

Effective Synthesis of 2-[4-(3-Methyl-2-butenyl)phenyl]propionic Acid via Hydromagnesation Reaction with Nickel or Titanium Catalysts

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(Received December 12, 1985)

Synopsis. 2-[4-(3-Methyl-2-butenyl)phenyl]propionic acid was synthesized in 82% yield via nickel(II) chloride or dichlorobis[η^5 -cyclopentadienyl]titanium-catalyzed hydromagnesation of 1-(3-methyl-2-butenyl)-4-vinylbenzene obtained in ca. 63–68% yield by the coupling reaction of 4-(3-methyl-2-butenyl)phenylmagnesium chloride with vinyl chloride.

In the course of our synthetic study of analgesic and antiinflammatory drugs, attention was focused on a convenient synthesis of 2-[4-(3-methyl-2-butenyl)phenyl]propionic acid (**1**).¹⁾ As the prenyl moiety of **1** was relatively unstable in acidic media or in the presence of oxygen, the method previously employed¹⁾ required multi-step reactions with troublesome handlings to obtain **1** of a high purity. On the other

hand, it has been well known that the hydromagnesation reaction of styrene with nickel²⁾ or titanium³⁾ catalysts afforded 1-phenylethylmagnesium halides in good yield, which prompted us to apply this reaction to 1-(3-methyl-2-butenyl)-4-vinylbenzene (**3**). Herein we wish to describe a practical three-step synthesis of **1** starting from 1,4-dichlorobenzene (Scheme).

The coupling reaction of the Grignard reagent of 1-chloro-4-(3-methyl-2-butenyl)benzene (**4**)⁴⁾ with vinyl chloride was carried out by using iron(III)⁵⁾ or nickel(II)⁶⁾ catalysts (0.4 mol% vs. **4**) such as iron(III) acetylacetonate, iron(III) chloride, or [1,3-bis(diphenylphosphino)propane]dichloronickel(II) to obtain **3** in 63, 64, and 68% yield, respectively. Rectification of **3** was carried out under reduced pressure to separate (3-

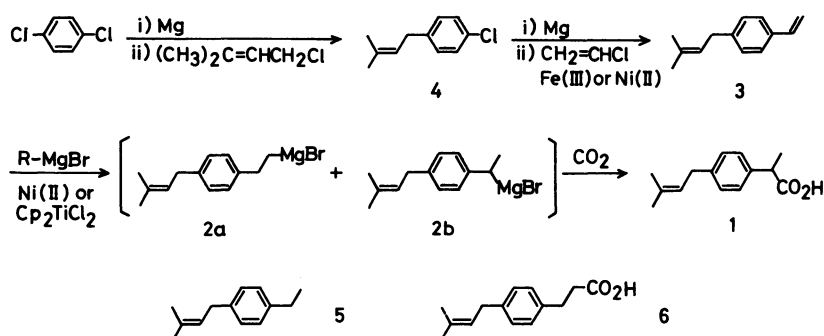


Table 1. Results of the Nickel-Catalyzed Hydromagnesation of **3**

Entry	R-MgBr ^{a)}	Catalysts ^{b)} (mol% vs. 3)	Reaction Temperature/°C	Reaction Time/h	Yield of 5 /%
1	<i>i</i> -C ₄ H ₉	NiCl ₂ (5)	17–20	4.25	57
2	C ₂ H ₅	NiCl ₂ (5)	0	5	51
3	C ₂ H ₅	NiCl ₂ (5)	15–20	1	52
				3	74
				5	79
4	C ₂ H ₅	NiCl ₂ (5)	30–40	1	36
5	C ₂ H ₅	NiCl ₂ (10)	15–20	1	55
6	C ₂ H ₅	NiCl ₂ (2.5)	15–20	2.5	64
7	<i>i</i> -C ₄ H ₉	NiBr ₂ (5)	15–20	4.5	34
8	<i>i</i> -C ₄ H ₉	Ni(acac) ₂ (5)	20	4.2	35
9	<i>i</i> -C ₄ H ₉	NiCl ₂ (PPh ₃) ₂ (5)	20	5.2	6

a) 1.5 Equivalent (vs. **3**) of the Grignard reagent was used in THF. b) Ni(acac)₂: Nickel(II) acetylacetonate.

c) Determined by GC (OV-1, 1m, 110 °C), using tridecane as the internal standard.

Table 2. Results of the Titanium-Catalyzed Hydromagnesation of **3**

Entry	R-MgBr ^{a)}	Solvent	Catalyst ^{b)} (mol% vs. 3)	Reaction Temperature/°C	Reaction Time/h	Yield of 5 /%
10	C ₃ H ₇	Et ₂ O	5	30	5	64
11	<i>i</i> -C ₃ H ₇	Et ₂ O	5	30	12	74
12	C ₃ H ₇	THF	5	50	1	66
					5	90
13	C ₃ H ₇	THF	2.5	50	5	70
14	C ₃ H ₇	THF	10	50	5	58
15	C ₃ H ₇	THF	5	reflux	5	65
16	<i>i</i> -C ₃ H ₇	THF	5	50	5	87
17	<i>t</i> -C ₄ H ₉	THF	5	50	5	40
18	<i>i</i> -C ₄ H ₉	THF	5	50	5	— ^{d)}

a) 1.22 Equivalent (vs. **3**) of the Grignard reagent was used. b) Catalyst: Dichlorobis[η^5 -cyclopentadienyl]titanium. c) Determined by GC (OV-1, 1m, 110°C), using tridecane as the internal standard. d) Only polymerization was observed.

methyl-2-butenyl)benzene (10%), unreacted **4** (ca. 2%), and a trace amount of 4-(3-methyl-2-butenyl)phenol (ca. 0.2%). Then, the optimum conditions of the hydromagnesation reaction of **3** with nickel(II) catalysts were investigated by measuring the yield of 1-ethyl-4-(3-methyl-2-butenyl)benzene (**5**) generated from the intermediary Grignard reagents (**2a,b**) by quenching with water (Table 1). The best yield of **5** was achieved by using ethylmagnesium bromide in the presence of nickel(II) chloride catalyst (5 mol% vs. **3**) at 15–20°C in THF solvent (Entry 3). Variation of the reaction temperature or the amount of catalyst resulted in the decrease of the yield of **5**. The Grignard reagents (**2a,b**) prepared according to the procedure of Entry 3, in turn, was reacted with carbon dioxide at –10°C to obtain **1** in 82% yield with a trace amount of 3-[4-(3-methyl-2-butenyl)phenyl]propionic acid (**6**, 1.5%).

An alternative method for hydromagnesation of **3** was also studied by using dichlorobis[η^5 -cyclopentadienyl]titanium catalyst (Table 2). The Grignard reagents (**2a,b**) prepared according to the best procedure of Entry 12 was reacted with carbon dioxide to obtain **1** in also 82% yield. In this case, however, the undesirable regio-isomer (**6**) was formed up to 8% yield, which made the purification process troublesome to some extent.

In conclusion, we employed nickel(II) chloride as the catalyst of the hydromagnesation reaction of **3** in large scale experiments and succeeded in developing a practical three-step method for **1** starting from 1,4-dichlorobenzene.

Experimental

The boiling and melting points were uncorrected. The IR spectra were recorded with a Digilab FTS-20 C/D spectrometer. The NMR spectra were taken with a Varian XL-200 (with hexamethyldisiloxane as an internal standard). GC analyses were made by Shimadzu GC-7AG gas chromatograph using a 3 mm×100 cm column of OV-1 on Celite 545 with He as the carrier gas. 1-Chloro-3-methyl-2-butene is commercially available from Kuraray Co. Ltd.,

NIC-division.

1-Chloro-4-(3-methyl-2-butenyl)benzene (4). The procedure previously reported was used.⁴⁾ Into a solution of 4-chlorophenylmagnesium chloride in THF (2500 ml), prepared from 1,4-dichlorobenzene (438 g; 3 mol) and magnesium (80 g; 3.3 atom) was added 1-chloro-3-methyl-2-butene (343 g 3.3 mol) at 10–15°C during 2 h. After stirring for 3 h, the reaction mixture was poured into aqueous ammonium chloride and extracted with ether to obtain **4** (361 g; 1.95 mol) in 65% yield. Bp 64–65.5°C/0.38 mmHg (1 mmHg=133.322 Pa) [lit,⁴⁾ bp 84–88°C/1.5 mmHg].

1-(3-Methyl-2-butenyl)-4-vinylbenzene (3). Into a mixture of magnesium (87.6 g; 3.6 atom) in THF (84 ml) was dropped a solution of **4** (542 g; 3 mol) in THF (300 ml) at 110–120°C during 2 h under nitrogen atmosphere and the mixture was stirred further for 5 h. Thus obtained viscous Grignard reagent of **4** was immediately diluted to 1.5 M solution (1M=1 mol dm⁻³) by addition of 1630 ml of THF. The Grignard solution was added slowly into a mixture of vinyl chloride (250 g; 4 mol) and iron(III) acetylacetonate (4.5 g; 0.12 mol) in THF (1500 ml) maintaining the reaction temperature at 25–32°C. After stirring for 2 h, the resulting mixture was poured into aqueous ammonium chloride and extracted with ether. Rectification of the products with a Shibata Fractional Distillation Apparatus Model HPC-A-1500-B (packing column, 70 theoretical plates) gave **3** (325 g; 1.9 mol) in 63% yield with a small amount of lower boiling products [bp 35–58°C/0.1 mmHg] consisted of (3-methyl-2-butenyl)benzene (41 g; 0.285 mol), unreacted **4** (11 g; 60 mmol), and 4-(3-methyl-2-butenyl)phenol (1 g; 6 mmol). Bp 68–70°C/0.2 mmHg. IR(neat) 2960, 2900, 1625, 1505, 980, 900, 820 cm⁻¹. ¹H NMR(in CDCl₃) δ =1.57–1.73 (m, 6H, 2×CH₃); 3.25 (d, *J*=7 Hz, 2H, CH₂); 5.0–5.4 (m, 2H, 2×=CH); 5.6 (d, *J*=18 Hz, 1H, =CH), 6.62 (dd, *J*=11 and 18 Hz, 1H, =CH); 7.0–7.35 (m, 4H, arom.). Found: C, 90.51; H, 9.42. Calcd. for C₁₃H₁₆: C, 90.64; H, 9.36.

2-[4-(3-Methyl-2-butenyl)phenyl]propionic Acid (1). Nickel-Catalyzed Hydromagnesation: Into a mixture of **3** (258 g 1.5 mol) and nickel(II) chloride (9.8 g; 75 mmol) in THF was slowly added a 1 M solution of ethylmagnesium bromide in THF (2250 ml; 2.25 mol) at 15–20°C to react for 5 h. The reaction mixture was cooled to ca. –20°C, and dry gaseous carbon dioxide was passed through the bottom of the apparatus maintaining the temperature below –10°C. After the exothermic reaction stopped, the reaction mixture was poured into aqueous ammonium

chloride and extracted with diisopropyl ether. The organic layer was extracted with 10% aqueous sodium hydroxide (1200 ml; 3 mol). Then, the aqueous layer was neutralized with 0.5 M sulfuric acid and extracted with hexane. The product was purified by distillation under reduced pressure to obtain **1** (268 g; 1.23 mol) in 82% yield. Bp 130–135 °C/0.1 mmHg. IR (neat) 3450–2500, 1700, 1225, 750 cm⁻¹. ¹H NMR (in CCl₄) δ=1.42 (d, *J*=7.2 Hz, 3H, CH₃), 1.68; 1.8 (s, 6H, 2×CH₃); 3.20 (d, *J*=7.2 Hz, 2H, CH₂); 3.54 (q, *J*=7.2 Hz, 1H, CH); 5.18 (t, *J*=7.2 Hz, 1H, =CH); 6.80–7.12 (m, 4H, arom.); 11.83 (s, 1H, OH). Found: C, 76.94; H, 8.39. Calcd. for C₁₄H₁₈O₂: C, 77.03; H, 8.31.

The distillation residue was purified by recrystallization from hexane to obtain 3-[4-(3-methyl-2-butenyl)phenyl]propionic acid **6** (2.2 g; 10 mmol) in 0.7% yield. Mp 61–62 °C. IR (neat) 3300–2550, 1700, 1290, 940, 820 cm⁻¹. ¹H NMR (in CDCl₃) δ=1.72, 1.75 (s, 6H, 2×CH₃); 2.67 (t, *J*=8 Hz, 2H, CH₂); 2.92 (t, *J*=8 Hz, 2H, CH₂); 3.32 (d, *J*=7 Hz, 2H, CH₂); 5.33 (t, *J*=7 Hz, 1H, =CH); 7.13 (s, 4H, arom.); 10.88 (bs, 1H, OH). Found: C, 76.85; H, 8.35. Calcd. for C₁₄H₁₈O₂: C, 77.03; H, 8.31.

Titanium-Catalyzed Hydromagnesation: Dichlorobis[η⁵-cyclopentadienyl]titanium (75 mg; 0.3 mmol) was added to a mixture of **3** (1 g; 6 mmol) and propylmagnesium bromide in THF (7.2 mmol in 6 ml) at room temperature under argon atmosphere and the mixture was stirred for 5 h

successively. After addition of a small pieces of solid carbon dioxide (ca. 3 g), the resulting mixture was treated as the same manner described before. The products were esterified with diazomethane and analyzed by GC (OV-1, 1 m, 140 °C) using nonadecane as an internal standard. The result showed the formation of **1** in 82% yield and **6** in 8% yield.

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