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

SPECIFIC DEUTERATION OF PHENOLS AND AROMATIC ETHERS USING BORON TRIFLUORIDE AND DEUTERIUM OXIDE

Ali R. Banijamali, Avgui Charalambous, Cornelis J. Van der Schyf□ and Alexandros Makriyannis *

**Section of Medicinal Chemistry & Pharmacognosy, School of Pharmacy and Institute of Materials Science
The University of Connecticut, Storrs, CT 06268**

SUMMARY

A number of phenols and aromatic ethers were deuterated in positions ortho and para to the phenolic groups using BF_3 etherate followed by quenching with Na_2CO_3 in D_2O. This method involves mild reaction conditions and should have wide applicability in the isotopic labeling of these compounds.

KEYWORDS: Deuterium labeled phenols, aromatic ethers, Boron trifluoride.

INTRODUCTION

An increasing number of publications involving *in vitro* and *in vivo* biochemical experiments make use of labeled phenols and illustrate a demand for the facile synthesis of such compounds (1). Phenols can generally be labeled through the reductive dehalogenation of the corresponding halo analogs using deuterium or tritium gas (2). This method is reliable and gives specifically labeled products (3). On the other hand, it may be tedious, requiring multistep sequences and cannot be used for compounds with groups susceptible to hydrogenation such as olefins, acetylenes or benzyl ethers (4).

An easier approach for the isotopic labeling of phenols is through the use of hydrogen exchange reactions. Such methods include hydrogen exchange in the presence of Raney nickel (5-7) as well

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□On sabbatical leave from the Dept. of Pharmaceutical Chemistry, Potchefstroom University for C.H.E., Potchefstroom 2520, R.S.A.

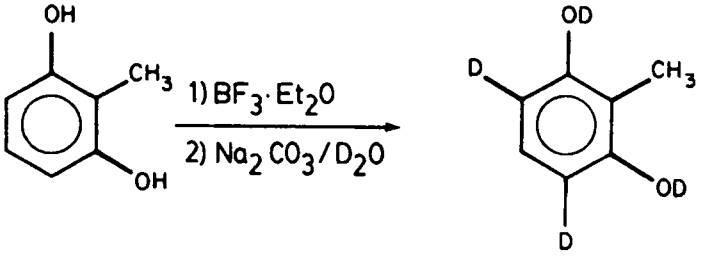
0362-4803/87/121479-04$05.00

Received March 31, 1987
Revised April 16, 1987

as acid catalyzed exchange with trifluoroacetic (8) or phosphoric acid (9). However, these procedures often suffer from lack of specificity in the labeling. Also, acid catalyzed reactions generally require heating and cannot be used with acid labile compounds. A phosphoric acid-boron trifluoride reagent (10), was found to be useful for labeling heat sensitive compounds at room temperature but also lacks specificity and cannot be used with acid labile compounds.

METHOD, RESULTS AND DISCUSSION

We would like to report here on a simple and highly effective method for the deuteration of phenols and phenyl ethers which makes use of boron trifluoride etherate followed by quenching with a solution of sodium bicarbonate in D_2O.



The reaction can be carried out in a variety of chlorinated hydrocarbons or aliphatic ethers, the choice of solvent being dictated by the reaction temperature and the solubility of the substrate.

The Table below illustrates the scope of this reaction with substituted phenols and phenyl ethers. As can be seen, deuteration occurs in relatively high yields and exclusively in positions ortho and para to the phenolic group. Ortho positions are generally favored over the para. Deuteration can be enhanced in all the positions to nearly quantitative yields by repeating the reaction. The reaction appears to require an electron rich aromatic ring since electron withdrawing substituents on the ring as in ortho- and para-hydroxyacetophenone, inhibit deuteration. Monophenols and 1,4 diphenols deuterate slowly at room temperature but the rate of deuteration can be increased if desired by refluxing the BF_3 etherate reaction mixtures. On the other hand, the more activated 1,3 diphenols

react with BF_3 etherate at much lower temperatures. This is especially useful for labeling labile phenols.

Hydrogen-Deuterium Exchange in Phenols using $BF_3 \cdot Et_2O/D_2O$

Compound	Solvent[1]	Time[2] (min)	% ^2H[3] at ring position number				
			2	3	4	5	6
1-OH,4-CH_3	CH_2Cl_2	30	70	0	--	0	70
1-OH,4-C_2H_5	i-Pr_2O	30	70	0	--	0	70
1-OH,3-CH_3	i-Pr_2O	30	65	--	65	0	90
1,2-OH,4-CH_3	Et_2O	30	--	80	--	43	80
1,3-OH,2-CH_3	Et_2O	30	--	--	90	0	90
1,3-OH,5-C_5H_{11}	CH_2Cl_2	30	85	--	85	--	85
1,4-OH,2-CH_3	i-Pr_2O	30	--	65	--	65	65
1,2,3,-OCH_3,5-CH_3	i-Pr_2O	60	--	--	50	--	50
1,3-OCH_3	i-Pr_2O	60	75	--	75	0	75
1-OH,2-$COCH_3$	i-Pr_2O	120	--	0	0	0	0
1-OH,3-$COCH_3$	i-Pr_2O	120	0	--	0	0	0

[1] Reactions done in i-Pr_2O were performed at 69°C, all others at 25°C or lower.

[2] Time to obtain amount of deuteration shown.

[3] Percent deuteration was determined from the ^1H NMR spectra of the products, obtained on a 200 MHz IBM WP-200 SY spectrometer.

All deuteration reactions represented in the Table above were performed according to the following general procedure. To a solution of 200 mg of a phenol in 10 ml of a dry solvent, 2 ml of $BF_3.Et_2O$ was added under nitrogen. The mixture was stirred at the temperatures and for the amount of time shown and then quenched using 3 ml of a 10% Na_2CO_3/D_2O solution and stirring was continued for 30 min. The organic layer was separated, washed with D_2O (2x2 ml) and dried over anhydrous Na_2SO_4. The solution was filtered and the solvent evaporated. The residue was purified by crystallization or chromatography.

Dedeuteration could similarly be accomplished by performing the same procedure on a deuterated substrate and quenching with H_2O to obtain quantitative isotopic hydrogen exchange.

The usefulness of this reaction with acid labile phenols is illustrated in our recently reported deuteration of acid labile tetrahydrocannabinoids in the phenolic ring (11). Reactions such as these could be carried out at temperatures of -30°C.

The reaction of $BF_3.Et_2O$ with phenols appears to result in boron trifluoride : phenol addition products which upon quenching with D_2O decompose to the deuterated phenol. The evidence for such a BF_3 : phenol covalent interaction comes from the proton NMR experiments where we observe the disappearance of the aromatic protons in the phenol spectrum upon addition of $BF_3.Et_2O$.

ACKNOWLEDGEMENTS

This research was supported by the National Institute on Drug Abuse (DA-3801) and the University of Connecticut Research Foundation (UCRF-35491). One of us (CJVdS) thanks the Foundation for Research Development, CSIR, Pretoria, for a sabbatical grant and Noristan Limited for support.

REFERENCES

1. N. A. Matwiyoff and T. E. Walker in: Stable Isotopes in the Life Sciences. Proceedings of a Technical Committee Meeting on Modern Trends in the Biological Applications of Stable Isotopes. International Atomic Energy Agency, Vienna 1977, pp 247-272.
2. M. Tashiro, A. Iwasaki, and G. Fukata, J. Org. Chem. 43, 196 (1978).
3. T. Pedersen and N. W. Larsen, J. Label. Compounds, 5, 195 (1969).
4. R. L. Burwell, Jr., and T. Nakajima, J. Catal., 13, 404 (1969).
5. P. M. Pojer, Tetrahedron Letters, 25, 2507 (1984).
6. M. Tashiro, K. Nakayama and G. Fukata, J. Chem. Soc. Perkin Trans. I, 2315 (1983).
7. A. C. Finlayson, R. K. M. R. Kallury and R. H. Prager, Aust. J. Chem., 32, 189 (1979).
8. M. L. Timmons, C. G. Pitt and M. E. Wall, Tetrahedron Letters, 3129 (1969).
9. J. L. G. Nilsson, I. M. Nilsson and S. Agurell, Acta Chem. Scand., 23, 2209 (1969).
10. E. A. Evans, "Tritium and its compounds" 2nd Ed., Wiley, New York (1974).
11. A. R. Banijamali, N. Abou-Taleb, C. J. Van der Schyf, A. Charalambous and A. Makriyannis. J. Label. Comp. Radiopharm. (Submitted).