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One-step exchange-labelling of piperidines, piperazines and dialkylamines with deuterium oxide: catalysis by various ruthenium complexes

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Abstract—A range of variously substituted piperidines, piperazines and dialkylamines can be conveniently deuterated in a single step by isotopic exchange with deuterium oxide in the presence of an appropriate ruthenium complex catalyst. The isotopic exchange can be carried out efficiently in dimethylsulfoxide, hence it is directly applicable to the deuteration of polar compounds such as pharmaceuticals. Isotopic incorporations are high, whilst recoveries are variable and generally moderate. Deuteration takes place at positions both α and β to the NH group.

The preparation of organic compounds labelled with isotopic hydrogen is of essential importance in the chemical, biological and environmental sciences. Hence numerous methodologies have been developed for the ^{2}H- and ^{3}H-labelling of organic substrates. Isotopic exchange techniques are well represented in these methodologies since they do not require the synthesis of labelling precursors and hence are suited to the rapid labelling approaches utilised in the pharmaceutical and related industries.[1] The development of parallel and combinatorial chemistry techniques over recent years has led to the incorporation of dialkylamines, particularly piperidines and piperazines, as scaffold fragments in many combinatorial libraries. Techniques for the labelling of these fragments with hydrogen isotopes are therefore of particular interest. Indeed, pioneering examples of the isotopic exchange of such compounds, under catalysis by tris-triphenylphosphineruthenium(II) dichloride, have already appeared in the literature.[1a,2]

As part of our programme to develop new isotopic labelling methods for polar molecules we have investigated the isotopic exchange of piperidines, piperazines and other secondary amines with deuterium oxide in dipolar aprotic solvents. We now report that several ruthenium-based complexes are effective catalysts for labelling the α- and β-methylene groups of such substrates (Scheme 1).

To identify active catalysts, a range of suitable group VIII metal complexes were screened for activity in the labelling of a solid commercially available piperazine substrate, 1-(5-trifluoromethylpyridin-2-yl)piperazine (**1**, Scheme 1), chosen for its ease of handling and of analysis by NMR and LC–MS. Screens were carried out in both DMF and DMSO. In the DMF screen, activity was noted for some iridium(I) based systems, particularly for Crabtree and co-workers[3] and Heys catalysts[4] and related complexes, though the degree of deuteration achieved by these systems was low. However, four commercially available ruthenium(II) complexes were identified which possessed high activity. These were, tris-triphenylphosphineruthenium(II) dichloride, already identified for the isotopic exchange of alcohols and primary amines,[5] the bis(benzene)- and bis(*p*-cymene)ruthenium(II) dichloride complexes and the tricarbonyldichlororuthenium(II) dimer. All of these

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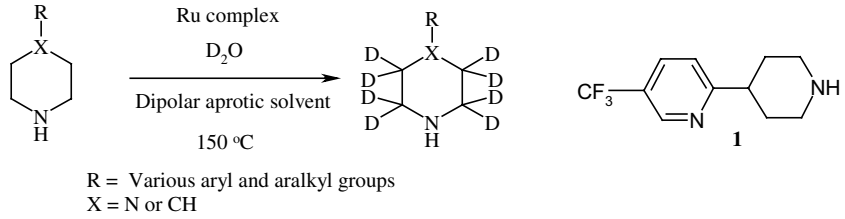

Scheme 1.

complexes proved most active in DMSO. Initial studies with these catalysts showed that the two bisarene complexes had very similar activity, hence only one, the bis(benzene) complex, was included in the more detailed studies.

Studies of the deuteration reaction were carried out in DMSO-d_6 to allow NMR monitoring and the process was optimised with respect to: time, temperature, molar ratio of catalyst to substrate and the quantity of deuterium oxide employed. None of the deuterium introduced into the substrate derived from the DMSO-d_6 co-solvent. Subsequently, the active catalysts were screened against a panel of commercially available piperidines, piperazines and dialkylamines to indicate the generality of the labelling procedure. The results of these studies are shown in Table 1.

Generally the most important parameter for a labelling reaction is the isotopic incorporation and this was satisfactorily high. Indeed it was often close to the equilibrium value (5.2 D/molecule) calculated for the exchangeable hydrogen isotope pool in the reaction, assuming no isotope effects and neglecting any contributions from solvent moisture content or ligand labelling.

The substrate recoveries were variable and generally moderate, due mainly to a competing methylation reaction presumably arising from activation of the DMSO-d_6 solvent by the catalyst. Carbonylation was also sometimes observed with the $(CO)_6Ru_2Cl_4$ catalyst. The importance of these side reactions varied with the substrate, however in those cases examined, both these impurities were removed by the simple formation and crystallisation of the amine oxalate salt.[6]

The results in DMSO were generally better than in DMF as evidenced by the data presented in parentheses for the $(PPh_3)_3RuCl_2$ catalyst.

The regiochemistry of the labelling reaction was investigated by ^1H NMR, ^2H NMR and MS for most substrates. Labelling was always observed at the methylenes both α and β to the NH group whilst no aromatic labelling or methine labelling was observed. However, the relative amount of deuterium at the α and β sites varied according to the catalyst. It was close to equal in the case of the $(CO)_6Ru_2Cl_4$ catalyst.

In contrast to $(PPh_3)_3RuCl_2$, the $(CO)_6Ru_2Cl_4$ catalyst labelled only secondary amines: model primary alcohols and amines and secondary alcohols were recovered unlabelled. Moreover, since some deuteration of the triphenylphosphine ligands was observed for the $(PPh_3)_3RuCl_2$ catalyst, the $(CO)_6Ru_2Cl_4$ catalyst should have particular advantages for tritium-labelling applications.

A typical small-scale deuteration procedure is given below.[6] The scale was chosen to model the preparation of tritiated compounds or of MS internal standards (where the analyte often has limited availability), however, it has been successfully scaled-up by 10-fold.

The nature of the actual catalytic species in these reactions is unknown. Ruthenium(II) DMSO complexes however, are well-known,[7] and are likely to be involved. In this context it is significant that ^{13}C NMR studies showed no remaining $(CO)_6Ru_2Cl_4$ resonances after brief heating in DMSO-d_6/D_2O, whilst gas evolution occurred during the initial dissolution. Some support for

Table 1. Labelling of piperidines, piperazines and dialkylamines

Substrate	Catalyst					
	$(PPh_3)_3RuCl_2$[c]		$C_{12}H_{12}Ru_2Cl_4$		$(CO)_6Ru_2Cl_4$	
	D/molecule[a]	%GC[b]	D/molecule[a]	%GC[b]	D/molecule[a]	%GC[b]
1-(3-Trifluoromethylphenyl)piperazine	4.9 (3.0)	88 (31)	3.4	61	4.8	77
1-(5-Trifluoromethylpyridin-2-yl)piperazine	2.8 (2.6)	85 (50)	2.2	76	5.0	30
1-Benzylpiperazine	4.7 (3.1)	60 (7)	5.7	13	4.8	27
1-Phenylpiperazine	4.7 (2.8)	63 (32)	5.0	32	5.1	10
1-Pyridin-2-ylpiperazine	2.4	13	1.0	15	3.8	<5
4-Benzylpiperidine	4.7 (2.9)	66 (19)	5.1	44	5.0	55
4-Phenylpiperidine	5.1 (3.4)	58 (12)	5.1	14	4.5	33
Dibutylamine	3.7 (2.6)	48 (51)	4.7	27	3.3	38
Dioctylamine	3.7 (4.0)	28 (3)	2.1	31	4.1	36

[a] Mean number of D atoms/molecule.
[b] % All related compounds in GC–MS total ion current trace.
[c] Figures in brackets are results using DMF as the co-solvent substrate 0.03 mmol, catalyst 0.01 mmol DMSO-d_6 (50 μl), D_2O (10 μl), 150 °C, 3 h.

an oxido-reductive mechanism[5] is provided by the promotion of the labelling by added isopropanol.

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6. [2,3,5,6-^{2}H]1-(3-Trifluoromethylphenyl)piperazinium oxalate.
   To a thick-walled screw-capped reaction vial was added $(CO)_6Ru_2Cl_4$ (6.8 mg) dry DMSO (50 μl) and D_2O (10 μl). 1-(3-Trifluoromethylphenyl)piperazine (10 mg) was then added and the vial capped, shaken and then heated for 3 h at 150 °C to yield a clear orange solution. The contents of the vial were cooled and added to saturated sodium bicarbonate solution (0.5 ml), extracted with diethyl ether (1.8 ml) and then again with ether (1 ml). The combined extracts were then washed with saturated sodium bicarbonate solution (0.25 ml) and the ether layer separated, filtered and blown to dryness under a stream of nitrogen. The resulting crude product was dissolved in ether (0.7 ml) and a saturated solution of oxalic acid in ether (50 μl, ca. 188 mg/ml) added. After standing overnight the supernatant was removed and the precipitated oxalate salt washed with ether (0.25 ml). The salt was dissolved in methanol (50 μl) and then ether (0.5 ml) was added slowly to induce crystallisation. After standing overnight the supernatant was removed and the product dried under vacuum to yield [2,3,5,6-^{2}H]1-(3-trifluoromethylphenyl)piperazinium oxalate (8.7 mg, 63%, mp 156–157 °C (authentic standard 157–158 °C), ^{1}H NMR (D_2O) δ 3.38 (1.76H, complex multiplet, residual $(CH_2)_2NH$ protons), 3.46 (1.72H, complex multiplet, residual $(CH_2)_2NAr$ protons), 7.25–7.29 (2H, overlapping doublets), 7.33 (1H, singlet), 7.47 (1H, triplet, $J = 7.8$ Hz) ppm. ^{2}H NMR (H_2O) δ 3.38 and 3.46, overlapping singlets) ppm, MS (CI, most intense ion at M+H+5D) gives 236.1418 amu, $C_{11}H_9D_5N_2F_3$ requires 236.1417 amu. The overall deuteration achieved, 4.5 D/molecule, constitutes ca. 80% of theory, assuming no isotope effects and no adventitious water in the reaction medium.
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