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ARTICLE TYPE

Three-Component Reaction between Substituted 2-(2-Nitrovinyl)-phenols, Acetylenedicarboxylate and Amines: Diversity-Oriented Synthesis of Novel Pyrrolo[3,4-*c*]coumarins

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An efficient and straightforward synthetic protocol has been developed for the preparation of pyrrolo[3,4-*c*]coumarins via $FeCl_3$-promoted three component reaction between substituted 2-(2-nitrovinyl)phenols, acetylenedicarboxylate and amines for the generation of a wide range of structurally interesting and pharmacologically significant compounds.

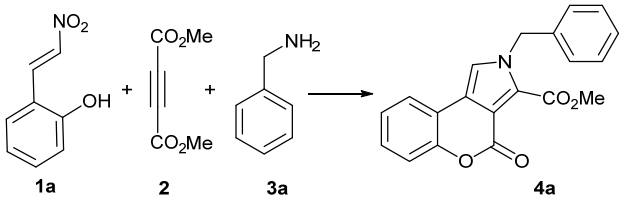
The coumarin ring is an important structure in a number of bioactive natural products.[1] Coumarins and their annulated derivatives display a wide spectrum of pharmacological profile[2], including anticancer activity,[3] steroid 5α-reductase,[4] inhibition of platelet aggregation,[5] and HIV-1 protease.[6] Coumarins have also been used as insecticides.[7] Additionally, 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,[8] dispersed fluorescent and laser dyes.[9] Recently, it is noteworthy that when coumarins are fused with other heterocycles possesses interesting properties. Studies have revealed that a number of biologically important properties of the coumarins fused with other heterocycles are dependent upon structural features of other heterocycles. Chemical modification of other heterocycles 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.[10,11] Specifically, those bearing a coumarin–pyrrole skeleton possess interesting properties like the family of lamellarins as potent cytotoxic agent against various tumor cells.[12] Similarly, pyrroles and their derivatives represent an important class of nitrogen-containing heterocycles.[13] They are core structural skeletons in a variety of natural and synthetic products exhibiting many ubiquitous and varied biological properties.[14-18] Additional, some investgations also reported that substituted pyrroles find application as dyes, pigments, and other functional materials.[19]

A combination of chromene with a pyrrole moiety in a single molecule has also been explored for the identification of promising bioactive molecules.[20] Among them, pyrrolo[*c*]coumarins, polycyclic systems in which a pyrrole ring is fused to the chromene unit, are of particular interest since they exhibit potent biological and pharmacological activity,[20e-f] as well as their potential applications as blue and green light-emitting fluorophores and electroluminescent materials for OLED devices.[21] In the light of the significance of pyrrolo-annulated coumarin systems and their diverse pharmacological properties, there has been a continuous effort to develop new, convenient, and versatile methods for synthesis of this class of compounds. A range of methods has been reported for their synthesis including Cu-mediated/MW-assisted C-O carboxylic lactonization of 2-halophenylindole carboxylic acids.[22] In the same way, using 4-(2-chlorophenyl)-1H-pyrrole-3-carboxylate as a starting material, heating a mixture of 4-(2-chlorophenyl)-1H-pyrrole-3-carboxylate and NaOH under refluxing, the following copper(I)-thiophene-2-carboxylate-mediated lactonization at high temperature (160 °C) in DMF also afforded pyrrolo[3,4-c]coumarins.[23] Zhou and co-workers described an appealing strategy to directly construct pyrrolo[3,4-*c*]coumarins by one-pot domino reactions from benzyl halides with pyridine and 3,4-dichlorocoumarin in the presence of potassium carbonate via in situ generated N-ylide intermediate.[24] Additionally, the pyrrolo[3,4-*c*]coumarins also were formed by the Fischer–Fink reaction starting from 4-chloro-3-formylcoumarin and α-aminoester derivatives.[25] Using isocyanides as starting materials, Ramazani and co-workers reported a novel procedure for the synthesis of pyrrolo[3,4-*c*]coumarins via the ring opening of coumarins and subsequent [4+1] cycloaddition reaction.[26] More recently, Alizadeh and co-workers reported that pyrrolo[3,4-*c*]chromene derivatives were synthesized starting from *p*-toluenesulfonylmethyl isocyanide as a synthetic reagent with commercially available salicylaldehydes and *β*-keto esters via a sequential three-component reaction in a one-step procedure.[27]

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. However there are only a few one-pot multicomponent reactions for the construction of structurally and stereochemically diverse pyrrolo[3,4-*c*]chromenes. The varied biological activity of the coumarins fused with other heterocycles, has encouraged research with regard to the procedures and substrates, which due to their versatility, allow the easy preparation of broad families of these compounds. Our continued interest in the synthesis of the

coumarins fused with other heterocycles[28] invokes us to search a novel route for fused pyrrolochromenes. Accordingly, we decided to investigate the three-component reaction of substituted 2-(2-nitrovinyl)phenols, acetylenedicarboxylate and amines in the synthesis of new coumarin derivatives.

Table 1 Optimization of reaction conditions in the synthesis of **4a**



1a **2** **3a** **4a**

Entry	Additive(eq.)	Solvent	T(°C)	t(h)	Yield(%)(**4a**)[a]
1	Et_3N(3.0)	MeOH	rt-ref	20	0
2	Et_3N(3.0)	EtOH	rt-ref	20	0
3	Et_3N(3.0)	CH_3CN	rt-ref	20	0
4	Et_3N(3.0)	PhMe	rt-ref	20	0
5	NaOH(1.0)	PhMe	rt-ref	20	0
6	PTSA(0.3)	PhMe	rt	20	0
7	$FeCl_3$(0.05)	PhMe	rt	20	35
8	$FeCl_3$(0.1)	PhMe	rt	20	38
9	$FeCl_3$(0.2)	PhMe	rt	20	50
10	$FeCl_3$(0.3)	PhMe	rt	16	78
11	$FeCl_3$(0.4)	PhMe	rt	10	90
12	$FeCl_3$(0.5)	PhMe	rt	10	90
13	$FeCl_3$(0.4)	PhMe	40	10	83
14	$FeCl_3$(0.4)	DMF	rt	10	75
15	$FeCl_3$(0.4)	Dioxane	rt	10	71

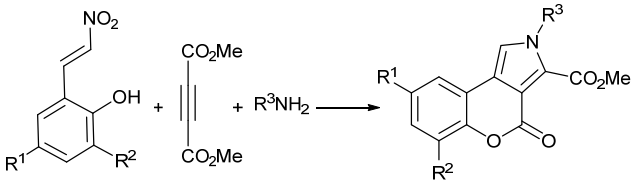
[a]isolated yield.

Based on our previous results[29], a basic reagent was usually used as a promoter for the addition reaction of electron-deficient *β*-nitrostyrenes and acetylenedicarboxylates, thus, our initial experiments focused on the identification of an appropriate basic agent. A generally organic base Et_3N was chosen as a promoter, using 2-(2-nitrovinyl)phenol (**1a**), dimethyl acetylenedicarboxylate (**2**) and benzylamine (**3a**) as the model substrate and methanol as the solvent, the reaction was carried out at rt for 10 h and under refluxing for 10 h, but the desired product was not obtained (Table 1). Next the replacement of MeOH by EtOH, CH_3CN or $PhCH_3$ respectively also did not give the desired product (Table 1, entries 2-4). Then the Et_3N was replaced with a strong base NaOH for the reaction under the same condition, no reaction still occurred (Table 1, entry 5). The above results indicted a large effect on the nature of the catalyst or promoter on this process. Further, we used *p*-methylbenzenesulfonic acid (PTSA) for this reaction at room temperature, no desired product was formed (Table 1, entry 6). However, under the same reaction conditions, by replacing PTSA with Lewis acid $FeCl_3$ (0.05 equiv.), the reaction afforded expected product in ca 35% yield within 20 h of reaction time (Table 1, entry 7).

Then our efforts further focused on the amount of Lewis acid $FeCl_3$, the yield was increased slightly when the amount of $FeCl_3$ was changed from 0.05 equiv. to 0.1 equiv. (Table 1, entries 7-8). When the amount of Lewis acid $FeCl_3$ was increased further to between 0.2 and 0.5 equiv., the yield of the desired product **4a** was obviously increased (entries 9-12). In the presence of 0.2, 0.3, 0.4, and 0.5 equiv. of $FeCl_3$, the yield of product **4a** obtained was 50, 78, 90, and 90%, respectively. Using 0.4 equiv. $FeCl_3$, the reaction was complete after 10 h and the isolated yield was the best (entry 11). Moreover, raising reaction temperature to 40 °C can not improve the reaction (entry 13). Pyrrolo[3,4-*c*]coumarin **4a** was produced in slightly lower yield when the reaction was performed in DMF, or dioxane (entries 14-15).

A series of experiments revealed that the optimal results were obtained when the reaction of 2-(2-nitrovinyl)phenol (**1a**), dimethyl acetylenedicarboxylateand (**2**) and benzylamine (**3a**) together with 0.4 equiv. $FeCl_3$ was carried out in toluene, the resultant mixture was stirred for 10 h at room temperature, whereby the yields of **4a** reached 90% (Table 1, entry 11).

Table 2. Synthesis of pyrrolo[3,4-*c*]coumarin derivatives[a]



1a-e **2** **3a-g** **4a-q**

Entry	R^1	R^2	R^3	Yield[b]
1	H	H	$C_6H_5CH_2$	90 (**4a**)
2	Br	H	$C_6H_5CH_2$	88 (**4b**)
3	H	CH_3	$C_6H_5CH_2$	62 (**4c**)
4	Cl	H	$C_6H_5CH_2$	92 (**4d**)
5	F	H	$C_6H_5CH_2$	80 (**4e**)
6	Br	H	*p*-$FC_6H_4CH_2$	78 (**4f**)
7	H	H	*p*-$FC_6H_4CH_2$	86 (**4g**)
8	H	H	*p*-$CH_3OC_6H_4$	75 (**4h**)
9	Cl	H	*p*-$CH_3OC_6H_4$	74 (**4i**)
10	Br	H	*m*-$CH_3C_6H_4$	65 (**4j**)
11	Br	H	n-C_8H_{17}	55 (**4k**)
12	H	H	n-C_8H_{17}	58 (**4l**)
13	H	CH_3	*p*-$ClC_6H_4CH_2$	72 (**4m**)
14	H	H	*p*-$O_2NC_6H_4$	70 (**4n**)
15	H	H	*p*-$ClC_6H_4CH_2$	89 (**4o**)
16	Br	H	*p*-$ClC_6H_4CH_2$	84 (**4p**)
17	F	H	*p*-$ClC_6H_4CH_2$	86 (**4q**)

[a] Reaction conditions: substituted 2-(2-nitrovinyl)-phenol **1a-e** (1 mmol), acetylenedicarboxylate (213 mg, 1.5 mmol), amines **3a-g** (1 mmol) and $FeCl_3$ (65 mg, 0.4 mmol), toluene (5 mL), 110 °C, 6 h. [b]isolated yield.

Under the optimized conditions as described in entry 11, Table 1, the generality of the reaction was examined. The reaction tolerates different substituents on the amines and substituted 2-(2-nitrovinyl)phenols, generally, amines with a range of substitutents such as benzyl, chlorobenzyl, fluorobenzyl, aryl, and aliphatic groups all worked well to give pyrrolo[3,4-*c*]coumarin derivatives. Substrate benzyl (chlorobenzyl, fluorobenzyl) amines gave the products in higher yields than aryl amines and general aliphatic amines. The electronic properties of the substituents on the benzene ring of benzylamines had a slight effect on the reaction. The introduction of an electron-withdrawing group such as chloro or fluoro speeded down the reaction and slightly decreased the yield of product. Additionally, 2-(2-nitrovinyl) phenol with substitutents such as fluoro, chloro, bromo, and methyl also worked well to give the corresponding products. However, we found substituted positions of phenyl groups of 2-(2-nitrovinyl)phenol mainly affected the reaction, the substitutents at C4 of 2-(2-nitrovinyl)phenol were propitious to the reaction compared with the substitutent at C6 (Table 2, entries 3 and 13). The molecular structures of all pyrrolo[3,4-*c*]coumarins **4a-q** were elucidated from their spectroscopic

analyses as described herein for **4a**. In the IR spectrum of **4a**, two sharp absorption bands at 1745 and 1689 cm^{-1}, three bands at 1580, 1530, and 1497 cm^{-1}, and two absorption bands at 1289 and 1167 cm^{-1} could be related to ArO*CO* and *CO*$_2$Me, C=C, and C–O stretching frequencies. The mass spectrum of **4a** displayed the molecular ion peak at *m*/*z* = 334.4 (M+1), which is in good agreement with the proposed structure. The ^{1}H NMR spectrum of **4a** exhibited three sharp singlet signals at 7.16 *ppm* (s, 1H), 5.59 *ppm* (s, 2H), 3.95 *ppm* (s, 3H) for *C*1-H, Ph*C*H$_2$ and CO$_2$*C*H$_3$, respectively. Characteristic ^{1}H chemical shift of C1-H, PhCH$_2$ and CO$_2$CH$_3$ unequivocally indicated the exclusive chemical environment of pyrrolo[3,4-*c*]coumarins **4a** protons. The ^{1}H-decoupled ^{13}C NMR spectrum of **4a** showed 18 distinct signals in agreement with the suggested structure. The important peaks were related to the ArO*C*O, *C*O$_2$Me, Ph*C*H$_2$ and CO$_2$*C*H$_3$ groups which appeared at δ = 169.1, 161.0, 53.4, and 52.7 *ppm* (see Supporting Information). Final confirmation for the formation of the reaction products was obtained by X-ray crystal structure analysis of compounds **4a** and **4o**. The structures of **4a** and **4o** was unambiguously solved by X-ray crystallography (Fig. 1).[30] X-ray crystallographic analysis determined that products **4a** and **4o** possess an alkyl and an ester contiguous substituents at N(2) and C(3) of pyrrolo[3,4-*c*]coumarin core.

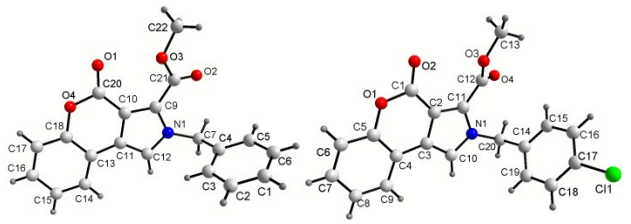
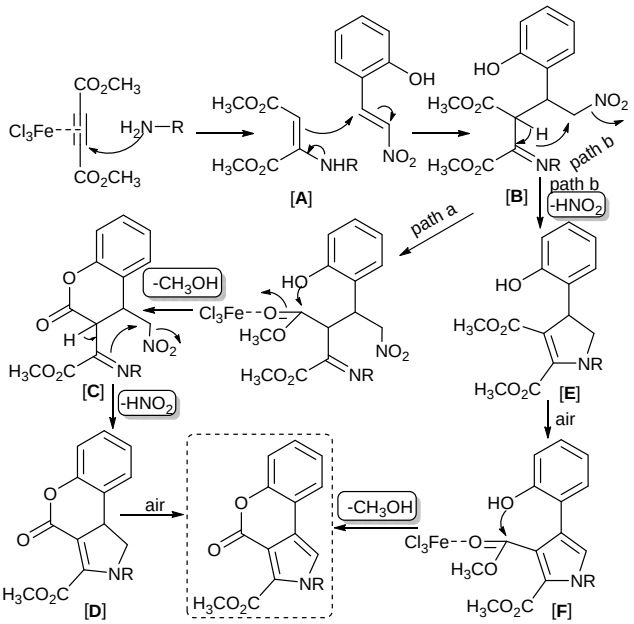


Figure 1. Molecular structure of pyrrolo[3,4-*c*]coumarins **4a** and **4o**



Scheme 1 Possible mechanism in the synthesis of pyrrolo[3,4-*c*]coumarins

For the readership understanding, we performed some control experiments. Under the optimized conditions, the model reaction of 2-(2-nitrovinyl)phenol (**1a**), dimethyl acetylenedicarboxylate (**2**) and benzylamine (**3a**) was carried out at rt for half of the optimized reaction time (5h) aimed at yielding some key intermediates and supporting the mechanistic proposal, but the reaction system was very complicated after workup, the desired intermediates were not isolated by flash chromatography. The results indicated there are some paths that lead to the final products. Based upon the above observation, we proposed a plausible reaction mechanism in Scheme 1. The key steps involved the generation of an aminobutene [A] via the nucleophilic addition of acetylenedicarboxylate with an amine in the presence of $FeCl_3$,[31] then the nucleophilic addition of [A] to 2-(2-nitrovinyl)phenol to give an intermediate imine [B]. The following $FeCl_3$-mediated intramolecular transesterification formed a coumarin core by path **a**, the removal of methanol gave a coumarin [C], the subsequent intramolecular nucleophilic substitution formed the dihydropyrrole intermediate [D] by the elimination of the nitro group.[32] Then, the air-mediated oxidative dehydrogenation of the dihydropyrrole intermediate [D] resulted in the formation of pyrrolo[3,4-*c*]coumarins.[33] We proposed another plausible reaction mechanism in path **b**. Initially, an intermediate imine [B] reacted through intramolecular nucleophilic substitution pathway to form the dihydropyrrole intermediate [E] by the elimination of the nitro group. Then, aerobic oxidation of the intermediate [E] yielded the pyrrole [F]. Finally, $FeCl_3$-mediated intramolecular transesterification formed a pyrrolo[3,4-*c*]coumarin.

Conclusions

In conclusion, we have developed a straightforward and efficient $FeCl_3$-promoted three component reaction between substituted 2-(2-nitrovinyl)-phenols, acetylenedicarboxylate and amines for the synthesis of novel pyrrolo[3,4-*c*]coumarins. This reaction involved the sequential $FeCl_3$-mediated nucleophilic addition of acetylenedicarboxylates, amines, and 2-(2-nitrovinyl)phenols, the following intramolecular transesterification to form a coumarin core. The subsequent intramolecular nucleophilic addition reaction gave the corresponding α-nitrousdihydropyrrole intermediates for the formation of tricyclic pyrrolo[3,4-*c*]coumarin core, the final removal of nitrous group promoted by $FeCl_3$ formed the products. The development of this strategy offered a complementary approach to substituted pyrrolo[3,4-*c*]coumarin compounds with advantages that included a variety of cheap and readily available reactants and a wide range of substrates with dense or flexible substitution patterns.

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Notes and references

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†Electronic Supplementary Information (ESI) available: [Reactions conditions and spectra.]. See DOI: 10.1039/b000000x/

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30 Crystallographic data for **4a** and **4o** have been deposited with the Cambridge Crystallographic Data Centre with the deposition number CCDC 1406217 and 1431800. These data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax (+44) 1223 336033, e-mail: deposit@ccdc.cam.ac.uk].

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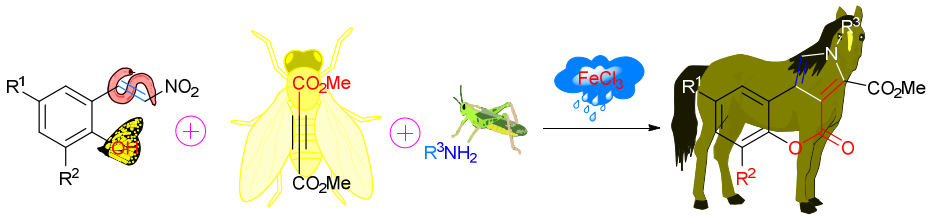

The diversity-oriented synthesis of pyrrolo[3,4-*c*]coumarins via $FeCl_3$-promoted three component reaction between substituted 2-(2-nitrovinyl)phenols, acetylenedicarboxylate and amines has been developed.