Trifluoroacetic acid-Promoted Michael Addition-Cyclization Reactions of Vinylogous Carbamates

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Trifluoroacetic acid-Promoted Michael Addition-Cyclization Reactions of Vinylogous Carbamates

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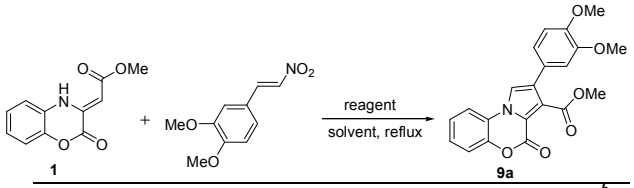
A simple and efficient methodology has been developed for the synthesis of pyrrolobenzoxazine and 3-arylamino coumarin derivatives promoted by trifluoroacetic acid. The initial step in the current protocol involves the Michael addition of the 1,4-benzoxazinone derivatives, a novel class of vinylogous carbamates to the Michael acceptors and subsequent cyclization.

Pyrrole fused heterocyclic compounds are wide spread in the nature and extensively found in many of the natural products and biologically active molecules.[1] These compounds possess a wide range of biological and pharmacological activities like antioxidant,[2] anticancer,[3,4] reversal of multidrug resistance (MDR),[5] antimicrobial activity,[6] human aldose reductase (h-ALR2) inhibition,[7] HIV-1 integrase inhibition and cell division inhibition.[8] The pyrrole fused compounds like pyrrolobenzoxazines and benzothiazines found to exhibit antihyperstensive and acts as central nervous system depressant agents.[9] In our laboratory we have developed novel methodologies for the synthesis of heterocyclic compounds of biological significance.[10] A green approach for the synthesis of 1,4-benzoxazinone derivatives from the readily available starting materials is one among them.[10c] Further we envisaged that these 1,4-benzoxazinone derivatives may serve as a new class of vinylogous carbamates. Herein we report the primary findings of the reactions of these vinylogous carbamates with Michael acceptors such as nitrostyrene and *p*-benzoquinones.

In our initial attempts, a mixture of benzoxazinone derivative **1** and 3,4-dimethoxy nitrostyrene in 1,2-dichloroethane (DCE) in presence of triflic acid was allowed to reflux for 5 h. The reaction proceeded smoothly and after purification by column chromatography a yellow coloured product was obtained. Upon careful analysis of the data obtained by ^{1}H, ^{13}C and DEPT NMR spectra, the product obtained was confirmed as a tetracyclic pyrrolobenzoxazine derivative **9a** (Table 1, entry 1). The initial step of the reaction takes place through the Michael addition and undergoes the subsequent intramolecular cyclization and concurrent elimination of nitro functionality to give the pyrrolobenzoxazine **9a**. Inspired with the results obtained, we further proceeded for the screening of various Brønsted and Lewis acids. Accordingly when the reaction was carried out with *p*-TSA.H_2O, the reaction was completed in 8 h with 73% yield and

Table 1. Optimization of Reaction Conditions[a]

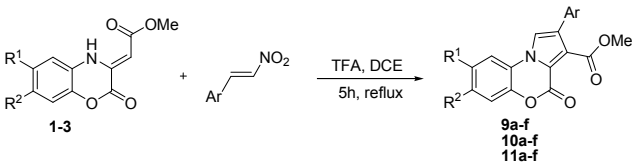


1 9a

Entry	Reagent	Solvent	Time (h)	Yield[b] (%)
1	TfOH	DCE	5	57
2	*p*-TSA.H_2O	DCE	8	73
3	TFA	DCE	5	82
4	$ZrCl_4$	DCE	5	68
5	$ZnCl_2$	DCE	5	61
6	$FeCl_3$	DCE	5	72
7	$SnCl_4$	DCE	5	64
8	BF_3.etherate	DCE	5	76
9	-	DCE	12	-
10	TFA	CH_2Cl_2	8	69
11	TFA	THF	5	74
12	TFA	CH_3CN	5	71
13	TFA	Toluene	5	76

[a]reactions were performed with **1** (0.5 mmol), 3,4-dimethoxy nitrostyrene (0.6 mmol) and reagent (0.75 mmol) in 4 mL of solvent. [b]yields of pure and isolated product **9a**.

Table 2. Substrate Scope[a]



Entry	R^1	R^2	Ar	Product	Yield[b] (%)
1	H	H	3,4-dimethoxy-phenyl	**9a**	82
2	H	H	4-methylphenyl	**9b**	77
3	H	H	4-chlorophenyl	**9c**	75
4	H	H	2-chlorophenyl	**9d**	71
5	H	H	1-naphthyl	**9e**	81
6	H	H	Phenyl	**9f**	84
7	H	Me	3,4-dimethoxy-phenyl	**10a**	76
8	H	Me	4-methylphenyl	**10b**	75
9	H	Me	4-chlorophenyl	**10c**	71
10	H	Me	2-chlorophenyl	**10d**	66
11	H	Me	1-naphthyl	**10e**	78
12	H	Me	Phenyl	**10f**	82
13	H	CO_2Me	3,4-dimethoxy-phenyl	**11a**	68
14	H	CO_2Me	4-methylphenyl	**11b**	66
15	H	CO_2Me	4-chlorophenyl	**11c**	62
16	H	CO_2Me	2-chlorophenyl	**11d**	56
17	H	CO_2Me	1-naphthyl	**11e**	71
18	H	CO_2Me	Phenyl	**11f**	75

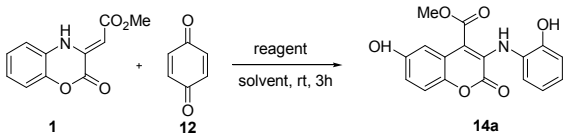
[a]reactions were performed with benzoxazinone derivative (**1-3,** 0.5 mmol), nitrostyrene derivative (0.6 mmol) and TFA (0.75 mmol) in 4 mL of DCE. [b]yields of pure and isolated products.

TFA afforded the corresponding product **9a** with 82% yield in 5 h. Further screening with various Lewis acids like $ZrCl_4$. $ZnCl_2$, $FeCl_3$, $SnCl_4$ and BF_3.etherate also afforded the product **9a** (Table 1, entries 4-8); nevertheless, the results revealed that they were less effective when compared to that of the trifluoroacetic acid. There was no formation of product in absence of the reagent (Table 1, entry 9). Subsequently, we have also tested various solvents such as toluene, CH_3CN, CH_2Cl_2, THF, However, DCE was found to be the better solvent for the current transformation (Table 1, entries 3 and 10-13). With the optimized conditions in hand, we further explored the scope and generality of the current protocol with diversely substituted 1,4-benzoxazinones **1-3** and nitrostyrene derivatives. Accordingly, a variety of aryl substituted nitroalkenes such as 3,4-dimethoxy, 4-methyl, 4-chloro, and 2-chloro substituted phenyl nitrostyrenes, were prepared and subjected to the Michael addition-cyclization strategy with vinylogous carbamate **1-3**. The desired products were obtained in high yields in all cases. The reaction of naphthyl and phenyl nitrostyrenes with 1,4-benzoxazinone **1** also underwent smoothly to afford the corresponding products in 81% and 84% yields, respectively. The 1,4-bezoxazinone **2** bearing methyl substituent also reacted well with the diversely substituted nitrostyrenes to furnish pyrrolobenzoxazines **10** in high yields (Table 2, entries 7-12). Under similar reaction conditions, when the benzoxazinone **3** bearing an ester (CO_2Me) moiety was reacted with the nitrostyrene derivatives, the corresponding products were obtained in slightly diminished yields when compared to those of other two benzoxazinone derivatives **1** and **2**. The reason might be the moderate nucleophilicity of **3**, due to presence of electron-withdrawing ester group. It is noteworthy to mention that the reactions of 1,4-benzoxazinones **1-3** with 2-chlorophenyl nitrostyrene furnished the products in lower yields (Table 2, entries 4, 10 and 16) when compared to that of the 4-chlorophenyl nitrostyrene, (Table 2, entries 3, 9 and 15) which may be attributed to the steric encumbrance of the ortho substituent.[11]

Further we focused on investigating the reactivity of these 1,4-benzoxazinone derivatives with other common Michael acceptors *p*-benzoquinone derivatives. Initially we started our investigation with the reaction of benzoxazinone **1** and *p*-benzoquinone (**12**). In a typical reaction procedure the 1,4-benzoxazinone **1** and *p*-benzoquinone were dissolved in 4 mL of CH_2Cl_2, then trifluoroacetic acid was added and allowed to stir at room temperature for 3 h. As the reaction proceeds the product started precipitating out of the reaction mixture. After completion of the reaction as shown by TLC, the reaction mixture was filtered to get coumarin derivative **14a** as yellow precipitate (Table 3, entry 1).

Encouraged with the results obtained, we have chosen the reaction of **1** and **12** as our model reaction and proceeded for the

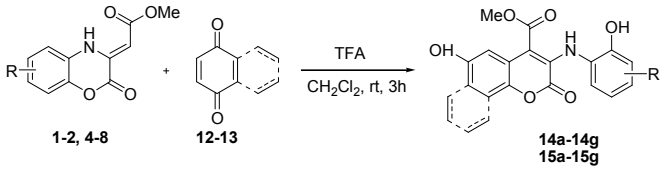
Table 3. Optimization of Reaction Conditions[a]

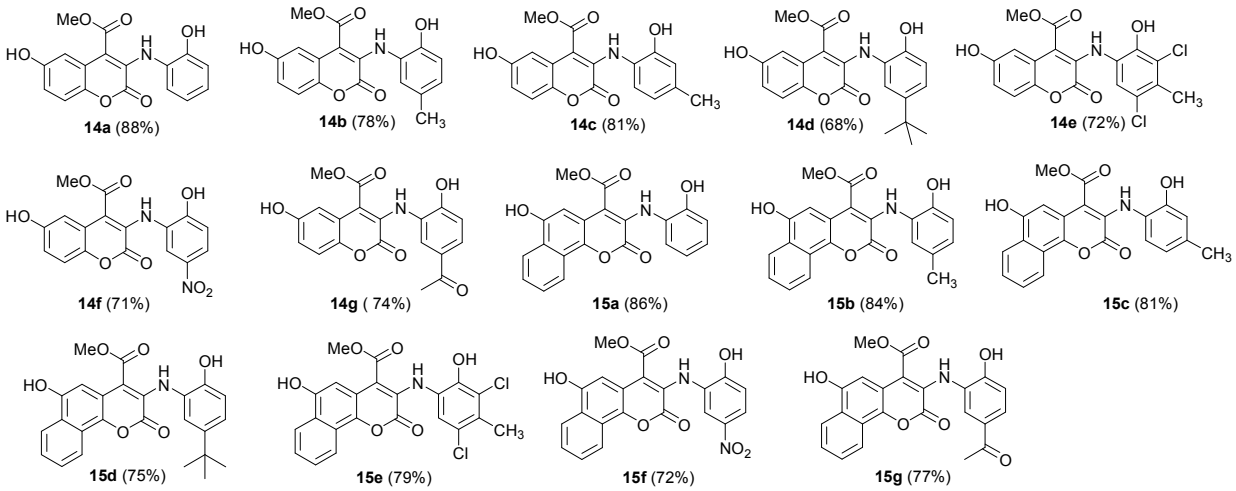


Entry	Reagent	Solvent	Yield[b] (%)
1	TFA	CH_2Cl_2	88
2	TfOH	CH_2Cl_2	-
3	*p*-TSA.H_2O	CH_2Cl_2	68
4	$ZrCl_4$	CH_2Cl_2	71
5	$FeCl_3$	CH_2Cl_2	76
6	$SnCl_4$	CH_2Cl_2	62
7	BF_3.etherate	CH_2Cl_2	79
8	TFA	DCE	85
9	TFA	Toluene	84
10	TFA	THF	80
11	TFA	CH_3CN	78

[a]reactions were performed with **1** (0.5 mmol), *p*-benzoquinone **12** (0.6 mmol) and TFA (0.6 mmol) in 4 mL of solvent. [b]yields of pure and isolated product **14a**.

Scheme 1. Substrate Scope[a]





[a]reactions were performed with **1** (0.5 mmol), *p*-benzoquinone (**12**) /naphthoquinone (**13**) (0.6 mmol) and TFA (0.6 mmol) in 4 mL of CH_2Cl_2.

optimization of reaction conditions. When the reaction was carried out with *p*-TSA.H_2O the desired product was obtained in 68% yield. However, no product was observed when the reaction was carried out with TfOH. Further on screening of various Lewis acids such as $ZrCl_4$, $FeCl_3$, $SnCl_4$, and BF_3.etherate afforded the desired product in moderate yields (Table 3, entries 1-7). Screening of various reagents disclosed that the trifluoroacetic acid affords the coumarin derivative **14a** in higher yield. Successive screening of various solvents like CH_2Cl_2, DCE, toluene, THF and CH_3CN, suggests that CH_2Cl_2 was the optimal solvent (Table 3, entries 1-7).

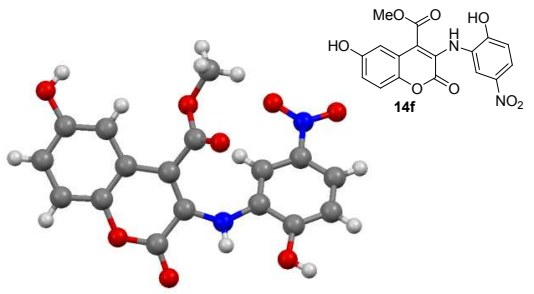


Figure 1. Single crystal X-ray structure of **14f**.

With the optimized protocol, we next set out to explore the substrate scope and limitation of the reaction. When the reaction of diversely substituted 1,4-benzoxazinone derivatives **1**-**2** and **4**-**8** was carried out with *p*-benzoquinone, all the reactions were proceeded smoothly to give the coumarin derivatives **14a**-**g** in excellent yields. The current methodology also tolerates a variety of functional groups. Further the reaction of 1,4-benzoxazinone derivatives **1**-**2** and **4**-**8** with 1,4-naphthoquinone (**13**) also delivered the corresponding coumarin derivatives **15a**-**g** in high yields. The single crystal X-ray analysis of the compound **14f**, corroborated the assigned structure to this coumarin derivative. Coumarin derivatives exhibit prominent biological activities,[12] and exclusively, the 3-amino substituted coumarins are found in the naturally occurring antibiotics like novobiocin,[13] chlorbiocin,[14] and coumermycin A1.[15] Moreover, the reported methods for synthesis of 3-aminocoumarin derivatives involves the multi-step procedures and expensive reagents.[16] Herein we reported a simple and efficient protocol for the synthesis of diversely substituted 3-amino coumarin derivatives from the readily available starting materials.

A possible mechanism for the formation of pyrrolobenzoxazine derivatives and 3-arylamino coumarin derivatives is depicted in scheme 2. In the presence of trifluoroacetic acid, initially the Michael addition of activated vinylogous carbamate takes place at the α-position of β-nitrostyrene, which further undergoes intra-molecular cyclization. The aromatization to pyrrole ring and concomitant exclusion of HNO and H_2O from species **A** results in the formation of pyrrolobenzoxazine derivative. In a similar fashion, the 1,4-benzoxazinone derivative undergoes Michael addition with *p*-benzoquinone in the presence of trifluoroacetic acid. The species **B** undergoues subsequent rearomatization and successive intra-molecular ring opening of oxazinone ring and cyclization to pyranone ring to generate 3-arylamino coumarin derivative.

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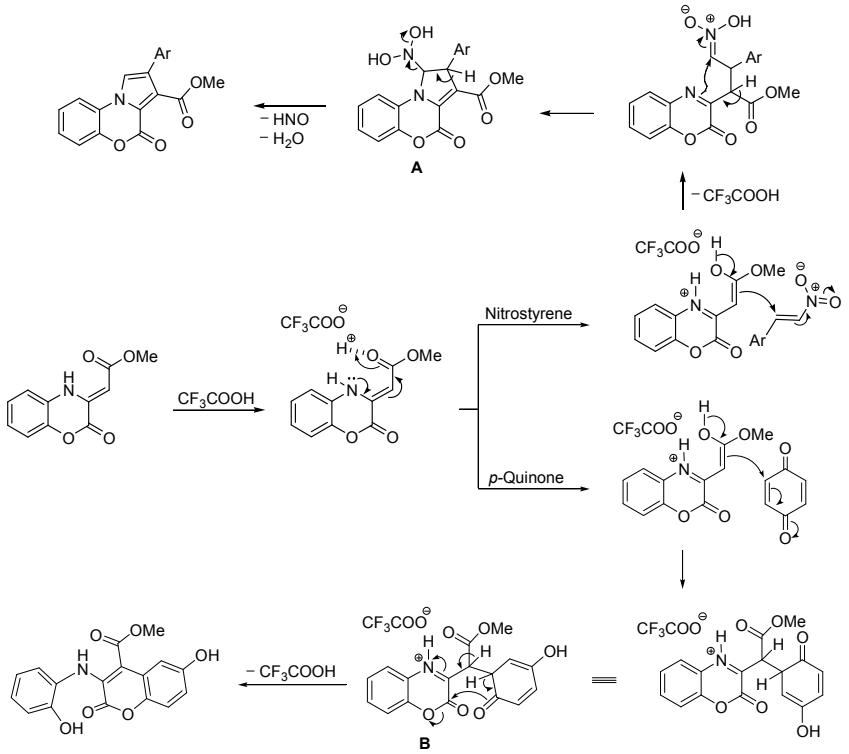
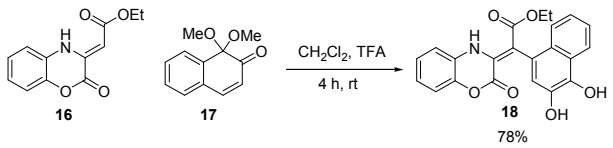
Scheme 2. A Plausible Mechanism for the Formation of Pyrrolobenzoxazine and 3-Arylamino Coumarin Derivatives.



In further investigation to evaluate the substrate scope, we have also carried out the reaction of 1,4-benzoxazinone **16** with *ortho*-naphthoquinone monoketal **17** in presence of TFA at room temperature for 4 h. The reaction underwent smoothly and after purification by column chromatography the product **18** was obtained in 78% yield. The structure of the product **18** was assigned by the collective information obtained from ^{1}H, ^{13}C NMR, DEPT, HRMS and single crystal X-ray analysis.

Scheme 3.



In conclusion, we have demonstrated a simple and efficient methodology for the synthesis of pyrrolobenzoxazine derivatives from the readily available starting materials and we have also developed a novel synthetic route for the synthesis of 3-amino coumarin derivatives from a new class of vinylogous carbamate. The current protocol obviates the purification by column chromatography and provides an easy access for the synthesis of diversely substituted 3-amino coumarin derivatives.

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§ Carried out crystallographic studies.

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Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/c000000x/

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