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September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

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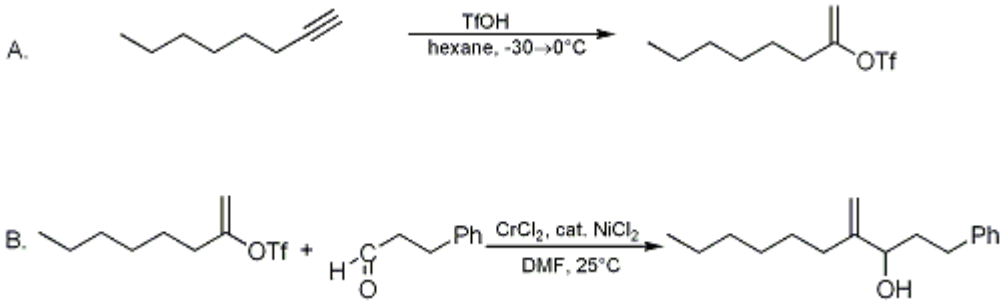
PREPARATION AND REACTIONS OF ALKENYLCHROMIUM REAGENTS: 2-HEXYL-5-PHENYL-1-PENTEN-3-OL



Submitted by Kazuhiko Takai[1], Koichi Sakogawa, Yasutaka Kataoka, Koichiro Oshima, and Kiitiro Utimoto[2].
Checked by Tadahiro Takemoto and Larry E. Overman.

1. Procedure

A. *1-Hexylethenyl triflate* (Note 1). A dry, 300-mL, three-necked, round-bottomed flask is equipped with a magnetic stirring bar, nitrogen inlet, rubber septum, and a 100-mL, graduated, pressure-equalizing addition funnel that is sealed with a rubber septum. The flask is charged with 1-octyne (11 g, 0.10 mol, (Note 2)) and dry hexane (100 mL, (Note 3)). The contents of the flask are cooled to −30°C (dry ice-methanol). The addition funnel is charged with neat trifluoromethanesulfonic acid (TfOH, 4.9 mL, 55 mmol, (Note 4)) which is then added dropwise at −30°C to the stirring solution over a period of 30 min. The addition funnel is rinsed with dry hexane (10 mL). The dark brown solution is warmed to 0°C and stirred at 0°C for 10 min. Saturated sodium bicarbonate ($NaHCO_3$) solution (20 mL) is introduced at 0°C to the reaction mixture. The organic layer is separated, washed with additional $NaHCO_3$ solution (2 × 50 mL), and then dried over potassium carbonate. The solvent is removed with a rotary evaporator. The crude product is distilled using a short-path still to give 9.6–10.4 g (67–73%) of 1-hexylethenyl triflate (Note 5), bp 97–98°C at 19 mm.

B. *2-Hexyl-5-phenyl-1-penten-3-ol*. A dry, 500-mL, four-necked, round-bottomed flask is equipped with a mechanical stirring bar, nitrogen inlet, rubber septum, and a 100-mL, graduated, pressure-equalizing addition funnel that is sealed with a rubber septum. In the flask are placed anhydrous chromium(II) chloride ($CrCl_2$) (10 g, 80 mmol, (Note 6)) and anhydrous nickel(II) chloride ($NiCl_2$) (52 mg, 0.40 mmol, (Note 7)) under an argon atmosphere. The flask is cooled to 0°C and dry, oxygen-free N,N-dimethylformamide (DMF, 250 mL, (Note 8)) is added to the flask with stirring. The salts are dissolved in a slightly exothermic process. The mixture is stirred at 0°C for 10 min. To the $CrCl_2$-$NiCl_2$ reagent at 25°C is added a solution of 3-phenylpropanal (2.7 g, 20 mmol, (Note 9)) in DMF (20 mL) by syringe. A solution of 1-hexylethenyl triflate (10 g, 40 mmol, (Note 5)) in DMF (60 mL) is added at 25°C through the addition funnel over a period of 5 min. The entire mixture is stirred at 25°C for 30 min. The reaction mixture is diluted with ether (200 mL), poured into ice-cooled water (400 mL), and extracted with ether (3 × 200 mL) repeatedly. The combined extracts are washed with aqueous sodium chloride solution (150 mL), dried over anhydrous sodium sulfate, and concentrated with a rotary evaporator (25°C, water bath). The crude product is distilled using a short-path still to give 4.0–4.6 g (82–94%) of 2-hexyl-5-phenyl-1-penten-3-ol, bp 109–111°C at 0.11 mm (Note 10) and (Note 11).

2. Notes

1. This procedure was reported by Stang and Summerville.[3]
2. 1-Octyne was distilled, bp 125–126°C.
3. Hexane was freshly distilled from sodium or calcium hydride.
4. Trifluoromethanesulfonic acid was distilled, bp 72–73°C at 20 mm.

5. The distilled triflate contained 3–9% of isomers, that were confirmed by capillary GLPC (Silicone OV-17, 50 m, 105°C, 1-hexylethenyl triflate: t_R = 11.1 min; isomers: t_R = 11.4 and 12.4 min) and ^{1}H NMR analysis. Because the isomers did not interfere with the second reaction, the triflate was employed without further purification. Spectral data of the distilled triflate was as follows: IR (neat) cm^{-1}: 2954, 2930, 2858, 1671, 1419, 1250, 1213, 1141, 943, 899, 703, 610; ^{1}H NMR ($CDCl_3$) δ: 0.89 (t, 3 H, J = 6.9), 1.2–1.4 (m, 6 H), 1.5–1.6 (m, 2 H), 2.34 (t, 2 H, J = 7.5), 4.93 (dt, 1 H, J = 3.5, 1.0), 5.08 (d, 1 H, J = 3.5), ^{1}H NMR peaks of the impurities appeared at δ 2.05–2.20 and 5.18–5.55; ^{13}C NMR ($CDCl_3$) δ: 13.9, 22.4, 25.9, 28.3, 31.3, 33.8, 103.9, 118.5 (q, J = 320, CF_3), 157.1.
6. Chromium(II) chloride (95% purity) was purchased from Aldrich Chemical Company, Inc., and used without further purification. The salt is easily oxidized and should be handled under an inert atmosphere.
7. Anhydrous nickel(II) chloride was purchased from Nacalai Tesque Co. and used without further purification. The salt is hygroscopic and should be handled under an inert atmosphere.
8. N,N-Dimethylformamide was refluxed in the presence of calcium sulfate under reduced pressure and distilled with nitrogen bubbling from a capillary, bp 76°C at 39 mm.
9. 3-Phenylpropanal was freshly distilled, bp 97–98°C at 12 mm.
10. The pot residue can be bulb-to-bulb distilled to give an additional 0.5–1 g of product to bring the combined yields to 94–95%. 2-Hexyl-5-phenyl-1-penten-3-ol has the following properties: R_f = 0.29 (ethyl acetate/hexane = 1/10); IR (neat) cm^{-1}: 3340, 3024, 2924, 2854, 1647, 1600, 1497, 1456, 1017, 900, 741, 697; ^{1}H NMR ($CDCl_3$) δ: 0.88 (t, 3 H, J = 6.8), 1.2–1.4 (m, 8 H), 1.7–2.2 (m, 5 H), 2.62 (ddd, 1 H, J = 6.6, 9.6, 13.9), 2.74 (ddd, 1 H, J = 6.1, 9.6, 13.9), 4.10 (dd, 1 H, J = 5.1, 7.5), 4.87 (d, 1 H, J = 1.5), 5.04 (s 1 H), 7.1–7.4 (m, 5 H). ^{13}C NMR ($CDCl_3$) δ: 14.1, 22.6, 27.9, 29.2, 31.4, 31.7, 31.9, 37.0, 74.7, 109.3, 125.7, 128.3, 128.4, 142.0, 152.0.
11. The following ratio of reactants, aldehyde/alkenyl triflate/$CrCl_2$/$NiCl_2$ = 1/2/4/0.02 gave the best results. When the ratio of reagents was reduced to aldehyde/alkenyl triflate/$CrCl_2$/$NiCl_2$ = 1/1/2/0.01, the reaction proceeded slowly. When the reaction was carried out at 25°C for 2 hr, 65% of the 2-hexyl-5-phenyl-1-penten-3-ol was isolated and 14% (GLPC analysis) of the 3-phenylpropanal remained.

Waste Disposal Information

Compounds of chromium and nickel are toxic. The aqueous layers from Step B and any other waste materials should be disposed of properly (see "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995).

3. Discussion

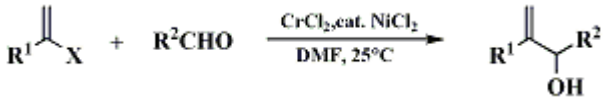
In the synthesis of a complex molecule, it is sometimes necessary to prepare an organometallic reagent under mild conditions. Because of the strong basicity and nucleophilicity of alkenyllithium and alkenylmagnesium compounds, only a few electrophilic functional groups are stable under the reaction conditions.[4] In contrast, the alkenylchromium reagents described here react with aldehydes to give adducts in good to excellent yields in the presence of ketones, esters, amides, acetals, ethers, silyl ethers, and nitriles.[5,6,7] The method is especially effective for highly oxygenated molecules.[6] Intramolecular cyclization of iodo aldehydes leading to 13-membered lactones has also been reported.[8]

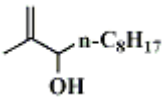
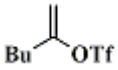
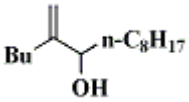
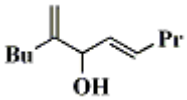
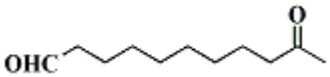
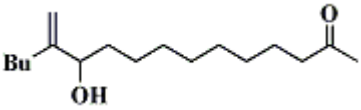
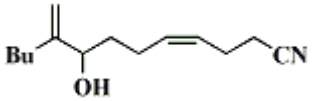
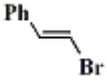
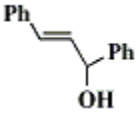
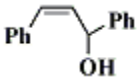
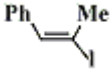
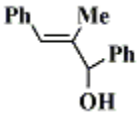
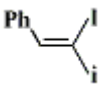
Addition of a catalytic amount of $NiCl_2$ to $CrCl_2$ is essential for the formation of alkenylchromium reagents.[5,6,7] However, a substantial amount of 1,3-diene, the coupling product of the alkenyl iodide, is produced if a higher content of $NiCl_2$ is employed.[9,10]

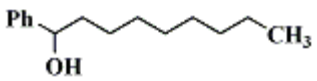
Reduction of alkenyl iodides and bromides to alkenylchromium reagents with $CrCl_2$ proceeds smoothly under the same conditions.[5,6,7] Several examples of the Grignard-type addition of alkenyl halides and triflates to aldehydes with the combination of $CrCl_2$ and $NiCl_2$ are shown in the Table. Iodoalkenes are more reactive than bromoalkenes (compare run 1 and 2). In the case of an α,β-unsaturated aldehyde, the 1,2-addition product is the main product (run 4). The alkenylchromium reagent adds to an aldehyde group selectively (runs 5–7), as do allyl-[11] and alkynylchromium reagents.[12] Steric interaction of substituents at a position cis to halogen causes cis-trans isomerization in some cases.[10] For example, while the reaction of (E)- and (Z)-2-bromostyrene and benzaldehyde proceeded stereospecifically (runs 8 and 9), both (E)- and (Z)-2-iodo-1-phenyl-1-propene reacted with

benzaldehyde to give (E)-1,3-diphenyl-2-methyl-2-propen-1-ol as the sole product (runs 10 and 11). The regiochemistry of double bonds is maintained during the coupling reaction. The $CrCl_2$-$NiCl_2$ system is also effective for the addition of iodobenzene to an aldehyde (run 12).[7]

TABLE
GRIGNARD-TYPE COUPLING BETWEEN ALKENYL HALIDES (OR TRIFLATES) AND ALDEHYDES, MEDIATED BY THE $CrCl_2$-$NiCl_2$ SYSTEM[a]



Run	Alkenyl Halide (or Triflate)	Aldehyde	Time hr	Product	Yield %
1		n-C_8H_{17}CHO	0.25		100
2		n-C_8H_{17}CHO	3		62
3		n-C_8H_{17}CHO	3		81
4		(E)-PrCH=CHO	4		64
5			1		87
6			2		78
7		PhCOMe	6	(recovery of PhCOMe, 87%)	
8		PhCHO	1		82
9		PhCHO	1		78
10		PhCHO	3		91[d]
11		PhCHO	3		90[d]
12	PhI	n-C_8H_{17}CHO	3		83



[a]A mixture of an alkenyl halide (or alkenyl triflate, 2.0 mmol) and an aldehyde (1.0 mmol) was treated at 25°C with $CrCl_2$ (4.0 mmol) and $NiCl_2$ (0.02 mmol) in DMF. [b]Products are isolated by column chromatography on silica gel. [c]The reaction mixture was heated at 60°C. [d]The absence of (Z)-isomer was confirmed by GLPC (Silicone SE-30) and NMR analysis.

References and Notes

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Appendix
Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

oxygen-free N,N-dimethylformamide

$CrCl_2$-$NiCl_2$

$NiCl_2$

$CrCl_2$

(E)- and (Z)-2-bromostyrene

(E)- and (Z)-2-iodo-1-phenyl-1-propene

n-$C_8H_{17}CHO$

PhI

potassium carbonate (584-08-7)

ethyl acetate (141-78-6)

ether (60-29-7)

sodium bicarbonate,
$NaHCO_3$ (144-55-8)

sodium chloride (7647-14-5)

sodium sulfate (7757-82-6)

nitrogen (7727-37-9)

benzaldehyde,
PhCHO (100-52-7)

calcium sulfate (7778-18-9)

nickel(0) (7440-02-0)

sodium (13966-32-0)

Iodobenzene (591-50-4)

N,N-dimethylformamide,
DMF (68-12-2)

hexane (110-54-3)

chromium(II) chloride (10049-05-5)

argon (7440-37-1)

calcium hydride (7789-78-8)

nickel(II) chloride (7718-54-9)

1-OCTYNE (629-05-0)

triflate

trifluoromethanesulfonic acid (1493-13-6)

3-phenylpropanal (104-53-0)

2-Hexyl-5-phenyl-1-penten-3-ol (187821-45-0)

1-Hexylethenyl triflate (98747-02-5)

(E)-1,3-diphenyl-2-methyl-2-propen-1-ol