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Complete List of Authors:	Chaskar, Atul; National Taiwan University, Department of Chemistry Kalmode, Hanuman; Institute of Chemical Technology, Department of Dyestuff technology Vadagaonkar, Kamlesh; Institute of Chemical Technology, Department of Dyestuff technology Murugan, Kaliyappan; National Taiwan University, Department of Chemistry Prakash, Sattey; University of Mumbai, National Centre for Nanosciences and Nanotechnology

Deep eutectic solvent: a simple, environmentally benign reaction media for regioselective synthesis of 2,3,4-trisubstituted 1*H*-pyrroles

Hanuman P. Kalmode,[a] Kamlesh S. Vadagaonkar,[a] Kaliyappan Murugan,[b] Sattey Prakash[c] and Atul C. Chaskar*[a,c]

[a]*Department of Dyestuff Technology, Institute of Chemical Technology, Mumbai 400019, India*
[b]*National Taiwan University, Taipei 10617, Taiwan*
[c]*National Centre for Nanosciences and Nanotechnology, University of Mumbai, Mumbai 400098, India. E-mail: achaskar25@gmail.com; Tel.: +91-22-33612706; Fax: +91-22-3361 1020.*

Abstract: Choline hydroxide have been successfully employed as an efficient base as well as reaction media in the synthesis of 2,3,4-trisubstituted 1*H*-pyrroles from methyl 2-isocyanoacetate and α,β-unsaturated ketones. Choline hydroxide used is inexpensive, non-toxic, recyclable and environmentally friendly. A mild reaction condition and easy workup procedure are the striking features of this protocol. This transformation proceeds through the 1,4-conjugate addition of methyl 2-isocyanoacetate with α,β-unsaturated ketones followed by intramolecular cyclization-oxidation reaction.

Keywords: Choline hydroxide, Green chemistry, 2,3,4-Trisubstituted 1*H*-pyrrole, α,β-Unsaturated ketones, Regioselectivity.

Introduction

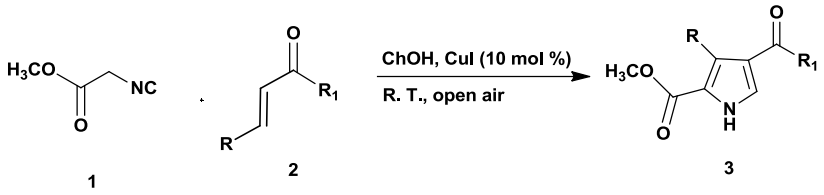
Pyrroles are common structural motif present in many natural products.[1] Moreover, they are employed as valuable intermediate in organic synthesis[2] and also utilized in other important fields such as materials,[3] medicinal chemistry and pharmacology.[4] In addition, pyrroles find promising application in organic semiconductors.[5] Consequently, they appear to be molecular scaffolds of considerable interest for synthetic chemists. The most frequently used methods for their preparation are the classic Hantzsch,[6] Knorr,[7] Paal-Knorr[8] procedures and Buchwald-Hartwig coupling[9]. Although these methods have been used during the last century, there are significant drawbacks which have triggered the search for new methodologies, such as transition-metal-catalyzed cyclizations,[10] cycloaddition reactions[11] and MCRs.[12] However, some of these new methods too have significant limitations such as tedious workup procedures, harsh reaction conditions, low yields, long reaction times or the requirement of an inert atmosphere.

All these aforementioned methods use large amounts of organic solvents, many of which are volatile, flammable and toxic. They are generally the largest single component by weight in most reactions and are a clear target for concern. Due to the increase in environmental consciousness in chemical research and industry, the challenge for a sustainable environment calls for clean procedures that avoid the use of harmful organic solvents. One of the important principles of green chemistry is the elimination of hazardous solvents in chemical synthesis, through which the use of expensive toxic solvents and the generation of waste can be avoided. Many alternative solvents have been proposed including water, supercritical fluids and room temperature ionic liquids (RTILs).[13] Ionic liquids (ILs), which are organic salts with a melting point lower than 100 ^{o}C, have attracted much attention in recent years.[14] They have some unusual properties, such as

negligible vapor pressure, low inflammability, high thermal stability, wide liquid temperature range, easy reusability and strong solvent power for both organic and inorganic substances.[15]

In this context, in recent years Paal-Knorr pyrrole synthesis in deep eutectic solvents has been achieved in quantitative yields.[16] Aydogan *et al.* reported Clauson-Kaas pyrrole synthesis catalyzed by acidic ionic liquid under microwave irradiation.[17] Eco-compatible synthesis of functionalized pyrrole was achieved in ionic liquid promoted multicomponent reaction.[18] Synthesis of tetrasubstituted pyrroles by the three-component condensation of acid chlorides, dialkylacetylenedicarboxylates and amino acids in the presence of various room-temperature ionic liquids as catalysts in water were described.[19] Polyethylene glycol (PEG) was found to be an inexpensive, non-toxic and effective medium for the one pot synthesis of highly functionalized pyrroles.[20] A green and practical method to synthesize novel *N*-(2-azetidinonyl) 2,5-disubstituted pyrroles, has been developed by Bandyopadhyay *et al*.[21] Despite of numerous diverse approaches towards the synthesis of substituted pyrroles, development of an easy, atom-economic, environmentally benign synthetic method still serve to be an attractive goal.

Thus, considering the literature reports and as a part of our endeavors for the designing and development of simple and green methodology for the synthesis of heterocycles[22], we herein wish to report simple, efficient and regioselective synthesis of novel 2,3,4-trisubstituted 1*H*-pyrroles from easily available starting materials.

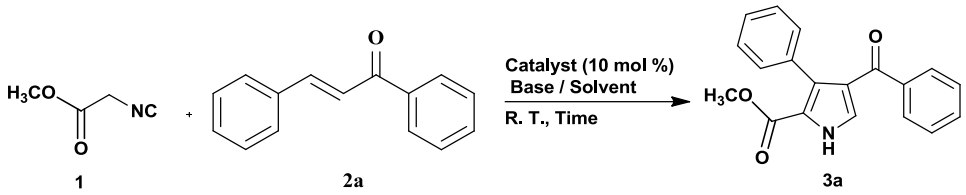


Scheme 2. General regioselective one-pot synthesis of 2,3,4-trisubstituted 1*H*-pyrrole

Results and discussion

Initially, the reaction of methyl 2-isocyanoacetate (**1)** with 1,3-diphenyl-2-en-1-one (**2a)** was selected as a model reaction, wherein the effect of different catalysts, bases and solvents were investigated. The reaction of methyl 2-isocyanoacetate (**1)** with CuI and chalcone (**2a**), was carried out in the presence of different bases such as Cs_2CO_3, K_2CO_3, NaOMe, K^{t}BuO and NaH (Table 1, entries 1-5). All these bases produced methyl 4-benzoyl-3-phenyl-1*H*-pyrrole-2-carboxylate (**3a**) in low to moderate yield (28-45%). Then we have screened the various organic bases such as DBU, 2,6-lutidine, pyridine and triethylamine (Table 1, entries 6-9) for the formation of **3a**. DBU, 2,6-lutidine and pyridine resulted in very low yields (10-18%) of **3a** whereas trace amount was observed in the case of triethylamine. To obtain the highest yield of **3a** we have screened various solvent such as water, MeOH, CH_3CN, THF and DCM in the presence of choline hydroxide as a base in equimolar amount (Table 1, entries 10-14). When we used water as a solvent **3a** was obtained in 22% yield whereas in the case of MeOH, CH_3CN, THF and DCM moderate yields (38-66%) of the product were obtained.

Table 1. Optimization of reaction conditions



Entry	Catalyst (mol %)	base	Solvent	Time (h)	Yield (%)[d]
1[a]	CuI	Cs_2CO_3	CH_3CN	2	43
2[a]	CuI	K_2CO_3	DMF	2	37
3[a]	CuI	NaOMe	MeOH	2	39
4[a]	CuI	K^{t}BuO	THF	2	45
5[a]	CuI	NaH	THF	2	28
6[a]	CuI	DBU	CH_3CN	2	12
7[a]	CuI	2,6-Lutidine	DCM	2	18
8[a]	CuI	Pyridine	DCM	2	10
9[a]	CuI	NEt_3	CH_3CN	2	Trace
10[a]	CuI	ChOH	Water	2	22
11[a]	CuI	ChOH	MeOH	2	66
12[a]	CuI	ChOH	CH_3CN	2	44
13[a]	CuI	ChOH	THF	2	49
14[a]	CuI	ChOH	DCM	2	38
15[b]	CuI	ChCl:PTSA	-	2	N. R.
16[b]	CuI	ChCl:Urea	-	2	N. R.
17[b]	CuI	ChOH	-	1	78
18[b]	CuI	ChOH	-	0.5	89
19[b]	CuCl	ChOH	-	0.5	34
20[b]	CuBr	ChOH	-	0.5	44
21[b]	$CuCl_2$	ChOH	-	0.5	24
22[b]	$CuBr_2$	ChOH	-	0.5	27
23[b]	$Cu(OAc)_2$	ChOH	-	0.5	30
24[c]	CuI	ChOH	-	0.5	N. D.

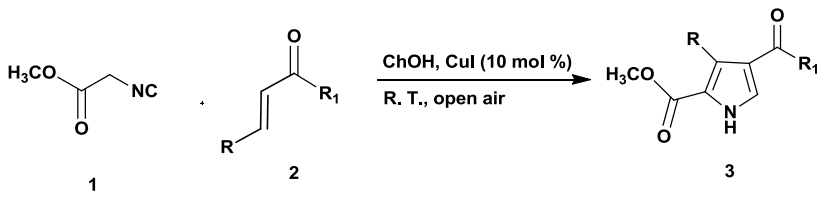
[a]Reaction conditions: methyl 2-isocyanoacetate **1** (1.0 mmol), 1,3-diphenyl-2-en-1-one **2a** (1.0 mmol), catalyst (10 mol %) and base (1.0 mmol) in 5 mL of solvent for 2 h, Open air. [b]Reaction conditions: methyl 2-isocyanoacetate **1** (1.0 mmol), 1,3-diphenyl-2-en-1-one **2a** (1.0 mmol), catalyst (10 mol %) and DES (3 mL), Open air. [c]Reaction conditions: methyl 2-isocyanoacetate **1** (1.0 mmol), 1,3-diphenyl-2-en-1-one **2a** (1.0 mmol), catalyst (10 mol %) and DES (3 mL), under N_2. [d]Isolated yields, N. R.= No Reaction, N. D.= Not Detected.

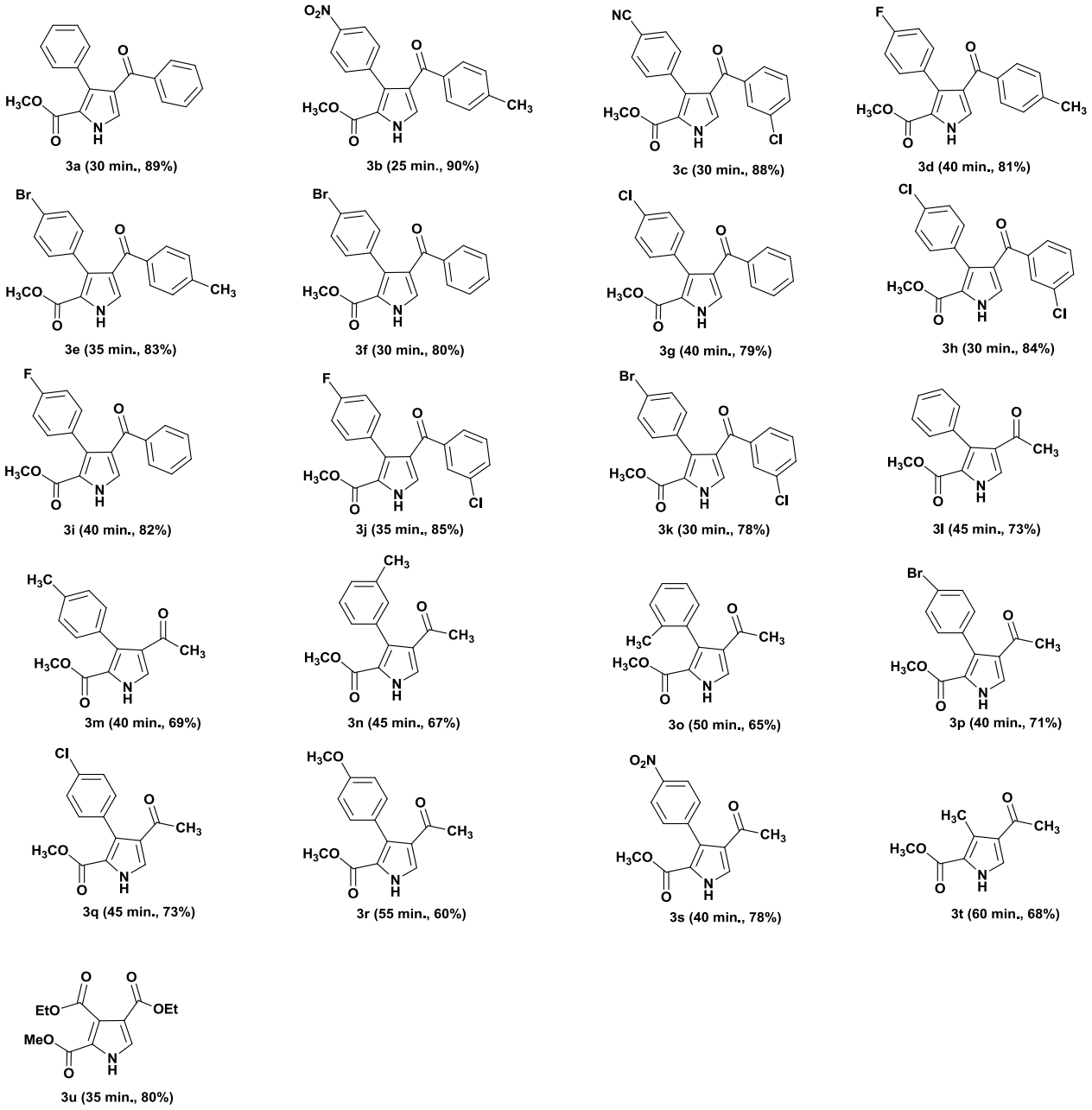
The formation of pyrrole (**3a**) was also studied in acidic, neutral and basic deep eutectic solvents. In acidic deep eutectic solvent such as ChCl:PTSA (Table 1, entry 15) no reaction was

observed in 2 h. Similarly, the reaction in a mixture of choline chloride:urea DES (Table 1, entry 16), formation of **3a** was not observed. Then we tried the reaction of methyl 2-isocyanoacetate (**1)** with CuI and chalcone (**2a**) in choline hydroxide as a base and reaction medium at room temperature for 1 h, the formation of **3a** was obtained in good yield (Table 1, entry 17). Delighted with this result, we decided to monitor the time required for completion of reaction. After varying time we found that the said reaction proceeded for completion within 0.5 h which was then selected as the optimized time (Table 1, entry 18). Various copper salts such as CuCl, CuBr, $CuCl_2$, $CuBr_2$ and $Cu(OAc)_2$ were tested under this condition for their catalytic activity but none of them was found to be as effective as CuI (Table 1, entries 19-23). The formation of **3a** was not detected under N_2 atmosphere (Table 1, entry 24), as oxygen present in the open air drives oxidation of pyrroline to pyrrole. Therefore, the synthesis of pyrrole (**3a**) by using CuI (10 mol %) as a catalyst, choline hydroxide as a base and reaction media was found to be the optimal reaction condition.

In order to investigate the scope and limitations of this novel greener protocol for the synthesis of 2,3,4-trisubstituted 1*H*-pyrroles, the reaction of methyl 2-isocyanoacetate (**1**) with various α,β-unsaturated aromatic and aliphatic ketones (**2**) were examined (Table 2). The reaction worked well and the corresponding pyrroles were obtained in 60-90% yield within 25-60 mins. Chalcones bearing electron withdrawing nitro and nitrile substituents on the phenyl ring of styryl portion offered excellent yields (88-90%) perhaps owing to the stability of olefinic double bond (Table 2, entries **3b** and **3c**). α,β-Unsaturated ketones bearing weakly activated or electron neutral substituents on the phenyl ring of acetophenone (such as methyl or halogens) portion and halogen substituents on the phenyl ring of styryl portion offered good yields (78-85%) of 2,3,4-trisubstituted 1*H*-pyrroles (Table 2, entries **3d**, **3e, 3h, 3j** and **3k**). The pyrroles (Table 2, entries **3f**, **3g** and **3i**) were obtained in 79-82% when chalcones bearing electron neutral or weakly activated substituents (such as halogens) on the phenyl ring of styryl portion were used.

Table 2. Scope of the formation of 2,3,4-trisubstituted 1*H*-Pyrroles[a, b, c]

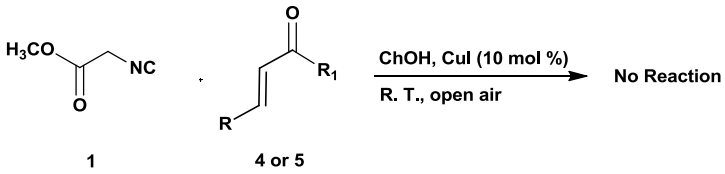




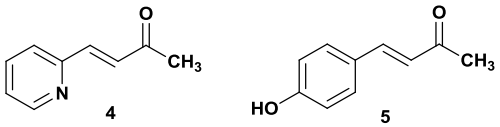
[a]Reaction conditions: methyl 2-isocyanoacetate **1** (1.0 mmol), chalcone **2** (1.0 mmol), catalyst (10 mol %) and DES (3 mL), Open air. [b]Isolated yields. [c]Time in minutes.

Encouraged with these results in hand, we have tried the reaction of methyl 2-isocyanoacetate (**1**) with methyl styryl ketone under optimum condition and corresponding pyrrole (**3l**) was obtained in 73% yield. Methyl styryl ketones bearing methyl substituent (4-Me, 3-Me and 2-Me) on the phenyl ring of styryl portion influenced the outcome of the reaction (Table 2, entries **3m**, **3n** and **3o**). The steric hindrance near the double bond of α,β-unsaturated ketones hampered the rate of reaction and the yield of product (65-69%). The reactivity order was observed to be *p*> *m* > *o*-isomer. Pyrroles **3p** and **3q** were obtained in 71 and 73% yield, respectively by the use of

methyl styryl ketones consisting of halogen substituents (4-Br, 4-Cl) on the phenyl ring of styryl portion. As expected (*E*)-4-phenylbut-3-en-2-one with an electron withdrawing -NO_2 group on phenyl ring required significantly shorter reaction time (40 min.) and offered a higher yield (78%) than that offered by its methoxy (Table 2, entries **3r** and **3s**) counterpart (55 min., 60%). Interestingly, (*E*)-pent-3-en-2-one and diethyl maleate also underwent the 1,4-conjugate addition followed by cyclization-oxidation reaction to afford 2,3,4-trisubstituted 1*H*-pyrroles (Table 2, entries **3t** and **3u**) in 68 and 80% yield, respectively.



Scheme 3. Control experiment



α,β-Unsaturated ketones with a 2-pyridyl substituent (**4**) and a 4-hydroxyphenyl substituent (**5**) at the β-position of chalcone do not undergo 1,4-conjugate addition followed by cyclization-oxidation reaction under these conditions (Scheme 3). This is due to the side reactions of catalyst and or base with the corresponding α,β-unsaturated ketones.

Recyclability of choline hydroxide (ChOH):

For large-scale operations, recovery and reuse of the DES is essential. In this context, the reaction between methyl 2-isocyanoacetate (**1**) and chalcone (**2a)** was examined under optimized reaction condition. After completion of reaction, the reaction mixture was dissolved in water (10 mL) and the product was extracted with ethyl acetate (3×10 mL). DES was recovered by evaporation of aqueous layer under vacuum. The recovered DES was then reused for the next run. As summarized in Table 3, DES can be recycled and reused up to four times without significant loss in activity.

Table 3. Recyclability study of DES for the synthesis of pyrrole (**3a**)[a, b]

Entry	Number of cycles	Yield[b] (%)
1	Fresh, non recycled	89
2	First	88

3	Second	87
4	Third	85
5	Fourth	85

[a]Reaction conditions: methyl 2-isocyanoacetate **1** (1.0 mmol), chalcone **2a** (1.0 mmol), catalyst (10 mol %) and DES (3 mL), Open air. [b]Isolated yields.

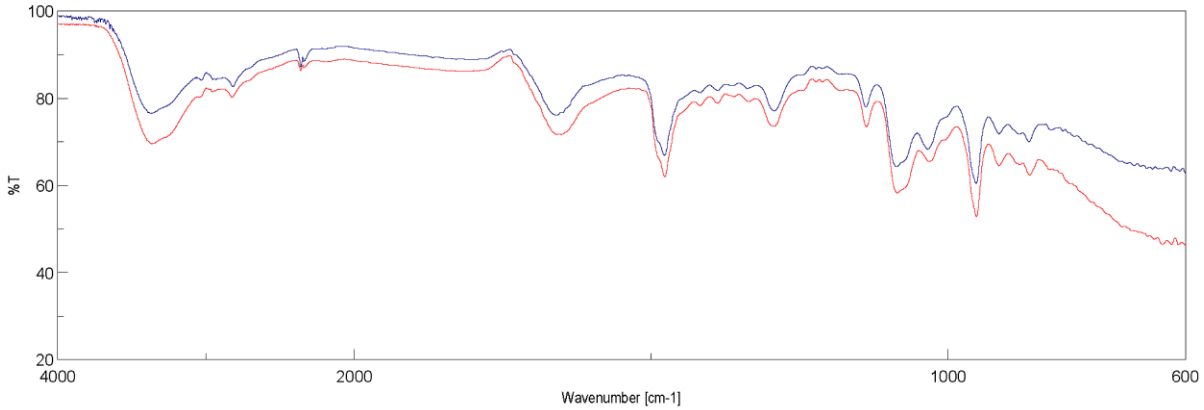
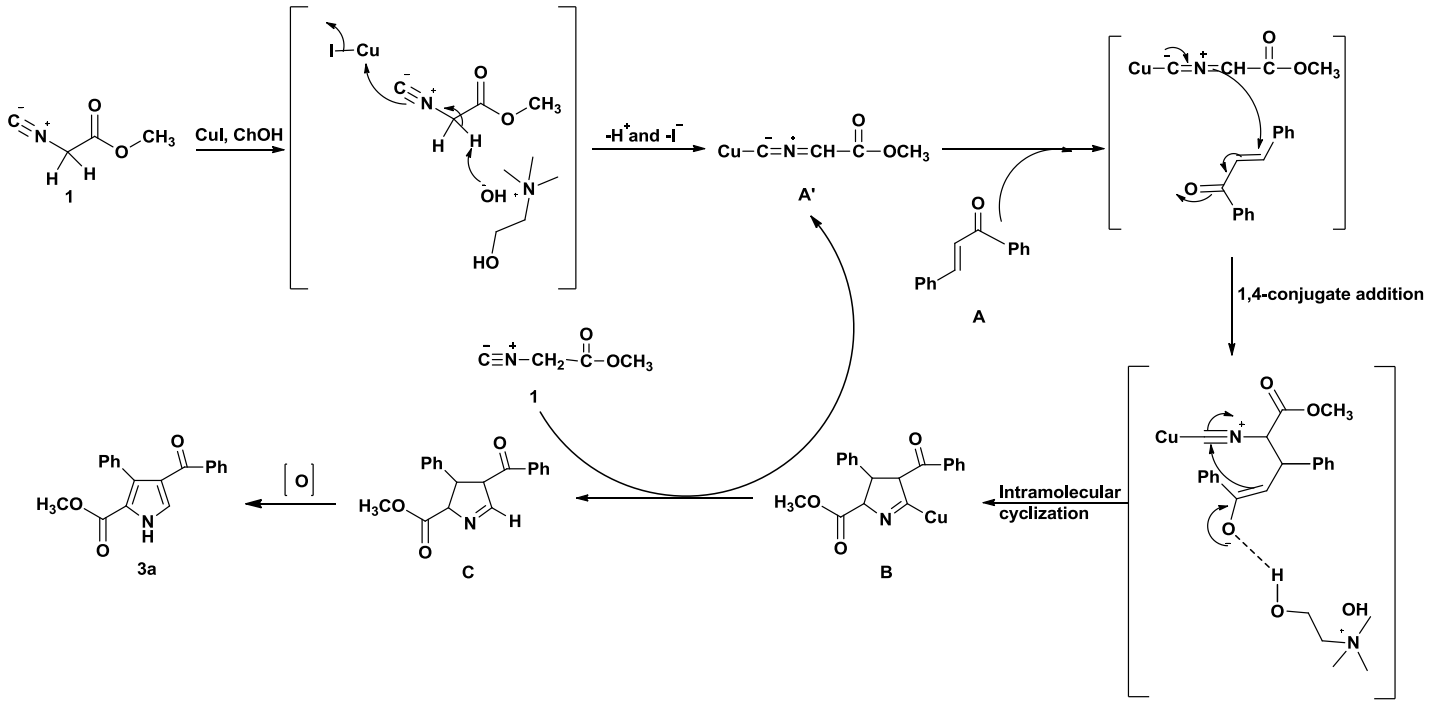


Fig. 1. FT-IR spectrum of a) ChOH before reaction (blue curve) b) ChOH after four runs (red curve).

FT-IR analysis

The compound having covalent bond absorbs various frequencies of electromagnetic radiation in the infrared region of the electromagnetic spectrum. Infrared spectrum was used to determine structural information of a molecule. FT-IR spectroscopy was used to characterize ChOH before and after reaction. The absorption peak at around 3363 cm^{-1} was the characteristic of -OH stretching frequency. The band at 1293 and 1085 cm^{-1} results from C-N and C-O stretching. Also band at 951 and 862 cm^{-1} was due to C-H bending frequency. There was no change observed in the IR spectra of ChOH before the reaction and after four runs (Fig. 1) so we can reuse it up to four cycles.

A plausible mechanistic pathway of the reaction of methyl 2-isocyanoacetate (**1**) and chalcone (**2a)** in choline hydroxide is depicted in Scheme 4. First the reaction of methyl 2-isocyanoacetate (**1**) with copper iodide in choline hydroxide gives α-cuprioisocyanide (**A′**). Then, 1,4-conjugate addition of α-cuprioisocyanide (**A′**) with chalcone (**2a**) followed by intramolecular cyclization gives a cyclic organocopper intermediate (**B**) which on copper hydrogen exchange affords 3,4-dihydro-2*H*-pyrrole (**C**). Oxidation of the latter offers the methyl 4-benzoyl-3-phenyl-1*H*-pyrrole-2-carboxylate (**3a**).[23]



Scheme 4. Proposed reaction mechanism

Conclusions

In conclusion, we have developed a simple, green and highly efficient protocol for the synthesis of 2,3,4-trisubstituted 1*H*-pyrroles using deep eutectic solvent. The functional group tolerant regioselective synthesis offered good to excellent yields of the products at room temperature in very short time. 2,3,4-Trisubstituted 1*H*-pyrroles have strong applications in the field of pharmaceuticals and agrochemicals.

Experimental section

General methods

Chemical reagents were obtained from commercial companies. All reactions were performed in round bottom flask and monitored by TLC performed on aluminium plates (0.25 mm, E. Merck) precoated with silica gel Merck 60 F-254. Developed TLC plates were visualized under a short-wavelength UV lamp. Reactions were conducted under open air and N_2 atmosphere in solvents such as water, CH_3CN, MeOH, DCM, THF and DMF. Yields refer to spectroscopically (^1H, ^{13}C NMR) homogeneous material obtained after column chromatography. Column chromatography was performed on silica gel (100-200 mesh size) supplied by S. D. Fine Chemicals Limited, India. IR spectra were recorded on a JASCO-FT/IR-4100 LE with attenuated total reflection (ATR) method. ^1H and ^{13}C NMR were recorded in $CDCl_3$ and CD_3OD solution with a Brüker 400 and Agilent 300 MHz spectrometers. Chemical shifts (δ) are reported relative to $SiMe_4$ (δ = 0.0) as an internal standard. The number of protons (*n*) for a given resonance is indicated by *n*H. Peak multiplicities are designated by the following abbreviations: s, singlet; d,

doublet; t, triplet; q, quartet; m, multiplet; dd, doublet of doublet; br, broad; *J*, coupling constant in Hz. High-resolution mass spectra were obtained by using positive as well as negative electrospray ionization (ESI) by Time of Flight (TOF) method.

General experimental procedure for the synthesis of choline hydroxide:

Choline chloride (1 mmol) and KOH (1 mmol) were dissolved in methanol (10 mL) at room temperature. This mixture was heated at 60 ºC for 12 h with constant stirring. After cooling to room temperature, the reaction mixture was filtered to remove solid KCl. The obtained filtrate was concentrated under vacuum to remove methanol and used without further purification.

General experimental procedure for the synthesis of 2,3,4-trisubstituted 1*H*-pyrroles:

A round bottom flask was charged with methyl 2-isocyanoacetate **1** (1.0 mmol), CuI (0.1 mmol), substituted chalcone **2** (1.0 mmol) and choline hydroxide (3 mL). The reaction mixture was stirred at R.T. for appropriate time. After completion of reaction, the reaction mixture was dissolved in water (10 mL) and the product was extracted with ethyl acetate (3×10 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The obtained crude product was purified by column chromatography on silica gel (100-200 mesh size) with *n*-hexane : ethyl acetate (75 : 25) as eluent to afford desired product **3a-3u**.

Methyl 4-benzoyl-3-phenyl-1*H*-pyrrole-2-carboxylate 3a.

Off white solid, mp 140-142 ºC; IR (ATR) ṽ (cm^{-1}): 3256, 1724, 1694, 1632, 1508, 1264 and 761; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.82 (bs, 1H), 7.72 (dd, *J* = 7.2, 1.2 Hz, 2H), 7.46 (t, *J* = 7.4 Hz, 1H), 7.36-7.32 (m, 5H), 7.29-7.23 (m, 3H), 3.74 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.20, 161.40, 138.97, 133.12, 132.49, 132.00, 130.32, 129.41, 128.02, 127.74, 127.30, 127.21, 125.15, 120.44, 51.65; HRMS (ESI): calc. for $[(C_{19}H_{15}NO_3)H]$ $[M+H]^-$ 306.1131, found 306.1130.

Methyl 4-(4-methylbenzoyl)-3-(4-nitrophenyl)-1*H*-pyrrole-2-carboxylate 3b.

Pale yellow solid, mp 162-164 ºC; IR (ATR) ṽ (cm^{-1}): 3421, 1720, 1695, 1627, 1601, 1509, 1437,1341 and 855; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.81 (bs, 1H), 8.15 (d, *J* = 8.4 Hz, 2H), 7.65 (d, *J* = 7.6 Hz, 2H), 7.50 (d, *J* = 8.8 Hz, 2H), 7.37 (d, *J* = 3.2 Hz, 1H), 7.19 (d, *J* = 8.0 Hz, 2H), 3.73 (s, 3H), 2.38 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.19, 160.86, 146.96, 143.42, 140.89, 136.07, 131.32, 130.08, 129.56, 129.10, 127.90, 125.09, 122.67, 121.03, 51.99, 21.66; HRMS (ESI): calc. for $[(C_{20}H_{16}N_2O_5)H]$ $[M+H]^+$ 365.1137, found 365.1111.

Methyl 4-(3-chlorobenzoyl)-3-(4-cyanophenyl)-1*H*-pyrrole-2-carboxylate 3c.

Off white solid, mp 182-184 ºC; IR (ATR) ṽ (cm^{-1}): 3273, 2234, 1727, 1707, 1644, 1517 and 746; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.57 (bs, 1H), 7.59 (distorted t, *J* = 7.2 Hz, 4H), 7.42 (distorted d, *J* = 7.6 Hz, 4H), 7.31 (t, *J* = 8.0, 7.2 Hz, 1H), 3.75 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.12, 160.77, 140.31, 138.41, 134.46, 132.33, 131.21, 130.35, 129.78, 129.41, 128.17, 127.28, 124.48, 121.21, 119.12, 111.04, 52.06; HRMS (ESI): calc. for $[(C_{20}H_{13}ClN_2O_3)H]$ $[M+H]^+$ 365.0693, found 365.0665.

Methyl 3-(4-fluorophenyl)-4-(4-methylbenzoyl)-1*H*-pyrrole-2-carboxylate 3d.

White solid, mp 128-130 ºC; IR (ATR) ṽ (cm^{-1}): 3316, 1728, 1692, 1634, 1517, 1263 and 841; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.56 (bs, 1H), 7.62 (d, *J* = 7.2 Hz, 2H), 7.34 (s, 1H), 7.28 (distorted t, *J* = 6.4. 6.0 Hz, 2H), 7.15 (d, *J* = 7.2 Hz, 2H), 6.95 (t, *J* = 8.4, 8.0 Hz, 2H), 3.74 (s, 3H), 2.37 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.74, 162.26 (d, J_{C-F} = 248.3 Hz), 161.25, 143.01, 136.26, 132.04 (d, J_{C-F} = 8.0 Hz), 131.99, 131.45, 129.65, 129.03, 128.88, 127.36, 125.34, 120.52, 114.40 (d, J_{C-F} = 21.4 Hz), 51.78, 21.64; HRMS (ESI): calc. for $[(C_{20}H_{16}FNO_3)H]$ $[M+H]^+$ 338.1192, found 338.1163.

Methyl 3-(4-bromophenyl)-4-(4-methylbenzoyl)-1*H*-pyrrole-2-carboxylate 3e.

Pale yellow solid, mp 166-168 ºC; IR (ATR) ṽ (cm^{-1}): 3262, 1730, 1692, 1636, 1504, 1261 and 754; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.57 (bs, 1H), 7.62 (d, *J* = 8.0 Hz, 2H), 7.39 (d, *J* = 8.0 Hz, 2H), 7.33 (d, *J* = 2.4 Hz, 1H), 7.20-7.15 (dd, *J* = 8.4, 8.0 Hz, 4H), 3.73 (s, 3H), 2.38 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.57, 161.21, 143.10, 136.23, 132.21, 132.04, 131.21, 130.57, 129.64, 128.94, 127.49, 125.19, 121.59, 120.54, 51.84, 21.66; HRMS (ESI): calc. for $[(C_{20}H_{16}BrNO_3)H]$ $[M+H]^+$ 398.0392, found 400.0354.

Methyl 4-benzoyl-3-(4-bromophenyl)-1*H*-pyrrole-2-carboxylate 3f.

Off white solid, mp 162-164 ºC; IR (ATR) ṽ (cm^{-1}): 3275, 1723, 1695, 1632, 1505, 1262 and 732; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.63 (bs, 1H), 7.71 (d, *J* = 7.6 Hz, 2H), 7.48 (t, *J* = 7.2 Hz, 1H), 7.40-7.34 (m, 5H), 7.19 (d, *J* = 8.0 Hz, 2H), 3.73 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.88, 161.20, 138.92, 132.28, 132.14, 132.03, 131.25, 130.57, 129.42, 128.25, 127.87, 124.99, 121.63, 120.69, 51.87; HRMS (ESI): calc. for $[(C_{19}H_{14}BrNO_3)H]$ $[M+H]^+$ 384.0235, found 386.0194.

Methyl 4-benzoyl-3-(4-chlorophenyl)-1*H*-pyrrole-2-carboxylate 3g.

Off white solid, mp 148-150 ºC; IR (ATR) ṽ (cm^{-1}): 3276, 1722, 1689, 1631, 1505, 1263 and 728; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.45 (bs, 1H), 7.71 (d, *J* = 7.2 Hz, 2H), 7.48 (distorted t, *J* = 7.2, 6.8 Hz, 1H), 7.36 (distorted t, *J* = 7.6, 7.2 Hz, 3H), 7.25 (s, 4H), 3.75 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.89, 161.19, 138.91, 133.33, 132.27, 131.71, 131.63, 131.24, 129.42, 128.23, 127.78, 127.64, 125.08, 120.72, 51.86; HRMS (ESI): calc. for $[(C_{19}H_{14}ClNO_3)H]$ $[M+H]^+$ 340.0740, found 340.0714.

Methyl 4-(3-chlorobenzoyl)-3-(4-chlorophenyl)-1*H*-pyrrole-2-carboxylate 3h.

White solid, mp 110-112 ºC; IR (ATR) ṽ (cm^{-1}): 3282, 1724, 1691, 1637, 1507, 1258 and 742; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.66 (bs, 1H), 7.62 (s, 1H), 7.57 (d, *J* = 7.6 Hz, 1H), 7.43 (d, *J* = 8.0 Hz, 2H), 7.30-7.23 (m, 5H), 3.74 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.52, 161.11, 140.42, 134.30, 133.48, 132.10, 131.68, 131.42, 131.09, 129.61, 129.49, 127.83, 127.69, 127.34, 124.72, 120.88, 51.92; HRMS (ESI): calc. for $[(C_{19}H_{13}Cl_2NO_3)H]$ $[M+H]^+$ 374.0350, found 374.0321.

Methyl 4-benzoyl-3-(4-fluorophenyl)-1*H*-pyrrole-2-carboxylate 3i.

White solid, mp 128-130 ºC; IR (ATR) ṽ (cm^{-1}): 3275, 1718, 1686, 1631, 1510, 1264 and 734; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.46 (bs, 1H), 7.69 (d, *J* = 7.2 Hz, 2H), 7.45 (d, *J* = 6.8 Hz, 1H), 7.37-7.25 (m, 5H), 6.94 (t, *J* = 8.0 Hz, 2H), 3.74 (s, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ

192.40, 162.10 (d, J_{C-F} = 243.7 Hz), 161.06, 139.18, 132.11 (d, J_{C-F} = 8.1 Hz), 131.86, 131.41, 129.92, 128.99, 128.86, 127.90, 124.13, 120.83, 113.53 (d, J_{C-F} = 21.5 Hz), 50.47; HRMS (ESI): calc. for $[(C_{19}H_{14}FNO_3)H]$ $[M+H]^+$ 324.1036, found 324.1005.

Methyl 4-(3-chlorobenzoyl)-3-(4-fluorophenyl)-1*H*-pyrrole-2-carboxylate 3j.

Off white solid, mp 104-106 ºC; IR (ATR) ṽ (cm^{-1}): 3296, 1715, 1686, 1637, 1513, 1260 and 739; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.60 (bs, 1H), 7.61 (s, 1H), 7.55 (d, *J* = 7.6 Hz, 1H), 7.41 (d, *J* = 3.2 Hz, 2H), 7.28 (s, 3H), 6.95 (t, *J* = 8.8, 8.4 Hz, 2H), 3.74 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.74, 162.26 (d, J_{C-F} = 244.8 Hz), 161.18, 140.42, 134.24, 132.08, 132.05 (d, J_{C-F} = 7.9 Hz), 131.31, 129.55, 129.51, 128.79, 127.79, 127.34, 124.83, 120.79, 114.46 (d, J_{C-F} = 21.3 Hz), 51.88; HRMS (ESI): calc. for $[(C_{19}H_{13}ClFNO_3)H]$ $[M+H]^+$ 358.0656, found 358.0623.

Methyl 3-(4-bromophenyl)-4-(3-chlorobenzoyl)-1*H*-pyrrole-2-carboxylate 3k.

White solid, mp 144-146 ºC; IR (ATR) ṽ (cm^{-1}): 3298, 1730, 1698, 1630, 1505, 1255 and 744; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.69 (bs, 1H), 7.62 (s, 1H), 7.56 (d, *J* = 7.6 Hz, 1H), 7.44-7.38 (m, 4H), 7.28 (t, *J* = 7.6 Hz, 1H), 7.16 (d, *J* = 8.4 Hz, 2H), 3.74 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.48, 161.11, 140.43, 134.31, 132.10, 131.98, 131.93, 131.09, 130.63, 129.63, 129.49, 127.89, 127.34, 124.65, 121.76, 120.85, 51.94; HRMS (ESI): calc. for $[(C_{19}H_{13}BrClNO_3)H]$ $[M+H]^+$ 417.9845, found 417.9822.

Methyl 4-acetyl-3-phenyl-1*H*-pyrrole-2-carboxylate 3l.

White solid, mp 170-172 ºC; IR (ATR) ṽ (cm^{-1}): 3250, 1728, 1697, 1638, 1512, 1270 and 768; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.81 (bs, 1H), 7.54 (d, *J* = 3.5 Hz, 1H), 7.37-7.34 (m, 3H), 7.30-7.28 (m, 2H), 3.63 (s, 3H), 2.02 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.43, 161.27, 134.02, 131.33, 129.83, 127.56, 127.47, 126.80, 126.37, 120.79, 51.49, 29.06; HRMS (ESI): calc. for $[(C_{14}H_{13}NO_3)]$ $[M]^-$ 243.0895 found 243.0817.

Methyl 4-acetyl-3-(*p*-tolyl)-1*H*-pyrrole-2-carboxylate 3m.

White solid, mp 184-186 ºC; IR (ATR) ṽ (cm^{-1}): 3253, 1726, 1694, 1642, 1516, 1268 and 765; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.85 (bs, 1H), 7.52 (d, *J* = 3.4 Hz, 1H), 7.24-7.15 (m, 4H), 3.64 (s, 3H), 2.37 (s, 3H), 2.03 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.61, 161.24, 137.11, 131.55, 130.83, 129.70, 128.33, 126.81, 126.41, 120.69, 51.44, 29.10, 21.24; HRMS (ESI): calc. for $[(C_{15}H_{15}NO_3)\text{-}H]$ $[M-H]^-$ 256.0973, found 256.0977.

Methyl 4-acetyl-3-(*m*-tolyl)-1*H*-pyrrole-2-carboxylate 3n.

White solid, mp 170-172 ºC; IR (ATR) ṽ (cm^{-1}): 3259, 1732, 1696, 1635, 1508, 1260 and 772; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.54 (bs, 1H), 7.54 (d, *J* = 3.5 Hz, 1H), 7.27 (d, *J* = 7.5 Hz, 1H), 7.15 (d, *J* = 7.6 Hz, 1H), 7.10-7.08 (m, 2H), 3.65 (s, 3H), 2.36 (s, 3H), 1.99 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.51, 161.13, 137.05, 133.79, 131.49, 130.48, 128.28, 127.47, 127.05, 126.90, 126.01, 120.69, 51.46, 29.10, 21.32; HRMS (ESI): calc. for $[(C_{15}H_{15}NO_3)\text{-}H]$ $[M-H]^-$ 256.0973, found 256.0974.

Methyl 4-acetyl-3-(*o*-tolyl)-1*H*-pyrrole-2-carboxylate 3o.

White solid, mp 162-164 ºC; IR (ATR) ṽ (cm^{-1}): 3248, 1731, 1687, 1629, 1502, 1255 and 774; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.77 (bs, 1H), 7.61 (d, *J* = 3.5 Hz, 1H), 7.27-7.16 (m, 3H), 7.11 (d, *J* = 7.9 Hz, 1H), 3.61 (s, 3H), 2.07 (s, 3H), 1.92 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ

194.36, 161.19, 136.39, 134.05, 130.53, 129.53, 129.49, 127.72, 126.72, 126.49, 125.26, 120.70, 51.52, 28.54, 19.94; HRMS (ESI): calc. for [($C_{15}H_{15}NO_3$)-H] [M-H]$^-$ 256.0973, found 256.0972.

Methyl 4-acetyl-3-(4-bromophenyl)-1*H*-pyrrole-2-carboxylate 3p.

Off white solid, mp 150-152 ^oC; IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3275, 1734, 1690, 1640, 1513, 1250 and 765; ^1H NMR (400 MHz, $CDCl_3$) δ 9.89 (bs, 1H), 7.51 (d, *J* = 3.3 Hz, 1H), 7.47 (d, *J* = 8.5 Hz, 2H), 7.17 (d, *J* = 8.5 Hz, 2H), 3.65 (s, 3H), 2.13 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.76, 161.09, 132.88, 131.61, 130.63, 129.90, 126.78, 126.19, 121.65, 120.96, 51.59, 28.92; HRMS (ESI): calc. for [($C_{14}H_{12}BrNO_3$)] [M]$^-$ 321.0001 found 320.9922.

Methyl 4-acetyl-3-(4-chlorophenyl)-1*H*-pyrrole-2-carboxylate 3q.

Off white solid, mp 134-136 ^oC; IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3278, 1728, 1689, 1637, 1510, 1253 and 773; ^1H NMR (400 MHz, $CDCl_3$) δ 9.67 (bs, 1H), 7.44 (d, *J* = 3.3 Hz, 1H), 7.25 (d, *J* = 8.3 Hz, 2H), 7.15 (d, *J* = 8.2 Hz, 2H), 3.57 (s, 3H), 2.04 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.71, 161.06, 133.45, 132.35, 131.28, 129.90, 127.72, 126.62, 126.35, 121.01, 51.59, 28.93; HRMS (ESI): calc. for [($C_{14}H_{12}ClNO_3$)H] [M+H]$^-$ 278.0585, found 278.0584.

Methyl 4-acetyl-3-(4-methoxyphenyl)-1*H*-pyrrole-2-carboxylate 3r.

White solid, mp 132-134 ^oC; IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3251, 1720, 1694, 1625, 1501, 1254 and 763; ^1H NMR (400 MHz, $CDCl_3$) δ 9.73 (bs, 1H), 7.52 (d, *J* = 3.5 Hz, 1H), 7.21 (d, *J* = 8.8 Hz, 2H), 6.90 (d, *J* = 8.7 Hz, 2H), 3.82 (s, 3H), 3.65 (s, 3H), 2.04 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.53, 161.24, 159.00, 131.19, 131.05, 126.85, 126.34, 125.89, 120.75, 113.05, 55.09, 51.47, 29.09; HRMS (ESI): calc. for [($C_{15}H_{14}NO_4$)-H] [M-H]$^-$ 272.0922 found 272.0923.

Methyl 4-acetyl-3-(4-nitrophenyl)-1*H*-pyrrole-2-carboxylate 3s.

Pale yellow solid, mp 144-146 ^oC; IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3415, 1724, 1698, 1632, 1605, 1513, 1443, 1345 and 858; ^1H NMR (400 MHz, $CDCl_3$) δ 9.78 (bs, 1H), 8.20 (d, *J* = 8.6 Hz, 2H), 7.56 (d, *J* = 3.3 Hz, 1H), 7.45 (d, *J* = 8.6 Hz, 2H), 3.65 (s, 3H), 2.25 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.72, 160.67, 147.08, 141.28, 130.99, 128.68, 126.98, 125.72, 122.54, 121.36, 51.77, 28.47; HRMS (ESI): calc. for [($C_{14}H_{12}N_2O_5$)H] [M+H]$^-$ 289.0825, found 289.0824.

Methyl 4-acetyl-3-methyl-1*H*-pyrrole-2-carboxylate 3t.

White solid, mp 130-132 ^oC; IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3254, 1732, 1690, 1633, 1505, 1261 and 763; ^1H NMR (400 MHz, $CDCl_3$) δ 9.47(bs, 1H), 7.43 (d, *J* = 3.4 Hz, 1H), 3.85 (s, 3H), 2.59 (s, 3H), 2.39 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.04, 162.02, 129.17, 127.20, 125.54, 121.16, 51.46, 28.25, 11.58; HRMS (ESI): calc. for [($C_9H_{11}NO_3$)H] [M+H]$^-$ 182.0818, found 182.0817.

3,4-diethyl 2-methyl-1*H*-pyrrole-2,3,4-tricarboxylate 3u.

Colorless oil; IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3247, 1676, 1655, 1499, 1443, 1259, and 898; ^1H NMR (300 MHz, $CDCl_3$) δ 9.48 (bs, 1H), 7.49 (d, *J* = 3.3 Hz, 1H), 4.42 (q, *J* = 7.2 Hz, 2H), 4.28 (q, *J* = 7.2 Hz, 2H), 3.86 (s, 3H), 1.39 (t, *J* = 7.2 Hz, 3H), 1.32 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.34, 162.70, 160.21, 126.22, 123.51, 121.05, 116.73, 61.90, 60.71, 52.38, 29.85, 14.36; HRMS (ESI): calc. for [($C_{12}H_{15}NO_6$)Na] [M+Na]$^+$ 292.0796, found 292.0845.

Author Contributions

[a]These authors contributed equally to this work.

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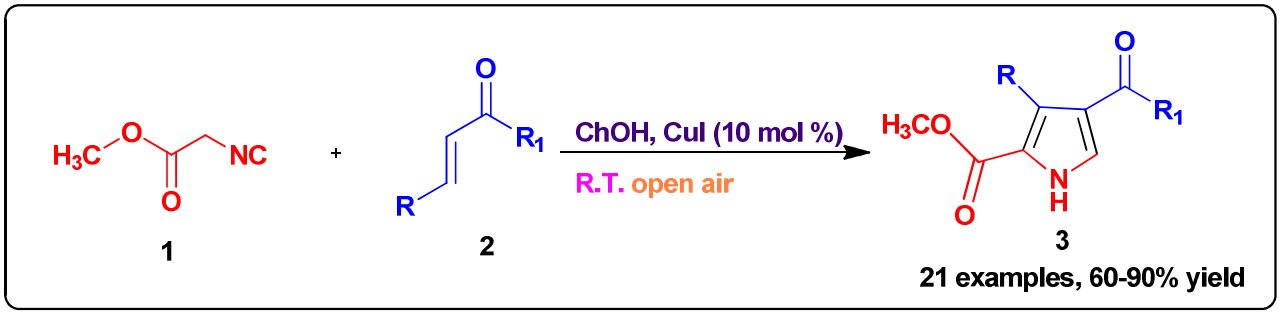
Graphical abstract

Deep eutectic solvent: a simple, environmentally benign reaction media for regioselective synthesis of 2,3,4-trisubstituted 1*H*-pyrroles

Greener, rapid and highly efficient synthetic protocol for the construction of pyrroles has been achieved.



Hanuman P. Kalmode,[a] Kamlesh S. Vadagaonkar,[a] Kaliyappan Murugan,[b] Sattey Prakash[c] and Atul C. Chaskar*[a,c]

[a]*Department of Dyestuff Technology, Institute of Chemical Technology, Mumbai 400019, India*
[b]*National Taiwan University, Taipei 10617, Taiwan*
[c]*National Centre for Nanosciences and Nanotechnology, University of Mumbai, Mumbai 400098, India. E-mail: achaskar25@gmail.com; Tel.: +91-22-3361 2706; Fax: +91-22-3361 1020.*