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NOTE

USE OF 2-DIMETHYLAMINOPYRIDINE IN TRITIUM AND DEUTERIUM EXCHANGE REACTIONS

Guvvala N. Reddy

Division of Radiopharmacy, Paul scherrer Institute, Switzerland,

Christopher J. Soares and Mark J. Kurth

Department of Chemistry, University of California, Davis, USA

and

Hank J. Segall
School of Veterinary Medicine, University of California, Davis, USA

Summary

Advantages of 2-dimethylaminopyridine as base in isotope exchange reactions that occur via enol formation are described for the preparation of deuterium and tritium labeled hexanal.

Key Words: 2-Dimethylaminopyridine, deuterium and tritium labelling, isotopic exchange, hexanal.

It has been reported that 4-hydroxyalkenals such as *trans* 4-hydroxy-2-hexenal, *trans* 4-hydroxy-2-nonenal are produced as metabolites following stimulated lipid peroxidation (1-5). 4-Hydroxyhexenal has also been detected as a metabolite of the pyrrolizidine alkaloid senecionine (5). These compounds are carcinostatic (6-9) and react with low molecular weight thiol compounds such as glutathione and cysteine (10,11). The biological effects that these compounds produce are thought to proceed via inactivation of functional sulfhydryl-containing compounds (6). In continuation of our studies with tritium labelled *trans* 4-hydroxyhexenal (12-14), we were interested in the preparation of tritium labelled hexanal which could then be elaborated to [5-^{3}H] *trans* 4-hydroxynonenal. Our synthesis of tritium-incorporated 4-hydroxyhexenal was carried out by the procedure of Erickson (15), starting with tritiated propanal. The preparation of [2-^{3}H] propanal was done following the procedure of D'Aniello and Barefield (16), by heating propanal,

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pyridine and a large amount of tritiated water in a sealed tube at 100° C for 4h and by distilling out the aldehyde-water azeotrope (47° C). However, the same procedure would not be applicable for the preparation of tritiated hexanal, as pyridine would co-distill with the hexanal-water azeotrope (hexanal, b.p. 131° C; pyridine 115° C). Our logical approach to an alternative method was to look for pyridine derivatives with a higher boiling range (> 135° C). Our immediate choice was to use either 2-dimethylaminopyridine (b.p. 191° C) or 4-dimethylaminopyridine (m.p. 108-110° C), the former being a liquid it was chosen. At this juncture, we had in mind the cost effectiveness of this method, as 2-dimethylaminopyridine and tritiated water were expensive reagents. This investigation shows the effectiveness of 2-dimethylaminopyridine at different mole percentage concentrations in incorporating the isotopic labelling.

Results and Discussion

As a model and to optimize the reaction conditions, the exchange reaction was carried out with hexanal and deuterium oxide (99%). The reaction conditions and the percentage of deuterium incorporation are given in the table below. The deuterium incorporation was estimated by the integration value of the two alpha protons as appeared in the ^1H NMR.

Table: Percentage incorporation of deuterium

Hexanal Concentration (5 mL, 0.042 mol); DMAP = 2-dimethylaminopyridine

DMAP(conc)	D_2O	Reaction Conditions	% Incorp.
1.2 eq.	1.2 eq	Reflux, 24 h	95%
10% mol eq.	1.2 eq	Reflux, 24h	58%
10% mol eq.	3.0 eq	Sealed tube, 105°, 4h	0%
10% mol eq.	2.0 eq.	Reflux, 48h	99%
30% mol eq.	1.2 eq.	Reflux, 62 h	99%
10% mol eq.	2.5 eq.	Sealed Tube, 135°, 24 h	130%

From the table of results it can be seen that the maximum incorporation was obtained when the reaction was carried out in a sealed tube at 135° C for 24 hours.

According to these conditions, hexanal (5.0 mL), 0.5 mL (0.01 mol) of 2-dimethylaminopyridine, 5.0 mL of tritiated water of 50 Curie total activity was heated in sealed tube at 135° C for 24 h. The reaction mixture was cooled to room temperature, and poured into dichloromethane. The reaction vessel was washed with dichloromethane and the washings were collected. The solution was dried over anhydrous $MgSO_4$, decanted into a round bottomed flask and distilled. The fraction boiling between 127°-131° C was collected. It exhibited an activity of 1.03 Curie / mL (125 mCi / mmol). The purity of the compound was established by radioTLC (silica gel plates) and Normal Phase HPLC (Waters analytical silica column). Tritium NMR also indicated single compound. The identity was further established by carrying through the compound into subsequent reactions.

To summarize the advantages of 2-dimethylaminopyridine: 1) only 10% mole equivalent is required; 2) large amounts of deuterium or tritium water are not necessary.

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