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A NOVEL ETHYNYLATION OF α-SUBSTITUTED MESITYL OXIDES

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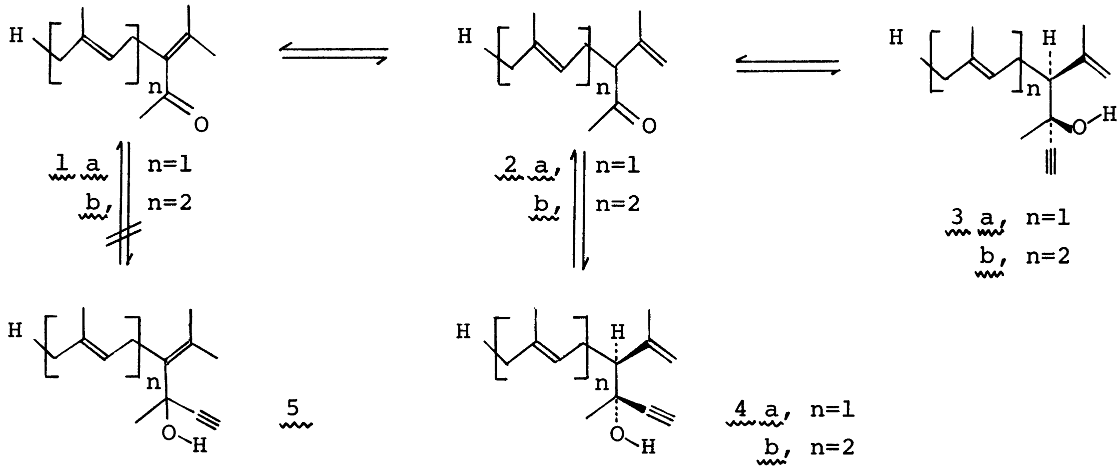
The ethynylation of ketone (**2**) in liquid ammonia at -33°C with stoichiometric sodium acetylide afforded the corresponding alcohol (**3** and **4**). Similar treatment of **1** resulted in only a little isomerization to **2**. Favorskii ethynylation under pressure at 0°C yielded a mixture of **1**, **2**, **3** and **4** without any detectable **5**, whichever ketone **1** or **2** being used.

Ethynylation of α,β-unsaturated ketones using stoichiometric potassium acetylide, lithium acetylide or calcium acetylide was reported to afford the corresponding ethynyl vinyl alcohol (e.g. **5**).[2] In the case of α-substituted α,β-unsaturated ketones (**1**), ethynylation was predicted to be complicated because of the accompanied isomerization to β,γ-unsaturated ketones (**2**) in the presence of potassium hydroxide or potassium amide.[3]

Recently, mesityl oxide has been shown to be a useful carbon-6 chain extender for the synthesis of terpenoid compounds *via* Cope rearrangement.[4] We now report a selective ethynylation to yield ethynyl allyl alcohols (**3** and **4**) which may be useful key-intermediates for the production of pseudoionone, squalane or isophytol *via* oxy-Cope rearrangement.[5]

The condensation reaction[3] of prenyl- or geranyl- chloride with 2 equiv. of mesityl oxide in the presence of 55 wt% of aquous sodium hydroxide (1.5 equiv.) using trimethylstearylammonium chloride as a catalyst at 60°C for 3 hrs gave a mixture of **1** and **2**, in ca. 80% yield (**1**:**2**=25:75). The ratio of **1**:**2** widely varied with reaction conditions, from 70:30 to 10:90. If desired, only **2** could easily and almost quantitatively be obtained, by continuous rectification under the condition of isomerization using 1,8-diazabicyclo [5,4,0] undecene-7 as a catalyst [1 wt% vs. (1 and 2)]. In the case of 2a, distillation condition was following: bottom temp., 140°C; top temp., 105°C; press., 40 mmHg.



Stoichiometric sodium acetylide ethynylation of 2a (2 mol) in liquid ammonia (1500 ml) at -33°C for 3 hrs, bubbling acetylene gas through the system, afforded a mixture of 1a, 2a and 4-isopropenyl-3,7-dimethyl-6-octen-1-yn-3-ol (3a and 4a) in a ratio of ca. 15, 5, 78 and 2%, respectively [analyzed by Vpc on a 10% PEG-20 M on Chromosorb W(AW) column (2 m) at 160°C]. 3a (purity 97%; bp 59-61°C/0.5 mm Hg) obtained by silica gel column chromatography ($n\text{-}C_6H_{14}:C_6H_6=6:4$) showed following spectra: ir(neat) 3440, 3300, 2120, 1640, 1030, and 900 cm^{-1}; nmr δ(in CCl_4) 1.40(s, CH_3, 3H), 1.60 and 1.64(s, CH_3, 6H), 1.72(s, CH_3, 3H), 2.00-2.40(m, CH_2CH, 3H), 2.30(s, ≡CH, 1H), ca. 4.83-5.00(m, =CH and $=CH_2$, 3H). On the other hand, similar treatment of 1a resulted in only a little isomerization to 2a (ca. 6%) and neither 3a and 4a nor the corresponding 5 expected could be observed.

Similar ethynylation of 2b gave a mixture of 1b, 2b and 4-isopropenyl-3,7,11-trimethyl-6,10-dodecatrien-1-yn-3-ol (diastereomers; 3b and 4b) in a ratio of ca. 30, 10, 57 and 3%, respectively. 3b (purity 95%; bp 120-125°C/0.3 mmHg) showed following spectra: ir(neat) 3450, 3290, 2117, 1630, 1025, 942, 920 and 895 cm^{-1}; nmr δ(in CCl_4) 1.40(s, CH_3, 3H), 1.53, 1.58 and 1.75(s, CH_3, 12H), ca. 1.87-2.50 (m, CH_2CH_2 and CH_2CH, 7H), 2.30(s, ≡CH, 1H), ca. 4.70-5.15(m, $=CH_2$ and =CH, 4H). Lower yield of alcohol (3b and 4b) was ascribed to the congelation of 2b under the reaction condition.

Contrariwise, the Favorskii ethynylation (molar ratio of acetylene:ketone=2.5 ∼7) in liquid ammonia (1500 ml) under pressure at the temperature range of -10 to 15°C, using 20 wt% of aquous potassium hydroxide (1-8 mol% vs. ketone) as a catalyst yielded a mixture of 1, 2, 3 and 4 without any detectable 5, whichever ketone

(1 mol) 1 or 2 might be employed. Stereochemistry of the diastereomers were not yet clarified, but the predominant production of 3a in the initial stage (see Fig. I), owing to the steric inequality of the conformation of 2a for a nucleophillic attack was suggested by conformational analysis[6).

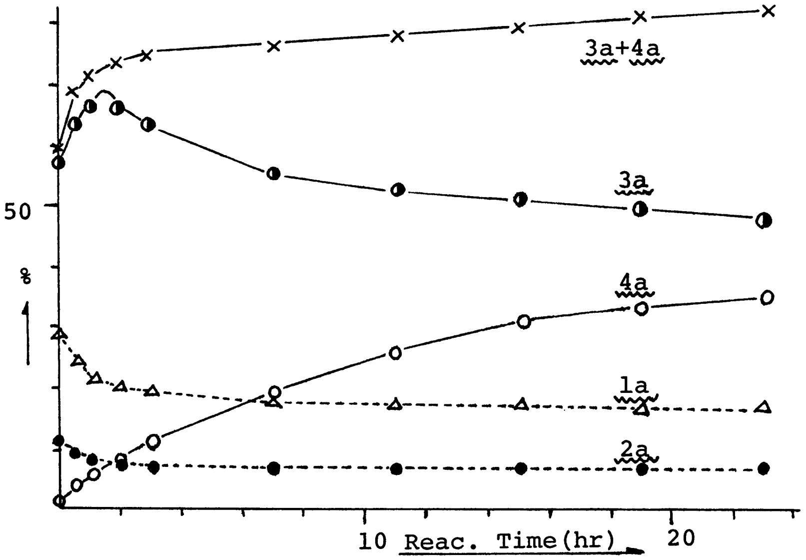


Fig. I Semicatalytic Ethynylation of 2a at 5°C. Molar Ratio of CH≡CH:2a=5; KOH:2a=0.08

Fractional distillation or silica gel column chromatography were ineffective for the separation of these two isomers (3 and 4). 4a separated and purified by preparative Vpc (PEG-20M, 2 m, 170°C) showed following spectra: ir(neat) 3430, 3290, 2116, 1638, 1110, 1030, 910, and 895 cm^{-1}; nmr δ(in CCl_4) 1.28(s, CH_3, 3H), 1.54 and 1.56(s, CH_3, 6H), 1.65(s, CH_3, 3H), ca. 1.90-2.55(m, CH_2CH, 3H), 2.30(s, ≡CH, 1H), 4.70(s, $=CH_2$, 2H), 4.92(t, =CH, 1H, J=7Hz)

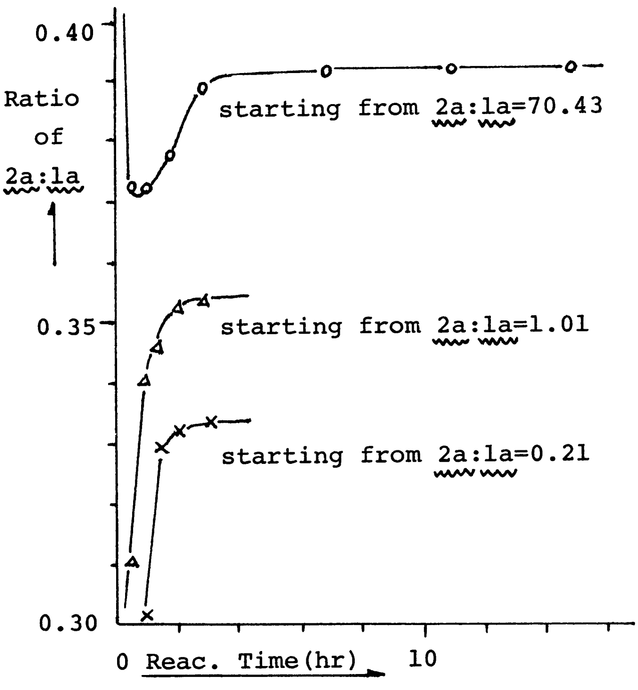


Fig. II Time Variation of Ratio of 2a:1a in Semicatalytic Ethynylation.

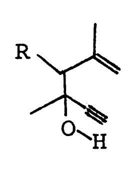
Production of 3a had a maximum in the first stage, and then, showed a decrease with the production of 4a, holding an approximately constant ratio of 3a to 2a. When 2a was used for the starting material, ratio of 2a:1a had a minimum which corresponded to the maximum of 3a, and then, approached to the isomerization equilibrium value (ca. 0.38 at 0°C). Furthermore, when 1a or the mixture of 1a and 2a (50:50) being used, no appreciable minimum of **2a**:**1a** could be observed (see Fig. II). It might be appropriate to set the rate-determining step to the isomerization process in the initial stage and to the ethynylation process afterward. Equilibrium value of the semicatalytic method was fundamentally defined by the molar ratio of acetylene to ketone. For instance, reaction of **2** in ammonia at 0°C for 2 hrs, in variation of molar ratio CH≡CH:ketone=2.5, 3 and 5, afforded a mixture of **3** and **4** in 65, 67 and 74%, respectively. On the other hand, treatment of **3a** with potassium hydroxide (5 mol%) in ammonia at 0°C for 3 hrs without acetylene, which condition might correspond to the molar ratio=1, gave a decomposed mixture of **1a**, **2a**, **3a** and **4a** in a ratio of 66, 26, 4 and 4%, respectively.

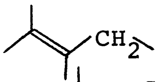
In summary, ethynyl allyl alcohols (**3** and **4**) were produced not only by stoichiometric sodium acetylide ethynylation of **2** (not **1**), but also by semicatalytic method regardless of the starting ketone being **1** or **2**. So the latter method is especially effective for the ethynylation of high boiling compounds in which separation of β,γ-unsaturated ketone is relatively difficult. As the ethynylation equilibrium of α-substituted mesityl oxide derivatives leaned to ketone side, relatively higher molar ratio of acetylene to ketone was needed to obtain **3** and **4**. Ethynyl vinyl alcohol (e.g. **5**) couldn't be formed by a usual procedure, owing to it's steric hindrance.

Kinetic studies on the reaction mechanism and synthetic application[7] of these compounds will be reported in due course.[8]

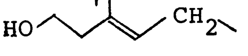
References and Notes

1) Dept. of Org. Synth., Faculty of Engineering, Kyushu University.
2) W. Oroshnik and A. D. Mebane, J. Am. Chem. Soc., 71, 2062 (1949).
3) M. Matsui, T. Yoshida, and H. Mori, Agr. Biol. Chem., 28, No 2, 95 (1964).
4) G. Büchi and H. Wüest, J. Am. Chem. Soc., 96, 7573 (1974).
5) We have succeeded in synthesis of pseudoionone etc. via solvent assisted oxy-Cope rearrangement and this will be reported in future communications.
6) Calculation was done according to the method of W. T. Wipke and P. Gund, J. Amer. Chem. Soc., 96, 299 (1974) and ibid, 98, 8107 (1976) with some modification.
7) **3'c**, **3'd**, **3'e** and **3'f** were obtained from the corresponding ketones (mixture of α,β-:β,γ-isomer=50:50) in ca. 74, 42, 73 and 68%, respectively (20 wt% of aquous potassium hydroxide 8 mol% vs. ketone, 7 equiv. of acetylene, at 0°C for 5 hrs).



3' **c**; R= 

[bp 89-92°C(2.3 mmHg)][9]

d; R= 

[bp 121-129°C(0.17 mmHg)]

e; R= $C_6H_5CH_2$- [bp 96-102°C(0.2-0.3 mmHg)]

f; R= 3,4-$Cl_2C_6H_3CH_2$- [bp 150-158°C(0.3 mmHg)]

8) We wish to thank Mr. Yoshiaki Ōmura, Mr. Sukeji Aihara, Dr. Fumio Mori, and Dr. Shoichi Ibata for stimulating discussions concerning the interpretation of this mechanism and Mr. Shigetoshi Amiya for the nmr spectral analyses.
9) **3'c** could be utilized for the synthesis of pseudoirone via oxy-Cope rearrangement.

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