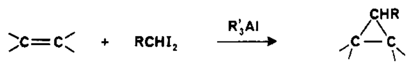
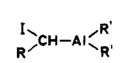
Communications

Trialkylaluminum-Alkylidene Iodide. A Powerful Cyclopropanation Agent with Unique Selectivity

Summary: A highly convenient and versatile method for the synthesis of cyclopropanes has been described which involves treatment of olefins with a variety of trialkylaluminums and alkylidene iodide under mild conditions.

Sir: The cyclopropanation of olefins is a highly useful synthetic operation in organic synthesis. The importance of this transformation stems from the occurrence of cyclopropane rings in many natural products and from the utility of cyclopropanes as synthetic intermediates for ring expansions and chain elaborations.[1] Here we wish to report a highly convenient and versatile method for the synthesis of cyclopropanes from olefins which was found to exhibit unique selectivity not observable in ordinary cyclopropanations, including the Simmons–Smith reaction and its modifications.[1f] The method simply involves treatment of olefins with a variety of trialkylaluminums and alkylidene iodide.[2]

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In 1964, Miller reported a cyclopropane synthesis using triethylaluminum–methylene iodide in disappointing yields,[3] and further investigations have not been carried out. However, making a survey of a range of aluminum reagents as well as manipulating experimental conditions, we have concluded that the stability of the dialkyl(α-iodoalkyl)aluminum species 1, the presumed cyclopropanation intermediate, is profoundly affected by the solvent employed.[2,4] Thus, in hydrocarbon solvent the use of equimolar amounts of trialkylaluminum and methylene iodide in the presence of olefins is essential for achieving reproducible results in the cyclopropanation process, though use of less than 1 equiv of trialkylaluminum is not detrimental. Apparently, the dialkyl(iodomethyl)aluminum 1 (R = H) undergoes decomposition in the absence of olefins[5] or by excess trialkylaluminum even in the presence of olefins[6] in hydrocarbon solvent. In contrast, the dimethyl(iodomethyl)aluminum 1 (R = H, R' = Me) is stable enough in methylene chloride even in the presence of excess trimethylaluminum.[7] Further, this reactive species generated in the proper solvent system has proved to be a powerful methylene transfer agent as demonstrated by the facile cyclopropanation of olefins at low temperature.[8]

The experimental procedure is straightforward and is illustrated here for the synthesis of *n*-decylcyclopropane. To a solution of 1-dodecene (3.37 g, 20 mmol) and methylene iodide (6.43 g, 24 mmol) in CH_2Cl_2 (40 mL) was added at 0 °C a 2 M *n*-hexane solution of triethylaluminum (24 mmol).[9] The mixture was stirred at room temperature for 3 h. The reaction was terminated by dilution with CH_2Cl_2 (40 mL) followed by successive treatment with sodium fluoride (4.03 g, 96 mmol) and water (1.3 mL, 72 mmol) at 0 °C.[10] Vigorous stirring of the resulting suspension was continued at 0 °C for 30 min. Filtration, washing with CH_2Cl_2, and removal of solvent left a crude oil, which was distilled to yield *n*-decylcyclopropane (3.39 g, 93% yield) as a colorless oil.

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(1) Reviews concerning the reactions, the natural occurrence, the synthesis, and the synthetic applications of cyclopropanes: (a) Lukina, M. Y. *Russ. Chem. Rev. (Engl. Transl.)* **1962**, *31*, 419. (b) Wendisch, D. In "Methoden der Organischen Chemie (Houben-Weyl)", 4th ed.; Müller, E., Ed.; Georg Thieme: Stuttgart, 1971; Vol. IV, Part 3, p 15. (c) Kirmse, W. "Carbene Chemistry"; Academic Press: New York, 1971. (d) Seyferth, D. *Acc. Chem. Res.* **1972**, *5*, 65. (e) Jones, M., Jr.; Moss, R. A. "Carbenes"; Wiley: New York, 1973. (f) Simmons, H. E.; Cairns, T. L.; Vladuchick, S. A.; Hoiness, C. M. *Org. React. (N.Y.)* **1973**, *20*, 1. (g) Ferguson, L. N. "Highlights of Alicyclic Chemistry"; Franklin: Palisade, NJ, 1973; Part 1, p 210. (h) Boyle, P. H. In "Rodd's Chemistry of Carbon Compounds", 2nd ed.; Ansell, M. F., Ed.; Elsevier: Amsterdam, 1974; Vol IIA Supplement, p 9 and the earlier volumes of this series. (i) Yanovskaya, L. A.; Dombrovskii, V. A. *Russ. Chem. Rev. (Engl. Transl.)* **1975**, *44*, 154. (j) Trost, B. M.; Melvin, L. S. "Sulfur Ylides"; Academic Press: New York, 1975. (k) Hiyama, T.; Nozaki, H. *J. Synth. Org. Chem., Jpn.* **1977**, *35*, 979. (l) Tunemoto, D.; Kondo, K. *Ibid.* **1977**, *35*, 1070. (m) Halton, B. In "Alicyclic Chemistry", Parker, W., Senior Reporter; The Chemical Society: London, 1977; Vol. 5, p 1 and the earlier volumes of this series. (n) Murakami, M.; Nishida, S. *J. Synth. Org. Chem., Jpn.* **1983**, *41*, 22.

(2) The present cyclopropanation using trialkylaluminum–methylene iodide may proceed via dialkyl(iodomethyl)aluminum as an intermediate, which can also be generated by the reaction of dialkylaluminum iodide with diazomethane. See: Hoberg, H. *Liebigs Ann. Chem.* **1962**, *656*, 1.

(3) Miller reported that the reaction of excess triethylaluminum with methylene iodide (1.5:1 molar ratio) in cyclohexene at 25 °C for 3 days gave norcarane in only 20% yield (Miller, D. B. *Tetrahedron Lett.* **1964**, 989). The low yield of norcarane may be ascribed to the partial decomposition of the intermediary diethyl(iodomethyl)aluminum by excess triethylaluminum. See ref 6.

(4) Reaction of methylene iodide with triisobutylaluminum (each 1 equiv) afforded nearly 1 equiv of isobutyl iodide as a product, suggesting the formation of diisobutyl(iodomethyl)aluminum in the solution.

(5) Initial treatment of methylene iodide with trialkylaluminum (Me_3Al, Et_3Al, and *i*-Bu_3Al) (1:1 molar ratio) in *n*-hexane or benzene at room temperature for 1–1.5 h and subsequent addition of 1-dodecene gave *n*-decylcyclopropane in 20–30% yield with recovery of the unreacted 1-dodecene (70–80% yield). The intermediary dialkyl(iodomethyl)aluminum 1 (R = H) decomposes to dialkylaluminum iodide and ethylene (see ref 2) or is assumed to participate in the facile intramolecular transfer via 1,2-migration to furnish $R'(R'CH_2)AlI$.

(6) Attempted cyclopropanation of 1-dodecene with excess triethylaluminum (2.4 equiv) and methylene iodide (1.2 equiv) in *n*-hexane gave *n*-decylcyclopropane in much lower yield (~48%; cf. entry 3 in the Table I). Diethyl(iodomethyl)aluminum derived from diethylaluminum iodide and diazomethane is reported to react with triethylaluminum. See: Hoberg, H. *Liebigs Ann. Chem.* **1967**, *703*, 1.

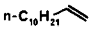
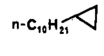
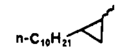
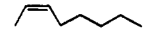
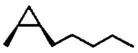
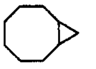
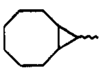
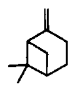
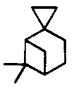
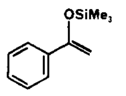
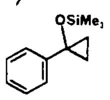
(7) For example, initial treatment of methylene iodide with trimethylaluminum (1:1 or 1:2 molar ratio) in CH_2Cl_2 at room temperature for 3 h and subsequent addition of 1-dodecene produced *n*-decylcyclopropane in 82–88% yields. However, the dialkyl(iodomethyl)aluminum derived from triethyl- or triisobutylaluminum are unstable in CH_2Cl_2 and on treatment with 1-dodecene gave *n*-decylcyclopropane in only 28–30% yields. Therefore, except with trimethylaluminum the present cyclopropanation should be carried out in the presence of olefins.

(8) Treatment of this species with 1-dodecene at −25 °C for 3 h yielded *n*-decylcyclopropane in 81% yield.

(9) We appreciate Toyo Stauffer Chemical Co., Ltd., for generous gift samples of trialkylaluminum.

(10) The NaF–H_2O workup offers an excellent method for product isolation in the reaction of organoaluminum compounds. See: Yamamoto, H.; Maruoka, K. *J. Am. Chem. Soc.* **1981**, *103*, 4186.

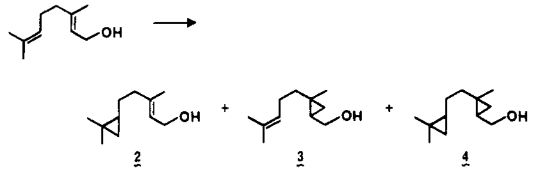
Table I. Cyclopropanation of Olefins with the Trialkylaluminum-Alkylidene Iodide System[a]

entry	olefin	R'_3Al (equiv)	$RCHI_2$ (equiv)	product	yield, %[b]
1		Me_3Al (1.2)	CH_2I_2 (1.2)		98, 91[c]
2		Me_3Al (0.6)	CH_2I_2 (1.2)		90
3		Et_3Al (1.2)	CH_2I_2 (1.2)		99, 94-96[d]
4		Et_3Al (0.6)	CH_2I_2 (1.2)		89[c]
5		i-Bu_3Al (1.2)	CH_2I_2 (1.2)		96
6		Me_3Al (3)	CH_3CHI_2 (3)		94[e]
7		i-Bu_3Al (3)	CH_3CHI_2 (3)		84[e]
8		Me_3Al (1.1)	CH_2I_2 (1.2)		75[c,f]
9		Et_3Al (1.2)	CH_2I_2 (1.2)		66
10		Me_3Al (1.2)	CH_2I_2 (1.2)		82, 75[c]
11		Et_3Al (1.2)	CH_2I_2 (1.2)		75
12		Me_3Al (3)	CH_3CHI_2 (3)		92[e]
13		Me_3Al (1.2)	CH_2I_2 (1.2)		46, 96[c]
14		i-Bu_3Al (1.2)	CH_2I_2 (1.2)		73[c]
15		Me_3Al (1)	CH_2I_2 (1.2)		57, 80[c]
16		n-Pr_3Al (1.2)	CH_2I_2 (1.2)		78[c]
17		Et_3Al (1.2)	CH_2I_2 (1.2)		86[c]

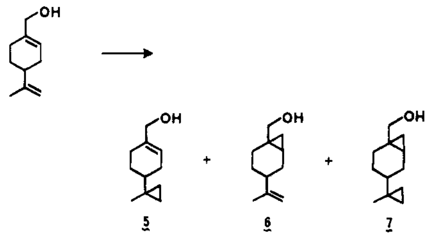
[a] Unless otherwise noted, the reaction was carried out in methylene chloride at room temperature for 3-8 h, and the mixture was worked up with NaF-H_2O or aqueous 10% NaOH. All compounds were identified by comparison of the spectral properties with those of authentic samples. [b] Isolated yield after silica gel column chromatography. [c] n-Hexane was used as solvent. [d] Use of benzene or chloroform as solvent. [e] Isomeric ratios of the products are 1.1:1 (entry 6), 0.7:1 (entry 7), and 6.3:1 (entry 12), respectively. [f] The stereospecificity of the cyclopropanation was determined by GC on a 25-m PEG-HT capillary column.

As revealed in Table I, a variety of combinations of trialkylaluminum with ethylene or methylene iodide can be utilized with equal efficiency in the preparation of cyclopropanes from olefins. Among these, the triisobutylaluminum-methylene iodide system is more selective than the others as described later in the cyclopropanation of geraniol and perillyl alcohol. Notably, even less than 1 equiv of trialkylaluminum is enough to complete the reaction, indicating the potential utility of dialkylaluminum iodide itself for cyclopropanation (entries 2 and 4).[11] The reaction proceeds under mild conditions for several hours (usually 3-5 h) in nonpolar solvents[12] and affords cyclopropanation products in good to excellent yields. It is stereospecific with respect to alkene substituents (entries 8 and 9) and is usually free from serious side reactions. Another characteristic of the method is its operational simplicity which enabled the ready adaptation to large-scale preparations.

From a synthetic point of view, we have noticed the remarkably high regioselectivity in the cyclopropanation of geraniol. This selectivity in the trialkylaluminum-promoted cyclopropanation reaction appears to be complementary to that obtained in existing methodologies.[1] Thus, treatment of geraniol with triisobutylaluminum (2 equiv)-methylene iodide (1 equiv) in CH_2Cl_2 at room temperature for 5 h gave rise to cyclopropanation products with some recovery of the starting material in 75% combined yield. GC analysis of their trimethylsilyl ethers indicated the ratio of **2**, **3**, **4**, and unreacted geraniol to be 76:1:4:19. Consequently, our methylene transfer reaction takes place almost exclusively at the C(6)-C(7) olefinic site far from the hydroxy group of geraniol and the C(2)-C(3) olefinic bond was left intact[13] In sharp contrast, however, the Simmons-Smith reagent and its variants exhibit totally opposite regioselectivity,[1f] and geraniol by exposure to diethylzinc-methylene iodide (2:1 molar ratio) in ether at room temperature for 3 h underwent a facile hydroxy-assisted cyclopropanation affording **2**, **3**, **4**, and unreacted



	2	3	4
i-Bu_3Al/CH_2I_2	76	1	4
Et_2Zn/CH_2I_2	2	74	3



	5	6	7
i-Bu_3Al/CH_2I_2	79	0	0
Et_2Zn/CH_2I_2	3	49	8

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(11) Diethylaluminum chloride and diethylaluminum iodide were actually found to be effective for the cyclopropanation of olefins. For example, reaction of 1-dodecene in CH_2Cl_2 with CH_2I_2 (1.2 equiv) and Et_2AlX (X = Cl or I; 1.2 equiv) at room temperature for 10-13 h produced n-decylcyclopropane in 85-94% yields.

(12) The use of polar solvents such as diethyl ether and tetrahydrofuran resulted in total recovery of the starting olefins.

(13) The triisobutylaluminum-methylene iodide system was found to be more selective than the other. For example, treatment of geraniol with tri-n-propylaluminum (2 equiv)-methylene iodide (1 equiv) in CH_2Cl_2 at room temperature for 5 h gave **2**, **3**, **4**, and unreacted geraniol in a ratio of 64:6:17:13 (88% combined yield). The use of trimethylaluminum-methylene iodide system afforded a number of side products.

geraniol in a ratio of 2:74:3:21 (93% combined yield). A similar tendency was also observed in the case of perillyl alcohol. Thus, the aluminum method under the comparable conditions as described above gave rise to a monocyclopropanation product **5** exclusively (64%) with recovery of unreacted perillyl alcohol (17%), although the zinc method yielded a mixture of **5**, **6**, **7**, and perillyl alcohol in a ratio of 3:49:8:40 (81% combined yield).

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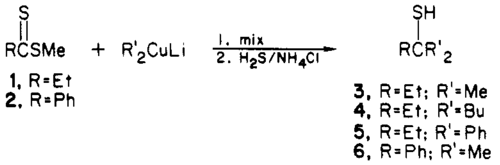
Reaction of Organocuprates with Dithio Esters: Double-Barrelled Carbophilic Addition and a New Synthetic Route to Tertiary Thiols[1a]

Summary: Organocuprates prepared from lithium reagents or Grignard reagents react with dithio esters to give high yields of tertiary thiols; in the absence of Cu(I), only thiophilic addition products are observed.

Sir: Thiocarbonyl compounds such as thioketones[2,3] and dithio esters[4] generally react with organometallic nucleophiles such as Grignard and lithium reagents via *thiophilic* addition,[5] e.g., these reagents convert thiobenzophenone[2] to alkyl or aryl benzhydryl sulfides and dithio esters to dithianes.[4] In contrast, we have discovered that organocuprates react with thiobenzophenone via *carbophilic* addition and with dithio esters via "double-barrelled" carbophilic addition (eq 1) to give excellent yields of tertiary thiols.



(1)

1, R=Et
2, R=Ph

3, R=Et; R'=Me
4, R=Et; R'=Bu
5, R=Et; R'=Ph
6, R=Ph; R'=Me

We have investigated this new reaction as a function of substrate (R = Et, Ph), cuprate (R′ = Me, Bu, Ph), organometallic precursor (R′Li, R′MgBr), copper(I) precursor (CuX, X = CN, Br, I, CF_3SO_3), solvent (ether, THF), and temperature (−78 °C, 0 °C) with the results summarized in Tables I and II. In all cases 2.0 mmol of Li or Mg reagent were used per 1.0 mmol of substrate; in the stoichiometric reactions 1.0 mmol of Cu(I) was used vs. 0.10 mmol in the catalytic reactions. The magnesiocuprates were prepared from CuO_3SCF_3 (Cu(I) triflate) in ether.

With methyl dithiopropionate (**1**) as the substrate and Me_2CuLi as the reagent, the yield of 2-methyl-2-butanethiol (**3**) is virtually quantitative (96–100%), and the best yields of 5-ethyl-5-nonanethiol (**4**) and 1,1-diphenyl-1-propanethiol (**5**) (using Bu_2CuLi and Ph_2CuLi, respectively, as reagents) are not far behind (93% and 97%, respectively). The best yield of α,α-dimethylbenzyl mercaptan (**6**) from methyl dithiobenzoate (**2**) and Me_2CuLi (88%) is not as good as the corresponding yield from **1** and Me_2CuLi, but it is very good nevertheless. Moreover, a 99% yield of **6** is obtained by treating **2** with 2 equiv of MeCu(SMe)Li. The yields from large-scale reactions are the same provided the same concentrations are used (see supplementary material).

Only traces (<0.1%) of thiophilic addition products (dithioacetals) are observed in any of the reaction mixtures. With **2** we also observe small amounts (up to 2%) of methyl 1-phenyl-1-ethyl sulfide, the product of an initial carbophilic attack followed by thiophilic attack on an intermediate thioketone (vide infra). The only situation in which we observe a significant amount of "carbophilic–thiophilic" product occurs when **1** and Bu_2CuLi from CuI are mixed at −78 °C in THF. Under these conditions the yield of butyl 3-heptyl sulfide is ~15%. Mixing the reactants at 0 °C in THF, or at either −78 °C or 0 °C in ether, results in just the "double-barrelled" carbophilic addition product, **4**.

When **1** and R'_2CuLi (R′ = Me, Bu, Ph) are mixed at −78 °C, samples withdrawn with a cold syringe and quenched with deoxygenated ammonium chloride solution contain neither starting material nor product by GLC. If the reaction mixture is then allowed to warm to 0 °C, a good yield of product appears. Apparently, an intermediate nonvolatile complex is formed first and yields product only upon warming. In some cases better yields are obtained by initiating the reactions at 0 °C rather than −78 °C (the optimal conditions are summarized in footnotes to Table I). Saturating the reaction mixtures with H_2S (−78 °C) before quenching with ammonium chloride solution gives slightly better yields from **1** and Me_2CuLi and has a negligible effect on yields from **1** and Bu_2CuLi. In contrast, H_2S treatment has a vital effect on yields from **1** and Ph_2CuLi, as it suppresses the formation of 1,1-diphenyl-1-propene (from elimination of H_2S from **5**). It also has a dramatic effect on the yields of **6** from **2** and Me_2CuLi—they are more than doubled in some cases.

We have verified that in the absence of Cu(I), **1** and **2** are converted to dithioacetals by MeLi, BuLi, and PhLi, and BuMgBr. (With MeMgBr and PhMgBr thioenolization of **1** occurs, yielding ketene dithioacetals upon quenching with benzyl bromide.) No products of carbophilic attack are observed in these reactions. Thus, the inclusion of Cu(I) has a profound effect upon the course of the reaction. For the thiophilic attack on thiobenzophenone, Beak and co-workers preferred a direct nucleophilic addition mechanism, since they found the yields of thiophilic products to be inversely proportional to the ability of a series of organometallics to transfer an electron.[2] On the other hand, Ohno et al.[3] proposed electron transfer followed by radical combination for the reaction of PhLi with di-*tert*-butyl thioketone, which affords both C-phenylated and S-phenylated products. An electron-

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[1] (a) Part 9 of a series on New Copper Chemistry, for part 8, see: Bertz, S. H.; Dabbagh, G. *Inorg. Chem.* **1985**, *24*, 3488; for part 7, see: Bertz, S. H.; Dabbagh, G.; Cook, J. M.; Honkan, V. *J. Org. Chem.* **1984**, *49*, 1739. (b) AT&T Bell Laboratories Summer Research Program for Minorities and Women, 1983 participant.

[2] Beak, P.; Yamamoto, J.; Upton, C. J. *J. Org. Chem.* **1975**, *40*, 3052.

[3] Under appropriate conditions, carbophilic addition is observed with aliphatic thioketones, see: Ohno, A.; Nakamura, K.; Shizume, Y.; Oka, S. *Bull. Chem. Soc. Jpn.* **1977**, *50*, 1003.

[4] The only documented examples of carbophilic attack on dithioesters involve allyl, benzyl, and propargyl Grignard reagents, see: Masson, S.; Saquet, M.; Thuillier, A. *Tetrahedron Lett.* **1976**, 4179; *Tetrahedron* **1977**, *33*, 2949. R. D. Miller and co-workers have observed carbophilic attack on some trithiocarbonates. (R. D. Miller, personal communication).

[5] For leading references, see: Duus, F. In "Comprehensive Organic Chemistry"; Barton, D., Ollis, W. D., Eds.; Pergamon: Oxford, 1979; Vol. 3, pp 391, 429. Scheithauer, S.; Mayer, R. In "Topics in Sulfur Chemistry"; Senning, A., Ed.; Georg Thieme: Stuttgart, 1979; Vol. 4, p 306. See also ref 7, p 1047.

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