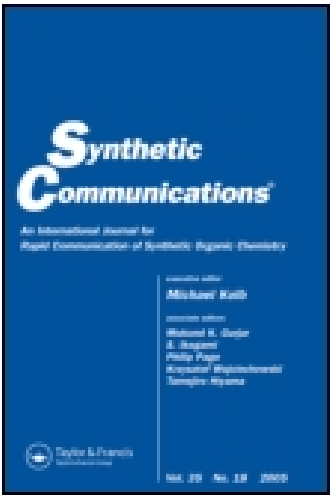

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Synthesis of [^{3}H] Dapsone

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ABSTRACT

An efficient synthesis of [^{3}H] dapsone at high specific activity is described.

Key Words: Dapsone; Tritium; Tritium NMR; Bromination; Dehalogenation.

4,4′-Sulfonylbisbenzeneamine (dapsone **1**) is a truly intriguing compound, possessing both valuable industrial polymer[1] and pharmaceutical applications. With regard to the latter, **1** has been successfully employed for leprosy[2] and is also the treatment of choice for dermatitis herpetiformis. Recently, it has been broadly prescribed in the treatment of *Pneumocystis carinii* in AIDS patients.[3] We were required to label **1** with tritium and now report a useful method.

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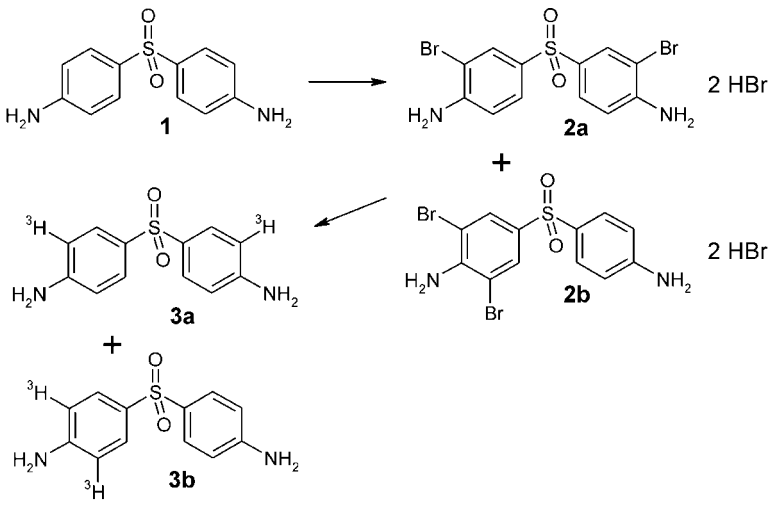
Although no report of the bromination of **1** was found in the literature, the mild preparation of dibromo analogues **2** was straightforward for us, as seen in Scheme 1. Product **2** appeared to be a mixture of bromine isomers substituted in large part *ortho* to the amines and also contained some tri- and tetrabromo analogues. These were anticipated not to interfere in the subsequent tritiation and even elevate product specific activity. Precursor mixture **2** was used without further purification and was smoothly converted to [^{3}H] dapsone **3** at high specific activity by catalytic tritium dehalogenation followed by high-performance liquid chromatography (HPLC) purification. Product **3** was found to be radiochemically homogeneous by HPLC and afforded the proton decoupled tritium nuclear magnetic resonance (NMR) as seen in Fig. 1, documenting the exclusive tritium incorporation into the phenyl positions *ortho* to the amines.

EXPERIMENTAL

General

Evaporations were carried out on a Buchi evaporator at bath temperatures less than 40°C. Analytical thin-layer chromatography (TLC) was performed on Analtech 5 × 15 cm glass plates coated with silica gel and developed with chloroform:methanol : ammonium hydroxide (10:1:0.1). Autoradiography was performed at 0°C after spraying with 2,5-diphenyloxazole (PPO) and exposing the plates to x-ray film. The TLC plates were also scanned



Scheme 1. Synthesis of **3**.

(~3 min) for applied radioactivity (~10 μCi). Analytical HPLC was performed on a Waters instrument with peak detection done simultaneously by ultraviolet (UV) (280 nm- Waters 440 UV detector) and liquid scintillation flow monitor. NMR spectra were obtained on a Bruker 300 MHz instrument, and chemical shift values are expressed in parts per million downfield from tetramethylsilane (TMS). All chemicals used were reagent grade.

Bromodapsone Mixture 2

To a three-neck, 100 mL round-bottom flask was added **1** (300 mg, 1.2 mmol) and 40 mL of acetic acid, followed by the drop-wise addition of bromine (0.25 mL, 4.8 mmol) in 5 mL of acetic acid. After stirring overnight at ambient temperature, the resulting solid was filtered, washed with water, and vacuum dried to yield 507 mg (74% yield) of **2** (TLC, R_f 0.75), which proved to be mostly a mixture of dibromodapsone isomers **2a** and **2b** by mass spectral analysis (M + 1: m/e 407) and ^{1}H NMR (acetone-d_6): complex multiplet from 6.9–8.0 ppm.

[^{3}H] Dapsone 3

To a 5 mL round-bottom flask was added 15 mg (0.026 mmol) of **2** and 2 mL of THF with 0.05 mL of triethylamine and 15 mg of 10% Pd/C catalyst.

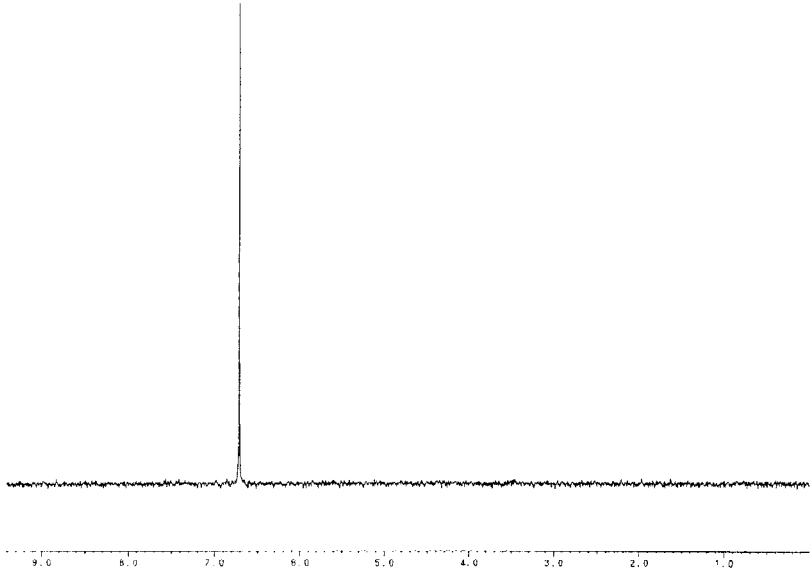


Figure 1. Proton decoupled tritium NMR (CD_2OD) of **3**.

The reaction was stirred at ambient temperature overnight with 60 Ci of tritium gas. After evacuation of the tritium gas, catalyst filtration and several vacuum evaporations of methanol, a radioassay revealed 2205 mCi of crude product. A portion (544 mCi) of this was purified by reverse-phase HPLC [10 mmol aqueous triethylammonium acetate (pH 4):acetonitrile (70 : 30)] to afford 119 mCi of **3** (an extrapolated 22% radiochemical yield based on precursor **2**), which was 97% radiochemically pure and cochromatographed with authentic **1** on HPLC (same system as above) and TLC. The specific activity of **3** was measured to be 81.9 Ci/mmol by UV (ethanol) assay (where $E_{296} = 29{,}399$ for **1**), and it provided the proton decoupled tritium NMR of Fig. 1.

REFERENCES

1. Kagathara, V.M.; Parsania, P.H. Thermal Analysis of Cured Chloro Epoxy Resins and Epoxy-Acrylate-Styrene Copolymers. Polymer Testing **2002**, *21*, 659–663.
2. Kataria, H.C.; Gupta, S.S. More Potential Drugs for Leprosy and Activity of Diaminodiphenyl Sulfones and Other Drugs and Dosages. Oriental Journal of Chemistry **1994**, *10*, 59–62.
3. Watson, J. Pneumocystis Carinii: Where Are We Now? Journal of HIV Therapy **2002**, *7*, 8–12.

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