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AN EXPEDITIOUS SYNTHESIS OF ALK-2-YN-1-OLS

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Abstract: A convenient inexpensive preparation of alk-2-yn-1-ols, commencing from terminal alkynes, has been developed. This procedure allows for using paraformaldehyde instead of gaseous formaldehyde for hydroxymethylation of alk-1-ynylmagnesium bromides.

Alkynylation is an important reaction widely used in organic synthesis. It has been traditionally carried out by using alkali metal alkynides or alkynyl Grignard reagents usually obtained from terminal acetylenes and ethylmagnesium bromide. Alkynylation of formaldehyde is of special importance because the propargyl alcohols thus formed are valuable intermediates which are useful in the synthesis of alk-2-yn-1-als[1] used for the preparation of 2,5-dialkylresorcinols[2] and alkynyl-halocarbenes[3] as well as for other synthetic applications including preparation of trisubstituted allenes[4], furans[5], and α,β-unsaturated aldehydes[6].

Either of two methods is generally proposed for alkynylation of formaldehyde. The first method uses gaseous formaldehyde generated

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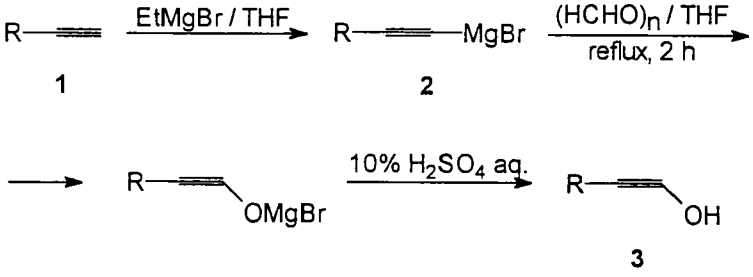
by the thermal depolymerization of paraformaldehyde[7] or 1,3,5-trioxane[8]. Formaldehyde is carried over into the alkynyl Grignard reagent by a current of dry nitrogen using a wide delivery tube which is prone to clogging. The second method involves the *in situ* generation of formaldehyde from dry paraformaldehyde reacting with ethereal solution or suspension of lithium acetylide[9]. Both aforementioned procedures are neither operationally simple nor rapid and economically attractive.



Scheme

We required a number of alk-2-yn-1-ols as starting materials for the stereospecific synthesis of (Z)-and (E)-allylamines. To meet our needs for a general, simple, and inexpensive entry to such propargyl alcohols we have decided to combine the use of alkynyl Grignard reagents with the *in situ* generation of formaldehyde from its linear polymer by changing the solvent from ether to tetrahydrofuran. This modification significantly simplifies the preparation of alk-2-yn-1-ols (**3**) from terminal acetylenes (**1**) (Scheme).

Commercially available terminal alkynes (**1**) were transformed into alk-1-ynylmagnesium bromides (**2**) by refluxing with tetrahydrofuran solution of freshly prepared ethylmagnesium bromide. Hydroxymethylation of (**2**) was accomplished by generating formaldehyde *in situ* from paraformaldehyde suspended in the reacting mixture. The reaction was practically completed after 2 hours in refluxing tetrahydrofuran. Upon conventional work-up with 10% aqueous sulfuric acid the crude alk-2-yn-1-ols (**3**) were purified by distillation under reduced pressure to give spectroscopically pure samples in good yields. Physical properties of all compounds (**3**) prepared were fully consistent with the literature data (Table).

Thus, a convenient and economically attractive synthesis of alk-2-yn-1-ols (**3**) starting from terminal alkynes (**1**) has been developed. The main advantage of our procedure is the possibility of using paraformaldehyde directly in the reaction medium without previous depolymerization. The use of lithium acetylides recommended for such preparative variant[9] is neither necessary nor economically justified.

It is also noteworthy that our synthetic modification can be directly extended to hydroxymethylation of other Grignard compounds. We were able to demonstrate that cyclohexylmethanol can be conveniently prepared from cyclohexylmagnesium chloride in 70% yield following exactly the procedure described in this paper. This is in contrast to the literature statement[10] that the yield is only 40-50% when paraformaldehyde is used directly in ethereal solution without depolymerization.

TABLE

Preparation of Alk-2-yn-1-ols (**3**).

Compound No.	R	Yield of (**3**) (%)*	b.p. of (**3**) (°C/mmHg)	n_D^{20} of (**3**)	Lit. data of (**3**)
3a	C_3H_7	75	71-72/15	1.4530	b.p. 88-91/60[2], n_D^{20} - 1.4550[11]
3b	C_4H_9	75	88-89/16	1.4526	b.p. 83/12[9], n_D^{20} - 1.4555[9]
3c	C_5H_{11}	73	96/11	1.4480	b.p. 93/10[2]
3d	C_6H_{13}	74	110/20	1.4556	b.p. 108/10[2]
3e	Ph	82	132/10	1.5830	b.p. 107/2[12], n_D^{25} - 1.5835[12]

* Yields of distilled, pure compounds.

EXPERIMENTAL

Analytically pure, absolute tetrahydrofuran was purchased from Fluka. All other reagents were commercially available and used without further purification. Boiling points are uncorrected. IR spectra were measured using a Specord M 80 (C. Zeiss) instrument. ^{1}H-NMR spectra were recorded at 80 MHz with a Tesla 587 FT spectrometer. FAB/MS were measured on a APO Electron (Ukraine) Modell MI 12001 E mass spectrometer equipped with a FAB ion source (thioglycerol matrix).

Preparation of alk-2-yn-1-ols (3a-e). General Procedure:

Ethylmagnesium bromide was prepared from magnesium grit (1.44 g, 60 mmol) and ethyl bromide (7.2 g, 66 mmol) in tetrahydrofuran (35 mL). A solution of alk-1-yne (1, 60 mmol) in tetrahydrofuran (10 mL) was then added dropwise with stirring and the reacting mixture was refluxed for 1.5 h. It was then cooled to room temperature and paraformaldehyde (dried in vacuo over P_2O_5, 2.4 g, 80 mmol) was added. The resultant mixture was refluxed with stirring for 2 h. It was then cooled (ice-water bath) and quenched with 10% aqueous sulfuric acid (100 mL) at room temperature. The organic phase was separated and the water layer was extracted with ether (2 x 10 mL). The extracts combined with the organic phase were washed with 5% $NaHCO_3$ aq. (10 mL) and water (10 mL), dried over anhydrous $MgSO_4$, evaporated, and distilled in vacuo to give pure alk-2-yn-1-ol (**3a** - **e**) as colorless liquid (see Table).

Hex-2-yn-1-ol (3a):

Yield: 75%. IR (film): ν = 3356, 2964, 2936, 2872, 2288, 2228, 1034, 1024 cm^{-1}.

^1H - NMR ($CDCl_3$ / TMS): δ = 0.98 (t, 3H, J = 7.2); 1.58 (sex, 2H, J= 7.2); 1.87 (s, 1H); 2.27 (tt, 2H, J = 7.2, J = 2.25); 4.37 (t, 2H, J = 2.25).

MS (m/z): 99 (M + 1), 81 (M - OH).

Hept-2-yn-1-ol (3b):

Yield: 75%. IR (film): ν = 3340, 2956, 2948, 2936, 2872, 2224, 1136, 1012 cm^{-1}.

^1H - NMR ($CDCl_3$ / TMS): δ = 0.82 (dist. t, 3H, J = 6.5); 1.35 - 1.61 (m, 4H); 1.94 (s, 1H); 2.15 - 2.38 (m, 2H); 4.27 (t, 2H, J = 2.25).

MS (m/z): 113 (M + 1), 95 (M - OH).

Oct-2-yn-1-ol (3c):

Yield: 73%. IR (film): ν = 3340, 2936, 2884, 2860, 2288, 2228, 1136, 1014 cm^{-1}.

^1H - NMR ($CDCl_3$ / TMS): δ = 0.98 (dist.t, 3H, J = 6.0); 1.20 - 1.60 (m, 6H); 1.87 (s, 1H); 2.15 - 2.33 (m, 2H); 4.37 (t, 2H, J = 2.25).

MS (m/z): 127 (M + 1), 109 (M - OH).

Non-2-yn-1-ol (3d):

Yield: 74%. IR (film): ν = 3344, 2932, 2884, 2860, 2264, 2228, 1138, 1014 cm^{-1}.

^1H - NMR ($CDCl_3$ / TMS): δ = 0.90 (dist.t, 3H, J = 6.0); 1.18 - 1.65 (m,

8H); 1.95 (s, 1H); 2.15 - 2.38 (m, 2H); 4.37 (t, 2H, J = 2.25).

MS (m/z): 141 (M + 1), 123 (M - OH).

3-Phenyl-prop-2-yn-1-ol (3e):

Yield: 82%. IR (film): ν = 3328, 2240, 1520, 1488, 1442, 1032, 756, 692 cm^{-1}.

^1H - NMR ($CDCl_3$ / TMS): δ = 1.96 (s, 1H); 4.49 (s, 2H); 7.41 - 7.80 (m, 5H).

MS (m/z): 133 (M + 1), 115 (M - OH).

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