THE DEUTERATION OF ACETANILIDES

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Summary

The base-catalysed exchange of a proton of the methyl groups in acetanilides can be used to incorporate deuterium into these amides. 4'-Hydroxy-2[^{2}H]acetanilide (acetaminophen, paracetamol) can be prepared by the demethylation with boron tribromide of 4'-methoxy-2[^{2}H]acetamide obtained by this base-catalysed exchange.

Key Words

[2-^{2}H]acetanilide, 4'-methoxy-[2-^{2}H]acetanilide, 4'-hydroxy-[2-^{2}H]acetanilide, base-catalysed exchange, 2,2,6,6-tetramethylpiperidine, [^{2}H]trifluoracetic acid

Introduction

The base-catalysed exchange of hydrogen atoms α- to a carbonyl group is a well established method for the introduction of deuterium into ketones and esters (1). This method can also be used for the isotopic labelling of carboxylic acids provided that a suitably strong base (e.g. butyl-lithium) is used for the removal of a proton α- to the carboxylate anion (2). As the protons α- to the carbonyl group in N,N-disubstituted carboxamides are less acidic than those in esters by about 4 pKa units in DMSO (3), the protons α- to the carbonyl group in N-monosubstituted amides should be more difficult to remove by base than the corresponding protons in carboxylic acids. However, the low cost of the isotopically-labelled starting material (^2H_2O or ^3H_2O) in such an exchange and the possibility of developing an experimentally simple method for the synthesis of the isotopically-labelled analgesic 4'-hydroxyacetanilide (acetaminophen, paracetamol) led us to explore this exchange reaction

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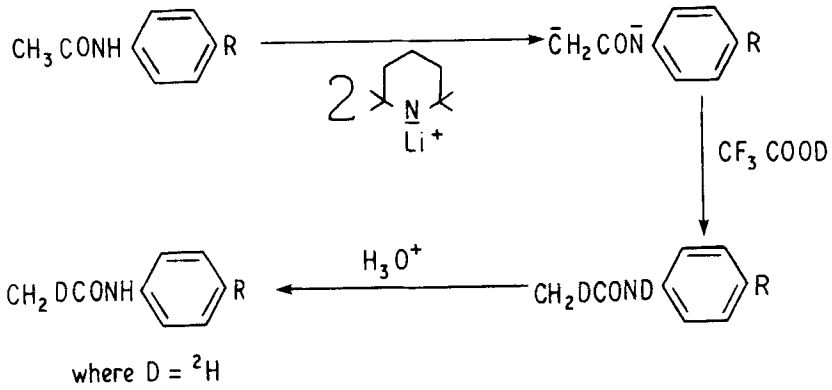
with aromatic amides. The base-catalysed deuterium exchange of the α-C-H protons in amides in $NaO^2H/^2H_2O$ at elevated temperatures has been reported (4) but this reaction has not been used preparatively. We now wish to report the ready proton exchange of the protons of the methyl groups of acetanilides at room temperature using the anion of 2,2,6,6-tetramethylpiperidine as base and [^{2}H]trifluoracetic acid as deuterium source.



Experimental

Preparation of 4-methoxy-[2-^{2}H]acetanilide - To a solution of 2,2,6,6-tetramethylpiperidine (3.5 ml, 20 mmole) in tetrahydrofuran (10 ml) at -78°C in a nitrogen atmosphere and with exclusion of moisture was added a solution of n-butyl-lithium in hexane (12.5 ml, 1.6 M, 20 mmole) dropwise with stirring. After 90 minutes, 4'-methoxyacetanilide (1.65 g, 10 mmole) in tetrahydrofuran (10 ml) was added and the mixture stirred for 1 hour at room temperature. Hexamethylphosphoramide (2 ml) followed by [^{2}H]trifluoracetic acid [prepared by adding ^2H_2O

(360 µl, 20 mmole) to trifluoracetic anhydride (1.39 ml, 20 mmole)] were added followed after 15 minutes by 1 M HCl (20 ml). The mixture was stirred overnight at room temperature and was then extracted with 40°/60° petroleum ether (3 x 25 ml). The petrol extracts were dried ($MgSO_4$) and evaporated *in vacuo* to leave deuterated 4'-methoxyacetanilide as a yellow oil. This was purified by chromatography on an alumina column. Elution with 60°/80° petroleum ether/diethyl ether (200 ml; 1/1; v/v) removed hexamethylphosphoramide and elution with diethyl ether gave 4'-methoxy-[2-^{2}H]acetanilide 620 mg (40%) m.p. 126-128° lit. (4'-methoxyacetanilide) 130°. The ^{1}H n.m.r. spectrum (220 MHz, $CDCl_3$) showed peaks at 2.10 (2 Hs), 3.75 (3Hs) and 6.75-7.40 (4Hm) confirming the location of the deuterium at the methyl group of the acetyl moiety. Comparison of peak areas showed that approximately one deuterium atom was incorporated per molecule. The e.i. mass spectrum had peaks at m/z 165 ($C_9{}^1H_{11}NO_2$) and 166 ($C_9{}^1H_{10}{}^2HNO_2$) and indicated a deuterium incorporation of 29%. Using the above method [2-^{2}H]acetanilide was prepared in 60% yield with a deuterium incorporation of 23%. The direct deuteration of 4'-hydroxyacetanilide could not be achieved by the above method.

Preparation of 4'-hydroxy-[2-^{2}H]acetanilide - To a solution of 4'-methoxy-[2-^{2}H]acetanilide (514 mg, 3 mmole) in dichloromethane (40 ml) was added a solution of boron tribromide (1.2 ml) in dichloromethane (15 ml). The reaction was stirred overnight at room temperature then water (45 ml) was added. The mixture was extracted with ethyl acetate (3 x 25 ml), the organic extracts were treated with an excess of solid K_2CO_3 and then an equal volume of dilute HCl was added. The ethyl acetate was separated and the aqueous phase extracted with a further portion of ethyl acetate (25 ml). The combined organic extracts were dried

($MgSO_4$) and evaporated *in vacuo* to leave deuterated 4'-hydroxy-acetanilide as an oil. This was purified by chromatography on alumina (elution with $CHCl_3/CH_3OH$, 9/1, v/v) to give 4'-hydroxy-[2-^{2}H]acetanilide, 121 mg (26 %) m.p. 172^o lit. (4'-hydroxy-acetanilide) 170^o. The ^{1}H n.m.r. spectrum (220 MHz, [^{2}H]$_6$-DMSO) showed peaks at 1.95 (2Hs) and 6.6-7.40 (4Hm) p.p.m. Comparison of the areas of the peaks showed that one hydrogen had been replaced in the acetyl group of 4'-hydroxyacetanilide. E.i. mass spectrometry confirmed that 27% deuterium was present indicating that virtually no loss of isotope had occurred during the demethylation.

Discussion

We have shown that the base-catalysed removal of protons from the methyl groups of acetanilides can occur despite the presence of an N-H group adjacent to the carbonyl group. Deuteration of the enolate ion so produced can be conveniently achieved using [^{2}H]trifluoracetic acid which can be readily prepared by the addition of ^2H_2O trifluoracetic anhydride. An additional advantage of this method is that isotopically labelled water is cheap and hence this is a low-cost synthesis compared with the preparation of 4'-hydroxy-[2-$^2H_3$] acetanilide from the amine and [$^2H_6$]acetic anhydride (6).

n-Butyl-lithium did not remove a proton from the acetyl group of acetanilide and reaction between the amide and the butyl carbanion appeared to occur. However, when a strong sterically-hindered base such as lithio 2,2,6,6-tetramethyl-piperidide (5) was used proton removal occurred unaccompanied by side reactions such as attack by the base on the amide. Our method can be used for the preparation of [2-^{3}H]acetanilide from ^3H_2O and trifluoracetic anhydride and hence this method should be of general use for the preparation of isotopically

labelled amides.

We have been unable to prepare 4'-hydroxy-[2-^{2}H]acetanilide by direct exchange. Presumably, the phenolic O-H and the amide N-H protons are ionised by lithio 2,2,6,6-tetramethylpiperidide making removal of a third proton from the acetyl group impossible under the reaction conditions employed. Demethylation of 4'-methoxy-[2-^{2}H]acetanilide by boron tribromide (7) occurred readily and 4'-hydroxy-[2-^{2}H]acetanilide was prepared by this route.

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