Synthesis of Methylcubane and Cyclopropylcubane. The Cubane-1,4-diyl Route

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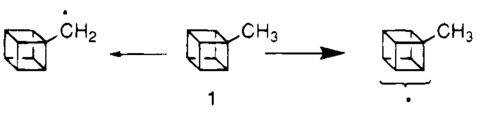
Received September 20, 1994[⊗]

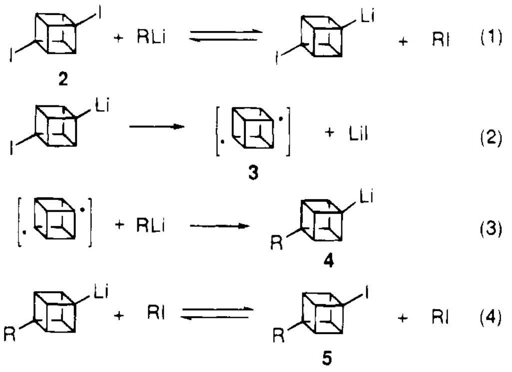
Details for preparation of 1,4-diiodocubane from cubane-1,4-dicarboxylic acid are given. The diiodide is used to generate cubane-1,4-diyl, a nonisolable intermediate. Additions to the diyl are shown to provide for the ready synthesis in good yield of methylcubane, 1,4-dimethylcubane, cyclopropylcubane, etc.

Calculations place the C−H bond dissociation energy of a cubyl C−H higher than that of a primary C−H by about 5 to 9 kcal/mol.[1−4] Yet, low temperature esr experiments with methylcubane (**1**) indicate that homolytic abstraction of H$^\bullet$ from cubyl C−H (any position) is favored over abstraction from the methyl C−H.[2] Product trapping experiments conducted at room temperature have confirmed this unexpected result.[5] Clearly, some kinetic (rather than thermodynamic) factor controls the reaction. Indeed, recent high level *ab initio* calculations show that abstractions of cubyl hydrogen by nucleophilic radicals (e.g. $CH_3{}^\bullet$) and particularly electrophilic radicals (e.g. $CH_3O^\bullet$) proceed via polarized transition states specially stabilized by charge delocalization into the cube.[4] As the dynamics of H$^\bullet$ abstraction from cubyl versus methyl C−H are quite different, and the products show entirely divergent behavior, methylcubane is coming to be an important probe in physical organic[6,7] and enzymatic studies,[8] including, for example, an investigation of the reaction pathways of P-450-containing enzymes and methane monooxygenase enzymes.[5]



We report here an interesting synthesis[9] of methylcubane utilizing the very versatile and extraordinary intermediate cubane-1,4-diyl.[10,11] It proceeds from the dimethyl ester of cubane-1,4-carboxylic acid,[12] the most available cubane,[13] *via* 1,4-diiodocubane. A high-yield variant of the Barton decarboxylation iodination[14] developed by Tsanaksidis[15] was used to prepare the diiodide. Details for the preparation of the diiodide are given in the Experimental Section of this paper.

1,4-Diiodocubane (**2**) on reaction with organolithiums undergoes exchange and elimination (eqs 1 and 2) giving cubane-1,4-diyl (**3**).[10,11] The diyl adds organolithiums to give 4-substituted cubyllithiums (**4**) in good yield (eq 3). These may react with organo iodides generated in the initial halogen/metal exchange of eq 1 to give 4-substituted cubyl iodides (eq 4). Whether this conversion is effective seems to depend on the equilibrium position of eq 4.



When RI is an aromatic iodide the equilibrium greatly favors the aryllithium (and hence the cubyl iodide),[10,11,16] in agreement with the higher acidity of an aromatic hydrogen over cubyl hydrogen,[17] a result of the somewhat higher s-character in the exocyclic carbon orbital (33 versus 31%). When RI is methyl iodide, eq 4 is expected to favor methyllithium (and hence the cubyl iodide) for different reasons—primary organolithiums are favored over tertiary ones because of inductive and associative effects. Indeed, when cubyl iodide itself was treated with excess methyllithium and the reaction mixture subsequently quenched with methanol, virtually no cubane was produced; the starting iodide could be recovered.[18]

[⊗] Abstract published in *Advance ACS Abstracts,* January 1, 1995.

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[18] However, reaction with *sec*-BuLi or *tert*-BuLi followed by methanol gives cubane in high yield.

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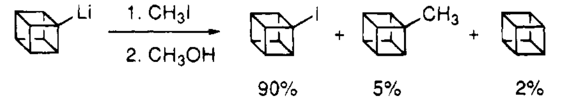
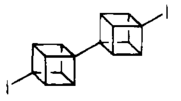
The converse experiment, treatment of cubyllithium[19] with methyl iodide followed by quenching with methanol, gave a good yield of cubyl iodide and very little methylcubane or cubane (eq 5)

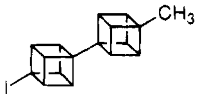


(5)

Our first attempt to prepare methylcubane by the reaction of 1,4-diiodocubane with an excess of methyllithium was provocative. The major products (60%) were the bicubyl compounds **6** and **7**. 4-Methylcubyl iodide (**8**)



6



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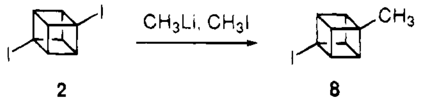
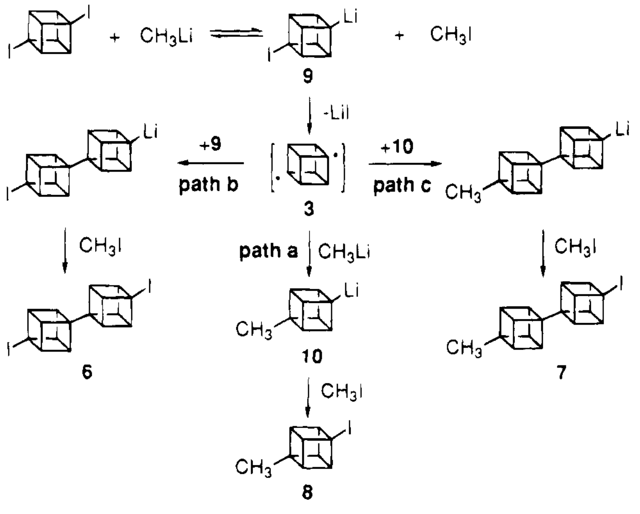
was formed in about 30% yield, and there was less than 5% each of methylcubane and cubane. The bicubyls, important compounds in their own right, are formed from intermediate cubyllithiums adding to cubane-1,4-diyl (Scheme 1).[10] This bypath could be suppressed by adding methyl iodide to the reaction. When excess methyllithium was added to a suspension of 1,4-diiodocubane in ether containing 10 equiv of methyl iodide, the reaction was much cleaner; the bicubyl byproducts were significantly reduced, and 4-methylcubyl iodide was formed in good yield (eq 6).



(6)

Scheme 1

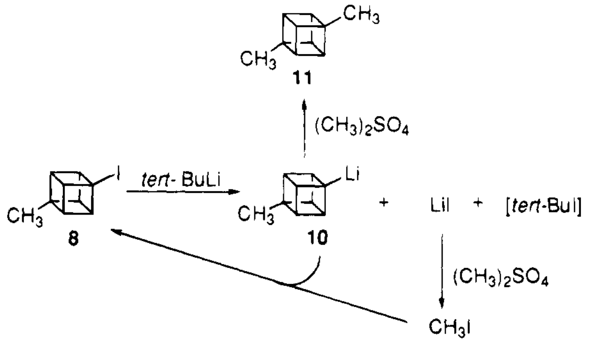


Inspection of Scheme 1 makes clear why the presence of excess methyl iodide favors formation of 4-methylcubyl iodide. There are three second order reaction pathways open to cubane-1,4-diyl; path a leads ultimately to the desired product, while paths b and c lead to the unwanted (at least here) bicubyls. In the presence of added methyl iodide, the transient concentration of (4-iodocubyl)lithium (**9**) is reduced, and path b is slowed. Similarly, the concentration of (4-methylcubyl)lithium (**10**) is reduced by added methyl iodide, and path c is less competitive.

4-Methylcubyl iodide (**8**) was isolated from the reaction mixture in 70% yield using a standard workup. It can be reduced to methylcubane easily using tri-*n*-butyltin hydride.[6,20] In our experiments, however, we instead took the crude mixture formed from the reaction of 1,4-diiodocubane with methyllithium and methyl iodide and, without any workup, added excess *tert*-BuLi to the same pot. This converted all the organoiodides to organolithiums; quenching with methanol produced the corresponding hydrocarbons. Purification by preparative gas chromatography gave methylcubane in 54% yield *overall* from 1,4-diiodocubane.

We could also obtain 1,4-dimethylcubane (**11**) by treating 4-methylcubyl iodide with *tert*-BuLi followed by dimethyl sulfate. A substantial amount of 4-methylcubyl iodide was recovered, no matter the care in running the reaction or the excess of dimethyl sulfate. A sample of the reaction mixture was taken before adding dimethyl sulfate and quenched with methanol. Methylcubane was found to be the only product. Therefore, in the original experiment, the methylcubyl iodide "recovered" had to have been formed after dimethyl sulfate was added. We ultimately found that methyl iodide is formed readily from reaction of dimethyl sulfate with the lithium iodide present in the reaction mixture from the initial halogen–metal exchange. A second halogen–metal exchange, now between (4-methylcubyl)lithium and methyl iodide, is responsible for the production of the 4-methylcubyl iodide isolated (Scheme 2).

Scheme 2



Methylcubane is of interest in high energy, air-breathing fuel programs. Cyclopropylcubane has even greater potential. The chemistry of cubane-1,4-diyl presented above provides neatly for the preparation of cyclopropylcubane. Treatment of 1,4-diiodocubane with 4 equiv of cyclopropyllithium followed by quenching with methanol gave 4-cyclopropylcubyl iodide (**12**) in 54% yield. The yield of **12** was much improved (to 86%) when cyclopropyl iodide was purposely added at the beginning of the reaction.[21] Presumably it plays the same role as methyl iodide does in the preparation of **8** (*cf.* Scheme 1).

Reduction of **12** to cyclopropylcubane (**13**) was effected by treatment with *tert*-BuLi followed by protonation. Just as in the synthesis of methylcubane, the conversion of 1,4-diiodocubane to cyclopropylcubane could be done in a single pot. Cyclopropylcubane, a stable material under ordinary conditions, was obtained in 63% overall yield (eq 7).

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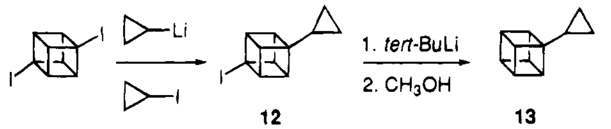
(19) Generated from cubyl iodide and *tert*-BuLi.

(20) This is particularly convenient when one has pure **8** on hand. Its reaction with the tin hydride can be run neat. Methylcubane is formed nearly quantitatively and can be obtained pure directly from the reaction mixture by vacuum sublimation through a small silica gel column. The procedure provides methylcubane free of solvent.

(21) Rather than prepare and add cyclopropyl iodide, it was formed *in situ* by reaction of cyclopropyllithium with iodine.



12 13 (7)

Experimental Section

Most cubanes are quite stable kinetically. Nonetheless, as they are all high-energy materials it is prudent to run reactions thereof behind safety shields. Crude reaction mixtures should not be concentrated at elevated temperature, particularly in the presence of acidic or metallic contaminants.

General. NMR spectra were run in chloroform-*d* at ambient probe temperature: ^{1}H NMR at 400 MHz and referenced to internal tetramethylsilane; ^{13}C NMR spectra at 100.6 MHz and referenced to the central line of the solvent. Proton chemical shifts are reported to a precision fo ±0.01 ppm; carbon chemical shifts, to a precision of ±0.1 ppm. DEPT ^{13}C-NMR experiments were used to distinguish C, CH, CH_2, and CH_3 carbon signals. Alkyllithium solutions were obtained from Aldrich and titrated prior to use. Anhydrous reaction solvents were prepared by usual procedures and used throughout. Preparative gas chromatography was done on an 1/4 in. × 5 ft aluminum column packed with 25% XE 60 on Chromosorb W column. Merck silica gel 60 (230–400 mesh) was employed for column chromatography.

1,4-Diiodocubane (2). Cubane-1,4-dicarboxylic acid (1.92 g, 9.99 mmol) was dissolved in 20 mL of pure thionyl chloride (warm), and the solution was heated to reflux for 1 h with a temperature-controlled oil bath. The solution was cooled, and the volatile components were removed at room temperature (!) under reduced pressure. **Do not heat!** The solid residue (the diacid chloride) was dissolved in dry benzene (40 mL) under nitrogen, and the solution was added dropwise over about 15 min to a magnetically stirred, irradiated (300 W tungsten lamp), boiling suspension of the anhydrous sodium salt of N-hydroxypyridine-2-thione (Sigma, dried in the dark at ca. 60 °C/0.01 Torr for 6–8 h, 3.24 g, 21.7 mmol) in dry benzene (40 mL), containing 2,2,2-trifluoroiodoethane (5.0 mL, 51 mmol) and 70 mg of 4-(*N,N*-dimethylamino)pyridine as catalyst. The mixture was heated under reflux for a further 2.5 h, cooled to room temperature, and washed with successive portions of water (50 mL), concentrated hydrochloric acid (50 mL), and water (50 mL). The organic layer was dried ($MgSO_4$, K_2CO_3) and taken to dryness by distillation at atmospheric pressure and then *in vacuo* to afford the crude diiodide as a yellow solid (3.0 g, 84%). Trituration with ether (5–10 mL) removed the color and left 2.85 g (80%) of off-white crystals. Crystallization (methanol/benzene) gave the pure 1,4-diiodide as colorless needles: mp 227–227.5 °C (lit.[22] 226–227 °C).

4-Methylcubyl Iodide (8). A suspension of 1,4-diiodocubane (1.0 g, 2.8 mmol) in iodomethane (1.8 mL, 28 mmol) and ether (40 mL) under nitrogen was stirred in a 100-mL flask in a 20–22 °C water bath. Methyllithium (20 mL, 28 mmol, 1.4 M in ether) was added in one portion. The diiodocubane dissolved gradually, and a pale yellow color developed. After 4.5 h the mixture was cooled to −70 °C (at this point it can be used in the preparation of methylcubane, *vide infra*) and quenched with methanol. Water was added to the resulting suspension. The organic layer was separated and washed with 2 N hydrochloric acid. The solvent was removed under vacuum at room temperature, and the residue was purified by sublimation (40 mtorr/60 °C) or by column chromatography using pentane as eluant. 4-Methylcubyl iodide was obtained as a white crystalline powder 0.48 g (70%): mp 79–81 °C; ^{1}H-NMR δ 1.29 (s, 3H, CH_3), 3.82 (m, 3H, cubyl H-3, 5, 7), 4.17 (m, 3H, cubyl H-2, 6, 8); ^{13}C-NMR δ 19.2 (CH_3), 40.6 (cubyl CI), 50.7 (cubyl C-3, 5, 7 or C-2, 6, 8), 54.4 (cubyl C-2, 6, 8 or C-3, 5, 7), 56.4 ppm (cubyl C-4). Anal. Calcd for C_9H_9I: C, 44.29; H, 3.72; I, 51.99. Found: C, 44.32; H, 3.71; I, 52.13.

Methylcubane (1). *tert*-BuLi in pentane (1.7 M, 25 mL, 42 mmol) was added dropwise over 30 min to the cold (acetone/CO_2 bath) reaction mixture identified above in the preparation of **1**. The resulting light brown solution was stirred for 10 min (at this point the solution can be used in the preparation of dimethylcubane, *vide infra*), and then the reaction was quenched with methanol. Water was added. The organic layer was separated, washed generously with water, 2 M hydrochloric acid, and then water again. After it was dried over anhydrous Na_2SO_4, the solution was concentrated by slow and careful distillation of the solvents at atmospheric pressure. The volume was reduced to 2–3 mL. Purification by gas chromatography gave 0.18 g (55%) of methylcubane as a colorless oil: mp −34 °C (DSC, 20 °C/min); ^{1}H-NMR δ 1.25 (s, 3H, CH_3), 3.64 (m, 3H, cubyl H-2, 6, 8), 3.84 (m, 3H, cubyl H-3, 5, 7), 4.05 ppm (m, 1H, cubyl H-4); ^{13}C-NMR δ 19.8 (CH_3), 43.8 (cubyl C-3, 5, 7 or C-2, 6, 8), 48.7 (cubyl C-4), 49.9 (cubyl C-2, 6, 8 or C-3, 5, 7), 55.5 ppm (cubyl C-1); HRMS calcd for C_9H_{10} (M^+) 118.0783, found 118.0782.

1,4-Dimethylcubane (11). Dimethyl sulfate (4.0 mL, 42 mmol) was added to the cold reaction mixture identified above in the preparation of **8**. The reaction mixture was warmed to room temperature. After 2 h, excess dimethyl sulfate was destroyed by adding aqueous ammonia. The mixture was stirred at room temperature overnight. Workup as described in the preparation of methylcubane and purification by preparative gas chromatography gave 0.16 g (43%) of 1,4-dimethylcubane as colorless needles: mp 41–42 °C; ^{1}H-NMR δ 1.26 (s, 6H, CH_3), 3.45 ppm (s, 6H, cubyl H); ^{13}C-NMR δ 20.0 (CH_3), 46.0 (cubyl CH), 56.5 ppm (cubyl C-1,4); HRMS calcd for $C_{10}H_{12}$ (M^+) 132.0939, found 132.0931.

4-Cyclopropylcubyl Iodide (12). A solution of cyclopropyl bromide (Aldrich, 1.3 g, 11 mmol) was dissolved in 20 mL of ether and cooled to −78 °C; *tert*-BuLi in pentane (1.7 M, 13 mL, 22 mmol) was added dropwise. The mixture was stirred at −78 °C for 10 min. The cyclopropyllithium solution so made was cannulated quickly into a well-stirred suspension of 1,4-diiodocubane (1.0 g, 2.8 mmol) and iodine[21] (0.71 g, 2.8 mmol) in ether (25 mL) under nitrogen in a 100-mL flask in a 20–22 °C water bath. The diiodide dissolved gradually, and a pale yellow color developed. After 50 min, the reaction flask was placed in an iced-water bath (at this point it can be used in the preparation of cyclopropylcubane, *vide infra*), and the reaction was quenched with methanol. Water was added. Standard workup followed by sublimation under vacuum (40 mtorr/60 °C) or by flash chromatography on silica gel with pentane as elutant gave 4-cyclopropylcubyl iodide as a white crystalline powder 0.65 g (86%): mp 76.5–77.5 °C; ^{1}H-NMR δ 0.14 and 0.43 (m, 4H, cyclopropyl CH_2), 1.00 (m, 1H, cyclopropyl CH), 3.79 (m, 3H, cubyl H-3, 5, 7), 4.13 (m, 3H, cubyl H-2, 6, 8); ^{13}C-NMR δ 0.1 (cyclopropyl CH_2), 11.7 (cyclopropyl CH), 40.2 (cubyl CI), 48.3 (cubyl C-3, 5, 7 or C-2, 6, 8), 54.3 (cubyl C-2, 6, 8 or C-3, 5, 7), 60.6 ppm (cubyl C-4). Anal. Calcd for $C_{11}H_{11}I$: C, 48.91; H, 4.11; I, 46.98. Found: C, 48.85; H, 4.11; I, 46.88.

Cyclopropylcubane (13). The reaction mixture at the point identified above in the preparation of **12** was cooled in a dry ice/acetone bath to < −70 °C. *tert*-BuLi in pentane (1.7 M, 9.9 mL, 17 mmol) was added dropwise over 15 min. The mixture was stirred cold for another 15 min and then worked-up as described for the preparation of methylcubane. Purification by gas chromatography gave 0.26 g (63%) of cyclopropylcubane as colorless oil: mp −31 °C (DSC, 20 °C/min); ^{1}H-NMR δ 0.15 and 0.38 (m, 4H, cyclopropyl CH_2), 0.98 (m, 1H, cyclopropyl CH), 3.64 (m, 3H, cubyl H-2, 6, 8), 3.80 (m, 3H, cubyl H-3, 5, 7), 4.01 ppm (m, 1H, cubyl H-4); ^{13}C-NMR δ −0.2 (cyclopropyl CH_2), 12.0 (cyclopropyl CH), 43.8 (cubyl C-3, 5, 7 or C-2, 6, 8), 47.3 (cubyl C-2, 6, 8 or C-3, 5, 7), 48.9 (cubyl C-4), 59.6 ppm (cubyl C-1); HRMS calcd for $C_{11}H_{12}$ (M^+) 144.0939, found 144.0935.

Acknowledgment. This work was supported by the National Science Foundation and the Office of Naval Research. We are grateful to John Tsanaktsidis for some of the early experiments.

JO941603U

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