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An efficient ultrasonic-assisted synthesis of imidazolium and pyridinium salts based on the Zincke reaction

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ABSTRACT

A mild and efficient method has been developed using ultrasound irradiation for the synthesis of imidazolium and pyridinium salts based on the Zincke reaction. Tertiary nitrogen nucleophiles such as pyridines and imidazoles can be alkylated with primary amine by simply using their ammonium form Zincke salts. In almost all cases, a clear yield increase results and a dramatic reduction of the reaction time accompanied by an improved quality of the products occurs.

1. Introduction

Over the course of the last decades, pyridinium and imidazolium-based salts have gained much attention for their versatile properties and variety applications in diverse areas ranging from synthetic and catalytic chemistry to biotechnology, electrochemistry, and material science [1]. One of the most practical and widely used routes for the synthesis of these compounds is direct alkylation of pyridine or 1-methylimidazole with an excess of alkyl halides [2]. However, using alkyl halides as alkylating agents can lead to preparative issues such as time-consuming and usually requiring a large molar excess of haloalkane (10–400%) to achieve good yields [3], these make syntheses both dirty and expensive, and most importantly, a number of halides such as *sec*-alkyl halides, *tert*-alkyl halides and aryl halides work difficult or even impossible [4]. So to find or explore another alternative synthetic strategy for the preparation of imidazolium and pyridinium salts has been the recent research focus. In earlier reports, dimethyl sulfate, diethyl sulfate, dimethyl carbonate and propylene oxide were successively used as an alternative alkylating agents [5], a series of imidazolium and pyridinium salts were prepared. Most recently, Bischoff and co-workers demonstrated the synthesis of imidazolium and pyridinium salts based on the Mitsunobu reaction, tertiary nitrogen nucleophiles such as pyridines and imidazoles can be alkylated with alcohols [6]. Fürstner et al. developed a novel route to synthesis unsymmetrical imidazolium salts bearing two different aryl groups on the *N*-atoms, which using various substituted anilines as well as secondary and tertiary amines as the reaction partners [4].

To our knowledge, The Zincke reaction is a versatile method in which a pyridine is transformed into a pyridinium salt by reaction with 2,4-dinitrochlorobenzene and a primary amine [7]. Synthesis of *N*-arylpyridinium salts from the Zincke salt was for the first time reported by Marvell and Ise [8]. Recently, pyridinium salts containing reactive hydroxyl, amine and/or pyridyl groups have also been synthesized [9]. In spite of their potential utility, however, some of draw-backs such as lower yield and relatively long reaction time commonly associated with this useful reaction [9,10]. Ultrasound irradiation has been considered as a clean and useful protocol in organic synthesis in the last three decades [11], compared with traditional methods, the procedure is more convenient. A large number of organic reactions can be carried out in higher yield, shorter reaction time or milder conditions under ultrasonic irradiation [12]. Due to the absence of reported ultrasonic-assisted Zincke reaction and our general interest in the development of clean chemical processes, herein, we wish to report an improved procedure for the Zincke reaction, under ultrasound irradiation, not only a variety of pyridinium salts but also many imidazolium salts were prepared with mild reaction conditions, short reaction time and moderate to high yields (Scheme 1).

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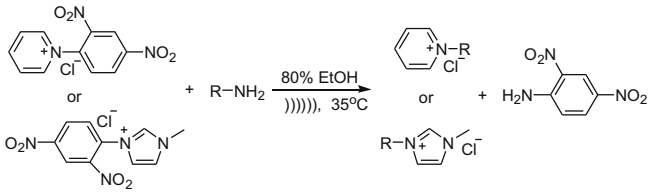

Scheme 1. Synthesis of imidazolium and pyridinium salts.

2. Experimental

2.1. Apparatus and analysis

Melting points were measured on WRS-1B digital Melting point meter and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were measured on a DRX300 NMR Spectrometer using TMS as an internal standard in D_2O, $DCCl_3$ or DMSO-d_6. The elemental analyses were performed in the Institute of Chemistry, Chinese Academy of Sciences. Sonication was performed in Kunshan KQ-400KDE ultrasonic cleaner (with a frequency 40 kHz and a nominal power 400 W), and the reaction temperature was controlled by exchange of the water in ultrasonic cleaning bath. Analytical thin layer chromatography (TLC) was carried out using MN Kieselgel G/UV_{254} (Art. 816320) glass backed plates.

2.2. N-(2,4-Dinitrophenyl)pyridinium chloride [13]

To a solution of finely powdered 1-chloro-2,4-dinitrobenzene (10.12 g, 50 mmol) in acetone (15 mL) was added pyridine (4.5 mL, 55 mmol), the reaction vessel equipped with a drying tube was then placed in a laboratory ultrasonic cleaning bath, and the reaction mixture was irradiated by 40 kHz ultrasound at 40 °C for 1.5 h. The resulting precipitate was collected, washed with acetone, and recrystallized from MeOH/AcOEt/hexane to give a product (12.39 g, 88%) as a slightly yellow crystal, m.p. 192.4–193.1 °C (lit. 197–200 °C). ^{1}H NMR (300 MHz, DMSO-d_6): δ = 9.40 (d, J = 6.9 Hz, 2H), 9.31 (s, 1H), 9.02 (t, J = 7.9 Hz, 1H), 8.97 (d, J = 8.7 Hz, 1H), 8.47 (d, J = 7.9 Hz, 2H), 8.38 (d, J = 8.7 Hz, 1H). ^{13}C NMR (300 MHz, DMSO-d_6): δ = 121.4, 128.0, 130.2, 131.9, 138.7, 143.2, 146.2, 148.8, 149.0.

2.3. General procedure for the synthesis of pyridinium chloride

A 50 mL round flask was charged with *N*-(2,4-dinitrophenyl)pyridinium chloride (1.41 g, 5.0 mmol), primary amine (5.5 mmol) and 15 mL 80% ethanol, the reaction flask was located in the cleaner bath, where the surface of reactants was slightly lower than the level of the water. Then the reaction mixture was irradiated by 40 kHz ultrasound at 35 °C under nitrogen. The reaction progress was monitored by TLC. After the solution was irradiated for the period as indicated in Table 2, 2,4-dinitroaniline precipitated from the reaction solution was removed by filtration. The solvent was evaporated under vacuum, and the resulting solid was washed with petroleum ether (3 × 10 mL). Evaporation of solvent under reduced pressure gave the desired product. For the new products, their structures were determined by ^{1}H and ^{13}C NMR spectroscopy and elemental analysis. For the known compounds, their structures were determined by ^{1}H and ^{13}C NMR spectroscopy and the spectral data of the products were identical to those previously reported [14].

2.3.1. 1-(4-Amino-phenyl)-pyridinium chloride (Table 2, entry **5**)

^{1}H NMR (300 MHz, DMSO-d_6): δ = 9.03 (d, J = 5.6 Hz, 2H), 8.78 ((t, J = 7.4 Hz, 1H), 8.21 (t, J = 6.7 Hz, 2H), 7.71 (d, J = 7.4 Hz, 2H), 6.79 (d, J = 8.8 Hz, 2H), 5.94 (s, 2H). ^{13}C NMR (300 MHz, DMSO-d_6): δ = 148.4, 142.8, 141.2, 134.3, 129.4, 126.4, 125.8. Anal. calcd. for $C_{11}H_{11}ClN_2{\cdot}0.5H_2O$: C, 61.25; H, 5.14. Found: C, 61.39; H, 5.47.

2.3.2. 1, 4-Bis (pyridinium) butane chloride (Table 2, entry **8**)

^{1}H NMR (300 MHz, D_2O): δ = 8.70 (d, J = 5.5 Hz, 4H), 8.48 (t, J = 7.8 Hz, 2H), 7.90 (t, J = 6.9 Hz, 4H), 4.74 (t, J = 7.2 Hz, 4H), 2.22 (m, 4H). ^{13}C NMR (300 MHz, D_2O): δ = 145.5, 144.1, 128.4, 62.2, 34.6. Anal. calcd. for $C_{14}H_{18}Cl_2N_2{\cdot}0.8H_2O$: C, 56.12; H, 6.06. Found: C, 56.41; H, 5.82.

2.3.3. 1,2-Bis (pyridinium) ethane chloride (Table 2, entry **9**)

^{1}H NMR (300 MHz, DMSO-d_6): δ = 8.72 (d, J = 5.5 Hz, 4H), 8.63 (t, J = 7.8 Hz, 2H), 8.10 (t, J = 6.9 Hz, 4H), 4.98 (s, 4H) ^{13}C NMR (300 MHz, DMSO-d_6): δ = 146.3, 139.8, 128.7, 62.9, 35.2. Anal. calcd. for $C_{12}H_{14}Cl_2N_2{\cdot}1.0H_2O$: C, 52.38; H, 5.13. Found: C, 52.59; H, 5.47.

2.4. N-(2,4-Dinitrophenyl)-3-methylimidazolium chloride [15]

To a solution of finely powdered 1-chloro-2,4-dinitrobenzene (10.12 g, 50 mmol) in acetone (15 mL) was added 1-methylimidazole (4.06 mL, 51 mmol), the reaction vessel equipped with a drying tube was then placed in a laboratory ultrasonic cleaning bath, and the reaction mixture was irradiated by 40 kHz ultrasound at 40 °C for 80 min. The resulting precipitate was collected, washed with acetone, and recrystallized from MeOH/AcOEt/hexane to give a product (13.09 g, 92%) as a white crystal. Mp 245.4–246.9 °C (lit. 244–247 °C). ^{1}H NMR (300 MHz, DMSO-d_6): δ = 9.20 (d, J = 2.51 Hz, 1H), 8.32–8.90 (m, 3H), 8.14 (d J = 2.05 Hz, 1H), 7.97 (d, J = 2.07 Hz, 1H), 4.16 (s, 3H). ^{13}C NMR (300 MHz, DMSO-d_6): δ = 149.6, 144.6, 132.8, 131.9, 129.6, 124.6, 124.5, 122.1, 36.3.

2.5. General procedure for the synthesis of imidazolium chloride

A 50 mL round flask was charged with 1-(2,4-dinitrophenyl)-3-methylimidazolium chloride (2.0 g, 7.0 mmol), primary amine (7.5 mmol) and 15 mL of 80% ethanol, the reaction flask was located in the cleaner bath, where the surface of reactants was slightly lower than the level of the water. Then the reaction mixture was irradiated by 40 kHz ultrasound at 35 °C under nitrogen. The reaction progress was monitored by TLC. After the solution was irradiated for the period as indicated in Table 3, 2,4-dinitroaniline precipitated from the reaction solution was removed by filtration. The solvent was evaporated under vacuum, and the resulting

Table 1
The effect of the reaction conditions on the synthesis of 1-(4-methoxy-phenyl)-pyridinium chloride[a].

Entry	Power (W)	Temperature (°C)	Irradiation time (min)	Yield (%)[b]
1	320	25	60	57
2	360	30	60	64
3	360	35	60	71
4	360	40	60	71
5	360	45	60	72
6	360	35	80	80
7	360	35	100	86
8	360	35	120	87
9[c]	0	Reflux	360	56
10[c]	0	Reflux	720	75

[a] Conditions: With irradiation frequency 40 kHz, *N*-(2,4-dinitrophenyl)pyridinium chloride (1.41 g, 5. 0 mmol) and 4-methoxy-phenylamine (0.68 g, 5. 5 mmol) were dissolved in 15 mL of 80% ethanol under N_2.
[b] Refers to work-up yield.
[c] Conventional method with magnetic stirring.