Reactions of Grignard reagents with 1,3-dicyanoadamantane

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Reactions of Grignard reagents RMgX (R = Me, Et, Pr, Bu; X = Br, I) with 1,3-dicyanoadamantane (1) were studied. Optimum conditions for the synthesis of monoaddition products of Grignard reagents to compound 1 were established. The first stage of the reaction of cyanoadamantane 1 with MeMgBr was studied by the MNDO-PM3 method. According to calculations, the more preferable reaction mechanism involves formation of a six-membered cyclic intermediate containing two Mg atoms, two C atoms, and one Br and one N atom.

Key words: adamantane, cyanoadamantanes, Grignard reagents, 1-cyano-3-oxo-adamantanes, quantum-chemical calculations, reaction mechanism.

Dicyanoadamantanes are intermediate compounds, which are used in the synthesis of some derivatives (in particular, diamines possessing various types of therapeutic activity¹) and polymeric materials with improved operating characteristics.² In this work we studied the reactions of 1,3-dicyanoadamantane (1) with Grignard reagents RMgX (R = Me, Et, Pr, Bu; X = Br, I) in Et₂O and Et₂O-THF mixture (Scheme 1).

Scheme 1



R = Me (a), Et (b), Pr (c), Bu (d); X = I (a, b), Br (c, d)

The starting point was to study the reactions of Grignard reagents with compound 1 in Et_2O . However, the reactions were complicated by the precipitation of

N-halomagnesiumketimine **2**, which made the yield of the target product **3** very low. The solubility of ketimine **2** can be enhanced by using THF as co-solvent; in this case the duration of the reaction somewhat increases. Therefore, subsequent experiments were performed with THF—Et₂O mixtures (the solvents were taken in a 1 : 1 to 1 : 2 (v/v) ratio).

The kinetics of the reactions under study are strongly affected by the structure of the substrate, as well as by the solvent nature and temperature. To ensure control of the course of the reactions and to establish the mechanism of the reactions of compound **1** with Grignard reagents, the first stage of the process was studied by the MNDO-PM3 method.

First, to be certain that nonvalent (bridging) bonds formed by the Mg atom are correctly described by this quantum-chemical method, we carried out a theoretical study of MeMgBr dimerization. The Grignard reagent molecules form associates in solution; the coordination sphere of the Mg atom can also contain some solvent molecules while the coordination number of Mg can vary from 4 to $6.^3$ The calculated geometric parameters of three possible MeMgBr dimers (Table 1) are in reasonable agreement with the experimental values for organomagnesium compounds.³ Based on the dimerization energies ΔE (see Table 1), the dimer with two bridging Br atoms is the most energetically favorable; this is consistent with the experimental data.³ The rather high ΔE values are due to the fact that the models chosen ignored the presence of solvent molecules within the coordination sphere of the metal atom (cf. $\Delta E = -17.6 \text{ kJ mol}^{-1} \text{ ob-}$

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Compound	ΔE /kJ mol ⁻¹	Q_{Mg}	r _{Mg-Br}	r _{Mg-C}
			Å	
CH ₃ —Mg—Br	_	+0.72	2.37	1.87
Br-Mg, Mg-Br CH ₃	-162.4	+0.69	_	2.15
Br-Mg, Mg-CH ₃	-228.8	+0.61	2.42	2.15
H ₃ C-Mg ^{Br} _{Mg} -CH ₃	-256.0	+0.67	2.38	_

 Table 1. Molecular and electronic structure of MeMgBr and its dimers

Note. $\Delta E = E_{\text{dimer}} - 2E_{\text{monomer}}$ is the dimerization energy, Q_{Mg} is the atomic charge of Mg, $r_{\text{Mg-Br}}$ and $r_{\text{Mg-C}}$ are the corresponding average bridging bond lengths (interatomic distances for MeMgBr).

tained in our calculations for MeMgBr with inclusion of these effects) (Scheme 2).

Scheme 2



Thus, the geometric parameters and energy characteristics of the bridging bonds in the Grignard reagent molecules can be qualitatively reproduced by the PM3 method, but obtaining quantitatively correct results requires the inclusion of solvent molecules within the coordination sphere of the metal. However, in order to make the calculations less difficult, because the exact number of solvent molecules involved in the reaction is unknown, and taking into account that the chemical properties of a Grignard reagent and its behavior in chemical reactions can always be qualitatively explained by the formula RMgX,⁴ subsequent computations were carried out without inclusion of solvent molecules.

A study⁵ on the kinetics of the first stage of the reaction between BuMgBr and benzonitrile revealed a rapid formation of an intermediate complex of the reactants and showed that intramolecular rearrangement in the complex is the rate-determining step for the overall reaction. Three possible mechanisms of the reactions between nitriles and Grignard reagents were proposed.^{5–9} All of them involve the formation of an intermediate product containing a four- or a six-membered ring (Scheme 3).



Note. Figures preceded by the "+" or "-" sign are the atomic charges; other figures are the bond orders.

To choose the preferred mechanism of the reaction of compound 1 with MeMgBr, we analyzed the results of calculations of intermediate products 4-6, carried out with full geometry optimization. The attainment of a global energy minimum was checked by performing calculations with modified initial molecular geometries. According to calculations, the formation of intermediates 4 and 5 is energetically favorable (Table 2). Structure 6 does not correspond to a minimum on the potential energy surface (geometry optimization leads to the starting compounds); therefore, the corresponding reaction route is hardly probable. We also calculated some other possible structures containing four- and six-membered rings with different types of arrangement of the constituent atoms; however,

Table 2. Energy characteristics of different reaction mechanisms

Intermediate complex	ΔE_1	ΔE_2	ΔE_3	
		kJ mol ⁻¹		
4	-153.9	+19.4	-134.5	
5	-163.9	+29.4	-134.5	
6	_	_	-134.5	

Note. ΔE_1 is the energy of formation of intermediate complexes (**4**-**6**) from **1**, ΔE_2 is the formation energy of the end product (rearrangement of **4**-**6** into **2**), and ΔE_3 is the energy of formation of *N*-halomagnesiumketimine **2** from **1**.

compounds **4** and **5** were found to be the most energetically favorable.

According to calculations, the four- and six-membered rings in molecules 4 and 5, respectively, are nearly planar. The atomic charge distribution patterns (alternation of negative and positive charges) for these rings are typical of rather stable cyclic structures (see Scheme 3). The bond orders for the newly formed C-Me and N-Mg bonds (0.90-0.96 and 0.81-1.05, respectively) are characteristic of single bonds. The multiplicities of the carbon-nitrogen bonds in molecules 4 and 5 are reduced to 2 (the corresponding bond orders lie between 1.90 and 1.99). This means that the intermediates 4 and 5 correspond to the situation where the addition of the Grignard reagent to dinitrile 1 is nearly completed. Namely, one should only cleave a weak Mg-Me bond (bond order is 0.06 and bond energy is $+19.4 \text{ kJ mol}^{-1}$) for 4 and eliminate a rather loosely bound MeMgBr (interaction energy is $+29.4 \text{ kJ mol}^{-1}$) for 5 (see Table 2) to obtain ketimine **2**.

Thus, the reaction of dinitrile 1 with MeMgBr can involve the formation of two cyclic intermediates, 4 and 5, the latter being somewhat more energetically favorable. The choice of particular reaction route seems to be dependent on many factors. In particular, if either molecule 1 or the Grignard reagent molecule produce some steric hindrances, only one RMgBr molecule is involved in the formation of the cyclic intermediate and the reaction proceeds via the four-membered ring 4. For instance, our calculations of structures of the types 4 and 5 for the reaction of compound 1 with sterically hindered PhCH₂MgBr showed that the structure with the fourmembered ring is by 38.3 kJ mol^{-1} more preferable than the structure containing the six-membered ring. The course of the reaction can also be strongly affected by the reagent concentrations. For instance, an increase in the RMgBr concentration should favor the reaction via the six-membered ring 5.

Based on the results of our calculations, this can be done with certainty using a twofold excess of the Grignard reagent. In practice, the use of a THF—Et₂O (1:2) mixture and a 2.8 to 3.2 excess of the Grignard reagent allows one to obtain the monoaddition products in 70—78% yields (Table 3). It should be noted that a reasonably high (up to 80%) yield of the diaddition product in the reaction of dinitrile **1** with MeMgI can be obtained if the molar excess of the Grignard reagent is greater than 4.4 and the substrate concentration is at least $0.1-0.2 \text{ mol L}^{-1}$.

Thus, we proposed the most probable mechanism of the reaction of 1,3-dicyanoadamantane with Grignard reagents, involving the formation of cyclic intermediates **4** and **5**. The route *via* the six-membered ring **5** is somewhat more energetically preferable (by 10 kJ mol^{-1}) than the

Table 3. Effect of substituents in the Grignard reagent molecules on the yields of ketonitriles 3a-d

Grignard reagent	Molar excess of Grignard reagent	Duration of first stage/h	Yield 3a—d (%)
MeMgI	2.8	3	78
EtMgI	3.2	3	75
PrMgBr	3.2	8	70
BuMgBr	3.2	12	72

Note. The concentration of substrate 1 was 0.3 mol L^{-1} .

route *via* the four-membered ring **4**. The choice of a particular reaction pathway is determined by the steric hindrances produced by reactants, by the reactant concentrations, and by the solvent nature. The conditions for the synthesis of alkyl(cyanoadamantyl)ketones in 70-78%yields are substantiated.

Experimental

IR spectra were obtained on a Specord-M82 spectrometer (KBr pellets) and ¹H NMR spectra were recorded on a Bruker AM-300 spectrometer (300.13 MHz) in DMSO-d₆ with Me₄Si as internal standard. GLC analyses were performed on a Perkin–Elmer–Sigma 2S chromatograph equipped with a flame-ionization detector and a stainless steel column (0.3×100 cm, 10% PPMS-4, Chromatone N-AW-DMCS, nitrogen as the carrier gas) with linear temperature programming in the range from 80 to 230 °C. Quantum-chemical calculations were carried out by the MNDO-PM3 method¹⁰ with full geometry optimization for all compounds involved in reactions.

3-Acetyl-1-cyanoadamantane (3a). A reactor equipped with a stirrer, a reflux condenser with a calcium chloride tube, and a dropping funnel was charged with Mg (8.16 g, 0.28 mol) and Et₂O (100 mL). Then, MeI (17.4 mL, 0.28 mol) dissolved in Et_2O (50 mL) and compound **1** (18.6 g, 0.10 mol) dissolved in THF (100 mL) were added successively from a dropping funnel over a period of 0.5 h. The reaction mass was stirred for 3 h, cooled, and then water (25 mL), 12% NaOH solution (40 mL), an additional 30 mL of water and NH₄Cl (5 g) was added. The precipitate that formed was filtered and extracted with THF (3×150 mL). The extract was evaporated and the stillage residue was distilled in vacuo. The yield was 15.8 g (78%), b.p. 165-168 °C (2 Torr). Recrystallization from PrⁱOH gave the target product of 98% (GLC monitoring), b.p. 98-102 °C. Found (%): C, 76.62; H, 8.38; N, 6.81. C₁₃H₁₇NO. Calculated (%): C, 76.81; H, 8.43; N, 6.89. IR spectrum, v/cm⁻¹: 2910, 2853 (≡C−H); 2230 (C≡N); 1704 (C=O). ¹H NMR, δ: 1.51–1.75 (m, 12 H, CH₂ adamantane); 1.97 (s, 2 H, CH adamantane); 2.10 (s, 3 H, Me).

1-Cyano-3-propionyladamantane (3b) was synthesized analogously to compound **3a** using EtI (25.6 mL, 0.32 mol) instead of MeI. The yield was 16.2 g (75%), b.p. 179–181 °C (2 Torr). Recrystallization from $Pr^{i}OH$ —hexane mixture (1 : 3, v/v) gave the target product of 97% purity (GLC monitoring), b.p. 58–62 °C. Found (%): C, 77.18; H, 8.72; N, 6.36. $C_{14}H_{19}NO.$ Calculated (%): C, 77.38; H, 8.81; N, 6.45. IR spectrum, v/cm⁻¹: 2911, 2850 (\equiv C–H); 2235 (C \equiv N); 1710 (C=O). ¹H NMR, δ : 0.82 (br.s, 3 H, Me); 1.49–1.71 (m, 12 H, CH₂ adamantane); 2.18 (s, 2 H, CH adamantane); 2.45 (q, 2 H, CH₂C=O, J = 7 Hz).

3-Butyryl-1-cyanoadamantane (3c) was synthesized analogously to compound **3a** using PrBr (29.1 mL, 0.32 mol) instead of MeI. The reaction was carried out over a period of 8 h. The yield was 16.2 g (70%), b.p. 187–190 °C (2 Torr). Found (%): C, 78.73; H, 9.07; N, 5.97. $C_{15}H_{21}NO.$ Calculated (%): C, 77.88; H, 9.15; N, 6.06. IR spectrum, v/cm⁻¹: 2912, 2852 (\equiv C–H); 2241 ($C\equiv$ N); 1706 (C=O). ¹H NMR, δ : 0.90 (t, 3 H, Me, J = 6 Hz); 1.28 (m, 2 H, CH₂CH₂Me); 1.51–1.71 (m, 12 H, CH₂ adamantane); 2.05 (s, 2 H, CH adamantane); 2.38 (t, 2 H, CH₂CH₂C=O, J = 7 Hz).

1-Cyano-3-pentanoyladamantane (3d) was synthesized analogously to compound **3a** using BuBr (33.7 mL, 0.32 mol) instead of MeI. The reaction was carried out over a period of 12 h. The yield was 17.6 g (72%), b.p. 197–200 °C (2 Torr). Found (%): C, 78.18; H, 9.36; N, 5.62. C₁₆H₂₃NO. Calculated (%): C, 78.32; H, 9.45; N, 5.71. IR spectrum, v/cm^{-1} : 2908, 2855 (=C-H); 2247 (C=N); 1701 (C=O). ¹H NMR, δ : 0.90 (t, 3 H, Me, J = 6.5 Hz); 1.23–1.33 (m, 4 H, CH₂CH₂CH₂); 1.63–1.92 (m, 12 H, CH₂ adamantane); 2.05 (s, 2 H, CH adamantane); 2.41 (t, 2 H, CH₂CH₂C=O, J = 7 Hz).

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