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Communications

Electroreductive Intermolecular Coupling of Ketones with Olefins[1]

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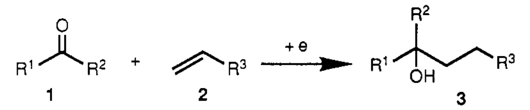
Summary: Electroreductive coupling of ketones with a variety of olefins such as 1-olefins, dienes, and trienes afforded the corresponding tertiary alcohols in good yields and high regioselectivity.

Sir: In our continuing studies on the cathodic coupling of a carbonyl group with unsaturated systems, we have already reported that the electroreduction of nonconjugated olefinic ketones affords the corresponding intramolecularly coupled alcohols with good yields and excellent regio- and stereoselectivities.[2-5]

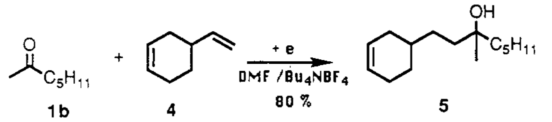
On the other hand, the cathodic intermolecular coupling[6] of ketones **1** with olefins **2** leading to the corresponding tertiary alcohols **3** (Scheme I) has not yet been achieved successfully, in spite of its high potentiality as a synthetic method. Namely, the electroreduction of a mixture of **1** and **2** under conditions similar to those used in the intramolecular coupling has not given the coupled products in satisfactory yields.[8]

We report herein our new findings that the cathodic intermolecular coupling of **1** with **2** is satisfactorily achieved by selecting the material of cathode and the type of solvent.

Scheme I



Scheme II



Thus, the coupling of methyl ethyl ketone (**1a**, R^1 = Me, R^2 = Et) with 1-octene (**2a**, R^3 = C_6H_{13}) was chosen as a model and carried out in a divided cell using a variety of cathodes (Pt, Pb, Sn, Zn, graphite,[9] or carbon fiber[11]) and solvents [dioxane–MeOH (10:1), i-PrOH, or DMF].

The use of carbon fiber and DMF gave the best result (yield of **3a**, R^1 = Me, R^2 = Et, R^3 = C_6H_{13}, 77%), whereas the use of other types of metal cathode resulted in the decrease in the yield of **3a** (solvent, DMF, Pt, 19%; Pb, 38%; Sn, 40%; Zn, 44%). In this coupling, the activity of the surface of the metal cathode is also important since the use of polished[12] metal cathodes (yield of **3a**; Pb, 50%; Sn, 52%; Zn, 58%) or addition of chlorotrimethylsilane (CTMS) into the reaction system to activate[13] the surface of the cathode resulted in the increase in the yield of **3a**

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[1] Electroorganic Chemistry. 118.

[2] Shono, T.; Mitani, M. *J. Am. Chem. Soc.* **1971**, *93*, 5284.

[3] Shono, T.; Nishiguchi, I.; Ohmizu, H. *Chem. Lett.* **1976**, 1233.

[4] Shono, T.; Nishiguchi, I.; Ohmizu, H. *J. Am. Chem. Soc.* **1978**, *100*, 545.

[5] Shono, T.; Kise, N.; Suzumoto, T.; Morimoto, T. *J. Am. Chem. Soc.* **1986**, *108*, 4676.

[6] We have previously reported that cathodic coupling of activated olefins with carbonyl compounds[7] is effectively promoted by the addition of chlorotrimethylsilane to the reaction system.

[7] Shono, T.; Ohmizu, H.; Kawakami, S.; Sugiyama, H. *Tetrahedron Lett.* **1980**, *21*, 5029.

[8] Shono, T.; Mitani, M. *Nippon Kagaku Kaishi* **1973**, 975.

[9] Disintegration of graphite electrodes was observed[10] under the conditions of electroreduction.

[10] Miller, E. K.; Mahachi, T. J. *J. Org. Chem.* **1985**, *51*, 1041.

[11] The carbon fiber used was carbonized polyacrylonitrile (Hi-Carbolon-3KS, diameter 7 μm, Asahi Kasei Carbon Fiber Co., Ltd.).

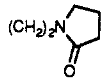
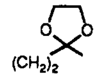
[12] The cathode (2 × 2 cm) was polished with emery paper, washed by 3 N HCl, and dried under reduced pressure. The electrochemical reaction was carried out under similar conditions (except the material of cathode) to that stated in ref 16.

[13] It has been reported that CTMS activates the metal surface.[14]

[14] Corey, E. J.; Pyne, S. G. *Tetrahedron Lett.* **1983**, *24*, 2821.

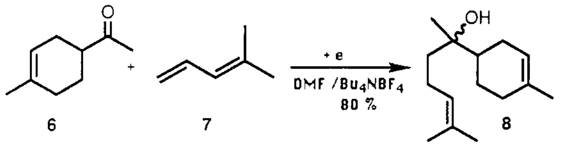
0022-3263/89/1954-6001$01.50/0

Table I. Electroreductive Coupling of Ketones with Olefins

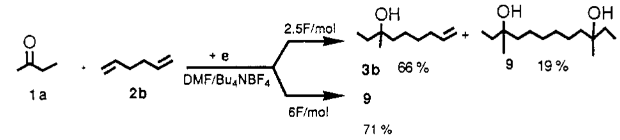
run	ketone 1 R^1	ketone 1 R^2		olefin 2 R^3		product 3 yield,[a] %
1	Me	Me	**1c**	C_8H_{17}	**2c**	63
2	Me	Bu	**1d**		**2c**	81
3	Me	i-Pr			**2c**	52
4	–$(CH_2)_6$–				**2c**	80
5	**1d**			$(CH_2)_2Ph$		82
6	**1d**			$(CH_2)_9OH$		71
7	**1d**			$(CH_2)_8CONMe_2$		78
8	Me	C_6H_{13}				70
9	Me	Et	**1a**			65

[a] Isolated yield obtained after 2.5 F/mol of electricity based on the ketone was passed.

Scheme III



Scheme IV



(Pb, 61%; Sn, 51%; Zn, 64%).[15]

The other results[16] obtained under the conditions of using the carbon fiber cathode in DMF are summarized in Table I, which shows that the coupling of ketones with 1-olefins having a variety of functional groups (runs 5–9) are also successful.

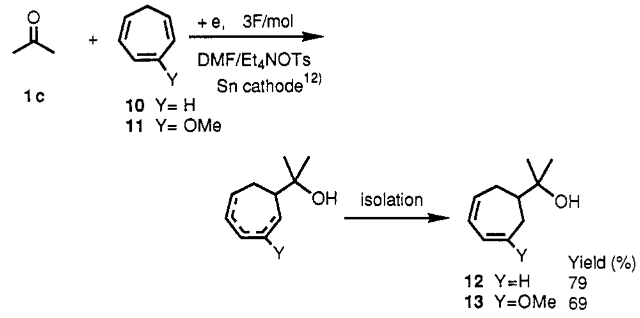
In addition, these couplings are regioselective since a single product was obtained in each coupling and the formation of other isomers was not observed.

Moreover, it was also found that this coupling was influenced by the type of olefins. Thus, the coupling of **1a** with a disubstituted terminal olefin, for instance, resulted in the remarkable decrease in the yield, and that with a 2-olefin did not yield the corresponding coupled product. This selectivity may be applied to organic synthesis.

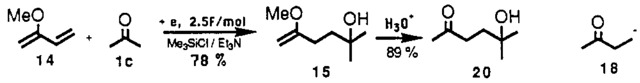
As shown in Scheme II, coupling of 2-heptanone (**1b**, R^1 = Me, R^2 = C_5H_{11}) with a diene **4** took place with high regioselectivity at the less substituted double bond of **4** to yield the product **5**.[18]

This remarkable regioselectivity led to the satisfactory one-step synthesis of a mixture (1:1) of diastereoisomers of bisabolol (**8**)[19] through coupling of a ketone **6** with 4-methyl-1,3-pentadiene (**7**) (Scheme III).

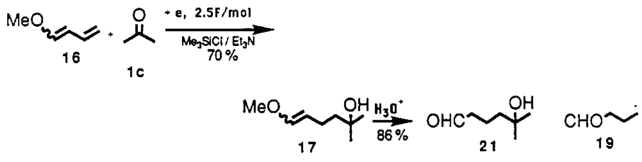
Scheme V



Scheme VI



Scheme VII



It is also interesting that in the reaction of **1a** with 1,5-hexadiene (**2b**) (Scheme IV) the formation of 1:1 or 2:1 adduct (**3b** or **9**[18]) was able to be controlled by the amount of electricity passed.

Moreover, coupling of acetone (**1c**) with a cyclic triene system[21] such as cycloheptatriene (**10**) or 3-methoxycycloheptatriene (**11**) also took place at terminal position (1-position) of **10** or **11**, yielding 1,3-cycloheptadiene derivative **12**[22] or **13**[23] as the single product (Scheme V).

The electroreduction of a solution of **1c** and a dienol ether **14** in DMF using the carbon fiber cathode gave the

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(15) The cathodic solution was dry DMF containing CTMS (10 mmol), **1a** (10 mmol), **2a** (2 mmol), and Bu_4NBF_4 (5 mmol).

(16) The cathodic reaction was carried out in a divided cell equipped with a bundle of carbon fiber[11] (three thousands carbon fiber filaments, 15-cm length) as a cathode, a platinum anode (2 × 2 cm), and a glass filter diaphragm. A solution of **1** (10 mmol) and **2** (2 mmol) in dry DMF (20 mL) containing Bu_4NBF_4 (5 mmol) as a supporting electrolyte was put into a cathodic chamber of the cell. The anodic solution was 15 mL of dry DMF containing Bu_4NBF_4 (5 mmol). After 2.5 F/mol of electricity based on **2** was passed through the cell under the constant current of 0.2 A,[17] the cathodic solution was poured into 100 mL of brine and extracted with ether. The residue obtained by evaporation of solvent was column chromatographed (silica gel, EtOAc–hexane, 1:10) in order to give **3**.

(17) Cathode potential was –2.5 to –2.7 V vs SCE.

(18) The product **5** or **9** was a mixture of diastereomers.

(19) The structure of **8** was confirmed by the analysis of its spectroscopic data.[20]

(20) Some spectroscopic data have been reported: Gutsche, C. D.; Maycock, J. R.; Chang, C. T. *Tetrahedron* **1968**, *24*, 859.

(21) The use of the carbon fiber cathode instead of a Sn cathode resulted in the decrease of the yield of **12** (50%).

(22) The skeleton of **12** was confirmed by the transformation of it to 1-methyl-1-cycloheptylethanol (Anal. Calcd for $C_{10}H_{20}O$: C, 76.86; H, 12.90. Found: C, 76.84; H, 13.19). The position of double bonds in **12** was determined by 400-MHz ^1H NMR [δ 5.92–5.75 (m, 4 H, olefinic protons), 2.55–2.03 (m, 4 H, allylic protons)].

(23) The structure of **13** was determined by spectroscopic analyses, and also by the transformation of it to 3-isopropylcycloheptanone.[24] This result indicates that the active species formed from **1c** attacked position 1 of **11**. The active species has an anionic character and, hence, the intermediate formed by the attacking on the position 6 of **11** is less stable than that formed by the attacking on the position 1, since in the former intermediate, some negative charge is developed at the carbon which has the MeO group. The transformation of **13** to β-dolabrin[25] was also successful.

(24) Miyashita, M.; Hara, S.; Yoshikoshi, A. *J. Org. Chem.* **1987**, *52*, 2602.

(25) Cavazza, M.; Pietra, F. *J. Chem. Soc., Perkin Trans 1* **1985**, 2283.

coupled product **15** in only 24% yield, while it was found as shown in Scheme VI that the addition of CTMS and Et_3N into this reaction system brought about the increase in the yield (78%) of **15**.[26] Under the latter reaction conditions, the coupling of dienol ether **16** with **1c** also gave the corresponding coupled product **17** in 70% yield (Scheme VII).

The fact that the acidic hydrolysis of the coupling product **15** or **17** forms the corresponding ketone **20** or aldehyde **21** indicates that the dienol ether **14** or **16** behaves in this coupling reaction as the equivalent for the anion **18** or **19** in which the negative charge is located at the β- or γ-position of the carbonyl group.

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[26] The cathodic solution of DMF (20 mL) containing CTMS (10 mmol), Et_3N (10 mmol), Bu_4NBF_4 (5 mmol), **14** or **16** (2 mmol), and **1c** (10 mmol) was electrochemically reduced under similar conditions described in ref 16.

Octamethylcalix[4]arene

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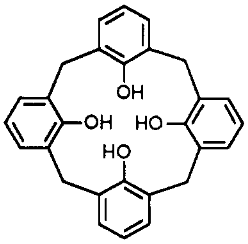
Summary: The sterically crowded octamethylcalix[4]arene (**2**) was synthesized in one step and shown to exist in a relatively flexible "boat" conformation.

Sir: In recent years extensive research has been carried out on macrocyclic hosts capable of including small guest molecules in their cavities.[1] A noteworthy family of these synthetic macrocycles consists of cyclic arrays of *n* phenol moieties linked by methylene groups. These compounds are commonly referred to by the trivial name (coined by Gutsche) "calix[*n*]arenes".[2] *p-tert*-butylcalix[*n*]arenes (*n* = 4, 5, 6, and 8) can be prepared in one step by base-catalyzed condensation of *p-tert*-butylphenols and formaldehyde under different experimental conditions.[3] In addition, several multistep syntheses have been developed for the synthesis of calixarenes.[4]

The conformational behavior of calix[4]arenes is commonly analyzed in terms of four conformations: cone, partial cone, and 1,3- and 1,2-alternate.[2,5] Spectroscopic evidence as well as X-ray diffraction data show that the parent compound (**1**) and its *p*-alkyl derivatives exist in solution as well as in the crystalline state in the cone conformation.[2,6] The energetic preference for the cone conformation is ascribed to the existence of a cyclic intramolecular hydrogen bond.

We report the (serendipitous) one-step preparation of the previously unknown sterically crowded octamethylcalix[4]arene (**2**),[7] a compound which displays novel conformational properties. Our initial goal was to synthesize **3** in which the OH groups are arranged in a *extra*-annular fashion (i.e. located in the outer periphery). However, when a solution of 2,6-dimethyl-4-hydroxybenzyl alcohol[8] (**4**) in nitrobenzene at 90 °C was treated with 0.5 equiv of $AlCl_3$ instead of the expected calixarene **3**,[9] we isolated an isomeric calixarene **2** (with *intra*-annular OH groups) as the sole product in 28% (not optimized) yield.[10] This remarkably simple preparation of **2** is notable since no one-step, synthetically useful cyclization of benzylic alcohols to yield calixarenes with *intra*-annular OH groups has been reported previously.[11] The reaction probably involves the rearrangement of **4** to 2,4-dimethyl-6-hydroxybenzyl alcohol[12] (**5**) prior to the tetramerization. Indeed, when **5** was submitted to the reaction conditions, **2** was obtained in ca. 50% yield.



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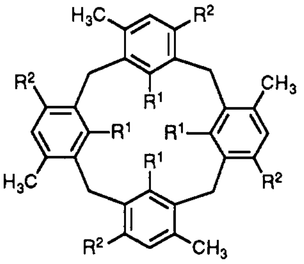
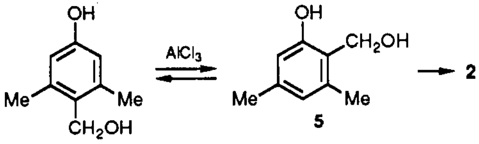


2: R^1 = OH; R^2 = Me
3: R^1 = Me; R^2 = OH



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[1] For recent reviews, see: (a) Molecular Inclusion and Molecular Recognition-Clathrates I. *Top. Curr. Chem.* **1987**, 140. (b) *Synthesis of Macrocycles: Design of Selective Complexing Agents*; Izatt, R. M.; Christensen, J. J.; Eds., Wiley: New York, 1987.

[2] For reviews, see: Gutsche, C. D. *Acc. Chem. Res.* **1983**, *16*, 161. Gutsche, C. D. *Topics in Current Chemistry*; Springer-Verlag: Berlin, 1984; Vol. 123, p 1. Gutsche, C. D. in ref 1a, p 93. Shinkai, S. *Pure Appl. Chem.* **1986**, *58*, 1523.

[3] *n* = 4: Gutsche, C. D.; Iqbal, M.; Stewart, D. *J. Org. Chem.* **1986**, *51*, 742. *n* = 5: Ninagawa, A.; Matsuda, H. *Makromol. Chem., Rapid Commun.* **1982**, *3*, 65. *n* = 6 and *n* = 8: Gutsche, C. D.; Dhawan, B.; No, K. H.; Muthukrisnan, R. *J. Am. Chem. Soc.* **1981**, *103*, 3782. See also: Dhawan, B., Chen, S. I., Gutsche, C. D. *Makromol. Chem.* **1987**, *188*, 921

[4] For some examples of multistep syntheses of calixarenes, see: (a) Kammerer, H; Happel, G. *Makromol. Chem.* **1980**, *181*, 2049. (b) Bohmer, V.; Marschollek, F.; Zetta, L. *J. Org. Chem.* **1987**, *52*, 3200.

[5] Cornforth, J. W.; D'Arcy Hart, P.; Nicholls, G. A.; Rees, R. J. W.; Stock, J. A. *Brit. J. Pharmacol.* **1955**, *10*, 73. Gutsche, C. D.; Dhawan, B.; Levine, J. A.; No, K. H.; Bauer, L. J. *Tetrahedron* **1983**, *39*, 409.

[6] Andreetti, G. D.; Ungaro, R.; Pochini, A. *J. Chem. Soc., Chem. Commun.* **1979**, 1005. Andreetti, G. D.; Pochini, A.; Ungaro, R. *J. Chem. Soc., Perkin Trans. 2* **1983**, 1773. Ungaro, R.; Pochini, A.; Andreetti, G. D.; Sangermano, V. *Ibid.* **1984**, 1979. Ungaro, R.; Pochini, A.; Andreetti, G. D.; Domiano, P. *Ibid.* **1985**, 197.

[7] CAS name for **2**: 4,6,10,12,16,18,22,24-octamethylpentacyclo[$19.3.1.1^{3,7}.1^{9,13}.1^{15,19}$]octacosa-1(25),3,5,7(28),9,11,13(27),15,17,19(26),21,23-dodecaene-25,26,27,28-tetrol.

[8] Auwers, K. *Ber.* **1907**, *40*, 2524.

[9] It has been reported that treatment of 2,6-dimethyl-4-methoxybenzyl alcohol with $AlCl_3$ yields the tetramethyl tetraether of **3**: Wu, T.-T.; Speas, J. R. *J. Org. Chem.* **1987**, *52*, 2330.

[10] Preparation of **2**. To a solution of **4** (0.5 g, 0.33 mmol) in 55 mL of $C_6H_5NO_2$ at 90 °C was added 0.277 mg of $AlCl_3$. After the mixture was stirred for 2 h, water was added, and the mixture was stirred at room temperature for 1 h. The phases were separated, and the organic phase was filtered through a sintered-glass funnel (no. 3). The filtrate was washed twice with water, and the organic phase was dried ($MgSO_4$). Evaporation of the solvent under low pressure yielded almost pure **2**. Recrystallization from DMF afforded 170 mg of **2**·DMF (28%). A solvent-free sample could be obtained by sublimation under reduced pressure: mp 330–332 °C; MS (EI, 70 eV) *m/z* 536 (M, 36), 135 ([M − (2,3,5-$Me_3C_6H_2OH$ − H)], B). Anal. Calcd for $C_{36}H_{40}O_4$: C, 80.56; H, 7.51. Found: C, 80.70; H, 7.38.

[11] $TiCl_4$-catalyzed alkylations have been used for the preparation of calixarenes, e.g. by reaction of 2,6-bisbromomethylated phenols with phenols. See for example ref 4b.

[12] Finn, S. R.; Musty, J. W. G. *J. Appl. Chem.* **1951**, *1*, 182.

0022-3263/89/1954-6003$01.50/0