



An efficient synthesis of pyrroles by a one-pot, three-component condensation of a carbonyl compound, an amine and a nitroalkene in a molten ammonium salt

Brindaban C. Ranu* and Suvendu S. Dey

Department of Organic Chemistry, Indian Association for the Cultivation of Science, Jadavpur, Calcutta-700 032, India

Received 20 December 2002; revised 1 February 2003; accepted 14 February 2003

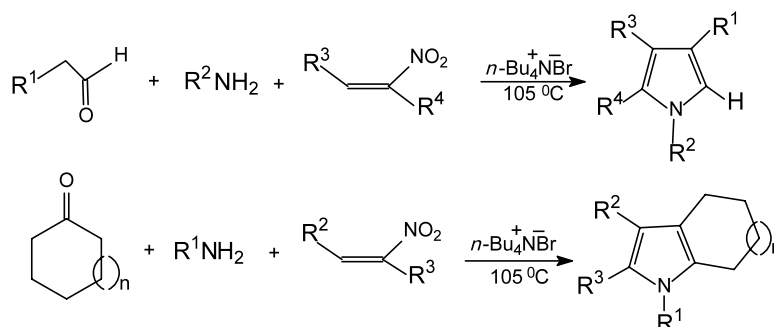
Abstract—A one-pot, three-component condensation of a carbonyl compound, an amine and a nitroalkene leading to an efficient synthesis of alkyl-substituted pyrroles has been carried out in molten tetrabutylammonium bromide. Neither a catalyst nor an organic solvent is required for this reaction and the molten ammonium salt is recyclable. © 2003 Elsevier Science Ltd. All rights reserved.

Because of the toxic and volatile nature of many organic solvents, particularly chlorinated hydrocarbons, ionic liquids are emerging as effective solvents for 'green' processes.¹ However, the high cost of most conventional room temperature ionic liquids and apprehension about their toxicity has led us to explore the use of more benign salts in the molten state as practical alternatives.² As a part of this program we initiated an investigation^{2e} to explore the efficacy of molten tetrabutylammonium bromide for useful reactions.

The pyrrole ring constitutes a basic heteroaromatic structure. It is a vital building block for the construction of porphyrins and a key unit in a number of

biologically active compounds.³ Several alkylated pyrrole derivatives have been shown to possess remarkable biological activity.⁴ Thus, the synthesis of pyrroles remains an extremely attractive topic.

Pyrroles are prepared primarily by using classical Knorr⁵ and Hantzsch⁶ procedures. However, the synthesis of alkylated pyrroles by these procedures is problematic, since mixtures of regioisomers are generally formed from non-stabilized enamine intermediates. Although several methods have been developed for the synthesis of this heterocyclic system recently⁷ these are not always satisfactory with respect to ease of operation, yield, general applicability and toxicity of reagents and solvents. We wish to report here a simple and green



Scheme 1.

Keywords: pyrrole; tetrabutylammonium bromide; condensation; solvent-free reaction.

* Corresponding author. Tel.: +91-33-24734971; fax: +91-33-24732805; e-mail: ocbcr@iacs.res.in

method for the synthesis of pyrroles by a three-component condensation of an aldehyde or ketone with an amine and an α,β -unsaturated nitroalkene⁸ in molten tetrabutylammonium bromide which does not require any other reagent or organic solvent (Scheme 1).

The experimental procedure is very simple. A mixture of the aldehyde or a ketone (1 mmol), an amine (1 mmol) and a conjugated nitroalkene (1 mmol) was added to molten tetrabutylammonium bromide (1 g) at 105°C and the mixture was heated with stirring at that temperature for the period of time required to complete the reaction (TLC). The reaction mixture was cooled and extracted three times with ethyl acetate. The combined organic extracts were washed with water, brine and dried. Evaporation of the solvent left the crude product, which was purified by column chromatography over silica gel to afford the pure pyrrole. The tetrabutylammonium bromide remaining in the reaction flask was washed with hexane, dried under vacuum and was recycled for subsequent use without any loss of efficiency. New compounds were properly characterized by their IR, ¹H and ¹³C NMR spectra and elemental

analysis, whereas the known compounds (entries 7–10 in Table 1 and entries 3–6, 8, and 10 in Table 2) were identified by comparison of their spectroscopic data with those reported values.^{7j}

A wide range of aldehydes was coupled with a variety of primary amines and α,β -unsaturated nitroalkenes by this procedure to provide the corresponding substituted pyrroles. The results are presented in Table 1. Surprisingly, open-chain ketones do not lead to pyrroles by this procedure, instead the reaction stops at the intermediate imine stage. When the reaction was carried out at a higher temperature, a mixture of unidentified products with considerable amounts of tar was formed. However, cyclic ketones, under the conditions of the present procedure, provided the corresponding fused pyrroles. The results are reported in Tables 1 and 2. As is evident from the results, this procedure can place alkyl or aryl substituents at any specific position in the pyrrole ring by proper choice of coupling components.

In general, the reactions are fast and clean. The yields are also high for a three-component coupling process.

Table 1. Synthesis of pyrroles by the coupling of aldehydes, amines and nitroalkenes

Entry	R ¹	R ²	R ³	R ⁴	Time(h)	Yield(%) ^a
1	C ₈ H ₁₇	CH ₃ (CH ₂) ₃	<i>p</i> -(NO ₂)C ₆ H ₄	CH ₃	1	82
2	C ₈ H ₁₇			CH ₃	1	75
3	C ₈ H ₁₇	PhCH ₂		CH ₃	1	75
4	C ₈ H ₁₇		<i>p</i> -(Cl)C ₆ H ₄	CH ₃	1	80
5	C ₈ H ₁₇	PhCH ₂	<i>p</i> -(Cl)C ₆ H ₄	CH ₃	0.75	85
6	CH ₃	PhCH ₂	<i>p</i> -(NO ₂)C ₆ H ₄	CH ₃	1	72
7	CH ₃ CH ₂	CH ₃ (CH ₂) ₂	Ph	CH ₃	1	70
8	CH ₃		Ph	CH ₃	1	73
9	CH ₃ CH ₂	CH ₃ (CH ₂) ₃	Ph	CH ₃	1	69
10	CH ₃	CH ₃ (CH ₂) ₃	<i>p</i> -(Cl)C ₆ H ₄	CH ₃ CH ₂	1	70

^aYields refer to those of pure isolated products characterized by spectroscopic data (IR, ¹H and ¹³C NMR).

Table 2. Synthesis of fused pyrroles by the coupling of cycloalkanones, amines and nitroalkenes

Entry	n	R ¹	R ²	R ³	Time(h)	Yield(%) ^a
1	1		<i>p</i> -(Cl)C ₆ H ₄	CH ₃	1	87
2	1	Ph	<i>p</i> -(Cl)C ₆ H ₄	CH ₃	1.5	68
3	1	PhCH ₂	<i>p</i> -(Cl)C ₆ H ₄	CH ₃ CH ₂	1	86
4	1		Ph	CH ₃	0.75	83
5	1	(CH ₃) ₂ CH	<i>p</i> -(Cl)C ₆ H ₄	CH ₃ CH ₂	1	73
6	1	PhCH ₂	<i>p</i> -(Cl)C ₆ H ₄	CH ₃	0.5	92
7	2	PhCH ₂	<i>p</i> -(Cl)C ₆ H ₄	CH ₃	1	80
8	2	CH ₃ (CH ₂) ₃	Ph	CH ₃	1	71
9	3	PhCH ₂	<i>p</i> -(Cl)C ₆ H ₄	CH ₃	0.75	85
10	3	CH ₃ (CH ₂) ₃	Ph	CH ₃	1	69
11	3	PhCH ₂	<i>p</i> (NO ₂)C ₆ H ₄	CH ₃	0.5	91
12	3	PhCH ₂		CH ₃	0.75	75

^aYields refer to those of pure isolated products characterized by spectroscopic data (IR, ¹H and ¹³C NMR).

This procedure neither involves any strong acid or base nor any toxic reagent or solvent. Presumably, the carbonyl compound combines with the amine to form the imine which then couples with the nitroalkene to produce the pyrrole. However, the reason for the lack of coupling of open-chain ketones is not clear to us.

In conclusion, the present procedure for the synthesis of pyrroles through a one-pot condensation of carbonyl compounds, amines and conjugated nitroalkenes demonstrates the potential of molten tetrabutylammonium bromide as a good medium and catalyst for coupling reactions and provides promise for further useful applications. Moreover, this methodology offers significant advantages with regard to simplicity of operation, yield of products, reaction times, choice of substituents on the pyrrole ring and, above all, recyclability and non-toxicity of the reaction medium used. Thus, it provides a better and greener alternative for the synthesis of pyrroles.

Acknowledgements

This investigation has enjoyed financial support from the CSIR [Grant No. 01(1739)/02], New Delhi. S.S.D. is thankful to the CSIR for his fellowship.

References

- (a) Welton, T. *Chem. Rev.* **1999**, 99, 2071; (b) Wasserscheid, P.; Keim, W. *Angew. Chem., Int. Ed.* **2000**, 39, 3773; (c) Sheldon, R. *Chem. Commun.* **2001**, 2399; (d) Namboodiri, V. V.; Varma, R. S. *Chem. Commun.* **2002**, 342; (e) Harjani, J. R.; Nara, S. J.; Salunkhe, M. M. *Tetrahedron Lett.* **2002**, 43, 1127.
- (a) Smietana, M.; Mioskowski, C. *Org. Lett.* **2001**, 3, 1037; (b) Amantini, C.; Fringuelli, F.; Pizzo, F.; Vaccaro, L. *J. Org. Chem.* **2001**, 66, 6734; (c) Selvakumar, K.; Zapt, A.; Beller, M. *Org. Lett.* **2002**, 4, 3031; (d) Ganchegui, B.; Bouquillon, S.; Henin, F.; Muzart, J. *Tetrahedron Lett.* **2002**, 43, 6641; (e) Ranu, B. C.; Das, A.; Samanta, S. J. *Chem. Soc., Perkin Trans. 1* **2002**, 1520.

3. (a) Jones, A.; Bean, G. P. *The Chemistry of Pyrroles*; Academic Press: London, 1977; (b) Jones, A. *Pyrroles*; Wiley: New York, 1990.
4. (a) Hayakawa, Y.; Kawasaki, K.; Seto, H. *Tetrahedron Lett.* **1992**, 33, 2701; (b) Yoshida, W. Y.; Lee, K. K.; Carroll, A. R.; Scheuner, P. *Helv. Chim. Acta.* **1992**, 75, 1721; (c) Lehuédu, J.; Fauconneau, B.; Barrier, L.; Ourakow, M.; Piriou, A.; Vierfond, J.-M. *Eur. J. Med. Chem.* **1999**, 34, 991.
5. Sundberg, R. J. In *Comprehensive Heterocyclic Chemistry*; Bird, C. W.; Cheeseman, G. W. H., Eds.; Pergamon Press: Oxford, 1984; Vol. 4, p. 331.
6. Eicher, T.; Hauptmann, S. *Chemie der Heterocyclen*; Thieme Verlag: Stuttgart, 1994; p. 94.
7. (a) Furstner, A.; Weintritt, H.; Hupperts, A. *J. Org. Chem.* **1995**, 60, 6637; (b) Periasamy, M.; Srinivas, G.; Bharathi, P. *J. Org. Chem.* **1999**, 64, 4204; (c) Danks, T. N. *Tetrahedron Lett.* **1999**, 40, 3957; (d) Shiraishi, H.; Nishitani, T.; Nishihara, T.; Sakaguchi, S.; Ishii, Y. *Tetrahedron* **1999**, 55, 13957; (e) Grigg, R.; Savie, V. *Chem. Commun.* **2000**, 873; (f) Burley, I.; Bilic, B.; Hewson, A. T.; Newton, J. R. A. *Tetrahedron Lett.* **2000**, 41, 8969; (g) Liu, J.-H.; Yang, Q.-C.; Mak, T. C. W.; Wong, H. N. C. *J. Org. Chem.* **2000**, 65, 327; (h) Langer, P.; Freifeld, I. *Chem. Commun.* **2002**, 2668; (i) Quiclet-Sire, B.; Wendeborn, F.; Zard, S. Z. *Chem. Commun.* **2002**, 2214; (j) Ranu, B. C.; Hajra, A. *Tetrahedron* **2001**, 57, 4767.
8. A similar procedure for the synthesis of pyrroles using lanthanide compounds was reported earlier by Shiraishi et al.^{7d}