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

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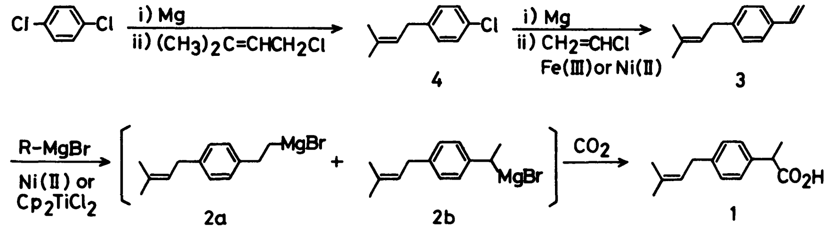
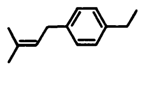
Synopsis. 2-[4-(3-Methyl-2-butenyl)phenyl]propionic acid was synthesized in 82% yield via nickel(II) chloride or dichlorobis[η^5-cyclopentadienyl]titanium-catalyzed hydromagnesation of 1-(3-methyl-2-butenyl)-4-vinylbenzene obtained in ca. 63—68% yield by the coupling reaction of 4-(3-methyl-2-butenyl)phenylmagnesium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

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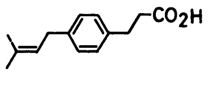
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Table 1. Results of the Nickel-Catalyzed Hydromagnesation of **3**

Entry	R-MgBr a)	Catalysts b) (mol% vs. **3**)	Reaction Temperature/°C	Reaction Time/h	Yield of **5**/% c)
1	*i*-C_4H_9	$NiCl_2$ (5)	17—20	4.25	57
2	C_2H_5	$NiCl_2$ (5)	0	5	51
3	C_2H_5	$NiCl_2$ (5)	15—20	1	52
				3	74
				5	79
4	C_2H_5	$NiCl_2$ (5)	30—40	1	36
5	C_2H_5	$NiCl_2$ (10)	15—20	1	55
6	C_2H_5	$NiCl_2$ (2.5)	15—20	2.5	64
7	*i*-C_4H_9	$NiBr_2$ (5)	15—20	4.5	34
8	*i*-C_4H_9	$Ni(acac)_2$ (5)	20	4.2	35
9	*i*-C_4H_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**/%[c)]
10	C_3H_7	Et_2O	5	30	5	64
11	i-C_3H_7	Et_2O	5	30	12	74
12	C_3H_7	THF	5	50	1	66
					5	90
13	C_3H_7	THF	2.5	50	5	70
14	C_3H_7	THF	10	50	5	58
15	C_3H_7	THF	5	reflux	5	65
16	i-C_3H_7	THF	5	50	5	87
17	t-C_4H_9	THF	5	50	5	40
18	i-C_4H_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-vinylbenene (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 viscid 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 $CDCl_3$) δ=1.57—1.73 (m, 6H, 2×CH_3); 3.25 (d, J=7 Hz, 2H, CH_2); 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 $C_{13}H_{16}$: 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 CCl_4) δ=1.42 (d, J=7.2 Hz, 3H, CH_3), 1.68; 1.8 (s, 6H, 2×CH_3); 3.20 (d, J=7.2 Hz, 2H, CH_2); 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 $C_{14}H_{18}O_2$: 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 $CDCl_3$) δ=1.72, 1.75 (s, 6H, 2×CH_3); 2.67 (t, J=8 Hz, 2H, CH_2) 2.92 (t, J=8 Hz, 2H, CH_2); 3.32 (d, J=7 Hz, 2H, CH_2); 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 $C_{14}H_{18}O_2$: C, 77.03; H, 8.31.

Titanium-Catalyzed Hydromagnesation: Dichlorobis[η^5-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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