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ELECTROREDUCTIVE INTRAMOLECULAR COUPLING OF γ- AND δ-CYANOKETONES[1]

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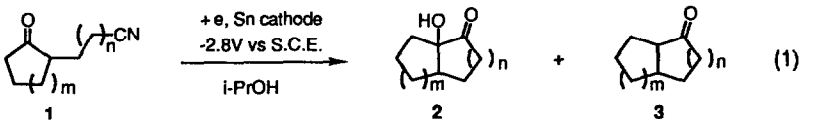
Summary: Electroreduction of γ- and δ-cyanoketones in i-PrOH gave cyclized products α-hydroxyketones and their dehydroxylated ketones, and this reaction was applied to the synthesis of dihydrojasmone, methyl dihydrojasmonate, and Rosaprostol.

We have previously reported some unique electroreductive intramolecular coupling reactions of nonconjugated olefinic,[2] acetylenic,[3] and aromatic ketones[4] yielding cyclic tertiary alcohols. Recently, we have found that the electroreduction of some cyclic γ- and δ-cyanoketones 1 led to intramolecular coupling between carbonyl and cyano groups, and formed bicyclic α-hydroxyketones 2 and their dehydroxylated ketones 3 (eq.1).



1 2 3 (1)

The electroreduction of cyclic γ- and δ-cyanoketones 1 (5 mmol) was carried out using a Sn cathode (5X10 cm^2) and a carbon rod anode in i-PrOH (40 mL) containing Et_4NOTs (10 g). The cathodic and anodic chambers were separated by a ceramic diaphragm. The electricity was passed with controlling the cathode potential at -2.8 V vs. SCE until almost all of the cyanoketone was consumed. The catholyte was worked up similarly to our previously reported method.[4]

The results obtained from several cyclic γ- and δ-cyanoketones 1 are shown in Table I. Although the product selectivity was lowered to some extent, the electroreduction could also be carried out at constant current of 0.2 A (run 3) or without using a diaphragm (run 4). As clearly shown in the Table I, the ratio of the products 2 and 3 was remarkably controlled by the reaction temperature. When the reaction was carried out at 25℃, the α-hydroxyketone 2 was obtained almost exclusively, whereas the dehydroxylated ketone 3 was mainly formed at 65℃.

The electroreduction with Ag cathode gave almost the same result as with Sn cathode (run 5). Using other materials as the cathode (Cd: 2b 64%, 3b 2%; Pb: 2b 40%, 3b 15%; Zn: 2b 30%, 3b trace) or DMF as solvent (Sn: 2b 20%) brought about the decrease in the yield.

Although the detail of reaction mechanism and the effect of cathode material are still not always clear, it is rather reasonable that the reaction is initiated by reduction of the carbonyl group, since the complete inertness of a cyano group under the

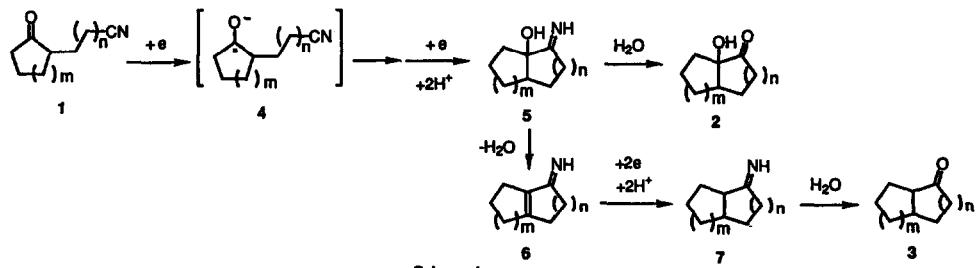
Table I. Electroreductive intramolecular coupling of cyclic γ- and δ-cyanoketones

Run		m	n	Temp.	F/mol	%yield[a] of	2		3
1	1a	1	1	25℃	3	2a	68[b]	3a	—
2	1b	2	1	25℃	3	2b	76[c]	3b	2
3[d]				25℃	3.5		63[c]		16
4[e]				25℃	4		65[c]		11
5[f]				25℃	4		74[c]		2
6				65℃	6		5		64
7	1c	3	1	25℃	4	2c	76[g]	3c	8
8				65℃	8		—		71
9	1d	8	1	25℃	6	2d	55[h]	3d	22
10				65℃	10		4		54
11	1e	1	2	25℃	3	2e	60[i]	3e	—
12	1f	2	2	25℃	4	2f	69[i]	3f	3
13				65℃	8		3		60

a. Isolated yields. Satisfactory spectroscopic and elemental analyses were obtained for all compounds. b. Obtained as a single stereoisomer. See ref. 5. c. Obtained as a single stereoisomer. See ref. 6. d. At constant current of 0.2A. e. Without using a diaphragm. f. Using Ag cathode. g. Obtained as a 2:1 mixture of two stereoisomers. See ref. 8. h. Obtained as a ca. 7:1 mixture of two stereoisomers. See ref. 9. i. Obtained as a single stereoisomer. See ref. 10. j. Obtained as a 2:1 mixture of two stereoisomers. See ref. 11.

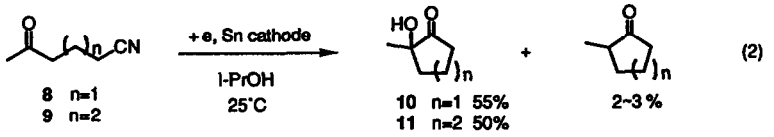
present reaction conditions was shown by the fact that 2-cyclohexylpropionitrile was quantitatively recovered when the electricity was passed through its solution under the same reaction conditions.

As shown in Scheme I, the active species such as anion radical 4 formed from the carbonyl group adds to the cyano group to give α-hydroxyimine 5. At an elevated temperature, dehydration of 5 takes place to form 6 which is immediately reduced to 7. Working-up of 5 and 7 with water gives the products 2 and 3 respectively.



Scheme I.

Electroreduction of acyclic γ- and δ-cyanoketones 8 and 9 similarly gave the corresponding cyclized products 10 and 11 together with small amounts of their dehydroxylated ketones (eq.2).

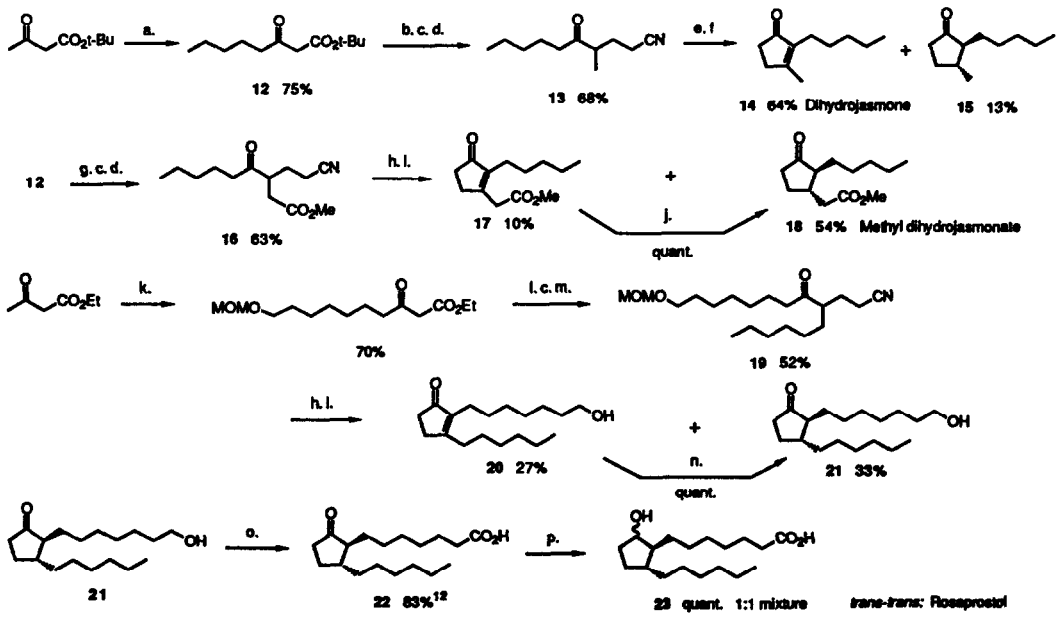


(2)

Since a variety of γ-cyanoketones can easily be synthesized from alkyl acetylacetonates, this electroreductive coupling of γ-cyanoketones offers a new synthetic method of 2,3-disubstituted cyclopentanones. Some of our preliminary results, namely, the synthesis of dihydrojasmone 14, methyl dihydrojasmonate 18, and Rosaprostol 23[13] are shown in Scheme II.

The electroreduction of γ-cyanoketone 13 and subsequent acid treatment gave dihydrojasmone 14 and its hydrogenated one 15. Methyl dihydrojasmonate 18 and its dehydrogenated one 17 were obtained from γ-cyanoketone 16 by the same method. Hydrogenation of 17 afforded 18 quantitatively.

Similarly, 19 gave 2,3-disubstituted cyclopentanone 21 and its dehydrogenated one 20. Jone's oxidation of 21 and the following reduction with $NaBH_4$ gave hydroxy carboxylic acid 23 as a 1:1 mixture of two stereoisomers. The trans,trans isomer of 23 is Rosaprostol.



a. NaH, n-BuLi, n-BuBr, THF, 0°C, 1h; b. NaH, MeI, DMF, r. t., 2h; c. CH_2=CHCN, cat. t-BuOH, reflux, 2h; d, cat. p-TsOH, 120°C, 30min; e. +e (-2.6V vs S.C.E.), Sn cathode, i-PrOH, r. t., 6F/mol; f. cat. p-TsOH, benzene, reflux, 2h; g. NaH, $BrCH_2CO_2Me$, DMF, r. t., 2h; h. +e, Sn cathode, i-PrOH, 65°C, 6F/mol; i. HCl, MeOH, r. t., 24h; j. H_2 (1atm), Pd/C, MeOH, r. t., 24h; k. NaH, n-BuLi, $MOM(CH_2)_6Br$, THF, 0°C, 1h; l. NaH, $n\text{-}C_6H_{13}Br$, DMF, 50°C, 6h; m, NaOH, EtOH/H_2O, r. t., 5days; n. Li, NH_3, -70°C, 1h; o. Jones oxd., 0°C, 2h; p. $NaBH_4$, MeOH, 0°C, 1h.

Scheme II.

References and Notes

1. Electroorganic Chemistry. 123.

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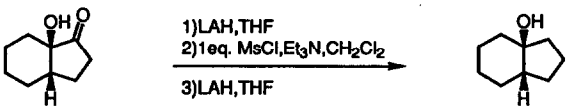
5. Stereoconfiguration of 2a should be cis. 2a: ^{13}C-NMR ($CDCl_3$) 23.90 (t), 24.30 (t), 31.87 (t), 35.02 (t), 37.14(t), 48.21 (d), 88.06 (s), 220.21 (s) ppm.

6. Stereoconfiguration of 2b was determined by transformation of it to the known compound 24[7] and the comparison of its ^{13}C-NMR spectrum with the reported data. 2b: ^{13}C-NMR ($CDCl_3$) 20.67 (2C,t), 20.94 (t), 24.40 (t), 29.11 (t), 33.15 (t), 40.77 (d), 77.67 (s), 219.94 (s) ppm.



2b 24

7. G. A. Molander and J. B. Etter, J. Org. Chem., 51, 1778 (1986).

8. Although the stereoisomers of 2c could be separated by column chromatography on silica gel, the stereostructure of each isomer could not be assigned. 2c (major): ^{13}C-NMR ($CDCl_3$) 21.75 (t), 25.71 (t), 25.74 (t), 30.59 (t), 32.38 (t), 32.52 (t), 34.84 (t), 47.02 (d), 81.04 (s), 221.78 (s) ppm. 2c (minor): ^{13}C-NMR ($CDCl_3$) 23.90 (t), 26.27 (t), 26.32 (t),26.47 (t), 27.01 (t), 34.67 (t), 36.32 (t), 45.45 (d), 78.11 (s), 219.02 (s) ppm.

9. The stereoisomers of 2d could not be separated. 2d (major): ^{13}C-NMR ($CDCl_3$) 19.40 (t), 21.71 (t), 22.08 (t), 22.11 (t), 22.39 (t), 24.03 (t), 24.11 (t), 25.23 (t), 25.89 (t), 26.13 (t), 30.84 (t), 36.84 (t), 38.52 (d),79.10 (s), 218.81 (s) ppm. 2d (minor): ^{13}C-NMR ($CDCl_3$) 19.62 (t),23.02 (t),23.27 (t), 23.80 (t), 24.06 (t), 24.17 (t), 24.48 (t), 25.35 (t), 25.96 (t),26.01 (t), 27.16 (t), 32.81 (t), 45.48 (d), 80.89 (s), 219.55 (s) ppm.

10. 2e: ^{13}C-NMR ($CDCl_3$) 21.33 (t), 26.11 (t), 30.03 (t), 30.59 (t), 37.18(t), 37.26 (t), 52.64 (d), 86.44 (s), 214.33 (s) ppm.

11. The stereoisomers of 2f could be separated by column chromatography on silica gel. 2f (major): ^{13}C-NMR ($CDCl_3$) 20.10 (t), 21.14 (t), 26.01 (t),26.39 (t), 27.47 (t), 31.39 (t), 37.24 (t), 44.62 (d), 78.05 (s), 214.40 (s) ppm. 2f (minor): ^{13}C-NMR ($CDCl_3$) 20.84 (t), 25.44 (t), 26.38 (t), 27.10(t), 27.41 (t), 31.16 (t), 37.46 (t), 46.72 (d), 76.19 (s), 213.43 (s) ppm.

12. 22: ^{13}C-NMR ($CDCl_3$) 14.02 (q), 22.57 (t), 24.54 (t), 26.59 (t), 26.97 (t), 27.01 (t), 27.90 (t), 28.80 (t), 29.43 (t), 29.47 (t), 31.76 (t), 33.96(t), 34.70 (t), 37.83 (t), 41.50 (d), 54.98 (d), 179.88 (s), 221.75 (s) ppm.

13. A prostaglandin analogue possessing antiulcer activity.[14]

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