# A Novel and Facile Method for the Synthesis of 2,3-Disubstituted Quinolines by a Three-Component Coupling Reaction

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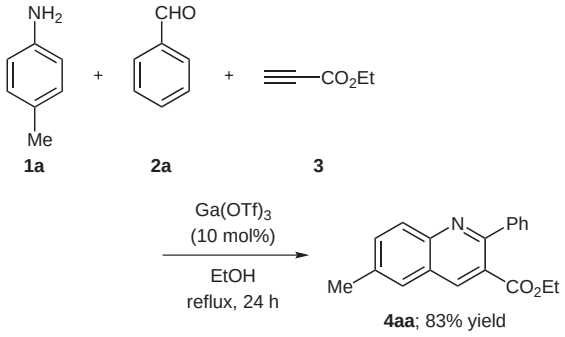
**Abstract:** A Lewis acid effectively catalyzed the three-component coupling reaction of an aromatic amine and aldehyde with ethyl propiolate, and the 2,3-disubstituted quinoline was regioselectively obtained in a good yield (up to 83% GC yield).

**Key words:** Lewis acid, quinolines, three-component coupling reaction, regioselectively

In 2001, Balalaie et al. reported that the three-component coupling reaction of amine, aldehyde, and ethyl propiolate was mediated by microwave irradiation and N-substituted 1,4-dihydropyridines (Hantzsch pyridines) were obtained in good yields.[1] However, it required expensive microwave apparatus and severe reaction conditions. So, we tried to perform this reaction using catalytic amount of Lewis acid. Then, we carried out the reaction of *p*-toluidine (**1a**; 0.5 mmol), benzaldehyde (**2a**; 0.54 mmol), and ethyl propiolate (**3**; 0.6 mmol) using $Ga(OTf)_3$ (10 mol%) at reflux in EtOH (5 mL) for 24 hours. Contrary to our expectations, the 2,3-disubstituted quinoline **4aa** bearing an ester group at the 3-position was obtained as a major product (83% yield) together with a small amount of the 1,4-dihydropyridines (<10%; Scheme 1). We are surprised at and interested in this reaction, which would be a useful method for the synthesis of substituted quinolines.




**Scheme 1**

Substituted quinolines play important roles in medicinal chemistry because quinoline-containing natural products have interesting biological activities and are widely used as antimalarials, antibacterials, psychopharmacological drugs, and so on.[2] Furthermore, these compounds are versatile synthons for the preparation of molecules having electronic and photonic characteristics.[3] Because of their importance, numerous methods have been developed for the construction of these substituted quinolines; for example, Friedländer reaction, Skraup reaction and Combes reaction.[4] Although these methods are convenient for obtaining the polysubstituted quinolines, the synthesis of 2-aryl-3-carboalkoxy quinoline has rarely been reported using these and other methods;[5] these methods would not have provided enough quinoline libraries. Therefore, a simple, expeditious and reasonable method is still required.

In this study, we have developed a novel and facile method for the synthesis of several 2,3-disubstituted quinolines bearing an ester group at the 3-position using the three-component coupling reaction of an amine, an aldehyde, and ethyl propiolate in the presence of a catalytic amount of Lewis acids.

We first investigated several solvents for the reaction of **1a** and **2a** with **3** using a catalytic amount of $Ga(OTf)_3$ (10 mol%; Table 1). When we used other alcoholic solvents, such as MeOH and *n*-PrOH, the yields of the quinoline **4aa** were lower than that with EtOH (entries 2 and 3). Toluene,[6] 1,2-dichloroethane and THF did not seem to be appropriate solvents, as the yields were unsatisfactory (entries 4–6). As a result, EtOH was revealed to be the solvent of choice.[7]

**Table 1** Effect of Solvent in the Reaction of *p*-Toluidine (**1a**), Benzaldehyde (**2a**) with Ethyl Propiolate (**3**) Using $Ga(OTf)_3$ (10 mol%)[a]

| Entry | Solvent | Yield (%)[b] |
|---|---|---|
| 1 | EtOH | 83 |
| 2 | MeOH | 56 |
| 3 | *n*-PrOH | 36 |
| 4 | Toluene | 37 |
| 5 | 1,2-dichloroethane | trace |
| 6 | THF | trace |

[a] Reaction conditions: $Ga(OTf)_3$ (0.05 mmol), **1a** (0.5 mmol), **2a** (0.54 mmol), **3** (0.6 mmol), solvent (5 mL), reflux for 24 h.
[b] GC yield.

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We next examined various Lewis acids in this reaction and these results are summarized in Table 2.[8] The reaction was smoothly mediated by several Lewis acids but hardly proceeded in the absence of Lewis acid (entry 1). $Ga(OTf)_3$ and $Sc(OTf)_3$ were the most effective catalysts that regioselectively produced the desired quinoline **4aa** in high yields without contamination of the regioisomers (entries 2 and 3). $In(OTf)_3$ and $Yb(OTf)_3$ also could catalyze the reaction and **4aa** was obtained in moderate yields (entries 4 and 5). The use of $BF_3{\cdot}OEt_2$, $AlCl_3$ and $InBr_3$ as a catalyst resulted in lower yields. The unreacted starting compounds were recovered or 1,4-dihydropyridines were produced (5–10%; entries 6–8). $TiCl_2(O\textit{i}\text{-}Pr)_2$ worked as effectively as $Sc(OTf)_3$. In this case, the yield of **4aa** was 77% (entry 9).

**Table 2** Effect of Lewis Acid in the Reaction of *p*-Toluidine (**1a**), Benzaldehyde (**2a**) with Ethyl Propiolate (**3**)[a]

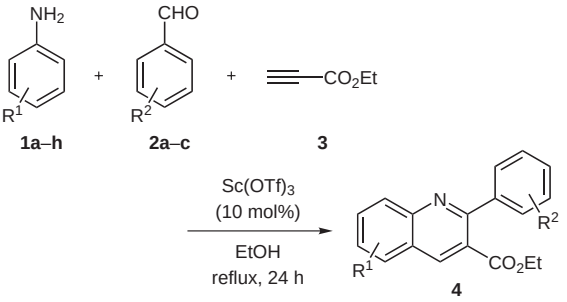
| Entry | Lewis Acid | Yield (%)[b] |
|---|---|---|
| 1 | none | 0 |
| 2 | $Ga(OTf)_3$ | 83 |
| 3 | $Sc(OTf)_3$ | 80 |
| 4 | $In(OTf)_3$ | 69 |
| 5 | $Yb(OTf)_3$ | 63 |
| 6 | $BF_3{\cdot}OEt_2$ | 55 |
| 7 | $AlCl_3$ | 56 |
| 8 | $InBr_3$ | 36 |
| 9 | $TiCl_2(O\textit{i}\text{-}Pr)_2$ | 77 |

[a] Reaction conditions: Lewis acid (0.05 mmol), **1a** (0.5 mmol), **2a** (0.54 mmol), **3** (0.6 mmol), EtOH (5 mL), reflux for 24 h.
[b] GC yield.

We then carried out the reaction of several amines **1a**–**h**, aldehydes **2a**–**c** with ethyl propiolate (**3**) using $Sc(OTf)_3$ or $Ga(OTf)_3$ (10 mol%) under the optimal conditions and these results are summarized in Table 3.[9] The reaction of *p*-ethylaniline (**1b**) and *p*-isopropylaniline (**1c**) smoothly proceeded to give the corresponding quinolines **4ba** and **4ca** in good yields, respectively (entries 3 and 4). We examined the substituent effect of the *para* position of aniline on the product yield, but no remarkable difference between electron-donating and electron-withdrawing groups was observed with respect to the yields (entries 5–7). The reaction of *o*-toluidine (**1g**) and *m*-toluidine (**1h**) gave the quinolines **4ga** and **4ha**[10] in low and moderate yields, respectively (entries 8–10). We investigated the reaction of *p*-chlorobenzaldehyde (**2b**) and *p*-fluorobenzaldehyde (**2c**) and obtained the desired quinolines in moderate yields (entries 11–13).

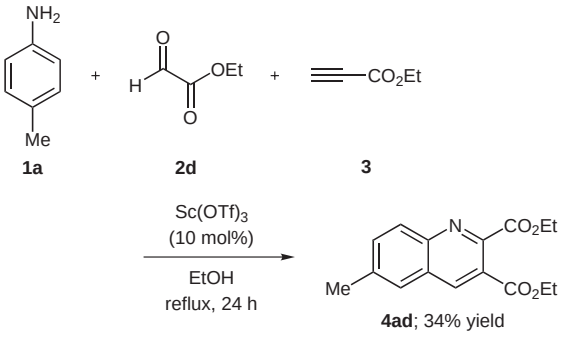
When we performed the reaction using ethyl glyoxalate (**2d**) instead of aromatic aldehyde under the same conditions (Scheme 2), we obtained the 2,3-dicarboethoxy quinoline **4ad** in moderate yield (34%).[11]

**Table 3** 2,3-Disubstituted Quinoline Synthesis by the Three-Component Coupling Reaction of Several Substrates Using $Sc(OTf)_3$ under Optimal Conditions[a]




| Entry | $R^1$ | $R^2$ | Product | Yield (%)[b] |
|---|---|---|---|---|
| 1 | *p*-Me (**1a**) | H (**2a**) | **4aa** | 80 |
| 2[c] | *p*-Me (**1a**) | H (**2a**) | **4aa** | 83 |
| 3[d] | *p*-Et (**1b**) | H (**2a**) | **4ba** | 70 (64)[e] |
| 4[d] | *p*-*i*-Pr (**1c**) | H (**2a**) | **4ca** | 79 (75)[e] |
| 5 | *p*-MeO (**1d**) | H (**2a**) | **4da** | 33 |
| 6 | H (**1e**) | H (**2a**) | **4ea** | 28 |
| 7 | *p*-Cl (**1f**) | H (**2a**) | **4fa** | 21 |
| 8 | *o*-Me (**1g**) | H (**2a**) | **4ga** | 15 |
| 9[d] | *m*-Me (**1h**) | H (**2a**) | **4ha** | 42 (40)[e,f] |
| 10[c] | *m*-Me (**1h**) | H (**2a**) | **4ha** | 34[f] |
| 11[d] | *p*-Me (**1a**) | *p*-Cl (**2b**) | **4ab** | 53[g] |
| 12 | H (**1e**) | *p*-Cl (**2b**) | **4eb** | 33 |
| 13 | H (**1e**) | *p*-F (**2c**) | **4ec** | 32 |

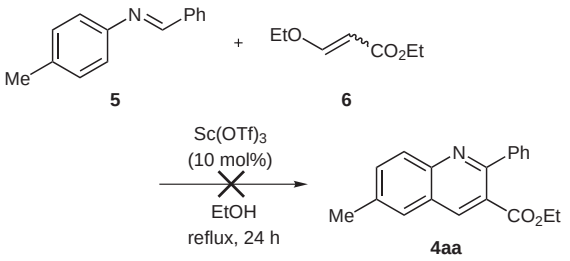
[a] Reaction conditions: $Sc(OTf)_3$ (0.05 mmol), **1a** (0.5 mmol), **2a** (0.54 mmol), **3** (0.6 mmol), EtOH (5 mL), reflux for 24 h.
[b] GC yield.
[c] $Ga(OTf)_3$ was used as a catalyst instead of $Sc(OTf)_3$.
[d] Double scale.
[e] Isolated yield is given in parentheses.
[f] The ratio of regioisomers (5-methyl/7-methyl) was not determined.
[g] Isolated yield.




**Scheme 2**

Ethyl 3-ethoxyacrylate (**6**), which could result from the 1,4-addition of ethanol to ethyl propiolate, might be involved in the reaction.[12] It would react with the imine to produce quinoline.[4a,13] So, we separately performed the reaction of ethyl 3-ethoxyacrylate (**6**) with imine **5** [or *p*-toluidine (**1a**) and benzaldehyde (**2a**)]. However, this reaction hardly gave the quinoline under the same conditions, and the starting imine **5** was recovered (Scheme 3).[14]

The reaction might proceed with the Diels–Alder-type cycloaddition of the imine with ethyl propiolate (**3**), although the regioselectivity of the product can not be explained.




**Scheme 3**

In conclusion, we have developed a useful method for the synthesis of the 2,3-disubstituted quinolines bearing an ester group at the 3-position by the three-component coupling reaction of an amine, aldehyde, and ethyl propiolate using a catalytic amount of $Sc(OTf)_3$. Further studies on the reaction mechanism are now in progress.

## Acknowledgment

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(6) When this reaction was carried out at reflux in toluene, the major product was the 1,4-dihydropyridines. The investigation regarding the synthesis of 1,4-dihydropyridines will be reported elsewhere in due course.

(7) We performed this reaction using TfOH (10 mol%) at reflux in EtOH, and obtained the quinoline **4aa** in 50% yield..

(8) **General Procedure**: To the EtOH (5 mL) solution of **1a** (53.9 mg, 0.5 mmol), **2a** (55 μL, 0.54 mmol) and Lewis acid (0.05 mmol, 10 mol%) was added **3** (61 μL, 0.6 mmol) using a microsyringe and then the mixture was refluxed for 24 h. The reaction was quenched with sat. aq $NaHCO_3$ and the mixture was extracted with EtOAc. The combined organic layers were dried over $MgSO_4$. The organic layer was filtered and concentrated under reduced pressure. The yield of **4aa** was determined by GC using biphenyl as the internal standard. The quinoline **4aa** was purified by preparative TLC ($SiO_2$; hexane–EtOAc, 7:1) and/or recycling preparative HPLC (GPC column, $CHCl_3$ as an eluent) and was fully characterized.
**Ethyl 6-Methyl-2-phenylquinoline-3-carboxylate (4aa)**: $^1$H NMR (300 MHz, $CDCl_3$): δ = 1.06 (t, *J* = 6.9 Hz, 3 H), 2.55 (s, 3 H), 4.17 (q, *J* = 6.9 Hz, 2 H), 7.44 (m, 3 H), 7.62 (m, 4 H), 8.07 (d, *J* = 9.0 Hz, 1 H), 8.55 (s, 1 H). $^{13}$C NMR ($CDCl_3$): δ = 13.6, 21.5, 61.4, 125.4, 125.8, 126.8, 128.1, 128.3, 128.4, 129.1, 133.8, 137.2, 138.3, 140.8, 146.9, 157.2, 168.1.

(9) The reaction with imine **5**, which was prepared from **1a** and **2a**, using $Sc(OTf)_3$ yielded the quinoline **4aa** in 60% yield.

(10) CCDC 650434 contains the supplementary crystallographic data for compound **4ha**. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: +44(1223)336033.

(11) **Typical Procedure (Scheme 2)**: To the EtOH (7 mL) solution of **1a** (107.2 mg, 1.0 mmol), **2d** (110 μL, 1.1 mmol), which was distilled from $P_2O_5$ before use, and $Sc(OTf)_3$ (49.2 mg, 0.10 mmol) was added **3** (122 μL, 1.2 mmol) using a microsyringe and then the mixture was refluxed for 24 h.

The reaction was quenched with sat. aq $NaHCO_3$ and the mixture was extracted with EtOAc. The combined organic layers were dried over $MgSO_4$. This organic layer was filtered and concentrated under reduced pressure. The residue was purified by short column chromatography (hexane–EtOAc, 6:1) and recycling preparative HPLC (GPC column, $CHCl_3$ as an eluent) to give the pure **4ad** in 34% yield.

**Diethyl 6-Methylquinoline-2,3-dicarboxylate (4ad)**: $^1$H NMR (300 MHz, $CDCl_3$): δ = 1.45 (m, 6 H), 2.57 (s, 3 H), 4.43 (q, *J* = 7.0 Hz, 2 H), 4.52 (q, *J* = 7.0 Hz, 2 H), 7.67 (m, 2 H), 8.09 (d, *J* = 5.8 Hz, 1 H), 8.67 (s, 1 H). $^{13}$C NMR ($CDCl_3$): δ = 14.1, 21.6, 61.4, 62.2, 122.5, 127.1, 127.3, 129.4, 134.6, 138.7, 138.9, 146.6, 147.0, 165.3, 166.9.

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