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Note

An Improved Synthesis of Tetramethylammonium Azide

*Dirk Schweitzer**

Department of Chemistry, University of Washington, Seattle, WA 98195, USA

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An improved synthesis of tetramethylammonium azide, $N(Me)_4^+N_3^-$, is presented. It involves a neutralization of tetramethylammonium hydroxide with sulfuric acid, followed by a metathetical reaction with sodium azide in methanol. Tetramethylammonium azide is then separated from the less soluble Na_2SO_4 *via* filtration. This method provides a convenient access to tetramethylammonium azide. It is therefore more usable in a typical academic laboratory setting than previously reported syntheses.

Key words: synthesis, tetramethylammonium, azide.

INTRODUCTION

The binding of the inhibitor azide to small model compounds is investigated in the course of studies aimed at understanding the reactivity of the active site of the metalloenzyme nitrile hydratase.[1,2] In an earlier system, the PF_6^- salt of a pentacoordinated model compound was reacted with N(*n*-Butyl)$_4$N$_3$.[2] The azide-bound model compound was then separated from the byproduct N(*n*-Butyl)$_4$PF$_6$ *via* crystallization. In comparison to this study,[2] it was found that in the current system[1] it is not possible to separate the byproduct N(*n*-Butyl)$_4$PF$_6$ from the azide-bound model compound. Therefore, another counter cation in the azide source was needed. It should be less soluble than tetra-*n*-butylammonium in an organic solvent, such as MeCN or CH_2Cl_2, but more soluble than an alkali cation. It was reasoned that tetramethylammonium azide will be a good choice. A literature search

* (E-mail: dirk@u.washington.edu)

showed that $N(Me)_4N_3$ has been prepared by the reaction of $N(Me)_4I$ with AgN_3,[3,4] by the neutralization of $N(Me)_4OH$ with HN_3,[5–10] or by the reaction of $N(Me)_4F$ with $Si(Me)_3N_3$.[11] All of these reactions have major disadvantages. They either involve explosive reagents (AgN_3 and HN_3)[3–10] or corrosive HF is needed to synthesize one of the starting materials ($N(Me)_4F$).[12] Therefore, it was decided to develop an improved method to synthesize $N(Me)_4N_3$. Since many metalloenzymes are known to be inhibited by azide, it seems likely that there is interest to have an azide source that has different solubility properties than the commercially available NaN_3 and $N(n\text{-Butyl})_4N_3$(TCI).

EXPERIMENTAL

All reagents and solvents were bought from commercial suppliers and used as received. The ^1H NMR spectrum was recorded at room temperature on an AF300 spectrometer with residual protio solvent used as the reference signal. The chemical shift is reported relative to TMS. The IR spectrum was recorded on a Perkin-Elmer 1600 spectrometer. The elemental analysis was performed by Atlantic Microlab (Norcross, GA, USA).

Tetramethylammonium Azide

An aqueous solution of $N(Me)_4OH \cdot 5\ H_2O$ (8.1 g, 44.7 mmol) was neutralized with H_2SO_4 (6 mL of a 3.90 M solution, 23.4 mmol). Once the solution was slightly acidic (pH ~5), it was evaporated to dryness using an oil pump vacuum. The remaining paste was heated under vacuum to 60 °C for at least 24 h. Thereafter, the white solid was dissolved in MeOH (40 mL) and NaN_3 (5.8 g, 89 mmol) was added. The suspension was vigorously stirred for 1 h. Then, Et_2O (15 mL) was added. After the suspension was stirred for another 30 min, it was filtered through Celite on an M frit. The solution was evaporated to dryness. The remaining solid was redissolved in MeOH (50 mL). Diethylether (10 mL) was added and the solution was filtered. Next, the solution was evaporated to dryness. The last dissolving/filtering/evaporation to dryness sequence was then repeated. The remaining white, crystalline solid ($N(Me)_4N_3$) was dried under vacuum. Yield: 4.8 g (41.3 mmol, 92%); m.p. 254–256 °C (decomposition); IR (KBr pellet): $\nu_a(N_3^-)$ = 2042 cm^{-1}. ^1H NMR (MeOH) δ/ppm: 3.23 (s).

Anal. Calcd. for $C_4H_{12}N_4$: C 41.36, H 10.41, N 48.23%; found: C 41.20, H 10.40, N 48.39%.

A qualitative test using aqueous $BaCl_2$ showed that no SO_4^{2-} was present.

RESULTS AND DISCUSSION

The method of $N(Me)_4N_3$ preparation reported herein utilizes, in the first step, the neutralization of $N(Me)_4OH$ by a strong acid (H_2SO_4). Thereafter, a metathetical reaction is performed. In MeOH as the solvent, NaN_3

dissolves, while the less soluble Na_2SO_4 precipitates. It is filtered off, and the solvent is evaporated to obtain pure $N(Me)_4N_3$.

$$2\ N(Me)_4OH + H_2SO_4 \xrightarrow{H_2O} (N(Me)_4)_2SO_4 + 2\ H_2O$$

$$(N(Me)_4)_2SO_4 + 2\ NaN_3(s) \xrightarrow{MeOH} 2\ N(Me)_4N_3 + Na_2SO_4(s)$$

The initial preparation of $(NMe_4)_2SO_4$ is necessary. Because of it, the second reaction yields insoluble Na_2SO_4 which can easily be separated from the more soluble NMe_4N_3. In comparison, if NMe_4Cl would be reacted with NaN_3 then a mixture of NMe_4N_3 and NMe_4Cl would be in solution even after the addition of Et_2O to precipitate the alkali salt.

The present procedure provides a convenient access to pure $N(Me)_4N_3$. In comparison to previously reported methods, it does not involve explosive AgN_3 or HN_3,[3–10] and it does not require the usage of corrosive HF.[11,12] Thus, the present procedure is more suitable for a typical academic laboratory. Further, no inert atmosphere conditions are required.

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SAŽETAK

Poboljšana priprava tetrametilamonijeva azida

Dirk Schweitzer

Prikazana je poboljšana priprava tetrametilamonijeva azida, $N(Me)_4^+N_3^-$. Tetrametilamonijev hidroksid neutralizira se sumpornom kiselinom, nakon čega slijedi metatetska reakcija natrijeva azida u metanolu. Zatim se tetrametilamonijev azid odvaja filtracijom od manje topljivog natrijeva sulfata. Ta metoda osigurava jednostavnu pripravu tetrametilamonijeva azida te je stoga prikladnija za tipičnu akademsku laboratorijsku uporabu od ranije objavljenih sinteza.