An Efficient Synthesis of Imidazo[1,2-*a*]pyridines

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Abstract

Imidazo[1,2-*a*]pyridines are useful building blocks for a number of biologically and pharmaceutically valuable compounds. Its synthetic method started from the reaction of 2-aminopyridines with acetophenones. However, the existing synthetic methods have drawbacks such as relatively high reaction temperatures, long reaction times and the difficult post-treatment. In this article, an improved synthetic method with high yield and simple steps for the synthesis of imidazo[1,2-*a*]pyridines was reported. It is an improved method that CsF-Celite was used in post-treatment, which enhanced the total yield, and the operations were effectually simplified by the one-pot method. Moreover, CsF-Celite can be recovered for subsequent reactions and reused without any loss of efficiency.

Keywords: Celite, Cesium Fluoride, One-pot synthesis

Introduction

In recent years, imidazo[1,2-*a*]pyridines have drawn considerable attentions due to their various advantages, especially in therapeutic activities such as antiviral (Gudmundsson, Williams, Drach, & Townsend, 2003; Gueiffier et al., 1998; Lhassani et al., 1999), antimicrobial (Chandra Mohan, Reddy Donthiri, Nageswara Rao, & Adimurthy, 2013), antiulcer (Starrett, Montzka, Crosswell, & Cavanagh, 1989), anti-inflammatory (Hieke et al., 2012), antipsychotic (Marcinkowska et al., 2016), anti HIV (Jenkinson et al., 2010), anticancer (Byth, Geh, Forder, Oakes, & Thomas, 2006; Hayakawa et al., 2007) and β-amyloid formation inhibitors. Among these therapeutic activities, some imidazo[1,2-*a*]pyridine scaffolds are readily available as marketed drugs including zolimidine, zolpidem, alpidem, olprinone, and saripidem. Additionally, the remarkable fluorescence properties of imidazo[1,2-*a*]pyridines have been recently discovered and applied to the application as amyloid plaques imaging probes in brain (Hodgkiss et al., 1992; Yousefi et al., 2012; Zhuang et al., 2003).

Various methods for the synthesis of imidazo[1,2-*a*]pyridines have been continually developed such as oxidative coupling (Bagdi, Rahman, Santra, Majee, & Hajra, 2013; Cao et al., 2014; Donohoe, Kabeshov, Rathi, & Smith, 2012; Meng, Wang, Yu, & Zhao, 2014; Zeng, Tan, Leow, & Liu, 2012), oxidative amination (Monir, Bagdi, Ghosh, & Hajra, 2014), aminooxygenation (Wang et al., 2011) and hydroamination (Chioua et al., 2013). The most attractive method is the condensation reaction of 2-aminopyridines with α-haloketones which exhibited several advantages compared to other synthetic methods such as simple operation and reduction in waste generation (Patil, Gaikwad, & Bobade). However, the lachrymatory property of α-haloketones (Karade, Kondre, Gampawar, & Shinde, 2009) is one of the main limitations of this approach. Hence, one-pot syntheses via Ortoleva-King without isolation of α-haloketone

are an alternative way to partly overcome these limitations (Kielesinski, Tasior, & Gryko, 2015; Stasyuk, Banasiewicz, Cyrański, & Gryko, 2012). The reaction mechanism involves two major steps: 1) formation of keto-ammonium salt intermediate (**3**) and 2) cyclization under basic condition (Saldabol & Giller, 1976) (Figure 1). However, the conventional methods for the synthesis of imidazo[1,2-*a*]pyridines require long reaction times, high reaction temperatures, difficult separation, and low yields.

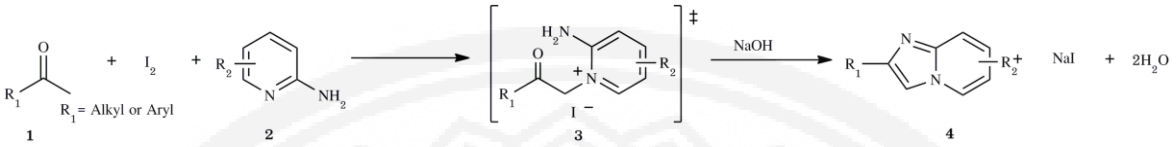


Figure 1 Formation of imidazo[1,2-*a*]pyridines

For recent decades, inorganic-solid-supported, such as KF-celite and CsF-celite, have attracted significant attention, due to their extremely versatile properties such as their high thermal stability, ease of handling and ability of H-bond formation with fluoride anion (Clark, 1980). These materials have been extensively studied and applied in organic synthesis, for example, alkylation (Ando & Yamawaki, 1979; Bloch & Orvane, 1981; Hayat et al., 2001), acylation (Mukaiyama, Pai, Onaka, & Narasaka, 1980), cyclization (Mali & Kulkarni-Joshi, 1999; Mohammed Khan et al., 2003), cyclocondensation (Chancharunee, Pinhom, Pohmakotr, & Perlmutter, 2009) and esterification (Lee & Choi, 1998; Oaksmith & Ganem, 2009).

We have recently reported an efficient method, using ionic liquids as catalyst under ultrasound irradiation (US), which allowed us to obtain imidazo[1,2-*a*]pyridines with shorter reaction time and under milder reaction conditions (Paengphua & Chancharunee, 2018). During our studies, we found that the types and amount of base play an important role to induce complete conversion to the product. The increasing popularity of ionic fluorides as bases has prompted us in further studies for improving the procedure for imidazo[1,2-*a*]pyridine synthesis. In continuation of our efforts to develop simple and general methods for the preparation of imidazo[1,2-*a*]pyridines, we herein report a simple one-pot synthesis approach of imidazo[1,2-*a*]pyridines using ionic liquids as catalyst and CsF-Celite as heterogeneous base under ultrasound irradiation.

Methods and Materials

Materials and Apparatus

All chemical reagents were carefully purified prior to the use in the reaction. A frequency of 40 kHz and a nominal power 150 W of ultrasonic cleaner bath was employed as energy source. Known compounds were identified by comparison of their melting points, ^{1}H NMR and ^{13}C NMR spectra with the reported values in literatures (Paengphua & Chancharunee, 2018). The CsF-Celite was prepared under the same manner as that of previously reported methods (Lee & Choi, 1998; Polshettiwar & Kaushik, 2005).

General procedure for the synthesis of imidazo[1,2-*a*]pyridines

To a 5 mL dried flat bottom capped vial, a mixture of acetophenone **1** (0.51 mmol), 2-aminopyridine **2** (1.17 mmol), iodine (0.61 mmol) and 20 mol% 1-butyl-3-methylimidazolium tetrafluoroborate ([BMIM]BF_4) (0.10 mmol) were added and equipped with magnetic bar. The mixture was irradiated at a frequency of 40 kHz for 1-3 hours at 30-45 ^{o}C. The temperature of ultrasonic bath was controlled manually by addition or removal of small amounts water. To complete the reaction, 0.76 mmol of CsF-Celite and 2 mL

of $CHCl_3$ were added to the reaction and further irradiated at the same frequency at 40-45 °C for 15 minutes. The solid was filtered and washed with 2x2 mL of $CHCl_3$and 2 mL of acetone. The combined organic phase was dried with Na_2SO_4 and concentrated under *vacuo* which was further purified by column chromatography to give the desired product. The used solid CsF-Celite has been recovered by washing three times with $CHCl_3$ followed by small portion of acetone. Then, the solid was further dried at 50 °C for 2 hours and reused successively.

2-Phenylimidazo[1,2-*a*]pyridine (**4a**); White solid, mp = 135-137 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (d, 6.5 Hz, 1H), 7.97 (d, 7.7 Hz, 2H), 7.84 (s, 1H), 7.65 (d, 8.9 Hz, 1H), 7.45 (m, 2H), 7.35 (t, 7.5 Hz, 1H), 7.16 (m, 1H), 6.74 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.2, 146.1, 134.2, 128.9, 128.2, 126.5, 126.0, 125.0, 117.9, 112.8, 108.5.

2-(4-Bromophenyl)imidazo[1,2-*a*]pyridine (**4b**); Pale yellow solid, mp = 214-215 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (d, 6.9 Hz, 1H), 7.87 (s, 1H), 7.85 (d, 8.3, 2H), 7.62 (d, 9.0 Hz, 1H), 7.57 (d, 8.6 Hz, 2H), 7.18 (m, 1H), 6.80 (t, 6.9 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.8, 144.7, 132.6, 131.7, 127.7, 125.5, 125.1, 122.0, 117.7, 112.8, 108.1.

2-(3-Methoxyphenyl)imidazo[1,2-*a*]pyridine (**4c**); Light yellow solid, mp = 61-63 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (dt, 6.7, 1.0 Hz, 1H), 7.87 (s, 1H), 7.65 (d, 9.0 Hz, 1H), 7.58 (dd, 2.8, 1.5 Hz, 1H), 7.52 (dt, 7.8, 1.5 Hz, 1H), 7.35 (t, 8.0 Hz, 1H), 7.19 (ddd, 9.0, 6.7, 1.0 Hz, 1H), 6.89 (d, 8.0 Hz 1H), 6.80 (t, 6.7, 1H), 3.89 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.1, 145.7(2), 135.3, 129.6, 125.5, 124.8, 118.7, 117.5, 114.2, 112.4, 111.1, 108.3, 55.2.

2-(4-Methoxyphenyl)imidazo[1,2-*a*]pyridine (**4d**); Pale yellow solid, mp = 134-136 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (d, 6.8 Hz, 1H), 7.90 (d, 8.8 Hz, 2H), 7.79 (s, 1H), 7.62 (d, 9.0 Hz, 1H), 7.16 (m, 1H), 6.99 (d, 8.8 Hz, 2H), 6.76 (t, 6.8 Hz, 1H), 3.86 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.8, 145.7, 145.6, 127.2, 126.5, 125.6, 124.4, 117.3, 114.3, 112.4, 107.3, 55.4.

2-(2-Nitrophenyl)imidazo[1,2-*a*]pyridine **(4e);** Yellow solid, mp = 152-153 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (d, 6.9 Hz, 1H), 8.02 (dd, 7.9, 1.2 Hz, 1H), 7.79 (s, 1H), 7.76-7.61 (m, 3H), 7.49 (dd, 7.9, 1.2 Hz, 1H), 7.24 (t, 6.1 Hz, 1H), 6.84 (t, 6.1, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.8, 145.6, 140.7, 132.3, 131.8, 128.8, 128.0, 126.1, 125.7, 123.9, 118.2, 113.2, 110.9.

2-(3-Nitrophenyl)imidazo[1,2-*a*]pyridine **(4f);** Yellow solid, mp = 202-204 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.75 (s, 1H), 8.47 (d, 7.8 Hz, 1H), 8.26-8.17 (m, 2H), 8.04 (s, 1H), 7.83 (d, 9.0 Hz, 1H), 7.68 (t, 7.6 Hz, 1H), 7.37 (m, 1H), 6.97 (t, 6.8, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.9, 145.7, 143.2, 135.3, 131.9, 129.7, 125.8, 125.7, 122.7, 120.7, 117.8, 113.3, 109.2.

2-(4-Nitrophenyl)imidazo[1,2-*a*]pyridine **(4g);** Yellow solid, mp = 266-267 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.67 (s, 1H), 8.59 (d, 6.6 Hz, 1H), 8.32 (d, 8.9 Hz, 2H), 8.25 (d, 8.9 Hz, 2H), 7.63 (d, 9.0 Hz, 1H,), 7.32 (m, 1H), 6.96 (t, 6.6 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 147.0, 145.7, 142.5, 141.0, 127.8, 126.9, 126.5, 124.7, 117.3, 113.5, 112.0.

2-(2-Hydroxyphenyl)imidazo[1,2-*a*]pyridine **(4h);** White solid, mp = 142-144 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.45 (br, 1H), 8.18 (d, 6.9 Hz, 1H), 7.89 (s, 1H), 7.62-7.51 (m, 2H), 7.30-7.17 (m, 2H), 7.05 (d, 8.0, 1H), 6.90-6.77 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.4, 145.3, 143.5, 129.7, 125.7, 125.3, 125.0, 119.1, 117.7, 116.6, 116.3, 113.2, 106.9

2-(4-(Methylsulfonyl)phenyl)imidazo[1,2-*a*]pyridine **(4i);** Off white solid, mp = 243-245 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16-8.13 (m, 3H), 8.01-7.99 (m, 3H), 7.66 (d, 8.9 Hz, 1H), 7.24 (m, 1H), 6.85 (t, 6.8 Hz, 1H), 3.07 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.0, 143.5, 139.2, 139.1, 127.8, 126.7, 125.8, 125.6, 117.7, 113.3, 109.8, 44.7.

7-Methyl-2-phenylimidazo[1,2-*a*]pyridine **(4j);** Off white solid, mp = 171-172 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (d, 6.9 Hz, 1H), 7.94 (d, 7.9 Hz, 2H), 7.80 (s, 1H), 7.44-7.36 (m, 3H), 7.30 (m, 1H), 6.62 (d, 6.9 Hz, 1H), 2.40 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.4, 145.8(2), 135.7, 134.2, 128.9, 128.0, 126.2, 125.0, 117.0, 115.3, 107.7, 21.4.

2-(4-Bromophenyl)-7-methylimidazo[1,2-*a*]pyridine **(4k);** Light yellow solid, mp = 204-206 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (d, 6.8 Hz, 1H), 7.76 (d, 8.5 Hz, 2H), 7.68 (s, 1H), 7.51 (d, 8.5 Hz, 2H), 7.33 (s, 1H), 6.57 (d, 6.8 Hz, 1H), 2.34 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.1, 144.2, 135.8, 133.0, 131.8, 127.5, 124.9, 121.7, 115.9, 115.3, 107.7, 21.5.

2-(3-Methoxyphenyl)-7-methylimidazo[1,2-*a*]pyridine **(4l);** Off white solid, mp = 77-78 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (d, 6.8 Hz, 1H), 7.73 (s, 1H), 7.55 (m, 1H), 7.48 (d, 7.5 Hz, 1H), 7.38 (s, 1H), 7.32 (t, 7.5 Hz, 1H), 6.84 (m, 1H), 6.57 (dd, 6.8, 1.3, 1H), 3.84 (s, 3H), 2.30 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.1, 146.0, 145.3, 135.7, 135.5, 129.7, 124.8, 118.5, 115.9, 115.1, 114.2, 110.8, 107.7, 55.5, 21.2.

2-(4-Methoxyphenyl)-7-methylimidazo[1,2-*a*]pyridine **(4m);** Pale yellow solid, mp = 161-163 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80-7.78 (m, 3H), 7.52 (d, 6.8 Hz, 1H), 7.27 (s, 1H), 6.98-6.87 (m, 2H), 6.47 (d, 6.8 Hz, 1H), 3.81 (s, 3H), 2.33 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.5, 146.1, 145.2, 135.2, 127.4, 126.8, 124.8, 115.5, 114.6, 114.1, 106.7, 55.3, 21.3.

7-Methyl-2-(2-nitrophenyl)imidazo[1,2-*a*]pyridine **(4n);** Yellow solid, mp = 148-150 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.46 (d, 7.1 Hz, 1H), 8.18 (s, 1H), 7.91 (d, 7.8 Hz, 1H), 7.83 (d, 7.8 Hz, 1H), 7.71 (t, 7.6 Hz, 1H), 7.56 (t, 7.6 Hz, 1H), 7.34 (s, 1H), 6.79 (d, 7.0 Hz, 1H), 2.35 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 149.3, 145.5, 139.9, 136.6, 132.4, 130.9, 129.2, 127.4, 126.7, 124.0, 115.6, 115.5, 110.9, 21.3.

7-Methyl-2-(3-nitrophenyl)imidazo[1,2-*a*]pyridine **(4o);** Yellow solid, mp = 185-187 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.73 (t, 1.6 Hz, 1H), 8.52 (s, 1H), 8.42 (d, 6.8 Hz, 1H), 8.35 (d, 7.8 Hz, 1H) , 8.14 (dd, 8.0, 1.6 Hz, 1H), 7.72 (t, 8.0 Hz, 1H), 7.39 (s, 1H), 6.79 (d, 6.8 Hz, 1H), 2.36 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 148.8, 145.9, 142.2, 136.7, 136.3, 132.1, 130.8, 126.8, 122.5, 120.1, 115.8, 115.5, 110.5, 21.3.

7-Methyl-2-(4-nitrophenyl)imidazo[1,2-*a*]pyridine **(4p);** Yellow solid, mp = 216-218 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 (d, 8.0 Hz, 2H), 8.07 (d, 8.0 Hz, 2H), 8.02 (d, 6.9 Hz, 1H), 7.90 (s, 1H), 7.39 (s, 1H), 6.67 (d, 6.9 Hz, 1H), 2.40 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.1, 146.5, 143.2, 140.5, 136.8, 126.4, 125.0, 124.2, 116.3, 115.9, 109.5, 21.4.

2-(7-Methylimidazo[1,2-*a*]pyridin-2-yl)-phenol **(4q);** Off white solid, mp = 139-140 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.70 (br, 1H), 8.04 (d, 6.8 Hz, 1H), 7.80 (s, 1H), 7.59 (d, 7.8 Hz, 1H), 7.37 (s,1H), 7.23 (t, 7.8, 1H), 7.04 (d, 8.4 Hz, 1H), 6.88 (m, 1H), 6.70 (d, 6.8 Hz, 1H), 2.43 (s,

3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.1, 144.8, 143.8, 136.2, 129.4, 125.7, 124.5, 119.0, 117.7, 116.5, 115.8, 115.3, 106.2, 21.4.

Results and discussion

The one-pot synthesis of imidazo[1,2-*a*]pyridines using acetophenone (**1a**) and 2-aminopyridine (**2a**) in the presence of iodine has been extensively studied. (Kielesinski, et al., 2015; Saldabol & Giller, 1976; Stasyuk, et al., 2012). This method involves high reaction temperatures, long reaction times and tedious work up with excess amount of aqueous base under highly elevated temperature, giving poor to moderate yield with less purity of the desired product. Recently, we have reported the ultrasound-assisted a one-pot synthesis of substituted imidazo[1,2-*a*]pyridines by using acetophenone (**1a**) and 2-aminopyridine (**2a**) in the presence of iodine and 1-butyl-3-methylimidazolium tetrafluoroborate ([BMIM]BF_4) as catalyst, followed by aqueous base. The present work was initiated with an aim to improve the procedure for imidazo[1,2-*a*]pyridines synthesis. We initiated our studies by using acetophenone (**1a**), 2-aminopyridine (**2a**), iodine and [BMIM]BF_4 with the mole ratios of 1:2.3:1.2:0.2, respectively as a model reaction (Figure 2). The reaction was carried out under ultrasonic irradiation for 2.5 hours followed by post-treatment both with and without base. The effect of base types and stoichiometry on the reaction were investigated. The results were shown in Table 1.

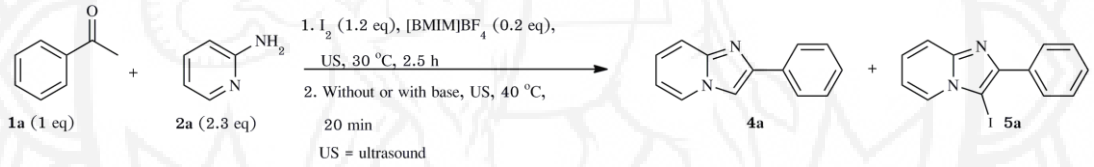
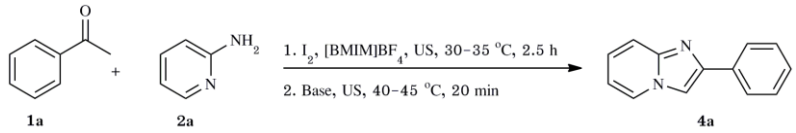


Figure 2 Synthesis of imidazo[1,2-*a*]pyridines

Initially, when acetophenone (**1a**) was allowed to react with 2-aminopyridine (**2a**) under ultrasound irradiation at 35 °C for 2.5 hours, without post-treatment with base, the imidazo[1,2-*a*]pyridine (**4a**) was obtained in low yield (45%). The desired product 4a was obtained in higher yield after treating the reaction mixture for 20 minutes with one equivalent of NaOH at 40-45 °C under ultrasound irradiation (Table 1, entry 1). The yield was increased with increasing mole ratio of NaOH (Table 1, entries 2-4) up to 16.0 moles per mole of acetophenone, but beyond 16.0 moles no further increase was observed. Next, we examined the use of aqueous base K_2CO_3. The moderate to high yields of the desired product (57-76%) were observed when 1.0-2.0 equivalents of K_2CO_3 were used in the reaction (Table 1, entries 5-7). The best yield (82%) was obtained when 4.0 equivalents of K_2CO_3 was used (Table 1, entry 8). Although, the use of aqueous base NaOH and K_2CO_3 could give the desired product in good yield, the difficulty of phase separation and high base concentration was required to complete the reaction resulting in limitation of this method. To further improve the reaction conditions, the reaction was investigated by using CsF-Celite as solid base.

Table 1 Synthesis of 2-Phenylimidazo[1,2-*a*]pyridine (**4a**) in various base.



1a 2a 4a

Entry	Base	Amount of Base (equiv.)	Time (min)	Isolated yield (%)
1	NaOH	1.0	20	53[a]
2	NaOH	1.5	20	66
3	NaOH	2.0	20	71
4	NaOH	16.0	20	78
5	K_2CO_3	1.0	20	57
6	K_2CO_3	1.5	20	73
7	K_2CO_3	2.0	20	76
8	K_2CO_3	4.0	20	82

Reaction conditions: **1a** (0.51 mmol), **2a** (1.17 mmol), iodine (0.61 mmol) and 20 mol% [BMIM]BF_4, US, 30-35 °C, 2.5 hours followed by various base, US, 40-45° C.

[a] The reaction carried out under the same condition without base treatment gave product **4a** in 45%.

In order to prove whether the reaction can be influenced by CsF-Celite, we began our studies by using the same model reaction. To gain insight into the information regarding reaction components, we conducted a series of experiment in a sealed NMR tube. The model reactions were carried under ultrasonic irradiation for 2.5 hours followed by post-treatment with CsF-Celite. At different time intervals, 2 mL of $CDCl_3$ were added to the reaction and further irradiated at the same frequency at 40-45 °C and the NMR spectrum was taken. The results were shown in Figure 3.

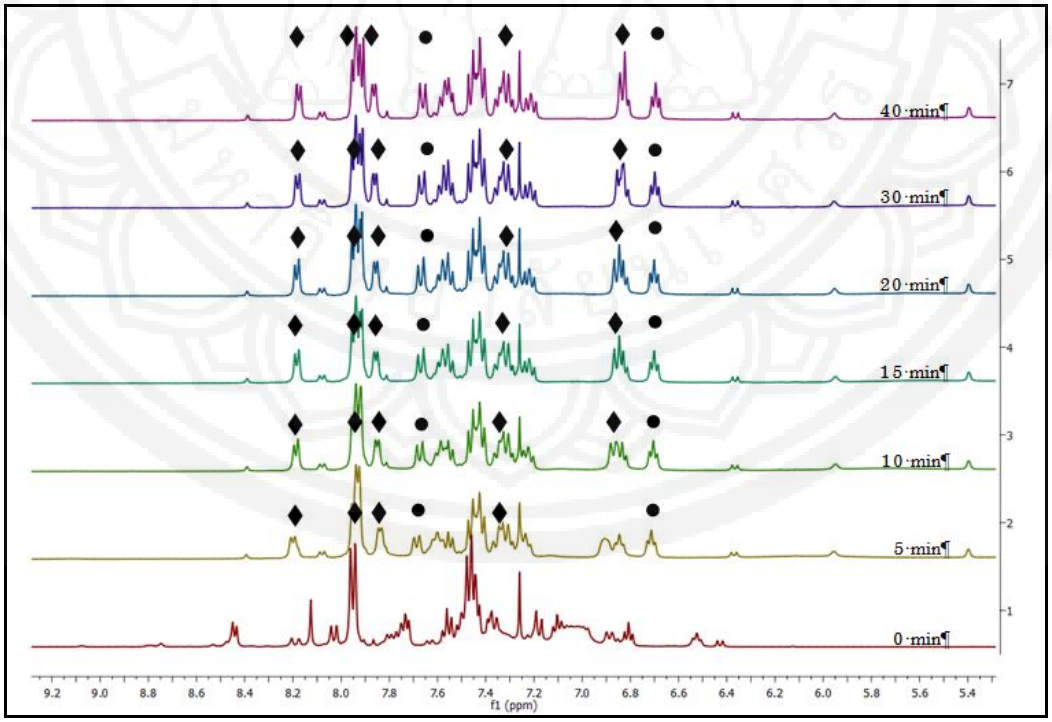


Figure 3 NMR experiment after added CsF-Celite in the reaction of imidazo[1,2-*a*]pyridines using **1a** (0.51 mmol), **2a** (1.17 mmol), iodine (0.61 mmol) and 20 mol% [BMIM]BF_4, US, 30-35 °C, 2.5 hours. (♦, **4a**) and (●, **5a**)

^{1}H NMR spectroscopic analysis of the mixture indicated that no product signal was observed after CsF-Celite was added to the mixture. After the reaction was sonicated for 5 min the product signals started to appear (signals at 8.19, 7.92, 7.83 and 7.34 ppm) together with the formation of the minor product **5a** (signals at 7.67 and 6.70 ppm). By extended the reaction time, an increasing of product signal was observed and it was constant after 15 min. Thus, these results demonstrated that the use of CsF-Ceilte as solid base for post-treatment led to significant work up process improvement with short reaction time. With this optimistic result, we further investigated the effect of the reactants ratio (CsF-Celite/acetophenone) on the product yield with a fixed reaction time of 15 min (Table 2). The results showed moderate to good yield when 1.0-1.5 equivalents of CsF-Celite was used, whereas a comparable yields was obtained when 2 equivalents of CsF-Celite was used (Table 2, entry 1-4).

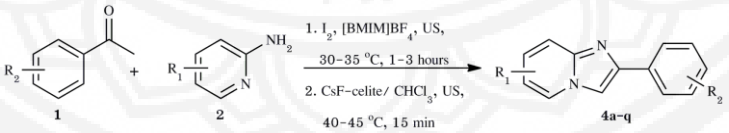
Table 2 Reaction of acetophenone (**1a**) and 2-aminopyridine (**2a**) with CsF-Celite.

Entry	Base	Amount of Base (equiv.)	Time (min)	Isolated yield (%)
1	CsF-Celite	0.5	15	45
2	CsF-Celite	1.0	15	60
3	CsF-Celite	1.5	15	81
4	CsF-Celite	2.0	15	82

Reaction conditions: **1a** (0.51 mmol), **2a** (1.17 mmol), iodine (0.61 mmol) and 20 mol% [BMIM]BF_4, US, 30-35 °C, followed by various amount of CsF-Celite, US, 40-45° C, 15 min.

After finding the optimized reaction conditions, we studied the scope and the generality of this new protocol for various ketones (**1**) and amines (**2**) under optimized conditions and the results are summarized in Table 3. Broad substrate scopes with respect to both substrates were observed. The result showed the substituted acetophenones, such as *p*-bromo, *m*-methoxy, *p*-methoxy, *o*-nitro, *m*-nitro groups and *p*-methylsulfonyl reacted smoothly to produce the target products in good to excellent yields (73-82%) (Table 3, entries 2-6 and 9). Whereas, the reaction of *p*-nitro and *o*-hydroxy acetophenones with **2a** provided the desired product **4g** and **4h** in moderate yield (Table 3, entries 7 and 8). This transformation was also applicable to 2-amino-4-methylpyridine (**2b**) and the desired products **4j-q** were obtained in high to excellent yields, 70-85% (Table 3, entries 10-17).

Table 3 Synthesis of substituted imidazo [1,2-*a*] pyridines



1 2 4a-q

Entry	R_1	R_2	Product	Time (hours)	Isolated Yield(%)
1	H	H	**4a**	2.5	82
2	H	4-Br	**4b**	2	73
3	H	3-OMe	**4c**	1	78
4	H	4-OMe	**4d**	2	73
5	H	2-NO_2	**4e**	2	82
6	H	3-NO_2	**4f**	3	74
7	H	4-NO_2	**4g**	1.5	58
8	H	2-OH	**4h**	2.5	57
9	H	4-SO_2Me	**4i**	3	73

Table 3 Cont.

Entry	R_1	R_2	Product	Time (hours)	Isolated Yield(%)
10	4-Me	H	**4j**	1.5	73
11	4-Me	4-Br	**4k**	2.5	81
12	4-Me	3-OMe	**4l**	1	70
13	4-Me	4-OMe	**4m**	1.5	78
14	4-Me	2-NO_2	**4n**	2.5	81
15	4-Me	3-NO_2	**4o**	3	85
16	4-Me	4-NO_2	**4p**	2	85
17	4-Me	2-OH	**4q**	2.5	79

Reaction conditions: **1** (0.51 mmol), **2** (1.17 mmol), iodine (0.61 mmol) and 20 mol% $[BMIM]BF_4$, US, 30-35 °C, followed by CsF-Celite/$CHCl_3$, US, 40-45° C, 15 min.

The reusability of CsF-Celite

The feasibility of recovery and reuse of CsF-Celite for post-treatment was also examined by using the model reaction, acetophenone and 2-aminopyridine under the established condition. After post-treatment process, the solid CsF-Celite was recovered and washed three times with $CHCl_3$ and small amount of acetone to remove the reaction residue which was further dried at 50 °C for 2 hours and the reused for four cycles. The result was summarized in Table 4. It was found that the reused CsF-Celite was reacted efficiently to subsequently reactions with no significantly yield decreasing.

Table 4 The study of CsF-Celite reusability.

Entry	Number of Cycles	Isolated yield (%)
1	1	81
2	2	80
3	3	79
4	4	78

Reaction conditions: **1a** (0.51 mmol), **2a** (1.17 mmol), iodine (0.61 mmol) and 20 mol% $[BMIM]BF_4$, US, 30-35 °C, followed by CsF-Celite/$CHCl_3$, US, 40-45° C, 15 min.

Conclusion and Suggestion

In summary, a convenient and efficient US-assisted two-step process was developed for the synthesis of imidazo[1,2-*a*]pyridines which involved US-promoted formation of keto-ammonium salt intermediate followed by and cyclization under basic condition using CsF-Celite as solid base. Compared with conventional post-treatment methods used to prepare these compounds, CsF-Celite reduced post-treatement time and generated the expected products 4a-4q in high yields. Moreover, this very attractive protocol offers various features such as operational simplicity in term of phase separation, especially the strong advantage in material reusability. This in turn makes the method more economical.

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