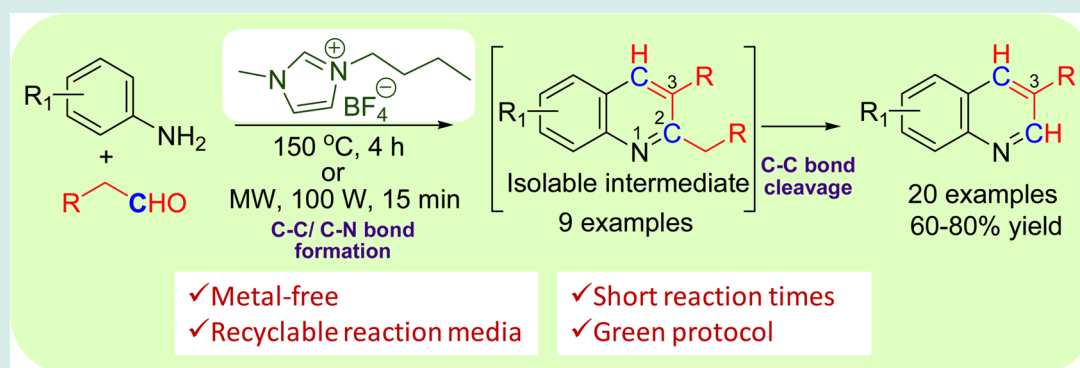


Metal-Free, Ionic Liquid-Mediated Synthesis of Functionalized Quinolines

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ABSTRACT: An expedient and metal-free synthetic protocol for construction of substituted quinolines has been developed from anilines and phenylacetaldehydes using imidazolium cation-based ionic liquids as the reaction medium. Mechanistic analysis indicated that the reaction occurs through C–C and C–N bond formation to produce isolable 2,3-disubstituted quinoline intermediates, which undergo C–C bond cleavage to produce 3-substituted quinolines. The reaction proceeds smoothly with a range of functionalities in good to excellent yields. Advantages of this protocol include metal-free, environmentally friendly, recyclable reaction media, higher yields and shorter reaction times, and thus is promising for the efficient combinatorial synthesis of structurally diverse 2,3-disubstituted and 3-substituted quinolines.

KEYWORDS: ionic liquids, metal-free, quinolines, heterocycle synthesis, green chemistry

INTRODUCTION

Metal-free synthetic protocols can diminish adverse environmental consequences of many organic reactions.^{1–4} Many efforts to establish metal-free reaction conditions use polar solvents and ionic liquids (ILs), the latter area focusing largely on water-soluble imidazolium cation-based systems.^{5–8} ILs have been considered as green solvents due to their properties of high thermal stability, nonflammable nature, immiscibility with a number of organic solvents, negligible vapor pressure, and recyclability.^{9,10} Furthermore, ILs are known to play roles both as solvent and catalyst.¹¹ For example, 1-butyl-3-methylimidazolium tetrafluoroborate ([Bmim]BF₄) has been used in a wide variety of reactions, including synthesis of vic-diamines,¹² Michael reaction,¹³ synthesis of 1,4-dihydropyridines,¹⁴ cleavage of ethers,¹⁵ Stille coupling,¹⁶ halogenation of alkenes,¹⁷ olefin metathesis,¹⁸ and Suzuki–Miyaura cross-coupling.¹⁹ The ILs are also widely used in the synthesis of heterocyclic compounds^{5,20,21} and inorganic materials.²²

Quinoline is one of the most widely occurring heterocyclic scaffolds in drugs and natural products, possessing a diverse range of pharmacological activities and therefore attracting the continued attention of medicinal and synthetic chemists. Apart

from conventional approaches,^{23–28} several new methods have been discovered for quinoline synthesis.^{29–32} Among these, the condensation of anilines and phenylacetaldehydes provides an elegant approach to substituted quinolines, for which two methods are reported in the literature (Table 1): (a) sulfamic acid catalyzed synthesis of 2,3-disubstituted quinolines (3)³³ and (b) CuBr/CF₃SO₃H catalyzed synthesis of 3-substituted quinolines (4).³⁴ In addition to these two reports, there exists another similar approach for synthesis of 3-substituted quinolines 4, which involves FeCl₃-catalyzed condensation of anilines and styrene oxides.³⁵

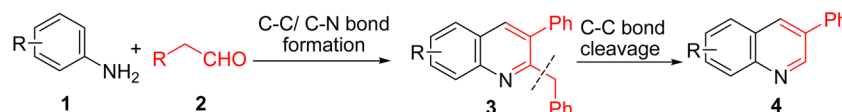
In the present paper, we report a green, facile, and efficient metal-free synthesis of 2,3-disubstituted 3 and 3-substituted quinolines 4 through sequential one-pot C–C/C–N bond formation and C–C bond cleavage (entries 3–5, Table 1). The advantages of the present protocol include the following: (a) ability to prepare both 2,3-disubstituted 3 and 3-substituted quinolines 4 using this reaction; (b) metal-free reaction

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Table 1. Methods for Quinoline Synthesis from Aniline and Phenylacetaldehyde



no.	ref	conditions	% yield of 3/4
1	33	NH ₂ SO ₃ H, 80 °C, 3–5 h	63–86/0 ^a
2	34	CuBr/CF ₃ SO ₃ H, DMSO, 110 °C	0 ^b /45–93
3	this work	[Bmim]BF ₄ , 150 °C, 4 h	8/78 ^c
4	this work	[Bmim]BF ₄ , 120 °C, MW, 100 W, 15 min	8/80 ^c
5	this work	[Bmim]BF ₄ , 110 °C, 0.5 h	35/50 ^c

^aOnly product 3 was formed. ^bOnly product 4 was formed. ^cYields are mentioned for products obtained from 2,3-dimethyl aniline.

condition; (c) recyclable and ecofriendly ionic liquid reaction media.

RESULTS AND DISCUSSION

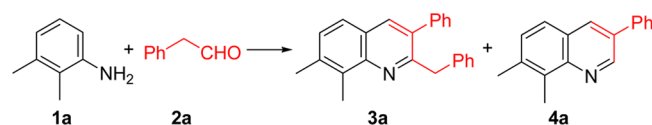
To establish a metal-free protocol for the synthesis of substituted quinolines, we explored the reaction of 2,3-dimethylaniline (**1a**) with phenylacetaldehyde (**2a**) in the presence of CuBr and 1-butyl-3-methylimidazolium tetrafluoroborate ionic liquid (as a replacement for CF₃SO₃H and DMSO in the published protocol³⁴) at 110 °C (Table 2, entry 1). Gratifyingly, the desired 3-substituted quinoline **4a** was obtained in good yield (entry 1), comparable to the Yan method (entry 2).³⁴ Control reactions without addition of CF₃SO₃H (entry 3) or CuBr (entry 4) established the essential nature of these reagents in the absence of IL. The Lewis acid FeCl₃ was an effective replacement for CuBr (giving **4a** in 70%

yield, entry 5), and the addition of ionic liquid gave a slightly better result (78% yield, entry 6). Most encouraging, however, was the formation of quinolines **3a** and **4a** in 12% and 70% yields, respectively, in the presence of ionic liquid [Bmim]BF₄ without the addition of any catalyst or additive (entry 7). Exploration of reaction temperature (entries 7–11) indicated 150 °C as optimal, with no reaction occurring at room temperature. When the reaction time was reduced from 4 h to 30 min, the 2,3-disubstituted quinoline **3a** could be isolated in 35% yield (entry 10). A different ionic liquid, 1-ethyl-3-methylimidazolium 1,1,2,2-tetrafluoroethanesulfonate ([emim]-[CHF₂CF₂SO₃]), was not successful (entry 12).

Since ILs have ability to absorb microwave energy and convert it into heat, microwave irradiation is an attractive alternative for thermally driven reactions in these media. Accordingly, the above model reaction was subjected to microwave irradiation (100 W) at 120 °C for 5–15 min (entries 13 and 14), which produced desired product **4a** in 80% yield (entry 14). Thus, the entries 8 and 14 are considered as optimized reaction conditions under conventional heating and microwave irradiation, respectively.

An exploration of aniline and phenylacetaldehyde scope using the conventional optimized reaction conditions (entry 8, Table 2) gave the results shown in Figure 1. Anilines substituted with electron-donating groups (**4a–4e**, **4g–4l**) and electron-withdrawing groups (**4m–4o** and **4s**) each participated well in this reaction. Similarly, nonsubstituted (**4a–4o**) as well as substituted (**4p–4s**) phenylacetaldehydes produced corresponding quinoline products in good yields. For the latter examples, the corresponding phenylacetaldehydes were prepared from phenyl epoxides by treatment with zeolite in methylene chloride.³⁶ The phenylacetaldehydes obtained by evaporation of the solvent were treated directly with anilines and ionic liquid in the same pot to produce the desired quinolines **4p–4s** (Figure 1). In contrast to anilines, cyclohexylamine did not produce the desired product.

Representative aliphatic aldehydes (*n*-butyraldehyde and phenylpropanal) also proved to be interesting (Figure 2). The 3-substituted quinoline product **4t** was obtained from the reaction of 2-bromoaniline with *n*-butyraldehyde, which was not possible using Yan and co-workers³⁴ protocol. However, in other cases, 2,3-disubstituted quinolines **3u–x** were obtained. As with CuBr/CF₃SO₃H,³⁴ the reaction of 3-phenylpropanal **2w** with aniline **1b** using our optimized reaction conditions led to formation of only 2,3-disubstituted product 3-benzyl-2-phenethylquinoline **3w** (Figure 2). Performing the reaction at 110 °C for 30 min gave both 2,3-disubstituted and 3-monosubstituted products (Table 3). The 2,3-disubstituted

Table 2. Optimization of Reaction Conditions^a

entry	catalyst	additive	reaction medium	temp ^b (°C)/ time	yield ^c (%) 3a/ 4a
1	CuBr	none	[Bmim]BF ₄	110/4 h	5/80
2	CuBr	CF ₃ SO ₃ H	DMSO	110/4 h	5/74
3	CuBr	none	DMSO	110/4 h	0/0
4	none	CF ₃ SO ₃ H	DMSO	110/4 h	0/0
5	FeCl ₃	none	CH ₃ CN	110/4 h	8/70
6	FeCl ₃	none	[Bmim]BF ₄	110/4 h	5/78
7	none	none	[Bmim]BF ₄	110/4 h	12/70
8^d	none	none	[Bmim]BF₄	150/4 h	8/78
9	none	none	[Bmim]BF ₄	180/4 h	8/80
10	none	none	[Bmim]BF ₄	110/30 min	35/50
11	none	none	[Bmim]BF ₄	25/4 h	0/0
12	none	none	[Emim] [CHF ₂ CF ₂ SO ₃]	110/4 h	0/0
13	none	none	[Bmim]BF ₄	120, MW, 100 W, 5 min	18/48
14^d	none	none	[Bmim]BF₄	120, MW, 100 W, 15 min	8/80

^a**1a** (1.0 mmol), **2a** (2.0 mmol), catalyst or additive (wherever mentioned), and solvent. ^bMW, microwave irradiation. ^cIsolated yields after silica gel column chromatography. ^dBold entries indicate optimized reaction conditions for synthesis of 3-substituted quinolines **4**.

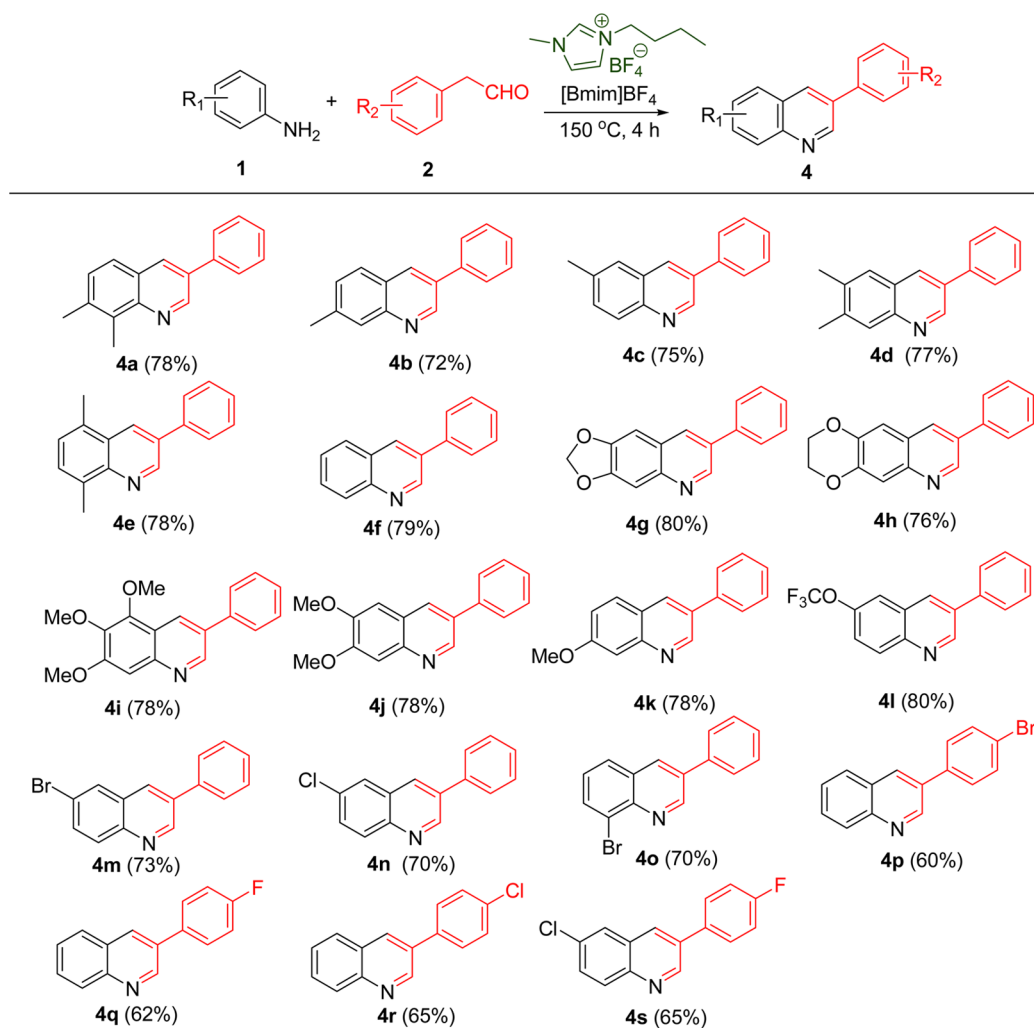


Figure 1. Metal-free synthesis of 3-substituted quinolines in ionic liquid under conventional heating.

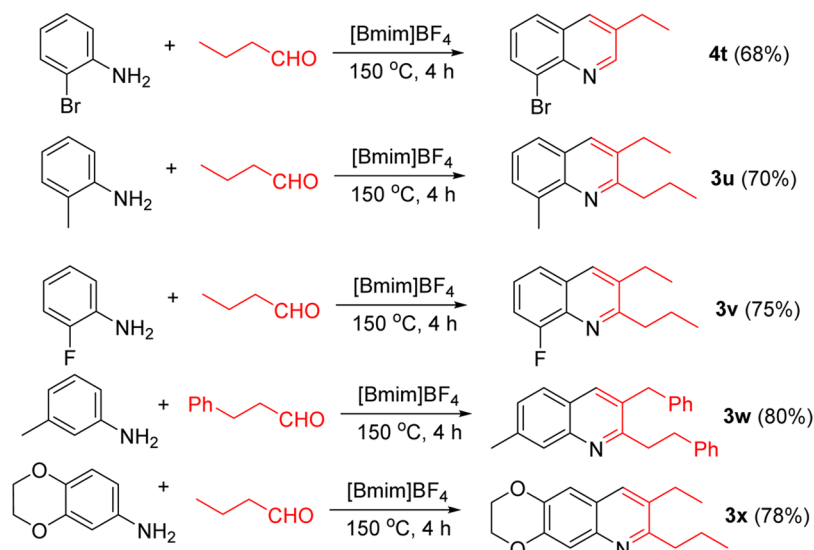
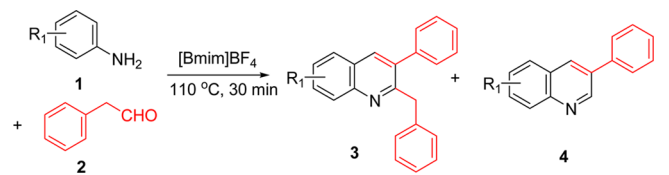


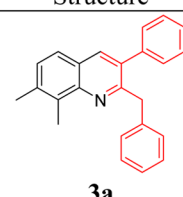
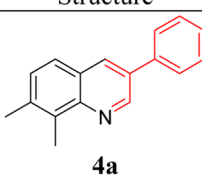
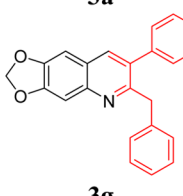
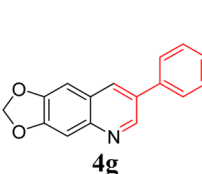
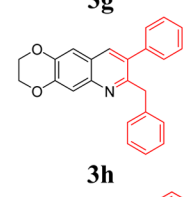
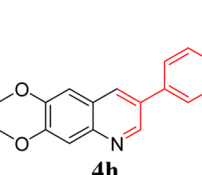
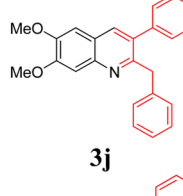
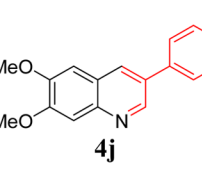
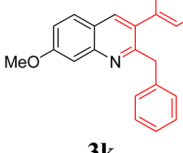
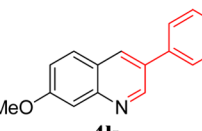
Figure 2. Metal-free synthesis of 3-substituted and 3,4-disubstituted quinolines in ionic liquid.

quinolines **3a** and **3g–3k** were obtained in 18–45% yields, along with 3-substituted quinolines **4a** and **4g–k** (38–50%).

The repeated reuse of the ionic liquid reaction medium was investigated using the model reaction between 2,3-dimethyl

aniline **1a** and phenylacetaldehyde **2a**. After completion of the reaction, products were extracted with diethyl ether, and the remaining ionic liquid after drying under reduced pressure was reused for next reaction. The desired product **4a** was obtained

Table 3. Synthesis of Mono- And Disubstituted Quinolines^a


Entry	Product 3		Product 4	
	Structure	%Yield ^b	Structure	%Yield ^b
1	 3a	35	 4a	50
2	 3g	28	 4g	42
3	 3h	30	 4h	45
4	 3j	18	 4j	38
5	 3k	26	 4k	40

^aAniline **1** (1.0 mmol), phenylacetaldehyde **2** (2.0 mmol), and ionic liquid was heated to reflux at 110 °C for 30 min. ^bIsolated yields after silica gel column chromatography.

in 70%, 68%, 65%, and 62% yield over four cycles, indicating good recyclability of the ionic liquid over several cycles.

Since ILs are known to activate carbonyl groups through hydrogen-bonding, we suggest that [Bmim]BF₄ activates the aldehyde electrophile by interaction with the carbonyl oxygen as illustrated in Figure 3 for the representative reaction of **1a** + **2a**. The ionic liquid [Bmim]BF₄ may also enhance the nucleophilicity of the amine through interaction of tetrafluoroborate with the N–H bond. The resulting imine intermediate undergoes self-condensation to generate **3a₁** as a key intermediate. This is supported by monitoring of the reaction by LC-ESI-MS at intermediate reaction time (30 min). As shown in Figure 4, 2,3-disubstituted quinoline intermediates **3a₁** and **3a₂** were observed along with product **4a**. At 4 h reaction time, the ratio of **4a**/**3a₂** changed from 37:35 to 70:0, suggesting that **3a₂** is a key intermediate in the formation of **4a** (section S3 of Supporting Information).

The cleavage process that takes **3** to **4** was found to be inhibited by a radical quencher: the reaction of **1a** + **2a** performed in the presence of TEMPO produced **3a₁** as the major product with **4a** formed only in trace amounts. In the absence of TEMPO, the cleavage event generates benzaldehyde as a byproduct (seen in TLC). These observations are consistent with the presumed formation of a benzylic radical **V** and hydroperoxide **VII** (Figure 3). Based on the literature precedence,^{37,38} we presume that IL plays a role in generating benzylic radical **V** from intermediate **3a₂**; however, the exact mechanism of radical generation is not clearly understood.

In summary, we have found that an ionic solvent allows for the direct synthesis of substituted quinolines without metal catalyst or additive, presumably by functioning both as a Lewis acid and Lewis base. The method is operationally simple and can be used to access both 2,3-disubstituted and 3-substituted quinolines. The ionic liquid [Bmim]BF₄ provides a recyclable and nonvolatile medium, simple workup, and high product

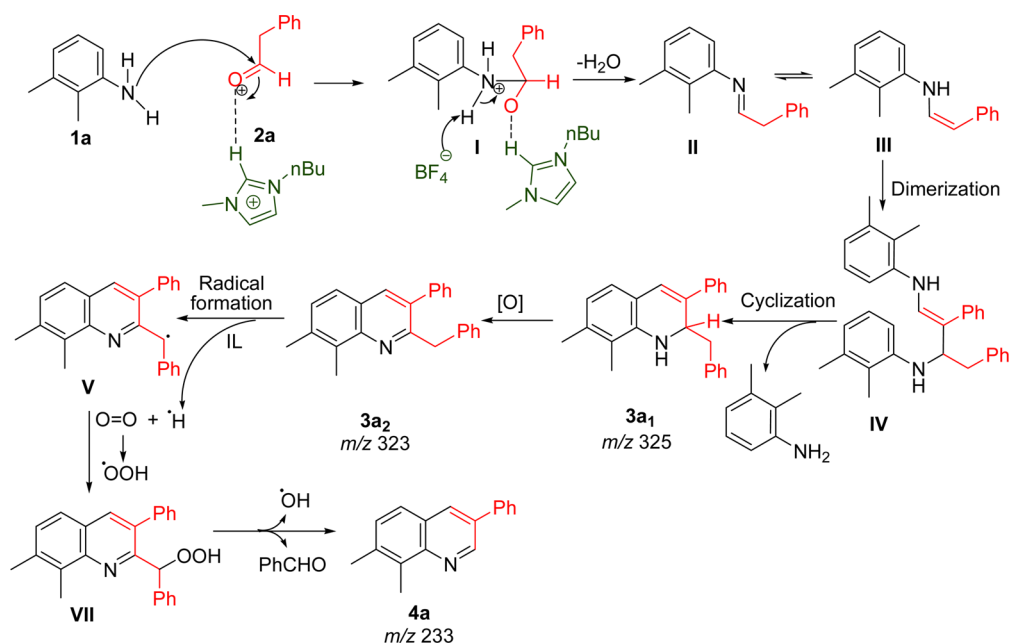


Figure 3. Plausible reaction mechanism showing formation of $3a_1$ and $3a_2$ as key intermediates during synthesis of 3-substituted quinoline $4a$.

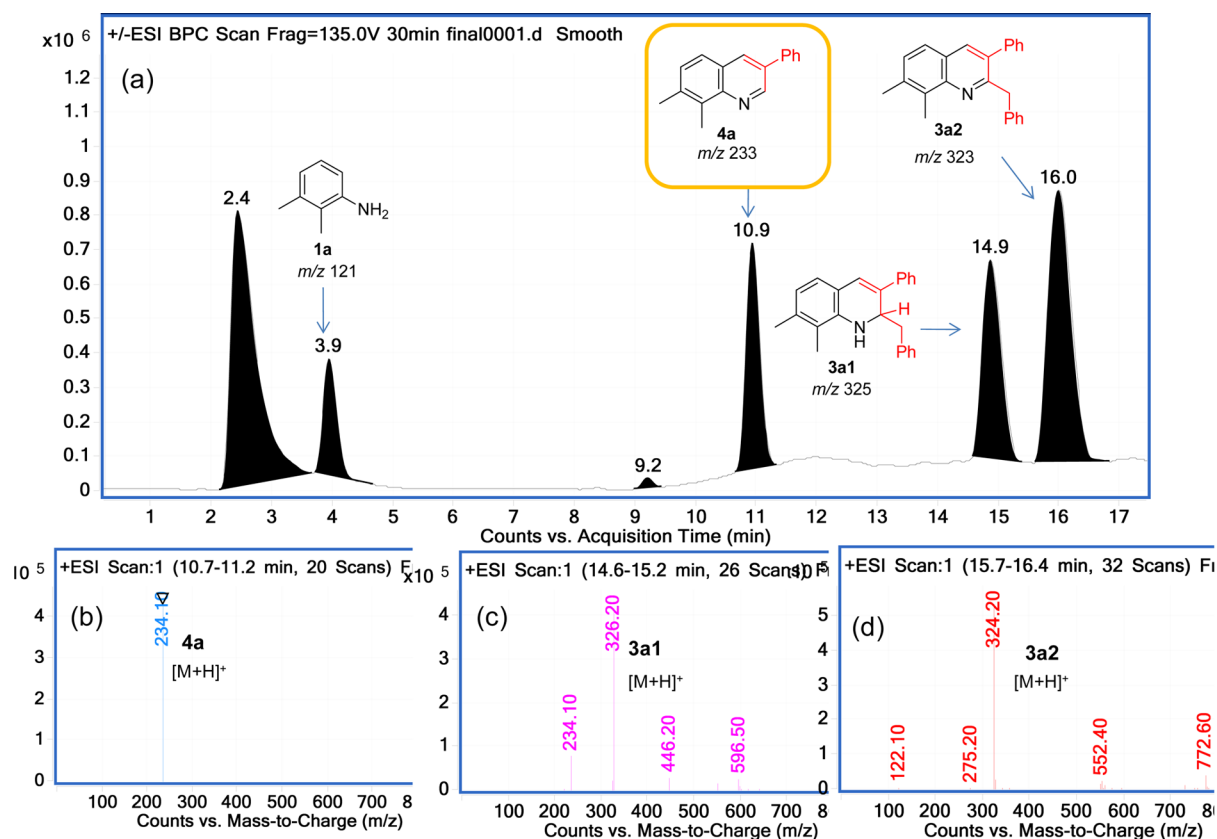


Figure 4. LC-ESI-MS analysis of reaction mixture after 30 min. (a) LCMS chromatogram showing product $4a$ and intermediates $3a_1$ and $3a_2$; (b–d) MS chromatograms of peaks appearing at t_R 10.9, 14.9, and 16.0 min, respectively.

yield, and therefore a useful alternative to existing processes for quinoline synthesis.

EXPERIMENTAL PROCEDURES

General Optimized Procedure for Synthesis of 3-Substituted Quinolines $4a$ – t . The ionic liquid 1-butyl-3-methylimidazolium tetrafluoroborate used in the present study was purchased from

Sigma-Aldrich. Although this IL is commercially available, it can be prepared starting from *N*-methylimidazole.³⁹ The mixture of aniline (1 , 1.0 mmol) and phenylacetaldehyde (2 , 2.0 mmol) in ionic liquid [Bmim]BF₄ (1 mL) was stirred at 150 °C in an oil bath in an open-air atmosphere for 4 h. After completion of the reaction, products were extracted with diethyl ether (50 mL \times 3). The remaining ionic liquid was further washed with diethyl ether and dried at 80 °C under

reduced pressure, for its reuse. The combined organic layer was evaporated under reduced pressure to give the crude product. Purification by silica gel column chromatography (mesh 100–200) using hexane–EtOAc as eluent gave quinolines **4a–4t** as major products in 60–80% yield. The spectral data for all synthesized quinolines **4a–4t** and **3a–x** is provided in the Supporting Information.

■ ASSOCIATED CONTENT

● Supporting Information

Experimental procedures and NMR spectra of all compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

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