Journal of Molecular Liquids 198 (2014) 259–262

Contents lists available at ScienceDirect

Journal of Molecular Liquids

journal homepage: www.elsevier.com/locate/molliq

L-(+)-Tartaric acid and choline chloride based deep eutectic solvent: An efficient and reusable medium for synthesis of *N*-substituted pyrroles via Clauson-Kaas reaction

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ARTICLE INFO

Article history:
Received 15 May 2014
Received in revised form 29 June 2014
Accepted 14 July 2014
Available online 27 July 2014

Keywords:
Deep eutectic solvent
Low melting mixture
L-(+)-Tartaric acid–choline chloride
Clauson-Kaas reaction
Pyrroles

ABSTRACT

L-(+)-Tartaric acid–choline chloride based deep eutectic solvent has been found to be an effective promoted medium for Clauson-Kaas reaction of aromatic amines and 2,5-dimethoxytetrahydrofuran. Structurally diverse *N*-substituted pyrroles were obtained in high to excellent yields under mild conditions. The deep eutectic solvent is inexpensive, non-toxic, reusable and biodegradable.

1. Introduction

Pyrroles constitute an interesting class of nitrogen-containing heterocycles that widely occur in bioactive natural products, pharmaceuticals, functional materials, ligands and synthetic building blocks [1]. Consequently, many approaches have been developed for the synthesis of substituted pyrroles including Paal–Knorr reaction [2], conjugate addition reactions [3], coupling reaction [4], cycloaddition reaction [5], Hantzsch procedure [6], annulation reactions [7], transition metal-mediated cyclization [8] as well as multi-component reactions [9–11]. Clauson-Kaas reaction is one of the most widely-used protocols for the synthesis of *N*-substituted pyrroles [12]. Despite some improved methods have been developed for this reaction [13–15], some of these procedures are associated with one or more disadvantages such as the use of volatile and hazardous organic solvents, the requirement of expensive catalyst and additional microwave oven. Thus, the development of a simple, efficient, economical and green procedure for the preparation of *N*-substituted pyrroles would be attractive.

Recently, deep eutectic solvents (DESs) have been emerged as new alternative renewable reaction media or catalyst for the development of environmentally benign organic transformations [16,17]. The properties of DESs are similar to that of conventional ionic liquids in terms of low vapour pressure and flammability. They often show low volatility, water-compatibility, non-toxicity, bio-compatibility, bio-degradability, and recyclability. DESs are mainly prepared by mixing quaternary ammonium salt such as choline chloride (ChCl) with hydrogen-bond donors such as urea, citric acid, and glycerol without any further purification steps. Moreover, most of materials are ready availability from bulk renewable resources. Some organic reactions such as Ugi reaction [18], esterification reaction [19], ring opening of epoxides [20], synthesis of aurones [21], quinolines [22], quinazolines [23], 1,8-dioxo-dodecahydroxanthene [24], benzopyran derivatives [25], β-functionalized ketonic derivatives [26], spirooxindoles [27], tetrasubstituted imidazoles [28] as well as reductive amination of aldehydes and ketones [29] have been reported to proceed using DESs as solvent or catalyst. As part of our ongoing studies devoted towards the development of novel and environmentally benign synthetic methodologies [30–40], herein we report L-(+)-tartaric acid–ChCl as reaction medium and catalyst for the synthesis of *N*-substituted pyrroles via Clauson-Kaas reaction (Scheme 1).

2. Experimental section

2.1. General

All reagents were obtained from local commercial suppliers and used without further purification. Melting points were determined on an X-4 apparatus and are uncorrected. NMR spectra were recorded on a Bruker DRX-500 spectrometer at 500 MHz (^{1}H) and 125 MHz (^{13}C)

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http://dx.doi.org/10.1016/j.molliq.2014.07.015
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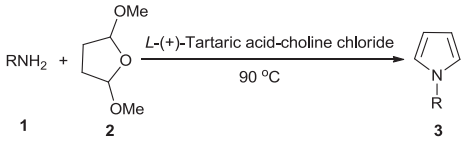


Scheme 1. Synthesis of *N*-substituted pyrroles via Clauson-Kaas reactions in DES.

using $CDCl_3$ as the solvent with TMS as internal standard. Mass spectra were operated at a ThermoFinnigan LCQ Advantage instrument with an ESI source (4.5 keV).

2.2. Typical procedure for the preparation of N-substituted pyrroles

Amine (1 mmol), 2,5-dimethoxytetrahydrofuran (1.1 mmol) and L-(+)-tartaric acid–choline chloride based DES (1.5 g) were added to a 50 mL round bottom flask and the reaction mixture was stirred at 90 °C. The progress of the reaction was monitored by TLC. After completion of the reaction, the mixture was cooled to room temperature and the product was extracted with ethyl acetate. After the evaporation of the solvent, the residue was purified by column chromatography on silica gel to afford the pure product. The DES was dried under vacuum and reused for the next cycle.

2.3. Spectra data of the products

1-Phenyl-1H-pyrrole (**3a**). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 6.36 (t, J = 2.0 Hz, 2H), 7.10 (t, J = 2.0 Hz, 2H), 7.24–7.26 (m, 1H), 7.40–7.45 (m, 4H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 110.5, 119.4, 120.6, 125.7, 129.6, 140.9 ppm; ESI-MS: m/z = 144 $(M + 1)^+$.

3-(1H-Pyrrol-1-yl)phenol (**3b**). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 4.88 (brs, 1H), 6.34 (t, J = 2.0 Hz, 2H), 6.70 (dd, J = 8.0 Hz, 2.0 Hz, 1H), 6.89 (t, J = 2.0 Hz, 1H), 6.98 (dd, J = 8.0 Hz, 2.0 Hz, 1H), 7.07 (t, J = 2.0 Hz, 2H), 7.27 (t, J = 8.0 Hz, 1H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 107.9, 110.7, 127.8, 113.1, 119.5, 130.8, 142.2, 156.6 ppm; ESI-MS: m/z = 160 $(M + 1)^+$.

1-(2-Methoxyphenyl)-1H-pyrrole (**3c**). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 3.85 (s, 3H), 6.34 (s, 2H), 7.01–7.05 (m, 4H), 7.28–7.32 (m, 2H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 55.7, 108.7, 112.2, 120.8, 121.9, 125.6, 127.4, 130.2, 152.6 ppm; ESI-MS: m/z = 174 $(M + 1)^+$.

1-(4-Methoxyphenyl)-1H-pyrrole (**3d**). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 3.84 (s, 3H), 6.32 (t, J = 2.0 Hz, 2H), 6.95 (d, J = 9.0 Hz, 2H), 7.00 (t, J = 2.0 Hz, 2H), 7.31 (d, J = 9.0 Hz, 2H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 55.6, 109.8, 114.6, 119.7, 122.2, 134.5, 157.7 ppm; ESI-MS: m/z = 174 $(M + 1)^+$.

1-(2-Tolyl)-1H-pyrrole (**3e**). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 2.25 (s, 3H), 6.35 (t, J = 2.0 Hz, 2H), 6.83 (t, J = 2.0 Hz, 2H), 7.27–7.32 (m, 4H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 17.7, 108.6, 121.9, 126.4, 126.5, 127.4, 130.9, 133.6, 140.5 ppm; ESI-MS: m/z = 158 $(M + 1)^+$.

1-(4-Tolyl)-1H-pyrrole (**3f**). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 2.38 (s, 3H), 6.34 (t, J = 2.0 Hz, 2H), 7.06 (t, J = 2.0 Hz, 2H), 7.22 (d, J = 8.0 Hz, 2H), 7.29 (d, J = 8.0 Hz, 2H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 20.9, 110.2, 119.5, 120.6, 130.1, 135.4, 138.6 ppm; ESI-MS: m/z = 158 $(M + 1)^+$.

1-(2,5-Dimethylphenyl)-1H-pyrrole (**3g**). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 2.34 (s, 3H), 2.51 (s, 3H), 6.49 (t, J = 2.0 Hz, 2H), 6.62 (t, J = 2.0 Hz, 2H), 7.25 (s, 2H), 7.33 (s, 1H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 17.6, 20.9, 108.8, 122.1, 127.4, 128.3, 130.6, 131.0, 136.4, 140.6 ppm; ESI-MS: m/z = 172 $(M + 1)^+$.

1-(2,6-Dimethylphenyl)-1H-pyrrole (**3h**). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 2.05 (s, 6H), 6.33 (s, 2H), 6.62 (s, 2H), 7.13 (d, J = 7.5 Hz, 2H), 7.21 (t, J = 7.5 Hz, 1H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 17.4, 108.6, 121.4, 128.0, 136.3, 140.0 ppm; ESI-MS: m/z = 172 $(M + 1)^+$.

1-(2,6-Diisopropylphenyl)-1H-pyrrole (**3i**). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 1.14 (d, J = 7.0 Hz, 12H), 2.39-2.48 (m, 1H), 6.32 (t, J = 2.0 Hz, 2H), 6.64 (t, J = 2.0 Hz, 2H), 7.22 (d, J = 7.5 Hz, 2H), 7.39 (t, J = 7.5 Hz, 1H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 24.7, 28.1, 108.4, 123.1, 123.4, 128.9, 137.1, 147.1 ppm; ESI-MS: m/z = 228 $(M + 1)^+$.

1-(4-(tert-Butyl)phenyl)-1H-pyrrole (**3j**). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 1.35 (s, 9H), 6.34 (t, J = 2.0 Hz, 2H), 7.07 (t, J = 2.0 Hz, 2H), 7.33 (d, J = 7.0 Hz, 2H), 7.44 (d, J = 7.0 Hz, 2H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 31.4, 34.5, 110.1, 119.4, 120.3, 126.4, 138.4, 148.7 ppm; ESI-MS: m/z = 200 $(M + 1)^+$.

1-(2-Fluorophenyl)-1H-pyrrole (**3k**). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 6.38 (t, J = 2.0 Hz, 2H), 7.06 (t, J = 2.0 Hz, 2H), 7.19–7.26 (mk, 3H), 7.41 (t, J = 8.0 Hz, 1H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 110.1, 117.1 (d, $^2J_{FC}$ = 20.3 Hz), 121.4 (d, $^4J_{FC}$ = 3.5 Hz), 124.8 (d, $^4J_{FC}$ = 3.8 Hz), 125.0, 127.2 (d, $^3J_{FC}$ = 7.9 Hz), 129.1 (d, $^3J_{FC}$ = 10.4 Hz), 155.1 (d, $^1J_{FC}$ = 247.8 Hz) ppm; ESI-MS: m/z = 162 $(M + 1)^+$.

1-(4-Fluorophenyl)-1H-pyrrole (**3l**). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 6.35 (t, J = 2.0 Hz, 2H), 7.02 (t, J = 2.0 Hz, 2H), 7.12 (t, J = 8.5 Hz, 2H), 7.35 (d, J = 8.5 Hz, 1H), 7.36 (d, J = 8.5 Hz, 1H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 110.5, 116.3 (d, $^2J_{FC}$ = 22.6 Hz), 119.6, 122.3 (d, $^3J_{FC}$ = 8.1 Hz), 137.2, 160.7 (d, $^1J_{FC}$ = 243.2 Hz) ppm; ESI-MS: m/z = 162 $(M + 1)^+$.

1-(3-Chlorophenyl)-1H-pyrrole (**3m**). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 6.30 (t, J = 2.0 Hz, 2H), 6.99 (t, J = 2.0 Hz, 2H), 7.12–7.20 (m, 2H), 7.25 (dd, J = 8.5, 2.0 Hz, 1H), 7.32 (d, J = 2.0 Hz, 1H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 141.5, 135.0, 130.4, 125.3, 120.4, 119.0, 118.1, 110.8 ppm; ESI-MS: m/z = 179 $(M + 1)^+$.

1-(4-Chlorophenyl)-1H-pyrrole (**3n**). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 6.36 (t, J = 2.0 Hz, 2H), 7.05 (t, J = 2.0 Hz, 2H), 7.33 (d, J = 8.5 Hz, 2H), 7.39 (d, J = 8.5 Hz, 1H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 110.9, 119.3, 121.6, 129.7, 131.1, 139.4 ppm; ESI-MS: m/z = 179 $(M + 1)^+$.

1-(2-Bromophenyl)-1H-pyrrole (**3o**). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 6.34 (t, J = 2.0 Hz, 2H), 6.99 (t, J = 2.0 Hz, 2H), 7.24 (td, J = 8.5, 1.5 Hz, 1H), 7.33 (dd, J = 8.5, 1.5 Hz, 1H), 7.39 (td, J = 8.5, 1.5 Hz, 1H), 7.69 (dd, J = 8.5, 1.5 Hz, 1H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 109.2, 119.8, 122.2, 128.1, 128.3, 133.7, 140.4 ppm; ESI-MS: m/z = 223 $(M + 1)^+$.

1-(3-Bromophenyl)-1H-pyrrole (**3p**). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 6.35 (s, 2H), 7.06 (s, 2H), 7.28 (t, J = 7.5 Hz, 1H), 7.33 (d, J = 7.5 Hz, 1H), 7.36 (d, J = 7.5 Hz, 1H), 7.55 (s, 1H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 111.1, 118.9, 119.3, 123.2, 123.5, 128.6, 130.9, 141.9 ppm; ESI-MS: m/z = 223 $(M + 1)^+$.

1-(4-Bromophenyl)-1H-pyrrole (**3q**). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 6.40 (s, 2H), 7.14 (s, 2H), 7.50 (d, J = 9.0 Hz, 2H), 7.69 (d, J = 9.0 Hz, 2H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 111.6, 119.1, 119.9, 126.9, 143.2 ppm; ESI-MS: m/z = 223 $(M + 1)^+$.

1-(4-Iodophenyl)-1H-pyrrole (**3r**). IR (KBr): 3130, 1587, 1496, 1409, 1330, 1247, 1126, 1078, 1001, 920, 815, 729 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 6.36 (t, J = 2.0 Hz, 2H), 7.05 (t, J = 2.0 Hz, 2H), 7.15 (d, J = 9.0 Hz, 2H), 7.73 (d, J = 9.0 Hz, 2H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 89.4, 111.0, 119.1, 122.2, 138.6, 140.4 ppm; ESI-MS: m/z = 270 $(M + 1)^+$.

1-(3-Nitrophenyl)-1H-pyrrole (**3s**). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 6.38 (t, J = 2.0 Hz, 2H), 6.82 (t, J = 2.0 Hz, 2H), 7.46-7.49 (m, 2H), 7.65 (t, J = 8.5 Hz, 1H), 7.85 (d, J = 8.6 Hz, 1H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 145.0, 133.9, 133.0, 127.6, 127.5, 124.7, 121.1, 110.8 ppm; ESI-MS: m/z = 189 $(M + 1)^+$.

1-(4-Nitrophenyl)-1H-pyrrole (**3t**). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 6.43 (t, J = 2.0 Hz, 2H), 7.18 (t, J = 2.0 Hz, 2H), 7.52 (d, J = 9.0 Hz, 2H), 8.31 (d, J = 9.0 Hz, 2H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 112.6, 119.1, 119.4, 125.6, 144.7, 145.2 ppm; ESI-MS: m/z = 189 $(M + 1)^+$.

1-(4-(1H-pyrrol-1-yl)phenyl)ethanone (**3u**). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 2.62 (s, 3H), 6.39 (t, J = 2.0 Hz, 2H), 7.17 (t, J = 2.0 Hz, 2H), 7.47 (d, J = 8.5 Hz, 2H), 8.03 (d, J = 8.5 Hz, 2H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 26.6, 111.7, 119.0, 119.3, 130.2, 133.9, 144.0, 196.8 ppm; ESI-MS: m/z = 186 $(M + 1)^+$.

1-(3-(Trifluoromethyl)phenyl)-1H-pyrrole (**3v**). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 6.39 (t, J = 2.5 Hz, 2H), 7.11 (t, J = 2.0 Hz, 2H), 7.50 (d, J = 7.5 Hz, 1H), 7.53-7.58 (m, 2H), 7.63 (s, 1H) ppm; ^{13}C NMR

($CDCl_3$, 125 MHz) δ: 111.4, 117.1 (q, $^3J_{FC}$ = 4.0 Hz), 119.2, 122.1 (q, $^3J_{FC}$ = 3.6 Hz), 123.4, 123.9 (q, $^1J_{FC}$ = 270.8 Hz), 130.3, 132.2 (q, $^2J_{FC}$ = 32.5 Hz), 141.2 ppm; ESI-MS: m/z = 212 $(M + 1)^+$.

1-(4-(Trifluoromethyl)phenyl)-1H-pyrrole (**3w**). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 6.40 (t, *J* = 2.0 Hz, 2H), 7.14 (t, *J* = 2.0 Hz, 2H), 7.50 (d, *J* = 8.5 Hz, 2H), 7.69 (d, *J* = 8.5 Hz, 2H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 111.5, 119.1, 119.9, 124.1 (q, $^1J_{FC}$ = 270.0 Hz), 126.9 (q, $^3J_{FC}$ = 3.6 Hz), 127.4 (q, $^2J_{FC}$ = 32.8 Hz), 143.2 ppm; ESI-MS: m/z = 212 $(M + 1)^+$.

Ethyl 4-(1H-pyrrol-1-yl)benzoate (**3x**). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 1.41 (t, *J* = 7.0 Hz, 3H), 4.39 (q, *J* = 7.0 Hz, 2H), 6.39 (t, *J* = 2.5 Hz, 2H), 7.16 (t, *J* = 2.5 Hz, 2H), 7.45(d, *J* = 8.5 Hz, 2H), 8.11(d, *J* = 8.5 Hz, 2H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 14.4, 61.1, 111.5, 119.1, 119.3, 127.3, 131.3, 143.9, 166.0 ppm; ESI-MS: m/z = 216 $(M + 1)^+$.

1-(Naphthalen-1-yl)-1H-pyrrole (**3y**). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 6.45 (t, *J* = 2.0 Hz, 2H), 7.04 (t, *J* = 2.0 Hz, 2H), 7.49–7.57 (m, 4H), 7.80 (d, *J* = 8.5 Hz, 1H), 7.90 (d, *J* = 8.5 Hz, 1H), 7.95 (d, *J* = 8.5 Hz, 1H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 109.3, 123.3, 123.4, 125.4, 126.7, 127.1, 128.0, 128.3, 130.0, 134.4, 138.4 ppm; ESI-MS: m/z = 194 $(M + 1)^+$.

2-(1H-Pyrrol-1-yl)pyridine (**3z**). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 6.45 (t, *J* = 2.0 Hz, 2H), 7.12 (dd, *J* = 8.0, 5.0 Hz, 1H), 7.33 (d, *J* = 8.0 Hz, 1H), 7.61 (t, *J* = 2.0 Hz, 2H), 7.74 (td, *J* = 8.0, 1.5 Hz, 1H), 8.48 (dd, *J* = 5.0, 1.5 Hz, 1H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 111.3, 111.5, 118.1, 120.2, 138.5, 148.7, 151.3 ppm; ESI-MS: m/z = 145 $(M + 1)^+$.

2-(1H-pyrrol-1-yl)pyrimidine (**3aa**). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 6.34 (t, *J* = 2.5 Hz, 2H), 7.05 (t, *J* = 4.5 Hz, 1H), 7.78 (t, *J* = 2.5 Hz, 2H), 8.62 (d, *J* = 4.5 Hz, 2H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 112.0, 117.1, 119.1, 158.4 ppm; ESI-MS: m/z = 146 $(M + 1)^+$; Anal. Calcd for $C_8H_7N_3$: C, C, 66.19; H, 4.86; N, 28.95. Found: C, 66.01; H, 5.02; N, 29.13.

4-(1H-pyrrol-1-yl)aniline (**3ab**). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 3.68 (br s, 2H), 6.30 (t, *J* = 2.0 Hz, 2H), 6.72 (d, *J* = 8.5 Hz, 2H), 6.97 (t, *J* = 2.0 Hz, 2H), 7.19 (d, *J* = 8.5 Hz, 2H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 109.5, 115.7, 119.7, 122.4, 133.0, 144.5 ppm; ESI-MS: m/z = 159 $(M + 1)^+$.

3. Results and discussion

The examination of the reaction conditions commenced with the reaction of aniline and 2,5-dimethoxytetrahydrofuran as model reaction. As shown in Table 1, only a trace amount of the target product was detected when the reaction was performed in low-melting mixtures, such as D-(−)-fructose-*N*,*N*-dimethylurea (DMU), lactose–DMU–NH_4Cl, glucose–urea–$CaCl_2$, glucose–urea–NaCl, sucrose–choline chloride and glucose–guanidinium HCl at their minimal melting temperature. When the reaction was conducted in mannose–DMU–NH_4Cl, the yield of desired product could be improved to 25% (Table 1, entry 8). Consider this reaction works well under acidic conditions, some acidic medium was investigated in order to obtain more satisfactory results. To our great delight, a significant improvement was observed when deep eutectic solvents such as L-(+)-tartaric acid–DMU and citric acid–DMU were used as the reaction medium (entries 9 and 10). Screening revealed that the use of L-(+)-tartaric acid–ChCl melt produced the best result (entry 11). In contrast, the reaction did not proceed in organic solvents such as MeOH, EtOH and MeCN in the presence of a catalytic amount of L-(+)-tartaric acid–ChCl (10 mol%) (entries 12–14).

In order to demonstrate the practical applicability of this process, the model reaction was carried out in a scale of 50 mmol. The reaction was completed in 1 h with 94% yield (entry 15). On the same scale, the recyclability of deep eutectic solvent was investigated. After completion of the reaction, the mixture was cooled to room temperature and the product was extracted with ethyl acetate. The DES was dried under vacuum and subjected to the next cycles without further purification. The results of five runs showed almost consistent yields (entry 16).

Having obtained satisfactory results, the substrate scope and generality of this novel process were evaluated under the above optimized conditions and the typical results are presented in Table 2. Anilines containing different substituents such as OH, OMe, Me, F, Cl, Br, NO_2, Ac and CF_3 were smoothly reacted with tetrahydro-2,5-dimethoxyfuran to provide expected *N*-substituted pyrroles in good to excellent yields. The electronic properties of the substituents on the phenyl ring of anilines had a little effect on the reaction. In general, anilines bearing an electron-donating group produced a slightly higher yield of products than those analogues bearing electron-withdrawing group. The steric effect of substituents had an obvious impact on the yield of the reaction. For example, Clauson-Kaas reaction of tetrahydro-2,5-dimethoxyfuran with *para*-, *meta*- and *ortho*-bromoaniline provided 86% of **3p** and 89% of **3q**, while the yield of **3o** was decreased to 79% (Table 2, entries 15–17). The same phenomenon was observed in the reaction of tetrahydro-2,5-dimethoxyfuran with *para*- and *ortho*-methoxyaniline (entries 3 and 4). Moreover, naphthylamine was proved applicable for this reaction, generating the desired product in 94% yield (Table 2,

Table 1
Optimization of the reaction conditions[a].

Entry	Solvent	Temperature (°C)	Time (min)	Yield (%)[b]
1	No	100	240	21
2	D-(−)-Fructose–DMU (70:30)	71	120	trace
3	Lactose–DMU–NH_4Cl (50:40:10)	88	160	trace
4	Glucose–urea–$CaCl_2$ (50:40:10)	75	180	trace
5	Glucose–urea–NaCl (60:30:20)	78	180	trace
6	Sucrose–ChCl (50:50)	80	180	trace
7	Glucose–guanidinium HCl (40:60)	70	180	trace
8	Mannose–DMU–NH_4Cl (50:40:10)	73	110	25
9	L-(+)-Tartaric acid–DMU (30:70)	70	60	77
10	Citric acid–DMU (40:60)	65	60	86
11	L-(+)-Tartaric acid–ChCl (50:50)	90	50	95
12[c]	MeOH	reflux	60	trace
13[c]	EtOH	reflux	60	trace
14[c]	MeCN	reflux	60	trace
15[d]	L-(+)-Tartaric acid–ChCl (50:50)	90	60	94
16[e]	L-(+)-Tartaric acid–ChCl (50:50)	90	50	95, 93, 92, 91, 90

[a] Reaction conditions: aniline (1 mmol), 2,5-dimethoxytetrahydrofuran (1.1 mmol), solvent (1.5 g).
[b] Isolated yields.
[c] The reaction was carried out in the presence of L-(+)-tartaric acid–ChCl (10 mol%), organic solvent (3 mL).
[d] The reaction was carried out in 50 mmol scale.
[e] L-(+)-Tartaric acid–ChCl was reused for 5 times.

Table 2
Synthesis of *N*-substituted pyrroles in L-(+)-tartaric acid–ChCl.

Entry	Amine	Product	Time (min)	Yield (%)[a]	Mp (°C)
1	$PhNH_2$	**3a**	50	95	60–61
2	$3\text{-}OHC_6H_5NH_2$	**3b**	50	92	62–63
3	$2\text{-}OCH_3C_6H_5NH_2$	**3c**	40	89	Oil
4	$4\text{-}OCH_3C_6H_5NH_2$	**3d**	30	95	111–112
5	$2\text{-}CH_3C_6H_4NH_2$	**3e**	40	90	Oil
6	$4\text{-}CH_3C_6H_4NH_2$	**3f**	30	95	82–83
7	$2,5\text{-}Me_2C_6H_3NH_2$	**3g**	60	89	52–53
8	$2,6\text{-}Me_2C_6H_3NH_2$	**3h**	80	86	46–47
9	$2,6\text{-}{}^{i}Pr_2C_6H_3NH_2$	**3i**	100	76	76–77
10	$4\text{-}{}^{t}BuC_6H_4NH_2$	**3j**	90	92	71–72
11	$2\text{-}FC_6H_4NH_2$	**3k**	90	83	Oil
12	$4\text{-}FC_6H_4NH_2$	**3l**	80	86	51–52
13	$3\text{-}ClC_6H_4NH_2$	**3m**	80	85	50–51
14	$4\text{-}ClC_6H_4NH_2$	**3n**	80	83	87–88
15	$2\text{-}BrC_6H_4NH_2$	**3o**	100	79	Oil
16	$3\text{-}BrC_6H_4NH_2$	**3p**	80	86	81–82
17	$4\text{-}BrC_6H_4NH_2$	**3q**	80	89	93–94
18	$4\text{-}IC_6H_4NH_2$	**3r**	90	82	130–131
19	$2\text{-}NO_2C_6H_4NH_2$	**3s**	110	78	Oil
20	$4\text{-}NO_2C_6H_4NH_2$	**3t**	100	89	187–188
21	$4\text{-}AcC_6H_4NH_2$	**3u**	80	88	120–121
22	$3\text{-}CF_3C_6H_4NH_2$	**3v**	90	83	48–49
23	$4\text{-}CF_3C_6H_4NH_2$	**3w**	90	90	112–113
24	$4\text{-}COOEtC_6H_4NH_2$	**3x**	80	90	76–77
25	Naphthalen-1-amine	**3y**	60	94	Oil
26	Pyridin-2-amine	**3z**	120	75	Oil
27	Pyrimidin-2-amine	**3aa**	80	85	83–84
28	Benzene-1,4-diamine	**3ab**	100	93	80 − 82

[a] Isolated yield.

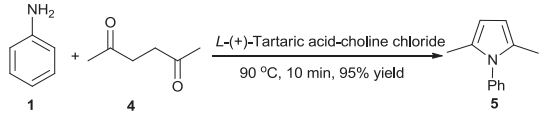
entry 25). Heteroaromatic amines such as pyridin-2-amine and pyrimidin-2-amine also underwent the reaction efficiently. Aromatic diamine such as benzene-1,4-diamine was also tested and the corresponding monopyrroles **3ab** was selectively formed (entry 28). However, aliphatic amines showed no reactivity under current conditions.

To extend the application of this DES, Paal–Knorr reaction was also examined [2]. As shown in Scheme 2, the reaction of aniline with acetonylacetone proceeded well, and the desired product **5** could also be obtained in 95% yield.

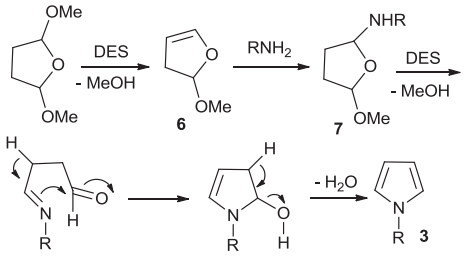
Based on previous reports [14], a tentative mechanism for the formation of *N*-substituted pyrroles is proposed in Scheme 3. The first step may involve the deprotection reaction of 2,5-dimethoxytetrahydrofuran to form intermediate **6**. Next, the reaction of intermediate **4** with amines **1** led to *N*-substituted pyrroles **3** by a nucleophilic addition, subsequent expulsion of MeOH, dehydration, and intramolecule aromatization steps. In this process, the acidity of the DES may play an important role for the deprotection of methoxy groups. The hydrogen bonding interactions between DES and aromatic amino group might assist in improving the nucleophilicity of aromatic amine **1** leading to its faster attack on intermediate **6**.

4. Conclusion

In summary, we have developed a simple, greener and efficient procedure for the synthesis of *N*-substituted pyrroles by Clauson-Kaas reaction of amines and 2,5-dimethoxytetrahydrofuran using a deep eutectic mixture as a novel and green medium. The present protocol offers some advantages such as operational simplicity, metal-free, wide range of substrates, high yields and environmentally benign reaction conditions.



Scheme 2. Synthesis of substituted pyrroles via Paal–Knorr reactions in DES.



Scheme 3. Plausible reaction mechanism.

Acknowledgments

Financial support from the National Natural Science Foundation of China (Nos. 21272053 and 21072042) is greatly appreciated.

References

[1] S.D. Joshi, U.A. More, V.H. Kulkarni, T.M. Aminabhavi, Curr. Org. Chem. 17 (2013) 2279–2304.
[2] Z.H. Zhang, J.J. Li, T.S. Li, Ultrason. Sonochem. 15 (2008) 673–676.
[3] Q.L. Chong, X.Y. Xin, C.X. Wang, F. Wu, B.S. Wan, Tetrahedron 70 (2014) 490–494.
[4] M.N. Zhao, Z.H. Ren, Y.Y. Wang, Z.H. Guan, Org. Lett. 16 (2014) 608–611.
[5] G. Lonzi, L.A. Lopez, Adv. Synth. Catal. 355 (2013) 1948–1954.
[6] V. Estevez, M. Villacampa, J.C. Menendez, Chem. Commun. 49 (2013) 591–593.
[7] S.Y. Wang, X.C. Zhu, Z. Chai, S.W. Wang, Org. Biomol. Chem. 12 (2014) 1351–1356.
[8] Y.H. Xu, T. He, Q.C. Zhang, T.P. Loh, Chem. Commun. 50 (2014) 2784–2786.
[9] B.L. Li, P.H. Li, X.N. Fang, C.X. Li, J.L. Sun, L.P. Mo, Z.-H. Zhang, Tetrahedron 69 (2013) 7011–7018.
[10] B.L. Li, H.C. Hu, L.P. Mo, Z.H. Zhang, Rsc Adv. 4 (2014) 12929–12943.
[11] B.L. Li, M. Zhang, H.C. Hu, X. Du, Z.H. Zhang, New J. Chem. 38 (2014) 2435–2442.
[12] F.P. Ma, P.H. Li, B.L. Li, L.P. Mo, N. Liu, H.J. Kang, Y.N. Liu, Z.H. Zhang, Appl. Catal. A Gen. 457 (2013) 34–41.
[13] C.C. Silveira, M.P. Fortes, S.R. Mendes, Curr. Org. Chem. 16 (2012) 1540–1548.
[14] X.X. Zhang, J.C. Shi, Tetrahedron 67 (2011) 898–903.
[15] H.J. Deng, Y.J. Fang, G.W. Chen, M.C. Liu, H.Y. Wu, J.X. Chen, Appl. Organomet. Chem. 26 (2012) 164–167.
[16] C. Ruβ, B. König, Green Chem. 14 (2012) 2969–2982.
[17] Q.H. Zhang, K. De Oliveira Vigier, S. Royer, F. Jérôme, Chem. Soc. Rev. 41 (2012) 7108–7146.
[18] N. Azizi, S. Dezfooli, M.M. Hashemi, C. R. Chim. 16 (2013) 1098–1102.
[19] V. De Santi, F. Cardellini, L. Brinchi, R. Germani, Tetrahedron Lett. 53 (2012) 5151–5155.
[20] N. Azizi, E. Batebi, Catal. Sci. Technol. 2 (2012) 2445–2448.
[21] I. Hawkins, S.T. Handy, Tetrahedron 69 (2013) 9200–9204.
[22] F.P. Ma, G.T. Cheng, Z.G. He, Z.H. Zhang, Aust. J. Chem. 65 (2012) 409–416.
[23] Z.H. Zhang, X.N. Zhang, L.P. Mo, Y.X. Li, F.P. Ma, Green Chem. 14 (2012) 1502–1506.
[24] P.H. Li, F.P. Ma, P. Wang, Z.H. Zhang, Chin. J. Chem. 31 (2013) 757–763.
[25] N. Azizi, S. Dezfooli, M. Khajeh, M.M. Hashemi, J. Mol. Liq. 186 (2013) 76–80.
[26] U.N. Yadav, G.S. Shankarling, J. Mol. Liq. 195 (2014) 188–193.
[27] N. Azizi, S. Dezfooli, M. Mahmoudi Hashemi, J. Mol. Liq. 194 (2014) 62–67.
[28] N. Aziizi, Z. Manochehri, A. Nahayi, S. Torkashvand, J. Mol. Liq. 196 (2014) 153–158.
[29] D. Saberi, J. Akbari, S. Mahdudi, A. Heydari, J. Mol. Liq. 196 (2014) 208–210.
[30] Z.H. Zhang, T.S. Li, J.J. Li, Monatsh. Chem. 138 (2007) 89–94.
[31] X.N. Zhang, Y.X. Li, Z.H. Zhang, Tetrahedron 67 (2011) 7426–7430.
[32] J. Deng, L.P. Mo, F.Y. Zhao, L.L. Hou, L. Yang, Z.H. Zhang, Green Chem. 13 (2011) 2576–2584.
[33] Y.H. Liu, J. Deng, J.W. Gao, Z.H. Zhang, Adv. Synth. Catal. 354 (2012) 441–447.
[34] J. Deng, L.P. Mo, F.Y. Zhao, Z.H. Zhang, S.X. Liu, ACS Comb. Sci. 14 (2012) 335–341.
[35] R.Y. Guo, Z.M. An, L.P. Mo, R.Z. Wang, H.X. Liu, S.X. Wang, Z.H. Zhang, ACS Comb. Sci. 15 (2013) 557–563.
[36] R.Y. Guo, Z.M. An, L.P. Mo, S.T. Yang, H.X. Liu, S.X. Wang, Z.H. Zhang, Tetrahedron 69 (2013) 9931–9938.
[37] R.Y. Guo, P. Wang, G.D. Wang, L.P. Mo, Z.H. Zhang, Tetrahedron 69 (2013) 2056–2061.
[38] P.H. Li, B.L. Li, Z.M. An, L.P. Mo, Z.S. Cui, Z.H. Zhang, Adv. Synth. Catal. 355 (2013) 2952–2959.
[39] P.H. Li, B.L. Li, H.C. Hu, X.N. Zhao, Z.H. Zhang, Catal. Commun. 46 (2014) 118–122.
[40] X.N. Zhao, H.C. Hu, F.J. Zhang, Z.H. Zhang, Appl. Catal. A Gen. 482 (2014) 258–265.