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ARTICLE

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Green synthesis of caffeine based on methylating reagent dimethyl carbonate and environmental friendly separating method

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Abstract

In this paper, a green process for the synthesis and separation of caffeine was reported. Theophylline sodium is used as the raw material, diazabicyclo[5.4.0]undec-7-ene as the catalyst, and Turkey red oil as the solvent, particularly, dimethyl carbonate was adopted in place of high toxic dimethyl sulfate to form a mixture of caffeine and by-product sodium bicarbonate. After converting sodium bicarbonate to sodium carbonate, the solubility difference between caffeine and sodium carbonate at 40°C was for the first time utilized to achieve the purpose of separating caffeine with an excellent yield of 98.4% and a purity of greater than 99.0%. Furthermore, both the reaction mother liquor and separation mother liquor can be recycled and reused during the reaction and separation processes, respectively, with little caffeine loss. No industrial waste was discharged in the process of the improved synthesis and separation, which is therefore environmental friendly.

KEYWORDS
caffeine, sodium carbonate, solubility difference

1 | INTRODUCTION

Caffeine, 1,3,7-trimethyl-2,3,6,7-tetrahydro-1H-purine-2,6-dione, is an important pharmaceutical raw material and a beverage additive.[1] Caffeine was firstly extracted from cocoa beans in 1820,[2] and then its chemical structure was confirmed by Stenhouse.[3,4] It was not until 1899 that caffeine was synthesized from cyanoacetic acid and urea or dimethyl urea for the first time.[5] Until now, the main source of caffeine is synthetic.[6]

In industrial production of caffeine, dimethyl sulfate (DMS) is still used as the methylating reagent.[7] However, DMS is highly toxic,[8] has strong irritancy and corrosiveness, there are also hidden safety risks in production and transportation, and a large number of wastewater containing salt and monomethyl sulfate will be produced, which makes sewage treatment very difficult.[9] Compared with DMS, dimethyl carbonate (DMC) is an environmental friendly methylating reagent[10] because of its low toxicity and little environmental impact.[11] It had been reported that DMC was used as the methylating reagent in the process of synthesizing caffeine, but the yield was only 67.0%, which did not meet the industrial production requirement.[12,13] Thus, DMC has the potential to be adopted in place of DMS or alkyl halides for methylating reactions.[14,15]

Nowadays, the solvent extraction method[16] is generally adopted for the separation of caffeine and by-product salt in industrial production.[17] Chloroform is an effective extractant, but it is volatile in use,[18] resulting in a significant loss per year and also affecting the health of practitioners. In addition, since chloroform can destroy the atmospheric ozone layer, the Montreal Protocol, which is in force internationally, has limited or prohibited the use of chloroform.[19] Herein, a new strategy that utilizes the solubility distinctions between caffeine and by-product salts at different temperatures to achieve the purpose of separating caffeine is proposed for the first time.

In this work, sodium theophylline is used as the starting raw material, DMC as the methylating agent in place of DMS, Turkish red oil as a solvent, and DBU as the catalyst for caffeine synthesis. Caffeine and by-products including methanol and sodium bicarbonate will be obtained. For caffeine separation, the solubility of caffeine, sodium bicarbonate, and sodium carbonate in water at different temperatures was evaluated (Figure 1).

2 | RESULTS AND DISCUSSION

2.1 | Characterization

The synthetic yield of caffeine is 98.4%, melting point (mp): 237–239°C. ^{1}H NMR (500 MHz, $CDCl_3$), δ 3.35 (s, 3H, CH_3), 3.41 (s, 3H, CH_3), 3.87 (s, 3H, CH_3), 7.89 (s, 1H, purine-7-*H*) ppm. ^{13}C NMR (125 MHz, $CDCl_3$), δ 28.6, 31.6, 35.0, 108.3, 140.8, 146.6, 151.7, 154.3 ppm. LC–MS, m/z: $[M+H]^+$, 195.2, found, 195.1. The purity of caffeine is 99.4%, $t = 7.987$ min (Supporting information).

2.2 | RML and SML circulation

The reaction mother liquor (RML) produced by the synthesis process mainly contains emulsifier, a small amount of DMC and caffeine, Turkish red oil, sodium bicarbonate, and methanol. As shown in Figure 2a, recycling and reusing of the RML almost do not reduce the yield of caffeine with a quantitative tendency of 98% after seven circles. In addition, the accumulated by-product methanol can be separated and recovered by distillation. For the separation

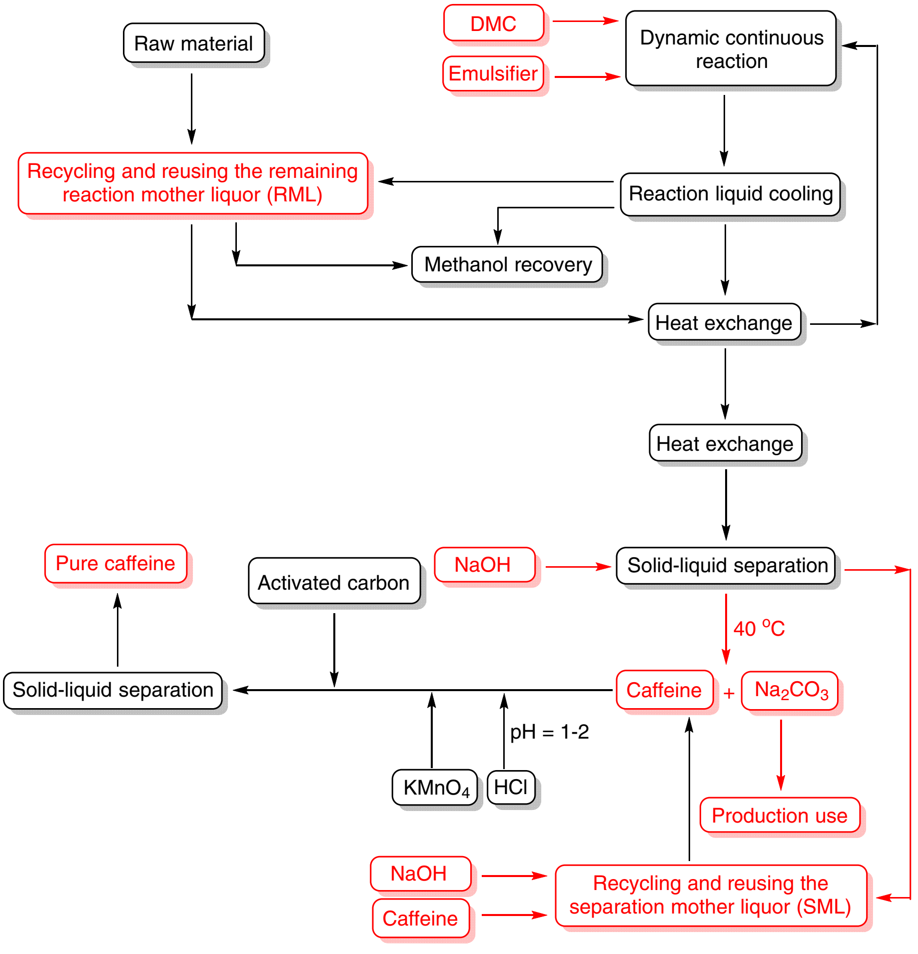


FIGURE 1 The flow chart for synthesis and separation of caffeine

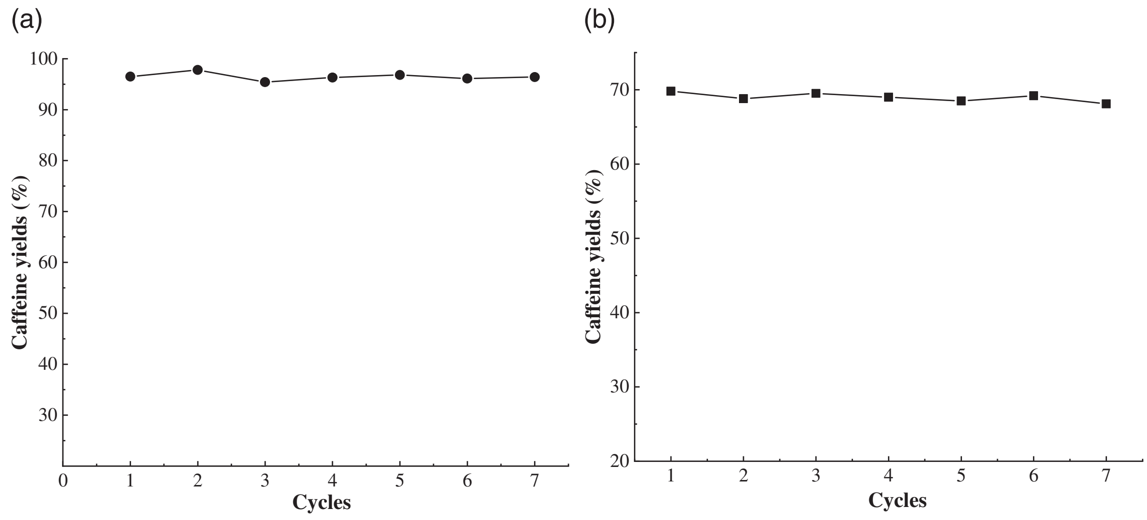


FIGURE 2 The yield change of caffeine after seven times recycling and reusing (a) RML and (b) SML

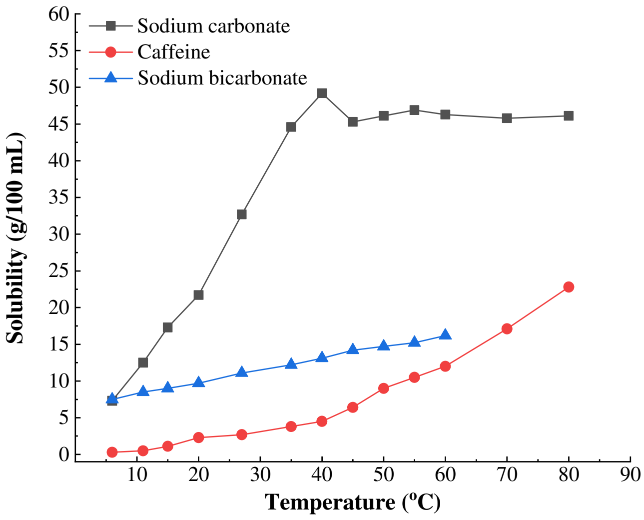


FIGURE 3 Solubility of pure caffeine, sodium bicarbonate, and sodium carbonate in water with different temperatures

mother liquor (SML) circulation (Figure 2b), the ochre caffeine is yielded 70.0%, which is kept well after more than seven times. Therefore, the RML and SML circulation has no effect on the yield of caffeine.

2.3 | Separation of caffeine

As shown in Figure 3, the solubility difference between caffeine and sodium carbonate at different temperatures is utilized to achieve the purpose of separating caffeine. In 100 mL water, when the solution temperature is 40°C, the solubility of caffeine is 4.5 g, that of sodium bicarbonate is 13.1 g and that of the sodium carbonate is 49.2 g, which is the maximum. When the temperature is 20°C, the solubility of caffeine reduces to 2.0 g, that of sodium bicarbonate decreases to 9.7 g, and that of sodium carbonate reduces to 21.7 g, compared with 40°C. In addition, for the solubility of sodium carbonate, when the temperature is higher than 40°C, it will decrease to 45.3–46.9 g. For the cases of caffeine and sodium bicarbonate, however, the solubility has an obvious increasing tendency, which is not beneficial for the separation of caffeine. Hence, the optimal temperature is 40°C for caffeine separation. Actually, caffeine exists in the aqueous solution of sodium carbonate, the lower solubility (0.1 g at 20°C and 0.2 g at 40°C) of caffeine under the same temperature condition will be observed, due to the specific gravity and polarity of the aqueous solution.

The solubility of sodium bicarbonate and caffeine in water with different temperatures is not much different; the separation of caffeine and sodium bicarbonate can only be carried out by the extraction method with high costs. However, that of sodium carbonate and caffeine is much different; hence, sodium bicarbonate is converted into sodium carbonate during the separation process.

It is an energy-saving process because the reaction process of sodium bicarbonate with sodium hydroxide is an exothermic process, which can make the temperature of the reaction system raise to 45°C. Also, the properties of the produced sodium carbonate and sodium bicarbonate are very similar, the addictive values of them as alkaline substances are not decreased and the costs are not increased. These results indicate that utilizing the solubility difference between caffeine and sodium carbonate at different temperatures for separating caffeine has no effect on the purity of caffeine, and the whole caffeine separation process is green environmental friendly without any waste generation.

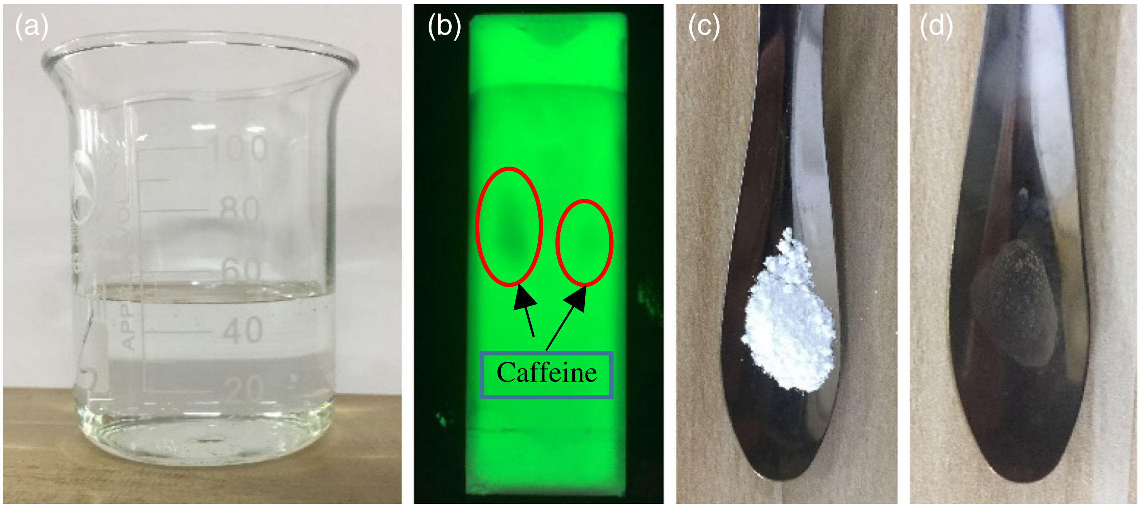
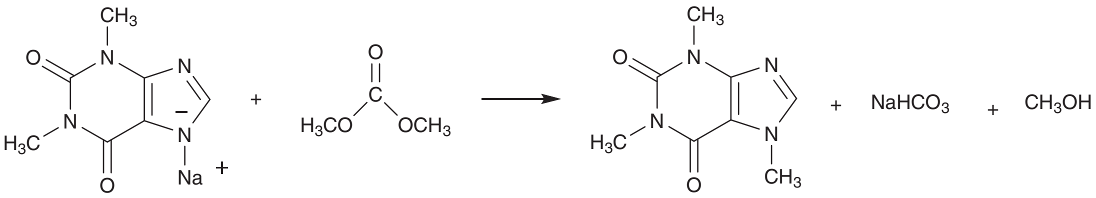


FIGURE 4 The (a) clarity, (b) TLC plate, (c) drying at 105°C, and (d) igniting of pure caffeine at 700–800°C



SCHEME 1 Synthetic route of caffeine

2.4 | Caffeine detection

In order to prove that the synthesized caffeine meets the requirements, the related indexes have been evaluated. The pure caffeine solution is clarified as shown in Figure 4a. There is nearly no impure spot that emerged in test solution A and control solution B based on the TLC (Figure 4b). According to Equations (1) and (2), the weight loss percent of pure caffeine after drying and weight percent of residue after igniting are 4.2 and 0.006%, respectively (Figure 4c,d). These suggest that the synthesized caffeine can be used directly as a commodity.

3 | EXPERIMENTAL

3.1 | Reagents and instruments

Sodium theophylline (98.0%) was obtained from Shandong Xinhua Pharm. Co., Ltd. Dimethyl carbonate (99.0%) and Turkey red oil (99.0%) were purchased from Zibo Hengzeng Chemical Co., Ltd. 1,8-Diazabicyclo [5.4.0]undec-7-ene (DBU, 99.0%) was achieved from Nanjin Apicci Pharm Technology Co., Ltd. Sodium hydroxide (99.7%) was obtained from Tianjin Hengxing Chemical Reagent Co., Ltd. Ethylene glycol (99.7%) was purchased from Zhengzhou Enming Chemical Product Co., Ltd. OP-10 emulsifier (99.7%) was achieved from Shanghai Aladdin Bio-Chem Technology Co., Ltd.

Visualization on thin-layer chromatography (TLC) was acquired using ultra violet (UV) light (254 nm). mp was measured on a melting point apparatus (WRS-1A). ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker Advance 500 (500 MHz) spectrometer using $CDCl_3$ as solvent. Mass spectra were obtained with Agilent Technologies 5975C mass spectrometer and LC-20A high-performance liquid chromatography. The following abbreviations were used to describe peak patterns: s = singlet, d = doublet, t = triplet, q = quadruplet, m = multiplet. Coupling constants (J) were expressed in hertz unit (Hz).

3.2 | Synthesis and separation of caffeine methods

3.2.1 | Synthetic method

Theophylline sodium (10.0 g, 0.075 mol) was dissolved in 60 mL of solution (m[water]: m[ethylene glycol]: m[OP-10] = 14:1:1]), with a resulting theophylline sodium concentration of 1.25 mol/L.[20,21] Then, DMC (0.15 mol) as the green methylating reagent, Turkish red oil (0.5 g) as the solvent, and DBU (0.5 g) as the catalyst were added and the mixture was placed in a 150 mL autoclave, heated at 135°C for 4 hr (Scheme 1). After the reaction was completed, cooled to room temperature, the crude caffeine as yellow solid was filtered for further separation and purification, and the remaining reaction mother liquor (RML) would be recycled and reused to synthesize caffeine.

3.3 | Separation method

Crude caffeine 19.3 g (70%) was dissolved in 25 mL of water, and sodium hydroxide solid (4.1 g) was added in batches with slow stirring. Upon completing the addition, the temperature was kept at 45°C and stirred for 5 min. The ochre caffeine was separated by hot suction filtration and weighed 13.3 g (98.4%) after drying. In addition, the separation mother liquor (SML) was cooled to 20°C, and a large amount of white hydrated sodium carbonate solid was precipitated and filtered, and the SML would be recycled and reused to separate caffeine.

3.4 | Recycling and reusing RML method

Theophylline sodium (10.0 g, 0.075 mol) and a certain amount of DMC were redissolved in the RML to further synthesize crude caffeine for seven cycles. In addition, the by-product methanol would be accumulated, which could be separated and recovered by distillation.

3.5 | Recycling and reusing SML method

The obtained crude caffeine was dissolved in the above SML, and sodium hydroxide solid was also added in batches with slow stirring. The ochre caffeine was separated by hot suction filtration and with a yield of 70.0%, and the SML would be further recycled and reused for caffeine separation for seven times.

3.6 | Purification method

An ochre caffeine solution of 11.0 mg/mL was obtained, and then hydrochloric acid was adopted to adjust the pH to 1–2.[22] An appropriate amount of food grade potassium permanganate and 0.5% active carbon were added into the caffeine solution for oxidization and decolorization, respectively. After removing excess active carbon and potassium permanganate through vacuum filtration, pure caffeine was obtained as white solid. The purity of caffeine could be checked by LC-20A high-performance liquid chromatography (column: C18-Wr 5 μm [4.6 mm × 250 mm]; injection volume: 20 μL; mobile phase: V_{methanol}:V_{water} = 60:40; flow rate 1.0 mL/min; detection wavelength: 275 nm; column temperature: 30°C).

3.7 | Caffeine detection methods

3.7.1 | Detection of clarity

Pure caffeine (1.0 g) was dissolved in water (50 mL), then heated to boiling, cooled, and the solution should be clarified.[23]

3.7.2 | Detection of related substances

The test solution A (20 mg/mL) was obtained from an amount of pure caffeine being dissolved in chloroform–methanol (v/v, 3/2). The control solution B (0.10 mg/mL) was achieved through appropriate amount solution A being quantitatively diluted with chloroform–methanol (v/v, 3/2). According to the TLC (General Rule 0502) test, the solutions A (10 μL) and B (10 μL) were aspirated and spotted on the same silica gel GF254 thin layer plate, n-butanol–acetone–trichloromethane–concentrated ammonia (v/v/v/v, 40/3/30/10) as the eluent, then dried and observed under UV light (254 nm). If there were impure spots of test solution A emerged, the color of these impure spots would not be deeper than the main spot of control solution B.[23]

3.7.3 | Detection of loss after drying

Pure caffeine (1.0 g) was dried at 105°C for 2 hr, the weight loss should be less than 8.5%.[23] For anhydrous caffeine, if dried at 105°C for 1 hr, the weight loss percent can be calculated based on Equation (1) and should not exceed 0.5%.

$$wt\% = [(W_0 - W)/W_0] \times 100\% \qquad (1)$$

where *wt%* represents the weight loss percent after drying, W_0 and W are the weights of before and after drying at 105°C for 2 hr.

3.7.4 | Detection of residue after igniting

Pure caffeine (1.0 g) was taken and placed in a constant weight crucible, slowly scorched until completely carbonified and cooled. Then, sulfuric acid (0.5 mL) was dropped for wetting the sample. After heating at the low temperature to removal sulfuric acid, the sample was completely ashed at 700–800°C, then moved into a dryer, cooled, weighed precisely. After that, the sample was ashed again at 700–800°C until obtaining a constant weight. The weight percent of residue can be calculated as Equation (2) and no more than 0.1%.[23]

$$w\% = [W_r/W_0] \times 100\% \tag{2}$$

where $w\%$ represents the weight percent of residue after igniting, W_0 and W_r are the weights of before and after igniting at 700–800°C.

4 | CONCLUSIONS

This work mainly reports the green synthesis of caffeine and separation of it with an environmental friendly method. Caffeine is obtained in a green way through methylating theophylline sodium with DMC reagent to reduce toxicity and environmental pollution, DBU as a catalyst, and Turkish red oil as an emulsifier and solvent to increase the solubility of theophylline sodium. In addition, the remaining RML would be recycled and reused to continuously synthesize caffeine. By-products are methanol and sodium bicarbonate, which will be converted into sodium carbonate in the following separation process. Because of the obvious distinction in solubility of caffeine and sodium carbonate, caffeine can be directly separated from the reaction solution, and the SML would be further recycled for caffeine separation for more than seven times. Thereby, this technique effectively avoids disadvantages of high cost and high consumption brought by the conventional process of chloroform extraction, and has significant benefits such as the ease of operation, high yield, no wastewater discharge, and eco-friendly. In a word, this improved process realizes a green and environmental friendly synthesis and separation of caffeine.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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