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of Reliable Methods
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Working with Hazardous Chemicals

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September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

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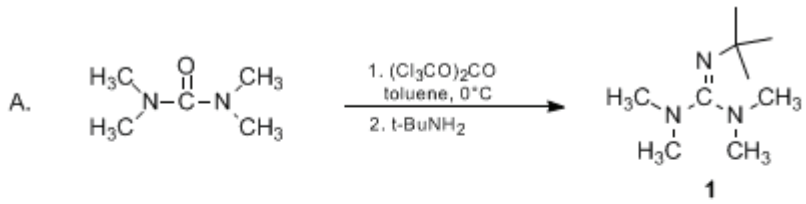
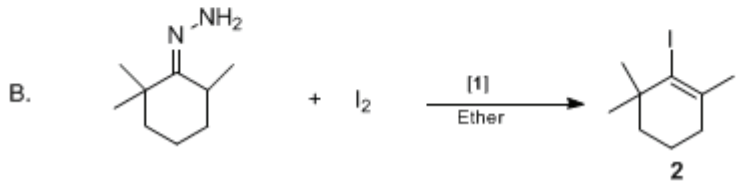
PREPARATION AND REACTIONS OF 2-tert-BUTYL-1,1,3,3-TETRAMETHYLGUANIDINE: 2,2,6-TRIMETHYLCYCLOHEXEN-1-YL IODIDE





Submitted by Derek H. R. Barton, Mi Chen, Joseph Cs. Jászberényi, and Dennis K. Taylor[1].
Checked by Richard A. Hartz and Amos B. Smith, III.

1. Procedure

CAUTION! These reactions, which involve toxic reagents, must be carried out (including workup) in an efficient fume hood.

A. *2-tert-Butyl-1,1,3,3-tetramethylguanidine* **(1)**. To an oven-dried, 500-mL, three-necked, round-bottomed flask, equipped with a nitrogen inlet with gas bubbler, magnetic stirring bar, thermometer, condenser, and a 250-mL dropping funnel, are added triphosgene (14.8 g, 0.05 mol) (Note 1), and anhydrous toluene (120 mL) (Note 2). The mixture is kept under argon and cooled to ≈10°C with the aid of an external ice bath. A solution of N,N,N',N'-tetramethylurea (18.0 mL, 0.15 mol) (Note 3) in dry toluene (50 mL) is slowly added to the mixture over 30 min (Note 4). After the addition is complete, the mixture is allowed to warm to ambient temperature, and stirring of the mixture is continued for an additional hour. During this time a white precipitate forms (Note 5). tert-Butylamine (47.3 mL, 0.45 mol) (Note 6) is slowly added to the mixture over 30 min (Note 7). After the addition is complete, the mixture is heated under reflux for 5 hr and then cooled to room temperature. Anhydrous ether (200 mL) (Note 8) is added and the white precipitate is quickly removed by filtration (Note 9). The precipitate is washed with a further quantity of anhydrous ether (300 mL) (Note 10) and immediately dissolved in aqueous 25% sodium hydroxide solution (100 mL). The mixture is then extracted with three portions of ether (300 mL). The combined organic layers are dried (potassium carbonate), filtered, and the solvent is removed under reduced pressure. The resulting colorless liquid is purified by distillation (bp 88–89° C/36 mm) to afford 18.7 g (73%) of 2-tert-butyl-1,1,3,3-tetramethylguanidine **1** (Note 11).

B. *2,2,6-Trimethylcyclohexen-1-yl iodide* **(2)**. To an oven-dried, 500-mL, three-necked, round-bottomed flask, equipped with a nitrogen inlet with gas bubbler, magnetic stirring bar, and a 250-mL dropping funnel, are added 2,2,6-trimethylcyclohexanone hydrazone (4.6 g, 0.03 mol) (Note 12), anhydrous ether (100 mL) (Note 8), and 2-tert-butyl-1,1,3,3-tetramethylguanidine **(1)** (46.25 g, 0.27 mol). The mixture is kept under argon at ambient temperature and an ethereal solution (100 mL) of iodine (15.25 g, 0.06 mol) is added to the mixture over 40 min with vigorous stirring. (Note 13). After the addition is complete, stirring is continued for an additional 30 min. The ether is removed under reduced pressure (Note 14) and the residue is heated at 90°C for 30 min (Note 15) under an inert

atmosphere. The reaction mixture is allowed to attain ambient temperature. Ether (100 mL) is added and the organic phase is washed twice with 2 N hydrochloric acid (30 mL), aqueous sodium thiosulfate solution (30 mL), aqueous sodium bicarbonate solution (30 mL) and saturated sodium chloride solution (30 mL). The organic phase is dried (sodium sulfate) and the solvent is removed under reduced pressure to afford crude iodide **(2)**. Purification of **2** can be achieved by flash chromatography (Note 16) affording pure iodide **(2)** (6.34 g, 85%) as a colorless oil. (Note 17).

2. Notes

1. Triphosgene was purchased from the Aldrich Chemical Company, Inc., and used as received.
2. Toluene is distilled from calcium hydride (CaH_2) under argon just prior to use.
3. N,N,N',N'-Tetramethylurea was purchased from the Aldrich Chemical Company, Inc., and purified by distillation prior to use.
4. Although no major temperature increase is observed, the reaction proceeds best with slow addition.
5. This salt is the corresponding Vilsmeier salt. See reference [2].
6. tert-Butylamine was purchased from the Aldrich Chemical Company, Inc., and dried prior to use by distillation from CaH_2 under argon.
7. No major temperature increase is observed.
8. Diethyl ether is distilled from sodium under argon just prior to use.
9. The white precipitate should be collected as quickly as possible to avoid hydrolysis to the starting urea. The precipitate turns pale yellow if hydrolysis is occurring. Additional ether (300 mL) may be needed to ensure complete transfer of the solids to the filtration apparatus.
10. The filtrate must be colorless, indicating that all impurities have been removed.
11. Distillation is not neccessary if the solids are washed correctly. Spectral data for **1** are as follows: IR (neat) cm^{-1}: 1620; ^1H NMR ($CDCl_3$) δ: 1.22 (s, 9 H), 2.67 (s, 12 H). **1** should be stored under argon in the refrigerator to prevent hydrolysis. The purity is estimated to be ≈95% by NMR and TLC analysis. The impurity is the starting urea and could not be avoided.
12. The hydrazone of 2,2,6-trimethylcyclohexanone is prepared according to a procedure outlined in reference [3]. To a solution of absolute ethanol (37 mL), hydrazine (26.0 g, 25.40 mL), and triethylamine (6.8 g, 9.43 mL) is added 2,2,6-trimethylcyclohexanone (6.3 g, 7.0 mL). The mixture is heated to 100°C for 2–3 days, cooled to ambient temperature, and the solvent removed under reduced pressure. Recrystallization of the residue from hexanes affords the hydrazone as white needles (4.85 g, 70%, mp 48–49°C). The spectra are as follows: ^1H NMR ($CDCl_3$) δ: 1.0–1.2 (m, 9 H), 1.40–1.92 (m, 6 H), 2.95 (m, 1 H), 4.51 (s, 2 H); ^{13}C NMR ($CDCl_3$) δ: 17.18, 17.39, 26.51, 28.92, 29.48, 31.68, 37.61, 40.43, 162.47.
13. Vigorous stirring is required as large quantities of precipitate form during the addition.
14. The nitrogen inlet is removed and replaced with a line to a water pump.
15. Heating causes most of the solids to liquify. The temperature refers to the outside oil bath temperature.
16. Flash chromatography was performed on standard Silica Gel 60Å, (230–400 mesh) with hexane, R_f = 0.75.
17. Spectral data for **2** are as follows: ^1H NMR ($CDCl_3$) δ: 1.09 (s, 6 H), 1.53–1.72 (m, 4 H), 1.87 (s, 3 H), 2.12 (t, 2 H); ^{13}C NMR ($CDCl_3$) d: 19.40, 31.08, 31.56, 33.69, 37.86, 39.51, 117.36, 137.70. Compound **2** deteriorates rapidly at ambient temperature, but is stable for several weeks if stored under argon in the refrigerator. The purity is estimated to be >98% by NMR and TLC analysis. No microanalytical data was obtained because of the instability of **2**.

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

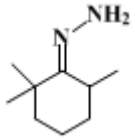
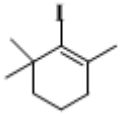
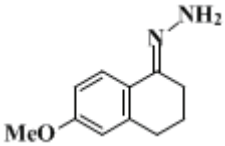
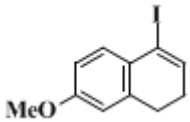
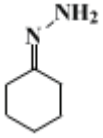
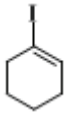
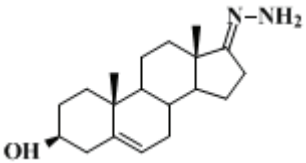
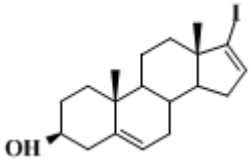
3. Discussion

The procedure described here allows the convenient preparation of large quantities of the strong, non-nucleophilic base 2-tert-butyl-1,1,3,3-tetramethyl-guanidine **(1)**. This reagent provides an inexpensive alternative to the amidine bases, 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) and 1,8-

diazabicyclo[5.4.0]undec-7-ene (DBU), which suffer from being easily alkylated.[4] Additionally, the hazards of using phosgene in the previous preparations of **1**[2,4,5] have been greatly reduced by employing triphosgene as a phosgene equivalent.[6]

The synthetic utility of this base **(1)** was demonstrated in the preparation of vinyl iodides in high yields from simple ketohydrazones and iodine (Table), a process that normally gives mixtures of vinyl iodides and geminal diiodides if less hindered bases are employed.[5] This base has also been used in the elimination of sulfonic acids from the corresponding sulfonates, the alkylation of compounds containing active methylene groups, the conversion of hydrazones to vinyl selenides, and the preparation of esters from sterically hindered acids.[4,5]

TABLE
PREPARATION OF VINYL IODIDES FROM HYDRAZONES

Entry	Hydrazone	Vinyl Iodide	% Yield
1			73
2			70
3			91
4			95

Other inexpensive, sterically hindered guanidine bases have also been synthesized and their reactivity is comparable to that described here.[2,4]

References and Notes

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Appendix
Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

hydrazone of 2,2,6-trimethylcyclohexanone

ethanol (64-17-5)

potassium carbonate (584-08-7)

hydrochloric acid (7647-01-0)

ether,
diethyl ether (60-29-7)

sodium hydroxide (1310-73-2)

sodium bicarbonate (144-55-8)

sodium chloride (7647-14-5)

sodium sulfate (7757-82-6)

sodium thiosulfate (7772-98-7)

iodine (7553-56-2)

toluene (108-88-3)

sodium (13966-32-0)

phosgene (75-44-5)

hydrazine (302-01-2)

guanidine (113-00-8)

hexane (110-54-3)

triethylamine (121-44-8)

argon (7440-37-1)

calcium hydride (7789-78-8)

2-tert-Butyl-1,1,3,3-tetramethylguanidine,
2-tert-butyl-1,1,3,3-tetramethyl-guanidine (34331-58-3)

2,2,6-TRIMETHYLCYCLOHEXEN-1-YL IODIDE (189633-81-6)

triphosgene (32315-10-9)

N,N,N',N'-tetramethylurea (632-22-4)

tert-Butylamine (75-64-9)

2,2,6-trimethylcyclohexanone hydrazone (189633-82-7)

2,2,6-trimethylcyclohexanone (2408-37-9)

1,5-diazabicyclo[4.3.0]non-5-ene

1,8-diazabicyclo[5.4.0]undec-7-ene (6674-22-2)