

Supporting Information

Reactive Behaviors of Isoquinoline Alkaloid in Green Reduction Process Assisted by Ionic Liquids and Solvent-Free Techniques

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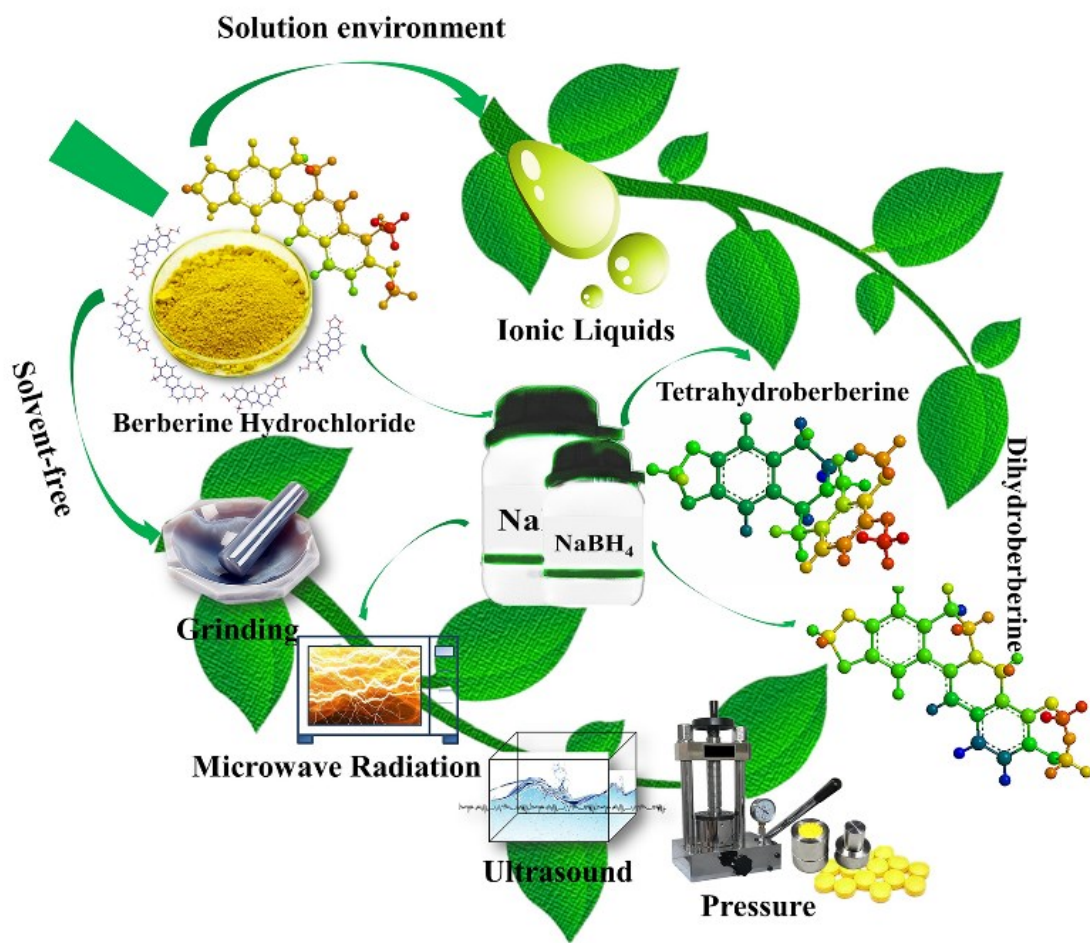
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1. Total scheme for green reduction process



Scheme S1 Total scheme for green reduction process

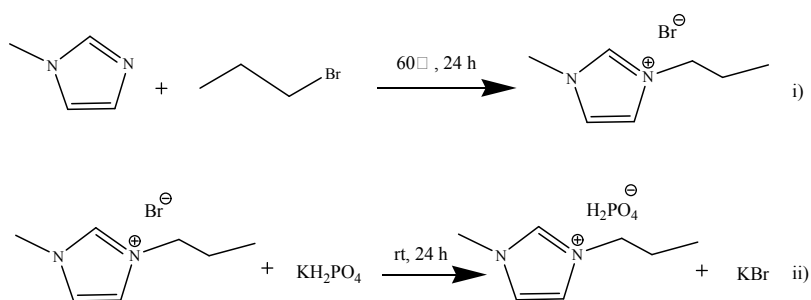
2. Reagents and materials

All of the reagents and solvents used in the present study were of analytical-reagent grade or higher. Synthetic reagents for ten ILs including 1-methylimidazole, bromoethane, 1-bromopropane, 1-bromobutane, potassium dihydrogen phosphate, potassium bisulfate, benzothiazole, 8-hydroxyquinoline, ethanol and ethyl acetate were purchased from Aladdin Chemical Reagent Co. Ltd. (Shanghai, China). Raw material of berberine hydrochloride (BH) was supplied by Bomei Biotechnology Co. Ltd. (analytical grade, purity >96.5%, Hefei, China), then was ground to 80 mesh powders and stored in vacuum drier for later use. Standard samples of DHB and THB (chromatographic purities above 99.5%) were procured from Bomei as well. Acetonitrile (chromatographic purity, above 98%) was purchased from Kelong Chemical Co. Ltd. (Chengdu, China). Moreover, deionized water was obtained from ultra-pure water purification system (0.4 mm filter membrane) provided by Youpu Equipment Co. Ltd. (Chengdu, China).

3. Synthesis of ionic liquids

(1) Synthesis of imidazolium ILs [S1]

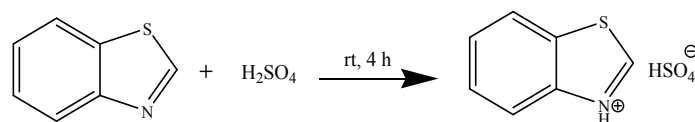
6 imidazole-based ILs were $[\text{C}_2\text{MIM}]\text{H}_2\text{PO}_4$, $[\text{C}_2\text{MIM}]\text{HSO}_4$, $[\text{C}_3\text{MIM}]\text{H}_2\text{PO}_4$, $[\text{C}_3\text{MIM}]\text{HSO}_4$, $[\text{C}_4\text{MIM}]\text{H}_2\text{PO}_4$ and $[\text{C}_4\text{MIM}]\text{HSO}_4$, all of them were prepared by two steps. For example, in the synthesis of $[\text{C}_3\text{MIM}]\text{H}_2\text{PO}_4$ (**Scheme 2**), 1-methylimidazole and 1-bromopropane (molar ratio=1:1.2) were first put together in a three-neck flask under the protection of N_2 at 60°C and reacted for 24 hours. The obtained light yellow viscous liquid $[\text{C}_3\text{MIM}]\text{Br}$ was extracted with ethyl acetate and washed for three times and then transferred to a vacuum drying oven at 50°C to remove ethyl acetate. Second, 0.01 mol of $[\text{C}_3\text{MIM}]\text{Br}$ was dissolved in 50 mL of anhydrous acetone, and 0.011 mol of KH_2PO_4 was added into the acetone solution, the reaction was stirred at room temperature for 24 h. After that, byproduct KBr and extra KH_2PO_4 were removed by filtration. The final product $[\text{C}_3\text{MIM}]\text{H}_2\text{PO}_4$ was washed with ethyl acetate for three times and dried for 24 h. Synthesis of $[\text{C}_3\text{MIM}]\text{HSO}_4$ was the same procedures. The brominated intermediate $[\text{C}_3\text{MIM}]\text{Br}$ and slightly excessive KHSO_4 were dissolved in acetone, reacted at room temperature for 24 hours, and the target ionic liquid was purified and dried as above. Other imidazole-based ILs were prepared in the same manner.



Scheme S2 Synthesis of $[\text{C}_3\text{MIM}]\text{H}_2\text{PO}_4$

(2) Synthesis of benzothiazolium ILs [S2]

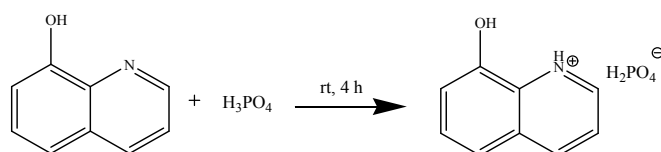
Taking the synthesis of [HBth]HSO₄ as an example (**Scheme S3**), 0.1 mol of benzothiazole was dissolved in 50 mL of ethanol in an ice bath, 0.11 mol of sulfuric acid was dropped in the solution in batches. After stirring for 4 h at room temperature, ethanol was removed by vacuum distillation. The residue was washed with ethyl acetate and recrystallized twice with anhydrous ethanol to obtain the colorless needle like crystal, which was the target product. Synthesis of [HBth]H₂PO₄ was conducted with the same process, but H₂SO₄ was replaced by H₃PO₄.



Scheme S3 Synthesis of [HBth]HSO₄

(3) Synthesis of quinolinium ILs [S3]

Like Benzothiazole-based ILs, 8-hydroxyquinoline based ionic liquids were synthesized by one-pot acid-base neutralization. For instance, synthesis of [Hyqu]H₂PO₄ was realized by dissolving 0.1 mol of 8-OH-quinoline in 100mL of anhydrous ethanol, and 0.11 mol of phosphoric acid was added dropwisely into the solutions. After stirring for 4 h in the ice bath, ethanol was removed by vacuum distillation, and the solid was recrystallized twice with anhydrous ethanol to obtain the yellow needle crystal as the final product (**Scheme S4**).



Scheme S4 Synthesis of [Hyqu]H₂PO₄

3. NMR, element analysis and melting points of ILs

Here ^1H NMR spectra of the ILs were performed on AV II-400 MHz spectrometer (Bruker, Switzerland), element analysis was operated on EA3000 elemental analyzer (Euro vector S.P.A, USA) and melting points for those ILs as solid at room temperature were measured on a TG 209 FI Iris analyzer (NETZSCH Company, Germany) with a heating rate of $10^\circ\text{C}/\text{min}$ from 30 to 700°C under N_2 .

$[\text{C}_2\text{mim}][\text{HSO}_4]$: $\text{C}_6\text{H}_{12}\text{N}_2\text{O}_4\text{S}$, C: 34.0%, N: 13.6%, S: 15.1%, O: 30.2%; ^1H NMR (400 MHz, CD_3CN , TMS) δ / ppm: 9.38 (s, 1H), 8.40 (s, 1H), 7.85 (s, 1H), 7.78 (s, 1H), 3.87 (s, 3H), 4.30 (m, 2H), 1.43 (t, 3H), which were similar to the reported data in previous study. ^[S4]

$[\text{C}_4\text{mim}][\text{H}_2\text{PO}_4]$: $\text{C}_8\text{H}_{17}\text{N}_2\text{O}_4\text{P}$, C: 13.3%, N: 12.1%, P: 12.8%, O: 26.8%, ^1H NMR (400 MHz, CD_3CN , TMS) δ / ppm: 0.83 (t, 3H), 1.25 (m, 2H), 1.75 (m, 2H), 3.85 (s, 3H), 4.16 (t, 2H), 7.50 (m, 2H, H-4, H-5), 8.99 (s, 1H, H-2), 11.02 (br s, 2H, H_2PO_4) which accorded with the reported data in previous study. ^[S5]

$[\text{C}_4\text{mim}][\text{HSO}_4]$: $\text{C}_8\text{H}_{16}\text{N}_2\text{O}_4\text{S}$, C: 13.2%, N: 12.4%, S: 13.6%, O: 26.3%; ^1H NMR (400 MHz, CD_3CN , TMS) δ / ppm: 8.55 (s, 1H), 8.40 (s, 1H), 7.40 (s, 1H), 7.17 (s, 1H), 4.15 (t, 2H), 3.86 (s, 3H), 1.90 (m, 2H), 1.35 (m, 2H), 0.95 (t, 3H), which were similar to those reported in previous study. ^[S4]

[HBth][H₂PO₄]: C₇H₈NO₄PS, C: 35.8%, N: 6.30%, O: 27.1%, S: 13.3%, P: 13.2%; melting point: 120.2~120.9°C; ¹H NMR (400 MHz, D₂O, TMS) δ / ppm: 7.43 (t, 1H), 7.51 (t, 1H), 7.83 (d, 1H), 7.91 (d, 1H), 9.60 (s, 1H), which were close to the reported data. [S6]

[HBth][HSO₄]: C₇H₇NO₄S₂, C: 36.1%, N: 6.20%, O: 27.3%, S: 27.4%; melting point: 130.2~130.8°C; ¹H NMR (400 MHz, D₂O, TMS) δ / ppm: 7.31 (t, 1H), 7.37 (t, 1H), 7.62 (d, 1H), 7.74 (d, 1H), 9.72 (s, 1H), which were similar to those reported in previous study. [S6]

[Hyqu][H₂PO₄]: C₉H₁₀NO₅P, C: 44.1%, N: 5.79%, P: 12.6%, O: 33.0%; ¹H NMR (400 MHz, CH₃DO, TMS) δ / ppm: 9.14 (m,1H), 9.05 (m,1H), 8.09 (t,1H), 7.78 (m,2H), 7.5 (m,1H), which accorded with the reported data in previous study. [S3]

[Hyqu][HSO₄]: C₉H₉NO₅S, C: 44.3%, N: 5.77%, S: 13.0%, O: 32.8%; melting point: 166.9~168.1°C; ¹H NMR (400 MHz, CH₃DO, TMS) δ / ppm: 9.18 (m,1H), 9.09 (q,1H), 8.11 (t,1H), 7.78 (m,2H), 7.52 (m,1H), which were similar to the reported data in previous study. [S3]

4. Process analysis for solution and non-solvent reduction

In order to track the reaction process and observe the reduction behaviors, near infrared spectroscopy and X-ray powder diffraction are recommended for solution reaction system and solid-phase reaction system, respectively. Near-infrared (NIR) spectra is suitable for analysis in solution conditions, and it is widely applied in online process monitoring. NIR is usually used to detect absorption of the hydrogen-containing vibration, such as C-H, N-H and O-H. These contain information about the composition and molecular structure of organic compounds. In order to investigate the reaction process, NIRQUEST512 near-infrared spectroscopy (Ocean Optics, Dunedin, USA) equipped with deuterium light source (DH-2000-BAL) and fiber optic probes (T300-UV-VIS, optical length = 1 cm) was applied to monitor the reaction after 20 min, 30 min and 40 min. Apparently, adsorption of all the chemical bonds of BH mentioned above was gradually reduced as the reaction proceeded. Furthermore, X-ray powder diffraction (XRPD) was a favorable tool to investigate solid information in reaction process, which was applied here to analysis the products obtained with different pressure time and explore the influence of the factor. An X' Pert PRO diffractometer (Panalytical, Eindhoven, The Netherlands) with $CuK\alpha 1$ radiation at 40 kV and 40 mA was used to obtain the spectra. The researchers can determine the presence and content of different products according to the attribution of related peaks, which provide useful information for the reaction development in whole solid phase

system.

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