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LITHIATION OF CHLORODIHYDROFURAN AND CHLORODIHYDROPYRAN. SYNTHESIS OF ACETYLENIC ALCOHOLS

Tariq R. Sobahi, Salem A. Basaif, Abdullah M. Asiri and Mohamed A. Hassan
Department of Chemistry, Faculty of Science, King Abdulaziz University,
Jeddah-21589, P.O.Box 80203, Saudi Arabia
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تم اصطناع الكحولات الأستيلينية من مركب ٣-كلورو-٤،٥-ثنائي هيدروفيوران و مشتقات ٢-الكيل له و كذلك مركب ٥-كلورو-٣،٤-ثنائي هيدرو-*H*٢-بيران ومشتقات ٦-الكيل له باستخدام فلز الصوديوم كقاعدة حفزية معتدلة لفتح الحلقة مع النـــزع بيتا في THF. كذلك تم ألكلة ملح ثنائي ليثيوم للكحولات-أوميجا-أستيلينية في THF/HMPT متبوعة بالتحلل المائي لتعطي الكحولات الأستيلينية ذات سلسلة الكيل طويلة.

Acetylenic alcohols were synthesized from 3-chloro-4,5-dihydrofuran and its 2-alkyl derivatives, and 5-chloro-3,4-dihydro-2*H*-pyran and its 6-alkyl derivatives *via* base catalyzed β-elimination using sodium metal in THF. Also, alkylation followed by hydrolysis of the dilithium salt of ω-hydroxy-alk-1-ynes in THF/HMPT gives the corresponding long chain acetylenic alcohols.

INTRODUCTION

Long chain acetylenic alcohols are expensive chemicals and they are very important as key starter for the synthesis of the natural phermones, fatty alcohols, acids and detergents [1-3].

We are aiming to synthesis acetylenic alcohols *via* economical and commercial methods using tetrahydrofuran (THF) and 3,4-dihydro-2*H*-pyran as cheap and commercial petrochemical products as starting materials.

EXPERIMENTAL

Tetrahydrofuran (THF) was distilled over KOH followed by distillation over sodium metal in the presence of benzophenone and stored under nitrogen. *n*- and *sec*-Butyllithium were standardized by the method of Watson and Eastham [4]. The infrared spectra were obtained by Nicolet Magna 520 FTIR spectrophotometer using CCl_4 as a solvent. ^{1}H NMR spectra were recorded by Bruker DP X 400 MHz spectrometer using $CDCl_3$ as a solvent and TMS as internal standard. The mass spectra were measured by Hewlett-Packard 5980A spectrophotometer using direct introduction technique at 70 eV. Elemental analysis were carried out using a Perkin Elmer 240B analyzer. A Hewlett-Packard 5750 gas chromatography was used for quantitative analysis using C-20M*, 8%, 3 m and OV-17, 10%, 3 m as stationary phases and decane was used as an internal standard.

3-Chloro-4,5-dihydrofuran (1).

A stream of dry chlorine gas was passed into tetrahydrofuran (THF) (100 ml), at -20°C. After the solution became yellow in color, it was warmed up to room temperature and then a stream of nitrogen was passed till solution became colorless. The solution was added dropwise to tributylamine (TBA) (223 g, 1.2 mol) in a three-necked flask (500 ml) fitted with condenser at 150°C under 150-160 mm.Hg pressure during 3h. Distillation using Widmer column at 32-35°C/18 mm.Hg gave 3-chloro-4,5-dihydrofuran (**1**, 57.8 g, 55% yield); ^{1}H NMR δ 6.38 (1H, s, olefinic C2-*H*), 4.36 (2H, t, C5-H_2), 2.78 (2H, t, allylic C4-H_2) ppm.

5-Chloro-3,4-dihydro-2*H*-pyran (2).

A stream of dry chlorine gas was passed into a solution of 3,4-dihydro-2*H*-pyran (84.0 g, 1.0 mol) in dry CCl_4 (600 ml) at -30°C. After the solution became yellow in color it was warmed up to room temperature and then a stream of nitrogen was passed till the solution became colorless. The solution was added dropwise to tributylamine

yellow solution], hept-3-yn-1-ol **(7c)** or hept-4-yn-1-ol **(7g)** (2.24 g, 20 mmol) was injected rapidly at 0°C with vigorous stirring for 2h and the mixture kept at 25°C for 2h. The reaction mixture was quenched by water (50 ml). The solution was extracted with ether (3X100 ml) and washed by HCl (4M aqueous solution). The ethereal solution was dried over $CaSO_4/K_2CO_3$. The solvent was removed by distillation and the product was distilled at 83-85°C/ 10mm.Hg to give hept-6-yn-1-ol **(8)** (2.1 g, 94% yield); IR ν_{max} 2130 (HC≡), 2950 (C≡C), and 3310 (OH) cm^{-1}; ^1H NMR δ 3.60 (2H, t, CH_2-O), 2.20 (2H, dt, ≡C-CH_2), 1.90 (1H, t, HC≡), 1.60 (1H, s, OH), 1.55 (6H, m, 2CH_3) ppm; MS m/e 80(100%), 112(3% M^+); $C_7H_{12}O$ (112.1), Calcd.: C, 74.94; H, 10.79. Found: C, 74.91; H, 10.90.

Synthesis of acetylenic alcohols (7b-g and h-j).

To a solution of ω-hydroxy-alk-1-yne (20 mmol) in dry THF (30 ml), *n*-butyllithium (40 mmol) was added dropwise at 0°C and the solution was stirred for 1h after complete addition and then the alkyl halide (20 mmol) in hexamethylphosphorous triamide (HMPT) (60 ml) was added at 0°C and left with stirring for 1h at 0°C and 2h at 25°C. The solution was poured into ice (100 g) and extracted with ether (3X50 ml). The ethereal solution was separated and washed with water (3X50 ml) and dried over $CaSO_4$. The solvent was distilled off and the product was distilled under vacuum (yield 68-75%) (Table 1).

7h: IR ν_{max} 2920 (C≡C), and 3350 (OH) cm^{-1}; ^1H NMR δ 4.20 (2H, t, CH_2-O), 3.50 (1H, s, OH), 1.80 (3H, t, CH_3) ppm; MS m/e 40(84%), 70(100% M^+); C_4H_6O (70), Calcd.: C, 68.55; H, 8.63. Found: C, 68.37; H, 8.72.

7i: ^1H NMR δ 3.90 (2H, t, CH_2-O), 2.60 (4H, m, CH_2-C≡C-CH_2), 1.80 (1H, s, OH), 1.40 (8H, m, 4CH_2), 0.98 (3H, t, CH_3) ppm; $C_{10}H_{18}O$ (154), Calcd.: C, 77.27; H, 11.67. Found: C, 77.16; H, 11.54.

7j: IR ν_{max} 2940 (C≡C), and 3360 (OH) cm^{-1}; ^1H NMR δ 3.58 (2H, t, CH_2-O), 2.13 (4H, m, CH_2-C≡C-CH_2), 2.05 (1H, s, OH), 1.45 (12H, m, 6CH_2), 0.88 (3H, t, CH_3) ppm; MS m/e 80(100%), 182(3% M^+); $C_{12}H_{22}O$ (182), Calcd.: C, 79.06; H, 12.16. Found: C, 79.21; H, 12.27.

1-Bromo-but-2-yne and 1-bromo-pent-3-yne (9a,b).

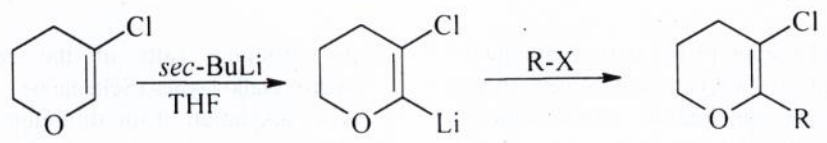
To a suspension of triphenylphosphine dibromide (120 mmol) in benzene (300 ml), but-2-yn-1-ol **(7h)** or pent-3-yn-1-ol **(7b)** (100 mmol) in dichloromethane (45 ml) was added dropwise at 0°C during 1h. The solution was stirred at 0°C for 2h after complete addition, and then kept at 25°C for 1h. The solution was filtered to remove triphenylphosphine oxide / HBr adduct and benzene was distilled of from the filtrate. The residue was taken up in hexane (100 ml) and purified by silica gel column chromatography to isolate the residual adduct. The solvent was distilled off and the product was distilled.

9a: distilled at 118-120°C/ 750mm.Hg (74% yield); IR ν_{max} 2920 (C≡C) cm^{-1}; ^1H NMR δ 3.85 (2H, t, CH_2Br), 1.85 (3H, t, CH_3) ppm; MS m/e 80(100%), 133(44% M^+); C_4H_5Br (133), Calcd.: C, 36.13; H, 3.99. Found: C, 36.03; H, 4.23.

9b: distilled at 64-66°C/ 40mm.Hg (84% yield); IR ν_{max} 2940 (C≡C) cm^{-1}; ^1H NMR δ 3.28 (2H, t, CH_2Br), 2.55 (2H, m, ≡C-CH_2), 1.75 (3H, t, CH_3) ppm; MS m/e 66(100%), 147(84% M^+); C_5H_7Br (147), Calcd.: C, 41.12; H, 4.83. Found: C, 40.91; H, 4.90.

Pent-3-ynyl-toluene-*p*-sulphonate (10).

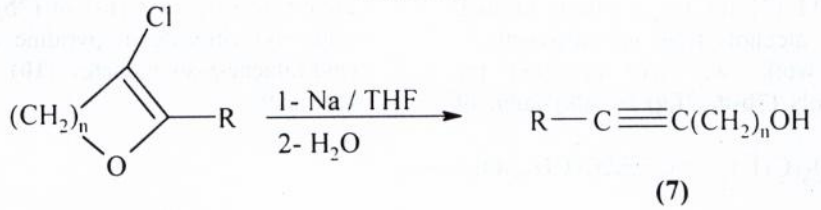
Pent-3-yn-1-ol (**7b**, 4.2 g, 50 mmol) was added during 45 min at 25°C to a stirred slurry of toluene-*p*-sulphonyl chloride (10.8 g) in pyridine (5 ml). After complete addition, the solution was stirred for 2h and then the mixture was poured into ice (100g) and extracted with ether (3X20 ml). The ether extract was washed by H_2SO_4 (2X10 ml, 6N) and then with a saturated aqueous solution of $NaHCO_3$ (5 ml) and finally, with water (5 ml), dried over anhydrous K_2CO_3 and the solvent was distilled off. The solid residue was crystallized from ethanol to give pent-3-ynyl-toluene-*p*-sulphonate (**10**, 9.6 g, 81% yield); mp 40-41°C; ^1H NMR δ 7.73-7.25 (4H, dd, Ar-H), 4.05 (2H, t, CH_2-OSO_2), 2.48 (2H, m, ≡C-CH_2), 2.42 (3H, s, Ar-CH_3), 1.68 (3H, t, ≡C-CH_3) ppm; $C_{12}H_{14}O_3S$ (238), Calcd.: C, 60.48; H, 5.92. Found: C, 60.38; H, 5.98.



(2) **(5)** **(6)**

a) R= CH_3
b) R= C_2H_5

Scheme 3



(1,4); n= 2
(2,6); n= 3

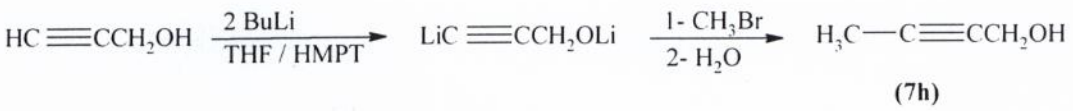
(7)

	n	R
a)	2	H
b)	2	CH_3
c)	2	n-C_3H_7
d)	2	n-C_4H_9
e)	3	H
f)	3	CH_3
g)	3	C_2H_5

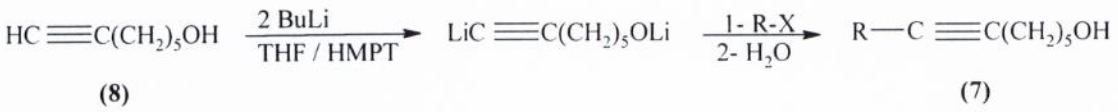
Scheme 4

Table 1: The physical data of acetylenic alcohols (7).

Compound	b.p/mm	Yield %	Analysis % found/calcd. C	H
7a	126°C/760	77	68.45 68.51	8.67 8.63
7b	57°C/13	78	71.32 71.39	9.58 9.59
7c	150°C/19	81	75.78 75.89	10.68 10.71
7d	89°C/7	84	76.07 76.13	11.08 11.19
7e	143°C/760	69	71.59 71.39	9.62 9.59
7f	74°C/8	73	73.38 73.47	10.13 10.20
7g	91°C/18	73	74.94 74.94	10.73 10.79



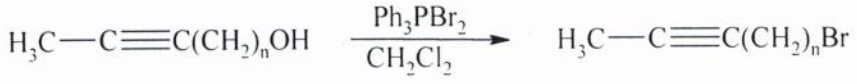
(7h)



(8) **(7)**

i) R= *n*-C_3H_7
j) R= *n*-C_5H_{11}

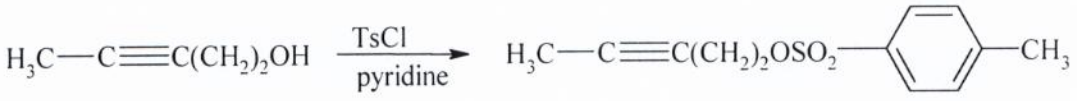
Scheme 7



(7) **(9)**

a) n= 1 ; **b)** n= 2 **a)** n= 1 ; **b)** n= 2

Scheme 8



(7b) **(10)**

Scheme 9

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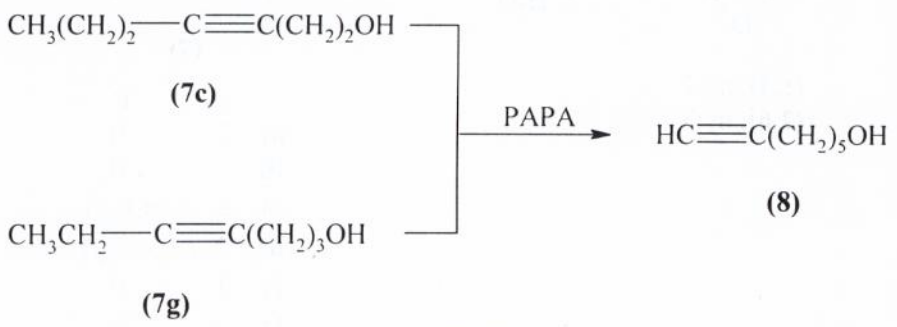
It was reported earlier [9,10] that potassium-3-aminopropylamide (PAPA) is used as new strong base for rapid, and quantitative multi-positional isomerization of the internal triple bond to the chain terminus. Treatment of hept-3-yn-1-ol **(7c)** or hept-4-yn-1-ol **(7g)** with PAPA at 0°C under argon as heavy inert gas in 3-aminopropylamine as solvent gives hept-6-yn-1-ol **(8)** in quantitative yield (Scheme 5).

On the other hand, there are many methods have been reported [11-13] for the synthesis of long chain acetylenic alcohols from ω-hydroxy-alk-1-ynes. In this work, we have prepared the acetylenic alcohols **(7b-d, 7f,g)** by alkylation of the dilithium salts of the corresponding ω-hydroxy-alk-1-ynes (Scheme 6).

Also, alkylation of the dilithium salt of propargyl alcohol or hept-6-yn-1-ol **(8)** under the same conditions yielded the corresponding acetylenic alcohol **(7i,j)** respectively (Scheme 7).

Treatment of but-2-yn-1-ol **(7h)** or pent-3-yn-1-ol **(7b)** with triphenylphosphine dibromide in dichloromethane gave 1-bromo-but-2-yne **(9a)** or 1-bromo-pent-3-yne **(9b)** respectively (Scheme 8). Treatment of pent-3-yn-1-ol **(7b)** with toluene-*p*-sulphonyl chloride in pyridine afforded pent-3-ynyl-toluene-*p*-sulphonate **(10)** as shown in scheme 9.



Scheme 5

(7)

	n	R
b)	2	CH_3
c)	2	n-C_3H_7
d)	2	n-C_4H_9
f)	3	CH_3
g)	3	C_2H_5

Scheme 6

RESULTS AND DISCUSSION

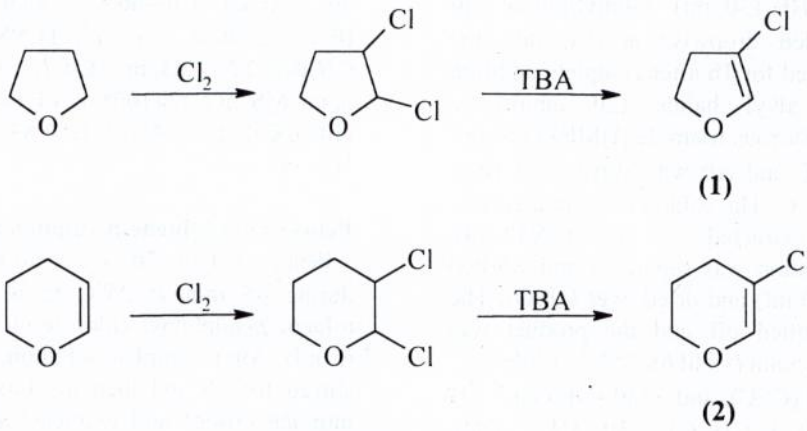
Chlorination of THF followed by dehydrochlorination using tributylamine (TBA) gives 3-chloro-4,5-dihydrofuran **(1)**. Also, chlorination of 3,4-dihydro-2*H*-pyran followed with dehydrochlorination by TBA gives 5-chloro-3,4-dihydro-2*H*-pyran **(2)** in a good yield (Scheme 1).

Treatment of 3-chloro-4,5-dihydrofuran **(1)** with *n*-butyllithium in THF at -78°C gives 3-chloro-4,5-dihydro-2-furyllithium **(3)** [5], which is quenched by alkyl halides at -78°C to give 2-alkyl-3-chloro-4,5-dihydrofuran **(4a-c)** [6] (Scheme 2).

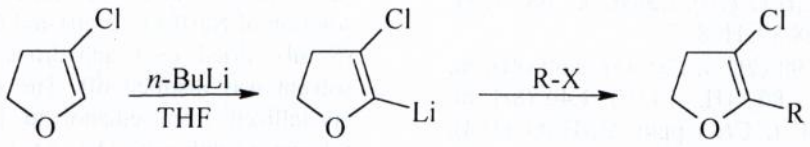
In an analogous steps, the treatment of 5-chloro-3,4-dihydro-2*H*-pyran **(2)** with *sec*-butyllithium in THF at -78°C gives 5-chloro-3,4-dihydro-2*H*-pyran-6-yllithium **(5)**, which is quenched by alkyl halides to give 6-alkyl-5-chloro-3,4-dihydro-2*H*-pyran **(6a,b)** [7] (Scheme 3).

It has been reported [5,8] that potassium-sodium alloy in THF is used as a base for ring opening with β-elimination of 3-chloro-2-methyl-4,5-dihydrofuran with subsequent isomerization to give a mixture of pent-3-yn-1-ol and pent-4-yn-1-ol.

We have modified the method to obtain high yield by convenient and simple method for the synthesis of the expected acetylenic alcohols without any isomerization. Sodium metal in THF is used as mild base at 25°C for ring opening with β-elimination of 3-chloro-4,5-dihydrofuran **(1)** or its 2-alkyl derivatives **(4)** and 5-chloro-3,4-dihydro-2*H*-pyran **(2)** or its 6-alkyl derivatives **(6)** to give after hydrolysis with water the corresponding acetylenic alcohols **(7)** in good yield as shown in scheme 4. Physical data of compounds **(7)** were given in Table 1.



Scheme 1



a) R= CH_3
b) R= n-C_3H_7
c) R= n-C_4H_9

Scheme 2

(223 g, 1.2 mol) in a three-necked flask (500 ml) fitted with condenser at 150°C under 150-160 mm.Hg pressure during 3h. The CCl_4 was removed by distillation and then further distillation using Widmer column at 43-45°C/ 18mm.Hg gave 5-chloro-3,4-dihydro-2*H*-pyran (**2**, 72.0 g, 61% yield); ^{1}H NMR δ 6.70 (1H, t, olefinic C6-*H*), 3.95 (2H, t, allylic C4-H_2), 2.84 (2H, t, C2-H_2), 2.12 (2H, dt, C3-H_2) ppm.

2-Alkyl-3-chloro-4,5-dihydrofuran (4a-c).

To a solution of 3-chloro-4,5-dihydrofuran **(1)** (52.0 g, 0.5 mol) in absolute THF (300 ml), *n*-butyllithium (1.5 M) in hexane (333.3 ml, 0.5 mol) was added dropwise during 1h at -78°C under nitrogen. 3-Chloro-4,5-dihydrofuryllithium **(3)** was precipitated during the addition. The solution was kept at -78°C for 2h after complete addition with stirring. The solution was warmed up gradually to -20°C and then methyl, *n*-propyl, or *n*-butyl iodide (0.55 mol) was added dropwise. The solution was kept for 2h at -20°C with stirring and then warmed up to room temperature. Water (500 ml) was added, and the aqueous layer was extracted with ether (3X100 ml) and added to organic layer, dried over $CaSO_4$ and the solvent was distilled using Widmer column. The product was distilled under vacuum to give 2-alkyl-3-chloro-4,5-dihydrofuran **(4a-c)** in 80-85% yield.

4a: distilled at 47-49°C/ 45mm.Hg; ^{1}H NMR δ 4.35 (2H, t, C5-H_2), 2.97 (2H, t, allylic C4-H_2), 1.80 (3H, s, C2-CH_3) ppm.

4b: distilled at 53-55°C/ 12mm.Hg; ^{1}H NMR δ 4.31 (2H, t, C5-H_2), 2.87 (2H, t, allylic C4-H_2), 2.48 (2H, t, C1-H_2 of *n*-C_3H_7), 1.49 (2H, m, C2-H_2 of *n*-C_3H_7), 1.03 (3H, t, CH_3) ppm.

4c: distilled at 64-66°C/ 45mm.Hg; ^{1}H NMR δ 4.29 (2H, t, C5-H_2), 2.83 (2H, t, allylic C4-H_2), 2.25 (2H, t, C1-H_2 of *n*-C_4H_9), 1.46 (4H, m, C2-H_2 and C3-H_2 of *n*-C_4H_9), 0.96 (3H, t, CH_3) ppm.

6-Alkyl-5-chloro-3,4-dihydro-2*H*-pyran (6a,b).

In a 250 ml three-necked flask containing 5-chloro-3,4-dihydro-2*H*-pyran **(2)** (11.8 g, 100 mmol) in dry THF (50 ml) at -78°C, *sec*-butyllithium (142.8 ml, 100 mmol of 0.7 M solution in hexane) was added dropwise during 1h, at -78°C under nitrogen atmosphere and the solution was stirred for 2h at -78°C after complete addition. Ethereal solution of methyl or ethyl iodide (120 mmol) was added and then the solution was kept at -78°C with stirring for 5h. The solution was gradually warmed to room temperature with stirring for 30 min, and then water (30 ml) was added. The solution was extracted with ether (3X50 ml) and the ethereal extracts were dried over $CaSO_4$. The solvent was then distilled off and the product was distilled.

6a: distilled at 58-60°C/ 18mm.Hg (69% yield); ^{1}H NMR δ 4.27 (2H, t, C2-H_2), 2.43 (2H, t, allylic C4-H_2), 2.02 (2H, dt, C3-H_2), 1.77 (3H, s, CH_3) ppm.

6b: distilled at 63-66°C/ 18mm.Hg (78% yield); ^{1}H NMR δ 4.23 (2H, t, C2-H_2), 2.39 (2H, t, allylic C4-H_2), 2.32 (2H, q, C6-CH_2-), 1.92 (2H, dt, C3-H_2), 1.05 (3H, t, CH_3) ppm.

Synthesis of acetylenic alcohols (7a-g).

Method A:

A mixture of 3-chloro-4,5-dihydrofuran **(1)** and its 2-alkyl derivatives **(4)** or 5-chloro-3,4-dihydro-2*H*-pyran **(2)** and its 6-alkyl derivatives **(6)** (50 mmol), were dissolved in dry THF (50 ml) and finely devided sodium metal (3.6 g, 150 mmol) was added with stirring at 25°C for 48h. The dark blue suspension was poured into ice (50g) and the solution was extracted with ether (3X50 ml) and dried over $CaSO_4$. The solvent was removed by distillation and then the products were distilled under vacuum (Table 1).

The IR spectra of alcohols **(7)** showed bands ranges at ν_{max} 2100-2130 (HC≡), 2930-2959 (C-C≡C-C), and 3300-3320 (OH) cm^{-1}. The ^{1}H NMR signals of alcohols **(7)** range are: δ 3.3-3.9 (2H, t, CH_2-CH_2-OH), 1.8-2.5 (2H, m, ≡C-CH_2), 1.7-2.1 (1H, t, *H*C≡), 1.5-1.8 (3H, m, ≡C-CH_3) ppm, and unfixed position for 1H of OH group. The mass spectra of **(7)** displayed peaks at m/e (abundance %): **7b** 40(100), 84(4); **7e** 40(100), 84(14); **7g** 80(100), 112(3).

Hept-6-yn-1-ol (8).

To a solution of PAPA (80 mmol) [prepared by adding 1,3-diaminopropane (50 ml) to potassium hydride (3.2 g, 80 mmol) under argon at 25°C till no hydrogen gas evolved with formation of clear