Journal of Labelled Compounds and Radiopharmaceuticals—Vol. XXVIII, No. 12

REGIOSPECIFIC TRITIUM LABELING OF AROMATIC ACIDS, AMIDES, AMINES AND HETEROCYCLICS USING HOMOGENEOUS RHODIUM TRICHLORIDE AND RUTHENIUM ACETYLACETONATE CATALYSTS.

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Summary

Homogeneous rhodium trichloride has been found to promote *ortho*-tritiation with high regioselectivity in a wide range of aromatic carboxylic acids, amides and aralkylamines. Less successful results were obtained using *o*-chlorobenzoic and *o*-anisic acids where some decomposition was seen, and in acids and amides of the phenolic type, where a degree of electrophilic exchange accompanies the *ortho*-exchange. The same catalyst has also been used to regiospecifically label a number of heterocyclics. In the course of investigations with other metal complexes ruthenium acetylacetonate has been identified as an excellent promoter of *ortho*-exchange in benzoic acids.

Introduction

Aromatic carboxylic acids, amides and aralkylamines are frequently used as intermediates in laboratory and industrial synthesis.

0362–4803/90/121427–10$05.00

Received June 7, 1990

Furthermore these functional groups are commonly found in many important pharmaceutical compounds. As it is frequently necessary to prepare selectively deuteriated and tritiated derivatives of these compounds it is important to investigate whether one-step catalytic reactions can be developed to replace the time consuming and somewhat demanding synthetic procedures that are often necessary. *Ortho*-deuteriated derivatives of these compounds have typically been prepared by multistep synthesis via the deuterium oxide hydrolysis of *ortho*-lithiated oxazolines[1], by permanganate oxidation of *ortho*-deuteriated toluenes[2], by dehalogenation of *ortho*-halobenzoic acids[3] and by reduction of *ortho*-thalliated acids[4]. In some of the cases mentioned the combination of forcing conditions and aggressive reagents leads to considerable side-product formation.

Metal catalysed hydrogen isotope exchange reactions have been widely used mainly under heterogeneous conditions.
Often such reactions have been employed to study mechanisms of catalysis rather than for the synthesis of labelled compounds. Considerably less work has been carried out with homogeneous metal complexes. However the development of ^{3}H-nmr spectroscopy, with its ability to delineate the pattern of labeling at the microcurie level of radioactivity, is likely to change this situation. Prominent amongst the homogeneous catalysts studied so far are K_2PtCl_4 (sometimes the sodium salt is preferred), Na_3IrCl_6 and $RhCl_3$. The latter is of particular interest as previous work [5,6] has shown that it can catalyse the *ortho*-deuteriation of aromatic acids, amides, aralkylamines and anilides with high regioselectivity. Less extensive studies[7] with tritium have shown that the same high regiospecificity can be achieved. The present paper describes a more extensive investigation to see if the catalyst can promote *ortho*-exchange in compounds with a wider range of functional groups and also in various heterocyclic compounds.

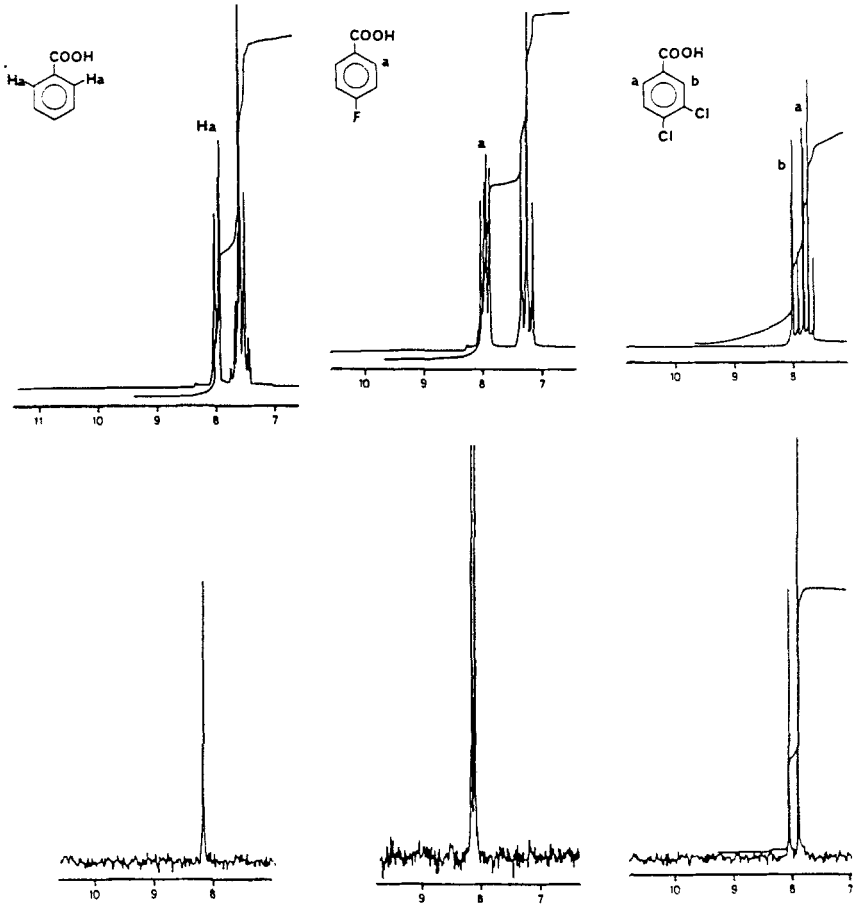
In addition an investigation has been carried out to see whether other metal complexes can be found which emulate rhodium trichloride.

Results and Discussion

The results in Table 1 show that homogeneous rhodium trichloride catalyses the *ortho*-tritiation of a wide range of aromatic acids, amides and aralkylamines with high regioselectivity. For illustrative purposes typical ^{3}H-nmr spectra are presented in the Figure. In most cases the products obtained after a very simple work-up procedure were of high radiochemical and chemical purity, thereby obviating the need for further purification by tlc or hplc. For the majority of the benzoic acids studied the regiospecificity was consistently 100%. The only exceptions to this high degree of regioselectivity were observed when decomposition occurred (*o*-chlorobenzoic acid, which underwent partial dechlorination and *o*-anisic acid which underwent partial demethylation to salicylic acid) or when electrophilic exchange was a competing reaction (*p*-hydroxybenzoic and *p*-aminobenzoic acids). Substitution in the *meta* position had no effect on the regioselectivity whilst substitution at the *ortho* position, with the exception of salicylic acid, merely ensured that the tritium was incorporated in the remaining *ortho* position. Of the three di- and tri-substituted benzoic acids studied, only in one case, that of the 3,4-dichloro compound, was steric hindrance sufficiently important as to alter the customary 50:50 distribution for the 2 and 6 positions to 36 and 64% respectively. A similar but more dramatic effect was seen in the case of isophthalic acid, where only 5% of the label was present in position 2 the remainder being located in the unhindered 4 and 6 positions.

The results for salicylic acid, which show a reduced selectivity, are consistent with previously reported deuteriation[5] and tritiation studies[7] and indicate the involvement of a competing

FIGURE. Proton and tritium N.M.R. spectra of representative tritiated benzoic acids.



electrophilic exchange pathway. The results are similar for salicylamide and salicylanilide with the important difference that in the latter compound some 49% of the label is present *ortho* to the anilide group rather than the amide group, where only 2% was present. This is the first reported instance of the anilide group acting as a directing group for tritium incorporation; it may not however be generally applicable as the results for acetanilide itself signify. The remaining amides and aralkylamines provide results in which satisfactorily high regioselectivities are observed.

Where comparison with previous deuteriation studies[5] is possible there is generally good agreement, the anilides being an exception. However, the experimental conditions for the deuteriation[5] and tritiation studies[7] are different. THO is generally used in much lower amounts than D_2O and the reaction is known to exhibit quite marked solvent effects[8]. Therefore this aspect needs to be borne in mind when comparisons between isotopes are made.

Extension of the work to incorporate additional functional groups showed (Table 2) that only the aldehyde group was effective, but since the specific activity of the tritiated benzaldehyde was only 10% of that normally obtained with the benzoic acids, the group can only be classified as a weak director at best. Even this may be an exaggeration as the group is sensitive to oxidation and labeling may occur via an oxidation-reduction step.

The complete lack of hydrogen isotope exchange in the case of methyl benzoate and the failure to incorporate any tritium in the ring in the case of phenylacetate suggests that the reaction mechanism is an example of a cyclometallation reaction involving the formation of a five-membered ring. These findings together with the kinetic aspects will be the subject of a separate publication.

The heterocyclic compounds were studied (Table 3) because although they are devoid of a functional group, chelation can take place between the catalyst, the nitrogen atom and an aromatic position in an adjacent ring. In all four cases studied high regiospecificity was observed, the only surprise being the result for 7,8-benzoquinoline, which by analogy with 2-phenylpyridine was expected to label in the C-12 position; the rigidity of the 7,8-benzoquinoline molecule may be the deciding factor in this case. Our search for other homogeneous metal catalyst complexes (Table 4)

led to the finding that ruthenium acetylacetonate was very effective in catalysing the tritiation of benzoic acid, even more so than rhodium trichloride, but that it was more limited in its scope.

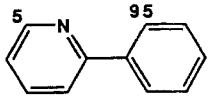
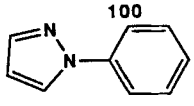
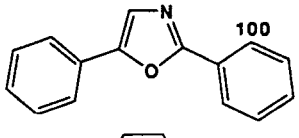
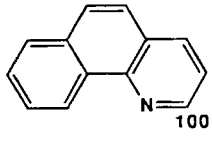
TABLE 1. Tritiation of aromatic acids, amides and aralkylamines using homogeneous $RhCl_3$ catalyst

Substrate	Positions labelled (regiospecificity)
Benzoic acid	2,6 (100%)
o-Toluic acid	6 (100%)
m-Toluic acid	2,6 (100%)
p-Toluic acid	2,6 (100%)
o-Anisic acid	decomp.
m-Anisic acid	2,6 (100%)
p-Anisic acid	2,6 (100%)
3,5-Dimethoxybenzoic acid	2,6 (100%)
3,4,5,-Trimethoxybenzoic acid	2,6 (100%)
o-Fluorobenzoic acid	6 (100%)
p-Fluorobenzoic acid	2,6 (100%)
m-Trifluoromethylbenzoic acid	2,6 (100%)
p-Trifluoromethylbenzoic acid	2,6 (100%)
o-Chlorobenzoic acid	decomp.
m-Chlorobenzoic acid	2,6 (100%)
p-Chlorobenzoic acid	2,6 (100%)
3,4-Dichlorobenzoic acid	2 (36%), 6 (64%)
p-Cyanobenzoic acid	2,6 (100%)
p-Nitrobenzoic acid	2,6 (100%)
p-Hydroxybenzoic acid	2,6 (94%), 3,5 (6%)
p-Aminobenzoic acid	2,6 (86%), 3,5 (14%)
Salicylic acid	6 (37%), 3 (24%), 5 (39%)
Salicylamide	6 (55%), 3 (25%), 5 (20%)
Salicylanilide	6 (2%), 3 (49%), 2,6 (49%)
1-Naphthoic acid	2 (100%)
2-Naphthoic acid	1 (10%), 3 (90%)
Isophthalic acid	2 (5%), 4,6 (95%)
Chromone-2-carboxylic acid	3 (100%)
Crotonic acid	α (50%) β (14%) γ (36%)
Cinnamic acid	decomp.
Benzamide	2,6 (100%)
o-Ethoxybenzamide	6 (100%)
Benzylamine	2,6 (100%)
α-Methylbenzylamine	2,6 (100%)
N-Benzoylbenzylamine	2,6 (100%)
Acetanilide	no incorporation (<50 μCi)

TABLE 2. Investigation of the influence of other functional groups on the regiospecificity of homogeneous $RhCl_3$ promoted hydrogen isotope exchange

Group	% Tritium (relative)	
	Ring	Side Chain
$Ar-CH_2COOH$	0	100
$Ar-CH_2CH_2COOH$	0	100
$Ar-CH(Me)COOH$	0	100
$Ar-COCH_3$	7	93
$Ar-CH_2CN$	4	96
$Ar-COOCH_3$	0	0

TABLE 3. Determination of the tritium distribution in heterocyclics labelled using homogeneous rhodium trichloride catalyst

Compound	Structure (relative tritium incorporation , %)
2-Phenylpyridine	
1-Phenylpyrazole	
2,5-Diphenyloxazole	
7,8-Benzoquinoline	

Unsuccessful attempts were made to tritiate benzimidazole, 2-phenylindole and nicotinic acid

TABLE 4. Tritiation of benzoic acid, benzamide and benzylamine using various homogeneous metal complexes.

Catalyst[a]	Specific activity obtained (mCi/mmole)		
	Benzoic acid	Benzamide	Benzylamine
$RhCl_3.3H_2O$	25	13	15
$Ru(acac)_3$	137	-	-
$Rh(acac)_3$	5	-	-
$RuCl_3$	1	b	b

a - Ir, Fe, Co, Ni, Pd, Pt, Mn, V and Cr acetylacetonates failed to induce significant exchange
b - Not determined

Experimental

Materials

All the substrates used were either obtained from Fisons plc or purchased from the Aldrich Chemical Company. So also were the catalysts with the exception of the iridium, platinum and palladium acetylacetonates which were gifts from Johnson Matthey plc. Tritiated water (50 Ci ml^{-1}) was obtained from Amersham International plc.

Tritiation Procedure

The catalyst eg rhodium trichloride (0.125 mmoles, 30 mg) and substrate (0.25 mmoles) were dissolved in dimethylformamide (1 ml) and transferred to a 3 ml capacity thick-walled reaction tube. Tritiated water (3 microlitres) was added, the tube cooled in liquid nitrogen, evacuated and sealed. The reaction was then allowed to proceed for between 18-24 hours at 110°C in a thermostat. On completion the tube was cooled, opened and the substrate purified by solvent extraction using one or other of the following methods:-

(a) Purification of the acids

The contents of the reaction tube were poured into an aqueous hydrochloric acid solution (4M, 5 ml) and extracted into ethyl acetate (3 x 10 ml). The volume of ethyl acetate was reduced to about 20 ml by evaporation before it was washed with water (2 x 2 ml) and back extracted with aqueous potassium hydroxide solution (1M, 3 x 2 ml). The potassium hydroxide fraction was filtered through a glass wool plug in a Pasteur pipette, re-acidified with aqueous hydrochloric acid solution (4M) and extracted with ethyl acetate (3 x 10 ml). The ethyl acetate solution was washed once with water (2 ml), dried with anhydrous sodium sulphate, before being evaporated down to dryness by passing nitrogen over the surface of the solution.

The sample was further freeze dried to remove any remaining traces of water.

(b) Purification of the amides

The contents of the reaction tube were poured into ethyl acetate (20 ml) and the fraction successively washed with sodium bicarbonate solution (50 g l^{-1}, 2 ml), aqueous hydrochloric acid (1M, 2 ml) and finally water (2 ml). Each aqueous fraction was re-extracted with a further 10 ml of ethyl acetate, and the various fractions combined. This solution was then dried over anhydrous sodium sulphate, filtered and evaporated to dryness as in (a) to leave the purified amide.

(c) Purification of the amines

The contents of the reaction tube were poured into an aqueous potassium hydroxide solution (1M, 5 ml) and extracted with ethyl acetate (3 x 10 ml). After washing with water (2 x 2 ml), the amines were back extracted into aqueous hydrochloric acid solution (4M, 3 x 2 ml). The acid fraction was cooled in ice and made alkaline by the addition of potassium hydroxide pellets. The amine was then extracted into ethyl acetate (3 x 10 ml) after which the organic fraction was washed once with water (2 ml), dried over anhydrous sodium sulphate, filtered and the solvent removed by passing nitrogen over the surface of the solution. Where necessary the amine hydrochloride was prepared by passing a stream of hydrochloric acid gas into a methanolic solution of the amine. The methanol was removed by rotary evaporation and any residual moisture removed by freeze drying.

^{3}H-Nmr Analysis

The detailed procedure has been provided in a recent publication[9].

Acknowledgements

Thanks are due to both the SERC and Amersham International plc for a Collaborative Grant to purchase the Bruker AC 300 MHz instrument and to SERC for a CASE studentship (to DH). Mr J P Bloxsidge is thanked for the nmr spectra and Mrs L Carroll for technical assistance. We are grateful to Johnson Matthey plc for the gifts of catalysts.

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