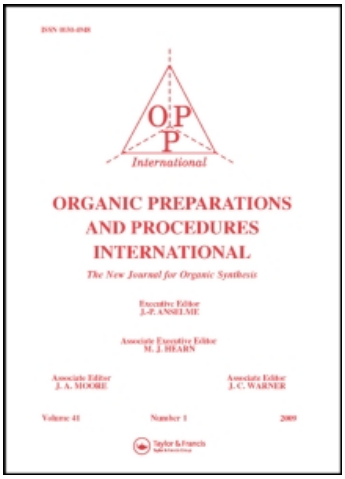

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AN EFFICIENT AND FACILE PREPARATION OF 2,2',4,4'-TETRABROMODIPHENYLAMINE

Xiaoxia Wang[a]; Cailan Wang[a]; Xiaoyang Wang[a]; Yulu Wang[a]
[a] Department of Chemistry, Henan Normal University, Henan, P. R, CHINA

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material, see A. Fujii, J. H. Bush, K. E. Shores, R. G. Johnson, R. J. Garascia, and E. S. Cook, *J. Pharm. Sci.*, **66**, 844 (1977). t-Butyl 4-bromobenzoate has also been used with N-vinylphthalimide, see J. E. Francis, R. L. Webb, G. R. Ghai, A. J. Hutchison and M. A. Moskal, *J. Med. Chem.*, **34**, 2570 (1991).

6. Reduction of **2** by electrolysis at a lead cathode has been reported, see K. H. Slotta and R. Kethur, *Chem. Ber.*, **71**, 59 (1938).

7. Methyl 4-formylbenzoate is commercially available at reasonable cost from Fluka ($0.44 per gram). Other suppliers are considerably more expensive. Alternatively, it may be prepared from 4-formylbenzoic acid, a by-product of terephthalic acid manufacture, by esterification with dimethyl sulfate.

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AN EFFICIENT AND FACILE PREPARATION OF 2,2',4,4'-TETRABROMODIPHENYLAMINE

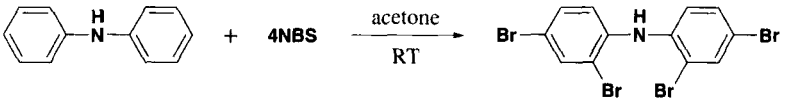
Submitted by (12/03/99) Xiaoxia Wang, Cailan Wang, Xiaoyang Wang and Yulu Wang*

Department of Chemistry
Henan Normal University, Xinxiang,
453002 Henan, P. R. CHINA

2,2',4,4'-Tetrabromodiphenylamine (**1**) and its N-alkyl derivatives (available by alkylation of 2,2',4,4'-tetrabromodiphenylamine) are important intermediates for the synthesis of phenazasiline compounds which possess excellent high-temperature stability coupled with antioxidant activity; these properties make them useful as antioxidants for high-temperature lubricants.[1] 2,2',4,4'-Tetrabromodiphenylamine and its N-alkyl derivatives themselves have also been used as fireproofing agents for plastics.[2]

Literature procedures for the preparation of **1** include bromination of diphenylamine with bromine in various solvents,[1, 3] with 1-bromo-2-methyl-2-imidazoline hydrobromide in EtOH (31% yield) and in CCl_4 (81% yield)[4] and with benzyltrimethylammonium tribromide in CH_2Cl_2-MeOH (90% yield).[5] Bromination with bromine, a highly toxic agent, can be undesirable for laboratory synthesis and industrial production. 1-Bromo-2-methyl-2-imidazoline hydrobromide is not readily available and benzyltrimethylammonium tribromide is tedious to prepare. Here we report a simple procedure for the preparation of **1** by bromination of diphenylamine with NBS in acetone.

In a typical experiment bromination of 0.169g (1 mmol) diphenylamine with 0.712g (4 mmol) NBS at room temperature gave **1** in 97% yield. However, a larger-scale preparation can give bromoacetone as a by-product. Lowering the temperature under which the experiment is conducted is an effective way of avoiding such a side-reaction. By removing the mixed solvent of water and acetone, succinimide was recovered form the filtrate almost quantitatively.



1

EXPERIMENTAL SECTION

All reagents and solvents were obtained from commercial sources and used without further purification. Melting points were determined on a Kofler micromelting apparatus and were uncorrected. IR spectra were recorded on an SP3-300 spectrophotometer in KBr. ^{1}HNMR spectra were measured on a JEOL-Fx-90Q spectrometer using TMS as internal standard. Elemental (C, H and N) analyses were carried out on a Carlo-Erba 1102 elemental analyzer.

Procedure: To a solution of NBS (4.272g, 24mmol) in acetone (45mL) was added diphenylamine (1.014g, 6mmol) in three portions within 3 minutes at 5°. After the third portion was added, the color of the reaction mixture changed immediately from light yellow to blue-black and soon to pink with white needles precipitating out. Cold water (50 mL) was then added to the mixture to complete precipitation of the product. The white needles were collected, washed with water, and dried. Recrystallization from toluene gave 2.65g (91%) of **1**, mp. 188.5-189.5°, *lit.*[5] 188-189°. ^{1}H NMR ($CDCl_3$): δ 6.35 (s, 1H, NH), 7.0-7.4 (dd, 4H, ArH), 7.72 (s, 2H, ArH).

Anal. Calcd for $C_{12}H_7Br_4N$: C, 29.73; H, 1.45; N, 2.89. Found: C, 29.75; H, 1.41; N, 2.90

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AN EFFICIENT AND SCALABLE SYNTHESIS OF METHYL 3-HYDROXYMETHYLBENZOATE

Submitted by M. H. Chen, J. G. Davidson, J. T. Freisler, E. Iakovleva and J. Magano*

(05/01/00)

Parke-Davis Pharmaceutical Research Division, Warner-Lambert Company 2800 Plymouth Road, Ann Arbor, MI 48105, U.S.A.

The preparation of the large quantities (from a few to several hundred grams or even kilograms) of biologically active compounds required by the pharmaceutical industry for both animal and human testing still represents, in many cases, a formidable challenge for the synthetic organic chemist. The procedures employed for the synthesis of small amounts of compounds are not always scalable due to technical difficulties (size of equipment, toxicity of starting materials and intermediates, safety issues, etc) or the cost of chemicals. Therefore, the necessity for short, high-yielding routes at a reasonable cost and where the intermediates are easy to isolate and purify is of paramount importance for successfully synthesizing the target molecule.

In an important anti-HIV project currently underway in our laboratories related to the synthesis of antagonists for the CCR5 co-receptor, the need for large quantities of the important intermediate methyl 3-hydroxymethylbenzoate (**3**) arose. In addition, we were interested in a methodology that allowed a simple isolation and the avoidance of time-consuming purification processes such as chromatography. This reagent is not commercially available and, to our surprise, a thorough bibliographic search revealed that it has been hardly cited in the past and, in most cases, included in the patent literature.[1] The use of the conditions previously reported, applied to our case in order to obtain large quantities of this intermediate, led to either incomplete reactions or crude materials that required additional purification. Therefore, an improvement of the existing methodology was needed. The synthetic route followed to prepare methyl 3-hydroxymethylbenzoate (**3**) is given below: