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LETTERS TO THE EDITOR

One-Pot Synthesis of Methyl 6-[3-(1-Adamantyl)-4-methoxyphenyl]-2-naphthenoate

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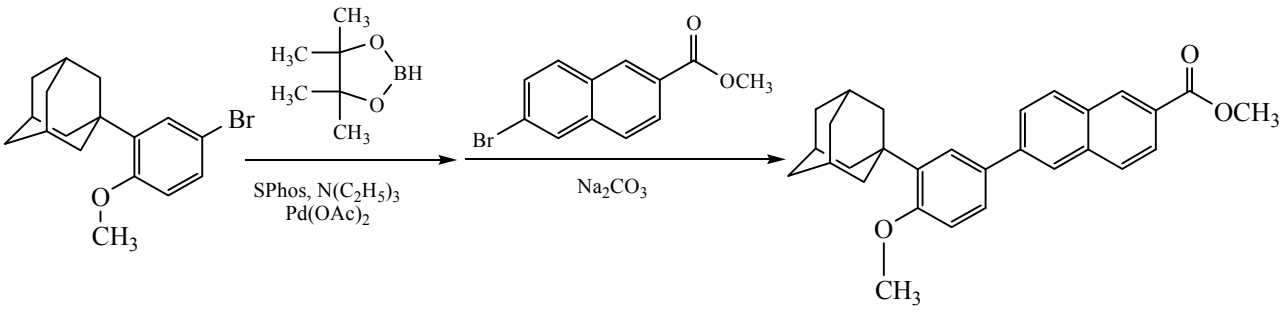
The key stage at the constructing backbone of 6-[3-(1-adamantyl)-4-methoxyphenyl]-2-naphthoic acid (Adapalene) molecule is the formation of a C–C bond between 3-(1-adamantyl)-4-methoxyphenyl and 2-carbomethoxy-6-naphthyl fragments. Among the most effective modern methods of C–C bond formation is known the process of catalytic coupling according to the method of Suzuki–Miyaura [1].

To use this method, one of the coupled fragments should bear a boron-containing functional group. For introducing such a group the most widely used method is the transmetallation of preliminarily prepared Grignard reagents or lithium derivatives at the action of a boron compounds with halogen or alkoxy residue as a leaving group.

An alternative method of introducing this functional group is catalytic coupling of boron-containing nucleophilic agent with electrophilic aryl substrate, which unlike the transmetallation reaction can be performed in one stage [2].

The main advantage of direct catalytic heterofunctionalization of aryl halides is its easy technological application. Conditions of this reaction differ only slightly from that of Suzuki–Miyaura cross-coupling reaction (the latter requires a stronger base), therefore it is possible to carry out these two processes without separation of the intermediate arylboric acid pinacol ester, that is, to arrange it as a *one-pot* synthesis [3, 4].

The main factors hampering wide technological application of the direct catalytic heterofunctionalization is the high cost of boron-containing nucleophilic reagents and a difficult selection an appropriate catalytic system providing acceptable yield of the product. According to our new data, the most effective ligand for the *one-pot* synthesis of methyl 6-[3-(1-adamantyl)-4-methoxyphenyl]-2-naphthenoate is 2-(dicyclohexylphosphino)-2',6'-dimethoxybiphenyl (Sphos). We found experimentally that pinacolborane is the optimal reagent for the heterofunctionalization.



Methyl 6-[3-(1-adamantyl)-4-methoxyphenyl]-2-naphthenoate. A 3-liter two-neck round-bottom flask was charged with 800 ml of dioxane, 100 g (0.31 mol) of 2-(1-adamantyl)-4-bromoanisole, 94 g (130 ml, 0.93 mol) of triethylamine, 3.5 g (0.0155 mol, 5 mol %) of palladium acetate, and 12.7 g (0.031 mol, 10 mol %) of 2-dicyclohexylphosphyno-2',6'-dimethoxybiphenyl (Sphos). The resulting solution was stirred for 30 min under argon, and 51 g (58 ml, 0.4 mol) of pinacol boronate solution in 300 ml of dioxane was added in one portion. The reaction mixture was refluxed at stirring under slow flow of dry argon for 12 h. Then the reaction mixture was cooled to room temperature, 61 g (0.23 mol) of methyl 6-bromo-2-naphthenoate was dissolved in it and a solution of 127 g (1.2 mol) of sodium carbonate in 600 ml water was added. The reaction was carried out under argon at vigorous mechanical stirring at 80°C for 4 h.

After the reaction completing, the mixture was cooled to ambient temperature and filtered without separating layers. The main part of the reaction product precipitated. To get the remaining part of the product, the organic layer was evaporated to 1/4 volume and cooled. The precipitates formed were filtered off and combined. The crude product was dissolved in 500 ml of *N*,*N*-dimethylacetamide, hot solution was filtered, evaporated to a volume of 300 ml, and then left for 16 h at room temperature for crystallization. The crystals formed were filtered off and dried at 150–180°C for 2 h. 87 g of methyl 6-[3-(1-adamantyl)-4-methoxyphenyl]-2-naphthenoate was obtained [yield 66% based on 2-(1-adamantyl)-4-bromoanisole], mp 222–225°C. Purity of the product obtained was higher than 99%.

^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.79 s (6H), 2.10 s (3H), 2.16 s (6H), 3.90 s (3H), 3.94 s (3H), 6.99 d (1H, J = 8 Hz), 7.51 s (1H), 7.52 d (1H, J = 8 Hz), 7.78 d (1H, J = 9 Hz), 7.94 d (1H, J = 9 Hz), 7.98–8.02 m (3H), 8.55 s (1H).

Use of dipalladium tris-(dibenzylideneacetone) [$Pd_2(dba)_3$] instead of palladium acetate is shown to change insignificantly the pinacol 3-(1-adamantyl)-4-methoxyphenylboronate yield. 2,2'-Bis-(diphenylphosphino)diphenyl ether (DPEphos) as a ligand reduces the methyl 6-[3-(1-adamantyl)-4-methoxyphenyl]-2-naphthenoate yield to 59%. Use of 1,1'-bis(diphenylphosphino)ferrocene or triphenylphosphine as the ligands decrease the product yield to 28% and 9% respectively. Application of bis-pinacolatodiboron as functionalizing agent led to a considerable decrease in the product yield.

The GLC analysis was performed on a Varian 3700 instrument with 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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