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ONE-STEP SYNTHESIS OF ETHYL QUINALDATES BY LEWIS ACID CATALYZED THREE-COMPONENT COUPLING REACTION OF AROMATIC AMINES, ALIPHATIC ALDEHYDES AND ETHYL GLYOXYLATE

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Abstract – A convenient, efficient and simple one-pot method for the synthesis of quinaldates was developed by three-component coupling reaction of an arylamine (1), ethyl glyoxylate and an aliphatic aldehyde (2) in the presence of Lewis acid catalyst. The reaction proceeded most effectively using Yb(OTf)₃ as a catalyst.

INTRODUCTION

2-Quinolinecarboxylic acid (quinaldic acid) and its derivatives form as tryptophan metabolites,^{1,2} and the quinaldyl moiety exist widely in natural products or synthetic biologically active compounds, such as thiostrepton² and enzyme inhibitors.³ Quinaldates are also used as chelating ligands, which are important for development of molecular catalysts⁴ or designing functional materials such as precipitating agents.⁵ Several synthetic methods of quinaldic acid are known, however, preparation of substituted quinaldates is scarcely reported.⁶ We have paid an attention to facile method for substituted quinaldates toward development of biologically active compounds or functional materials. Recently we have reported a synthesis of substituted quinolines by three-component coupling reaction of anilines, aromatic aldehydes and aliphatic aldehydes using iridium catalyst.⁷ The method is applicable to the synthesis of quinaldates by replacing aromatic aldehydes with ethyl glyoxylate (EG), and we examined the reaction using several Lewis acids and metal catalysts. As reported in this paper we have found that Lewis acids catalyze the three-component coupling reaction effectively, and ytterbium triflate is active catalyst for quinaldate synthesis.

RESULTS AND DISCUSSION

The results of several Lewis acid catalyzed synthesis of the quinaldate (**3a**) from *p*-anisidine (**1a**), ethyl glyoxylate (EG) and *n*-valeraldehyde (**2a**) are listed in Table 1. At first the reaction of **1a**, **2a** with EG was carried out as follows. The mixture of **1a** (1.0 mmol) and EG (1.2 mmol) was stirred at room temperature in DMSO. To the mixture 1.0 mol% of SnCl₂ and **2a** (1.1 mmol) were added, and the resulting mixture was heated at 90 °C under oxygen for 16 h to give ethyl 6-methoxy-3-propylquinaldate (**3a**) in 88% yield after chromatographic purification. Similarly reaction using ZnCl₂ and TiCl₄ catalysts gave **3a** in high yields. Instead of ordinary metal chloride Lewis acids, lanthanoid triflates are also effective catalysts. Among them, Yb(OTf)₃ catalyzed the reaction most actively to give **3a** in 94% yield. When 0.5 mol% of Yb(OTf)₃ was used, the product was obtained in 87% yield. However, 5 mol% of the catalyst was employed, the yield was decreased in 83% yield.

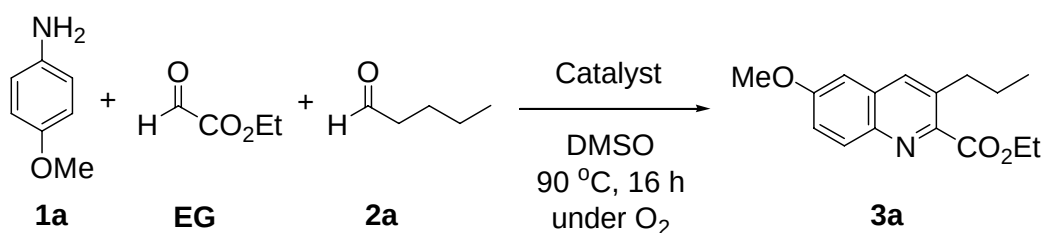


Table 1 Effect of catalysts on three-component coupling reaction

Entry	Catalyst		Yield / % ^{a)}
1	SnCl ₂	(1.0 mol%)	88
2	ZnCl ₂	(1.0 mol%)	88
3	TiCl ₄	(1.0 mol%)	81
4	La(OTf) ₃	(1.0 mol%)	88
5	Yb(OTf) ₃	(5.0 mol%)	83
6	Yb(OTf) ₃	(1.0 mol%)	94
7	Yb(OTf) ₃	(0.5 mol%)	87

a) Isolated yield based on arylamine (**1a**).

Various substituted quinaldates were obtained in good yields using ytterbium-catalyzed three-component coupling reaction in a one pot (Table 2). The reactions using *p*-methoxy- or *p*-methylaniline were carried out similarly as in the reaction in Table 1, and the reactions proceeded smoothly to give the products in good yields except for in the case of acetaldehyde (Entry 2) as an aliphatic aldehyde. However, in the case of arylamines with electron-withdrawing substituent such as *p*-Br, *p*-F and *p*-CO₂Me, the results were unsatisfactory. The reaction is considered to proceed involving imine formation from **1** and EG, and in the case of electron deficient anilines the formation of corresponding imines was slow. Therefore

preformation of the imines at higher temperature (120 °C) before addition of the catalyst and aliphatic aldehyde **2** is preferable.⁸

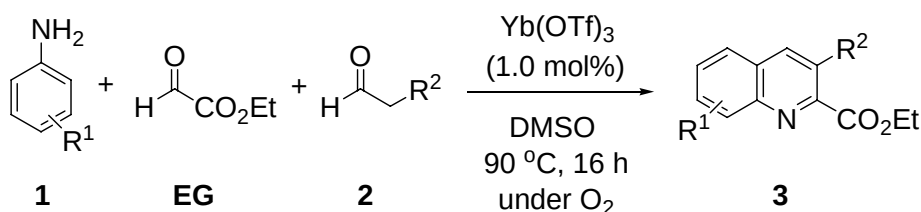
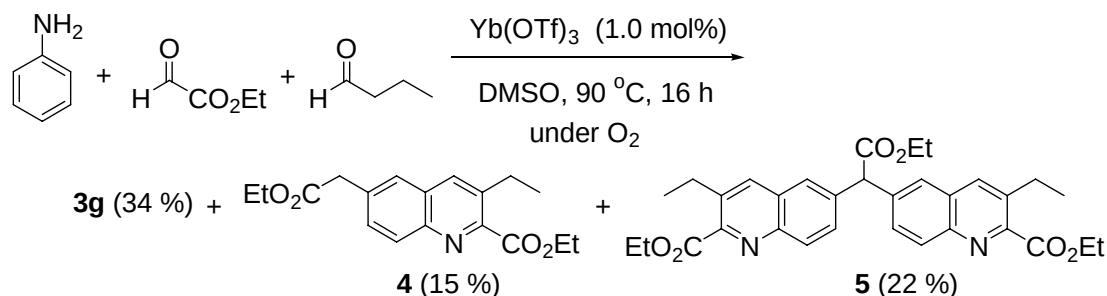


Table 2 Synthesis of quinaldates by ytterbium-catalyzed three-component coupling reaction

Entry	R ¹	R ²	3 (Yield / %) ^{a)}	Entry	R ¹	R ²	3 (Yield / %) ^{a)}
1	<i>p</i> -OMe	<i>n</i> -Pr	3a (94)	7	H	Et	3g (34)
2	<i>p</i> -OMe	H	3b (45)	8	<i>o</i> -OMe	Et	3h (41)
3	<i>p</i> -OMe	Me	3c (84)	9	<i>p</i> -Me	Et	3i (90)
4	<i>p</i> -OMe	Et	3d (99)	10 ^{b)}	<i>p</i> -Br	Et	3j (90)
5	<i>p</i> -OMe	<i>i</i> -Pr	3e (92)	11 ^{b)}	<i>p</i> -F	Et	3k (73)
6	<i>p</i> -OMe	Bn	3f (91)	12 ^{b)}	<i>p</i> -CO ₂ Me	Et	3l (53)

a) Isolated yield based on arylamine (**1**). b) Preformation of the imine at 120 °C was carried out prior to addition of **2** and Yb(OTf)₃.

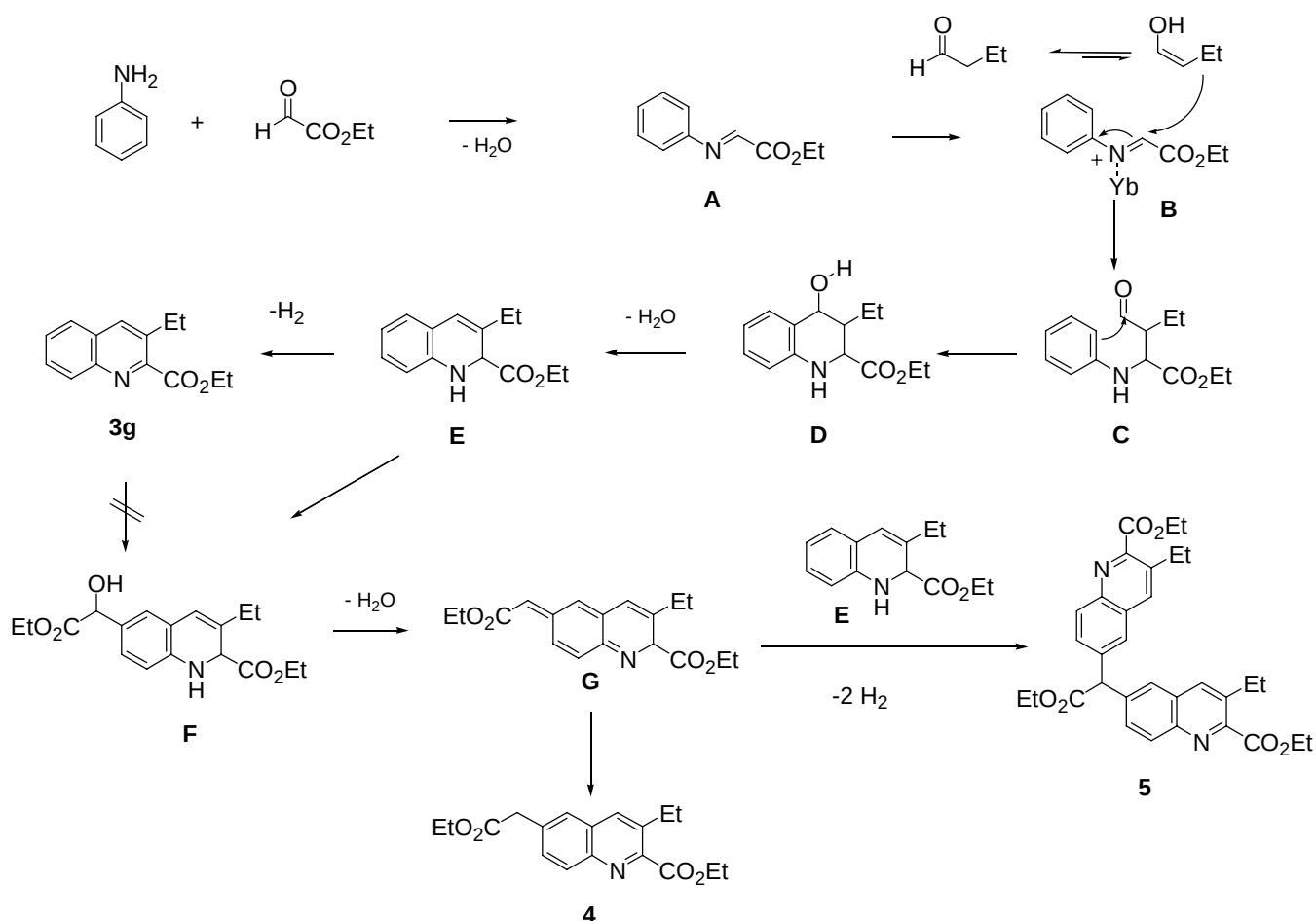
When aniline was employed, the quinaldate (**3g**) was obtained in 34% yield. In this case substitution reaction at C-6 was observed to yield the diester (**4**) and triester (**5**) in 15% and 22% yields respectively based on aniline. The structures of **4** and **5** were elucidated by NMR and HRMS spectrum.



Scheme 1 Three-component coupling reaction of aniline, EG and butanal

The mechanism for the formation of quinaldates (**3g**, **4** and **5**) from aniline can be explained in Scheme 2. At first formation of imine from aniline and EG followed by reaction of butanal gives the aldehyde **C**, which is cyclized under acidic conditions by intramolecular Friedel-Crafts type reaction to give **D**.

Dehydration of **D** gives the dihydroquinaldate **E**, which is dehydrogenated to give the quinaldate (**3g**). The formation of **4** and **5** seems to be explained by Friedel-Crafts type reaction of **3g** with EG. The reaction starting with **3g** and EG was examined separately in order to confirm the process from **3g** to **4** and **5** via **F**, but no reaction proceeded under the same reaction conditions of three component coupling reaction. Therefore the C-C bond forming reaction at C-6 in the quinaldate is supposed to proceed prior to dehydration of **E** to **3g**. The precise mechanism for the formation of **4** and **5** is not clear, but the reaction of **E** with EG is plausible. Thus, reaction of **E** with EG gives **F** followed by dehydration to afford the intermediate **G**, which is isomerized to furnish the (quinolin-6-yl)acetate derivative (**4**). Furthermore, Friedel-Crafts type reaction of **E** proceeds with the intermediate **G** followed by loss of two hydrogen molecules to afford the bis(quinolin-6-yl)acetate (**5**).⁹



Scheme 2 Plausible reaction mechanism for the formation of **3g**, **4** and **5**

SUMMARY

We have developed an efficient one-pot synthesis of 2-ethoxycarbonylquinoline derivatives (quinaldates) from aromatic amines, ethyl glyoxylate (EG) and aliphatic aldehydes in the presence of a catalytic amount of Yb(OTf)₃, which provides a promising method for preparation of substituted quinaldates.

EXPERIMENTAL

All melting points were measured on a Yamato Model MP-21 and were uncorrected. ^1H NMR and ^{13}C NMR spectra were recorded in CDCl_3 as a solvent using TMS as an internal standard on JEOL Lambda 500 spectrometers. Multiplicities are indicated as br (broadened), s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet). High-resolution mass (HRMS) spectroscopy and elemental analysis were performed by the Material Characterization Central Laboratory of Waseda University.

General procedure for the synthesis of 3a – 3i. A mixture of arylamine (**1**) (1.0 mmol), ethyl glyoxylate (1.2 mmol, 0.273 mL, Polymer form 47% in toluene) in DMSO (3 mL) was stirred at rt for 1 h. Then alkyl aldehyde (**2**) (1.1 mmol) and $\text{Yb}(\text{OTf})_3$ (6.2 mg, 0.01 mmol) were added to the mixture successively, and the resulting mixture was stirred at 90 °C for 16 h under oxygen. The reaction mixture was washed with phosphate buffered saline solution (PBS, 50 mL) and extracted with AcOEt (20 mL $\times$ 3). The organic layer was dried over MgSO_4 . Removal of the solvent in vacuo, followed by chromatography on silica gel column (AcOEt / hexane = 5 / 95), afforded **3**.

Ethyl 6-methoxy-3-propylquinaldate (3a): pale yellow oil (257 mg, 94 %), ^1H NMR (500 MHz, CDCl_3) δ 0.97 (t, J = 7.3 Hz, 3H, CH_3), 1.43 (t, J = 7.1 Hz, 3H, OCH_2CH_3), 1.69 (m, 2H, CH_2), 2.93 (m, 2H, CH_2), 3.90 (s, 3H, OCH_3), 4.48 (q, J = 7.1 Hz, 2H, OCH_2CH_3), 6.99 (d, J = 2.7 Hz, 1H, aromatic H), 7.30 (dd, J = 9.2, 2.7 Hz, 1H, aromatic H), 7.88 (s, 1H, aromatic H), 8.02 (d, J = 9.2 Hz, 1H, aromatic H), ^{13}C NMR (125 MHz, CDCl_3) δ 13.9 (s, CH_3), 14.2 (s, OCH_2CH_3), 24.3 (s, CH_2), 34.8 (s, CH_2), 55.5 (s, OCH_3), 61.8 (s, OCH_2CH_3), 104.0, 122.4, 130.1, 131.3, 134.7, 135.9, 141.9, 147.5, 158.9 (s, aromatic C); 166.9 (s, CO), HRMS (FAB) calcd for $\text{C}_{16}\text{H}_{20}\text{NO}_3$ [$\text{M} + \text{H}$] $^+$ 274.1443, found 274.1444.

Ethyl 6-methoxyquinaldate (3b): colorless crystals (from AcOEt / hexane, 104 mg, 45 %), mp 127-128 °C, ^1H NMR (500 MHz, CDCl_3) δ 1.46 (t, J = 7.1 Hz, 3H, OCH_2CH_3), 3.93 (s, 3H, OCH_3), 4.52 (q, J = 7.1 Hz, 2H, OCH_2CH_3), 7.08 (d, J = 2.7 Hz, 1H, aromatic H), 7.40 (dd, J = 9.3, 2.7 Hz, 1H, aromatic H), 8.11 – 8.13 (m, 2H, aromatic H), 8.17 (d, J = 9.3 Hz, 1H, aromatic H), ^{13}C NMR (125 MHz, CDCl_3) δ 14.4 (s, OCH_2CH_3), 55.6 (s, OCH_3), 62.0 (s, OCH_2CH_3), 104.6, 121.5, 123.4, 130.8, 132.3, 135.6, 143.8, 145.8, 159.4 (s, aromatic C); 165.6 (s, CO), HRMS (FAB) calcd for $\text{C}_{13}\text{H}_{14}\text{NO}_3$ [$\text{M} + \text{H}$] $^+$ 232.0974, found 232.0985, Anal. Calcd for $\text{C}_{15}\text{H}_{19}\text{NO}$: C, 67.52; H, 5.67; N, 6.06. Found: C, 67.42; H, 5.48; N, 6.15.

Ethyl 6-methoxy-3-methylquinaldate (3c): pale yellow oil (206 mg, 84 %), ^1H NMR (500 MHz, CDCl_3) δ 1.43 (t, J = 7.1 Hz, 3H, OCH_2CH_3), 2.61 (s, 3H, CH_3), 3.87 (s, 3H, OCH_3), 4.47 (q, J = 7.1 Hz,

2H, OCH₂CH₃), 6.93 – 6.94 (m, 1H, aromatic H), 7.28 (dd, $J = 9.3, 2.7$ Hz, 1H, aromatic H), 7.84 (s, 1H, aromatic H), 8.02 (d, $J = 9.3$ Hz, 1H, aromatic H), ¹³C NMR (125 MHz, CDCl₃) δ 14.2 (s, OCH₂CH₃), 19.9 (s, CH₃), 55.5 (s, OCH₃), 61.7 (s, OCH₂CH₃), 103.8, 122.3, 130.2, 130.7, 131.3, 136.6, 141.9, 146.9, 159.1 (s, aromatic C); 166.6 (s, CO), HRMS (FAB) calcd for C₁₄H₁₆NO₃ [M + H]⁺ 246.1130, found 246.1123.

Ethyl 6-methoxy-3-ethylquinaldate (3d): pale yellow oil (257 mg, 99 %), ¹H NMR (500 MHz, CDCl₃) δ 1.28 (t, $J = 7.5$ Hz, 3H, CH₃), 1.42 (t, $J = 7.1$ Hz, 3H, OCH₂CH₃), 2.97 (q, $J = 7.5$ Hz, 2H, CH₂), 3.87 (s, 3H, OCH₃), 4.47 (q, $J = 7.1$ Hz, 2H, OCH₂CH₃), 6.97 (d, $J = 2.7$ Hz, 1H, aromatic H), 7.28 (dd, $J = 9.3, 2.7$ Hz, 1H, aromatic H), 7.87 (s, 1H, aromatic H), 8.01 (d, $J = 9.0$ Hz, 1H, aromatic H), ¹³C NMR (125 MHz, CDCl₃) δ 14.2 (s, OCH₂CH₃), 15.1 (s, CH₃), 25.8 (s, CH₂), 55.4 (s, OCH₃), 61.7 (s, OCH₂CH₃), 104.0, 122.3, 130.2, 131.2, 134.9, 136.1, 141.8, 147.4, 158.9 (s, aromatic C); 166.8 (s, CO), HRMS (FAB) calcd for C₁₅H₁₈NO₃ [M + H]⁺ 260.1287, found 260.1287.

Ethyl 6-methoxy-3-isopropylquinaldate (3e): pale yellow oil (251 mg, 92 %), ¹H NMR (500 MHz, CDCl₃) δ 1.30 (d, $J = 6.8$ Hz, 6H, CH₃), 1.40 (t, $J = 7.1$ Hz, 3H, OCH₂CH₃), 3.48 (m, 1H, CH), 3.86 (s, 3H, OCH₃), 4.46 (q, $J = 7.1$ Hz, 2H, OCH₂CH₃), 7.00 (d, $J = 2.7$ Hz, 1H, aromatic H), 7.27 (dd, $J = 9.2, 2.7$ Hz, 1H, aromatic H), 7.97 – 7.99 (m, 2H, aromatic H), ¹³C NMR (125 MHz, CDCl₃) δ 14.1 (s, OCH₂CH₃), 23.7 (s, CH₃), 28.9 (s, CH₂), 55.4 (s, OCH₃), 61.7 (s, OCH₂CH₃), 104.3, 122.4, 130.1, 130.9, 132.0, 140.0, 141.6, 148.1, 158.7 (s, aromatic C); 167.2 (s, CO), HRMS (FAB) calcd for C₁₆H₂₀NO₃ [M + H]⁺ 274.1443, found 274.1415.

Ethyl 6-methoxy-3-benzylquinaldate (3f): pale yellow crystals (from AcOEt / hexane, 292 mg, 91 %), mp 96–97 °C, ¹H NMR (500 MHz, CDCl₃) δ 1.26 (t, $J = 7.1$ Hz, 3H, CH₃), 3.84 (s, OCH₃), 4.35 (q, $J = 7.1$ Hz, 2H, CH₂), 4.36 (s, 2H, CH₂), 7.11 – 7.13 (m, 2H, aromatic H), 7.16 – 7.18 (m, 1H, aromatic H), 7.23 – 7.25 (m, 2H, aromatic H), 7.29 (dd, $J = 9.2, 2.7$ Hz, 1H, aromatic H), 7.75 (s, 1H, aromatic H), 8.01 (d, $J = 9.2$ Hz, 1H, aromatic H) ¹³C NMR (125 MHz, CDCl₃) δ 14.1 (s, OCH₂CH₃), 38.4 (s, CH₂), 55.5 (s, OCH₃), 61.8 (s, OCH₂CH₃), 104.2, 122.7, 126.3, 128.5, 129.2, 130.1, 131.3, 133.3, 136.6, 139.6, 142.0, 147.4, 159.1 (s, aromatic C); 166.7 (s, CO), HRMS (FAB) calcd for C₂₀H₂₀NO₃ [M + H]⁺ 322.1443, found 322.1452, Anal. Calcd for C₂₀H₁₉NO₃: C, 74.75; H, 5.96; N, 4.36. Found: C, 74.53; H, 5.76; N, 4.06.

Ethyl 3-ethylquinaldate (3g): pale yellow oil (78 mg, 34 %), ¹H NMR (500 MHz, CDCl₃) δ 1.30 (t, $J = 7.5$ Hz, 3H, CH₃), 1.43 (t, $J = 7.1$ Hz, 3H, OCH₂CH₃), 2.96 (q, $J = 7.5$ Hz, 2H, CH₂), 4.49 (q, $J = 7.1$ Hz,

2H, OCH₂CH₃), 7.50 – 7.53 (m, 1H, aromatic H), 7.62 – 7.65 (m, 1H, aromatic H), 7.73 (dd, *J* = 8.2, 1.3 Hz, 1H, aromatic H), 7.99 (s, 1H, aromatic H), 8.12 (d, *J* = 9.0 Hz, 1H, aromatic H), ¹³C NMR (125 MHz, CDCl₃) δ 14.2 (s, OCH₂CH₃), 15.0 (s, CH₃), 25.6 (s, CH₂), 61.9 (s, OCH₂CH₃), 126.9, 127.8, 128.8, 129.2, 129.7, 135.2, 136.1, 145.7, 150.4 (s, aromatic C); 166.8 (s, CO), HRMS (FAB) calcd for C₁₄H₁₆NO₂ [M + H]⁺ 230.1181, found 230.1182.

Ethyl 8-methoxy-3-ethylquinaldate (3h): pale yellow oil (106 mg, 41 %), ¹H NMR (500 MHz, CDCl₃) δ 1.28 (t, *J* = 7.5 Hz, 3H, CH₃), 1.43 (t, *J* = 7.1 Hz, 3H, OCH₂CH₃), 3.00 (q, *J* = 7.5 Hz, 2H, CH₂), 4.03 (s, 3H, OCH₃), 4.47 (q, *J* = 7.1 Hz, 2H, OCH₂CH₃), 6.97 (dd, *J* = 7.7, 0.7 Hz, 1H, aromatic H), 7.31 (dd, *J* = 8.2, 0.7 Hz, 1H, aromatic H), 7.44 – 7.48 (m, 1H, aromatic H), 7.98 (s, 1H, aromatic H), ¹³C NMR (125 MHz, CDCl₃) δ 14.1 (s, OCH₂CH₃), 15.0 (s, CH₃), 25.6 (s, CH₂), 55.9 (s, OCH₃), 61.8 (s, OCH₂CH₃), 107.2, 118.6, 128.4, 130.1, 136.2, 136.3, 137.7, 148.8, 155.6 (s, aromatic C); 166.6 (s, CO), HRMS (FAB) calcd for C₁₅H₁₈NO₃ [M + H]⁺ 260.1287, found 260.1286.

Ethyl 6-methyl-3-ethylquinaldate (3i): pale yellow oil (219 mg, 90 %), ¹H NMR (500 MHz, CDCl₃) δ 1.28 (t, *J* = 7.5 Hz, 3H, CH₂CH₃), 1.42 (t, *J* = 7.1 Hz, 3H, OCH₂CH₃), 2.47 (s, 3H, CH₃), 2.95 (q, *J* = 7.5 Hz, 2H, CH₂), 4.47 (q, *J* = 7.1 Hz, 2H, OCH₂CH₃), 7.44 – 7.46 (m, 2H, aromatic H), 7.88 (s, 1H, aromatic H), 8.00 (d, *J* = 8.6 Hz, 1H, aromatic H), ¹³C NMR (125 MHz, CDCl₃) δ 14.1 (s, OCH₂CH₃), 15.1 (s, CH₂CH₃), 21.6 (s, CH₃), 25.6 (s, CH₂), 61.7 (s, OCH₂CH₃), 125.6, 128.9, 129.3, 131.5, 135.4, 137.9, 144.2, 149.3 (s, aromatic C); 166.8 (s, CO), HRMS (FAB) calcd for C₁₅H₁₈NO₂ [M + H]⁺ 244.1338, found 244.1324.

General procedure for the synthesis of 3j – 3l. A mixture of arylamine (**1**) (1.0 mmol), ethyl glyoxylate (1.2 mmol, 0.273 mL, Polymer form 47 % in toluene) and DMSO (3 mL) was stirred at 120 °C for 1 h. Then alkyl aldehyde (**3**) (1.1 mmol) and Yb(OTf)₃ (6.2 mg, 0.01 mmol) were added to the mixture, and the resulting mixture was stirred at 90 °C for 16 h under oxygen (balloon). The reaction mixture was washed with PBS buffer solution (50 mL) and extracted with AcOEt (20 mL × 3). The organic layer was dried over MgSO₄. Removal of the solvent in vacuo, followed by chromatography on silica gel column (AcOEt / Hexane = 5 / 95), afforded **3**.

Ethyl 6-bromo-3-ethylquinaldate (3j): pale yellow oil (275 mg, 90 %), ¹H NMR (500 MHz, CDCl₃) δ 1.30 (t, *J* = 7.5 Hz, 3H, CH₃), 1.44 (t, *J* = 7.1 Hz, 3H, OCH₂CH₃), 2.97 (q, *J* = 7.5 Hz, 2H, CH₂), 4.49 (q, *J* = 7.1 Hz, 2H, OCH₂CH₃), 7.71 (dd, *J* = 9.0, 2.1 Hz, 1H, aromatic H), 7.91 – 7.92 (m, 2H, aromatic H), 7.98 (d, *J* = 9.0 Hz, 1H, aromatic H), ¹³C NMR (125 MHz, CDCl₃) δ 14.2 (s, OCH₂CH₃), 14.9 (s,

CH₃), 25.6 (s, CH₂), 62.1 (s, OCH₂CH₃), 122.0, 129.0, 129.8, 131.4, 132.8, 135.0, 136.4, 144.2, 150.8 (s, aromatic C); 166.5 (s, CO), HRMS (FAB) calcd for C₁₄H₁₅NO₂Br [M + H]⁺ 308.0286, found 308.0289.

Ethyl 6-fluoro-3-ethylquinaldate (3k): pale yellow oil (180 mg, 73 %), ¹H NMR (500 MHz, CDCl₃) δ 1.31 (t, *J* = 7.5 Hz, 3H, CH₃), 1.44 (t, *J* = 7.1 Hz, 3H, OCH₂CH₃), 2.99 (q, *J* = 7.5 Hz, 2H, CH₂), 4.50 (q, *J* = 7.1 Hz, 2H, OCH₂CH₃), 7.36 (dd, *J* = 8.8, 2.7 Hz, 1H, aromatic H), 7.41 – 7.45 (m, 1H, aromatic H), 7.96 (s, 1H, aromatic H), 8.14 (dd, *J* = 9.2, 5.3 Hz, 1H, aromatic H), ¹³C NMR (125 MHz, CDCl₃) δ 14.2 (s, OCH₂CH₃), 15.0 (s, CH₃), 25.6 (s, CH₂), 62.0 (s, OCH₂CH₃), 109.9 (d, *J*_{CF} = 23 Hz, aromatic C), 119.7 (d, *J*_{CF} = 27 Hz, aromatic C), 129.6 (d, *J*_{CF} = 9.7 Hz, aromatic C), 132.4 (d, *J*_{CF} = 9.7 Hz, aromatic C), 135.5 (d, *J*_{CF} = 5.6 Hz, aromatic C), 136.4, 142.8 (s, aromatic C), 149.8 (d, *J*_{CF} = 3.2 Hz, aromatic C), 161.3 (d, *J*_{CF} = 256 Hz, aromatic C), 166.6 (s, CO); HRMS (FAB) calcd for C₁₄H₁₅NO₂F [M + H]⁺ 248.1087, found 248.1080.

Ethyl 6-methoxycarbonyl-3-ethylquinaldate (3l): colorless crystals (from hexane, 152 mg, 53 %), mp 84-85 °C, ¹H NMR (500 MHz, CDCl₃) δ 1.32 (t, *J* = 7.5 Hz, 3H, CH₃), 1.44 (t, *J* = 7.1 Hz, 3H, OCH₂CH₃), 2.98 (q, *J* = 7.5 Hz, 2H, CH₂), 3.96 (s, 3H, OCH₃), 4.51 (q, *J* = 7.1 Hz, 2H, OCH₂CH₃), 8.11 (s, 1H, aromatic H), 8.15 (d, *J* = 8.8 Hz, 1H, aromatic H), 8.23 (dd, *J* = 8.8, 1.6 Hz, 1H, aromatic H), 8.53 (d, *J* = 1.6 Hz, 1H, aromatic H), ¹³C NMR (125 MHz, CDCl₃) δ 14.2 (s, OCH₂CH₃), 14.9 (s, CH₃), 25.5 (s, CH₂), 52.5 (s, OCH₃), 62.1 (s, OCH₂CH₃), 127.9, 128.7, 129.2, 130.0, 130.1, 136.0, 137.3, 147.4, 152.6 (s, aromatic C); 166.4, 166.5 (s, CO), HRMS (FAB) calcd for C₁₆H₁₈NO₄ [M + H]⁺ 288.1236, found 288.1251, Anal. Calcd for C₁₅H₁₉NO: C, 66.89; H, 5.96; N, 4.88. Found: C, 66.69; H, 5.79; N, 4.89.

Ethyl 6-(ethoxycarbonylmethyl)-3-ethylquinaldate (4): pale yellow oil (47 mg, 15 %, obtained along with **3g**), ¹H NMR (500 MHz, CDCl₃) δ 1.20 (t, *J* = 7.1 Hz, 3H, OCH₂CH₃), 1.29 (t, *J* = 7.5 Hz, 3H, CH₃), 1.42 (t, *J* = 7.1 Hz, 3H, OCH₂CH₃), 2.96 (q, *J* = 7.5 Hz, 2H, CH₂CH₃), 3.75 (s, 2H, CH₂), 4.13 (q, *J* = 7.1 Hz, 2H, OCH₂CH₃), 4.48 (q, *J* = 7.1 Hz, 2H, OCH₂CH₃), 7.58 (dd, *J* = 8.8, 1.8 Hz, 1H, aromatic H), 7.65 (d, *J* = 1.8 Hz, 1H, aromatic H), 7.96 (s, 1H, aromatic H), 8.08 (d, *J* = 8.8 Hz, 1H, aromatic H), ¹³C NMR (125 MHz, CDCl₃) δ 14.1, 14.2 (s, OCH₂CH₃), 15.0 (s, CH₃), 25.6 (s, CH₂CH₃), 52.5 (s, OCH₃), 61.0, 61.9 (s, OCH₂CH₃), 126.9, 128.7, 129.8, 130.9, 134.0, 135.6, 135.9, 144.8, 150.2 (s, aromatic C); 166.7, 171.0 (s, CO), HRMS (FAB) calcd for C₁₈H₂₂NO₄ [M + H]⁺ 316.1549, found 316.1550.

Ethyl 2,2-bis(2-ethoxycarbonyl-3-ethylquinolin-6-yl)acetate (5): pale yellow oil (119 mg, 22 %, obtained along with **3g**), ¹H NMR (500 MHz, CDCl₃) δ 1.25 (t, *J* = 7.1 Hz, 3H, OCH₂CH₃), 1.29 (t, *J* = 7.5 Hz, 6H, CH₃), 1.43 (t, *J* = 7.1 Hz, 6H, OCH₂CH₃), 2.96 (q, *J* = 7.5 Hz, 4H, OCH₂CH₃), 4.26 (q, *J* =

7.1 Hz, 2H, OCH₂CH₃), 4.49 (q, J = 7.1 Hz, 4H, OCH₂CH₃), 5.35 (s, 1H, CH), 7.64 (dd, J = 9.0, 2.0 Hz, 2H, aromatic H), 7.72 (d, J = 2.0 Hz, 2H, aromatic H), 7.99 (s, 2H, aromatic H), 8.11 (d, J = 9.0 Hz, 2H, aromatic H), ¹³C NMR (125 MHz, CDCl₃) δ 14.1, 14.2 (s, OCH₂CH₃), 15.0 (s, CH₃), 25.6 (s, CH₂CH₃), 56.8 (s, CH), 61.7, 62.0 (s, OCH₂CH₃), 126.4, 128.8, 130.1, 130.3, 135.9, 136.4, 137.9, 144.9, 150.7 (s, aromatic C); 166.7, 171.6 (s, CO), HRMS (FAB) calcd for C₃₂H₃₅N₂O₆ [M + H]⁺ 543.2495, found 543.2495.

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