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Note

Base-catalyzed deuterium and tritium labelling of 1-biphenyl-4-ylpropane-1,2-dione and deuteration of aryl methyl ketones

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Summary

A synthesis and a base-catalyzed exchange reaction was developed under mild conditions to deuterate and subsequently tritiate the methyl group of the base sensitive diketone 1-biphenyl-4-ylpropane-l,2-dione depicted in Figure 1. Using Et_3N as base, deuterium incorporation of the methyl group was 88.9% and the tritium incorporation gave a specific radioactivity of 119 mCi/mmol. The scope of the exchanges was extended to methyl aryl ketones **2**−**4**. Copyright © 2004 John Wiley & Sons, Ltd.

Key Words: base-catalyzed exchange; tritium; labelled compounds; aryl methyl ketone; diketone

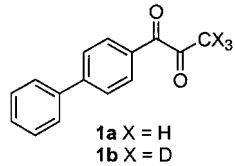

Figure 1. Structure of 1-Biphenyl-4-ylpropane-1,2-dione

Introduction

In the course of our medicinal chemistry efforts, we were seeking a fast and efficient method of labelling a methyl aryl diketone and several aryl methyl ketones with deuterium or tritium for use in enzyme and pharmacokinetic studies. Recently, we have completed a base-catalyzed exchange reaction

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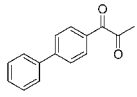
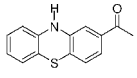
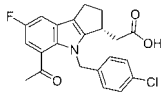
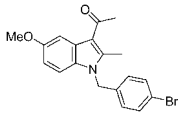
Table 1. Comparative deuterium exchanges on diketone and aryl methyl ketones using DBU and Et_3N as bases

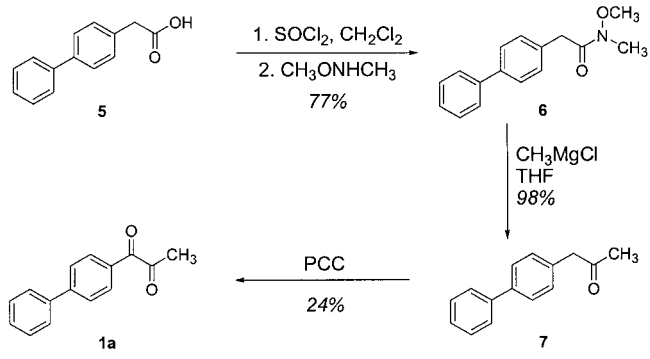
Compound	Substrate	Deuteration DBU	Deuteration Et_3N
1		Decomposition	1.2% d_0 3.9% d_1 21.5% d_2 73.3% d_3
2		0.6% d_0 0.0% d_1 4.0% d_2 95.4% d_3	0.4% d_0 2.4% d_1 21.9% d_2 75.3% d_3
3		1.5% d_0 6.1% d_1 17.7% d_2 74.7% d_3	0.5% d_0 10.1% d_1 24.9% d_2 64.5% d_3
4		0.0% d_0 0.4% d_1 0.0% d_2 99.6% d_3	71.6% d_0 20.8% d_1 6.9% d_2 0.7% d_3

method that we used to deuterate and tritiate aryl methyl sulfones and we decided here to extend the scope of this method to aryl methyl ketones. In this respect, we successfully used 1,8-diazabicyclo [5,4,0] undecen-7-ene (DBU) and triethylamine (Et_3N) as bases for the exchanges and the results are listed in Table 1. Although compounds **2**−**4** were not required tritiated for the studies, this methodology is readily applicable for tritiation with tritiated water (compounds **2**−**4** were obtained from our in-house sample collection). The deuterium incorporation for the methyl groups was calculated using mass spectrometry and the isotopic incorporation ranged from 88.5 to 99.7% with DBU as base and from 12.2 to 90.7% with Et_3N.

Results and discussion

α-Hydrogens of ketones are readily exchanged under basic conditions with the rates of exchange depending upon the base and on the medium employed.[1] DBU, which is a stronger base than triethylamine induced exchange more rapidly and very high conversion was obtained after 18 h for ketones **2**−**4**. The base sensitive diketone **1** decomposed upon treatment with DBU but a successful deuteration or tritiation using triethylamine as a milder base was achieved. In contrast, the exchange using triethylamine on the vinylogous ketone **4** provided only a low deuterium incorporation.

To study enzyme kinetics, **1** was required as either ^{14}C or ^{3}H labelled and having a specific activity preferably greater than 90 mCi/mmol. Direct tritium



Scheme 1. Synthesis of 1a

labelling was a much more attractive option than a radioactive total synthesis with carbon-14. Tritiated **1c** was obtained by direct exchange with a 50% yield after a straightforward chromatography and the specific activity obtained was 119 mCi/mmol. The synthesis of non-labelled compound **1a** is depicted in Scheme 1. Both the syntheses of **1a** and the intermediate l-biphenyl-4-ylacetone **7** were already reported but each by totally different pathways.[2] Scheme 1 had certain advantages useful for our own needs. A Grignard reaction on the Weinreb[3] amide **6** gave **7** in 98% yield. Compound **7** was subsequently oxidized with pyridinium chlorochromate to the diketone **1a** in 24% yield using a method developed by Bonadies and Bonini.[4] Exchanges were then carried out as described in the Experimental Section using the typical procedure for deuterium or tritium exchanges.

Experimental

Deuterium incorporation was calculated based on the intensities of protonated molecules and their isotopic peaks using a linear matrix program on a Micromass Quattro LC (electrospray mode) coupled with a Waters 2790 HPLC. Radioactivity measurements were perfonned on a Beckmann Coulter LS6000SC liquid scintillation counter using Ultima Gold XR (Packard Bioscience #6013119).

Typical procedure for deuterium or tritium exchanges

To a solution of the substrate (20 mg) in THF (500 µl) containing DBU (5 µl) or Et_3N (10 µl) was added deuterium oxide (200 µl, 99.9 at% D) or tritiated water (200 µl, 80 mCi/mmol). The mixture was stirred in a closed vial at room temperature for 18 h. To the mixture was added ethyl acetate (2 ml) and 1 N HC1 (1 ml) containing saturated brine (3 drops). The mixture was stirred for 30 s and most of the top layer removed and transferred to a new vial. The bottom layer was re-extracted with ethyl acetate (1 ml) twice and the combined

extracts washed twice with dilute brine (1 ml). The combined organics were dried (Na_2SO_4) and the solutions pipetted off from the salts. The clear solutions were concentrated and pumped on to obtain exact weights. Typical yields of the deuterated products were between 16 and 19 mg and the detailed exchange results are listed in Table 1.

Conclusion

In summary, we have developed an efficient synthesis of labelled l-biphenyl-4-ylpropane-l,2-dione **1** by using deuterated or tritiated water and triethylamine in a base-catalyzed exchange reaction. The method was extended to deuterate aryl methyl ketones with DBU or Et_3N as bases and is applicable to tritiation. Depending upon requirements, advanced substrates such as compounds **2**−**4** can be labelled rapidly in good yield.

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