Electrogenerated Acid-catalyzed Cyclization of Isoprenoids

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Synopsis. Biogenetic-type cyclization of some isoprenoids (geranyl phenyl sulfone, methyl geranate, pseudoionone, and 6,10-dimethyl-2,5,9-undecatrien-4-one) has been performed by use of an electrogenerated acid in 1,2-dichloroethane.

The biogenetic cyclization of polyisoprenoids to cyclic terpenoids has been performed by the action of strong acids such as boron trifluoride, tin(IV) chloride, and concentrated sulfuric acid.[1] For instance, pseudoionone is converted into ionone in concentrated sulfuric acid[2] and geranyl phenyl sulfone in concentrated sulfuric acid–acetic acid[3] or stannic tetrachloride in dichloromethane.[4] The requirement of a large amount of bases to neutralize the strong acid is unfavorable for the practical process.

Recently, the electrogenerated acid (EGA) has been recognized as a powerful acid-catalyst for epoxide ring opening,[5] acetalization[6] cyanation,[7] and conversion of nerolidol to bisaborol.[8] We describe an EGA-catalyzed cyclization of polyisoprenoids, demonstrating that a very small quantity of the EGA does promote the cyclization and the neutralization is easy for workup.

The electrolysis of **1a** (500 mg) in a distilled 1,2-dichloroethane (DCE) in the presence of lithium perchlorate (50 mg) and tetraethylammonium perchlorate (50 mg) was performed by use of platinum foil electrodes in an undivided cell. Constant current (1.7 mA/cm^2) was passed for 25 min (0.04 F/mol). If it is assumed that a proton of EGA is produced by one-electron oxidation of a trace amount of water existed in the solvent employed,[9] the amount of the EGA must be very small since 0.04 F/mol of electricity is enough to complete the cyclization. Therefore, a few drops of pyridine can neutralize the solution. The yield (95%) is comparable to that (87—94%) obtained in concentrated sulfuric scid.[3]

Lithium perchlorate is an essential electrolyte for generation of EGA, but tetraethylammonium perchlorate was employed as a coelectrolyte so as to get an enough conductivity of the solution. The use of tetraethylammonium perchlorate or tetraethylammonium tosylate alone is less effective for the purpose. 1,2-Dichloroethane is highly effective solvent while mixing of about 7% of more polar solvent such as ethyl acetate (81%, 0.8 F/mol), acetone (73%, 1.0 F/mol), and THF (42%, 2.1 F/mol) as a cosolvent resulted in decrease of both yield and reaction rate.

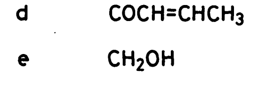
In order to elucidate the behavior of the EGA in this cyclization, two types of electrolysis procedure were examined. On electrolyzing the solution in the absence of **1a** (0.5 F/mol), and then adding **1a** in the pre-electrolyzed solution and allowing to react at 55 °C for 20 min, **2a** was obtained in almost the same yield (92%) as compared with that (95%) obtained in the electrolysis in the presence of **1a**. However, at the lower temperature (20 °C), both electrolysis procedures revealed a marked difference as shown in Table 1 (entry 5 and 7), clearly demonstrating that the cyclization proceeds faster on electrolyzing in the presence of a substrate. The EGA would be concentrated during the electrolysis at the anode surface to make the proximity of the anode extremely acidic so that the cyclization proceeds even with a small amount of EGA.[9]

Table 1. EGA Catalyzed cyclization of **1a**[a)]

Entry	Electrolyte[b)]	Temp °C	F/mol	2a %	1a %
1	$LiClO_4$–Et_4NClO_4	55	0.04	95	0
2	Et_4NClO_4	55	1.6	15	38
3	Et_4NOTs	55	2.0	trace	71
4	$LiBF_4$–Et_4NClO_4[e)]	55	1.0	54	15
5	$LiClO_4$–Et_4NClO_4	20	2.1	60	0
6[c)]	$LiClO_4$–Et_4NClO_4	55	0.5	92	0
7[d)]	$LiClO_4$–Et_4NClO_4	20	2.1	12	80

a) Substrate (0.36 mmol) in 8 ml of DCE. b) Electrolyte (50 mg for each). c) Pre-electrolyzed conditions (0.5 F/mol). d) Pre-electrolyzed conditions (2.1 F/mol). e) Because of the low solubility of $LiBF_4$ in DCE, Et_4NClO_4 was employed as a coelectrolyte.

The cyclization of **1a** and **1b**[10] proceeds successfully by the EGA catalysis [95% (α:β:γ=86:9:5) and 88% (α:γ=89:11)], respectively. Also pseudoionone **1c** afforded ionone in 57% yield. α-Damascone **2d**[11] was prepared in 30% yield from **1d**. In contrast, geraniol **1e** behaved somewhat differently and dehydrative cyclization occurred exclusively rather than the desired cyclization leading to the formation of a mixture of limonene and terpinolene (78%, limonene:terpinolene =36:64). And cyclization of **3** provided **4** (72%, α-H_9:β-H_9=34:64).[12]



1 **2**

1a R = CH_2SO_2Ph
b CO_2Me
c $CH{=}CHCOCH_3$
d $COCH{=}CHCH_3$
e CH_2OH

3 **4**

Experimental

Boiling points are indicated by an air bath temperature and uncorrected. The IR spectra were obtained with a JASCO IRA-1 spectrometer. ^{1}H-NMR spectra were measured with a JNM FX-100 spectrometer at 100 MHz in $CDCl_3$ using Me_4Si as an internal standard. Substrates **1a**,[13] **1b**,[10] **1d**,[11] and **3**[12] were prepared as reported in the literatures. Geraniol and pseudoionone were the samples which were manufactured in Kuraray Co. Ltd., to which the authors are grateful. 1,2-Dichloroethane and ethyl acetate were refluxed over P_2O_5 and distilled. THF was refluxed over NaOH and then $LiAlH_4$, and finally distilled from a sodium-benzophenone drying system. Acetone was stirred over dry $MgSO_4$ for overnight, filtered, and distilled. Electrolytes, $LiClO_4$, Et_4NClO_4, $LiBF_4$, and Et_4NOTs were commercially available and dried under the reduced pressure. A typical electrolysis is described below and the products, **2a**,[2,3] **2b**,[10] **2c**, **2d**,[11] and **4**[12] were idientified in comparison with the authentic samples.

*Electrolysis of **1a** in a 1,2-Dichloroethane-$LiClO_4$-Et_4NClO_4 system.* A solution of **1a** (500 mg, 1.8 mmol) $LiClO_4$ (50 mg), and Et_4NClO_4 (50 mg) dissolved in 1,2-dichloroethane (8 ml) was added in a beaker-type (10 cm in height and 3 cm in diameter) undivided cell settled with two platinum foil electrodes (2×1.5 cm^2) and electrolyzed at 55 °C under a constant current (1.7 mA/cm^2) for 25 min (0.04 F/mol). Saturated $NaHCO_3$ was added to the electrolysis mixture. After evaporation of the solvent under reduced pressure, the residue was extracted with ether three times. The combined extracts were washed with brine, dried (Na_2SO_4), and concentrated *in vacuo*. The residue was chromatographed (SiO_2, hexane:AcOEt=20:1) to give **2a** as a mixture (476 mg, 95%, isomer ratio α:β:γ=86:9:5). The pure γ-isomer of **2a** was obtained by column chromatography, and β-isomer was recrystallized from a mixture of α- and β-isomers. The structures of α- and β-isomers were identified in comparison with the authentic samples.[2,3]

*1,1-Dimethyl-3-methylene-2-(phenylsulfonylmethyl)cyclohexane (γ-**2a**)*: bp 113—115 °C/1.9 Pa; IR (neat) 3060, 2930, 2860, 1645 (C=C), 1443, 1300 (SO_2), 1136 (SO_2), 910, 730 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.80 (s, 3H, CH_3), 0.92 (s, 3H, CH_3), 1.20—1.70 (m, 4H, CH_2), 2.02 (t, J=6 Hz, 2H, CH_2), 2.45 (dd, J_1=8.3 Hz, J_2=3.6 Hz, 1H, CH), 3.24 (dd, J_1=14.6 Hz, J_2=3.7 Hz, 1H, CH_2), 3.42 (dd, J_1=14.6 Hz, J_2=8.3 Hz, CH_2), 4.60 (br s, 1H, =CH_2), 4.77 (br s, 1H, CH_2), 7.50—8.10 (m, 5H, ArH). Found: C, 69.25; H, 8.13%. Calcd for $C_{16}H_{22}O_2S$: C, 69.03; H, 7.96%.

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