An unusual reaction of propargylamines with CH_2I_2 and Et_3Al

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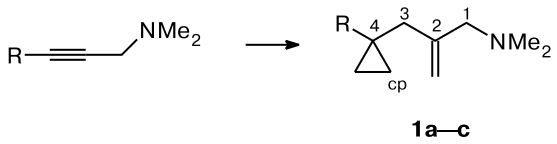
N-{2-[(1-R-Cyclopropyl)methyl]prop-2-enyl}-*N*,*N*-dimethylamines were prepared in 80—90% yields by the reaction (5 h, 23—25 °C) of propargylamines R—C≡C—CH_2NMe_2 (where R = alkyl, Ph) with a system of reactants CH_2I_2—Et_3Al taken in the molar ratio [propargylamine] : [Et_3Al] : [CH_2I_2] = 1 : 6 : 6. In the case of phenyl-substituted propargylamine, *N*-({1-[(1-phenylcyclopropyl)methyl]cyclopropyl}methyl)-*N*,*N*-dimethylamine is selectively formed in 76% yield upon the elongation of the reaction time to 4 days.

Key words: cyclopropanes, propargylamines, diiodomethane, triethylaluminum.

Compounds of the cyclopropane series are important intermediates in organic synthesis, because many of them are biologically active.[1] We have previously[2—4] found that alkyl- and phenyl-substituted acetylenes react with CH_2I_2 in the presence of Et_3Al to form cyclopropane compounds. The role of various functional substituents in biological activity induction is very high and, hence, the reactions of functionally substituted acetylene compounds with diiodomethane in the presence of trialkylalanes was studied to develop a general method of transformation of acetylenes into cyclopropanes. Substituted propargyl alcohols and amines were chosen as objects of transformation due to their accessibility and wide use in organic synthesis. It was found that substituted propargyl alcohols react with the systems of reactants CH_2I_2—R_3Al to form bis-cyclopropanes in good yields.[5] In this work, we present the results of the reaction of this system of reactants with propargylamines.

N,*N*-Dimethyl-*N*-(non-2-yn-1-yl)amine reacts with CH_2I_2 and Et_3Al under mild conditions (23—25 °C, 5 h) to form *N*-{2-[(1-hexylcyclopropyl)methyl]prop-2-en-1-yl}-*N*,*N*-dimethylamine (**1a**) in 83% yield (Scheme 1).

Scheme 1



1a—c

R = *n*-C_6H_{13} (**a**), Bu^n (**b**), Ph (**c**)

Reagents, conditions, and yields: CH_2I_2 (6 equiv.), Et_3Al (6 equiv.); CH_2Cl_2, 23—25 °C, 5 h; 83% (**a**), 79% (**b**), 89% (**c**).

The signals in the ^1H and ^{13}C NMR spectra of compound **1a** were assigned on the basis of the 2D NMR HSQC, COSY, and HMBC experiments. The ^1H NMR spectrum exhibits the characteristic multiplet signal with δ_H = 0.25—0.4 belonging to the strongly coupled four-spin system AA′BB′ of protons of the 1,1-disubstituted cyclopropane moiety. In the HMBC spectrum, this multiplet has cross-peaks with the C(3), C(4), and C(5) carbon atoms, and the singlet signals of protons of the $C(3)H_2$ group gives cross-peaks with C(1), C(2), and $=CH_2$. All interactions observed in the COSY and HMBC spectral also confirm the structure of compound **1a**.

The products of transformation of other propargylamines were synthesized and identified analogously, being substituted cyclopropanes **1b**,**c**.

It is difficult to cyclopropanate propargylamines by the systems of reactants CH_2I_2—Et_3Al because of the possible side formation of quaternary ammonium salts from CH_2I_2 or EtI (the latter is formed upon the generation of aluminum carbenoid by the exchange reaction). We established that *N*,*N*-dimethyl-*N*-(non-2-yn-1-yl)-amine in the presence of equimolar amounts of Et_3Al and CH_2I_2 form no quaternary ammonium salt because of the formation of the strong donor-acceptor bond N→Al. For this reason we proposed the following order of loading of the reactants: propargylamine, Et_3Al, and CH_2I_2. However, the organoaluminum complex should be decomposed with an aqueous solution of NaOH in order to isolate the reac-

Published in Russian in *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 8, pp. 1623—1625, August, 2010.

1066-5285/10/5908-1668

tion product. In this case, the reaction mixture can contain CH_2I_2 and EtI. It is known that EtMgBr reacts well with iodine-containing organic compounds yielding cross-coupling products. Therefore, to prevent the formation of quaternary ammonia salts, before hydrolysis the reaction mixture was treated with an ethereal solution of EtMgBr. The use of these manipulations allowed us to enhance the yield of the reaction products.

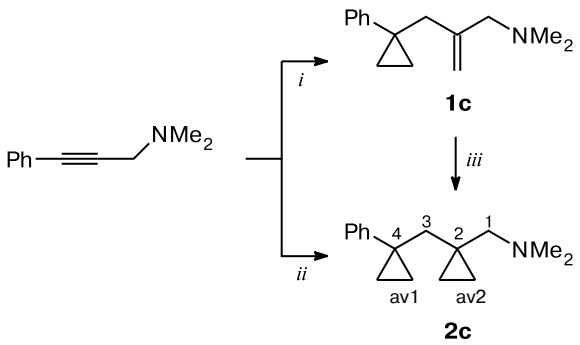
The influence of the nature of the organoaluminum compound on the yield and composition of the reaction products was studied. The highest yield of compound **1a** is observed when Et_3Al is used. The replacement of Et_3Al by $Bu^i{}_3Al$ decreases the yield of compound **1a** to 45% because of the incomplete conversion of the starting acetylene and formation of by-products. Compound **1a** is not formed in the case of Me_3Al.

The highest yield of compound **1a** was achieved when the reaction was carried out in dichloromethane and dichloroethane. The reaction does not occur in ether solvents (THF, diethyl ether).

The products of double bond cyclopropanation in compounds **1a**—**c** are slowly accumulated with the elongation of the reaction time to 4 days at room temperature. In the case of *N*,*N*-dimethyl-*N*-(3-phenylprop-2-inyl)-amine, bis-cyclopropane **2c** is formed selectively in 76% yield (Scheme 2). The addition of 2 equivalents of Et_3Al and CH_2I_2 to the reaction mixture on the next day after the starting the reaction does not accelerate cyclopropanation. Alkyl-substituted propargylamines are transformed into bis-cyclopropane compounds **2b**,**c** in 40—50% yields. In these cases, the reaction is non-selective with the side formation of unidentified isomeric compounds (according to the GC—MS data) in amounts of 30—40%. It is difficult to isolate individual compounds, because their R_f are close. A more convenient approach to bis-cyclopropane derivatives **2a**—**c** includes the isolation of compounds **1a**—**c** followed by their next cyclopropanation with CH_2I_2 and Et_3Al according to the Yamamoto procedure.[6]

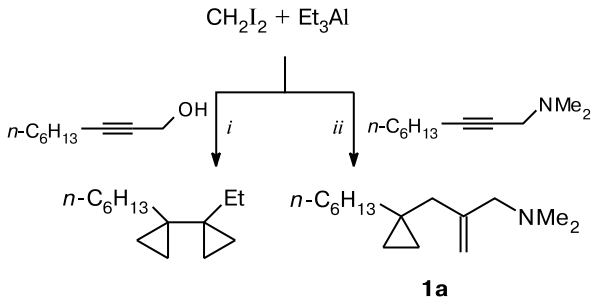
Unlike propargyl alcohols, propargylamines react with CH_2I_2—Et_3Al without elimination of the functional group (Scheme 3). The structure of 2-(cyclopropylmethyl)-allylamines **1** formed indicates that the scheme of transformations differs from that proposed for propargyl alcohols and alkyl-substituted acetylenes.[4,5] Thus, the nature of the functional group of propargyl derivatives substantially affects the direction of their interaction with the system of reactants CH_2I_2—Et_3Al. We are planning to carry out further experiments with other nitrogen-containing unsaturated compounds, which, as we hope, would elucidate the mechanism of this unusual transformation.

Scheme 2



Reagents, conditions, and yields: *i.* CH_2I_2 (6 equiv.), Et_3Al (6 equiv.), CH_2Cl_2, 23—25 °C, 3 h, 89%; *ii.* CH_2I_2 (6 equiv.), Et_3Al (6 equiv.), CH_2Cl_2, 23—25 °C, 4 days, 76%; *iii.* CH_2I_2 (2 equiv.), Et_3Al (2 equiv.), CH_2Cl_2, 23—25 °C, 6 h, 91%.

Scheme 3



Conditions and yields: *i.* CH_2Cl_2, ~20 °C, 3 h, 77%; *ii.* CH_2Cl_2, ~20 °C, 5 h, 83%.

Experimental

Commercially available reagents were used. Dichloromethane was distilled over P_2O_5. Reaction products were analyzed on a Carlo Erba chromatograph (Ultra-1 glass capillary column (Hewlett Packard) 25 m×0.2 mm, flame-ionization detector, temperature of the thermostat 50—170 °C, helium as carrier gas). Mass spectra were measured using a Finnigan 4021 instrument with an electron impact ionization energy of 70 eV and the temperature of the ionization chamber 200 °C. The elemental composition of the samples was determined on a Carlo Erba elemental analyzer (model 1106). ^1H and ^{13}C NMR spectra were recorded on a Bruker Avance 400 spectrometer (^1H, 400 MHz; ^{13}C, 100 MHz) using $SiMe_4$ and $CDCl_3$, respectively, as internal standards. The yields of compounds **2b**,**c** were determined by GC using an internal standard. TLC was carried out on Silufol UV-254 plates in an EtOAc—petroleum ether (1 : 4) system. Compound **1c** was cyclopropanated to form product **2c** according to the Yamamoto procedure.[6]

Synthesis of substituted cyclopropanes 1 (general procedure). A 25-mL glass reactor immersed in an ice bath and mounted on a magnetic stirrer was consecutively loaded in an inert gas atmosphere with CH_2Cl_2 (5 mL), propargylamine (2 mmol), Et_3Al (12 mmol), and CH_2I_2 (0.97 mL, 12 mmol). This sequence

of loading prevents the formation of ammonium salts. The mixture was stirred at ~20 °C for 5 h to obtain **1a—c** and for 4 days to obtain **2a—c**). Then a 3 *M* solution (10 mL) of EtMgBr in Et_2O was added to the reaction mixture (to decompose CH_2I_2 and EtI). The mixture was stirred for 1 h, hydrolyzed with a 25% aqueous solution of NaOH, and filtered through the paper filter. The aqueous layer was extracted with diethyl ether, and the extract was combined with the organic layer, dried with anhydrous $CaCl_2$, and concentrated *in vacuo*. Individual products were isolated on a column with silica gel. The eluent was EtOAc—petroleum ether (gradient 1 : 10→1 : 3).

***N*-{2-[(1-Hexylcyclopropyl)methyl]prop-2-en-1-yl}-*N*,*N*-dimethylamine (1a).** The yield was 0.37 g (83%), R_f 0.63. Found (%): C, 80.42; H, 12.88; N, 6.07. $C_{15}H_{29}N$. Calculated (%): C, 80.65; H, 13.08; N, 6.27. ^{1}H NMR, δ: 0.25—0.40 (m, 4 H, C(av)H_2); 0.88 (t, 3 H, C(10)H_3, J = 7.0 Hz); 1.15—1.40 (m, 10 H, C(5)H_2, C(6)H_2, C(7)H_2, C(8)H_2, C(9)H_2); 2.02 (s, 2 H, C(3)H_2); 2.18 (s, 6 H, Me_2N); 2.83 (s, 2 H, C(1)H_2); 4.95 (s, 2 H, =CH_2). ^{13}C NMR, δ: 11.79 (2 C, C(m)); 14.07 (C(10)); 17.69 (C(4)); 22.65 (C(9)); 26.45 (C(6)); 29.60 (C(7)); 31.91(C(8)); 35.75 (C(3)); 40.11 (C(5)); 45.34 (2 C, Me_2N); 65.47 (C(1)); 113.48 (=CH_2); 145.66 (C(2)). MS, m/z (I_{rel} (%)): 223 $[M]^+$ (1), 222 $[M - H]^+$ (10), 208 $[M - Me]^+$ (8), 194 $[M - C_2H_5]^+$ (15).

***N*-{2-[(1-Butylcyclopropyl)methyl]prop-2-en-1-yl}-*N*,*N*-dimethylamine (1b).** The yield was 0.21 g (79%), R_f 0.71. Found (%): C, 79.15; H, 12.90; N, 7.17. $C_{13}H_{25}N$. Calculated (%): C, 79.55; H, 13.02; N, 6.93%. ^{1}H NMR, δ: 0.30—0.40 (m, 4 H, C(av)H_2); 0.88 (t, 3 H, C(8)H_3, J = 7.2 Hz); 1.15—1.40 (m, 6 H, C(5)H_2, C(6)H_2, C(7)H_2); 2.03 (s, 2 H, C(3)H_2); 2.17 (s, 6 H, Me_2N); 2.84 (s, 2 H, C(1)H_2); 4.96 (s, 2 H, =CH_2). ^{13}C NMR, δ: 11.78 (2 C, C(av)); 14.16 (C(8)); 17.67 (C(4)); 22.97 (C(7)); 28.74 (C(6)); 35.41 (C(5)); 40.12 (C(3)); 45.35 (2 C, Me_2N); 65.46 (C(1)); 113.58 (=CH_2); 145.57 (C(2)). MS, m/z (I_{rel} (%)): 195 $[M]^+$ (1), 194 $[M - H]^+$ (8), 180 $[M - Me]^+$ (8), 166 $[M - C_2H_5]^+$ (20), 152 $[M - C_3H_7]^+$ (9), 138 $[M - C_4H_9]^+$ (7), 135 (19).

***N*-{2-[(1-Phenylcyclopropyl)methyl]prop-2-en-1-yl}-*N*,*N*-dimethylamine (1c).** The yield was 0.38 g (89%), R_f 0.45. Found (%): C, 83.79; H, 9.57; N, 6.31. $C_{15}H_{21}N$. Calculated (%): C, 83.67; H, 9.83; N, 6.50. ^{1}H NMR, δ: 0.80—0.95 (m, 4 H, C(av)H_2); 2.13 (s, 6 H, Me_2N); 2.50 (s, 2 H, C(3)H_2); 2.75 (s, 2 H, C(1)H_2); 4.70—4.90 (m, 2 H, =CH_2); 7.30—7.40 (m, 5 H, Ph). ^{13}C NMR, δ: 13.93 (2 C, C(av)); 23.48 (C(4)); 43.31 (C(3)); 45.32 (2 C, Me_2N); 65.91 (C(1)); 114.44 (=CH_2); 125.50 (C(8)); 127.87, 128.06 (4 C, C(6), C(6′), C(7), C(7′)); 145.62 (C(2)). MS, m/z (I_{rel} (%)): 215 $[M]^+$ (1).

***N*-({1-[(1-Hexylcyclopropyl)methyl]cyclopropyl}methyl)-*N*,*N*-dimethylamine (2a).** The yield was 48%, R_f 0.54. Found (%): C, 80.21; H, 12.79; N, 6.01. $C_{16}H_{31}N$. Calculated (%): C, 80.94; H, 13.16; N, 5.90. ^{1}H NMR, δ: 0.15—0.45 (m, 8 H, C(cp1)H_2, C(av2)H_2); 0.89 (t, 3 H, C(10)H_3, J = 6.8 Hz); 1.20—1.35 (m, 10 H, C(5)H_2, C(6)H_2, C(7)H_2, C(8)H_2, C(9)H_2); 2.11 (s, 2 H, C(3)H_2); 2.18 (s, 6 H, Me_2N); 2.22 (s, 2 H, C(1)H_2). ^{13}C NMR, δ: 10.49, 11.77 (4 C, C(av1), C(av2)); 14.13 (C(10)); 16.88 (C(4)); 18.21 (C(2)); 22.61 (C(9)); 26.51 (C(6)); 29.48 (C(7)); 31.83 (C(8)); 39.69 (C(3)); 40.04 (C(5)); 45.74 (2 C, Me_2N); 65.72 (C(1)). MS, m/z (I_{rel} (%)): 237 $[M]^+$ (1), 236 (1), 235 (1), 222 $[M - Me]^+$ (5), 208 $[M - C_2H_5]^+$ (5), 194 $[M - C_3H_7]^+$ (12), 180 $[M - C_4H_9]^+$ (10).

***N*-({1-[(1-Butylcyclopropyl)methyl]cyclopropyl}methyl)-*N*,*N*-dimethylamine (2b).** The yield was 41%, R_f 0.5. Found (%): C, 79.73; H, 12.32; N, 6.50. $C_{14}H_{27}N$. Calculated (%): C, 80.31; H, 13.00; N, 6.69. ^{1}H NMR, δ: 0.15—0.45 (m, 8 H, C(av1)H_2, C(av2)H_2); 0.88 (t, 3 H, C(8)H_3, J = 7.2 Hz); 1.20—1.40 (m, 6 H, C(5)H_2, C(6)H_2, C(7)H_2); 2.09 (s, 2 H, C(3)H_2); 2.17 (s, 6 H, Me_2N); 2.20 (s, 2 H, C(1)H_2). ^{13}C NMR, δ: 10.49, 11.76 (4 C, C(av1), C(av2)); 14.16 (C(8)); 23.12(C(7)); 28.89 (C(6)); 35.90 (C(5)); 39.72 (C(3)); 45.73 (2 C, Me_2N); 65.74 (C(1)). MS, m/z (I_{rel} (%)): 209 $[M]^+$ (1), 208, 207 (1) (1), 194 $[M - Me]^+$ (5), 180 $[M - C_2H_5]^+$ (5), 166 $[M - C_3H_7]^+$ (10).

***N*-({1-[(1-Phenylcyclopropyl)methyl]cyclopropyl}methyl)-*N*,*N*-dimethylamine (2c).** The yield was 0.35 g (76%), R_f 0.57. Found (%): C, 83.29; H, 10.11; N, 6.11. $C_{16}H_{23}N$. Calculated (%): C, 83.51; H, 9.92; N, 6.17. ^{1}H NMR, δ: –0.15—0.00 (m, 4 H, C(av1)H_2); 0.80—0.90 (m, 4 H, C(av2)H_2); 1.67 (s, 2 H, C(3)H_2); 2.10 (s, 2 H, C(1)H_2); 2.20 (s, 6 H, Me_2N); 6.90—7.50 (m, 5 H, Ph). ^{13}C NMR, δ: 10.42, 11.98 (4 C, C(av2), C(av2)); 17.02 (C(2)); 24.34 (C(4)); 44.48 (C(3)); 45.59 (2 C, Me_2N); 65.88 (C(1)); 125.79 (C(8)); 128.64, 129.82 (4 C, C(6), C(6′), C(7), C(7′)); 146.30 (C(5)). MS, m/z (I_{rel} (%)): 229 $[M]^+$ (1).

This work was financially supported by the Council on Grants at the President of the Russian Federation (Program for State Support of the Leading Scientific Schools of the Russian Federation, Grant NSh-4105.2010.3) and the Division of Chemistry and Materials Science of the Russian Academy of Sciences (Program No. 1).

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Received March 10, 2010;
in revised form May 12, 2010