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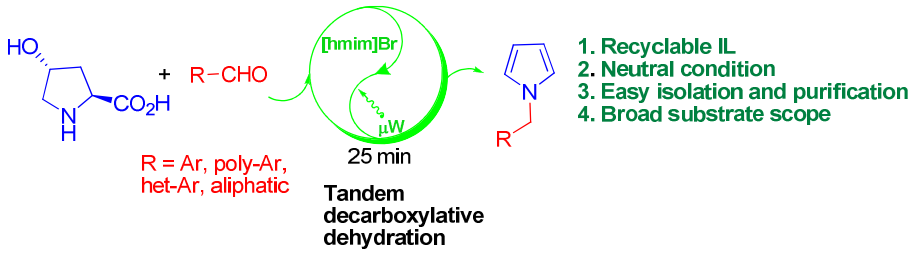
Synthesis of *N*-alkyl pyrroles via decarboxylation/ dehydration in neutral ionic liquid under catalyst-free condition

Veena D. Yadav, Shashikant U. Dighe and Sanjay Batra*

A catalyst-free benign route to *N*-alkyl pyrroles by reacting aromatic, heteroaromatic or aliphatic aldehydes with 4-hydroxyproline in neutral ionic liquid under microwave irradiation is presented.



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ARTICLE TYPE

Synthesis of *N*-alkyl pyrroles via decarboxylation/ dehydration in neutral ionic liquid under catalyst-free condition

Veena D. Yadav,[a] Shashikant U. Dighe[a] and Sanjay Batra*[a,b]

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A general route to *N*-alkyl pyrroles by reacting aromatic, heteroaromatic or aliphatic aldehydes with 4-hydroxyproline in ionic liquid under neutral condition was developed. The ionic liquid can be readily recovered and reused up to 5 reaction cycles without any effect on the yield of the product formed. The utility of the protocol for one-pot synthesis of 9*H*-benzo[*e*]pyrrolo[2,1-*b*][1,3]oxazines is also presented.

Introduction

N-substituted pyrroles are important class of compounds due to significant medicinal and material properties associated with them.[1-2] Therefore the synthesis of diverse *N*-substituted pyrroles had been an area of continuous research in synthetic chemistry.[3] The classical methods of synthesis of *N*-alkyl pyrrole involve harsh acidic/ basic conditions such as refluxing amine with 2,5-dimethoxy tetrahydrofuran in glacial acetic acid or direct heating of pyrrole with benzyl halide in ionic liquid in the presence of KOH or K_2CO_3.[4-5] In 2007, Tunge et al. reported the redox-neutral approach to the synthesis of *N*-alkyl pyrroles from 3-pyrroline and aldehyde or ketone in catalytic amount of acid.[6] Subsequently, Pan's and Seidel's groups independently reported the synthesis of *N*-substituted indole via reaction between indoline and aldehyde in the presence of acid.[7-8] The reaction proceeded via intramolecular hydride transfer to the azomethine ylide that was generated as intermediate during the reaction to afford product. In further advancement of the methodology Kumar and Rao reported synthesis of *N*-alkyl pyrroles by reaction between 4-hydroxy proline and aldehyde in DMSO which was required to be added slowly for efficient reaction.[9] Later Seidel et al. reported the synthesis of *N*-alkyl pyrrole via reaction of similar substrates in the presence of benzoic acid at 240 ^oC under microwave irradiation.[10] Subsequently, Hong and Wei and co-workers reported synthesis of *N*-alkyl pyrroles from identical substrates in DMF in the presence of acid.[11] In this case however, addition of aldehyde was required to be carried out slowly in hot DMF. In an ongoing project related to decarboxylative coupling reaction we became interested to develop a more sustainable alternative to the synthesis of *N*-alkyl pyrroles under neutral conditions. Analysis of the mechanism proposed by Seidel reflects that the acid is required to catalyze the dehydration of the enamine intermediate that is formed during the reaction. An insight into the literature revealed that the dehydration of the activated hydroxyl group leading to an alkene can be readily achieved via ionic liquid.[12] Taking a cue from these reports, we reasoned that if the reaction of 4-hydroxyproline and aldehyde is performed in a suitable ionic liquid there is a possibility that the use of acid is eliminated and the reaction could be performed at a lower temperature under neutral conditions. Working towards this objective we have discovered that the reaction between 4-hydroxyproline and the aldehyde is successful in neutral ionic liquid under microwave conditions at 130 ^oC to efficiently produce the *N*-alkyl pyrroles and we report details of this study herein. Remarkably the ionic liquid can be recovered from the reaction and can be reused without any loss of reactivity in subsequent runs.

Results and Discussion

We commenced our investigations by screening the reaction of 4-chlorobenzaldehyde (1.0 equiv) with 4-hydroxyproline (1.2 equiv) in 1-butyl-3-methylimidazolium bromide ([bmim]Br) under microwave irradiation (Table 1). The reaction was initially performed at 90 ^oC to be completed in 45 min to afford a product (70%) which was identified to be the required pyrrole derivative **2a** (entry 1). Next we investigated the reaction at higher temperatures and found that at 130 ^oC the reaction was completed in 25 min to afford the product in 80% yield (entry 2,3). Subsequently we evaluated other ionic liquids for the success of the reaction and discovered that as compared to the butyl-based ionic liquid 1-hexyl-3-methylimidazolium bromide ([hmim]Br) gave superior yield (82%) of **2a** (entries 4-7). We also investigated the reaction in organic solvents and found that yields of **2a** were inferior as compared to the one in ionic liquid. Besides the work up procedure with ionic liquid was easy as partitioning the reaction mixture in ethyl acetate and evaporating the solvent gave the product. Thus the optimized conditions which worked efficiently for us were aldehyde (1.0 equiv), 4-hydroxyproline (1.5 equiv) in [hmim]Br as medium under microwave at 130 ^oC for 25 min.

Next we tested the scope of the protocol using a variety of aldehydes and the results are summarized in Scheme 1. It was found that in all cases the reaction was successful to afford the desired *N*-alkyl pyrroles. The benzaldehydes bearing electron withdrawing substituents such as chloro, nitro or cyano furnished

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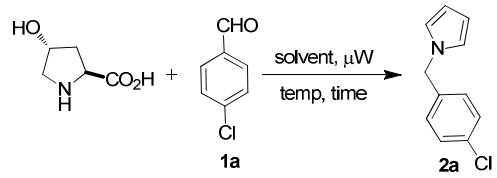
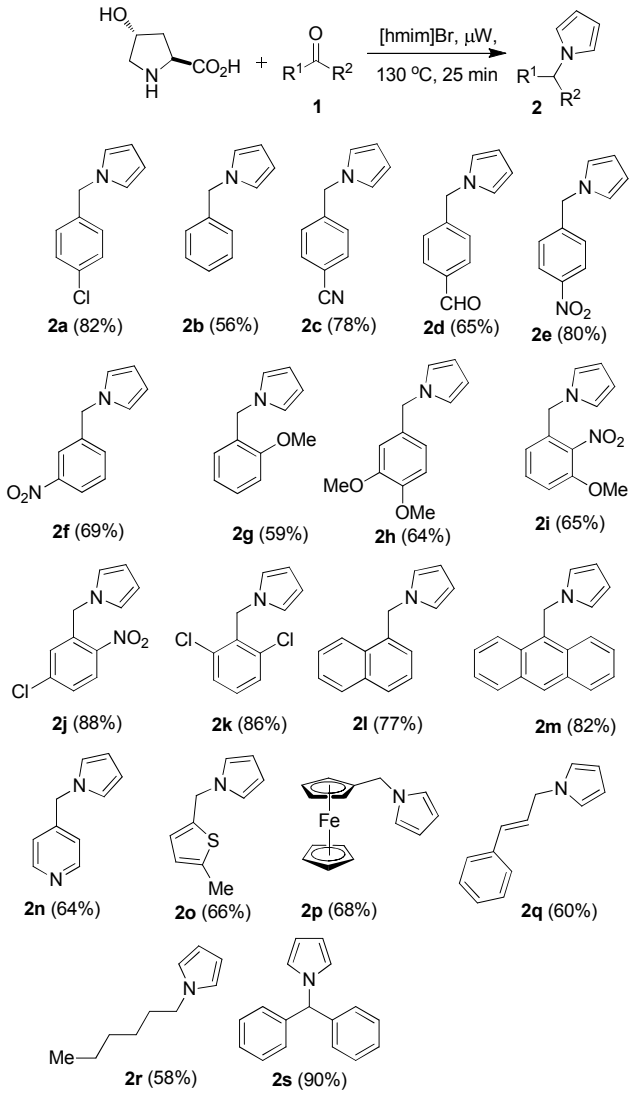
Table 1 Results of the optimization study[a]



Entry	Solvent	Temp (°C)	Time (min)	Yield (%)
1	[bmim]Br	90	45	70
2	[bmim]Br	110	30	77
3	[bmim]Br	130	25	80
4	[bmim]BF_4	130	25	42
5	[bmim]PF_6	130	25	41
6	[bmim]OH	130	25	48
7	**[hmim]Br**	**130**	**25**	**82**
8	Toulene	130	25	26
9	DMSO	130	25	38
10	DMF	130	25	18

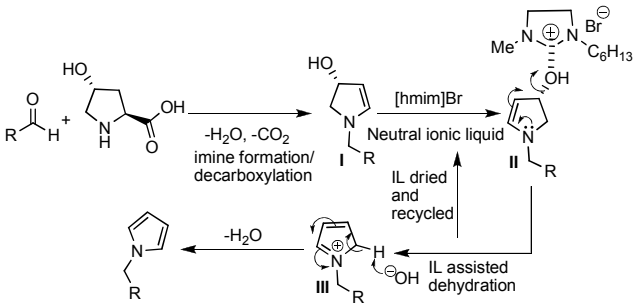
[a] All reactions were carried out with 100 mg (0.71 mmol) of **1a** and 99 mg (0.85 mmol) of 4-hydroxyproline in 1.0 mL of solvent under microwave.



Scheme 1. Scope of the reaction. All reactions were performed at 100 mg scale of aldehyde using 1.2 equiv of 4-hydroxyproline under microwave heating using 1 mL of ionic liquid.

the respective pyrroles **(2a, 2c, 2e-2f, 2j-2k)** in good yields. It was observed that the yield of the product **2b** prepared from unsubstituted benzaldehyde was relatively low. Besides the benzaldehydes carrying the electron donating substituent such as methoxy group also afforded the product **(2g-2h)** in moderate yields. Notably when terephthaldehyde was employed as substrate the corresponding product **2d** was isolated in 65% yields. Perhaps the presence of a formyl group in **2d** offers option for further derivatisation. Gratifyingly, ferrocenecarbaldehyde also smoothly afforded the pyrrole **2p** in 68% yield. The reaction worked well even with the polycyclic benzenes and heterocyclic aldehydes to afford **2l-2o** in 64-82% yields. We also investigated the aliphatic aldehydes in the protocol which gave the respective pyrrole derivatives **2q** and **2r** in 58-60% yields. Benzophenone which was examined too gave the product **2s** in 90% yield.

A plausible mechanism for the formation of *N*-alkyl pyrroles is delineated in Scheme 2. In the first stage the enamine **I** is produced via decarboxylation and imine formation as proposed by Seidel et al. This is followed by ionic liquid assisted dehydration leading to the formation of the pyrrole to afford the intermediate **III** that undergoes a deprotonation to furnish the product. After completion of the reaction, the mixture was extracted with ethyl acetate or ether (three times) and the residual ionic liquid was dried under vacuum and reused for 5 cycles without any significant effect on the yield of the product. This result suggests that this approach for preparing *N*-alkyl pyrroles is environmentally benign compared to the processes reported earlier.



Scheme 2. Plausible mechanism for ionic liquid promoted formation of *N*-alkyl pyrrole under neutral conditions.

With a view to use this methodology for the synthesis of pyrrole-fused system, we performed the reaction between salicylaldehyde **(A)** and 4-hydroxyproline in the presence of iodine. The initially formed 2-((1*H*-pyrrol-1-yl)methyl)phenol undergoes an in situ electrophilic cyclization to afford 9*H*-benzo[*e*]pyrrolo[2,1-*b*][1,3]oxazine **(3A)** in 78 % yield (Scheme 3). Subsequently, 4-bromosalicylaldehyde **(B)** and 3-methoxysalicylaldehyde **(C)** were also subjected to identical

Scheme 3. Synthesis of 9*H*-benzo[*e*]pyrrolo[2,1-*b*][1,3]oxazine via iodine-mediated electrophilic cyclization

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reaction. Whereas, 4-bromosalicylaldehyde gave the corresponding product **3B** in 35% yield, 3-methoxysalicylaldehyde gave a mixture of products from which the product **3C** could not be isolated in pure form.

Conclusion

In summary, we have demonstrated a sustainable approach for the synthesis of *N*-alkyl pyrroles in ionic liquid. This protocol is attractive as the reaction is performed under neutral and mild conditions and the ionic liquid used as the solvent could be readily recovered and reused. We have also extended the protocol for the one-pot synthesis of 9*H*-benzo[*e*]pyrrolo[2,1-*b*][1,3]oxazines.

Experimental

General. All experiments were monitored by thin layer chromatography (TLC) performed on pre-coated silica gel plates. After elution, plate was visualized under UV illumination at 254 nm for UV active materials. Further visualization was achieved by staining with $KMnO_4$ and charring on a hot plate. Column chromatography was performed on silica gel (100-200 mesh) by standard techniques eluting with solvents as indicated. IR spectra were recorded using Perkin Elmer's FTIR spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker 400 MHz spectrometer, using TMS as an internal standard (chemical shifts in δ). Peak multiplicities of NMR signals were designated as s (singlet), bs (broad singlet), d (doublet), dd (doublet of doublet), t (triplet), m (multiplet) etc. The ESI-MS were recorded on Ion Trap Mass spectrometer and the HRMS spectra were recorded as ESI-HRMS on a Q-TOF LC-MS/MS mass spectrometer. Commercial grade reagents and solvents were used without further purification. All reactions were carried out inflame-dried reaction vessels with Teflon lined snap caps in Biotage initiator 2.5 microwave synthesizer. The identity of the *N*-alkyl pyrrole products was confirmed by comparison to the reported NMR spectra of known compounds. The recovery of ionic liquid for solid compounds was made with EtOAc whereas for oily products diethylether was used.

General procedure for the synthesis of *N*-alkyl pyrroles as exemplified for 1-(4-Chlorobenzyl)-1*H*-pyrrole 2a

A clean oven-dried 2-5 mL reaction vial was charged with 4-chlorobenzaldehyde **1a** (100 mg, 0.71 mmol), 4-hydroxyproline (99 mg, 0.85 mmol) and [hmim]Br (1.0 mL). The resulting solution was stirred under microwave irradiation at 130 °C for 25 min. On completion, the reaction mass was allowed to cool to ambient temperature and extracted with EtOAc (3 x 5 mL). The combined organic layer was dried over anhyd. Na_2SO_4 and concentrated under reduced pressure to obtain a residue. The residue was purified through column chromatography on silica gel using hexanes/ EtOAc (9.5:0.5, v/v) as eluent to furnish **2a** (0.11 g, 82%) as a colorless oil.

1-(4-Chlorobenzyl)-1*H*-pyrrole (**2a**). R_f = 0.45 (Hexanes: EtOAc, 9:1, v/v); IR (neat) ν_{max}: 761, 1017, 1216, 1283, 1407, 1676, 2926 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.95 (s, 2H), 6.17 (t, J = 2.1 Hz, 2H), 6.62 (t, J = 2.1 Hz, 2H), 6.97 (d, J = 8.3 Hz, 2H), 7.23 (d, J = 8.3 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 52.7, 109.1, 121.3, 128.6, 129.1, 133.6, 137.1. MS (ESI+): m/z = 192.0. ESI-HR-MS calculated for $C_{11}H_{10}ClN$ (M^++H): 192.0580, found: 190.0583.

Typical experimental procedure for the synthesis of 9*H*-benzo[*e*]pyrrolo[2,1-*b*][1,3]oxazine 3A

An oven-dried 2-5 mL microwave reaction vial was charged with [hmim]Br (1.5 mL), salicylaldehyde (100 mg, 0.81 mmol), 4-hydroxyproline (113 mg, 0.98 mmol) and molecular iodine (205 mg, 0.81 mmol). The reaction vial was heated under stirring in a microwave reactor at 130 °C for 25 min. On completion, the reaction was cooled with compressed air flow and quenched with aq solution of $Na_2S_2O_3$ (5.0 mL) and extracted with EtOAc (3 x 10 mL). The combined organic layer was dried over anhyd Na_2SO_4 and concentrated under reduced pressure to obtain a residue. The residue was purified through column chromatography on silica gel using hexanes/ EtOAc (8.5:1.5, v/v) as eluent to furnish **3** (0.109 g, 78%) as a brown solid.

9*H*-Benzo[*e*]pyrrolo[2,1-*b*][1,3]oxazine (**3A**). Mp 85-87 °C; R_f = 0.45 (Hexanes: EtOAc, 9:1, v/v); IR (KBr) ν_{max}: 925, 1215, 1565, 3012 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.84 (dd, J_1 = 15.3 Hz, J_2 = 15.3 Hz, 2H), 6.53 (d, J = 8.4 Hz, 1H), 6.97-7.02 (m, 2H), 7.24-7.28 (m, 2H), 7.48 (d, J = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 55.7, 106.6, 108.5, 119.6, 121.6, 128.6, 128.9, 129.3, 132.0, 141.1, 144.4. MS (ESI+): m/z = 172.1. ESI-HR-MS calculated for $C_{11}H_9NO$ (M^++H): 172.0762, found: 172.0768.

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[a] *Medicinal & Process Chemistry Division, CSIR-Central Drug Research Institute, BS-10/1, Sector 10, Jankipuram Extension, PO Box 173, Lucknow-226031, UP, India. Fax: +91-522-2771941; Tel: +91-522-2772450/2772550 Extn. 4705, 4727; E-mail: batra_san@yahoo.co.uk*
[b] *Academy of Scientific and Innovative Research, New Delhi, India.*

† Electronic Supplementary Information (ESI) available: [^{1}H and ^{13}C-NMR spectra of all compounds are provided]. See DOI: 10.1039/b000000x/

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