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A novel Friedlander-type synthesis of 3-aryl quinolines from 3-oxo-2,3-diaryl-propionaldehydes

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ABSTRACT

3-Aryl quinolines are readily synthesized by a novel Friedländer-type reaction with 3-oxo-2,3-diaryl-propionaldehydes and 2-amino arylaldehydes. A preliminary mechanism of this novel one pot, two-step synthesis has been explored with the proofs of isolation of the enaminone intermediate and the eliminated benzoic acid in this reaction.

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1. Introduction

Many quinoline containing compounds exhibit a wide variety of pharmacological and biological activities,[1] such as antiasthmatic,[2] anti-inflammatory,[3] anti-HIV-1[4] and tyrosine kinase inhibiting properties.[5] Therefore, exploration of efficient synthetic methods to construct quinoline framework has continually drawn great attentions for many decades. As a result, many quinoline syntheses, such as Combes, Skraup, Döbner–Von Miller, Conrad–Limpach, Pfitzinger, Friedländer and Povarov reactions, etc. have been developed.[6] However, many of these classic synthetic approaches suffer from limited source of precursors, harsh reaction conditions, low yields or selectivity. Hence, variant or modified approaches of these classic quinoline syntheses continue to emerge with significant improvements in terms of the synthetic feasibility. For instance, some modified Friedländer syntheses have been recently described, either catalyzed with organometal catalysts, such as ruthenium,[7] or without expensive transition metal catalysts.[8] By using these methods, 2-substituted or 2,3-substituted quinolines could be successfully synthesized in good yields.

In our recent work for preparation of biological active heterocycles, we expected to synthesize a series of 3-aryl substituted quinolines by the Friedländer approach. However, the less accessibility of aryl acetaldehydes combined with the instability of *o*-amino arylaldehydes under the reaction conditions indicated less feasible syntheses with unsatisfactory yields. These disadvantages urged us to seek a new, mild condition variation of the Friedländer synthesis with readily available precursors to achieve our target compounds. It is known that less reactive α-methylenecarbonyl counterparts (e.g., aryl acetaldehydes) usually require more drastic reaction conditions, therefore increase the self-condensation tendency of *o*-amino arylaldehydes and thus result in low yields. In light of this mechanism understanding, we envisaged that replacing the hydrogen with an electron-withdrawing group on the α-methylene position of aryl acetaldehydes could activate these reactants, thus milder reaction conditions could be employed to diminish the yield deterioration caused by *o*-amino arylaldehydes self-condensation. Importantly, this introduced auxiliary electron-withdrawing group should be readily eliminated under the same reaction conditions after fulfilling its mission. Herein, we describe a new Friedländer-type approach to synthesize 3-aryl quinolines starting from 3-oxo-2,3-diaryl-propionaldehydes, which could be obtained efficiently from chalcone epoxides.[9] The auxiliary acyl (substituted benzoyl) groups eliminate during the reactions to give the same products while the normal aryl acetaldehydes are used as precursors (Scheme 1). To the best of our knowledge, this novel modification of the Friedländer-type quinoline synthesis is the first report of its type.

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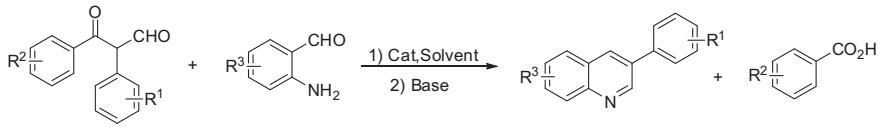


Scheme 1. Synthesis of 3-aryl quinolines.

2. Results and discussion

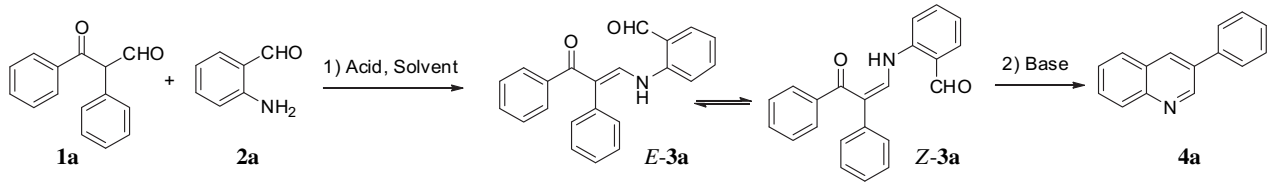
We started our investigation by subjecting our model substrates, 3-oxo-2,3-diphenylpropionaldehyde (**1a**) and *o*-amino benzylaldehyde (**2a**) to base-catalyzed Friedlander reaction conditions. Unfortunately, the reaction failed with messy results, and the self-condensation of **2a** was observed. Then, we turned our attention to the regular acid-catalyzed Friedländer conditions. Disappointingly, no quinoline product was obtained while either a Lewis acid $BF_3 \cdot Et_2O$ or a Brønsted acid TfOH was used as the catalyst (Table 1, entries 1 and 2). Instead, an enaminone intermediate **3a** (a mixture of *E*-, *Z*-isomers; *E*/*Z*=~7:3) was isolated and identified. However, while a base KO^{t}Bu was directly added to the reaction mixture containing the enaminone intermediate **3a**, the quinoline **4a** was formed rapidly in good yield in both cases (74% and 77%; Table 1, entries 3 and 4). Encouraged by these exciting results, we further explored the effects of various reaction parameters, such as acid catalysts (Table 1, entries 3–7), acid catalyst loading (Table 1, entries 4, 8 and 9), solvents (Table 1, entries 8 and 10–15), reaction temperature (Table 1, entries 8, 16 and 17) and bases (Table 1, entries 8 and 18–22). Under the optimized reaction (Table 1, entry 8), the quinoline **4a** was obtained in high yield (82%). Compared to the modest yields (31–53%)[10] achieved in classic Friedländer syntheses for the same product, this new protocol significantly improves the synthetic feasibility of 3-phenylquinoline **4a**.

Since one of the reactants, 3-oxo-2,3-diphenylpropionaldehyde (**1a**), is not a typical substrate for the classic Friedländer reaction, we speculated that an unusual reaction pathway could exist. Therefore, we are especially interested in understanding the mechanism of this novel Friedländer-type reaction and collecting the evidences to support our hypothesis. Thus, we subjected the isolated enaminone intermediate **3a** to the basic reaction condition. After work-up and purification, 3-phenylquinoline **4a** was obtained in 94% yield. In addition, benzoic acid **5** was also isolated as another product of the same reaction in 88% yield (Scheme 2).

The generality of this novel modification of the Friedländer synthesis has been investigated and the results are shown in Table 2. A series of condensation partners bearing substituents with various electronic (both electronic rich and deficient) properties at different (*ortho*-, *meta*- and *para*-) positions on the aromatic rings were subjected to this optimized reaction system and all afforded the 3-aryl quinolines **4** in good to high yields (Table 2).

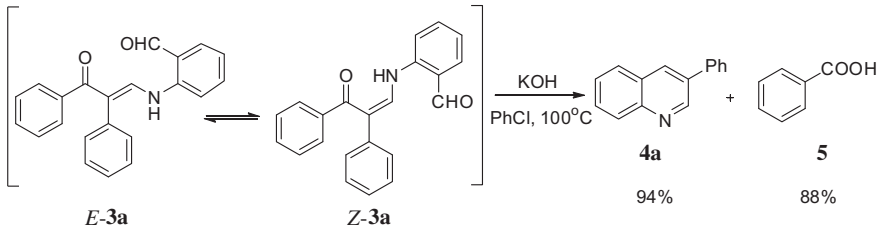
In general, the variation of electronic properties of R^1 groups only has slight influence on yields although electron-donating substituents help to achieve relatively better yields than electron-withdrawing substituents do (Table 2, entries 1–7), and the methyl group, instead of phenyl group, substituted substrate 3-oxo-2-methyl-3-phenylpropionaldehyde also gave moderate yield (Table 2, entry 16). An exception was observed that thienyl group as R^1 caused a significant decreasing in yield (Table 2, entries 13),

Table 1
Optimization of reaction conditions for a novel Friedländer-type synthesis of 3-phenylquinolines[a]



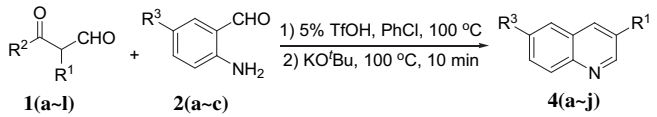
Entry	Acid (mol %)	Solvent	Base	*T* (°C)	Yield[b] (%)
1	$BF_3 \cdot Et_2O$ (10)	C_6H_5Cl	—	100	—
2	TfOH (10)	C_6H_5Cl	—	100	—
3	$BF_3 \cdot Et_2O$ (10)	C_6H_5Cl	KO^{t}Bu	100	74
4	TfOH (10)	C_6H_5Cl	KO^{t}Bu	100	77
5	$FeCl_3$ (10)	C_6H_5Cl	KO^{t}Bu	100	66
6	TsOH (10)	C_6H_5Cl	KO^{t}Bu	100	60
7	TFA (10)	C_6H_5Cl	KO^{t}Bu	100	72
8	TfOH (5)	C_6H_5Cl	KO^{t}Bu	100	82
9	TfOH (2)	C_6H_5Cl	KO^{t}Bu	100	68
10	TfOH (5)	EtOH	KO^{t}Bu	Reflux	26
11	TfOH (5)	DCE	KO^{t}Bu	Reflux	65
12	TfOH (5)	CH_3CN	KO^{t}Bu	Reflux	60
13	TfOH (5)	Toluene	KO^{t}Bu	100	76
14	TfOH (5)	Dioxane	KO^{t}Bu	100	63
15	TfOH (5)	DMF	KO^{t}Bu	100	62
16	TfOH (5)	C_6H_5Cl	KO^{t}Bu	80	78
17	TfOH (5)	C_6H_5Cl	KO^{t}Bu	120	54
18	TfOH (5)	C_6H_5Cl	KOH	100	77
19	TfOH (5)	C_6H_5Cl	Li_2CO_3	100	Trace
20	TfOH (5)	C_6H_5Cl	Cs_2CO_3	100	75
21	TfOH (5)	C_6H_5Cl	TEA	100	Trace
22	TfOH (5)	C_6H_5Cl	DBU	100	78

[a] Reaction conditions: **1a** (0.25 mmol), **2a** (0.375 mmol), solvent (1.5 mL); then base (0.5 mmol).
[b] Isolated yield.



Scheme 2.

Table 2
Synthesis of 3-aryl quinolines[a]



Entry	R^1	R^2	R^3	Product	Yield[b] (%)
1	Ph	Ph	H	**4a**	82
2	*p*-$CH_3OC_6H_4$	Ph	H	**4b**	80
3	*m*-$CH_3OC_6H_4$	Ph	H	**4c**	75
4	*o*-$CH_3OC_6H_4$	Ph	H	**4d**	76
5	*p*-$CH_3C_6H_4$	Ph	H	**4e**	77
6	*p*-BrC_6H_4	Ph	H	**4f**	77
7	*p*-FC_6H_4	Ph	H	**4g**	75
8	Ph	*p*-$CH_3OC_6H_4$	H	**4a**	72
9	Ph	*p*-$CH_3C_6H_4$	H	**4a**	77
10	Ph	*p*-BrC_6H_4	H	**4a**	86
11	Ph	*p*-$O_2NC_6H_4$	H	**4a**	88
12	Ph	Me	H	**4a**	30
13	Thiophene	Ph	H	**4h**	61
14	Ph	Ph	CH_3O	**4i**	67
15	Ph	Ph	Br	**4j**	76
16	Me	Ph	H	**4k**	67
17	Ph	Ph	NO_2	**4l**	34

[a] Reaction conditions: **1** (0.5 mmol), **2** (0.75 mmol), TfOH (0.025 mmol), C_6H_5Cl (3.0 mL), 100 °C 15 h; then KO^{t}Bu (1 mmol), 100 °C, 10 min.
[b] Isolated yield.

which could be due to the instability of thiophene moiety under the reaction conditions to form undesired by-products. Furthermore, an electron-withdrawing removable auxiliary group R^2CO helps to increase the yield while an electron-donating one does the opposite. The trend was clearly demonstrated from the experimental results: the yields gradually deceased when R^2 was switched from a strong electron-withdrawing group (*p*-$O_2NC_6H_4$) to a strong electron-donating one (*p*-$MeOC_6H_4$) (Table 2, entries 11, 10, 1, 9 and 8); an alkyl group (Me) could significantly reduce the yield to a very low level because of its strongest electron-donating property compared to those of the aryl substituents (Table 2, entry 12 vs entries 11, 10, 1, 9 and 8). Finally, the electronic properties of R^3 groups don't have a linear effect on the yields although a strong electron-withdrawing group (*p*-$O_2NC_6H_4$) could exceptionally reduce the yield (Table 2, entries 1, 14, 15 and 17).

According to all the experimental data, we proposed a possible reaction mechanism of this novel Friedländer-type synthesis (Scheme 3): TfOH catalyzes the reaction of **1a** with **2a** to produce an isolable enaminone intermediate **3a** (a mixture of *E*-, *Z*-isomers; *E*/*Z*=~7:3) as previously described. Strong base can deprotonate **3a** to form enaminone anion **6a**, which can then tautomerize to form imine anion **7a**. The highly reactive imine anion **7a** readily undergoes an intramolecular aldol-type condensation to form a hydroxyimine anion **8**, which proceeds to a benzoate anion **10** via an unstable four-membered ring lactol intermediate **9**. The benzoate anion **10** undergoes aromatization by losing a benzoate **5′** to form the desired quinoline **4a**.

Evidences in support of this mechanistic proposal exist as follows: (1) isolated enaminone **3a** clearly self-explains that it is the reaction intermediate. (2) Strong bases can smoothly promote quinoline synthesis with high yields while weak bases only give trace amount of products (Table 1, entries 8 and 18–22). This proves that formation of enaminone anion **6a** is the rate limiting step. (3) The generation of 1 equiv of benzoic acid **5** implies the transformations from enaminone anion **6a** to the final product quinoline **4a** although more evidence collecting is in due course.

3. Conclusions

We have demonstrated a novel one pot, two-step Friedländer-type reaction with broad substrate scope to synthesize 3-aryl quinolines in high yields. Since this methodology is the first report of using a type of unusual Friedländer substrates (3-oxo-2,3-diaryl-propionaldehydes) for the synthesis of 3-aryl quinolines, a new pathway may exist. Therefore, we proposed a preliminary mechanism based on the experimental results. Further expending substrate scope and deeper understanding the reaction mechanism are currently undergoing in our lab.

4. Experimental

4.1. General methods

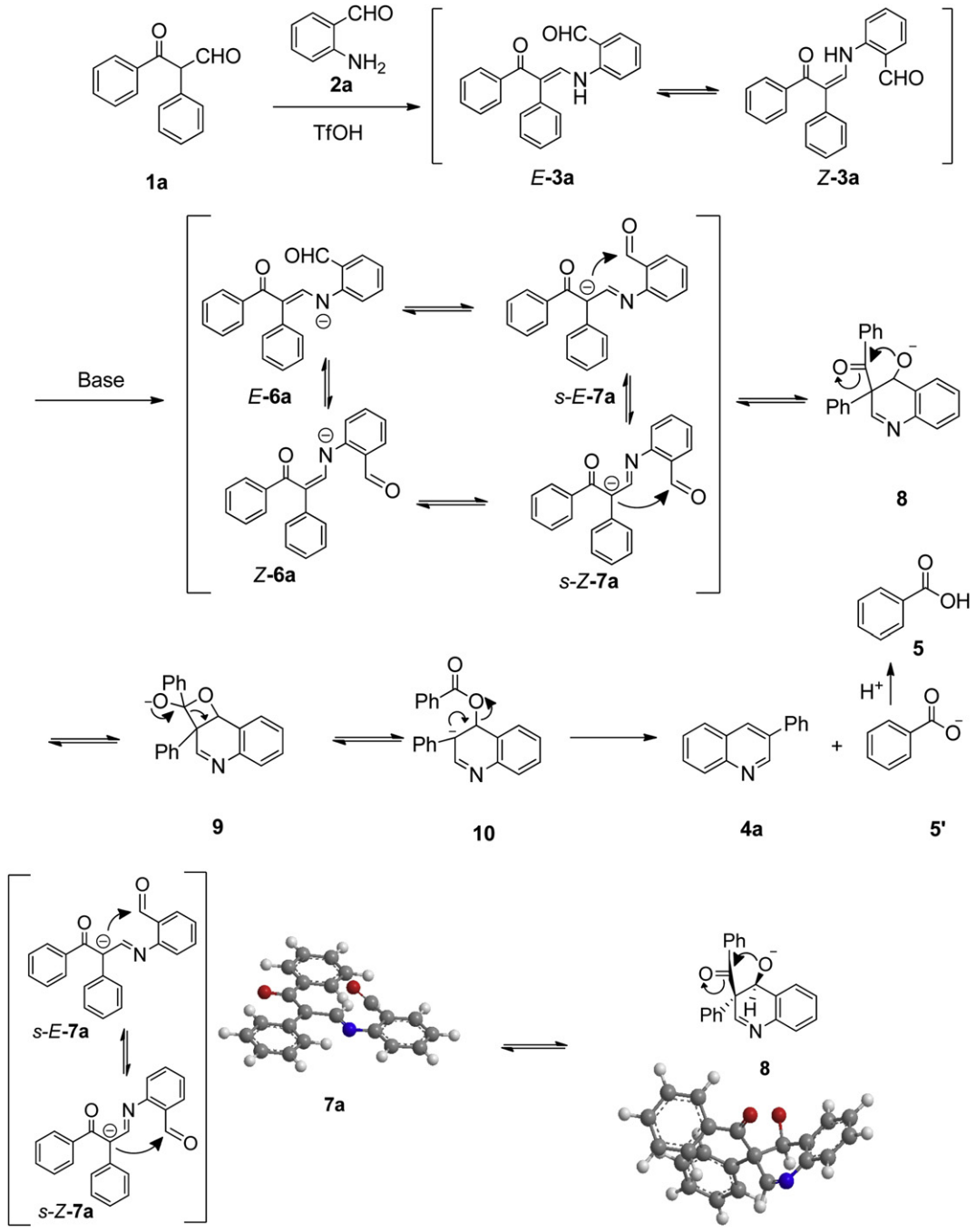
All reagents were purchased from commercial sources and used without treatment. ^1H and ^{13}C NMR spectra were recorded at 400 (or 500) and 100 MHz, respectively, using TMS as the internal standard. HRMS were recorded on a Bruker micrOTOF II spectrometer (ESI ionization).

4.2. Synthesis of the enaminone intermediate 3a

3-oxo-2,3-diphenylpropionaldehyde (112 mg, 0.5 mmol) and 2-aminobenzaldehyde (61 mg, 0.5 mmol) were dissolved in chlorobenzene (3.0 mL). Anhydrous $MgSO_4$ (180 mg) was added followed by the addition of TfOH (2.2 μL, 0.025 mmol), and the mixture was stirred at 100 °C for 1.5 h under nitrogen atmosphere (monitored by TLC). Then the solvent was evaporated, and the crude product was purified by silica gel column chromatography with EtOAc/petroleum ether (1:5, v/v) to afford the enaminone intermediate **3a** as a yellow solid (121 mg, 69%).

4.3. General procedure for the synthesis of 3-aryl quinolines

3-oxo-2,3-diarylpropanal (0.5 mmol) and 2-aminobenzaldehyde (0.75 mmol) were dissolved in chlorobenzene (3.0 mL), TfOH (0.025 mmol) was added and the mixture was stirred at 100 °C for 1.5 h (monitored by TLC). Then KO^{t}Bu (1.0 mmol) was added, the reaction mixture was stirred at 100 °C for another 10 min until the enaminone disappeared. The reaction mixture was extracted with ethyl acetate. The combined organic fractions were dried over anhydrous Na_2SO_4, and then evaporated in vacuo and



Scheme 3. Possible mechanism of this novel Friedländer-type synthesis.

purified by silica gel column chromatography (EtOAc/petroleum ether=1:5 to 1:10) to afford the corresponding 3-aryl quinoline.

*4.3.1. 3-Phenylquinoline (**4a**)*[11]. Yellow oil; IR (KBr): ν 3058, 3032, 2925, 2853, 1493, 902, 786, 762, 697 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 9.18 (1H, d, J=2.0 Hz), 8.28 (1H, d, J=2.0 Hz), 8.14 (1H, d, J=8.0 Hz), 7.86 (1H, d, J=8.0 Hz), 7.73–7.69 (3H, m), 7.58–7.49 (3H, m), 7.44–7.41 (1H, m). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 149.9, 147.3, 137.9, 133.8, 133.2, 129.3, 129.2, 129.1, 128.1, 128.0 (2CH), 127.5 (2CH), 127.4, 127.0. HRMS (ESI): $[M+H]^+$ calcd for $C_{15}H_{12}N$: 206.0964; found: 206.0987.

*4.3.2. 3-(4-Methoxyphenyl)quinoline (**4b**)*[12]. White solid; 80% yield; mp: 80–80.5 °C; IR (KBr): ν 3068, 2995, 2957, 2935, 2827, 1609, 1520, 1492, 1287, 1249, 1185, 1029, 830, 753 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 9.16 (1H, d, J=2.2 Hz), 8.23 (1H, d, J=2.2 Hz), 8.12 (1H, d, J=8.0 Hz), 7.84 (1H, d, J=8.0 Hz), 7.71–7.63 (3H, m), 7.57–7.53 (1H, m), 7.06–7.04 (2H, m), 3.87 (3H, s); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 159.9, 149.9, 147.1, 133.5, 132.4, 130.4, 129.2, 129.1, 128.6, 128.2 (2CH), 127.9, 127.0, 114.7 (2CH), 55.3.

*4.3.3. 3-(3-Methoxyphenyl)quinoline (**4c**)*[13]. White solid; 75% yield; mp: 62–62.5 °C; IR (KBr): ν 3052, 3012, 2961, 2936, 2838, 1600, 1579, 1489, 1434, 1293, 1242, 1210, 1170, 1038, 874, 810, 789, 749, 699 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 9.17 (1H, d, J=2.2 Hz), 8.29 (1H, d, J=2.2 Hz), 8.14 (1H, d, J=8.0 Hz), 7.87 (1H, d, J=8.0 Hz), 7.74–7.70 (1H, m), 7.59–7.55 (1H, m), 7.46–7.41 (1H, m), 7.30–7.23 (2H, m), 6.99–6.97 (1H, m), 3.89(3H, s). ^{13}C NMR ($CDCl_3$, 100 MHz)

δ 160.2, 149.9, 147.4, 139.3, 133.7, 133.3, 130.2, 129.4, 129.2, 129.0, 127.9, 127.0, 119.8, 113.4, 113.2, 55.4.

*4.3.4. 3-(2-Methoxyphenyl)quinoline (**4d**)*[14]. Yellow oil; 76% yield; mp: 62–63 °C; IR (KBr): ν 3062, 3030, 3009, 2977, 2936, 2835, 1595, 1493, 1461, 1438, 1243, 1181, 1056, 1022, 952, 908, 790, 753 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 9.12 (1H, d, *J*=2.2 Hz), 8.25 (1H, d, *J*=2.2 Hz), 8.13 (1H, d, *J*=8.0 Hz), 7.84 (1H, d, *J*=8.0 Hz), 7.72–7.68 (1H, m), 7.56–7.52 (1H, m), 7.43–7.38 (2H, m), 7.12–7.03 (2H, m), 3.83 (3H, s). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 156.7, 152.0, 146.8, 135.4, 131.6, 130.9, 129.6, 129.1, 129.1, 127.9, 127.1, 126.5, 121.1 (2CH), 111.2, 55.5.

*4.3.5. 3-(4-Tolyl)quinoline (**4e**)*[15]. White solid; 77% yield; mp: 81–81.5 °C; IR (KBr): ν 3063, 3022, 2953, 2923, 2853, 1491, 1340, 953, 908, 815, 786, 749 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 9.17 (1H, d, *J*=2.0 Hz), 8.27 (1H, s), 8.13 (1H, d, *J*=8.0 Hz), 7.86 (1H, d, *J*=8.0 Hz), 7.72–7.54 (4H, m), 7.34–7.32 (2H, m), 2.43 (3H, s). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 150.0, 147.3, 138.1, 135.1, 133.9, 132.9, 130.0, 129.3 (2CH), 129.2, 128.2, 128.0, 127.3 (2CH), 127.0, 21.1. HRMS (ESI): $[M+H]^+$ calcd for $C_{16}H_{14}N$: 220.1121; found: 220.1105.

*4.3.6. 3-(4-Bromophenyl)quinoline (**4f**).* White solid; 77% yield; mp: 141–141.5 °C; IR (KBr): ν 3059, 3030, 1492, 1431, 1354, 1078, 1006, 954. 906, 823, 785, 750 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 9.13 (1H, d, *J*=2.2 Hz), 8.26 (1H, d, *J*=2.2 Hz), 8.14 (1H, d, *J*=8.0 Hz), 7.87 (1H, d, *J*=8.0 Hz), 7.75–7.71 (1H, m), 7.66–7.63 (2H, m), 7.60–7.56 (3H, m). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 149.4, 147.5, 136.8, 133.1, 132.6 (2CH), 132.3, 129.6, 129.3, 129.0 (2CH), 128.0, 127.9, 127.2, 122.5. HRMS (ESI): $[M+H]^+$ calcd for $C_{15}H_{11}BrN$: 284.0075; found: 284.0088.

*4.3.7. 3-(4-Fluorophenyl)quinoline (**4g**)*[12]. White solid; 75% yield; mp: 105–105.4 °C; IR (KBr): ν 3065, 3047, 3025, 1603, 1518, 1494, 1237, 1166, 951, 905, 832, 747 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 9.13 (1H, d, *J*=2.2 Hz), 8.25 (1H, d, *J*=2.2 Hz), 8.14 (1H, d, *J*=8.0 Hz), 7.87 (1H, d, *J*=8.0 Hz), 7.74–7.65 (3H, m), 7.60–7.56 (1H, m), 7.23–7.19 (2H, m). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 164.3, 161.8, 149.8, 147.4, 134.1, 133.1, 133.0, 129.5, 129.3, 129.2, 129.1, 128.0, 127.2, 116.3, 116.1. HRMS (ESI): $[M+H]^+$ calcd for $C_{15}H_{11}FN$: 224.0876; found: 224.0897.

*4.3.8. 3-(Thiophen-2-yl)quinoline (**4h**).* White solid; 61% yield; mp: 70–70.3 °C; IR (KBr): ν 3065, 3034, 2983, 2920, 1492, 1429, 1346, 824, 782, 749, 692 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 9.21 (1H, d, *J*=2.2 Hz), 8.27 (1H, d, *J*=2.2 Hz), 8.10 (1H, d, *J*=8.0 Hz), 7.83 (1H, d, *J*=8.0 Hz), 7.71–7.67 (1H, m), 7.57–7.49 (2H, m), 7.40–7.39 (1H, m), 7.17–7.15 (1H, m). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 148.6, 147.3, 140.7, 131.3, 129.3, 129.3, 128.4, 127.9, 127.8, 127.5, 127.2, 126.1, 124.4.

*4.3.9. 6-Methoxy-3-phenylquinoline (**4i**)*[16]. White solid; 67% yield; mp: 120–122 °C; IR (KBr): ν 3056, 2996, 2964, 2923, 2851, 1621, 1502, 1456, 1246, 1216, 1027, 901, 829, 700 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 9.02 (1H, d, *J*=2.2 Hz), 8.19 (1H, d, *J*=2.2 Hz), 8.03–8.01 (1H, m), 7.71–7.69 (2H, m), 7.54–7.50 (2H, m), 7.45–7.41 (1H, m), 7.38–7.35 (1H, m), 7.13–7.12 (1H, m), 3.95 (3H, s). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 158.2, 147.5, 138.1, 134.2, 132.1, 130.7, 129.2 (2CH), 129.1 (2CH), 128.1, 127.5 (2CH), 122.2, 105.3, 55.5.

*4.3.10. 6-Bromo-3-phenylquinoline (**4j**).* White solid; 76% yield; mp: 114–114.5 °C; IR (KBr): ν 3055, 3037, 2956, 2924, 2853, 1594, 1483, 1451, 1398, 1330, 1059, 954, 891, 826, 757, 700 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 9.17 (1H, d, *J*=2.2 Hz), 8.18 (1H, d, *J*=2.2 Hz), 8.03–7.99 (2H, m), 7.79–7.76 (1H, m), 7.70–7.68 (2H, m), 7.55–7.51 (2H, m), 7.47–7.44 (1H, m). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 150.3, 145.8, 137.3, 134.7, 132.8, 132.0, 130.9, 129.9, 129.3 (2CH), 129.2, 128.4, 127.5 (2CH), 120.9.

*4.3.11. 3-Methylquinoline (**4k**)*[17]. Yellow oil; 67% yield; IR (KBr): ν 3064, 3031, 2921, 2857, 1495,1400, 1328, 1123, 977, 887, 785, 749 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) : δ 8.76 (s, 1H), 8.06 (d, *J*=8.4 Hz, 1H), 7.89 (s, 1H), 7.72 (d, *J*=8.1 Hz, 1H), 7.65 (m, 1H), 7.49 (m, 1H), 2.50 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 152.4, 146.5, 134.6, 130.4, 129.1, 128.4, 128.1, 127.1, 126.5, 18.7.

*4.3.12. 6-Nitro-3-phenylquinoline (**4l**).* White solid; 34% yield; mp: 159–161 °C; IR (KBr): ν 3055, 3037, 2956, 2924, 2853, 1606, 1518, 1489, 1440, 1420, 1348, 1085, 934, 911, 826, 751, 690 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 9.35 (d, *J*=2.5 Hz, 1H), 8.86 (d, *J*=2.5 Hz, 1H), 8.49–8.47 (m, 2H), 8.29–8.27 (m, 1H), 7.74–7.73 (m, 2H), 7.59–7.56 (m, 2H), 7.52–7.49 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 153.5, 149.2, 146.0, 136.7, 135.8, 134.6, 131.2, 129.5, 129.0, 127.6, 127.05, 124.8, 122.8. HRMS (ESI) for $C_{15}H_{11}N_2O_2$ $[M+H]^+$: calcd 251.0815, found 251.0812.

*4.3.13. (E)-2-(3-Oxo-2,3-diphenylprop-1-enylamino)benzaldehyde (E-**3a**) with (Z)-2-(3-oxo-2,3-diphenylprop-1-enylamino)benzaldehyde (Z-**3a**).* Yellow solid. ^1H NMR ($CDCl_3$, 500 MHz) δ 13.38 (0.3H, d, *J*=12.5 Hz, NH of *Z*-Configuration), 10.78 (0.7H, d, *J*=13.0 Hz, NH of *E*-Configuration), 10.5 (0.3H, s, CHO of *Z*-Configuration), 9.75 (0.7H, s, CHO of *E*-Configuration), 8.01 (0.7H, d, *J*=13.0 Hz, =CH–N of *E*-Configuration), 7.71 (0.3H, d, *J*=8.0 Hz, =CH–N of *Z*-Configuration), 7.66–7.63 (2.1H, m,), 7.58–7.55 (0.9H, m), 7.53–7.42 (4H, m), 7.38 (3H, t, *J*=7.5 Hz), 7.30 (0.3H, t, *J*=7.5 Hz), 7.25–7.11 (3H, m), 7.05 (0.7H, t, *J*=7.5 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 194.7 (0.7C, C=O of *E*-Configuration), 194.6 (0.3C, C=O of *Z*-Configuration), 194.3 (0.7C, CHO of *E*-Configuration), 193.2 (0.3C, CHO of *E*-Configuration), 142.9 (0.7C), 142.2 (0.3C), 141.1 (0.3C), 140.2 (0.7C), 140.1 (0.3C), 139.5 (0.7C), 136.6 (0.3C), 136.5 (0.7C), 136.0 (0.7C), 135.5 (0.3C), 134.2 (0.7C), 130.8 (0.6C), 130.6 (0.3C), 130.2 (0.6C), 129.5 (0.6C), 129.3 (0.6C), 129.2 (1.4C), 129.1 (1.4C), 128.4 (1.4C), 128.1 (1.4C), 128.0 (1.4C), 127.5 (0.6C), 126.3 (0.7C), 122.2 (0.3C), 121.6 (0.3C), 121.0 (0.7C), 120.4 (0.7C), 116.1 (0.3C), 113.2 (0.3C), 112.8 (0.7C). HRMS (ESI) for $C_{22}H_{17}NO_2Na$ $[M+Na]^+$: calcd 350.1175, found 350.1187.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2011.07.004.

References and notes

1. (a) Gildchrist, T. L. *Heterocyclic Chemistry*, 1st ed.; Pitman Publishing LTD: London, 1985; (b) Joshi, A. A.; Narkhede, S. S.; Viswanathan, C. L. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 73–76; (c) Roma, G.; Di Braccio, M.; Grossi, G.; Mattioli, F.; Ghia, M. *Eur. J. Med. Chem.* **2000**, *35*, 1021–1035; (d) Narender, P.; Srinivas, U.; Ravinder, M.; Rao, B. A.; Ramesh, C.; Harakishore, K.; Gangadasu, B.; Murthy, U. S. N.; Rao, V. J. *Bioorg. Med. Chem.* **2006**, *14*, 4600–4609; (e) Martirosyan, A. R.; Rahim-Bata, R.; Freeman, A. B.; Clarke, C. D.; Howard, R. L.; Strobl, J. S. *Biochem. Pharmacol.* **2004**, *68*, 1729–1738.
2. Dube, D.; Blouin, M.; Brideau, C.; Chan, C.; Desmarais, S.; Ethier, D.; Falgueyret, J. P.; Friesen, R. W.; Girard, M.; Girard, Y.; Guay, J.; Tagari, P.; Young, R. N. *Biorg. Med. Chem. Lett.* **1998**, *8*, 1255–1260.
3. Kalluraya, B.; Sreevinasa, S. *Farmaco* **1998**, *53*, 399–404.

4. Strekowski, L.; Mokrosz, J. L.; Honkan, V. A.; Czarny, A.; Cegla, M. T.; Wydra, R. L.; Patterson, S. E.; Schinazig, R. F. *J. Med. Chem.* **1991**, *34*, 1739–1746.
5. Maguire, M. P.; Sheets, K. R.; McVety, K.; Spada, A. P.; Zilberstein, A. *J. Med. Chem.* **1994**, *37*, 2129–2137.
6. (a) Manske, R. H. *Chem. Rev.* **1942**, *30*, 113–114; (b) Bergström, F. W. *Chem. Rev.* **1944**, *35*, 77–277; (c) Povarov, L. S. *Russ. Chem. Rev.* **1967**, *36*, 656–670; (d) Hisano, T. *Org. Prep. Proced. Int.* **1973**, *5*, 145–193; (e) Thummel, R. P. *Synlett* **1992**, 1–12; (f) Chan, B. K.; Ciufolini, M. A. *J. Org. Chem.* **2007**, *72*, 8489–8495; (g) Hormi, O. E.; Peltonen, C.; Heikkila, L. *J. Org. Chem.* **1990**, *55*, 2513–2515; (h) Zong, R.; Zhou, H.; Thummel, R. P. *J. Org. Chem.* **2008**, *73*, 4334–4337; (i) Ivachtchenko, A. V.; Kobak, V. V.; Ilyin, A. P.; Khvat, A. V.; Kysil, V. M.; Williams, C. T.; Kuzovkova, J. A.; Kravchenko, D. V. *J. Comb. Chem.* **2005**, *7*, 227–235; (j) Hadden, M.; Stevenson, P. J. *Tetrahedron Lett.* **1999**, *40*, 1215–1218; (k) Powell, D. A.; Batey, R. A. *Org. Lett.* **2002**, *4*, 2913–2916; (l) Cho, I. S.; Gong, L.; Muchowski, J. M. *J. Org. Chem.* **1991**, *56*, 7288–7291; (m) Riesgo, E. C.; Jin, X.; Thummel, R. P. *J. Org. Chem.* **1996**, *61*, 3017–3022; (n) Wu, Y.; Liu, L.; Li, H.; Wang, D.; Chen, Y. *J. Org. Chem.* **2006**, *71*, 6592–6595; (o) Denmark, S. E.; Venkatraman, S. *J. Org. Chem.* **2006**, *71*, 1668–1676; (p) Matsugi, M.; Tabusa, F.; Minamikawa, J.-I. *Tetrahedron Lett.* **2000**, *41*, 8523–8525.
7. (a) Vander Mierde, H.; Van Der Voort, P.; De Vos, D.; Verpoort, F. *Eur. J. Org. Chem.* **2008**, 1625–1631; (b) Vander Mierde, H.; Ledoux, N.; Allaert, B.; Van Der Voort, P.; Drozdzak, R.; De Vos, D.; Verpoort, F. *New J. Chem.* **2007**, *31*, 1572–1574.
8. Vander Mierde, H.; Van Der Voort, P.; Verpoort, F. *Tetrahedron Lett.* **2008**, *49*, 6893–6895.
9. Mathew, P.; Mathew, D.; Asokan, C. V. *Synth. Commun.* **2007**, *37*, 661–665.
10. Muchowski, J. M.; Maddox, M. L. *Can. J. Chem.* **2004**, *82*, 461–478.
11. Hogan, A. M. L.; O'Shea, D. F. *Org. Lett.* **2006**, *8*, 3769–3772.
12. Denmark, S. E.; Smith, R. C.; Chang, W. T. T.; Muhuhi, J. M. *J. Am. Chem. Soc.* **2009**, *131*, 3104–3118.
13. Rueping, M.; Theissmann, T.; Raja, S.; Bats, J. W. *Adv. Synth. Catal.* **2008**, *350*, 1001–1006.
14. Pena, M. A.; Sestelo, J. P.; Sarandeses, L. A. *J. Org. Chem.* **2007**, *72*, 1271–1275.
15. Dawood, K. M.; El-Deftar, M. M. *ARKIVOC* **2010**, *9*, 319–330.
16. Wang, Y.; Xin, X.; Liang, Y. J.; Lin, Y. G.; Zhang, R.; Dong, D. W. *Eur. J. Org. Chem.* **2009**, *24*, 4165–4169.
17. Huiban, M.; Huet, A.; Barré, L.; Sobrio, F.; Fouquet, E.; Perrio, C. *Chem. Commun.* **2006**, 97–99.