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2,3-Dichloro-5,6-Dicyano-1,4-Benzoquinone (DDQ)-Mediated Tandem Oxidative Coupling/Intramolecular Annulation/Dehydro-Aromatization for the Synthesis of Polysubstituted and Fused Pyridines

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Abstract: A DDQ-mediated tandem reaction of 1,3-diarylpropenes and β-enaminoesters/4-aminocoumarins is disclosed. It involves oxidative coupling, intramolecular annulation and dehydro-aromatization reaction, which provides an efficient and mild method for the synthesis of polysubstituted and fused pyridines under metal-free conditions.

Keywords: Annulation; DDQ; Oxidation; Pyridine; Tandem reaction

Introduction

Pyridine is the simplest and most fundamental *N*-heterocycle which widely exists as moiety in natural products, pharmaceuticals, and functional materials.[1] It could be used as ancillary ligand and organo-catalyst in homogeneous reactions.[2] As a consequence, considerable efforts have been devoted to developing efficient approaches for the preparation of pyridines. The traditional methods include the Hantzsch reaction,[3] Kröhnke pyridine synthesis,[4] Chichibabin reaction,[5] and Bohlmann-Rahtz reaction.[6] During the past few decades, a large number of alternative strategies for preparing pyridines have been successfully established such as metal-mediated cycloaddition,[7] metal-free multicomponent reaction,[8] transition-metal-catalyzed coupling of ketoxime acetates,[9] ring-expansion reaction,[10] and so on.[11] However, many of these reported methods suffer from the disadvantages such as harsh reaction conditions, functionalized starting materials, and use of transition-metal catalysts in the synthesis of polysubstituted pyridines. Due to the compelling attractions of the pyridine motif in several fields, it's still desirable to develop versatile and efficient synthetic routes for such a structure containing pyridine ring from readily available reactants under mild reaction conditions.

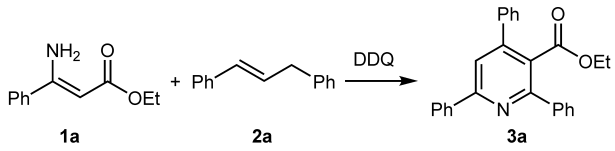
Push-pull enamine is a class of versatile synthetic building blocks and has been widely applied in the synthesis of *N*-heterocycles such as pyridines, pyrazoles, and chromones.[12] Recently, by utilizing push-pull enamines as the substrates, our group has developed some new methods for constructing diverse compounds via oxidative reaction in the presence of DDQ or I_2/benzoyl peroxide.[13] In aim of further expanding the application of enamines for the synthesis of *N*-heterocycles and our longstanding research interest in the oxidative reaction of 1,3-diarylpropenes,[13a,c–d,14] herein we wish to report a tandem reaction of β-enaminoesters and 1,3-diarylpropenes mediated by DDQ via oxidative coupling/intramolecular annulation/dehydro-aromatization, which gives the polysubstituted pyridines under metal-free condition. Moreover, this process is also applicable for 4-aminocoumarins, which generates the fused pyridocoumarins in moderate to good yields.

Results and Discussion

Initially, β-enaminoester **1a** and 1,3-diphenylpropene **2a** were chosen as model substrates. The reaction was

performed with 1.2 equiv. DDQ in $ClCH_2CH_2Cl$ (DCE) at room temperature. After 2 hours, extra 2.1 equiv. DDQ was added, and the reaction was continuously stirred for another 0.5 hour. Delightfully, the desired polysubstituted pyridine **3 a** was obtained, although the yield was only 29% (Table 1, entry 1).

Table 1. Optimization of the tandem reaction conditions.[a]



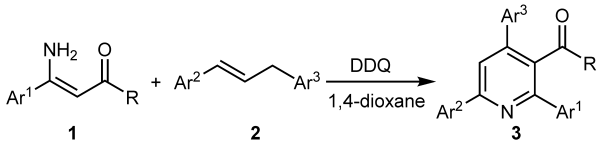
Entry	Solvent	DDQ (equiv)	Yield (%)[b]
1	DCE	1.2 + 2.1	29
2	1,4-dioxane	1.2 + 2.1	80
3	THF	1.2 + 2.1	58
4	$CHCl_3$	1.2 + 2.1	40
5	CH_2Cl_2	1.2 + 2.1	43
6	CH_3NO_2	1.2 + 2.1	53
7	CH_3CN	1.2 + 2.1	36
8	DMSO	1.2 + 2.1	34
9[c]	1,4-dioxane	1.2 + 2.1	56
10[d]	1,4-dioxane	1.2 + 2.1	63
11	1,4-dioxane	3.3	38
12	1,4-dioxane	1.2 + 2.0	70
13	1,4-dioxane	1.2 + 2.2	79

[a] **2 a** (0.24 mmol) and DDQ (0.24 mmol) in solvent (3 mL) were stirred for 10 mins at rt, **1 a** (0.2 mmol) was added and stirred for 2 hrs, then DDQ (0.42 mmol) was added and stirred for another 0.5 hr.
[b] Isolated yield.
[c] At 10 °C.
[d] At 40 °C.

Then, various solvents such as 1,4-dioxane, THF, $CHCl_3$, CH_2Cl_2, CH_3NO_2, CH_3CN, and DMSO were conducted (entries 2–8). It showed that 1,4-dioxane was the best option (entry 2). Increasing or decreasing the reaction temperature made the yield lower than that under best condition (entries 9–10). Finally, the dosage of DDQ was examined (entries 11–13). 3.3 equiv. DDQ was added in one portion to make the reaction complex, and only 38% yield was given (entry 11). Increasing the total dosage of DDQ to 3.4 equiv. could not promote the reaction yield (entry 13).

With the optimal reaction conditions in hand, various β-enaminoesters were investigated by new developed method (Table 2). β-Enaminoesters **1 b**–**1 s**, which contained electron-donating or electron-withdrawing group on the benzene ring, could react with 1,3-diphenylpropene **2 a** smoothly (entries 2–19). The corresponding polysubstituted pyridines **3 b**–**3 s** were obtained in 60–90% yields. No evidence of electron effect or hindrance effect was observed from the experimental data, regardless of their distinctive electronic property or position. β-Enaminoesters with

Table 2. The tandem reaction of β-enaminoesters and 1,3-diarylpropenes.[a]



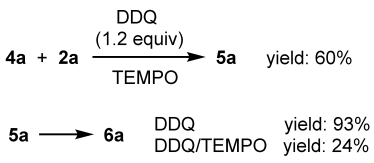
Entry	Ar^1, R, **1**	Ar^2, Ar^3, **2**	**3**	Yield (%)[b]
1	C_6H_5, OEt, **1 a**	C_6H_5, C_6H_5, **2 a**	**3 a**	80
2	2-FC_6H_4, OEt, **1 b**	**2 a**	**3 b**	73
3	3-FC_6H_4, OEt, **1 c**	**2 a**	**3 c**	78
4	4-FC_6H_4, OEt, **1 d**	**2 a**	**3 d**	76
5	2-ClC_6H_4, OEt, **1 e**	**2 a**	**3 e**	90
6	3-ClC_6H_4, OEt, **1 f**	**2 a**	**3 f**	71
7	4-ClC_6H_4, OEt, **1 g**	**2 a**	**3 g**	77
8	3-BrC_6H_4, OEt, **1 h**	**2 a**	**3 h**	83
9	4-BrC_6H_4, OEt, **1 i**	**2 a**	**3 i**	83
10	4-IC_6H_4, OEt, **1 j**	**2 a**	**3 j**	60
11	2-$CH_3C_6H_4$, OEt, **1 k**	**2 a**	**3 k**	75
12	3-$CH_3C_6H_4$, OEt, **1 l**	**2 a**	**3 l**	93
13	4-$CH_3C_6H_4$, OEt, **1 m**	**2 a**	**3 m**	87
14	2-$CH_3OC_6H_4$, OEt, **1 n**	**2 a**	**3 n**	70
15	3-$CH_3OC_6H_4$, OEt, **1 o**	**2 a**	**3 o**	83
16	4-$CH_3OC_6H_4$, OEt, **1 p**	**2 a**	**3 p**	76
17	4-$CF_3C_6H_4$, OEt, **1 q**	**2 a**	**3 q**	85
18	3,5-$Cl_2C_6H_3$, OEt, **1 r**	**2 a**	**3 r**	85
19	3,4-$F_2C_6H_3$, OEt, **1 s**	**2 a**	**3 s**	75
20	1-naphthyl, OEt, **1 t**	**2 a**	**3 t**	78
21	2-thienyl, OEt, **1 u**	**2 a**	**3 u**	83
22	2-furyl, OEt, **1 v**	**2 a**	**3 v**	46
23	C_6H_5, OCH_3, **1 w**	**2 a**	**3 w**	83
24	C_6H_5, OBu-*t*, **1 x**	**2 a**	**3 x**	82
25	C_6H_5, OBn, **1 y**	**2 a**	**3 y**	79
26	CH_3, OEt, **1 z**	**2 a**	–	–[c]
27	4-$CH_3C_6H_4$, Ph, **1 aa**	**2 a**	**3 z**	30
28	C_6H_5, CH_3, **1 bb**	**2 a**	–	–[c]
29	**1 a**	C_6H_5, 4-ClC_6H_4, **2 b**	**3 aa**	74[d]
30	**1 a**	C_6H_5, 4-$CH_3OC_6H_4$, **2 c**	**3 bb**	70[d]

[a] **2** (0.24 mmol) and DDQ (0.24 mmol) in 1,4-dioxane (3 mL) were stirred for 10 mins at rt, **1** (0.2 mmol) was added and stirred for 2 hrs, then DDQ (0.42 mmol) was added and stirred for another 0.5 hr.
[b] Isolated yield.
[c] The desired product could not be obtained.
[d] Both α- and γ- positional isomeric products were obtained. According to the NMR, the ratios of isomers of **3 aa** and **3 bb** are 9:11 and 3:2, respectively.

heteroaryl substituents **1u**–**1v** were also suitable for the reaction conditions (entries 21–22). β-Enaminoesters with different alkoxylcarbonyl groups **1w**–**1y** were surveyed (entries 23–25). The expected products were given in 79–83% yields, which indicated that the property of the examined alkoxylcarbonyl groups had no significant effect on the reaction. The desired product was not obtained when β-enaminoester **1z** was used as the substrate (entry 26). β-Enaminone **1aa** could react with 1,3-diphenylpropene with only 30% yield, while **1bb** could not (entries 27–28). 1,3-Diarylpropenes **2b**–**2c** with a mixture of α- and γ- isomers were prepared and surveyed in the reaction (entries 29-30). According to the ^{1}H NMR, the products obtained were also a mixture of α- and γ- isomers. However, the ratios between isomers were different from those of the corresponding 1,3-diarylpropenes, which indicated that the allylic radicals or cations generated in the reaction process.

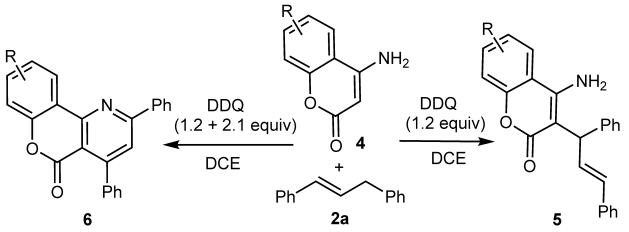
In consideration of 4-aminocoumarins have similar structure unit to β-enaminoesters, we turned our attention to the reaction of 4-aminocoumarins and 1,3-diphenylpropene for the construction of coumarins fused with pyridines. Pyridocoumarins have become the research focus in recent years because these privileged scaffolds exhibit a broad spectrum of pharmacological activities and remarkable photochemical properties.[15] Based on the previous reaction conditions, we found that DCE was the best solvent instead of 1,4-dioxane (Table 3, entries 1–2). The coupling product **5a** could be obtained when the dosage of DDQ was 1.2 equiv. The pyridocoumarin product **6a** was obtained when extra 2.1 equiv. DDQ was added to the reaction mixture. 4-Aminocoumarins **4b**–**4j** with halo, methyl or methoxyl substituent on the benzene ring could react with 1,3-phenylpropene **2a** successfully to give the corresponding products **5b**–**5j** and **6b**–**6j** under the different dosage of DDQ, respectively (entries 3–11).

To explore the tandem reaction mechanism, some control experiments were surveyed (Scheme 1). The yield of coupling product **5a** was decreased to 60% when 2 equiv. radical scavenger TEMPO was applied to the reaction mixture of **4** and **2a**. The cyclization of coupling product **5a** was examined in DCE in the presence of 2.2 equiv. DDQ, and the cyclization product **6a** was obtained in 93% yield within 1 hour. The yield was sharply decreased to 24% when 2 equiv.



Scheme 1. Control Experiments.

Table 3. The reaction of 4-aminocoumarins and 1,3-diphenylpropene.



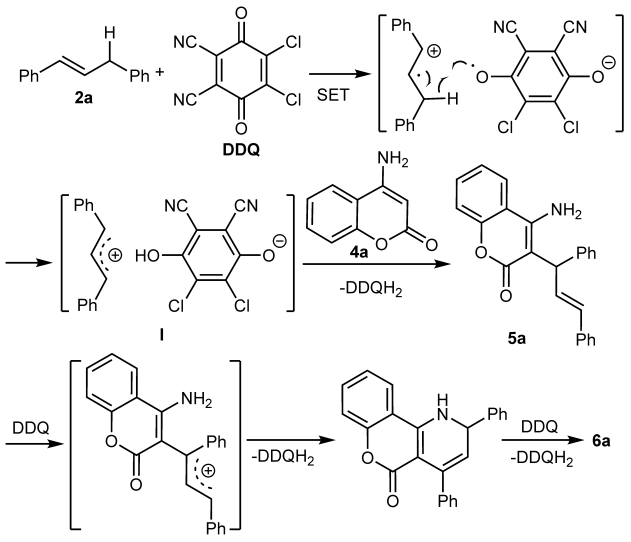
Entry	R, **4**	**5**,[a] Yield (%)[b]	**6**,[c] Yield (%)[b]
1	H, **4a**	**5a**, 90	**6a**, 84[d]
2	H, **4a**	**5a**, 98	**6a**, 90
3	6-F, **4b**	**5b**, 84	**6b**, 71
4	7-Cl, **4c**	**5c**, 94	**6c**, 76
5	6-Br, **4d**	**5d**, 93	**6d**, 85
6	7-Br, **4e**	**5e**, 92	**6e**, 85
7	6-CH_3, **4f**	**5f**, 92	**6f**, 70
8	7-CH_3, **4g**	**5g**, 88	**6g**, 79
9	5-CH_3O, **4h**	**5h**, 87	**6h**, 72
10	6-CH_3O, **4i**	**5i**, 85	**6i**, 70
11	7-CH_3O, **4j**	**5j**, 82	**6j**, 60

[a] **2a** (0.24 mmol) and DDQ (0.24 mmol) in DCE (3 mL) were stirred for 10 mins at rt, **4** (0.2 mmol) was added and stirred for 4 hrs.
[b] Isolated yield.
[c] **2a** (0.24 mmol) and DDQ (0.24 mmol) in DCE (3 mL) were stirred for 10 mins at rt, **4** (0.2 mmol) was added and stirred for 4 hrs, then DDQ (0.42 mmol) was added and stirred for another 2 hrs.
[d] 1,4-Dioxane as solvent.

TEMPO was added to the system. These results indicated that a single-electron-transfer (SET) was involved in the reaction. Based on above experiment results and the literature,[16] a possible mechanism was proposed in Scheme 2. Initially, 1,3-diphenylpropene **2a** reacts with DDQ to give the ion pair **I** through hydrogen abstraction after a single-electron-transfer from allylic double bond to DDQ. Subsequently, nucleophilic attack of **4a** takes place to allylic cation of the ion pair **I** to give the intermediate **5a**. Similarly, **5a** could react with DDQ to give the allylic cation, followed by the intramolecular nucleophilic attack of amino group and the dehydro-aromatization to produce the final product **6a**.

Conclusion

In conclusion, we have developed a tandem reaction of 1,3-diarylpropenes and β-enaminoesters/4-aminocoumarins. The procedure involves oxidative coupling/intramolecular annulation/dehydro-aromatization reaction. It provides an efficient and mild method for the



Scheme 2. Possible Mechanism.

synthesis of polysubstituted and fused pyridines under metal-free conditions.

Experimental Section

General information. Column chromatography was carried out on silica gel (200–300 mesh). ^{1}H NMR spectra were recorded on a 500 MHz spectrometer (Bruker AVANCE III 500 MHz nuclear magnetic resonance Spectrometer) or 600 MHz spectrometer (Bruker Ascend™ 600 MHz superconducting nuclear magnetic resonance spectrometer). ^{13}C NMR spectra were recorded on a 125 MHz spectrometer (Bruker AVANCE III 500 MHz nuclear magnetic resonance spectrometer) or 150 MHz spectrometer (Bruker Ascend™ 600 MHz superconducting nuclear magnetic resonance spectrometer). Chemical shifts were reported in parts per million (δ) relative to the internal standard TMS (0 ppm) for $CDCl_3$ or DMSO. The coupling constants, *J*, were reported in Hertz (Hz). High-resolution mass spectra (HRMS) were recorded on ESI-TOF (Agilent 6210 TOF LC/MS). Melting points were measured using a SGW X-4. The reagents were purchased from commercial chemical reagent companies and used without further purification unless otherwise stated. β-enaminoesters **1**,[17] 1,3-diarylpropenes **2**,[18] and 4-aminocoumarins **4**[19] were prepared according to the literatures.

General procedure for the synthesis of 3: To a solution of 1,3-diarylpropene **2** (0.24 mmol) in 1,4-dioxane (3 mL), DDQ (0.24 mmol, 0.055 g) was added. The mixture was stirred for 10 mins at room temperature, β-enaminoester **1** (0.2 mmol) was added and stirred for 2 hrs. Then extra DDQ (0.42 mmol, 0.095 g) was added and the mixture was stirred for another 0.5 hr. After the completion of the reaction, the solvent was concentrated under reduced pressure. Purification was done by column chromatography on silica gel (200–300 mesh) with petroleum ether and ethyl acetate (20:1–30:1) as the eluent to give the pure product **3**.

General procedure for the synthesis of 5: To a solution of 1,3-diphenylpropene **2** (0.24 mmol, 0.047 g) in $ClCH_2CH_2Cl$ (3 mL), DDQ (0.24 mmol, 0.055 g) was added. The mixture was stirred for 10 mins at room temperature, 4-aminocoumarin **4** (0.2 mmol) was added and stirred for 4 hrs. After the completion of the reaction, the solvent was concentrated under reduced pressure. Purification was done by column chromatography on silica gel (200–300 mesh) with petroleum ether and ethyl acetate (3:1–6:1) as the eluent to give the pure product **5**.

General procedure for the synthesis of 6: To a solution of 1,3-diphenylpropene **2** (0.24 mmol, 0.047 g) in $ClCH_2CH_2Cl$ (3 mL), DDQ (0.24 mmol, 0.055 g) was added. The mixture was stirred for 10 mins at room temperature, 4-aminocoumarin **4** (0.2 mmol) was added and stirred for 4 hrs. Then extra DDQ (0.42 mmol, 0.095 g) was added and the mixture was stirred for another 2 hrs. After the completion of the reaction, the solvent was concentrated under reduced pressure. Purification was done by column chromatography on silica gel (200–300 mesh) with petroleum ether and ethyl acetate (10:1–20:1) as the eluent to give the pure product **6**.

Acknowledgements

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FULL PAPER

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D. Cheng*, Z. Deng, X. Yan, M. Wang, X. Xu*, J. Yan*