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LETTERS TO THE EDITOR

Synthesis of 3-(1-Adamantyl)-4-methoxyphenylboric Acid

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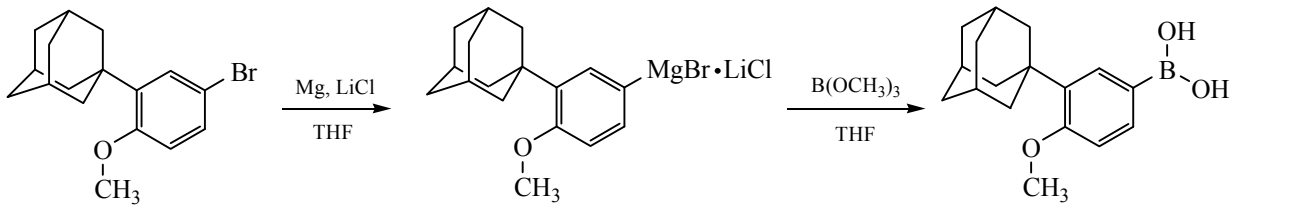
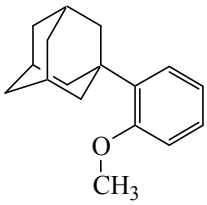
3-(1-Adamantyl)-4-methoxyphenylboric acid is the key intermediate in the synthesis of active pharmaceutical ingredient (API) 6-[3-(1-adamantyl)-4-methoxyphenyl]-2-naphthoic acid (Adapalene). We found that a direct Grignard synthesis involving 2-(1-adamantyl)-4-bromoanisole in the presence of dry lithium chloride led to increase in the 3-(1-adamantyl)-4-methoxyphenylboric acid yield to 70–72%.



Synthesis of 3-(1-adamantyl)-4-methoxyphenylmagnesium bromide by the classical reaction of 2-(1-adamantyl)-4-bromoanisole with metallic magnesium in an aprotic polar solvents, like THF or diethyl ether affords the target products in the yield no more than 11%. The main product of the reaction corresponds formally to the reduction product of the aryl halide. Thus, 2-(1-adamantyl)-4-bromoanisole furnishes 2-(1-adamantyl)anisole in 78% yield.



The GLC analysis of the reaction mixture showed that the conversion of 2-(1-adamantyl)-4-bromoanisole was complete that indicates the high reactivity of initial substrate toward magnesium under the conditions of classical Grignard reaction.

We succeeded to solve the problem of the low yield by using lithium chloride additive in the synthesis of the Grignard reagent. We found experimentally that the optimum molar ratio of 2-(1-adamantyl)-4-bromoanisole to lithium chloride in carrying out the Grignard reaction is 1:1.2. Our results showed that the increase in the molar content of lithium chloride from 0.1 to 1.2 increased the Grignard reagent yield, the lithium chloride excess up to 2 equivalents did not lead to a significant change in the yield. The Grignard reagent concentration in the reaction mixture was determined by titration according to the procedure described in [1].

Use of the lithium chloride also allowed the performance of the reaction between organomagnesium compound and trialkylborate at significantly higher temperature (from 0 to +5°C, ice water cooling) than the recommended as optimal for the boric acids synthesis (–70°C [2]).

3-(1-Adamantyl)-4-methoxyphenylboric acid. A one-liter three-neck round-bottom flask was dried by

heating with flame and charged with 8 g of magnesium turnings (0.33 mol), 200 ml of THF, and 8 g (0.19 M, 1.2 equiv.) of freshly powdered anhydrous lithium chloride. All operations were carried out under a slow stream of dry argon. While stirring vigorously the reaction mixture was heated to 40ºC and 11 g (5 ml, 0.06 mol) of 1,2-dibromoethane was added dropwise to initiate the reaction. After the end of boiling and gas evolution, a solution of 50 g (0.16 mol) of 2-(1-adamantyl)-4-bromoanisole in 400 ml of anhydrous THF was added to the hot reaction mixture maintaining the mixture at slight boiling. When the reagent was added completely, the mixture was gently boiled for 30 min. Then stirring was stopped and the solution of Grignard reagent was decanted into a flask preliminarily flushed with argon. The flask was then maintained in a refrigerator at 0ºC for 2 h.

A one-liter dry three-neck round-bottom flask was purged with argon and charged with 33 g (36 ml, 0.35 mol) of trimethylborate and 100 ml of anhydrous THF. The reaction mixture was cooled in ice bath (0 to +5°C) and at vigorous stirring a solution of Grignard reagent was added during 10 min. The flask was stoppered and the solution was allowed to stand in a refrigerator (0ºC) for 16 h.

The reaction mixture was then decomposed by adding 50 ml of hydrochloric acid and 50 ml of water at stirring without additional cooling. Organic layer was separated; water layer was extracted with 2× 100 ml of diethyl ether. Combined organic layers were dried over sodium sulfate. The solvent was distilled off under a reduced pressure at 50°C. The residue was treated with 200 ml of ethyl acetate and left overnight in a refrigerator (0ºC). The resulting precipitate was filtered off with suction, washed with cold ethyl acetate, and dried at 100°C. 3-(1-Adamantyl)-4-methoxyphenylboric acid yield was 32 g (72%), mp ~300°C.

^{1}H NMR spectrum of 3-(1-adamantyl)-4-methoxyphenylboric acid corresponds to a mixture of the acid itself and its cyclic trimer (boroxine) in a random ratio. Therefore spectral identification of the product was carried out after synthesis of cyclic pinacol ester of the acid. The ester was synthesized without additioanal acid catalysis by heating a mixture of 3-(1-adamantyl)-4-methoxyphenylboric acid and 2,3-dimethyl-2,3-butane-diol (pinacol) in equimolar amounts in toluene and distilling off the formed water.

3-(1-Adamantyl)-4-methoxyphenylboric acid pinacol ester. One-liter round-bottom flask, equipped with a Dean-Stark trap was charged with 100 g (0.35 mol) of 3-(1-adamantyl)-4-methoxyphenylboric acid, 45.5 g (0.39 mol) of 2,3-dimethyl-2,3-butanediol (pinacol), and 500 ml of toluene. The reaction mixture was refluxed for 2 h until the expected volume of water (~13 ml) was collected. On completing the reaction the solvent was distilled off under a reduced pressure at heating with a water bath at 60°C. The residue was dissolved in 200 ml of ethyl acetate and maintained at 0°C for 16 h. The precipitate formed was filtered off, washed with the smallest volume of cold ethyl acetate, and dried at 80°C. Yield 108 g (84%) of pinacol 3-(1-adamantyl)-4-methoxyphenylboronate, mp 162–164°C.

^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.30 s (12H), 1.76 s (6H), 2.07 s (3H), 2.09 s (6H), 3.85 s (3H), 6.83 d (1H, J = 8 Hz), 7.49 s (1H), 7.50 d (1H, J = 8 Hz).

The GLC analysis was performed on a Varian 3700 chromatograph with a flame-ionization detector. The ^{1}H NMR spectra were recorded on a Bruker AMX-500 spectrometer from solutions in DMSO-d_6 using TMS as internal reference.

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