Aluminum carbenoid Et_2AlCH_2I – a new cyclopropanation agent for the transformation of unsaturated amines into cyclopropyl amines

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Introduction.

Despite the ease of obtaining aluminum carbenoids by the reaction of CH_2I_2 and trialkylaluminums, their chemistry has been little studied. Over the last few years the authors have developed a new approach to the synthesis of cyclopropane compounds based on the reaction of substituted alkynes and allenes with aluminum carbenoids [1,2]. Substituted propargyl alcohol and amines have been successfully involved in the reaction [3,4]. At the same time, only a few examples for the cyclopropanation of functionally-substituted alkenes by aluminum carbenoid are known, such as geraniol, perillyl alcohol, γ-silicon substituted allylic alcohols [5-7]. In order to develop a general method for the preparation of functionally-substituted cyclopropanes, in this paper we have studied the reaction of aluminum carbenoids with unsaturated amines, such as allyl amines and enamines.

Resultes and discussion.

We found that substituted allyl amines (allyldiethylamine, allyl piperidine, allyl *tert*-octyl amine) react with two equivalents of Et_3Al and CH_2I_2 at room temperature in dichloromethane to give corresponding substituted cyclopropylmethyl amines **1a-d** in high yield (71-87%) (Scheme 1). The cyclopropanation proceeds successfully in hexane as well. However, the use of benzene or toluene as a solvent is undesirable due to the side reaction of

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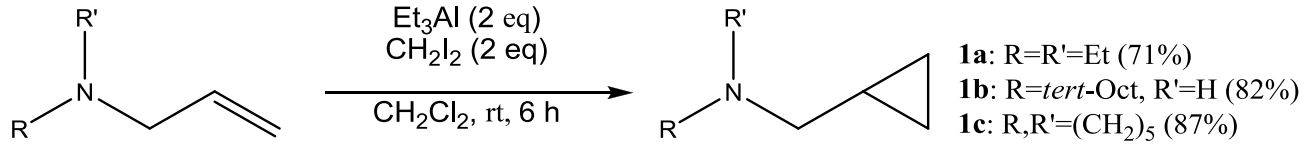
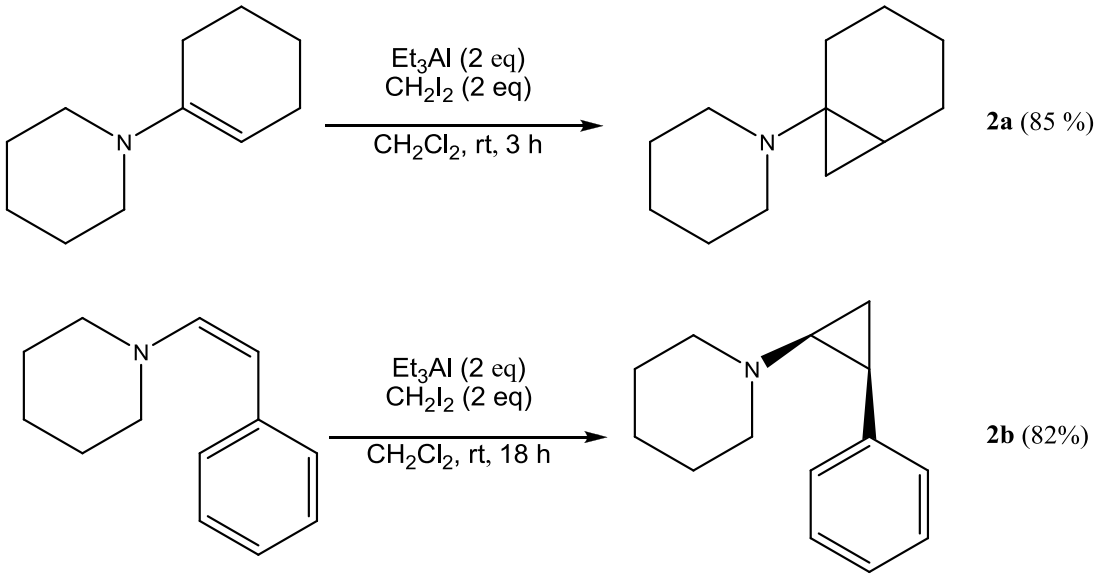
aromatic ring alkylation. Carrying out the reaction in tetrahydrofuran of diethyl ether inhibits the process of aluminum carbenoid formation from CH_2I_2 and Et_3Al. The reaction is complete in 6 hours typically.

Scheme 1.



Thus, the presence of a nitrogen atom in the structure of unsaturated compound did not prevent the cyclopropanation of the double bond. Of the particular interest was the extension of the reaction to the enamines, where the nitrogen atom is directly attached to the double bond. We found that the reaction of substituted enamines (1-cyclohexenylpiperidine, (*Z*)-1-styrylpiperidine) with two equivalents of Et_3Al and CH_2I_2 in the conditions described above results in the formation of corresponding substituted cyclopropyl amines **2a,b** in high yields () (Scheme 2). The reaction is complete in 3-18 hours depending on the amine structure. The transformation proceeds with retention of configuration of the substituents at the double bond in (*Z*)-1-styrylpiperidine.

Scheme 2.



The advantage of the proposed methodology is conveniently illustrated by the cyclopropanation of 1-cyclohexenylpyrrolidine. Cyclopropanation product was obtained only

in 8% yield using Simmons-Smith procedure (CH_2I_2-Cu/Zn) [8], 48% yield with Furukawa reagent [9] and 22% yield by means of CH_2Br_2-Zn/Cu-AcCl reagent [10] (Scheme 3). The best result (61%) was achieved using $CuCl_2$-diazomethane method [9]. CH_2I_2-Et_3Al reagent allows the preparation of 1-aminobicyclo[n.1.0]alkanes in high yield. There was no trace of starting enamine remaining in the resulting reaction mixture that is important because the product of the cyclopropanation is difficult to separate from enamine by conventional distillation or rectification due to the proximity of boiling points. We should mention another method of enamine cyclopropanation by Mg-CH_2Cl_2-[Ti] reagent which gives the product in high yield also [11] . However the latter reagent cannot be used for the cyclopropanation of allyl amines.

Experimental part.

General Procedures

The reagents were obtained from Aldrich or Acros. Dichloromethane was distilled over P_2O_5. Mass spectra were obtained on a Finnigan 4021 instrument. Nuclear Magnetic Resonance spectroscopy was performed on a Brucker Avance-400. The ^{1}H NMR spectra were recorded at 400 MHz and ^{13}C NMR spectra at 100 MHz in $CDCl_3$. The chemical shifts are reported in ppm relative to tetramethylsilane (TMS) as the internal standard. The numbering of atoms in the ^{13}C- and ^{1}H-NMR spectra of the compounds **1a-c, 2a** and **2b** is shown in Figure 1.

Synthesis of substituted cyclopropanes

To a solution of 2 mmole of substituted allyl amine or enamine in CH_2Cl_2 (5 mL), 4 mmole of Et_3Al (*caution: organoaluminums are pyrophoric and can ignite on contact with air, water or any oxidizer*) and 4 mmole of CH_2I_2 (0.32 mL) were added at 0 ^{o}C under an argon atmosphere. The mixture was stirred at room temperature until reaction complete. The reaction was terminated by dilution with CH_2Cl_2 (5 mL) followed by treatment with a 10N NaOH. The aqueous layer was extracted with CH_2Cl_2 (3x10 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.

N-(Cyclopropylmethyl)-N-ethylethanamine (1a). Bp 136-140°C. ^{1}H NMR δ 0.05-0.15 (m, 2H, C(3,4)H_a), 0.3-0.45 (m, 2H, C(3,4)H_b), 0.85-0.95 (m, 1H, C(2)H), 1.03 (t, $^{3}J_{CH}$ = 7.4 Hz, 6H, C(6,8)H_3), 2.52 (d, $^{3}J_{CH}$ = 7.2 Hz, 2H, C(1)H_2), 2.80 (q, $^{3}J_{CH}$ = 7.4 Hz, 4H, C(5,7)H_2). ^{13}C NMR δ 3.80 (2C, C(3,4)), 7.68 (C(2)), 9.24 (2C, C(6,8)), 46.00 (2C, C(5,7)), 56.29 (C(1)).

N-(Cyclopropylmethyl)-2,4,4-trimethylpentan-2-amine (1b). Bp 82-85°C (10 mm Hg). ^{1}H NMR δ 0.0-0.1 (m, 2H, C(3,4)H_a), 0.4-0.6 (m, 2H, C(3,4)H_b), 0.85-0.95 (m, 1H, C(2)H), 0.98 (s, 9H, C(8,11,12)H_3), 1.10 (s, 6H, C(9,10)H_3), 1.39 (s, 2H, C(6)H_2), 2.37 (d, $^{3}J_{CH}$ = 6.8 Hz, 2H, C(1)H_2). ^{13}C NMR δ 3.32 (2C, C(3,4)), 11.88 (C(2)), 28.92 (2C, C(9,10)), 31.57 (C(7)), 31.68 (3C, C(8,11,12)), 47.23 (C(1)), 52.83 (C(6)), 53.79 (C(5)).

1-(Cyclopropylmethyl)piperidine (1c). Bp 71-75°C (13 mm Hg). ^{1}H NMR δ 0.05-0.15 (m, 2H, C(3,4)H_a), 0.45-0.55 (m, 2H, C(3,4)H_b), 0.85-0.95 (m, 1H, C(2)H), 1.4-1.5 (m, 2H, C(7)H_2), 1.55-1.65 (m, 4H, C(6,8)H_2), 2. 23 (d, $^{3}J_{CH}$ = 6.8 Hz, 2H, C(1)H_2), 2.47 (br.s., 4H, C(5,9)H_2). ^{13}C NMR δ 3.97 (2C, C(3,4)), 8.39 (C(2)), 24.47 (C(7)), 25.95 (2C, C(6,8)), 54.64 (2C, C(5,9)), 64.63 (C(1)).

1-(Bicyclo[4.1.0]heptan-1-yl)piperidine (2a). Bp 88-90°C (3 mm Hg). ^{1}H NMR δ 0.15-0.25 (m, 1H, C(2)H_a), 0.6-0.7 (m, 1H, C(2)H_b),), 0.9-1.0 (m, 1H, C(3)H), 1.0-1.65 (m, 14H, C(4-7,9-11)H_2), 2.45-2.65 (m, 4H, C(8,12)H_2). ^{13}C NMR δ 19.65 (C(2)), 20.79, 21.28, 21.52, 22.64, 24.41, 24.76, 26.25 (2C, C(9,11)), 43.51 (C(1)), 49.33 (2C, C(8,12)).

1-(Cis-2-phenylcyclopropyl)piperidine (2b). Bp 105-108°C (1 mm Hg). ^{1}H NMR δ 0.9-1.0 (m, 1H, C(3)H_a), 1.1-1.2 (m, 1H, C(3)H_b), 1.4-1.55 (m, 2H, C(6)H_2), 1.4-1.5 (m, 2H, C(7)H_2), 1.55-1.65 (m, 4H, C(5,7)H_2), 1.8-1.9 (m, 1H, C(1)H), 2.0-2.1 (m, 1H, C(2)H), 2.62 (br.s., 4H, C(4,8)H_2), 7.0-7.5 (m, 5H, Ph). ^{13}C NMR δ 16.47 (C(3)), 24.42 (C(6)), 24.50 (C(2)), 25.83 (2C, C(5,7)), 49.75 (C(1)), 54.48 (2C, C(4,8)), 125.50 (C(12)), 126.08 (2C, C(10,14)), 128.21 (2C, C(11,13)), 142.43 (C(9)).

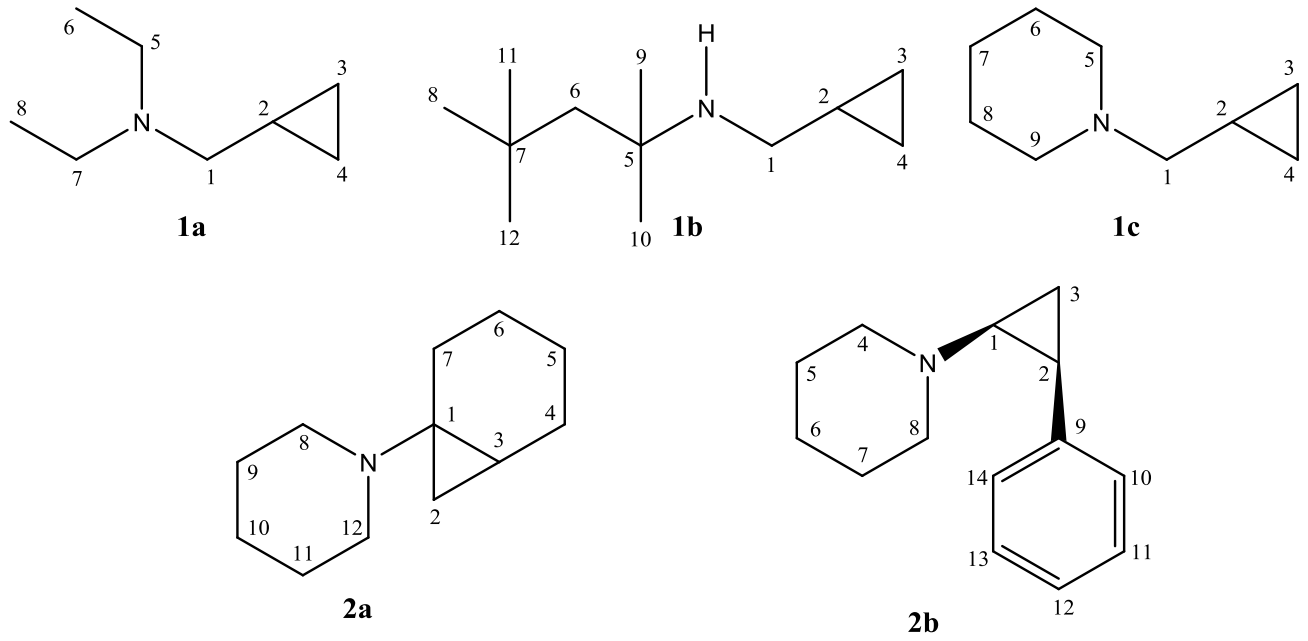


Figure 1. The numbering of atoms in the ^{13}C- and ^{1}H-NMR spectra of the compounds **1a-c, 2a** and **2b.**

Acknowledgments

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