

Notes

Lithium Bronze as a Stoichiometric Reagent for the Conjugate Reduction of α,β -Unsaturated Ketones

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
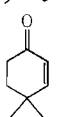
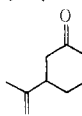
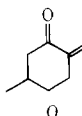

The lithium-ammonia 1,4-reduction of α,β -unsaturated ketones has proved to be an extremely valuable reaction in synthetic organic chemistry.^{1a} These reductions traditionally have been performed using blue solutions of lithium in liquid ammonia. An alternative to "lithium blue" reduction has been developed by Mel'nikova and Pivnitskii,² who discovered that ether suspensions of lithium tetraammine (Li·4NH₃, lithium bronze) effect the reduction of many steroidal enones in high yield and conversion. However, these workers specify^{2b} the use of an approximately 25-fold (i.e., 2500%) excess of the reagent, which detracts considerably from the utility of the method. We have found that, at least with monocyclic enones, this huge excess is unnecessary; a mere 5–10% excess is sufficient to cause virtually complete ($\geq 97\%$) reduction. With this modification, the Li bronze method is a very attractive alternative to Li blue reductions (in which the molar ratio of Li/NH₃ generally ranges from 1:60 to 1:200^{1b}). The major advantages of the Li·4NH₃ procedure are those of convenience and economy; much less NH₃ needs to be used, dried, distilled into the reaction vessel, and evaporated at the end of the reaction, with the attendant great savings in time, effort, expense, and flask size. In addition, the yields and cleanliness of the products compare favorably with those obtained using the Li blue procedure.^{1c} The method is also easily adaptable to large scale.

Li·4NH₃ may be prepared conveniently by condensing a slight excess of NH₃ into a flask containing Li metal. The reagent, fiery bronze in color with a metallic luster, is a liquid reminiscent of elemental mercury in its physical appearance but with a density of only ca. 0.5 g/mL.³ Addition of ether solutions of the enones 3,5-dimethylcyclohex-2-enone (1), 4,4-dimethylcyclohex-2-enone (2), (-)-carvone (3), (+)-pulegone (4), and isophorone (5) admixed with an equimolar quantity of *tert*-butyl alcohol to a vigorously stirred ether suspension of Li·4NH₃ results in rapid and efficient reduction to the ketone enolates and on workup the saturated ketones. The ketone product so obtained is generally quite pure, contaminated with only small amounts of unreduced enone and saturated alcohol. Experimental results are shown in Table I. Reductions on a 0.5-mol scale can be conducted in a 2-L flask less than half full; a typical Li blue reduction on this scale would require the use of at least a 5-L flask filled close to capacity.

In some cases, the regiospecific enolate generated in this fashion can be alkylated cleanly with methyl iodide.^{1a} Thus, treatment of the enolate produced by reduction of carvone (3; ca. 0.25 M in tetrahydrofuran with 1 equiv of ethanol as the proton source) with methyl iodide (6.5 equiv, -40 °C, 2 h) produced 2,2-dimethyl-5-isopropenylcyclohexanone in 84% distilled yield with a purity of ca. 93%. Less substituted enolates, however, gave significant polyalkylation (as much as 20–30%) as a consequence of reenolization caused by the alkoxide base generated in the reduction step.

We expect that Li·4NH₃ will also prove useful for many of the transformations more commonly effected by Li blue reduction.

Table I. Enone Reductions

enone	scale, no. mmol	product composition, % ^a			yield, %
		ketone(s)	enone	alcohol(s)	
	1 10	96 ^b	3	1	66, ^c 98 ^d
	2 10	93	3	4	64, ^c 93 ^d
	3 10 300 ^f	98 ^e	3	1	95 ^c
		99 ^e	1	1	90 ^c
	4 10	97 ^g	1	2	93 ^c
	5 10 500	97	1	2	82 ^c
		98	1	1	90 ^c

^a By thermal conductivity VPC integration. ^b Cis/trans, 87:13. ^c Distilled yield. ^d By VPC integration against an internal standard prior to solvent removal. ^e Cis/trans, 17:83. ^f Experiment by Professor F. E. Ziegler. ^g Cis/trans, 24:76.

Experimental Section.

3,5-Dimethylcyclohex-2-enone⁴ and 4,4-dimethylcyclohex-2-enone⁵ were obtained by synthesis. Isophorone, carvone, and pulegone were purchased from Aldrich Chemical Co. The enones were fractionally distilled to >99% purity. VPC analysis was performed on a Varian 1400 thermal conductivity instrument with 5 ft \times 1/8 in. columns of 5% OV-101 and 5% Carbowax 20M on 110/120 Anakrom ABS.

Reduction of Isophorone (3,5,5-Trimethylcyclohex-2-enone, 5) to 3,3,5-Trimethylcyclohexanone. A 2-L three-neck flask was fitted with a mechanical stirrer (glass blade), a dry ice condenser with an Ar inlet, and a 500-mL addition funnel. The apparatus was flame-dried while flushing with Ar and then maintained under positive Ar pressure. Lithium wire (7.35 g, 1.05 mol, 2-cm lengths) was added after the glassware had cooled. The dry ice condenser was filled, and ammonia (ca. 95 mL) was distilled from Na into the slowly stirred reaction vessel. Gradually the Li became coated with bronze globules, and eventually a bronze-colored liquid with a smooth mirror finish was formed. As a small excess of NH₃ had been used, the excess dripped from the condenser and cooled the flask contents.⁶ When bronze formation was complete (no chunks of Li metal remained), 100 mL of anhydrous Et₂O was added and the stirring speed was increased to disperse the reagent as well as possible. A solution of 69.1 g (0.50 mol) of isophorone and 37.1 g (0.50 mol) of dry *tert*-butyl alcohol was added over 60 min at such a rate that the NH₃ liberated did not reflux too rapidly. After the addition was complete, the reaction mixture was stirred another 15 min. Excess Li was destroyed by the dropwise addition of just enough of an Et₂O solution equimolar in dry acetone and ethanol. Just sufficient water (ca. 200 mL) to dissolve the Li salts was then added. The mixture was transferred to a separatory funnel; the water layer was separated and extracted with 200 mL of hexane. The combined organic layer was dried over MgSO₄ and the solvent removed on a rotary evaporator. The residue was distilled [57–58 °C (3.5 torr)] to afford 63.0 g of 3,3,5-trimethylcyclohexanone.

Reactions conducted on a 10-mmol scale were performed in a 250-mL flask. The molar proportions of reactants and solvents were similar to those described above except that 100 mL of Et₂O was added after formation of the bronze was complete.

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Registry No.—1, 1123-09-7; 2, 1073-13-8; 3, 6485-40-1; 4, 89-82-7; 5, 78-59-1; *cis*-3,5-dimethylcyclohexanone, 7214-52-0; *trans*-3,5-dimethylcyclohexanone, 7214-49-5; 4,4-dimethylcyclohexanone, 4255-62-3; *cis*-2-methyl-5-(1-methylethenyl)cyclohexanone, 3792-53-8; *trans*-2-methyl-5-(1-methylethenyl)cyclohexanone, 5948-04-9; *cis*-5-methyl-2-(1-methylethyl)cyclohexanone, 491-07-6; *trans*-5-methyl-2-(1-methylethyl)cyclohexanone, 89-80-5; 3,3,5-trimethylcyclohexanone, 873-94-9; lithium bronze, 19453-81-7; 2,2-dimethyl-5-isopropenylcyclohexanone, 54497-33-5.

References and Notes

- (1) (a) Review: D. Caine, *Org. React.*, **23**, 1 (1976). (b) Calculated from ref 1a, p 75, taking the density of liquid ammonia as 0.68 g/mL. (c) Cf. ref 1a, Table II.
- (2) (a) V. I. Mel'nikova and K. K. Pivnitskii, *J. Org. Chem. USSR (Engl. Transl.)*, **6**, 2635 (1970); (b) *ibid.*, **8**, 2138 (1972); (c) *ibid.*, **10**, 1024 (1974).
- (3) Li·4NH₃ reportedly (ref 2b) may be kept in a closed container at 20 °C for 2–3 weeks, but exposure to air (especially in a dispersed form) or heat can initiate exothermic decomposition. An attempt to transfer the reagent using a glass syringe proved troublesome and hazardous, as the material coated the walls of the syringe and sparked and sputtered at the tip of the needle. The reagent may, with appropriate precautions, be transferred through polyethylene tubing using positive, inert gas pressure.
- (4) E. C. Horning, M. O. Denekas, and R. E. Field, "Organic Syntheses", Collect. Vol. 3, Wiley, New York, 1955, p 317.
- (5) G. Opitz and H. Holtmann, *Justus Liebigs Ann. Chem.*, **684**, 79 (1965).
- (6) If desired, the excess NH₃ can be allowed to evaporate to give the reagent at room temperature. As the refluxing ammonia served to moderate the reaction temperature, we kept the dry ice condenser filled during the addition of the substrate; if the addition is commenced with the flask at room temperature, the NH₃ liberated as the reaction proceeds can cause a dramatic pressure surge, sufficient to blow out stoppers, etc.

Bicyclo[2.2.1]heptane-2,5-dione: Its Preparation and Reaction with Nucleophiles

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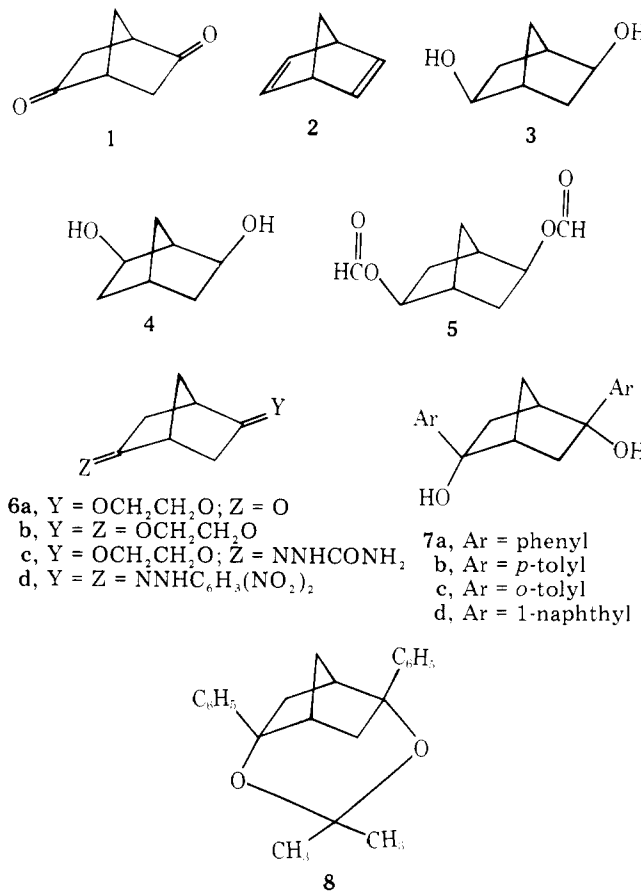
We have been exploring multigram syntheses of bicyclo[2.2.1]heptane-2,5-dione, a ketone^{3,4,5} with potentially interesting stereochemistry.

Dione 1 from Diene 2 by Hydroboration–Oxidation. Bicyclo[2.2.1]hepta-2,5-diene (**2**) has been subjected to hydroboration–oxidation.^{6–8} However, the literature does not identify the chief diol obtained. From studies of simpler model systems, one can infer that attachment of B should be *exo,exo* at positions 2 and 5, with retention of configuration upon alkaline hydrogen peroxide oxidation. We have shown that the hydroboration–oxidation must, in fact, proceed as expected, and that the predominant diol is indeed *exo,exo*-bicyclo[2.2.1]heptane-2,5-diol (**3**). We have shown that other diols are also formed: depending upon the experimental conditions, *exo,exo*-bicyclo[2.2.1]heptane-2,6-diol (**4**), and yet another diol have been detected in the reaction mixtures. It appears, however, that diol **3** predominates by about 10:1 over diol **4** in terms of isolated yields, and that the unknown third diol is obtained in still smaller amounts.

Hydroboration–oxidation⁹ of **2** in our laboratory has provided 50–60% isolated yields of the diol **3**, along with about 5% of the diol **4**, and other byproducts in minor amounts. All our attempts to prepare the dione **1** directly by oxidation of the organoboron compounds resulted in very poor yields of low purity product. Our efforts at Jones oxidation of the diol to the dione proceeded in yields up to about 41%. Thus the process of converting diene **2** to dione **1** was achieved in yields of 21–25%.

Dione 1 from Diene 2 by Formylation–Oxidation. Because of difficulties with hydroboration and oxidation in obtaining dione **1**, we explored an alternative route: formylation of the diene **2** to diformate ester **5** and oxidation of that to the dione **1**. There is precedent¹⁰ in the formylation of bicyclo[2.2.1]hept-2-ene to an *exo* ester. While our diformate ester appears to be previously undescribed, we have assigned it the 2,5-*exo,exo* configuration by analogy since it yields the dione **1**. The diformate ester was obtained in yields of 80%. Chromate oxidation in acetone resulted in 45% yields of the dione, this being 36% overall isolated yields from the diene.

Derivatives Obtained from Aryl Grignard Reagents and Dione 1. In accordance with expectations, we observed *exo* aryl products from the reaction of aryl Grignard reagents with the dione **1**.¹¹ That the attack was *exo*, at least in the case of phenyl Grignard reagent, was shown by the conversion of the *endo,endo*-diol **7a** into an acetonide **8**. Since only an *en-*



do,endo diol would be expected to give ring closure in this fashion, we have assigned *endo* configurations to **7a** and the other diols.

Derivatives of Bicyclo[2.2.1]heptane-2,5-dione. The mono(ethylene ketal), **6a**, the bis(ethylene ketal), **6b**, the semicarbazone of the mono(ethylene ketal), **6c**, and the bis(2,4-dinitrophenylhydrazone), **6d**, were prepared.

Experimental Section

Melting points were determined on a calibrated A. H. Thomas-Hoover melting point apparatus in capillary tubes. Elemental analyses were performed by M-H-W Laboratories of Garden City, Mich., or Chemalytics, Inc., of Tempe, Ariz. Infrared spectra were obtained on a Perkin-Elmer Model 457 spectrophotometer and proton magnetic resonance spectra on Varian Models A-60 and EM-390 spectrometers. GC/MS data were obtained from a Hewlett-Packard 5710A GC coupled with a 5980A MS interfaced with a 5934A data system.

Hydroboration–Oxidation of Diene 2. Several procedures were tried successfully, including (1) generation of the diborane *ex situ* from NaBH₄ and BF₃·etherate in diglyme; (2) generation *in situ* from the same reactants in THF with the etherate being added to the other reactants; (3) generation *in situ* as in (2) but with the etherate and