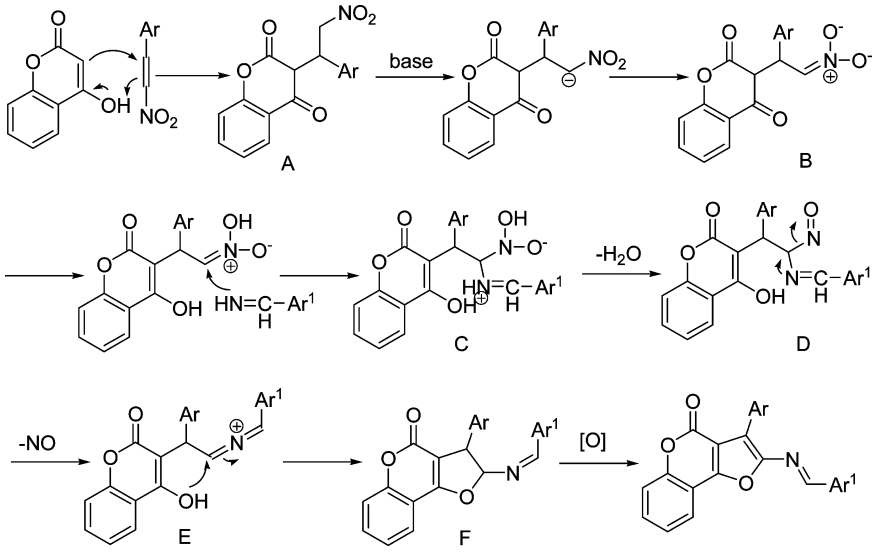
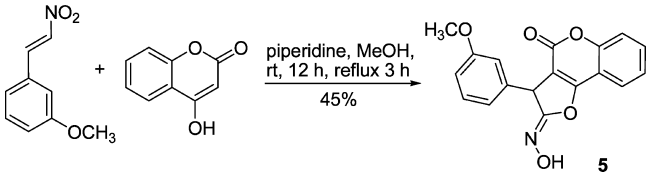
Scheme 1. Possible Mechanism for the Formation of Products 4a{*1,1,1*}−4s{*5,9,1*}



Scheme 2. Two-Component Reaction of Nitrostyrene and 4-Hydroxycoumarin



CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 600 MHz) δ (ppm) 8.80 (s, 1H), 7.89 (d, J = 6.6 Hz, 1H), 7.85 (d, J = 7.2 Hz, 2H), 7.79 (d, J = 9.0 Hz, 2H), 7.46 (t, J = 7.2 Hz, 1H), 7.43 (t, J = 7.8 Hz, 2H), 7.38 (d, J = 7.8 Hz, 1H), 7.33 (d, J = 7.2 Hz, 1H), 7.31 (t, J = 7.8 Hz, 1H), 6.90 (d, J = 9.0 Hz, 2H), 3.81 (s, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ (ppm) 161.84, 156.43, 154.88, 153.02, 151.96, 151.80, 130.06, 129.90, 129.80, 128.41, 128.11, 126.92, 126.77, 123.40, 119.92, 116.22, 115.82, 113.41, 111.37, 109.52, 54.48; IR (KBr, cm^{-1}) 2984, 2851, 1731, 1594, 1515, 1489, 1383, 1095, 1027, 901, 845, 739; MS(EI) (M + 1) 396.44 (100%); Anal. Calcd. for $C_{25}H_{17}NO_4$ (%) C 75.94, H 4.33, N 3.54; Found C 76.18, H 4.49, N 3.47.

■ ASSOCIATED CONTENT

Supporting Information

Additional experimental details, general information, and ^{1}H and ^{13}C NMR spectra for all products. This material is available free of charge via the Internet at http://pubs.acs.org.

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(22) Crystallographic data for **4r**{*6,2,1*} have been deposited with the Cambridge Crystallographic Data Centre with the deposition number CCDC 937473. These data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, U.K. [fax (+44) 1223 336033, e-mail deposit@ccdc.cam.ac.uk].