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ISOMERIZATION AND FOLLOWING ALKYLATION OF (Z,E)-2-OCTEN-4-YN-1-OL AS A ONE POT PROCEDURE IN SUPER BASIC MEDIA

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Abstract. Anionotropic isomerization of the enynic block of (Z,E)-2-octen-4-yn-1-ol in super basic media $MNH(CH_2)_2NH_2/H_2N(CH_2)_2NH_2$ (M = Li, Na) and the following alkylation *in situ* of the metallated product was studied. The influence of the strength of the super base and the structure of the alkylating agent to the yield and isomeric composition of products were determined.

Key words: isomerization, conjugated enynols, super bases, alkylation.

INTRODUCTION

Conjugated enynic compounds are very useful building blocks for the synthesis of biologically active compounds, particularly for the preparation of pheromones, eicosanoides, and vitamins [1, 2]. Several classical methods for the synthesis of 2-alken-4-yn-1-ols have been described [3, 4], but the preparation of longer enynols with a terminal enynic block has remained a difficult problem so far.

The anionotropic isomerization of internal triple bond(s) of alkynes [5], alkynols [6, 7], tertiary alkynyl amines [8], conjugated alkadiynes, and hydroxyalkadiynes [9] to the terminal position in super bases $[MNH(CH_2)_nNH_2/H_2N(CH_2)_nNH_2$ $(M = Li, Na, K; n = 2, 3)]$ is well documented. The products of isomerization are in metallated form in the reaction mixture, which offers a good possibility for these alkylations. Remizova and co-workers have tried to alkylate carbanions of terminal conjugated diynes in the reaction mixture with ω-protected bromoalkanoles, but the alkylation gave only 30–50% of the corresponding products [8–11]. There are no data available on the anionotropic isomerization of conjugated or nonconjugated enynic alcohols or other derivatives. The alkylation of the metal derivative of the triple bond is well known [3], but according to our information the alkylation of carbanions of enynols in ethylenediamine in the presence of a large excess of a very strong base ($pK_a = 38$ [12]) has not yet been described.

In the present work we have investigated the possibilities of the isomerization of (Z,E)-2-octen-4-yn-1-ol and the alkylation *in situ* of the metallated derivative of (Z,E)-5-octen-7-yn-ol.

EXPERIMENTAL

Infrared spectra were recorded on a Specord M82 (Carl Zeiss, Jena) spectrometer. The ^{1}H and ^{13}C NMR spectra were measured with a Bruker AC200P spectrometer at 200 MHz and 50 MHz, respectively. Chemical shifts are reported relative to TMS in $CDCl_3$. GLC analyses were performed on a Fractovap 4160 series (Carlo Erba Strumentazione) capillary gas chromatograph and Chrom 5 (Laboratorni Przistroje, Praha) equipped with FID, using fused silica capillary columns OV-101 25 m × 0.2 mm, Nordibond NB 20M 25 m × 0.32 mm, and glass column 2.5 m × 3 mm packed with 5% Carbowax 20M on Chromosorb W AW-DMCS 80–100 mesh.

All experiments were carried out in an atmosphere of dry, CO_2 and O_2 free argon. Ethylenediamine (EDA) was distilled several times from sodium wire and kept over molecular sieves 4Å.

(Z,E)-2-octen-4-yn-1-ol was synthesized as described earlier [4]. The product was prepared as a mixture of Z- and E-isomers (1 : 1). Yield 46%. In isomerization the mixture of Z/E isomers 1 : 2 was used, which was obtained by careful rectification.

^{13}C NMR of Z-isomer δ = 13.5 (C-8); 21.6 (C-6); 22.5 (C-7); 60.7 (C-1); 77.1 (C-4); 90.8 (C-5); 111.2 (C-3); 140.9 (C-2).
of E-isomer δ = 13.5 (C-8); 21.7 (C-6); 22.5 (C-7); 62.6 (C-1); 79.3 (C-4); 96.4 (C-5); 110.8 (C-3); 140.8 (C-2).

IR (cm^{-1}): 3304 (—OH); 1012 (—C—O); 2221 (C≡C); 3031 (═CH—); 1681, 958 (E C═C), 1639, 738 (Z C═C).

Typical isomerization procedure

Lithium ethylenediamide (LiEDA) and NaEDA were prepared in EDA (5 ml) from Li grains (63 mg, 9 mmol) and $NaNH_2$ (0.39 g, 7.4 mmol), respectively, by stirring on a magnetic stirrer at room temperature for 1.5 h. Then (Z,E)-2-octen-4-yn-1-ol (186 mg, 1.5 mmol) was injected to the solution of a super base. The reaction was observed by GLC. Results of the isomerization are given in Table 1.

Table 1

Isomerization of (Z,E)-2-octen-4-yn-1-ol with LiEDA/EDA and NaEDA/EDA

Superbase /solvent	Time, h	Temperature, °C	Ratio of Z-, E-isomers	Yield as GLC, %
LiEDA/EDA	0.3	5–10	68:32	94
LiEDA/EDA	0.5	20	78:22	93
LiEDA/EDA	0.5	50	67:33	95
LiEDA/EDA	0.5	70	68:32	96
LiEDA/EDA: THF (1:1)	0.5	20	68:32	92
LiEDA/EDA: THF (1:1)	0.5	50	69:31	94
NaEDA/EDA	0.25	20	56:44	95
	0.5		42:58	
	0.9		26:74	97
NaEDA/EDA	0.25	50	65:35	98
	1		23:77	
NaEDA/EDA: THF (1:1)	0.16	20	78:22	90
	0.3		75:25	94
	0.5		62:38	96
NaEDA/EDA: THF (1:1)		50	68:32	98

For the separation of the product the reaction mixture was poured into ice water, extracted with diethyl ether three times, acidified with diluted HCl to pH 2, washed with brine to neutral, dried on $MgSO_4$, the solvent was evaporated, and the residue purified by column chromatography on silica (eluent hexane/diethyl ether 1 : 1). The yield was 128 mg of pure (Z,E)-5-octen-7-yn-1-ol.

^{13}C NMR of Z-isomer δ = 24.9 (C-3); 29.9 (C-4); 32.1 (C-2); 62.5 (C-1); 75.8 (C-8); 82.5 (C-7); 108.6 (C-6); 145.5 (C-5).

of E-isomer δ = 24.8 (C-3); 32.1 (C-2); 32.7 (C-4); 62.6 (C-1); 76.5 (C-8); 81.4 (C-7); 109.0 (C-6); 146.3 (C-5).

IR (cm^{-1}): 3400 (—OH); 1060 (—C—O); 3290 (≡C—H); 2100, 640 (C≡C); 3020 (═CH—); 1680, 960 (E C═C), 1641, 738 (Z C═C).

Alkylation procedure

After isomerization of (Z,E)-2-octen-4-yn-1-ol with six equivalents of LiEDA at 40°C for 20–30 min the reaction mixture was cooled to 5°C and the alkylating agent (six equivalents) was added dropwise. The reaction was observed by GLC. Yields of alkylations were calculated from GLC data and are presented in Table 2.

Table 2

Alkylation of dilithium derivative of (Z,E)-5-octen-7-yn-1-ol

RX	Time, min	Yield as GLC, %
n-BuI	15	60
n-BuI+THF	30	65
n-BuBr	20	35
n-BuBr+THF	20	~50 (impurities)
n-BuCl	20	40
n-BuCl+THF	30 min–1 h	37
n-BuTos	20	14
CH_3I	20	25
$H_2C{=}CHCH_2Br$	20 min–1 h	9
C_6H_5Br	30 min–1 h	no reaction
$C_6H_5CH_2Cl$	30 min–1 h	no reaction

The product of butylation was isolated as described in the previous experiment. Then, 208 mg of a mixture consisting of 60% of the alkylation product and 40% of (Z,E)-5-octen-7-yn-1-ol was prepared.

^{13}C NMR of Z-isomer δ = 13.6 (C-12); 19.1 (C-9); 22.0 (C-11); 25.1 (C-3); 29.7 (C-4); 31.0 (C-10); 32.2 (C-2); 62.8 (C-1); 78.2 (C-7); 85.1 (C-8); 110.0 (C-6); 141.8 (C-5).

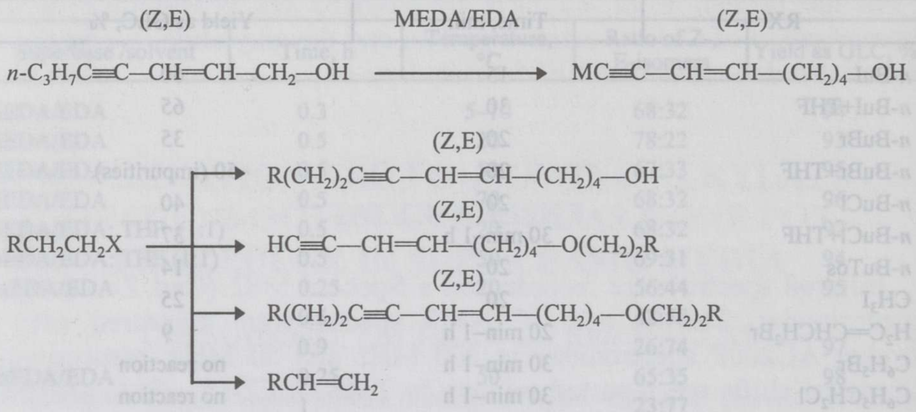
of E-isomer δ = 13.6 (C-12); 19.2 (C-9); 22.0 (C-11); 25.1 (C-3); 32.6 (C-4); 31.0 (C-10); 32.2 (C-2); 62.8 (C-1); 78.2 (C-7); 85.1 (C-8); 110.5 (C-6); 142.6 (C-5).

IR (cm^{-1}): 3400 (—OH); 1054 (—C—O); 2209 ($C\equiv C$); 3025 (=CH—); 1668, 958 (E C=C), 1641, 738 (Z C=C); 1380 (CH_3).

DISCUSSION

Isomerization of the triple bond of (Z,E)-2-octen-4-yn-1-ol was relatively fast even with LiEDA/EDA. The reaction was complete after 20 min at 5–10 °C. Temperature and the addition of THF as a cosolvent had no significant influence on the isomeric composition of the product. When a stronger super base NaEDA/EDA was used substantial isomerization of Z-enynol to E-isomer was detected. The ratio of Z/E isomers decreased at higher temperatures and at longer reaction times from the value of 3 : 1 to 1 : 3. The addition of THF decreased the basicity of the system and Z-E isomerization to the extent of only a few per cent was observed.

By alkylation *in situ* of the metallated derivative of (Z,E)-5-octen-7-yn-1-ol several routes of the reaction are possible:



LiEDA is a very strong base and causes a reasonable elimination of the alkylating agent. Even the dilithium derivative of (Z,E)-5-octen-7-yn-1-ol seems to be strong enough for the elimination. As a result of this undesirable reaction the dilithium derivative will be demetallated and the alkylation cannot be brought to completion. It was tried to reduce the basicity of reagents by adding THF. However, the addition of THF increased the yield of alkylation with *n*-BuI and *n*-BuBr only by 5 and 15%, respectively. The highest yield of alkylation was obtained by using butyl iodide, which is the best soft electrofile compared to other reagents used. As expected, by the alkylation of the dilithium derivative only traces of O-alkylation products were detected. In case of NaEDA/EDA a very complicated mixture of C-, O-, C,O-alkylation and some other products was obtained, as expected.

We conclude that the anionotropic isomerization of (Z,E)-2-octen-4-yn-1-ol is an excellent reaction for the preparation of terminal enynols and it could be useful for other homologues. The alkylation *in situ* is also very promising and could be improved after decreasing the basicity of the system.

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(Z,E)-2-OKTEEN-4-ÜÜN-1-OOLI ISOMERISATSIOON JA JÄRGNEV ALKÜLEERIMINE KUI "ÜHEPAJA" SÜNTEES SUPERALUSELISES KESKKONNAS

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On uuritud (Z,E)-2-okteen-4-üün-1-ooli enüünse bloki anionotroopset isomerisatsiooni erinevates superalustes $MNH(CH_2)_2NH_2/H_2N(CH_2)_2NH_2$ (M = Li, Na) ja saadud metalleeritud derivaadi vahetut alküleerimist. On käsitletud superaluse tugevuse ja alküleerivate agentide mõju isomerisatsiooni- ja alküleerimisproduktide saagisele ning koostisele.