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A NOVEL ELECTROREDUCTIVE ALKYLATION OF CYCLOHEPTATRIENE SYSTEMS AND ITS APPLICATION TO FACILE SYNTHESIS OF β–THUJAPLICIN[1]

Tatsuya Shono,* Tetsuo Nozoe,[2] Yoshihide Yamaguchi, Manabu Ishifune,
Masashi Sakaguchi, Haruhisa Masuda, and Shigenori Kashimura,

Department of Synthetic Chemistry, Faculty of Engineering, Kyoto University,
Yoshida, Sakyo, Kyoto 606, Japan

Electroreduction of cycloheptatriene or substituted cycloheptatrienes in the presence of an alkyl halide was found to be a unique and effective method for introducing regioselectively an alkyl group into seven-membered ring system and it was applied to a new synthesis of β–thujaplicin (hinokitiol).

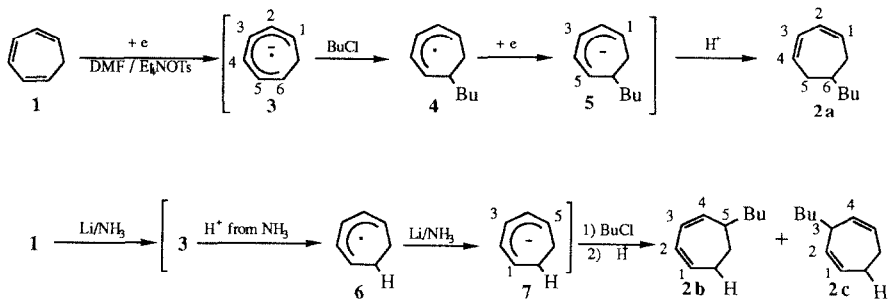
It has been found in our continuing studies on the cathodic reduction of olefinic systems[3,4] that the anionic active species formed by the electroreduction of activated olefins such as α,β-unsaturated ketones, esters, and nitriles possess unique reactivities and selectivities in their reaction with electrophiles.

It was found in the present study that 1,3,5-cycloheptatriene (CHT) and substituted CHTs such as 1-methoxy- and 3-methoxy-CHTs were electrochemically reducible[5] and the resultant anionic intermediates were regioselectively alkylated with alkyl halides to afford 6-alkyl-1,3-cycloheptadiene and 1-methoxy-6-alkyl-1,3-cycloheptadiene as the main products respectively. In addition, β-thujaplicin (hinokitiol) was effectively synthesized by using this new electroreductive alkylation as the key reaction.[7]

The electroreduction of CHT (**1**) in DMF in the presence of butyl chloride gave 6-butyl-1,3-cycloheptadiene (**2a**) as the main product[10] (Scheme 1). The fact that this electroreductive method gave **2a** as the main product is important since it has been reported that the reductive alkylation of **1** using Li metal as the reducing agent in liquid ammonia (Li/NH_3) gave a mixture of 5-butyl-1,3-cycloheptadiene (**2b**) and 3-butyl-1,4-cycloheptadiene (**2c**) in which **2c** was the main product (Scheme 1).[11,12] These differences in the regioselectivity of the alkylation of **1** would mainly be explained by the difference of the electrophiles which reacted with the first active intermediate formed from **1**.

Thus, the first active intermediate formed by one electron transfer to **1** is an anion radical species **3** in both electrochemical and Li-metal reductions.[6,11] Since the electroreduction of **1** was carried out in the presence of butyl chloride in aprotic solvent (DMF), the intermediate **3** reacted with butyl chloride before it was protonated by solvent and afforded the second intermediate **4**. It would be reasonable that **3** reacted with butyl chloride at its 1- and 6-positions since the density of negative charge is the highest at these two positions. In the third intermediate **5** formed by one-electron reduction of **4**, the negative charge was mainly located at 1-, 3-, and 5-positions. The counter cation of the anion **5** was, however, bulky tetraethylammonium ion and hence the anion **5** would be the most reactive at 5-position. Thus, the final main product was **2a**. On the other hand, in the

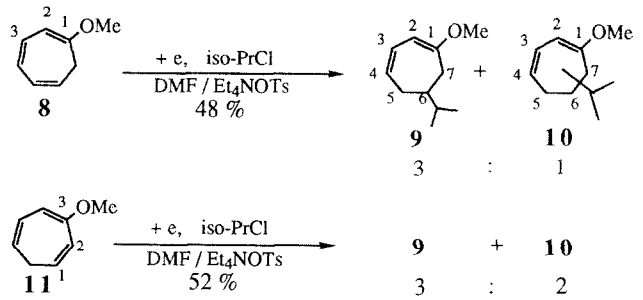
reduction of **1** with Li/NH_3, butyl chloride was absent when **3** was formed and hence it was easily protonated by NH_3 at 1- and 6-positions to yield a radical intermediate **6**. In the anion intermediate **7** formed by one-electron reduction of **6**, the negative charge is located at 1-, 3-, and 5-positions.[12] Hence, the products were **2b** and **2c**.



Scheme 1

The unique regioselectivity of electroreductive alkylation of CHT system was also studied with respect to some methoxylated CHTs. Thus, the electroreduction of a solution of 1-methoxy-CHT (**8**)[13] and iso-PrCl in DMF containing Et_4NOTs as a supporting electrolyte was found to give mainly 1-methoxy-6-isopropyl-1,3-cycloheptadiene (**9**) together with a mixture of minor products (**10**), that is, isomers of **9** (**9** : **10**=3 : 1)[14,15] (Scheme 2).

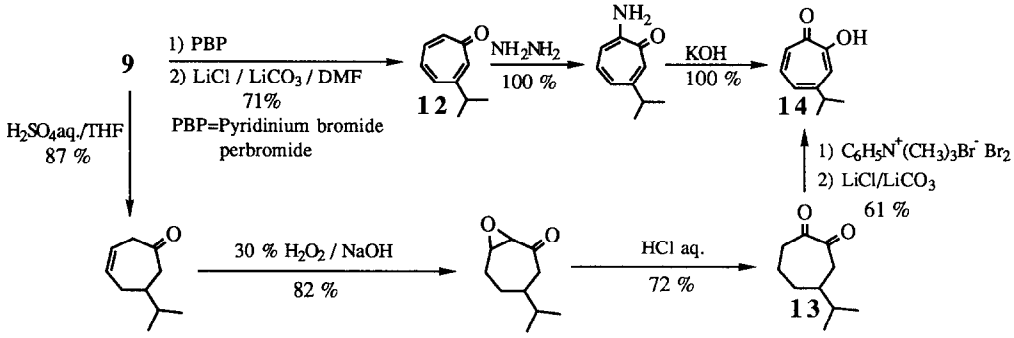
Interestingly, it was also found that the electroreduction of 3-methoxy-CHT (**11**)[13] in the presence of iso-PrCl under the same reaction conditions as the reduction of **8** also gave **9** as the main product though the regioselectivity of the alkylation was lower than **8** (**9** : **10**=3 : 2)[14] (Scheme 2).



Scheme 2

This unique electroreductive alkylation was applied to a novel synthesis of β–thujaplicin (**14**). The hitherto known methods of preparation of **14** often require rather troublesome procedures for the construction of seven-membered ring system[17] or for the introduction of an isopropyl group to a given position of the ring system.[18]

On the other hand, we found that **9** was easily transformed to two different key intermediates **12** and **13** (Scheme 3). Their transformation to **14** was attained by the known methods.[17]



Scheme 3

Typical procedure for the electroreductive alkylation of **8** was as follows: Into a cathodic chamber of an electrolysis cell equipped with a platinum cathode (2 x 2 cm) was added a solution of **8** (5 mmol) and iso-PrCl (15 mmol) in dry DMF (15 ml) containing Et4NOTs (7 mmol) as a supporting electrolyte. The anodic solution was 15 ml of DMF containing Et4NOTs (7 mmol), and a platinum anode (2 x 2 cm) was used. The electroreduction was carried out under constant current conditions (0.2 A) and the electrolysis cell was externally cooled with ice water. After 3 F/mol of electricity (based on **8**) was passed, the reaction mixture was poured into brine (100 ml) and the aqueous solution was extracted with ether (50 ml x 3). All products were purified by distillation under reduced pressure, and their structures were determined by the spectroscopic analyses (^{1}H-,^{13}C-NMR, and IR), and high resolution mass spectroscopy (HRMS).

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References and Notes

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5. The electroreduction of CHT has been studied from mechanistic point of view, and its reduction potential has been reported to be -2.6 V *vs.* SCE.[6]
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7. We have already reported that the synthesis of α-[8] and γ-thujaplicin[9] was easily attained by utilizing the anodic oxidation of CHT as a key procedure.
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10. ^{1}H-NMR, UV, and HRMS of **2a** gave satisfactory values for the assigned structure. **2a**; NMR ($CDCl_3$) δ 5.93-5.64 (m, 4H), 2.51-1.99 (m, 4H), 1.98-1.60 (m, 1H), 1.56-1.22 (m,6H), 0.92 (t, 3H, J=10 Hz) . UV (λ_{max}=247 nm ; ε= 7850 ; c =2.46 x 10^{-4}). HRMS Calcd for $C_{11}H_{18}$: 150.1409; Found: 150.1422.

The structures of the minor products were not determined.

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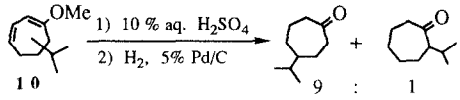
12.K.Hafner and W.Rellensmann, *Chem. Ber.*, **95**, 2567 (1962).

13.It has already been reported in our previous study that **8** and **11** were prepared with good yields by the anodic oxidation of **1** followed by the thermal rearrangement of the oxidation product 7-methoxy-CHT.[8]

14.The minor products (**10**) were determined to be the regioisomers of **9** in which the isopropyl group was located at 5- or 7-position, since hydrolysis of **10** obtained by the electroreduction of **8** and subsequent hydrogenation of the hydrolysis products gave a 9:1 mixture of 4-isopropylcycloheptanone[16] and 2-isopropylcycloheptanone.[16,17]



15.IR, ^{1}H-NMR spectra, and HRMS of **9** gave satisfactory values for the assigned structure.
9; IR(neat) 3025, 2845, 1655, 1625, 1220, 1160, 700 cm-1, NMR ($CDCl_3$) δ 0.83 (d,6H,J=7.0Hz), 1.77 (m,2H), 2.23 (m,4H), 3.50 (s,3H), 4.87 (d,1H,J=6.0Hz), 5.63 (m,2H). HRMS Calcd for $C_{11}H_{18}O$: 166.135; Found: 166.134. The structure of **9** was also confirmed by the transformation of **9** to the known 3-isopropylcycloheptanone.[17]

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