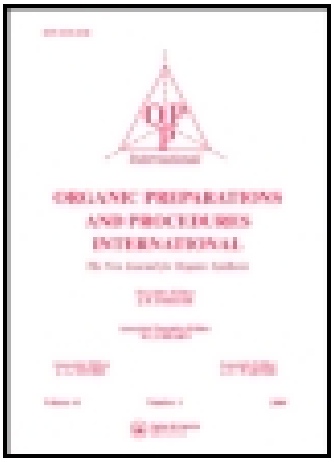

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AN EFFICIENT SYNTHESIS OF 3-BROMO-2-(BROMOMETHYL)-1-PROPENE

Theodore Axenrod [a], Kajal K. Das [a], Hamid Yazdekhasti [a], Paritosh R. Dave [b] & Alfred G. Stern [c]

[a] Department of Chemistry, The City College of the CUNY, New York, NY, 10031, USA

[b] Geo-Centers, Inc., at ARDEC, 762 Route 15 South Lake, Hopatcong, NJ, 07849, USA

[c] Energetic Materials Research and Technology Department, Naval Surface Warfare Center, Indian Head, MD, 20640, USA

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AN EFFICIENT SYNTHESIS OF 3-BROMO-2-(BROMOMETHYL)-1-PROPENE

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Theodore Axenrod*, Kajal K. Das and Hamid Yazdekhasti

Department of Chemistry, The City College of the CUNY
New York, NY 10031, USA

Paritosh R. Dave
Geo-Centers, Inc., at ARDEC, 762 Route 15 South
Lake Hopatcong, NJ 07849, USA

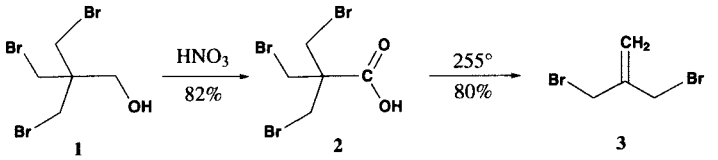
Alfred G. Stern
Energetic Materials Research and Technology Department
Naval Surface Warfare Center, Indian Head, MD 20640, USA

Allylic dihalides, such as 3-chloro-2-(chloromethyl)-1-propene, are key starting materials in the synthesis of azetidines,[1] 1,5-diazacyclooctanes and[1,2] higher cyclic oligomers[3] as well as other azaheterocyclic compounds which are of biological interest.[4,5] Cyclization of these bifunctional allylic halides with appropriate nucleophilic reagents also provides a straightforward and facile entry into other difficultly accessible heteroatom-containing bicyclic[5] and novel propellane[5,6] ring systems. In addition, when mediated by indium, these dihalides function as the valuable synthetic equivalent of the trimethylenemethane dianion, giving the corresponding 1,5-diols in their reactions with carbonyl compounds.[7]

Despite the importance of such simple allylic dihalides as synthetic intermediates, extensive use of these materials is impeded by their cost[8] and the relatively inefficient preparative procedures available for obtaining them. The best available route for the synthesis of 3-chloro-2-(chloromethyl)-1-propene proceeds from pentaerythritol[6,9,10] which is converted into a mixture of tri- and tetrachlorides by reaction with thionyl chloride in pyridine. Nitric acid oxidation of the crude mixture affords the *tris*(chloromethyl)acetic acid which after separation of the tetrachloride, is thermally decarboxylated to yield the product. Other methods that have been employed, each with particular disadvantages, include (i) chlorination of either methallyl chloride,[11,12] or (ii) methylenecyclopropane[13] and (iii) the reaction of 2-methylene-1,3-propanediol with thionyl chloride.[14] The corresponding diiodide has been prepared by treatment of 3-chloro-2-(chloromethyl)-1-propene with potassium iodide in acetone.[15]

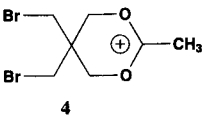
In like manner, the dibromide has been prepared by methods which also have unattractive features. For example, the 3-bromo-2-(bromomethyl)-1-propene **3** has been prepared by a number of routes including: (i) thermolysis of 9,10-ethano-9,10-dihydro-11,11-bis(bromomethyl)anthracene,[16] (ii) bromination of methylenecyclopropane,[13] (iii) reaction of 2-methylene-1,3-propanediol with phosphorus tribromide[14] and (iv) by halogen exchange in the reaction of 3-chloro-2-(chloromethyl)-1-propene with lithium bromide in acetone.[7] However, none of these procedures is conveniently adaptable to large-scale economical preparation of pure product. Thus, an improved synthetic method would be desirable.

This report details an efficient synthesis of 3-bromo-2-(bromomethyl)-1-propene **3** from pentaerythritol through the reaction steps, outlined in Scheme I. This strategy parallels the synthesis of



Scheme 1

the corresponding dichloride, but with the substantial advantage that the HBr / HOAc treatment of pentaerythritol in this procedure leads in good yield[17-19] to *tris*(bromomethyl)ethanol that is not contaminated with pentaerythrityl tetrabromide. This has been attributed[20] to the catalytic effect of the acetic acid which proceeds through an intermediate cyclic six-membered 1,3-dioxan-2-ylium cation **4**. This ion, unlike neopentyl alcohols which normally show very low S_N2 reactivity, apparently reacts readily with nucleophiles. Thus, the conversion of pentaerythritol to the *tris*(bromomethyl)ethanol **1** stage is promoted.[20] The latter compound is commercially available at a very reasonable price.[8]



4

Oxidation of *tris*(bromomethyl)ethanol **1** with hot nitric acid readily produces the *tris*(bromomethyl)acetic acid **2** in 82% yield. Thermal decarboxylation of the neat acid occurs smoothly at 255° and the pure 3-bromo-2-(bromomethyl)-1-propene **3** is obtained in 80% yield. The oxidation procedure has been carefully optimized and the conversions described here have been carried out with success on both large and small scales. Although no uncontrolled reactions have been encountered in our laboratories, the use of concentrated nitric acid in the oxidation step does lead to the evolution of toxic nitrogen oxides and appropriate precautions (well-ventilated hood, safety glasses, shields, heavy gloves) should be observed.

Thus, in contrast to the synthesis of the corresponding dichloride, this sequence leading to the dibromide is a superior protocol. The lowered yields arising from any tetrahalo by-product and the need to separate the latter from the *tris*(halomethyl)acetic acid before decarboxylation are conveniently avoided.

EXPERIMENTAL SECTION

^1H NMR spectra were measured at 300 MHz and ^{13}C NMR spectra were measured at 75 MHz on a Bruker AC300 spectrometer. Chemical shifts in $CDCl_3$ are reported in δ (ppm) relative to tetramethylsilane and were measured against the solvent as an internal standard. Melting points are uncorrected. Tris(bromomethyl)ethanol **1** was obtained from commercial sources[8] and used without further purification.

***tris*(Bromomethyl)acetic acid (2).**- Solid *tris*(bromomethyl)ethanol (**1**; 73.5 g, 0.23 mol) was added, in small portions during 2 hrs, to a stirred mixture of conc. nitric acid (sp. gr. 1.40; 210 mL) and

fuming nitric acid (sp. gr.1.52; 23 mL) maintained at 110°. The evolution of reddish-brown fumes of nitrogen dioxide became increasingly apparent after about one fifth (ca. 30 min) of the alcohol had been added and this was accompanied by a drop in the temperature of the reaction mixture to ~ 90°. After completion of the addition of the alcohol, stirring was continued at 80-90° for an additional 1.5 hrs and then, to avoid crystallization, the warm reaction mixture was poured into ice-water (500 mL). The resulting colorless solid was collected by filtration and washed with ice-water to yield 60.0 g (83%) of crude *tris*(bromomethyl)acetic acid **2**. After drying, NMR analysis indicated the crude material so obtained to be of excellent purity suitable for direct use in the subsequent decarboxylation step; mp. 98-100°, lit.[17] mp. 97-99°.^{1}H NMR ($CDCl_3$): δ 3.78 (s, 6H), 11.3 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 32.40, 53.22, 174.75.

3-Bromo-2-(bromomethyl)-1-propene (3).- A stirred melt of the crude neat *tris*(bromomethyl)acetic acid (**2**; 7.43 g, 0.022 mol) contained in a 50 mL round-bottomed flask fitted with a short path still head was gradually heated in a silicone oil bath until the temperature reached 255° where it was maintained. The stirred reaction mixture slowly darkened and eventually became black as gas evolution ensued and the product began to distill. 3-Bromo-2-(bromomethyl)-1-propene **3** (3.74 g, 80%), judged by NMR analysis to be of excellent purity,[13-15] was collected as a clear, colorless liquid, bp. 155°. ^{1}H NMR ($CDCl_3$): δ 4.13 (s, 4H), 5.33 (s, 2H); ^{13}C NMR ($CDCl_3$): δ 32.80, 119.17, 141.77.

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A CONCISE SYNTHESIS OF SYMMETRIC 1,3,5-C_3-TRISUBSTITUTED BENZENES

Submitted by M. W. Majchrzak*, J. N. Zobel, D. J. Obradovich and G. A. Peterson

Cambridge Chemical, Inc.
N115 W19392 Edison Drive
Germantown, WI 53022, USA

1,3,5-Trisubstituted benzenes represent an important class of compounds because of their unique symmetry, and their importance in the syntheses of cascade macromolecules.[1,2] They also have shown interesting pharmacological properties, such as anticoagulant and antiplatelet effects.[3] Their preparation has been based either upon 1,3,5-triacetylbenzene[3] or benzene-1,3,5-tricarboxylic acid,[4,5] but unfortunately, the syntheses of the three-carbon chain congeners required the application of laborious chain elongation procedures.[3-5]