Tetrahedron Letters,Vol.23,No.37,pp 3819-3822,1982 0040-4039/82/373819-04$03.00/0
Printed in Great Britain

REGIOSELECTIVE DEUTERATION OF AROMATIC AND α,β-UNSATURATED CARBOXYLIC ACIDS VIA RHODIUM(III) CHLORIDE CATALYSED EXCHANGE WITH DEUTERIUM OXIDE

W J S Lockley

Department of Metabolic Studies,
Fisons plc, Pharmaceutical Division, S and T Laboratories,
Bakewell Road, Loughborough, Leicestershire LE11 0QY
England

Abstract: Ortho-deuterated aromatic carboxylic acids and β-deuterated α,β-unsaturated carboxylic acids may be prepared with high regioselectivity by exchange deuteration of the unlabelled acids in the presence of rhodium(III) chloride.

Ortho-deuterated aromatic acids are currently prepared via deuterium oxide hydrolysis of ortho-lithiated oxazolines[1], by the permanganate oxidation of ortho-deuterotoluenes[2], and by the complex hydride reduction of ortho-thalliated[3] or ortho-halo[4] derivatives. These procedures involve the use of aggressive reagents likely to effect unwanted transformations to easily reduced or base sensitive substituents. Metal catalysed hydrogen isotope exchange with deuterium oxide or tritiated water, on the other hand, generally exhibits low regioselectivity and is more suited to the preparation of perdeuterated[5] or non-specifically tritiated acids. The results reported in this paper, however, demonstrate that high regioselectivity can be obtained if deuterium exchange is performed in the presence of rhodium(III) chloride. Thus, whilst homogeneous rhodium catalysed exchange deuteration of alkyl-, halo-, or nitro-substituted benzenes demonstrates little regioselectivity[6], the introduction of a carboxylic acid group produces a marked change. In this case, labelling takes place exclusively, or predominantly at positions β to the carboxylic acid group.

The specificity of labelling found for a range of substituted benzoic acids and related α,β-unsaturated compounds after deuteration in the presence of rhodium(III) chloride is summarised in the table.

In these studies the substrate (100 mg) and rhodium(III) chloride trihydrate (20 mg) dissolved in a mixture of N,N-dimethylformamide (2 cm^3) and deuterium oxide (99.8 atom % D, 1 cm^3) were heated at 110^o for an 18 hour period. After deuteration the labelled substrates were isolated by solvent extraction, labile deuterium removed by treatment with sodium bicarbonate solution followed by dilute hydrochloric acid, and the substrates purified, if necessary, by crystallisation from methanol or water.

Either the free carboxylic acid or the derived sodium salt may be employed as substrate in the reaction. Generally the sodium salt deuterates more rapidly than the corresponding acid.

Substrate	Percentage of Molecular Ions with One or More Deuterium Atoms	Percentage of Total Deuteration at Positions β to the Carboxylic Acid Group[a]
o-anisic acid	67	95
p-anisic acid	30	95
benzoic acid	42	95
sodium benzoate	98	95
o-chlorobenzoic acid	30	95
p-chlorobenzoic acid	33	95
trans-cinnamic acid	50	90
crotonic acid	52	90
furan-3-carboxylic acid	87	80[b]
isophthalic acid	52	90
1-naphthoic acid	98	90[c]
2-naphthoic acid	92	95
salicylic acid	58	90
o-toluic acid	56	90[d]
m-toluic acid	56	95
p-toluic acid	37	95
chromone-2-carboxylic acid	97	95
1-thiochromone-2-carboxylic acid	94	95
4-hydroxyquinoline-2-carboxylic acid	53	90
ethyl benzoate	2	ND[e]
2-phenylchromone (flavone)	0	0
2-methylchromone	0	0

[a] Determined by comparison of ^{1}H-nmr resonance intensities with molecular ion isotope distribution after correction for heavy isotope contributions at natural abundances.

[b] Labelled at position 2; the residual labelling (20%) occurred at position 5.

[c] Position 8 was ca. 10% labelled.

[d] Around 5% of the label was present in the methyl group.

[e] Not determined.

More complete deuteration may be obtained, if desired, by decreasing the amount of N,N-dimethylformamide co-solvent used or by increasing the catalyst/substrate ratio. The need to increase this ratio in particular cases arises from the slow thermal decomposition of rhodium(III) chloride to yield metallic rhodium which occurs with some substrates during the course of the reaction. Neither the metallic rhodium prepared from rhodium(III) chloride in the absence of substrate nor the hydrochloric acid released in the reaction were found to catalyse the deuteration of sodium benzoate under the standard reaction conditions used. The exact nature of the catalytic species is unknown however, since the formation of undetected colloidal rhodium metal during the course of the reaction cannot be entirely excluded and the aqueous chemistry of rhodium(III) chloride is complex[7]. It is interesting to note, however, that a stable chelate complex having a metal-sp^2-carbon bond has been isolated from the reaction between a rhodium(III) complex and 2-vinylpyridine[8] and that a similar chelate complex between ruthenium(II) and methyl methacrylate may be cleaved by deuterium chloride to yield methyl cis-β-deuteromethacrylate[9].

It is noteworthy that steric inhibition of β-deuteration is observable with certain of the substrates studied. Thus, isophthalic acid, meta-trifluoromethylbenzoic acid and meta-toluic acid are less easily deuterated at the 2-position than at the alternative "ortho" sites. 2-Naphthoic acid also demonstrates considerably less deuteration at the hindered peri-position (27%) than at the alternative 3-position (92%), though whether this effect is steric or may be ascribed to double bond localisation[10] is uncertain.

Whilst deuteration β to the carboxyl group is generally observed, the regioselectivity of the reaction is lowered in some cases by concomitant labelling at other sites. Thus a degree of labelling at electrophilically activated positions is observed with salicylic acid and furan-3-carboxylic acid, whilst ortho-toluic acid and 1-naphthoic acid are labelled to a small extent in the methyl group and at the 8-position respectively, sites which are in close proximity to the carboxyl function.

The absence of significant deuteration observed with ethyl benzoate, flavone and 2-methylchromone argues strongly that the carboxyl group or carboxylate anion is actively involved in the mechanism of the reaction, presumably by complexation with the catalytic rhodium species.

Interestingly, the β-deuteration noted with both crotonic and cinnamic acids is accompanied by a small degree of multiple labelling of the type previously observed in studies of the rhodium(III) chloride catalysed deuteration of alkylbenzenes[6].

Whilst catalysis by rhodium trichloride demonstrates wide generality, regioselective β-deuteration is also observed in the presence of other Group VIII metal chlorides in some cases. Thus, both ruthenium trichloride and iridium trichloride may also be used for the deuteration of sodium benzoate under conditions comparable to those used for the rhodium trichloride catalysed exchange.

In summary, the experiments described demonstrate that hydrogen isotope exchange in the presence of rhodium(III) chloride provides a simple procedure for the regioselective hydrogen isotope labelling of α,β-unsaturated and aromatic carboxylic acids. Such compounds, by virtue of their functionality, are potentially useful intermediates for the synthesis of a wide range of further labelled materials. A full and detailed account of the use of rhodium trichloride catalysis in the preparation of regioselectively tritiated chromone-2-carboxylates will be reported elsewhere.

Acknowledgements

The author would like to express his thanks to Mr Z R Cybulski for the patient recording and analysis of numerous mass spectra and to Mr D Hunter for his experiments and advice on the assignment of the ^{1}H-nmr spectra.

References

1. A.I. Meyers, E.D. Mihelich, J. Org. Chem., 40, 3158 (1975).

2. R.N. Renaud, D. Kovachic, L.C. Leitch, Can. J. Chem., 39, 21 (1961).

3. R.B. Herbert, Tetrahedron Lett., 1375 (1973).

4. T.R. Bosin, M.G. Raymond, A.R. Buckpitt, Tetrahedron Lett., 4699 (1973).

5. J.L. Garnett, L.J. Henderson, W.A. Sollich, Tetrahedron Lett., 516 (1961).

6. M.R. Blake, J.L. Garnett, I.K. Gregor, W. Hannan, K. Hoa, M.A. Long, J.C.S. Chem. Comm., 930 (1975).

7. E. Blasius, W. Preetz, Chromatog. Rev., 6, 191 (1964).

8. R.J. Foot, B.T. Heaton, J.C.S. Chem. Comm., 838 (1973).

9. S. Komiya, T. Ito, M. Cowie, A. Yamamoto, J. Ibers, J. Amer. Chem. Soc., 98, 3874 (1976).

10. R.J. Hodges, J.L. Garnett, J. Phys. Chem., 73, 1525 (1969).

(Received in UK 9 July 1982)