LITHIATED 2-METHYL-5-PHENYLOXAZOLES, FORMATION AND REACTIONS WITH ELECTROPHILES‡

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Abstract——The methyl group of 2-methyl-5-phenyloxazole (**1**) has been lithiated with lithium diisopropylamide (LDA) and the resulting lithio derivative has been reacted with electrophiles to obtain 2-alkyl-5-phenyloxazoles.

Previously, we reported the ozonolysis of unsubstituted oxazole to afford formylformamide which acted as the efficient and convenient formylating reagent for the various nucleophiles such as amines and alcohols.[1] In addition, 2,4-disubstituted oxazoles afforded diacylamines, while 4,5-disubstituted and 2,4,5-trisubstituted oxazoles were inert to ozone.[2] On the contrary, ozonolysis of 2,5-disubstituted oxazoles gave acid anhydrides as well as isocyanic acid.[2] Especially, oxazoles which had two different kinds of substituents gave mixed acid anhydrides such as acetic benzoic anhydride from 2-methyl-5-phenyloxazole.

In order to explore the synthetic utilities of this ozonolysis reaction, we required various kinds of 2-alkyl substituted 5-phenyloxazoles. However, a great majority of preparative methods of oxazoles of this type include some practical inconveniences. Namely they use starting materials which may be either unstable or available with difficulties.[3] For example, the oxazole derivatives have been prepared from isonitriles,[4] diazoketones,[5] or ketoazides,[6] which are labile and require the rigorous reaction conditions for the promotion of the product yields. The preparations from the commercially available starting materials require drastic reaction conditions such as heating with concentrated sulfuric acid or phosphorous oxychloride.[7] The introduction of substituent groups on the oxazole ring has been attempted by the use of lithiooxazoles.[8,9] Although 5-lithiooxazoles react with

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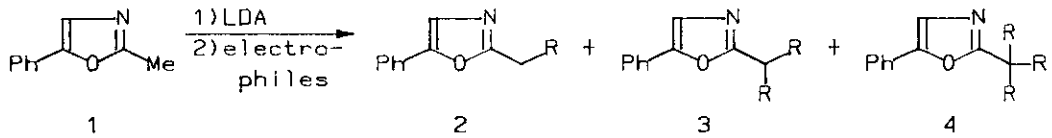
alkyl halides to give 5-alkyloxazoles,[8] 2-lithiooxazoles do not give any useful product due to the ring-chain tautomerism.[9]

Since methyl groups on heterocycles such as pyridines,[10] pyrimidines[11] and isoxazoles[12] are activated by the electron-withdrawing effect of the heterocycles, the methyl group generally reacts with various electrophiles in the presence of strong bases. This chemical tendency of heterocycles may also be expected for oxazoles. In fact, 2,4,5-trimethyloxazole was lithiated on the C-2 methyl group with lithium diisopropylamide (LDA) and then reacted with various electrophiles.[13] However phenyl substituted 2-methyloxazoles did not give any product upon treatment with LDA, while they reacted with electrophiles by the use of butyllithium.[13] These facts indicated that the methyl group on oxazole ring is quite sensitive to the nature of lithiating agents. Therefore, the reaction of 5-phenyl-2-methyloxazole (**1**) was performed with electrophiles by the use of LDA or butyllithium for the preparation of phenyloxazoles having the various substituent groups at C-2 carbon on the oxazole ring.

Results and Discussion

Although **1** was treated with butyllithium followed with methyl and ethyl iodide according to the Lipshutz's conditions,[13] none of the desired product could be obtained and the starting material was recovered completely. Next, the reaction of **1** with methyl iodide using LDA was performed. When an equimolar amount of methyl iodide and LDA was used for the introduction of a methyl moiety, only low yield was realized, and therefore 5 equivalents each of methyl iodide and LDA were required in order to increase the yields of products. When the ratio of methyl iodide to LDA was increased, the formation of 2-isopropyl-5-phenyloxazole (**3a**) was suppressed. Further, **1** was treated with the mixture of LDA and methyl iodide, no product was detected and **1** was recovered. From these facts, methyl iodide seemed to consume LDA very rapidly by the formation of N-methyldiisopropylamine. Therefore, **1** was treated with excess amount of LDA and then methyl iodide was added in portions with intervals. As the result, the yield of **3a** increased to 70 %, while the formation of 2-t-butyl-5-phenyloxazole (**4a**) was also formed. When methyl tosylate was used as a methylating reagent, the main product was found to be **2a**, but its yield was rather low.

In the cases of the other alkyl halides, the reaction profile of **1** was different from that of methyl iodide, because the electrophilicity of bulky alkyl halides such as ethyl iodide was depressed toward LDA. When an equimolar amount of ethyl iodide was treated with **1**, 2-propyl-5-phenyloxazole (**2b**) was formed predominantly. Otherwise, 2-(3-pentyl)-5-phenyloxazole (**3b**) was mainly obtained by the treatment



1 2 3 4

a: R= Me **b**: R= Et **c**: R= $PhCH_2$ **d**: R= p-Tol-CO **e**:R= p-Tol-CHOH

Table. Reaction of Electrophiles on 2-Methyl Group of **1**

Run	Electrophile*	Base	Mol Ratio			Yield (%)		
			1 :	Base :	Electrophile	**2**	**3**	**4**
1	MeI	BuLi	1 :	1.5 :	1.2	0	0	0
2	EtI	BuLi	1 :	1.5 :	1.2	0	0	0
3	MeI	LDA	1 :	3 :	3	trace	0	0
4	MeI	LDA	1 :	4 :	4	17	0	0
5	MeI	LDA	1 :	5 :	5	68	0	0
6	MeI	LDA	1 :	6 :	6	66	0	0
7	MeI	LDA	1 :	5 :	0.8	39	0	0
8	MeI	LDA	1 :	5 :	1	33	32	0
9	MeI	LDA	1 :	5 :	1.5	49	32	0
10	MeI	LDA	1 :	5 :	3	54	trace	0
11	MeI**	LDA	1 :	5 :	3	0	70	15
12	MeOTs	LDA	1 :	5 :	1.5	16	4	0
13	EtI	LDA	1 :	3.5 :	1.2	60	0	0
14	EtI	LDA	1 :	5 :	5	16	58	0
15	$PhCH_2$	LDA	1 :	3.5 :	1.2	62	0	0
16	$PhCH_2$	LDA	1 :	5 :	5	0	65	0
17	p-TolCHO	LDA	1 :	4.9 :	1.3	63	0	0
18	p-$TolCO_2Me$	LDA	1 :	5.5 :	1.5	58	0	0

* Electrophile was added in one portion to the reaction mixture.

** Methyl iodide was added in three portions with 30 min interval to the reaction mixture.

of **1** with excess amount of ethyl iodide. Also, an equimolar amount of benzyl bromide reacted with **1** to afford 2-(2-phenyl)ethyl-5-phenyloxazole (**2c**), while excess benzyl bromide gave 2-(1,3-diphenyl-2-propyl)-5-phenyloxazole (**3c**). Similarly, the reaction of **1** with 4-methylbenzaldehyde and methyl 4-methylbenzoate afforded 2-[2-hydroxy-2-(4-methylphenyl)ethyl]-5-phenyloxazole (**2d**) and 2-(4-methylbenzoyl)methyl-5-phenyloxazole (**2e**) respectively.

In conclusion, the 2-methyl group of **1** was lithiated with LDA and the resulting lithio derivative reacted with various electrophiles to achieve the preparation of various 2-alkyl substituted 5-phenyloxazoles in moderate yields.

EXPERIMENTAL

The infrared spectra were measured on a *JASCO A-3 infrared spectrophotometer*. ^{1}H- and ^{13}C-nmr were recorded Using JEOL-100 (100 MHz) spectrometer with tetramethylsilane as the internal standard. All melting points are uncorrected.

Preparation of 2-Methyl-5-phenyloxazole (1).

A mixture of 1-phenyl-1-hydroxy-2-ethylamine (10.9 g, 0.08 mol), acetyl chloride (6.3 g, 0.08 mol) and triethylamine (16 ml) in dichloromethane (230 ml) was stirred for 17 h at room temperature. After removal of volitile material, the residue was dissolved in acetone (200 ml). The chromic acid solustion, which was prepared from chromium trioxide (16 g), conc. sulfuric acid (16 ml) and water (70 ml), was gradually added to the acetone solution and stirred at room temperature for another 17 h. The reaction mixture was extracted with dichloromethane. The organic layer was washed with water, dried over anhydrous magnesium sulfate, and concentrated. The residue was heated at 140°C with conc. sulfuric acid (10 ml) for 15 min. After neutralization of the reaction mixture with 5 % aqueous sodium hydroxide, the product was extracted with dichloromethane, and the combined organic layer was washed with water, dried over anhydrous magnesium sulfate, and concentrated. 2-Methyl-5-phenyloxazole (**1**) was obtained by distillation, bp 100-110°C/5 mmHg, mp 56-57°C (lit.[5] mp 59°C), yield 4.4 g (35 %).

General Procedure.

Compound **1** in THF was added at -78°C to the THF solution of LDA, which was prepared from lithium, butyl chloride and diisopropylamine according to the method of Einhorn.[14] After stirring for 30 min at -78°C, the appropriate amount of electrophile was added at -78°C, and the solution was stirred for 17 h at room temperature. The reaction mixture was quenched with water, and extracted with dichloromethane. The organic layer was washed with water, dried over anhydrous magnesium sulfate, and concentrated. The residue was chromatographed on silica gel with benzene-ethyl acetate mixture. Results were summarized in the Table. By the

comparison of the spectral data and the gas chromatography, **2a** and **3a** were identified with the authentic samples.[5]

2-t-Butyl-5-phenyloxazole (4a).

Bp 65-70°C/5 mmHg; ^{1}H-nmr (δ, $CDCl_3$): 1.44 (9H, s), 7.20 (1H, s), and 7.2-7.7 ppm (5H, m); ^{13}C-nmr (δ, $CDCl_3$): 28.6 (q), 33.8 (s), 121.5 (d), 124.0 (d), 128.0 (d), 128.4 (s), 128.8 (d), and 150.6 ppm (s); Mass Calcd for $C_{13}H_{15}NO$: 201.1154. Found: m/z 201.1157.

2-Propyl-5-phenyloxazole (2b).

Bp 60-65°C/5 mmHg; ^{1}H-nmr (δ, $CDCl_3$): 1.03 (3H, t, J=7.3 Hz), 1.85 (2H, sex, J=7.3 Hz), 2.79 (2H, t, J=7.3 Hz), 7.20 (1H, s), and 7.25-7.7 ppm (5H, m); ^{13}C-nmr (δ, $CDCl_3$): 13.7 (q), 20.5 (t), 30.1 (t), 121.7 (d), 123.9 (d), 128.0 (d), 128.2 (s), 128.7 (d), 150.8 (s), and 164.3 ppm (s); Mass calcd for $C_{12}H_{13}NO$: 187.0998. Found: m/z 187.0999.

2-(3-Pentyl)-5-phenyloxazole (3b).

Bp 80-85°C/5 mmHg; ^{1}H-nmr (δ, $CDCl_3$): 0.91 (6H, t, J=7.3 Hz), 1.58-2.01 (4H, m), 2.78 (1H, quint, J=6.3 Hz), 7.15 (1H, s), and 7.1-7.7 ppm (5H, m); ^{13}C-nmr (δ, $CDCl_3$): 11.7 (q), 26.2 (t), 42.9 (d), 121.5 (d), 123.9 (d), 127.8 (d), 128.3 (s), 128.7 (d), 150.5 (s), and 167.0 ppm (s); Mass Calcd for $C_{14}H_{17}NO$: 215.1311. Found: m/z 215.1309; Anal. Calcd for $C_{14}H_{17}NO$: C, 78.10; H, 7.96; N, 6.51. Found: C, 77.87; H, 8.03; N, 6.49.

2-(2-Phenyl)ethyl-5-phenyloxazole (2c).

Bp 130-140°C/5 mmHg; mp 43-44°C; ^{1}H-nmr (δ, $CDCl_3$): 3.13 (4H, s), and 7.1-7.7 ppm (11H, m); ^{13}C-nmr (δ, $CDCl_3$): 30.1 (t), 33.2 (t), 121.8 (d), 124.0 (d), 126.4 (d), 128.1 (d), 128.3 (d), 128.5 (d), 128.8 (d), 140.3 (s), 151.0 (s), and 163.5 ppm (s); Anal. Calcd for $C_{17}H_{15}NO$: C, 81.90; H, 6.06; N, 5.62. Found: C, 81.69; H, 6.03; N, 5.57.

2-(1,3-Diphenyl-2-propyl)-5-phenyloxazole (3c).

Bp 140-145°C/5 mmHg; ^{1}H-nmr (δ, $CDCl_3$): 2.8-3.3 (4H, m), 3.56 (1H, quint, J=6.8 Hz), and 6.8-7.6 ppm (16H, m); ^{13}C-nmr (δ, $CDCl_3$): 39.6 (t), 43.5 (d), 121.7 (d), 124.0 (d), 126.4 (d), 128.0 (d), 128.4 (d), 128.7 (d), 128.9 (d), 129.9 (s), 139.0 (s), 150.7 (s), and 165.5 ppm (s); Mass Calcd for $C_{24}H_{21}NO$: 339.1624. Found: m/z 339.1620; Anal. Calcd for $C_{24}H_{21}NO$: C,84.92; H, 6.24; N, 4.13. Found: C, 84.42; H, 6.36; N, 4.16.

2-(4-Methylbenzoyl)methyl-5-phenyloxazole (2d).

The mixture of **2d** and their enol isomer was prepared from **1** and methyl 4-methylbenzoate, mp 99-100°C (from hexane). Ir ($CHCl_3$): 1690 cm^{-1}; ^{1}H-nmr (δ, $CDCl_3$): 2.38 (3H, s), 4.48 (1.4H, s), 6.12 (0.3H, s), 7.2-7.8 (8H, m), and 7.92 ppm (2H, d, J=8.3 Hz); ^{13}C-nmr (δ, $CDCl_3$): 21.4 (q), 39.1 (t), 122.3 (d), 123.8 (d), 124.2

(d), 125.4 (d), 128.0 (d), 128.3 (d), 128.7 (d), 129.2 (d), 129.5 (d), .pa 133.4 (s), 144.7 (s), 152.2 (s), 157.9 (s), 163.6 (s), 192.4 (s), 21.4 (q), 83.5 (d), 129.9 (s), 131.5 (s), 140.2 (s), and 162.6 ppm (s) ; Anal. Calcd for $C_{18}H_{15}NO_2$: C, 77.96; H, 5.45; N, 5.05. Found: C, 77.78; H, 5.51; N, 4.97.

2-[2-(4-Methylphenyl)-2-hydroxy]ethyl-5-phenyloxazole (2e).

Mp 126.5-127°C (from benzene-hexane mixture); ^{1}H-nmr (δ, $CDCl_3$): 2.33 (3H, s), 3.19 (2H, d, J=6.9 Hz), 4.0-4.5 (1H, broad s), 5.21 (1H, t, J=6.8 Hz), and 7.0-7.65 ppm (10H, m); ^{13}C-nmr (δ, $CDCl_3$): 21.1 (q), 37.8 (t), 71.2 (d), 121.5 (d), 124.1 (d), 125.7 (d), 127.9 (s), 128.3 (d), 128.8 (d), 129.2 (d), 137.4 (s), 139.9 (s), 151.2 (s), and 162.1 ppm (s); Anal. Calcd for $C_{18}H_{17}NO_2$: C, 77.40; H, 6.13; N, 5.01. Found: C, 77.39; H, 6.18; N, 4.84.

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