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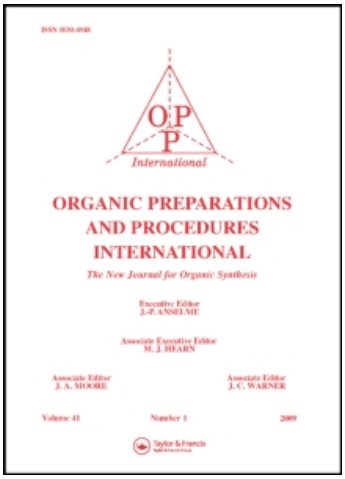

Organic Preparations and Procedures International
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

TRIMETHYLSILYL TRICHLOROACETATE AS A CHLOROFORM ALTERNATIVE FOR THE SYNTHESIS OF α-(TRICHOLOROMETHYL)-3-NITROBENZYL ALCOHOL

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To cite this Article Weissman, Steven A.(1995) 'TRIMETHYLSILYL TRICHLOROACETATE AS A CHLOROFORM ALTERNATIVE FOR THE SYNTHESIS OF α-(TRICHOLOROMETHYL)-3-NITROBENZYL ALCOHOL', Organic Preparations and Procedures International, 27: 5, 590 — 592
To link to this Article: DOI: 10.1080/00304949509458512
URL: http://dx.doi.org/10.1080/00304949509458512

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TRIMETHYLSILYL TRICHLOROACETATE AS A CHLOROFORM ALTERNATIVE FOR THE SYNTHESIS OF α-(TRICHOLOROMETHYL)-3-NITROBENZYL ALCOHOL

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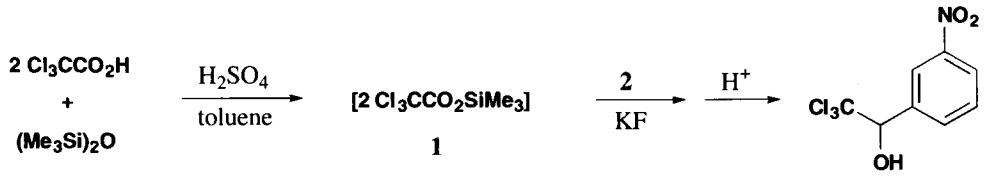
The desire to eliminate halogenated solvents and/or reagents such as chloroform, methylene chloride and carbon tetrachloride from the manufacture of pharmaceuticals has become an industry-wide goal, owing to the health and environmental concerns raised by their use.[1] We sought to develop a chloroform-free synthesis of α-(trichloromethyl)-3-nitrobenzyl alcohol (**3**), a precursor in the synthesis of clorsulon, a compound used in the treatment of liver flukes in animals.[2]



3

Traditionally, aromatic α-(trichloromethyl)carbinols are prepared by condensing the corresponding aldehyde or ketone with trichloromethide anion, generated by the action of base (such as KOH)[3] on chloroform (usually in >100% excess) or by the decomposition of trichloroacetic acid (or its sodium salt) in DMSO.[4] The presence of strong base in the former method often promotes the competing Cannizzaro reaction.[3] These methods have been employed for the synthesis of **3** in 98%[5] and 60% yield,[4a] respectively. Recently, trimethylsilyl trichloroacetate (**1**) (TMS-TCA), conveniently prepared *via* the sulfuric acid-catalyzed reaction between trichloroacetic acid and hexamethyldisiloxane[6] has been employed as an alternative trichloromethide synthon.[7] Herein, the utility of this reagent is described for the one-pot synthesis of **3** in excellent yield.

TMS-TCA (**1**) was generated and reacted with *m*-nitrobenzaldehyde (**2**) in the presence of a catalytic amount of potassium carbonate and 18-crown-6[7a] in the absence of solvent for 5 hrs at 70°.[8]

Completion of the reaction was monitored by cessation of CO_2 evolution. Acid-catalyzed cleavage of the intermediate TMS ether gave the desired alcohol in 78% yield (2% unreacted aldehyde remained). Application of the Larson methodology[7b] (KF catalysis in refluxing THF for 6 hrs), using distilled TMS-TCA, followed by an acidic workup provided **3** in 88% yield. The utility of this method was further improved by performing the TMS-TCA synthesis, the KF-catalyzed condensation with **2** and the TMS-ether hydrolysis *all in one-pot.* Thus, using 1.33 equiv. of **1** (formed *in situ*), the trichloro carbinol **3** was produced in 90% yield. This reaction required the use of 20-25 mole% of KF catalyst. The use of a reduced charge of the *in situ* generated TMS-TCA (1.15 equiv) gave an 84% yield of alcohol **3**, while 5% unreacted aldehyde was detected.

The application of TMS-TCA for the synthesis of **3** demonstrates: a) that it is a suitable chloroform replacement that minimizes the risk of competing side reactions; b) the ability to employ this reagent in a one-pot synthesis, eliminating the need for isolation and c) the compatibility of the reagent with aromatic nitro groups.

EXPERIMENTAL SECTION

Melting points were determined using a Buchi 510 apparatus and are uncorrected. NMR spectra were performed in $CDCl_3$ and recorded on a Varian Gemini 200, 200 MHz spectrometer using TMS as an internal standard.

α-(Trichloromethyl)-3-nitrobenzyl Alcohol (3).- Trichloroacetic acid (16.3 g; 100 mmol), hexamethyl disiloxane (42.5 mL; 200 mmol), sulfuric acid (1.1 g) and toluene (30 mL) were charged in a round bottom flask equipped with a Dean-Stark trap and mechanical stirrer (or magnetic stir bar). The reaction mixture was heated to reflux (111°) for 2 hrs during which time the theoretical amount of water (0.9 mL) was collected. The flask was then cooled to 40° and the volatiles were removed *in vacuo* (15-20 mmHg) over a 3 hr period to give a colorless residue. To the crude **1** was added THF (25 mL),[9] *m*-nitrobenzaldehyde (11.3 g; 75 mmol) and potassium fluoride (1 g; 17 mmol). The mixture was then heated to reflux for 1 hr, a second portion of KF (0.34g; 6 mmol) was added and the reflux continued for 5 hrs. The completion of the reaction was indicated by the change in the color of the reaction mixture from yellow to dark red. The flask was allowed to cool to 25° and 2N HCl in MeOH (25 mL) was added, followed by stirring for 3 hrs at 30°. The volatiles were evaporated *in vacuo* at 30° to provide 23.0 g of crude **3** as a caramel-colored syrup that contained 18.09 g of product (90% yield, based on LC assay vs reference standard material). Crystallization from 3:1 toluene-hexane gave 16.8 g of **3** as an tan solid (92.8% recovery), mp 89-91°, lit.[10] mp = 92°. ^{1}H NMR: δ 3.68 (d, 1H J = 1 Hz), 5.38 (d, 1H J = 1 Hz), 7.58 (apparent t, 1H J = 8 Hz), 7.98 (d, 1H J = 8 Hz), 8.27 (dd, 1H, J = 1 Hz, 8 Hz), 8.52 (apparent t, 1H J = 2 Hz). ^{13}C NMR: δ 148.14, 137.27, 135.93, 129.27, 124.88, 124.85, 102.65, 83.76.

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SYNTHESIS OF 1,3-DIMETHYLAZULENE

Submitted by (03/28/95) Nicholas M. Irvine and Marek Majewski*

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Azulene and substituted azulenes (e.g., **1**) continue to attract attention of researchers (both chemists and non-chemists alike) due to their unusual spectral, chemical and physiological properties.[1,2] Although a number of methods for preparing alkylazulenes exist, many of the older methods incorporate at least one very inefficient step.[1,3] Amongst the newer methods, the Ziegler-Hafner synthesis from cyclopentadiene[4] (annulation of a seven-membered ring) and the enamine method,[5] based on 3-substi-