

Reaction of Grignard Compounds with 4-Chloro-2-methyl-3-butyn-2-ol in Diethyl Ether Equivalents

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Abstract—Reactions of $\text{RMgX} \cdot \text{THF}$ complexes with 4-chloro-2-methyl-3-butyn-2-ol in aromatic hydrocarbons were studied. The complexes formed by arylmagnesium halides require the presence of anisole for the reaction to occur. 4-Chloro-2-methyl-3-butyn-2-ol can be synthesized by reaction of 2-methyl-3-butyn-2-ol with sodium hypochloride in the two-phase system water–benzene.

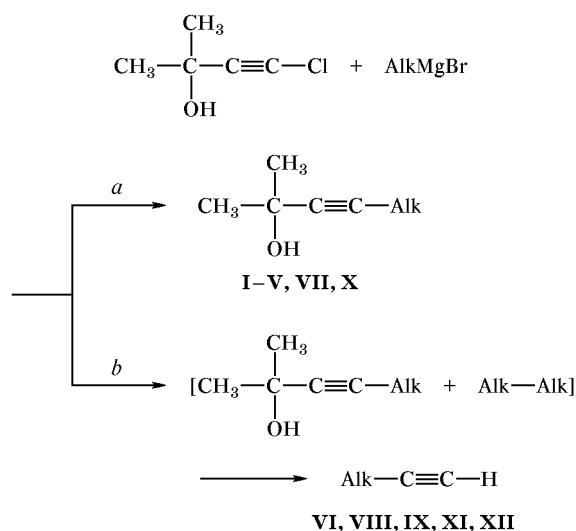
Reactions of Grignard compounds with 4-chloro-2-methyl-3-butyn-2-ol provide a convenient method for preparation of tertiary acetylenic alcohols which are used in the synthesis of monosubstituted acetylenes [1], herbicide stabilizers [2], and antitumor compounds [3]. However, from the viewpoint of safety, the use of diethyl ether as solvent [4] involves some difficulties due to risk of fire and explosion. Therefore, we examined the possibility for replacing

diethyl ether by more safe solvents. Specifically, the reactions of alkylmagnesium halides with 4-chloro-2-methyl-3-butyn-2-ol were carried out in benzene containing an equimolar (with respect to the Grignard compound) amount of tetrahydrofuran (THF).

As a rule, the reaction followed pathway *a* shown in Scheme 1, but in some cases the resulting mixture of target acetylenic alcohols and Wurtz condensation products was subjected to alkaline fission to isolate monosubstituted acetylenes (pathway *b* in Scheme 1).

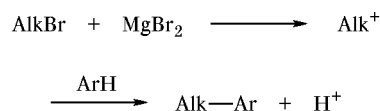
In keeping with published data, negative factors are the heterogeneity of the process and the possibility for alkylation of the aromatic solvent with alkyl halide activated by the liberated Lewis acid (Scheme 2) [5].

Scheme 1.



I, Alk = *i*-Pr; II, Alk = *i*-Bu; III, Alk = Bu; IV, Alk = *iso*-C₃H₁₁; V, Alk = C₅H₁₁; VI, Alk = C₆H₁₁; VII, Alk = C₆H₁₃; VIII, Alk = C₇H₁₅; IX, Alk = C₈H₁₇; X, Alk = C₉H₁₉; XI, Alk = C₁₀H₂₁; XII, Alk = C₁₂H₂₅.

Scheme 2.



Our experiments showed that, regardless of the structure of the Grignard compound, no benzene alkylation occurred. Presumably, originally weak acceptor properties of MgBr_2 are weakened even more strongly by solvation in THF.

The formation of Grignard compounds and replacement of chlorine in 4-chloro-2-methyl-3-butyn-2-ol were considerably hindered since the reaction mixture was heterogeneous (by contrast to the reaction in diethyl ether). It is known that, as the length of the carbon chain in the initial bromide increases, the

Reactions of 4-chloro-2-methyl-3-butyn-2-ol with Grignard compounds

AlkX	Mg/AlkX	Method	Yield, %
<i>iso</i> -C ₃ H ₇ Br	1.5	A	60.3
<i>iso</i> -C ₄ H ₉ Br	1.1	A	55.7
C ₄ H ₉ Br	1.1	B	45.7
C ₄ H ₉ Br	2	B	64.3
C ₄ H ₉ Cl	1.1	A	71.4
<i>iso</i> -C ₅ H ₁₁ Br	1.1	A	72.0
C ₅ H ₁₁ Br	1.1	B	55.2
C ₅ H ₁₁ Br	2	B	63.2
<i>cyclo</i> -C ₆ H ₁₁ Br	1.1	B	47.2 ^a
C ₆ H ₁₃ Br	1.1	B	55.4
C ₆ H ₁₁ Br	2	B	70.2
C ₇ H ₁₅ Br	1.1	B	58.0 ^a
C ₈ H ₁₇ Br	1.1	A	40.1 ^a
C ₈ H ₁₇ Br	1.1	B	57.5 ^a
C ₉ H ₁₉ Br	1.1	B	73.5
C ₁₀ H ₂₁ Br	1.1	B	52.3 ^a
C ₁₂ H ₂₅ Br	1.1	B	56.0 ^a

^a Yield of terminal alkyne obtained by alkaline fission of the primary product, acetylenic alcohol.

Barbier–Grignard procedure in diethyl ether gives much better results than the two-step Grignard process [4]. A different and more complex pattern is observed in a hydrocarbon medium: increase in the length of the alkyl radical, on the one hand, favors the Wurtz reactions and, on the other, increases the solubility of magnesium halide alkoxide, thus reducing the contribution of side processes.

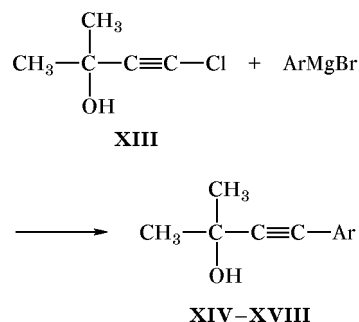
The contribution of the Wurtz reaction can be minimized by slow addition of alkyl bromide, and application of the two-step procedure is justified only for short radicals (up to C₆), since the Barbier–Grignard method does not favor formation of organo-magnesium compound because of the low solubility of magnesium halide alkoxide. This obstacle can be circumvented by using twofold excess of magnesium: the results become comparable with those obtained by the two-step procedure.

In going to longer hydrocarbon radicals (beginning with C₇), there is no need of applying excess magnesium, the second factor (solubilization of magnesium halide alkoxide; see above) becomes predominating, and the Barbier–Grignard procedure is preferable (see table). Unlike diethyl ether, the process in benzene allows higher temperature to be applied, and the

structure of the Grignard compound becomes less significant: alkyl derivatives with both normal and iso structure react with equal efficiency. The yields of the target products are 55–72%. However, we failed to obtain the corresponding alcohol from *tert*-butyl-magnesium chloride. This fact gives one more evidence in favor of the commonly accepted concerted reaction mechanism involving formation of a four-membered transition state [6].

The Wurtz reaction was the main process in the reactions of 4-chloro-2-methyl-3-butyn-2-ol with aryl-magnesium halides, which were carried out in hydrocarbons containing THF. Obviously, the reason is that the process is heterogeneous. In the reaction with phenylmagnesium bromide the yield of the corresponding acetylenic alcohol was 18% in benzene and 35% in toluene (according to the GLC data). When these reactions were performed in the presence of anisole and equimolar amount of THF (with respect to ArMgBr), the mixture became homogeneous, and the yield of the target products attained 60–67% (Scheme 3).

Scheme 3.



XIV, Ar = C₆H₅; **XV**, Ar = *o*-CH₃C₆H₄; **XVI**, Ar = *m*-CH₃-C₆H₄; **XVII**, Ar = *p*-CH₃C₆H₄; **XVIII**, Ar = *o*-CH₃OC₆H₄.

The structure of products **I–III** and **V–XVIII** was proved by comparing their properties with published data [1, 4, 7, 8]. The IR spectra of compounds **I–V**, **VII**, **X**, and **XIII–XVIII** contained absorption bands typical of C≡C bond (2220–2230 cm^{−1}) and OH group (3350–3400 cm^{−1}). Compounds **XIV–XVIII** also showed in the IR spectra a band at 1600 cm^{−1} due to aromatic ring vibrations. The terminal acetylenic bond in **VI**, **VIII**, **XI**, and **XII** gives rise to characteristic absorption bands at 2100–2110 (C≡C) and 3300 cm^{−1} (≡C–H).

Protons of the isopropyl group in **I** give a doublet at δ 1.00 ppm and a septet at δ 2.63 ppm (*J* = 6 Hz) in the ¹H NMR spectrum; the methyl group protons

appear as a singlet at δ 1.50 ppm, and the singlet at δ 4.31 ppm belongs to the hydroxy proton. In the ^1H NMR spectrum of **XVI** we observed signals from aromatic protons at δ 6.95–7.20 ppm and hydroxy group at δ 4.53 ppm. Protons of the methyl groups attached to the carbinol moiety appear at δ 1.59 ppm, and the aromatic methyl group protons give a singlet at δ 2.38 ppm. According to the GLC data, the purity of **XVI** was 94.3% after single distillation.

EXPERIMENTAL

The IR spectra were obtained from thin films or KBr discs using a UR-20 spectrometer. The ^1H NMR spectra were recorded on a Tesla BS-587A instrument operating at 80 MHz; cyclohexane- d_{12} was used as solvent, and TMS, as internal reference. GLC was performed on a Khrom-5 chromatograph; flame-ionization detector; 3.5-m glass column; stationary phase 3% of SP2100 on Chromaton N-AW-DMCS; carrier gas helium.

Initial 4-chloro-2-methyl-3-butyn-2-ol was synthesized by treatment of 2-methyl-3-butyn-2-ol with sodium hypochlorite at room temperature. Unlike the procedure reported in [9] which employs diethyl ether, we used benzene as solvent. As a result, the process was simplified, and the target product was isolated in 90% yield.

2,5-Dimethyl-3-hexyn-2-ol (I). 4-Chloro-2-methyl-3-butyn-2-ol, 5.9 g (0.05 mol), was added dropwise with stirring to the Grignard compound obtained from 7.2 g (0.23 mol) of metallic magnesium and 18.5 g (0.15 mol) of isopropyl bromide in benzene containing 10.8 g (0.15 mol) of THF. The mixture was heated for 5 h at 60°C and decomposed with 3% hydrochloric acid on cooling. The organic phase was dried over magnesium sulfate and evaporated, and the residue was distilled at 145–147°C to isolate 3.8 g (60.3%) of 2,5-dimethyl-3-hexyn-2-ol, n_D^{20} 1.4425; published data [4]: bp 48–50° (12 mm) n_D^{20} 1.4411. Compounds **II–IV** were synthesized in a similar way; their yields are given in table.

2,7-Dimethyl-3-octyn-2-ol (IV). bp 71–73°C (4 mm), n_D^{20} 1.4460, d_4^{20} 0.8451. Found, %: C 77.84; H 11.72. $\text{C}_{10}\text{H}_{18}\text{O}$. Calculated, %: C 77.92; H 11.69.

Reaction of *tert*-butylmagnesium chloride with 4-chloro-2-methyl-3-butyn-2-ol. The reaction was carried out as described above for isopropyl bromide. As a result, 1.9 g (33.3%) of the initial alcohol was recovered from the reaction mixture.

2-Methyl-3-nonyn-2-ol (V). Pentyl bromide, 3.8 ml (2.25 g, 0.015 mol), was added to a mixture of

4.0 g (0.166 mol) of metallic magnesium, 1.5 ml of THF, and 30 ml of benzene. When a reaction started, 5.5 ml (5.9 g, 0.05 mol) of 4-chloro-2-methyl-3-butyn-2-ol, 16.9 ml (20.40 g, 0.135 mol) of pentyl bromide, and 11 ml of THF in 60 ml of benzene were simultaneously added dropwise at 50–65°C over a period of 3 h. The mixture was heated for 4 h at that temperature and decomposed with 3% hydrochloric acid on cooling. The organic phase was separated and dried over magnesium sulfate, and volatile compounds were distilled off. Vacuum distillation of the residue at 93–95°C (12 mm) gave 4.25 g (55.2%) of 2-methyl-3-nonyn-2-ol, n_D^{20} 1.4465; published data [4]: bp 94–96°C (10 mm), n_D^{22} 1.4489.

Compounds **III**, **VII**, and **X** were synthesized in a similar way. Products **III**, **V**, and **VII** were also obtained by the same procedure but with a twofold excess of magnesium. The yields are given in table.

2-Methyl-4-(3-tolyl)-3-butyn-2-ol (XVI). 3-Bromotoluene, 1.8 ml (2.56 g, 0.015 mol), was added to a mixture of 4 g (0.16 mol) of metallic magnesium, 30 ml of anisole, and 1.2 ml of THF. When a reaction started, 5.5 ml (5.9 g, 0.05 mol) of 4-chloro-2-methyl-3-butyn-2-ol, 15.9 ml (23.1 g, 0.135 mol) of 3-bromotoluene, and 11 ml of THF in 40 ml of anisole were simultaneously added in a dropwise manner at 40–45°C over a period of 3 h. The mixture was heated for 4 h at that temperature and decomposed with 3% hydrochloric acid on cooling. The organic phase was separated and dried over magnesium sulfate, and volatile fractions were distilled off. Vacuum distillation of the residue at 105–108°C (3 mm) gave 5.5 g (63.2%) of 2-methyl-4-(3-tolyl)-3-butyn-2-ol, n_D^{20} 1.5498; published data [4]: bp 92–93.5°C (1.5 mm), $n_D^{16.5}$ 1.5485.

Compounds **XIV**, **XV**, **XVII**, and **XVIII** were synthesized by a similar procedure and with similar yields. In the reaction of phenylmagnesium bromide with 4-chloro-2-methyl-3-butyn-2-ol in toluene we isolated a fraction containing 41.8% (GLC) of the corresponding arylacetylenic alcohol and 58.2% of biphenyl (overall yield 83.8%, calculated on the expected 2-methyl-4-phenyl-3-butyn-2-ol).

1-Decyne (IX). Octyl bromide, 5.2 ml (5.80 g, 0.03 mol), was added to a mixture of 6.0 g (0.25 mol) of metallic magnesium, 60 ml of benzene, and 1.5 ml of THF. When a reaction started, 8.3 ml (8.9 g, 0.075 mol) of 4-chloro-2-methyl-3-butyn-2-ol, 34.4 ml (38.60 g, 0.20 mol) of octyl bromide, and 16 ml of THF in 80 ml of benzene were simultaneously added dropwise at 50–65°C over a period of 3 h. The mixture was heated for 4 h at that temperature and was

decomposed with 3% hydrochloric acid on cooling. The organic phase was separated and dried over magnesium sulfate, and volatile fractions boiling up to 83°C (3 mm) were distilled off. Potassium hydroxide, 1.0 g, was added to the residue, 18.35 g, and the mixture was heated at a bath temperature of 160–200°C. A fraction distilled in the temperature range from 56 to 180°C was dried over magnesium sulfate and distilled again. Yield of 1-decyne 5.95 g (57.5%), bp 165–166°C, n_D^{20} 1.4376; published data [8]: bp 162–165°C, n_D^{20} 1.4320.

Compounds **VI**, **VIII**, **XI**, and **XII** were obtained in a similar way. 1-Decyne (**IX**) was also synthesized by the two-step procedure (see above). The yields of the products are given in table.

4-Chloro-2-methyl-3-butyn-2-ol (XIII). Sodium hydroxide, 440 g, was dissolved in 1250 ml of water, the solution was cooled to room temperature, and gaseous chlorine prepared from 316 g KMnO_4 and 1600 ml of hydrochloric acid was passed through the solution. A solution of 97.5 ml (84.1 g, 1.0 mol) of 4-chloro-2-methyl-3-butyn-2-ol in 200 ml of benzene was added at 25–35°C, the mixture was stirred for 1 h, and the organic phase was separated, dried over magnesium sulfate, and distilled. Yield 107.2 g (90.5%), bp 134–136°C, n_D^{20} 1.4554; published data [9]: bp 70°C (50 mm), n_D^{20} 1.4571.

REFERENCES

1. Vasil'eva, R.L., Ashirbekova, A.K., Belyakova, V.A., Alimova, N.A., and Shchelnkunov, A.V., Available from VINITI, 1987, no. 1192–77.
2. Jeasure, I.K. and Josephs, M.I., *Weeds*, 1961, vol. 9, p. 103.
3. US Patent 3028438, 1962; *Ref. Zh., Khim.*, 1964, no. 1N337P.
4. Vasil'eva, R.L., Ashirbekova, A.K., and Shchelnkunov, A.V., Available from VINITI, 1975, no. 295–75.
5. Bryce-Smith, D. and Owen, W., *J. Chem. Soc.*, 1960, p. 3319.
6. Pal'm, V.A., *Vvedenie v teoreticheskuyu organicheskuyu khimiyu* (Introduction to Theoretical Organic Chemistry), Moscow: Vysshaya Shkola, 1974, p. 316.
7. Yasnopol'skii, V.D., *Fiziko-khimicheskie konstanty organicheskikh soedinenii s atsetilenovoi svyaz'yu* (Physicochemical Constants of Organic Compounds Containing an Acetylenic Bond), Baku: Akad. Nauk Azerb. SSR, 1966., pp. 18–27.
8. Shchelnkunov, A.V. and Ivanova, N.N., *Fiziko-khimicheskie konstanty atsetilenovykh soedinenii* (Physicochemical Constants of Acetylenic Compounds), Alma-Ata: Nauka Kazakh. SSR, 1988, pp. 128–163.
9. US Patent 298568, 1961; *Ref. Zh., Khim.*, 1962, no. 13L47P.