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The synthesis of 1,1′-disubstituted bis-cyclopropanes by the reaction of substituted propargylic alcohols with CH_2I_2–R_3Al

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ABSTRACT

A new efficient method for the synthesis of 1,1′-disubstituted bis-cyclopropanes is described, which involves treatment of 2-alkyn-1-ols with trialkylaluminium and diiodomethane.

We have previously reported the reaction of alkyl- and phenyl-substituted alkynes with CH_2I_2–Et_3Al which gave cyclopropylic compounds.[1] To extend the scope of this transformation, we examined the reaction of heteroatom-substituted acetylenic compounds with CH_2I_2 in the presence of trialkylaluminiums.

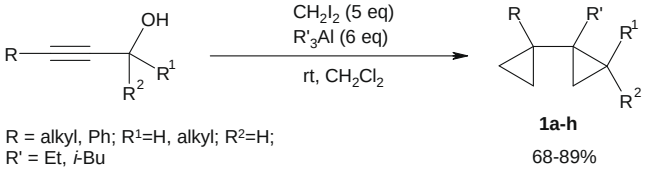
Here we report a convenient and versatile one-pot method for the synthesis of bis-cyclopropanes from readily available substituted propargylic alcohols, CH_2I_2 and trialkylaluminiums (Scheme 1).

The identification of polycyclopropanated natural compounds[2] and their biological activity[3] has promoted studies on the development of stereoselective methods to prepare polycyclopropanes.[4] The Simmons-Smith reaction is widely used for the preparation of 2,2′-disubstituted bis-cyclopropanes.[5]

The reaction of 2-nonyn-1-ol with CH_2I_2 and Et_3Al in CH_2Cl_2 gave 1-ethyl-1′-hexyl-bis-cyclopropane **1a** in 77% yield after 3 h at room temperature (Table 1, entry 1).[6] The reaction proceeds in hexane but does not occur in ethereal solvents (tetrahydrofuran and diethyl ether).

The complete structure elucidation of bis-cyclopropane **1a** was carried out by a variety of NMR correlation methods (COSY, HSQC and HMBC).[7]

The alkyl- and phenyl-substituted propargylic alcohols RC≡CCH_2OH (where R = *n*-Bu, *n*-Am, Ph) reacted in the same way to give the products **1b–d**. 2-Alkyl-substituted 2-alkyn-1-ols (3-octyn-2-ol, 5-decyn-4-ol) gave mixtures of regioisomeric bis-cyclopropanes in 1:1 ratios in 81% (**1e**) and 68% (**1f**) overall yields. On the other hand, a 2,2-dimethyl-substituted 2-alkyn-1-ol (2-methyl-3-octyn-2-ol) did not react with CH_2I_2–Et_3Al. The terminal propargylic alcohols (propargylic alcohol, 3-methyl-1-pentyn-3-ol, 1-ethynylcyclohexanol and 1-hexyn-3-ol) and their esters (2-propyn-1-yl acetate and 2-propyn-1-yl propionate) did not afford expected bis-cyclopropanes **1k–n**. 2-Butyn-1,4-diol and its dimethyl ether were not active in this reaction. However, the methyl ether of 2-nonyn-1-ol gave bis-cyclopropane **1a** in 82% yield. Hence, the chemistry of substituted propargylic alcohols, their esters and ethers is the same in this reaction.



R = alkyl, Ph; R¹=H, alkyl; R²=H;
R' = Et, *i*-Bu

1a-h
68-89%

Scheme 1. The synthesis of bis-cyclopropanes from propargylic alcohols.

Table 1
The synthesis of bis-cyclopropanes from propargylic alcohols[a]

Entry	R	R′	R^1	R^2	Bis-cyclopropane	GC yield (%)
1	*n*-C_6H_{13}	Et	H	H	**1a**	77
2	*n*-Bu	Et	H	H	**1b**	87
3	*n*-C_5H_{11}	Et	H	H	**1c**	89
4	Ph	Et	H	H	**1d**	72
5	*n*-Bu	Et	Me	H	**1e**	81
6	*n*-Bu	Et	*n*-Pr	H	**1f**	68
7	*n*-Bu	*i*-Bu	H	H	**1g**	85
8	Ph	*i*-Bu	H	H	**1h**	74
9	*n*-Bu	Me	H	H	**1i**	–
10	*n*-Bu	Et	Me	Me	**1j**	–
10	*n*-Bu	Et	Me	Me	**1j**	–
11	H	Et	H	H	**1k**	–
12	H	Et	*n*-Pr	H	**1l**	–
13	H	Et	Me	Et	**1m**	–
14	H	Et	–$(CH_2)_5$–		**1n**	–
15	CH_2OH	Et	H	H	**1o**	–

[a] Reaction conditions: alkyne:CH_2I_2:R_3Al = 1:5:6, CH_2Cl_2, 20–25 °C.

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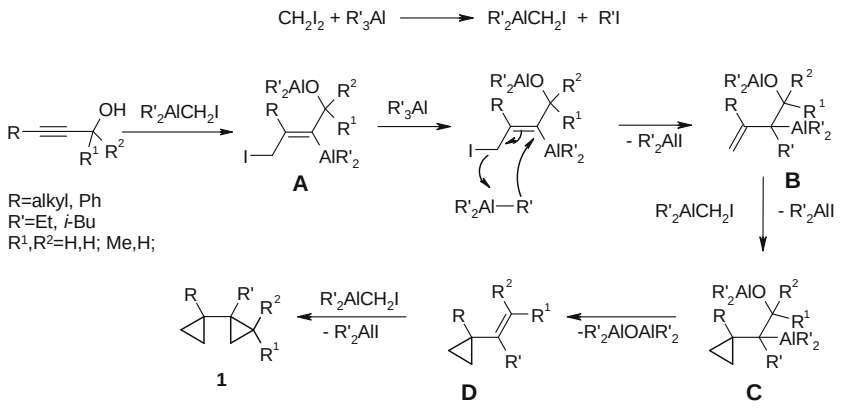
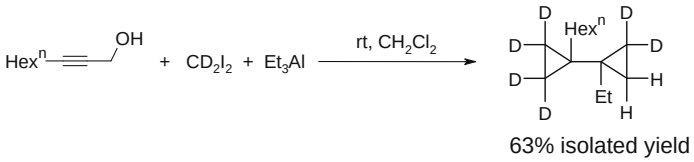


Scheme 2. A possible mechanism for the transformation.



Scheme 3. The reaction of 2-nonyn-1-ol with CD_2I_2 and Et_3Al.

The use of *i*-Bu_3Al instead of Et_3Al resulted in the formation of *iso*-butyl-substituted bis-cyclopropanes **1g, h** in high yields (74–85%). However, the reaction of 2-heptyn-1-ol with CH_2I_2–Me_3Al did not give the expected methyl-substituted bis-cyclopropane **1i**. The reaction of 2-nonyn-1-ol with CH_2I_2 in the presence of *i*-Bu_2AlH, *i*-Bu_2AlCl or Et_2AlCl did not proceed.

We assume that mechanistically the generation of dialkyl(iodomethyl)aluminium[8] occurs initially followed by carboalumination of the propargylic alcohol with the formation of iodo-containing alkenylaluminium **A**[9] (Scheme 2). Rearrangement under the action of R'_3Al affords unsaturated organoaluminium compound **B**. Cyclopropanation of the double bond[10] and elimination of $(R'_2Al)_2O$ give substituted vinylcyclopropane **D**. Finally, cyclopropanation of the latter leads to the formation of substituted bis-cyclopropane **1**.

We carried out the reaction of 2-nonyn-1-ol with CD_2I_2 and Et_3Al to confirm the proposed mechanism (Scheme 3) and obtained the corresponding deuterated bis-cyclopropane. The positions of the deuterium atoms in the product were determined by comparison of its ^1H and ^{13}C NMR spectra with those of **1a** and were as expected.

As follows from the mechanism, the low reactivity of terminal propargylic alcohols and 2-methyl-3-octyn-2-ol in this reaction could result from hindered carboalumination of the triple bond by dialkyl(iodomethyl)aluminium. We assume that the low reactivity of terminal propargylic alcohols was caused predominantly by electronic factors,[11] whereas in the case of the 2,2-disubstituted 2-alkyn-1-ol, it may be explained by steric hindrance. As noted above, Me_3Al did not react with propargylic alcohols probably as a result of its low reactivity[12] with CH_2I_2 and its greater tendency to form aggregates (compared to Et_3Al and *i*-Bu_3Al).[13] The same is true for Bu_2AlH, *i*-Bu_2AlCl and Et_2AlCl.

Acknowledgments

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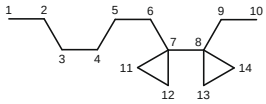
6. *Synthesis of 1-ethyl-1′-hexyl-bis-cyclopropane* (**1a**): To a solution of 2-nonyn-1-ol (0.42 g, 3 mmol) and diiodomethane (4.02 g, 15 mmol) in CH_2Cl_2 (15 mL), triethylaluminium (2.7 mL, 18 mmol) was added at 0 °C under an argon atmosphere. The mixture was stirred at room temperature for 3 h. The reaction was terminated by dilution with CH_2Cl_2 (20 mL) followed by treatment with a 7 wt% aq solution of HCl. The aqueous layer was extracted with CH_2Cl_2 (3×10 mL). The combined organic layers were then washed with saturated $NaHCO_3$ solution and dried over anhydrous $CaCl_2$. The solvent was removed under reduced pressure and the residue distilled to yield 0.40 g of an oily product (69% isolated yield, 77% GC yield). Bp 67–70 °C (1 Torr).
7. The ^1H NMR spectrum of **1a** in $CDCl_3$ shows an AA′BB′ multiplet for the cyclopropyl hydrogen atoms at 0.05–0.15 ppm which is typical for unsymmetrical 1,1-disubstituted cyclopropanes. The spectral parameters of the AA′BB′ multiplet are not discussed due to overlapping of the signals of the two cyclopropane fragments. The APT spectrum of **1a** shows resonances due to the CH_2 groups of two three-membered cycles at 9.10 and 9.20 ppm. There are four cross peaks in the HMBC spectrum between the hydrogen atoms of the cyclopropyl moieties and the carbon atoms C(6), C(7), C(8) and C(9). The spectrum shows cross peak between the hydrogen atoms of $C(10)H_3$ and carbon C(8). ^1H NMR (δ, ppm): 0.05–0.15 (m, 8H, $C(11–14)H_2$), 0.90 (t, $^3J_{CH}$ = 7.0 Hz, 3H, $C(1)H_3$), 0.96 (t, $^3J_{CH}$ = 7.4 Hz, 3H, $C(10)H_3$), 1.2–1.5 (m, 12H, $C(2–6,9)H_2$). ^{13}C NMR (δ, ppm): 9.10 and 9.20 (4C, C(11–14)), 11.13 (C(10)), 14.05 (C(1)), 20.06 (C(7)), 20.69 (C(8)), 22.70 (C(2)), 26.79 (C(5)), 29.81 (C(9)), 29.91 (C(4)), 31.96 (C(3)), 37.24 (C(6)). EIMS *m/z* (relative intensity, %): 194 (1)

$[M]^+$, 166 (65) $[M\text{-}C_2H_4]^+$, 137 (20), 123 (17), 109 (51), 96 (53), 95 (70), 81 (100). Anal. Calcd for $C_{14}H_{26}$: C, 86.52; H, 13.48. Found: C, 86.89; H, 13.11.



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11. In the case of 1-ethynylcyclohexanol, deuterolysis of the reaction mixture did not result in 1-(deuteroethynyl)cyclohexanol which indicates that metallation processes can be excluded from consideration.
12. Treatment of CH_2I_2 with Et_3Al or *i*-Bu_3Al (1:1 molar ratio) in CH_2Cl_2 at room temperature resulted in the disappearance of CH_2I_2 in 5 min due to aluminium carbenoid formation. In the case of Me_3Al, the conversion of CH_2I_2 was 73% after 2 h.
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