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Cleavage of C-O Bonds of Iminoethers and Methyl Hydroxamates with Grignard Reagents and Butyllithium

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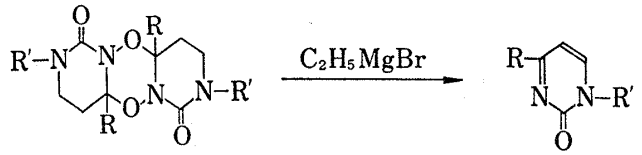
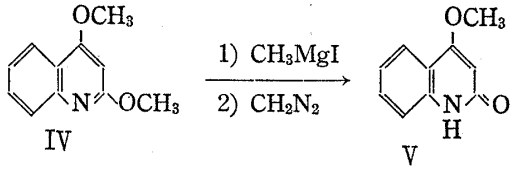
C–O bond in some cyclic iminoethers and methyl hydroxamates were cleavaged by methylmagnesium iodide and butyllithium in a good yield. This reaction was applied to the cleavage of the C–O bond of 4-methoxy-2,3-dihydrofuro[2,3-*b*]quinoline to give 4-hydroxy-3-propylcarbostyril. By the reaction of 3,6-diisobutyl-1-methoxy-2-oxo-1,2-dihydropyrazine with methylmagnesium iodide, neoaspergillic acid was obtained.

Keywords——Grignard reagent; iminoether; methyl hydroxamate; butyllithium; quinoline; pyrazine

It is already well known that the ether linkage and methylenedioxy ring are cleaved by Grignard reagents and alkyllithium.[2,3] Recently the cleavage shown in equation (1) has also been reported.[4] In the course of our investigation on N-heterocycles we applied this reaction to cleave the C–O bond in cyclic iminoethers and methyl hydroxamates, and the required products were obtained in a high yield.



(1)



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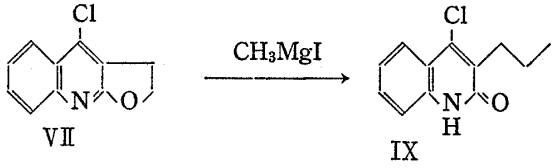
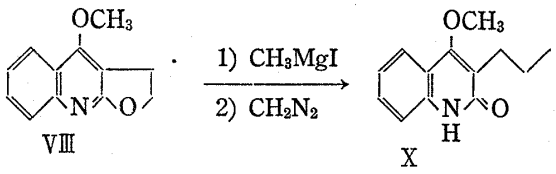
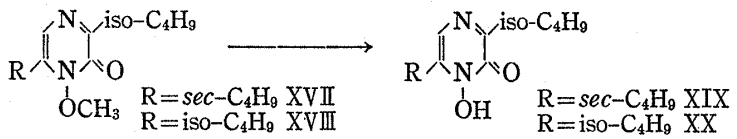


VII IX (3)



VIII X (4)



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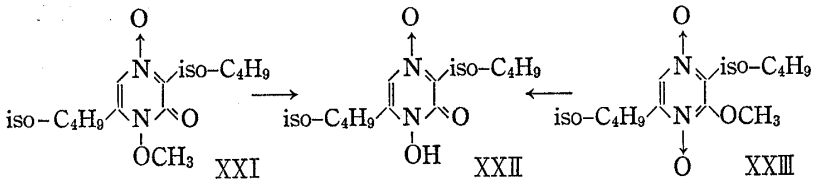

(6)

Table I. Cleavage of C-O Bonds with Grignard Reagents and Butyllithium

Compound No.	Reagent[a]	Solvent	Reaction temp. (°C)	Reaction time (hr)	Product	Yield (%)
I	MeMgI	neat	150	0.5	II	78
III	MeMgI	neat	160	1.0	carbostyril	89
	BuLi	hexane	r.t.	48	carbostyril	74
IV[b]	MeMgI	neat	150	0.5	IV+V	33+53
	MeMgI[c]	neat	160	0.5	VI	27
VII	MeMgI	neat	160	1.0	IX	91
	PhMgBr	neat	160	1.0	4-chloro-3-(β-phenethyl) carbostyril	62.8
VIII[b]	MeMgI	neat	150	1.0	X	36
	MeMgI	mesitylene	reflux	2.0	X	34
	PhMgBr	neat	150	1.0	4-methoxy-3-(β-phenethyl)-carbostyril	8
	isoPrMgBr	neat	150	1.0	4-methoxy-3-isohexyl-carbostyril	6.2
XIII	MeMgI	neat	150	1.0	XV	75
XIV	MeMgI	neat	150	0.5	XVI	84[d]
	MeMgI[c]	ether	reflux	2.0	XVI	65
XVIII	MeMgI	neat	150	0.5	XX	87[d]
	MeMgI[c]	ether	reflux	2.0	XX	43
XXI	MeMgI	neat	190	0.5	XXII	95
XXIII	MeMgI	neat	100	2.0	XXII	62
	MeMgI	neat	130	0.25	XXII	8

a) Three epuivalents of the reagent were used.
b) The products were treated with diazomethane.
c) One equivalent of the reagent was used.
d) yield of the crude product

In this work, the cleavage reactions are carried out using 3—4 equivalents of the Grignard reagents and butyllithium, under heating or at room temperature. The results obtained are shown in Table I.

Although 7-methoxy-3,4,5,6-tetrahydro-2H-azepine (I), prepared from caprolactam (II), was quantitatively recovered on heating without a Grignard reagent, I returned to II in 90% yield, on heating with methylmagnesium iodide. 2-Methoxyquinoline (III) and 2,4-dimethoxyquinoline (IV) were also demethylated in a high yield. On heating with excess of methylmagnesium iodide, IV gave a mixture of hydroxyquinolines, which was treated with an ether solution of diazomethane and purified by column chromatography to be separated into 4-methoxycarbostyril (V) and the starting material (IV). It is already known that the treatment[5] of 2,4-dihydroxyquinoline and 2-methoxy-4-hydroxyquinoline (VI) with diazomethane affords V and IV, respectively. Therefore this experiment indicates that 2,4-dihydroxyquinoline and VI were produced by demethylation of IV. However, on heating with equimolar methylmagnesium iodide, IV interestingly gave only VI. This result may be due to the difference of reactivity between an arylether and an iminoether.

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By the reaction of 4-chloro-2,3-dihydrofuro[2,3-*b*]quinoline[6] (VII) and dihydrodictamnine[7] (VIII), the dihydrofuran ring was cleaved. Namely VII gave 4-chloro-3-propylcarbostyril (IX), on being heated with methylmagnesium iodide, while VIII gave a mixture of 4-methoxy-3-propylcarbostyril (X) and the starting material, on being heated with methylmagnesium iodide and by following treatment with diazomethane. This result indicates that VIII gave a mixture of 4-hydroxy-3-propylcarbostyril (XI) and 4-hydroxy-2,3-dihydrofuro[2,3-*b*]quinoline (XII) by the cleavage reaction. The structure of IX and X were verified by comparing the UV spectra of the products with the spectra of 4-methoxy-[8] and 4-chloro-carbostyril,[9] respectively (Fig. 1), and by measuring their NMR spectra. The signals of propyl protons of IX in the NMR spectrum appeared as a multiplet at 1.70 ppm (2H, J=8 Hz), and two triplets at 1.06 ppm (3H, J=8 Hz), and two triplets at 1.06 ppm (3H, J=8 Hz) and 2.90 ppm (2H, J=8 Hz). The pattern of propyl protons in the NMR spectrum of X was almost same as that of IX.

The reaction of methoxypyrazines, such as 2-methoxy-5,6-diphenylpyrazine[10] (XIII) and 2-methoxy-3,6-diisobutylpyrazine (XIV), was also successful to give 2-hydroxy-5,6-diphenylpyrazine[11] (XV) and flavacol[12] (XVI), respectively in a high yield, on heating with methylmagnesium iodide without a solvent or in refluxing ether.

Demethylation of methyl cyclic hydroxamates such as XVII and XVIII, using hydriodic acid, was already reported in the course of the synthesis of aspergillic acid[13] (XIX) and neoaspergillic acid[12] (XX). In the present work, demethylation of 3,6-diisobutyl-1-methoxy-2-oxo-1,2-dihydropyrazine (XVIII) and its 4-oxide (XXI), using methylmagnesium iodide, is also achieved.

The NMR spectrum of a colorless crystalline product, obtained by treatment of XXII with diazomethane, showed two singlets at 4.04 and 4.16 ppm, whose intensity ratio was 4: 1. This NMR spectrum indicates that the crystals are composed of XXI and XXIII, which could not be separated into respective compounds by column chromatography. Without further purification, this crystalline mixture was submitted to the demethylation reaction to afford XXII in 95% yield. On the basis of this experiment, it seemed reasonable to assume that the cleavage of C–O bonds occurred in both compounds.

The deoxygenation products of the mixture of XXI and XXIII indicated two peaks (intensity ratio 4: 1) in gas chromatography. This product was chromatographed to be separated into XVIII, indicating a band at 1640 cm^{-1} in its IR spectrum, and XIV in the ratio of 3.9: 1. XVIII was submitted to the reaction with methylmagnesium iodide without purification to afford XX and flavacol under various conditions and the

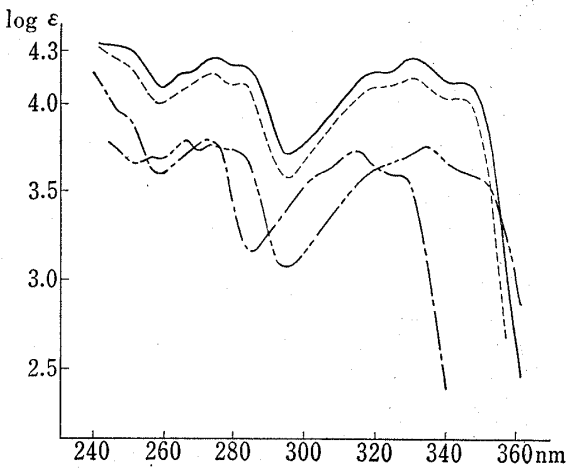

Fig. 1. UV-Spectra of Carbostyril Derivatives
———: X
·····: IX
———: 4-methoxycarbostyril
———: 4-chlorocarbostyril

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yields are listed in Table I. The reaction condition to afford XX described in this paper is much milder than the reported condition.[12]

In conclusion, the reaction of Grignard reagents with iminoethers and alkyl hydroxamates would provide a facile cleavage of a C–O bond.

Experimental[14]

Demethylation of 7-Methoxy-3,4,5,6-tetrahydro-2H-azepine (I)——In a usual manner an ether solution of MeMgI was prepared from 73 mg (3 mg-atom) of Mg. After ether was evaporated by distillation, 127 mg (1 mmol) of I was added to the residue and heated at 150° for 0.5 hr in an oil bath. When cooled, 1 ml of H_2O was added to the reaction mixture, which was then slightly acidified with 10% HCl and extracted with $CHCl_3$. The organic layer was dried over Na_2SO_4 and evaporated to dryness. The residue was purified by distillation to yield 88 mg (78%) caprolactam.

Demethylation of 2-Methoxyquinoline (III)——i) A mixture of 159 mg (1 mmol) of III and MeMgI, prepared from 73 mg (3 mg-atom) of Mg, was heated at 160° for 1 hr. The reaction mixture was treated similarly as in the case of I to give 129 mg (89%) carbostyril.

ii) After stirring a mixture of 80 mg (0.5 mmol) of III and 0.64 ml (1.6 mmol) of 15% BuLi–hexane solution at room temperature for 2 days, the reaction mixture was acidified with 30% AcOH and extracted with $CHCl_3$. The $CHCl_3$ layer was washed with aq. $NaHCO_3$ and H_2O, and after usual work-up, gave a product, which was recrystallized from MeOH–H_2O to give 106 mg (74%) of carbostyril.

Demethylation of 2,4-Dimethoxyquinoline (IV)——i) A mixture of 190 mg (1 mmol) of IV and MeMgI, prepared from 146 mg (3 mg-atom) of Mg, was heated at 150° for 0.5 hr. The reaction mixture was worked up similarly to the case of I to give a mixture of hydroxyquinolines, which was treated with an ether solution of CH_2N_2. The products were chromatographed over 3 g of Wakogel C-200 with benzene to give 92 mg (53%) of V and 62 mg (33%) of the starting material (IV).

ii) A mixture of 190 mg (1 mmol) of IV and MeMgI, prepared from 27 mg (1.1 mg-atom) of Mg, was heated at 160° for 0.5 hr. After working up, a brown substance (176 mg) was obtained and purified by column chromatography to yield IV (98 mg, 52%) and VI (47 mg, 27%).

Cleavage of the Ether Bond in 4-Chloro-2,3-dihydrofuro[2,3-*b*]quinoline (VII)——A mixture of 206 mg (1 mmol) of VII and MeMgI, prepared from 73 mg (3 mg-atom) of Mg, was heated at 160° for 1 hr. A usual work-up gave 220 mg of crude IX, which was recrystallized from MeOH to afford colorless needles (202 mg, 91%) of mp 194—195°. *Anal.* Calcd. for $C_{12}H_{12}ONCl$ (IX): C, 65.01; H, 5.46; N, 6.32. Found: C, 65.10; H, 5.71; N, 6.30. IR ν_{max}^{KBr} cm^{-1}: 1660, 1600. NMR ($CDCl_3$) δ: 1.06 (3H, t, J=8 Hz), 1.70 (2H, m, J=8 Hz), 2.90 (2H, t, J=8 Hz), 7.20 (3H, m), 7.90 (1H, d, J=8 Hz). Mass Spectrum *m/e*: 221 (M^+), 186 (–Cl), 178 ($-C_3H_7$).

Cleavage of the Ether Bonds in 2,3-Dihydrodictamnine (VIII)——A mixture of 201 mg (1 mmol) of VIII and MeMgI, prepared from 146 mg (6 mg-atom) of Mg, was heated at 150° for 1 hr. When cooled, the reaction mixture was treated with 10% HCl to be slightly acidified and evaporated to dryness *in vacuo*. The residue was extracted with hot $CHCl_3$. After $CHCl_3$ was removed by distillation *in vacuo*, the residue, in which the starting material was not detected any longer by TLC, was treated with an ether solution of CH_2N_2. The methylated products were separated by column chromatography (on 5 g of Wakogel C-200) to yield X (78 mg, 36%) as a colorless semisolid and the starting material (17 mg, 18%). A mixture of 201 mg (1 mmol) of VIII and 3 equivalents of MeMgI in 20 ml of mesitylene was refluxed and a usual work-up gave 73 mg (34%) of X. *Anal.* Calcd. for $C_{13}H_{15}O_2N$ (X): C, 71.87; H, 6.96; N, 6.45. Found: C, 72.01; H, 6.92; N, 6.46. IR ν_{max}^{KBr} cm^{-1}: 1663, 1595. NMR ($CDCl_3$) δ: 1.04 (3H, t, J=8 Hz), 1.71 (2H, m, J=8 Hz), 2.88 (2H, t, J=8 Hz), 3.82 (3H, s). Mass Spectrum *m/e*: 217 (M^+), 202 ($-CH_3$), 186 ($-CH_3O$), 174 ($-C_3H_7$), 143 ($-CH_3O$, $-C_3H_7$).

2-Methoxy-3,6-diisobutylpyrazine (XIV)——A mixture of 3.371 g (15 mmol) of 2-chloro-3,6-diisobutylpyrazine and a MeOH solution of NaOMe, prepared from 1.035 g (45 mg-atom) of Na and 30 ml of MeOH, was heated in a sealed tube at 130° for 2 hr to afford a colorless oil, which was purified by distillation at 102—104°/3 Torr to give 3.148 g (94%). *Anal.* Calcd. for $C_{13}H_{22}ON_2$ (XIV): C, 70.23; H, 9.97; N, 12.60. Found: C, 69.97; H, 10.14; N, 12.37. UV $\lambda_{max}^{95\%EtOH}$ nm (log ε): 217 (4.01), 280 (3.72), 298 (3.87). NMR ($CDCl_3$) δ: 0.91 (6H, d, J=7 Hz), 2.10 (2H, m), 2.51 (2H, d, J=7 Hz), 2.63 (2H, d, J=7 Hz), 3.90 (3H, s), 7.82 (1H, s).

Demethylation of Mixture of XXI and XXIII——A crystalline mixture of 254 mg (1 mmol) of XXI and XXIII, obtained from XXII by treatment with CH_2N_2, was heated at 190° for 30 min with 3 equivalents of MeMgI and worked up as usual to give 227 mg (95%) of XXII as colorless crystals. Recrystallization from EtOH gave colorless needles of mp 195°.

14) All melting and boiling points were uncorrected. IR spectra were measured with Shimadzu IR-400, UV spectra were recorded with Hitachi Model 323, NMR spectra were taken with JEOL JNM-PS-100 using tetramethylsilane as an internal standard, and mass spectra were measured with Hitachi RMU-7L spectrometer.

Preparation of 3,6-Diisobutyl-1-methoxy-2-oxo-1,2-dihydropyrazine (XVIII)——Colorless crystals, prepared from 480 mg (2 mmol) of XXII by treatment with CH_2N_2, were warmed at 40° for 30 min with 1 ml of PCl_3 in 80 ml of anhydr. AcOEt. The reaction mixture was poured into ice-water, made alkaline with K_2CO_3, and the AcOEt layer was separated. The usual work-up gave a yellowish oil (259 mg), which indicated two peaks (intensity ratio, 4: 1) in GLC (1.5% SE-30 on Shimalite; 1.5 m×3 mm; column temp., 75°; N_2 flow rate, 40 ml/min) and was chromatographed over silica gel (Wakogel C-200, 5 g), eluted with a mixture of benzene and acetone to give 178 mg (42%) of XVIII as a colorless semisolid and 45 mg (11%) of XIV. XVIII thus obtained was used for the demethylation reaction without further purification.

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Percutaneous Absorption of α-Olefin Sulfonate (AOS) in Rats[1]

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Percutaneous absorption of α-olefin sulfonate (AOS) was investigated in rats by using ^{14}C-labeled compound. The solution of ^{14}C–AOS was applied to the dorsal skin under various conditions: (a) the intact skin dried naturally after application, (b) the intact skin wiped off 0.5 hr after application, (c) the intact skin wiped off 1.5 hr after application, (d) the intact skin with a plastic cup containing ^{14}C–AOS solution and (e) the damaged skin without the *stratum corneum* dried naturally after application.

When rats were applied with 0.5 ml of a 0.2% solution of ^{14}C–AOS under the condition of (a), the recoveries of radioactivity were 0.33% in the urine, 0.08% in the bile and 0.21% in the main organs at 24 hr after application. It was thus estimated that the total amount absorbed through the skin was about 0.6% of the applied dose. Comparing the results obtained under the conditions of (a), (b) and (c), the percutaneous absorption of ^{14}C–AOS applied on the skin was almost finished by 1.5 hr after application. The excretion of radioactivity into the urine and bile was approached to the highest rate around 3—6 hr, then gradually decreased, and continued even 70—90 hr after application. When a 0.02% solution of ^{14}C–AOS was always in contact with the skin under the condition of (d), a small amount of the surfactant was continuously absorbed from the skin.

On the other hand, when the skin was damaged and ^{14}C–AOS was applied on it under the condition of (e), a greater amount of radioactivity was excreted into the urine and bile, and the recoveries were 36.26% in the urine, 1.83% in the bile and 12.28% in the main organs 30 hr after application, being about 50% in total.

Keywords——surfactant; percutaneous absorption; α-olefin sulfonate; dermal application; damaged skin; biliary excretion; uriary excretion

The main surfactant used previously as domestic detergent was tetrapropylene benzene sulfonate (ABS). Since it was pointed out that ABS was resistant to biodegradation and caused the pollution in environment, more biodegradable surfactants such as linear alkyl benzene sulfonate (LAS), higher alcohol sulfate (AS), alkyl ethoxy sulfonate (AES), and α-olefin sulfonate (AOS) have been widely used.

In order to assess the safety of these surfactants, many toxicological studies have been performed. As for AOS which was introduced as a new surfactant with the claims of

1) A part of this work was presented at the 96th Annual Meeting of the Pharmaceutical Society of Japan, Nagoya, April 1976.

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