A ONE-POT TRITIATION OF ALDEHYDES AT THE FORMYL POSITION: A SIMPLE ROUTE FOR THE LABELLING OF ANTIBIOTICS

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(Received for publication March 6, 1979)

Thiamine pyrophosphate is an important cofactor catalyzing four types of enzymatic reactions where a keto acid is involved[1].

These reactions involve the same hydroxyalkyl pyrophosphate **1** which is in resonance with an ylid of formula **2**. The most important characteristics of the intermediate **2** is that the carbon atom of the potential aldehyde R-CHO is transitorily nucleophilic. When reacted with aldehydes, thiazolium salts **3** can allow for the formation of an intermediate ylid **4** by the same type of reactions.

These intermediates lead to a simple synthesis of acyloins and γ-diketones[2]. If introduced in a medium containing tritiated water, **5** must be obtained and subsequently cleaved into the starting thiazolium salt **3** and the tritiated aldehyde **5'**. This concept appeared as a simple means for the synthesis of tritiated aldehydes at formyl position. Recently, this approach has been used for the preparation of deuterated aromatic aldehydes[3]. We describe here our preliminary results concerning the tritiation of aliphatic aldehydes.

Three different compounds have been tritiated by this method: hydratropic aldehyde **6**, spiramycin **7** and ribose **8**. Table 1 shows the results of our experiments.

The yield of recovered aldehyde is generally low (10%) due to major side reactions (acyloin formation particularly). The exchange reaction occurs also with low yield. This means that the procedure is not suitable for the synthesis of deuterated aldehydes where high incorporation is needed. It appears however to be a suitable method for the "one-pot" synthesis of tritiated

Fig. 1. The structures of the adduct obtained by the addition of an aldehyde to thiamine pyrophosphate.

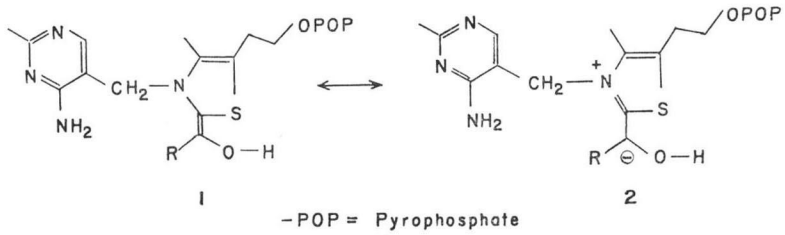

Fig. 2. The mechanism by which an aldehyde can be tritiated.

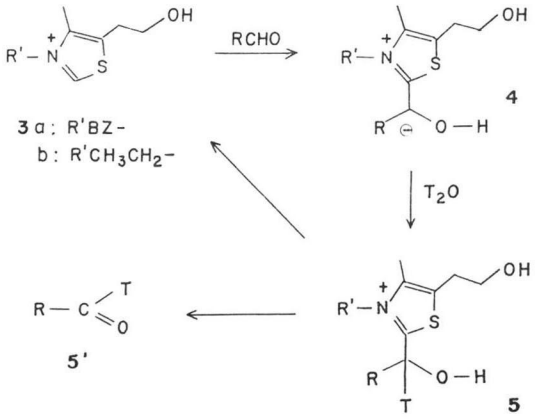

Fig. 3. The structure of the molecules which have been tritiated by our new method.

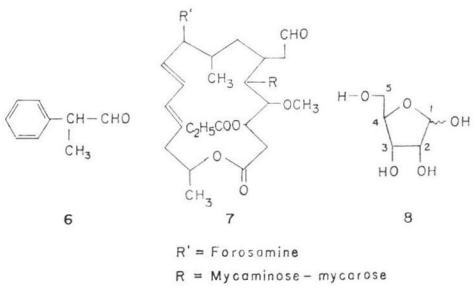

Table 1.

Substance used	Formula	% of recovered aldehyde	Specific radioactivity incorporated(*)
Hydratropic aldehyde	**6**	10	9.2 mCi/mole 2%
Spiramycin	**7**	10	13.7 mCi/mole 3%
Ribose	**8**	90	3.5 mCi/mole 0.8%

(*) In each experiment, 1 ml of tritiated water (specific radioactivity 0.90 Ci/mole) was used.

aldehydes which can be used for different purposes.

The specific radioactivity incorporated depends exclusively on the tritiated water used and on the nature of R: when this group is bulky, acyloin formation is not favored as compared to the exchange reaction and the recovery of the labelled aldehyde is acceptable. When the aldehyde is polyfunctional, a protection of the function not involved in the reaction is necessary. Spiramycin **7** can be protected by the labile trimethylsilyl group, whereas the alcoholic functions of ribose **8** have to be protected as 5-trityl 2,3-acetonide prior to tritiation.

The general experimental procedure we have used is the following:

A solution of the aldehyde ($5 \cdot 10^{-4}$ mole) in 1 ml of dimethylformamide with one equivalent of the thiazolium salt **3a** or **3b** are heated at 80°C. To this solution, are added 60 μl of triethylamine and after 3 minutes, one equivalent or more tritiated water (usually 1 ml). The solvent is then eliminated by distillation (in the case of spiramycin, 1 drop of trifluoroacetic acid is added to the mixture prior to distillation of the solvent) and the residue is purified by chromatography. The specific radioactivity incorporated into the sample is determined by liquid scintillation.

Other examples including the tritiation of streptomycin and rosamycin are under study in this laboratory.

Summary

When reacted with aldehydes, thiazolium salts catalyze the exchange of aliphatic formyl proton by tritium in tritiated water. This simple method is an efficient procedure for the one-pot synthesis of tritiated aldehydes, especially when they are bulky.

References

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