ChemComm

A highly efficient synthetic procedure for deuteriating imidazoles and imidazolium salts

Christopher Hardacre,*[ab] John D. Holbrey[b] and S. E. Jane McMath[a]

[a] *School of Chemistry, The Queen's University of Belfast, Belfast BT9 5AG, Northern Ireland*
[b] *The QUILL centre, The Queen's University of Belfast, Belfast BT9 5AG, Northern Ireland.*
E-mail: c.hardacre@qub.ac.uk; Fax: +44 28 9038 2117; Tel: +44 28 9027 4592

Received (in Cambridge, UK) 13th November 2000, Accepted 17th January 2001
First published as an Advance Article on the web 8th February 2001

Both substituted imidazoles and 1,3-dialkylimidazolium salts can be fully deuteriated on the heterocyclic ring using D_2O over heterogeneous Pd catalysts: deuteriated 1-alkyl-3-methylimidazolium chloride and hexafluorophosphate ionic liquids can also be prepared in good yields utilising readily available and relatively low cost sources of deuterium.

Imidazole and imidazolium salts are key systems in nature (in, for example, histidine and vitamin B_{12}, and as components in DNA base-pair structure, biotin, *etc*).[1] As such they have a tremendous range of applications in pharmaceutical, veterinary and agrochemical products. Other important applications include formulation of high temperature polymers and corrosion inhibitors,[2] for the formation of carbenes (as replacements for phosphine ligands in transition metal catalysis),[3] and as the basis for ionic liquids - clean solvents for catalysis, extraction technology and electrochemical applications.[4]

For our ongoing investigations of the liquid structure of ionic liquids by neutron diffraction, access to deuteriated materials in order to provide neutron-scattering contrast was required. For these studies, it was necessary to prepare significant quantities (3–5 g) of both fully deuteriated and selectively deuteriated (exchange on the ring positions only) samples of 1,3-dimethylimidazolium chloride or hexafluorophosphate and 1-ethyl-3-methylimidazolium chloride or hexafluorophosphate. Only one of these materials, 1-ethyl-3-methylimidazolium-d_{11} chloride, is currently commercially available and is supplied in small quantities and at prohibitively high cost for this experiment. This paper describes a versatile low cost methodology to prepare these deuteriated materials. Although ionic liquids research provided the driving force behind this investigation, these molecules are also of significant interest as mechanistic probes, particularly in biochemical studies, especially where ^{1}H and ^{2}D NMR spectroscopies are utilised.[5]

Ring deuteriation of imidazolium cations has been performed using D_2O by Dieter *et al*.[6] In this study, shaking with D_2O was sufficient to exchange the most acidic ring-hydrogen, H(2); however, exchange of the ring-hydrogens, H(4/5), was found to require more forcing conditions, *i.e.* heating in D_2O–K_2CO_3. Using this method, the ring-deuteriated salt, 1-ethyl-3-methylimidazolium-d_3 chloride could be prepared. In contrast, imidazoles are much less susceptible to H/D exchange (10^6–10^8 times slower) than the corresponding imidazolium salts.[7,8] Full ring deuteriation of imidazole is also possible under forcing acidic conditions. Lui *et al.* incorporated 90% deuterium using D_2O–D_2SO_4 at 200 °C for 4 h after two passes.[5] Here we show that by using D_2O and a heterogeneous catalyst, both imidazolium salts and substituted imidazoles can be ring deuteriated easily under mild, neutral conditions.

The deuteriation of 1-methylimidazole and 1,3-dimethylimidazolium chloride was screened using palladium and platinum catalysts on a variety of supports† (Table 1). The deuteriations were performed following a pre-reduction of the catalyst in flowing dihydrogen at rt. The substrate dissolved in D_2O was added to the catalyst and underwent a number of freeze-pump thaw cycles, after which the temperature was raised to 100 °C and left for 1 h. This technique has been used extensively for the deuteriation of other heterocycles, commonly pyridines and related molecules.[9] Using this method, 1,3-dimethylimidazolium chloride was deuteriated at the ring H(2) (99%) and H(4/5) (90%) positions using a 10% Pd/C catalyst. The general applicability of this system was demonstrated by deuteriation of imidazole, 1-methylimidazole and 1,3-dimethyl-, 1-ethyl-3-methyl- and 1,3-dibutylimidazolium chlorides with 90–96% deuterium incorporation at the ring H(4/5) positions after one cycle. Exhaustive deuteriation of alkylimidazolium salts was tested at elevated temperatures, and showed that, although exchange of the alkyl group hydrogens is possible, it is inefficient. For example, the maximum deuterium incorporation in methyl side chains on 1,3-dimethylimidazolium chloride at 250 °C over any catalyst was 43% after 12 h.

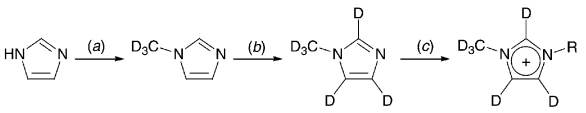
Table 1 Percentage deuterium incorporation at the ring H(4/5) positions in (i) 1,3-dimethylimidazolium chloride and (ii) 1-methylimidazole using various catalysts

	% Of ring H(4/5) deuteriated	
Catalyst[a]	(i)	(ii)
10% Pd/C	90	91
—	99[b]	—
10% Pd/Al_2O_3	95	87
5% Pt/C	33	0
5% Pt/Al_2O_3	45	5

[a] Little difference was found varying the catalyst loading between 5 and 10%. [b] Second deuteriation cycle.

In general, palladium catalysts are much more active for the exchange reaction than platinum catalysts in both imidazole and imidazolium-based systems. The lack of H/D exchange at the H(4/5) positions using platinum is not well understood at present. Explanations include a change in molecular adsorption geometry between the two metals or site blocking by strongly adsorbed molecules (originating *via* a surface reaction of the imidazole).[10,11] Experiments are currently underway to understand this process more fully.

Using the methodology described above to deuteriate the ring positions, a general procedure was devised in which the synthesis and deuteriation of the 1,3-dialkylimidazolium salts is divided into three discrete steps which can be manipulated in a modular fashion (Scheme 1). This involved a sequence in which imidazole is alkylated to 1-alkylimidazole, then ring-deuter-



Scheme 1 (*a*) CD_3OD, $RuCl_3$/(*n*-BuO)$_3$P; (*b*) D_2O, 10% Pd/C; (*c*) RX (CD_3Cl, C_2D_5I).

DOI: 10.1039/b009097m

iated with subsequent quaternisation with a second alkylating agent to yield the desired deuteriated 1,3-dialkylimidazolium salt. The order of the sequence depends on the relative efficiency of each step and the nature of the anions in the final 1,3-dialkylimidazolium salt. It is also important to consider whether deuteriation of the ring should be performed before or after the quaternisation. This is dependant on the relative stability of the H/D exchanged hydrogens with respect to scrambling in the subsequent reactions, *e.g.* quaternisation.

Here, the initial alkylation of the imidazole could not be performed cleanly using conventional procedures,[12] since a number of by-products were also formed. For example, methylation of imidazole with iodomethane under neutral conditions led to the formation of a mixture of 1H-imidazolium iodide, 1-methylimidazole and 1,3-dimethylimidazolium iodide. Under these reaction conditions, the imidazole acts as a base for the alkylation. However, since 1-methylimidazole is more reactive towards methyl iodide than imidazole itself, this leads to a final product mixture, which cannot easily be separated. Due to this problem, this method can only be applied to symmetrically substituted 1,3-dialkylimidazolium salts. In the field of room temperature ionic liquids, cation asymmetry is an important feature in order to provide the variation in properties such as melting point, viscosity and density, which allows their use as tuneable solvents.[13]

Alkylimidazoles may be synthesised *via* a number of other routes. Arduengo *et al.*[14] prepared 1,4,5-trimethyl-d_9-imidazole as a precursor to perdeuteriated carbenes *via* a cyclisation route using perdeuteriated methylamine, prepared by deuteriation of deuteriated nitromethane. Alkylation of imidazole has also been performed catalytically with methanol over a homogeneous ruthenium–tributylphosphite catalyst; Tanaka *et al.*[15] claimed 99.5% conversion and greater than 98% selectivity for the production of methylimidazole. This presents a potentially more effective route than that of Arduengo *et al.*[14] for the formation of 1-methyl-d_3-imidazole using deuteriated methanol as a low-cost methylating agent and also gives the opportunity to utilise longer-chain alcohols (for instance, deuteriated ethanol).

Here, 1,3-dimethylimidazolium-d_9 chloride was prepared from imidazole in three steps, introducing deuteriatated functionality at one nitrogen (*via* an alkyl group), to the ring and finally in a quaternisation step adding a deuteriated methyl group to the second nitrogen.‡ In the first step, imidazole was *N*-methylated with deuteriated methanol to 1-methyl-d_3-imidazole over a homogeneous ruthenium–tributylphosphite catalyst in 1,4-dioxane at 200 °C/40 bar pressure[15] with overall 75% yield (based on recovered imidazole) and was isolated by vacuum distillation. The resulting 1-methyl-d_3-imidazole was then deuteriated on the ring with D_2O over a Pd/C catalyst to give the fully perdeuteriated 1-methylimidazole. This was then alkylated with chloromethane-d_3 to give the 1,3-dimethylimidazolium-d_9 chloride, and with iodoethane-d_5 to 1-ethyl-3-methylimidazolium-d_{11} iodide in good overall yields. This approach allows the greatest flexibility in the chemistry and permits the selective introduction of deuterium to any of the functional areas of the imidazolium cation using relatively inexpensive and readily available deuteriated starting materials. The hexafluorophosphate salts were obtained by metathesis from the halide salt with $Na[PF_6]$ in D_2O. 1-Ethyl-3-methylimidazolium-d_{11} chloride was then isolated from the corresponding hexafluorophosphate salt by metathesis with LiCl in acetone-d_6. All the salts were collected as colourless crystals. ^1H and ^{13}C NMR spectra were obtained to assess the levels of deuteriation in the salts and in all cases the deuterium incorporation was greater than 97%. It should be noted that, for the ring deuteriations, this required two cycles in order to increase the deuterium level from 90 to >97%.

This procedure (Scheme 1) enables the preparation of ionic liquids and other 1,3-dialkylimidazolium salts (*i.e.* as precursors to carbene ligands) in which deuteriation of the cation can be selectively applied to any position; one or two *N*-alkyl substituents and ring. Moreover, combined with the lability of the ring H(2) in aqueous solution, it is also possible to selectively control the H/D substitution of the ring H(2) and H(4/5) by H/D exchange.

Financial support from the Department of Education in Northern Ireland (S. E. J. M.) and the Queen's University Ionic Liquids Laboratory (S. E. J. M., J. D. H) is gratefully acknowledged. Johnson Matthey and Degussa are thanked for the generous donation of the carbon catalysts and aluminium oxide respectively.

Notes and references

† Oxide supported catalysts were synthesised by wet impregnation from $PdCl_2$ and H_2PtCl_6 precursors on Degussa Alumina grade C, the catalysts were then calcined and reduced under hydrogen. ICP analysis of metal content was used to confirm catalyst loading. Pd/C and Pt/C catalysts were supplied by Johnson Matthey.

‡ Methanol-d_4 (99.8%) from Apollo Scientific Ltd. All other reagents were obtained from Aldrich and used as supplied.

1-Methyl-d_3-imidazole. Ruthenium chloride hydrate (0.63 g, 2.41 mmol), tri(*n*-butyl)phosphite (2.30 g, 9.19 mmol) and imidazole (10.78 g, 0.158 mol) were sequentially dissolved in 1,4-dioxane (300 cm^3) in a stirred 1 L autoclave. After addition of methanol-d_4 (20 g, 0.554 mol), the mixture was heated at 200 °C under 40 bar pressure of nitrogen for 18 h. Following reaction, the liquid was decanted from the spent catalyst and solvent/excess methanol were removed. The resulting pale yellow oil was vacuum distilled at 100 °C to give 1-methyl-d_3-imidazole as a colourless oil (6.5 g, 49%) and analysed by GC-MS. *m/z* (EI) 85, accurate mass 85.072 (Calc for $C_4H_3N_2D_3$, 85.072), NMR δ_H/ppm ($CDCl_3$) 7.49 (1H, s), 7.01 (1H, s), 7.86 (1H, s); δ_C/ppm ($CDCl_3$) 135.26 (C2), 126.93 (C4), 118.05 (C5), 30.59 ($-CD_3$); δ_D/ppm ($CDCl_3$) 29.64 ($-CD_3$). Unreacted imidazole (34%) was recovered from the distillation flask. Overall yield, based on imidazole was 75%, unreacted deuteriated methanol was recovered from the solvents by distillation and could be reused.

1-Methylimidazole-d_6. Palladium on activated carbon (2 g, 10% Pd) was reduced under dihydrogen (1 atm), for 1 h at rt. 1-Methylimidazole (10 g, 0.117 mol) was dissolved in pure D_2O (50 g, 0.28 mol), and added to the reduced catalyst. The reaction mixture was degassed by three freeze pump thaw cycles, then heated with stirring at 100 °C for 1 h. The reaction mixture was filtered to remove the catalyst, and the aqueous solvent was removed under reduced pressure, and then *in vacuo* to give the ring-deuteriated 1-methylimidazole (9.4 g, 91%). Extent of deuteriation was analysed by loss in ^1H and changes in ^{13}C NMR.

1,3-Dimethylimidazolium-d_9 chloride. Chloromethane-d_3 (1.0 g, 18.7 mmol) was condensed onto 1-methylimidazole-d_6 (1.0 g, 11.4 mmol) in a carius tube cooled to −180 °C with liquid nitrogen. The tube was then sealed and brought to rt, then heated at 80 °C for 15 h to give the 1,3-dimethylimidazolium-d_9 chloride as a colourless crystalline solid (1.6 g, 99%).

1 R. J. Sundberg and R. B. Martin, *Chem. Rev.*, 1974, **74**, 471.
2 F. Eng and H. Ishida, *J. Mater. Sci.*, 1986, **21**, 1561.
3 W. A. Herrmann, L. J. Goossen, C. Kocher and G. R. J. Artus, *Angew. Chem., Int. Ed. Engl.*, 1996, **35**, 2805.
4 T. Welton, *Chem. Rev.*, 1999, **99**, 2071.
5 K. Lui, J. Williams, H. R. Lee, M. M. Fitzgerald, G. M. Jensen, D. B. Goodin and A. E. McDermott, *J. Am Chem. Soc.*, 1998, **120**, 10 199.
6 K. M. Dieter Jr., C. J. Dymek, N. E. Heimer, J. W. Rovang and J. S. Wilkes, *J. Am. Chem. Soc.*, 1988, **110**, 2722.
7 O. Clement, A. W. Roszak and E. Buncel, *J. Am. Chem. Soc.*, 1996, **118**, 612; E. Buncel, O. Clement and I. Onyido, *J. Am. Chem. Soc.*, 1994, **116**, 2679; J. R. Jones and S. E. Taylor, *Chem. Soc. Rev.*, 1981, **10**, 329.
8 J. L. Wong and J. Keck Jr., *J. Org. Chem.*, 1974, **39**, 2398.
9 For example, J. A. Elvidge, J. R. Jones, R. B. Mane and J. M. A. Al-Rawi, *J. Chem. Soc., Perkin Transactions 2*, 1979, 386; G. E. Calf, J. L. Garnett and V. A. Pickles, *Aust. J. Chem.*, 1968, **21**, 961.
10 K. Pekmez and A. Yildiz, *Z. Phys. Chem.*, 1996, **96**, 109.
11 R. T. Carlin, T. H. Cho and J. Fuller, *Proceedings of the 12th International Symposium on Molten Salts*, ed. P. C. Truelove, H. C. De Long, G. Stafford and S. Deki, PV99-41, p. 90, The Electrochemical Proceedings Series, Pennington NJ, 1999; K Anderson, P. Goodrich, C. Hardacre, S. E. J. McMath, in preparation.
12 M. R. Grimmett, *Imidazole and benzimidazole synthesis*, 1997, Academic Press, London.
13 A. S. Larsen, J. D. Holbrey, F. S. Tham and C. A. Reed, *J. Am. Chem. Soc.*, 2000, **122**, 7264.
14 A. J. Arduengo III, H. V. R. Dias, D. A. Dixon, R. L. Harlow, W. T. Klooster and T. F. Koetzle, *J. Am. Chem. Soc.*, 1994, **116**, 6812.
15 N. Tanaka, M. Hatanaka and Y. Watanabe, *Chem. Lett.*, 1992, 575.