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REACTION OF 6-METHYL-2-PHENYL-4*H*-1,3-OXAZIN-4-ONE WITH OXIME DIANIONS[1]

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Abstract-- 6-Methyl-2-phenyl-4*H*-1,3-oxazin-4-one (**1**) undergoes novel ring transformation upon treatment with oxime dianions to give isoxazoles (**3a-d**) and pyridine N-oxides (**4c-f**). The reaction of **1** with cycloheptanone oxime (**2a**) or cyclododecanone oxime (**2b**) in the presence of two equivalents of butyllithium affords isoxazole (**3a** or **3b**). With acetophenone oxime (**2c**) or acetoxime (**2d**), pyridine N-oxide (**4c** or **4d**) is formed as a minor product in addition to isoxazole (**3c** or **3d**). Treatment with cyclopentanone oxime (**2e**) or cyclohexanone oxime (**2f**) yields pyridine N-oxides (**4e** or **4f**) as a sole product.

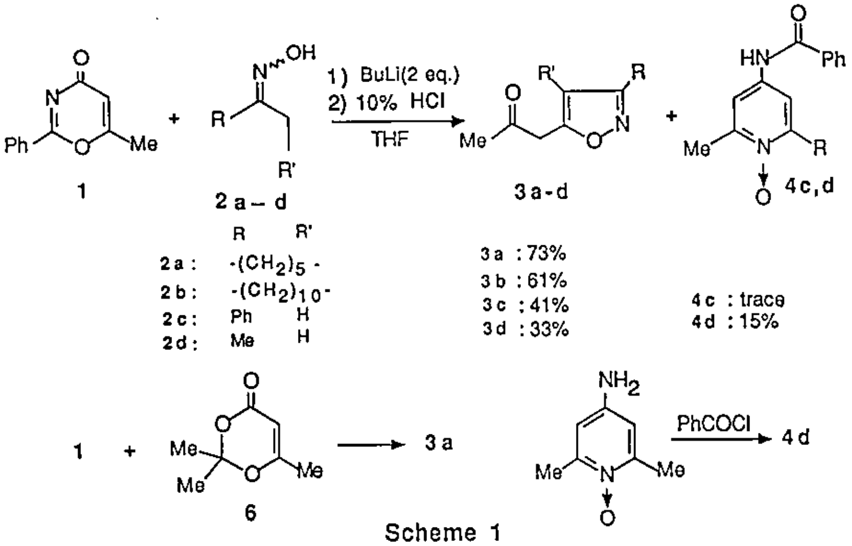
Ring transformation of 4*H*-1,3-oxazin-4-one derivatives with several nucleophiles to give a variety of heterocycles has been well investigated.[2] These ring transformation reactions involve the initial attack of the nucleophiles on the carbon at the 2-, 4-, or 6-position of the oxazine ring. For instance, carbanions derived from various ketones, esters, lactones and nitriles initially attack the 2-position of the oxazine ring to give 2-pyridone derivatives.[3] On the other hand, dianions derived from lactams, such as ε-capro-, δ-valero-, and γ-butyrolactams, attack the 4-position of the oxazine ring to afford the corresponding α-substituted lactams.[4] In this paper, we wish to report the novel ring transformation of 6-methyl-2-phenyl-4*H*-1,3-oxazin-4-one (**1**) with several oxime dianions into isoxazoles **3** and/or pyridine N-oxides **4** which involves the initial attack of the carbanion to the 4-position of the oxazine ring.

Treatment of **1** with cycloheptanone oxime (**2a**) in tetrahydrofuran (THF) at -70°C in the presence of two equivalents of butyllithium (BuLi), followed by quenching with 10% HCl at 0°C gave 5-acetonyl-3,4-cycloheptenoisoxazole (**3a**) in 73% yield together with benzamide. The structure **3a** was determined by the comparison of the ir spectrum with that of an authentic sample prepared from **2a** and 2,2,6-trimethyl-1,3-dioxin-4-one in the presence of two equivalents of BuLi. Cyclododecanone oxime (**2b**) similarly reacted with **1** to give the corresponding isoxazole derivative **3b** in 61% yield.

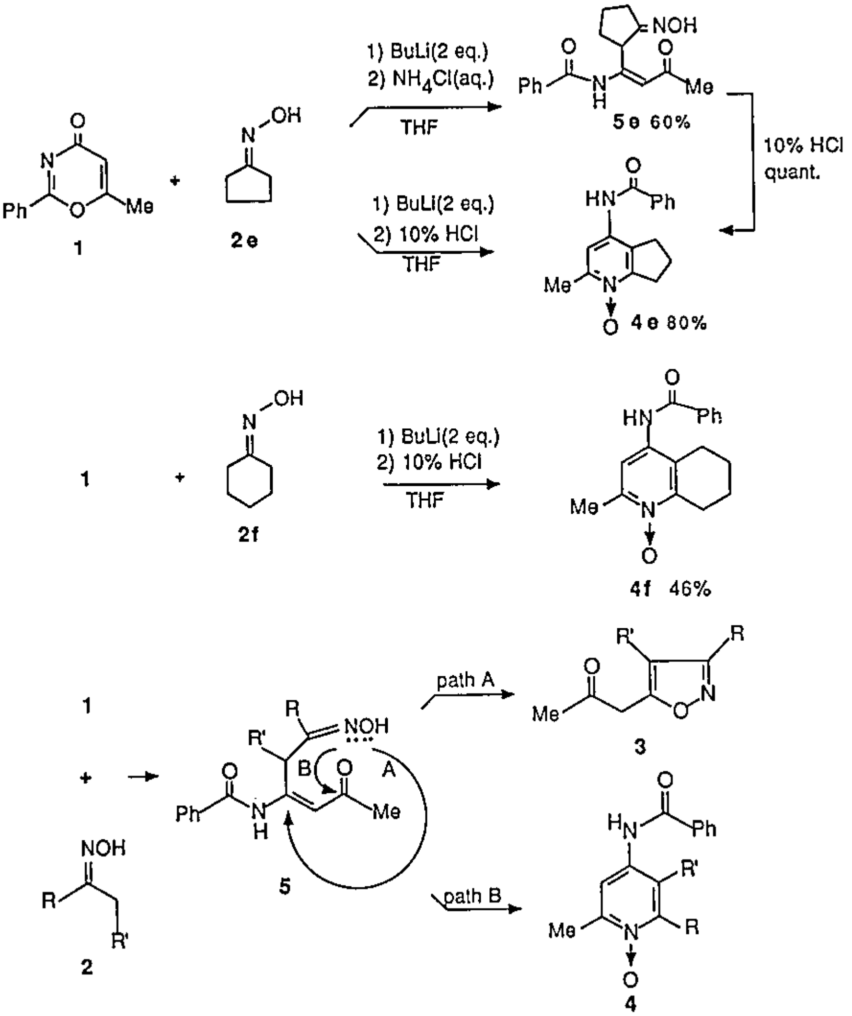
However, the reactions of **1** with acetophenone oxime (**2c**) or acetoxime (**2d**) were found to occur leading to pyridine N-oxide derivatives **4c,d** besides the corresponding isoxazole derivatives **3c,d**. The structural assignment of **4d** was accomplished on the basis of analytical and spectroscopic data such as ir, nmr, and ms. Further, the ir spectrum of **4d** was identical with that of a sample prepared by benzoylation of 4-amino-2,6-dimethylpyridine N-oxide[5] (Scheme 1).

On the other hand, the reaction of **1** with cyclopentanone oxime (**2e**) resulted in the formation of pyridine N-oxide **4e** as a sole product (Scheme 2). Thus, treatment of **1** with **2e** in THF at -70°C in the presence of two equivalents of BuLi, followed by quenching with 10% HCl in an ice-cooled bath produced **4e** in 80% yield. Employment of ammonium chloride as a quenching agent instead of 10% HCl at the same temperature gave rise to oxime **5e**[6] in 60% yield. The oxime **5e** was quantitatively transformed into the N-oxide **4e** by treatment with 10% HCl at room temperature. The reaction of **1** with cyclohexanone oxime (**2f**) similarly proceeded leading to the corresponding pyridine N-oxide **4f** in 46% yield (Scheme 2).

The ring transformation of 1,3-oxazine **1** into the isoxazole **3** and the pyridine N-oxide **4** could be explained in terms of the following two-step sequence. The first step is initiated by the attack of a carbanion on the carbon atom of C=O group in the oxazine ring, followed by ring-opening into the oxime **5**.



Scheme 1



Scheme 2

The second one is the recyclization of **5** to **3** and **4**, by path A and B respectively, as depicted in Scheme 2. The reaction patern involved in the second step seems to be mainly affected by steric factors rather than electronic ones. The mechanistic investigation on the cyclization *via* paths A and B is in progress and will appear in near future.

Table. Formation of Isoxazoles **3a-d** and Pyridine N-Oxides **4c-e**

Product	mp(°C) (solvent)	Formula (M^+)	Ir(KBr) cm-1	Nmr[a] δ : ppm
3a	66-67 (hexane)	$C_{11}H_{15}NO_2$ (193)	1720	1.42-2.95(10H,m), 2.18(3H,s), 3.73(2H,s)
3b	74-75 (hexane)	$C_{16}H_{25}NO_2$ (263)	1720	1.20-2.95(20H,m), 2.19(3H,s), 3.76(2H,s)
3c	69-70 (hexane)	$C_{12}H_{11}NO_2$ (201)	1720	2.15(3H,s), 3.75(2H,s), 6.45(1H,s), 7.2-8.05(5H,m)
3d	61-62 (hexane)	$C_7H_9NO_2$ (139)	1720	2.05(3H,s), 2.16(1H,s), 3.73(3H,s),6.15(1H,s)
4c	225-226 (acetone)	$C_{19}H_{16}N_2O_2$ (304)	1665 1200	2.36(3H,s), 7.50-8.15(12H,m), 10.45(1H,br)
4d	216-217 (acetone)	$C_{14}H_{14}N_2O_2$ (242)	1665 1200	2.40(6H,s), 7.76(2H,s), 7.50-8.00(5H,m),10.5(1H,br)
4e	213-215 (acetone)	$C_{16}H_{16}N_2O_2$ (268)	1665 1220	1.90-2.50(2H,m), 2.83-3.33(4H, m), 2.43(3H,s),7.23-8.03(6H,m), 9.30(1H,br)
4f	205-207 (acetone)	$C_{17}H_{19}N_2O_2$ (282)	1660 1200	1.50-3.00(8H,m), 2.40(3H,s), 7.30-8.00(6H,m), 9.57(1H,br)

a) Spectra were recorded on a JEOL JNM-PMX60 instrument with tetramethylsilane as reference in $CDCl_3$ (3a-d) and $CDCl_3$-DMSO-d_6 (4c-f).

REFERENCES AND NOTES

1. This forms Part XVI of " 1,3-Oxazines and Related Compounds".
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4. Y. Yamamoto and Y. Morita, *Chem. Pharm. Bull.,* 1984, **32**, 2555.
5. T. Kato and F. Hamaguchi, *Chem. Pharm. Bull.*, 1956, **4**, 174.
6. Mp 135-136°C. Ir(KBr)cm^{-1} : 1690, 1640. Nmr($CDCl_3$) δ: 1.42-2.08(2H,m), 2.02(3H,s), 2.55-3.00(4H,m), 6.83(1H,s), 7.33-8.17(6H,m).

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