ISSN 1070-3632, Russian Journal of General Chemistry, 2013, Vol. 83, No. 6, pp. 1170–1171. © Pleiades Publishing, Ltd., 2013.
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## LETTERS TO THE EDITOR

# Synthesis of 2-Hydroxy-2-carboxyalkyladamantanes

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Received February 14, 2013

**DOI:** 10.1134/S1070363213060327

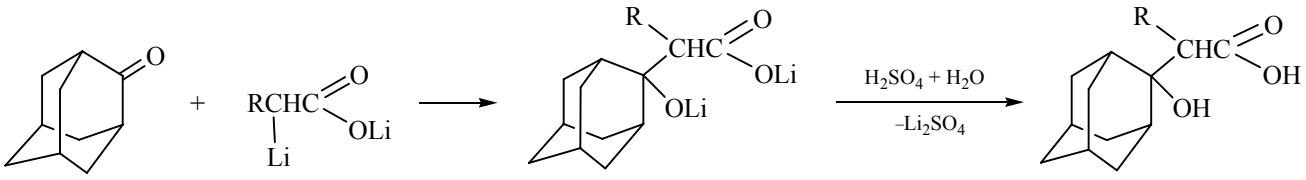
Organolithium compounds along with organomagnesium compounds are widely used as metallating agents in various syntheses. Usually these reactions are carried out in the presence of strong bases, acting as lithium carriers (*n*-butyllithium and lithium diisopropylamide) in tetrahydrofuran at –78°C [1–3]. This method is time-consuming as it involves the use of an inert atmosphere, maintaining a low temperature, and having a difficult isolation step.

We developed a method of synthesis of 2-hydroxy-2-carboxyalkyladamantanes **IVa**, **IVb** via the reaction of adamantan-2-one **I** with dilithium salt of acetic **IIa** or propionic acid **IIb**. Synthesis was performed at room temperature using lithium bis(trimethylsilyl)-amide as transmetallating agent.

Lithium hexamethyldisilamide was prepared from lithium hexamethyldisilazane and phenyllithium at the molar ratio of 1:(1.4–1.5) for a more rapid and complete transmetalation. Next, in the same reaction volume was synthesized dilithium salt **II** by reaction of lithium hexamethyldisilamide with lithium acetate or propionate in a molar ratio of 1:1.2, respectively. Dilithium salts of 2-hydroxy-2-carboxyalkyladamantanes **IIIa**, **IIIb** were obtained by reacting compounds **I** and **IIa**, **IIb** at a molar ratio of 1:(1.3–1.5). The isolation of the desired products **IVa**, **IVb** was carried out by treating compounds **IIIa**, **IIIb** with diluted sulfuric acid. The whole process of the synthesis proceeds in a one pot in anhydrous tetrahydrofuran medium at a temperature of 0–45°C over 5–6 h. Yield of 2-hydroxy-2-carboxyalkyladamantanes **IVa**, **IVb** is 76 and 87%, respectively. The structure of the synthesized compounds was confirmed by the $^1$H NMR and IR spectroscopy, and the composition, by elemental analysis.

Due to the presence of two functional groups, the resulting hydroxy acids **IVa**, **IVb** are capable of forming heterocyclic compounds promising for studying their pharmacological activity [3].

**General procedure for the synthesis of 2-hydroxy-2-carboxyalkyladamantanes (IV).** To 0.3 mol of thinly sliced metal lithium in 20 ml of THF under vigorous stirring was added by portions 0.15 mol of bromobenzene with a rate not allowing the temperature to rise above 20–25°C. After lithium dissolution, to the cooled mixture was added by portions 0.25 mol of hexamethyldisilazane. The mixture was heated for 1–1.5 h at 20°C. Then to the mixture was added 0.3 mol of lithium acetate or propionate. The reaction mixture was stirred for 1–1.5 h at 20°C, then to it was poured a solution of 0.1 mol of compound **I** in THF. The mixture was heated at reflux with stirring for 2 h and cooled. Organolithium compound was decomposed with a large excess of water. The mixture was




**I** **IIa, IIb** **IIIa, IIIb** **IVa, IVb**

R = H (**a**), $CH_3$ (**b**).

separated into two layers: an aqueous layer was extracted with ether and the organic layer was washed with aqueous solution of sodium hydroxide. The combined aqueous extracts were treated with diluted sulfuric acid until slightly acidic medium. The precipitate was filtered off and dried. Yield 76–85%.

**2-Hydroxy-2-(carboxymethyl)adamantane (IVa).** Yield 76%, mp 124–127°C. IR spectrum, ν, $cm^{-1}$: 1738 (C=O), 3352 (OH). $^1H$ NMR spectrum, δ, ppm: 1.32–2.15 m (14H, 2,2-Ad), 2.50 s (2H, $CH_2$). Found, %: C 68.61; H 8.53. $C_{12}H_{18}O_3$. Calculated, %: C 68.57; H 8.57.

**2-Hydroxy-2-(carboxyethyl)adamantane (IVb).** Yield 87%, mp 138–141°C. IR spectrum, ν, $cm^{-1}$: 1756 (C=O), 3364 (OH). $^1H$ NMR spectrum, δ, ppm: 0.91 d (3H, $CH_3$), 1.31–2.18 m (14H, 2,2-Ad), 2.87 q [1H, CHC(O)]. Found, %: C 69.61; H 8.91. $C_{13}H_{20}O_3$. Calculated, %: C 69.64; H 8.93.

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