Title

SYNTHESIS OF MONOTRITIOMETHYL IODIDE FROM THIOETHERS: HYDROGENOLYSIS IN THE PRESENCE OF THIOETHERS

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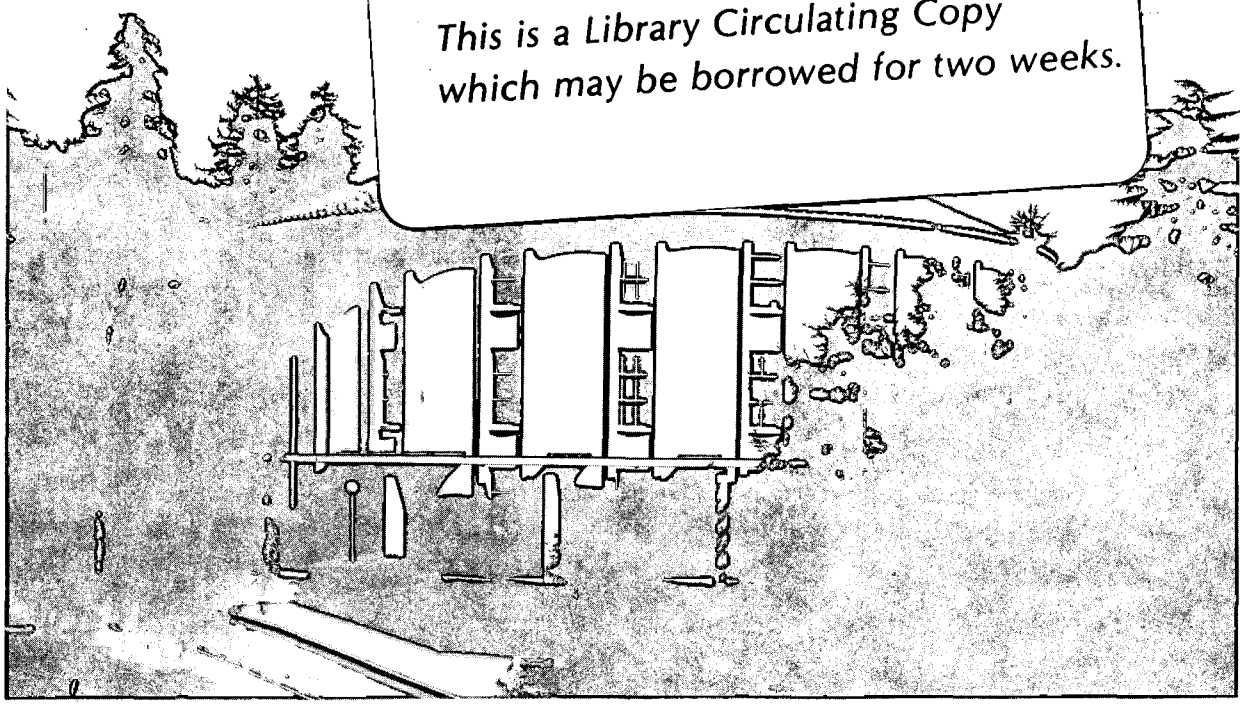

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DISCLAIMER

Synthesis of Monotritiomethyl Iodide from Thioethers. Hydrogenolysis in the Presence of Thioethers.

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Abstract

Tritiodehalogenation of chloromethyl phenyl sulfide with tritium gas over Pd/C in ethyl acetate gave the corresponding monotritiothioether with a specific activity of 28.5 Ci/mmole. Reaction of the [$^3H_1$]sulfide with benzyl iodide liberated monotritiomethyl iodide in one step in 92% yield through the intermediate formation of [$^3H_1$]methyl benzyl phenyl sulfonium iodide. The sulfonium salt readily thermally generates benzyl phenyl sulfide and [$^3H_1$]methyl iodide. Radio-HPLC analysis of the precursor showed complete radiochemical purity, and the specificity of the labeling was determined by tritium NMR spectroscopy. It is interesting and unexpected that such a hydrogenolysis proceeds with facility in the presence of thioethers.

Synthesis of Monotritiomethyl Iodide from Thioethers.
Hydrogenolysis in the Presence of Thioethers.

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Monotritiomethyl iodide with high specific activity is a valuable reagent for the incorporation of tritiated methyl group and has attracted much attention in recent years.[1] The reagent can be used for specific tritium labeling of amines, alcohols, thiols, and C-methylation of peptidic amino acid residues.[2,3] This reagent was previuosly prepared from bis-chloromethyl ether at nearly theoretical specific activity.[4] However, this technique has received limited applications because the precursor is known to be a powerful carcinogen and the resulting tritiated ether is highly volatile (bp -24.8 ^{o}C) and difficult to control under the reaction conditions.

We recently reported a new procedure for the synthesis of monotritiomethyl iodide by the preparation of chloromethyl esters, followed by tritiodehalogenation with carrier free tritium gas and subsequent cleavage of the [$^{3}H_{1}$]ester by lithium iodide.[5] Due to the time necessary for C-Cl bond hydrogenolysis in these esters (normally 12 hours), we observed significant isotopic dilution and the theoretical specific activity was not attainable. Also, in most cases, only 75-80% of the precursors' specific activity could be preserved in the N-methylated products. To overcome these deficiencies, we have continued our investigations and now report a more convenient and superior procedure.

Monotritiomethyl iodide can now be prepared from monotritiomethyl phenyl sulfide (**2**) as the precursor. When chloromethyl phenyl sulfide (**1**) was exposed to deuterium gas in the presence of Pd/C, we observed that hydrogenolysis of the C-Cl bond in this compound occurred within 3 hours at room temperature and gave a single product in 95% yield. The product was identified as monodeuteriomethyl phenyl sulfide (GC and deuterium NMR evidence). This result was surprizing because sulfides have long been known to poison the catalyst through the direct linkage of the heteroatom to the catalyst.[6] The hydrogenolysis of the precursor with carrier-free tritium gas and 10% Pd/C gave the desired product in 95% yield and with a specific activity of 20 Ci/mmole. The reaction was much faster with 30% Pd/C as the catalyst (less than one hour). In this case, at one atmosphere of carrier -free tritium gas, the rapid uptake of tritium was complete after one hour and the monotritiothioether was obtained with a specific activity of 28.5 Ci/mmole (theoretical

value, 29 Ci/mmole). The ^3H nmr spectrum of the precursor showed a singlet at 2.7 ppm for the CH2T attached to sulfur (Figure 1). In all cases, after the reaction was complete, the catalyst was filtered off and the filterate containing the tritiated sulfide was analysed by Radio-HPLC. The chromatograms showed tritiated thioanisole (**2**, R_t 4.6 min), isolated in 95% yield, as the only radioactive product.

For the generation of [$^3H_1$]methyl iodide, the filtrate was mixed with excess of benzyl iodide and heated for 48 hours at 150°C. The liberated monotritiomethyl iodide (**3**) was passed into N-methylaniline in DMF in the presence of anhydrous potassium carbonate and the product, [$^3H_1$]N,N-dimethylaniline (**5**),was isolated and analysed by radio-HPLC (specific activity 28.5 Ci/mmol). The ^3H nmr spectrum of the product showed a singlet at 3.0 ppm for the CH2T attached to the nitrogen (Figure 2). These results demonstrated that 100% of the precursor's specific activity can be preserved in the N-methylated product and that the faster the tritiodehalogenation, the less isotopic dilution occurred. Our preliminary work in a different investigation strongly suggests that adsorbed hydrogen on the catalyst as well as OH groups on the glassware are the major sources of dilution. When [$^2H_1$]methyl iodide was generated in the same procedure using D_2 gas and N-methylbenzylamine was used to capture the methyl iodide under the same conditions a much better yield (69%) of the N-methylated product, [$^2H_1$]N,N-dimethylbenzylamine (**6**), was obtained.

Cleavage of the sulfide (**2**) with benzyl iodide is a facile and convenient process. Through the intermediacy of the sulfonium salt, methyl iodide is liberated and the new sulfide, benzyl phenyl sulfide (**4**), is formed.

Experimental Section

Tritium gas was purchased from Oak Ridge National laboratory and contained 97.9% T_2,with the largest contaminant being DT(1.76%). Chloromethyl phenyl sulfide was purchased from Aldrich Chem. Co. and purified prior to use; EtOAc was distilled from P_2O_5 and Et_3N from BaO prior to use. Proton and triton NMR spectra were recorded on an IBM-AF-300 NMR spectrometer. HPLC analyses of the precursor and the N-methylated products were performed by using a water C-18 radial pak column with a mobile phase of $MeOH/H_2O/NH_4OH$ (50/50/1,3mL/min). Gas chromatographic analyses were performed on a Varian 3700 instrument using a carbowax 20M column. Tritiated samples were counted with a Packard 2002 liquid Scintillation counter.

Synthesis of Monotritiomethyl Phenyl Sulfide (2). a) Chloromethyl phenyl sulfide (**1**, 30μL,0.26mmol) and triethylamine (30μl,0.22mmol) were dissolved in purified, dried ethyl acetate (2 mL), Pd/C (10%, 66mg) was added, and the substrate was hydrogenolysed under one atmosphere of T_2 for 3 hours. Rapid uptake of tritium gas was complete after 2 hours,and the reaction was continued for an additional hour. The catalyst was filtered off and a portion of the filtrate was analysed by Radio-HPLC. The radiochromatogram showed a clean peak for [$^3H_1$]thioanisole: yield 28μL (95%); specific activity 20 Ci /mmole; ^3H nmr ($CDCl_3$); δ 2.6(s,T).

b) Chloromethyl phenyl sulfide (**1**, 30μL,0.26mmol) and triethylamine (30μl,0.22mmol) were dissolved in ethyl acetate (2mL), Pd/C (30%, 22mg) was added, and the substate was tritiated under one atmosphere of T_2 for 1 hour. Rapid uptake of tritium gas was complete after 40 min. The reactiom was discontinued at this stage,the catalyst was filtered off, and a portion of the filterate was analysed by Radio-HPLC.The radiochromatogram showed the corresponding peak for [$^3H_1$]thioanisole: yield 28μL (96%); specific activity 28.5 Ci /mmole; ^3H nmr ($CDCl_3$); δ 2.6 (s,T).

Synthesis of Monotritiomethyl Iodide (3) from [$^3H_1$]Thioanisole (2). a) [$^3H_1$]Thioanisole (**2**, 30 μL,0.26mmol) in ethyl acetate (2 mL) was mixed with benzyl iodide (300μL, 2.3mmol) and placed in the generation flask of a special apparatus. The system was kept at a pressure of 1/2 atmosphere. In the reaction flask was placed N-methylaniline (30μL, 0.27mmol), DMF (0.5mL) and anhydrous potassium carbonate (150mg). The generation flask was then heated at 150°C for 48 hours and the liberated tritiated methyl iodide passed over into the reaction flask where it reacted with the substrate. After this 48 hours, the solvent containing some methyl iodide was vacuum transferred into the reaction flask and the whole mixture was stirred overnight.

Analysis by Radio-HPLC and GC showed that the generation flask contained unreacted [$^{3}H_1$]thioanisole (**2**, 8%) and benzyl phenyl sulfide (**4**, 90%): mp 39°C (lit. [7] mp 41-43°C); ^{1}H NMR ($CDCl_3$) δ 4.1(s, 2H), 7.2-7.3 (m, 10H). Similarly, the reaction flask was shown to contain [$^{3}H_1$]N,N- dimethylaniline (**5**, 25%), sp. act. 28.5 Ci/mmole.

b) [$^{2}H_1$]Thioanisole (30 μL,0.26 mmole) was synthesized by the same procedure and used as the precursor. [$^{2}H_1$]Methyl iodide was generated and reacted with N-methylbenzylamine (40 μL, 0.31mmol) in DMF (0.5mL) and anhydrous potassium bicarbonate (150 mg). Gas chromatographic analysis of the reaction flask showed a single peak corresponding to [$^{2}H_1$]N,N-dimethylbenzylamine (**6**, 69%): ^{1}H NMR ($CDCl_3$); δ 2.3 (s, 5H), 3.5 (s, 2H), 7.4 (m, 5H); ^{2}H NMR ($CHCl_3$); δ 2.3 (s,1D).

Aknowledgement

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References

(1) Bloxsidge, J.P.; Elvidge, J.A.; Jones, J.R., Evans, E.A.; Kitcher, J.P.; Warell, D.C. *Org. Magn. Reson.* **1981**,*15*, 214.

(2) Bloxsidge, J.P.; Elvidge, J.A.; Gower, M.; Jones, J.R.; Evans, E.A.; Kitcher, J.P.; Warell, D.C. *J. Labelled Compound. Radiopharm.* **1981**,*18*, 1141.

(3) Johnstone , R.A.W.; Rose, M.E. *Tetrahedron* **1979**,*35*, 2169.

(4) Schwob, R. ; Wuersch, J. *J. Labelled Compound. Radiopharm.* **1978**,*14*, 355.

(5) Saljoughian, M., Morimoto, H., Dorsky, A.M., Rapoport, H., Andres, H., Tang,T.S. and Susan, A. *J. Labelled Compound. Radiopharm.* (In press).

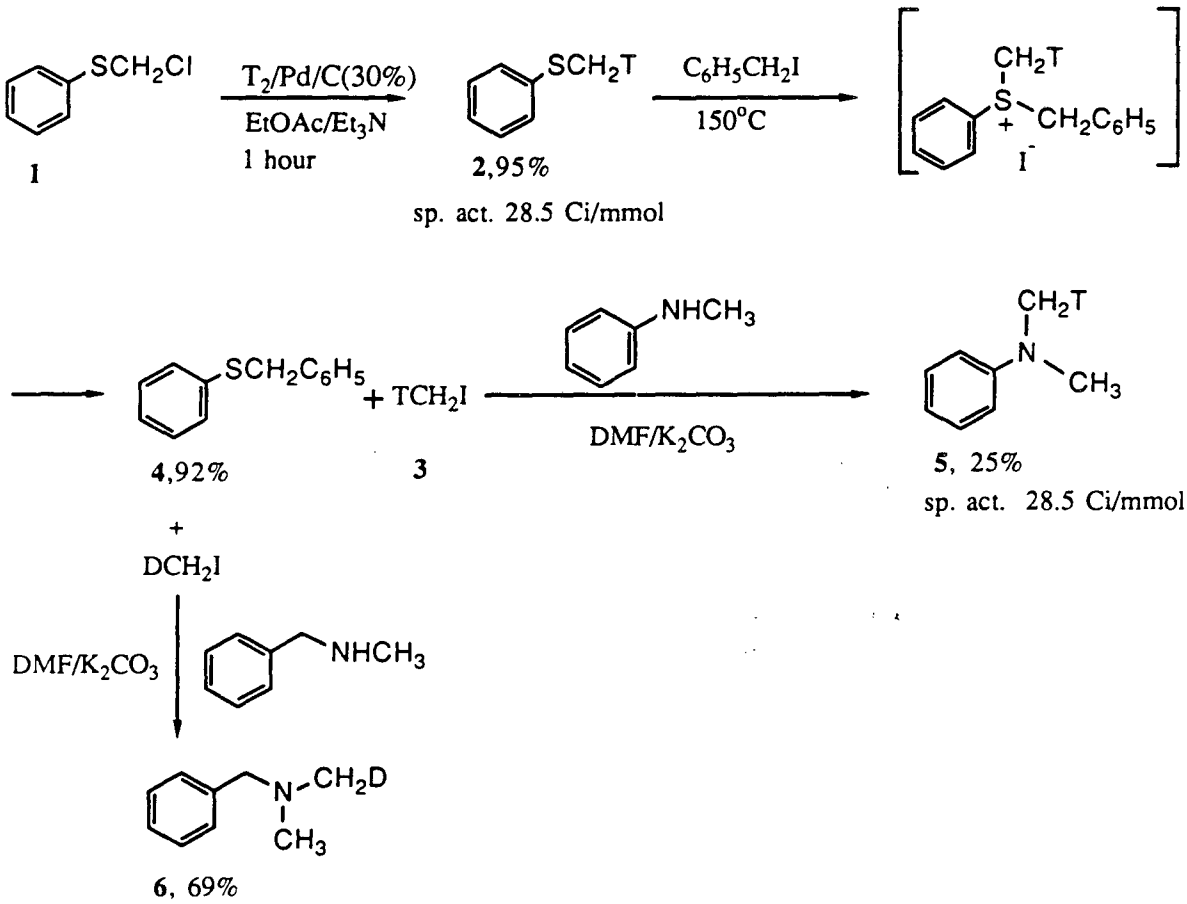
(6) Brown, W.G.; Calf, G.E. ; Garnett, J.L. *Chem. Comm.* **1967**,1066.

(7) Tuleen , D.L.; Marcum, V.C. *J. Org. Chem.* **1967**,*32*, 204.

Figure 1. NMR spectra of methyl phenyl sulfide (**2**) in $CDCl_3$: a., ^3H spectrum; b., ^1H spectrum.

Figure 2. NMR spectra of N,N-dimethlyaniline (**5**) in $CDCl_3$: a., ^3H spectrum; b., ^1H spectrum.

Scheme



1

2,95%

sp. act. 28.5 Ci/mmol

4,92%

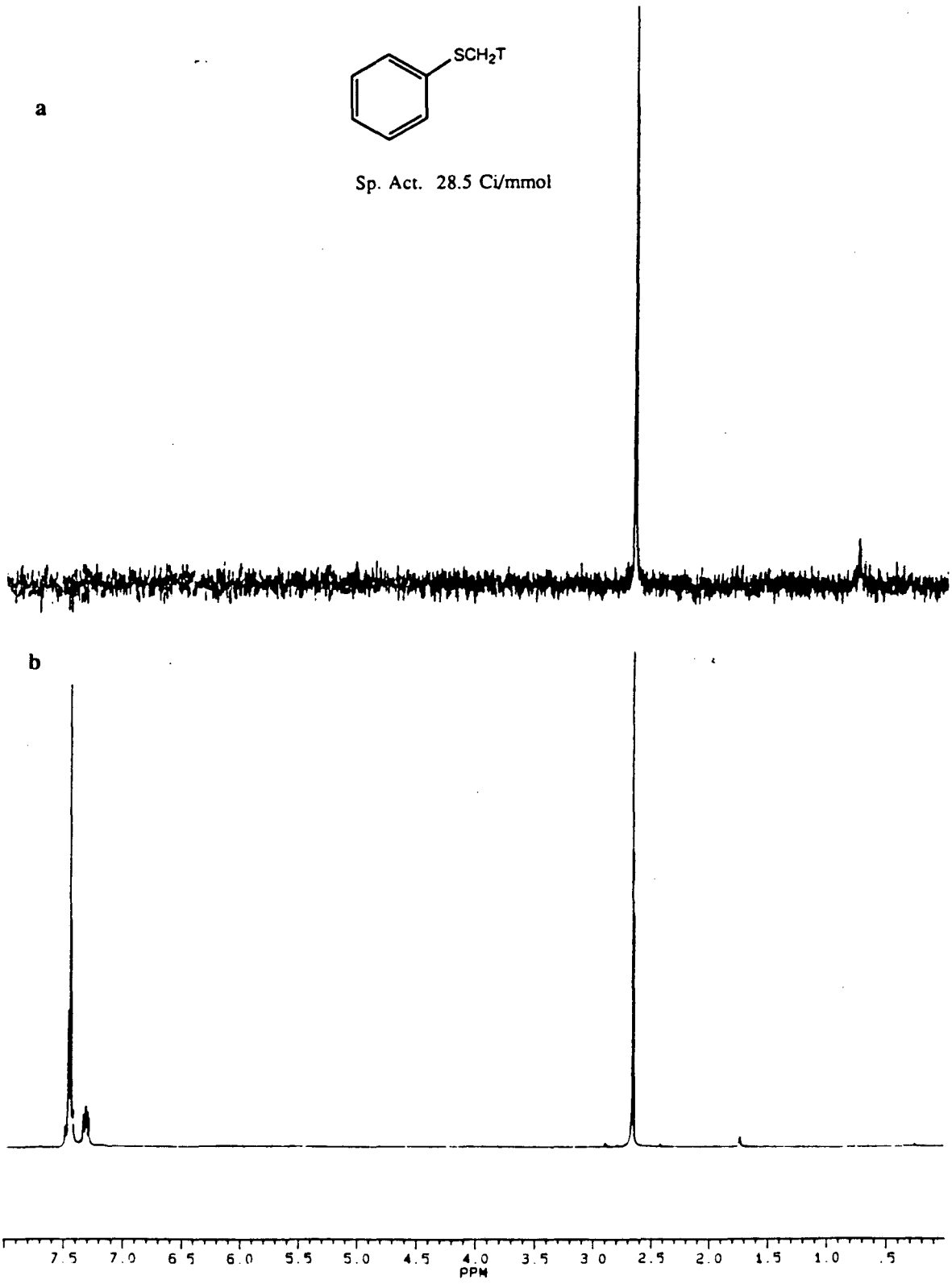
3

5, 25%

sp. act. 28.5 Ci/mmol

6, 69%

XBL 892-557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SCH2T
Sp. Act. 28.5 Ci/mmol
b
7.5
7.0
6.5
6.0
5.5
5.0
4.5
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1.5
1.0
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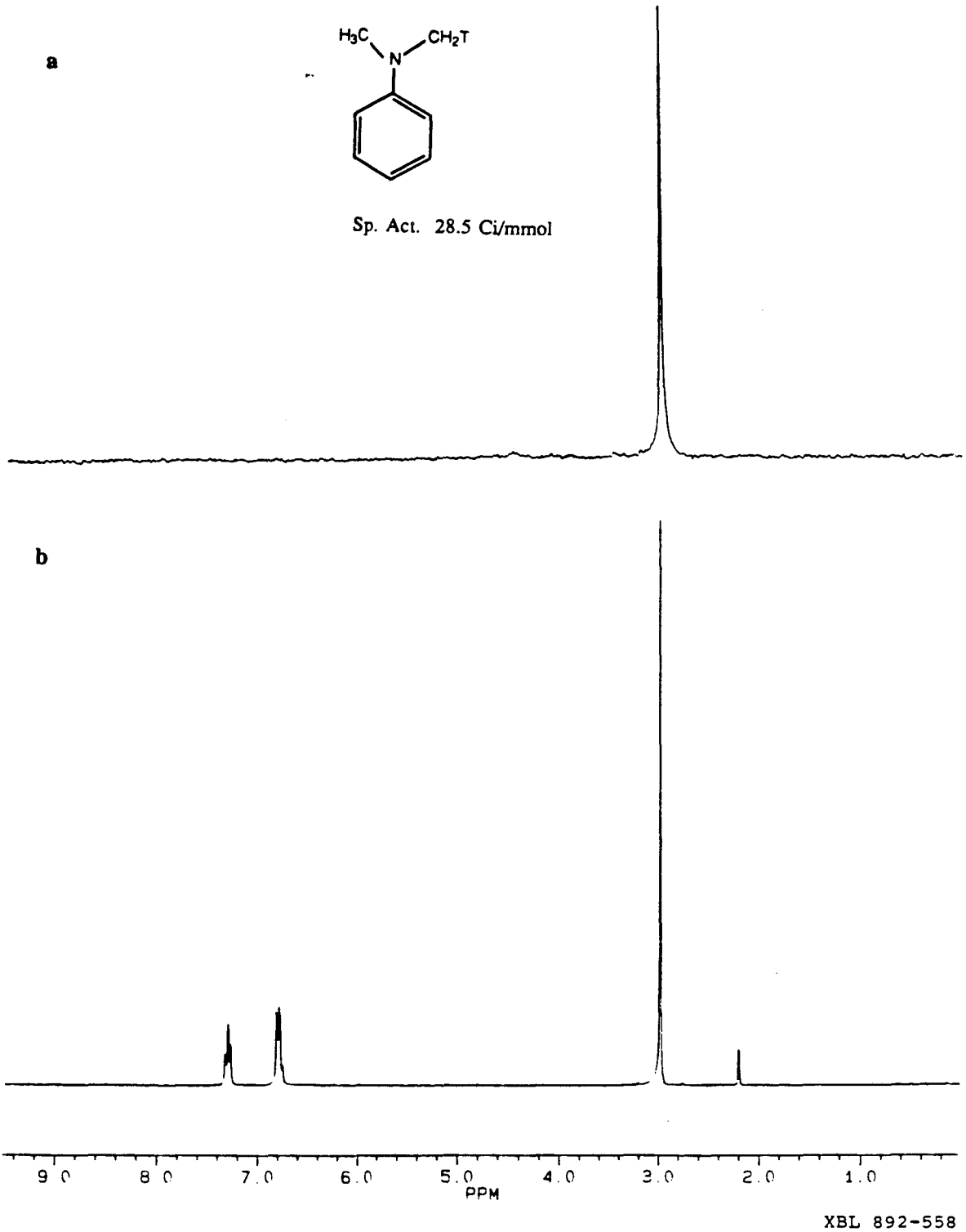
PPM

XBL 892-559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CH2T
Sp. Act. 28.5 Ci/mmol
b
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8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
PPM
XBL 892-558

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