2-1994

Bridgehead intermediates in organic synthesis. A reproducible synthesis of adamantane-containing compounds

George A. Kraus
Iowa State University, gakraus@iastate.edu

Tiberiu M. Siclovan
Iowa State University

Bridgehead intermediates in organic synthesis. A reproducible synthesis of adamantane-containing compounds

Abstract

Compounds containing the adamantane subunit have long been of interest to chemists due to the rigid structure and well-defined substitution chemistry of adamantane.l The discovery of the potent antiviral activity of amantadine (1-aminoadamantane) and rimantadine (a-methyl-l-adamantylmethylamine) has stimulated interest in the synthesis of adamantane-containing compounds.2 The significant neuroprotective properties of the NMDA antagonist memantine3 (l-amino-3,5-dimethyladamantane) have also prompted interest in adamantane synthesis

Notes

Bridgehead Intermediates in Organic Synthesis. A Reproducible Synthesis of Adamantane-Containing Compounds

George A. Kraus* and Tiberiu M. Siclovan

Department of Chemistry, Iowa State University, Ames, Iowa 50011

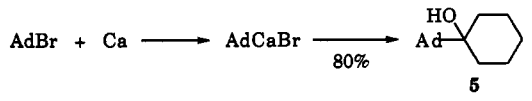
Received August 23, 1993

Compounds containing the adamantane subunit have long been of interest to chemists due to the rigid structure and well-defined substitution chemistry of adamantane.[1] The discovery of the potent antiviral activity of amantadine (1-aminoadamantane) and rimantadine (α-methyl-1-adamantylmethylamine) has stimulated interest in the synthesis of adamantane-containing compounds.[2] The significant neuroprotective properties of the NMDA antagonist memantine[3] (1-amino-3,5-dimethyladamantane) have also prompted interest in adamantane synthesis.

Although the carbocation chemistry of the adamantane system has been extensively studied, the chemistry of adamantyl bridgehead anions has been addressed in only a few isolated publications. No study of the scope and limitations of adamantyl bridgehead anions has been reported. Moreover, the literature of this bridgehead anion

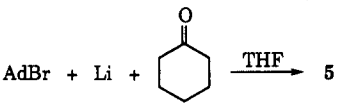
AdBr (1) AdMgBr (2) AdCaBr (3) AdLi (4)

is complicated by problems related to reproducibility of experimental protocols. Dubois and co-workers report that stirring a two-phase mixture of bromoadamantane (AdBr) and magnesium actually decreased the yield of Grignard reagent **2** compared with allowing the two-phase mixture to stand without stirring.[4] Dubois also reported that the use of the activated magnesium preparation developed by Rieke did not afford **2**. Yurchenko developed a quite different set of optimal conditions. He observed significant amounts (38–48%) of radical-derived products.[5] Organolithium **4** has been prepared and treated with nonenolizable ketones to provide hindered alcohols in modest yields.[6] Recently, Rieke and co-workers prepared an activated calcium reagent which reacted with adamantyl bromide to generate an organocalcium reagent **3** which, upon reaction with cyclohexanone, afforded an 80% yield of alcohol **5**.[7]



5

In the context of our continuing interest in bridgehead intermediates,[8] we tried the procedures of Dubois, Yurchenko, and Rieke using adamantyl bromide. Attempts to make Grignard **2** and trap it with cyclohexanone gave low yields of alcohol **5** with much recovered starting material and some adamantane. Our experiments using the calcium reagent developed by Rieke afforded a 20% yield of **5** with much returned unreacted **1**. These experiments were not conducted using drybox techniques, and such techniques appear to be essential.[9] However, the most widely used synthetic organometallic reactions can be conducted without having to resort to drybox techniques, so we searched for reaction conditions that were more convenient.



Metal–halogen exchange, a useful method for the generation of organometallic compounds, was then tried.[10] Interestingly, Lansbury has reported that the exchange reaction between 1-iodoadamantane and *tert*-butyllithium does not proceed to completion.[11] However, the reaction of **1** with lithium wire containing 1–2% sodium in THF at 0 °C in the presence of cyclohexanone produced alcohol **5** in 72% isolated yield, presumably via the intermediacy of **4**.

The reaction of **1** with Li and isobutyraldehyde furnished only a 32% yield of alcohol **6**. Since alcohol **6** was an early intermediate in one of our synthetic routes, we studied the effects of varying reaction parameters. Table 1 depicts our results. The optimal conditions involved the sonication of a mixture of **1**, isobutyraldehyde and lithium at 0 °C in ether. The reaction of representative carbonyl compounds using these conditions is collated in Table 2. The comparison of the results with isobutyraldehyde and pivaldehyde suggests that competitive deprotonation by the resulting alkoxide might be attenuating the yields. The failure of α-chloroisobutyraldehyde was unexpected and may be due to the facile reduction of the aldehyde carbonyl group. Although no chloro alcohol was isolated, the intermediate alkoxide would likely have generated a volatile epoxide by the displacement of the chlorine.

The reaction of the in situ generated adamantyllithium reagent with other functional groups was also investigated. Although acetonitrile and propylene oxide did not react, adamantanecarboxaldehyde (**11**) was isolated in 36% yield when DMF was subjected to our standard conditions.

$$\mathrm{AdBr + Li + DMF \rightarrow \underset{\mathbf{11}}{AdCHO}}$$

Our preparation of adamantyl carbinols via an in situ generated organolithium reagent affords reproducible

(1) Bingham, R. C.; von R. Schleyer, P. *Fortschr. Chem. Forsch.* **1971**, *18*, 1–102.
(2) Kirschbaum, J. *Analytical Profiles of Drug Substances*; Florey, K., Ed.; Academic Press: New York, 1983; Vol. 12, pp 1–36.
(3) Gupta, R. C.; Dettbarn, W. D. *Neurotoxicology* **1992**, *13*, 649.
(4) Molle, G.; Bauer, P.; Dubois, J. E. *J. Org. Chem.* **1982**, *47*, 4120.
(5) Yurchenko, A. G.; Fedorenko, T. V.; Rodionov, V. N. *J. Org. Chem. USSR* **1985**, *21*, 1529.
(6) Molle, G.; Briand, S.; Bauer, P.; Dubois, J. E. *Tetrahedron* **1984**, *40*, 5113.
(7) Wu, T.-C.; Xiong, H.; Rieke, R. D. *J. Org. Chem.* **1990**, *55*, 5045.
(8) Kraus, G. A.; Hon, Y.-S.; Thomas, P. J.; Laramay, S.; Liras, S.; Hansen, J. *Chem. Rev.* **1989**, *89*, 1591.
(9) Dr. Rieke informed us that the preparation and reactions of his reactive Ca reagent have been done using a drybox.
(10) Wakefield, B. J. *Chemistry of Organolithium Compounds*; Wiley: New York, 1972; pp 51–62.
(11) Lansbury, P. T.; Sidler, J. D. *Tetrahedron Lett.* **1965**, 691.

0022-3263/94/1959-0922$04.50/0

Table 1. Reactions of Bromoadamantane, Lithium, and Isobutyraldehyde

iPrCHO/1	Li/1	solvent	yield (%)
0.83	2.08	THF	32
1	1.5	THF	40
4	4	THF	7
1	1.5	Et_2O	46
1	1.5	Et_2O	56[a]

[a] Sonication.

Table 2. Reactions of Bromoadamantane, Lithium, and Carbonyl Compounds

carbonyl compd	RCOR'/1	Li/1	solvent	yield (%)	compd
iPrCHO	1	1.5	Et_2O	56	**6**
cyclohexanone	2	5	THF	72	**5**
cyclohexanone	2	5	Et_2O	74	**5**
2-cyclohexenone	0.83	2.08	THF	58	**7**
Me_3CCHO	2	5	THF	75	**8**
Me_3CCHO	2	5	Et_2O	80	**8**
PhCHO	0.83	2.08	THF	36	**9**
PhCHO	0.83	2.08	Et_2O	44	**9**
$Me_2C(Cl)CHO$	2	5	THF	0	**10**
$Me_2C(Cl)CHO$	2	5	Et_2O	10	**10**

[a] Sonication.

yields and is very convenient. It has been conducted on scales ranging from 1 mmol to 30 mmol. This work will facilitate the preparation of many compounds bearing the adamantane unit.

Experimental Section

Unless otherwise noted, materials were obtained from commercial suppliers and were used without purification. H:EA refers to hexanes/ethyl acetate solvent mixtures for TLC and silica gel flash chromatography (sgc). The purity of all title compounds was determined to be >95% by 300-MHz proton NMR and/or elemental analysis.

General Procedure. Li wire (6 mm in length, 3-mm diameter, 9.6 mmol) was cut into small pieces under N_2 and was added to a dry, N_2-flushed flask. Et_2O (8 mL) was then added, followed by a solution of anhydrous AdBr (410 mg, 1.9 mmol) in 2 mL of Et_2O. The flask was placed in an ultrasound bath containing water and crushed ice and sonication was started. The appropriate amount of aldehyde (3.8 mmol) was added dropwise via a syringe over 1 h. The mixture was further sonicated for 5 h. Depending on the aldehyde used, Li wire soon became clean and shiny as it reacted. The flask was then removed from the bath, 15 mL of H_2O was added, the mixture was stirred for 5 min. The organic layer was separated, the aqueous layer was extracted with Et_2O (3 × 10 mL), and the combined organic layers were dried over Na_2SO_4. The product was separated by sgc with hexanes/ethyl acetate as eluant. Compounds **5**,[7] **9**,[4] and **11**[5] had been previously prepared.

1-Adamantyl-2-methylpropanol (6): NMR ($CDCl_3$) δ 0.90 (d, J = 6.6 Hz, 3 H), 0.99 (d, J = 6.7 Hz, 3 H), 1.24 (d, J = 6 Hz, 1 H), 1.5–2.1 (complex multiplet, 15 H), 2.12–2.24 (broad singlet, 1 H), 2.90 (br d, J = 3.9 Hz, 1 H); IR (CCl_4) (3495 br), 2954, 2846, 1465, 1008, 786, 762 cm^{-1}; MS m/e 207, 165, 135, 107, 93, 70, 55; HRMS m/e for $C_{14}H_{24}O$ calcd 208.18272, found 208.18246; mp 48–49 °C; TLC (H:EA (7:1)) R_f = 0.47.

1-Adamantyl-2-cyclohexenol (7): NMR ($CDCl_3$) δ 1.4–2.2 (complex m, 21 H), 4.15–4.3 (br s, 1 H), 5.85 (complex m, 1 H), 6.09 (d, J = 9.9 Hz, 1 H); IR (CCl_4) 3630, 2910, 2853, 1454, 1289, 1027, 809, 761 cm^{-1}; MS m/e 135, 107, 79, 65; ^{13}C NMR ($CDCl_3$) δ 18.90, 25.28, 28.51, 29.54, 35.72, 37.15, 38.45, 67.82, 72.58, 128.79, 131.31; mp 71–72 °C; TLC (H:EA (10:1)) R_f = 0.44.

1-Adamantyl-2,2-dimethylpropanol (8): NMR ($CDCl_3$) δ 1.03 (s, 9 H), 1.45 (d, J = 6.3 Hz, 1 H), 1.60–2.02 (complex multiplet, 15 H), 2.78 (d, J = 6.6 Hz, 1 H); IR (CCl_4) 3648, 3530–3450 broad, 2906, 2849, 1481, 1363, 1005, 787, 763 cm^{-1}; MS m/e 222, 207, 165, 135, 107, 79, 67; HRMS m/e for $C_{15}H_{26}O$ calcd 222.19837, found 222.19820; mp 113–114 °C; TLC (H:EA (7:1)) R_f = 0.61.

Acknowledgment. We thank the National Institutes of Health (Grant GM33604) for financial support. G.K. thanks Brad Andersh for preliminary experiments.

Supplementary Material Available: ^1H NMR and IR spectra of **6–8** (7 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.