1,3-Oxazines and Related Compounds. VIII.1) Reaction of 6-Methyl-2-phenyl-4H-1,3-oxazin-4-one with Lactams and Their Derivatives

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6-Methyl-2-phenyl-4H-1,3-oxazin-4-one (1) underwent initial attack of the anions of lactams (2), such as ε-capro- (2a), δ-valero- (2b), and γ-butyro-lactams (2c), at the 4-position of the ring to give the corresponding α-substituted lactams (3a—c). Reaction of 1 with N-trimethylsilyl derivatives (6a—c) of 2 in the presence of lithium diisopropylamide afforded the 2,3-dihydro-4H-1,3-oxazin-4-one derivatives (7a—c), respectively. Similar treatment of 1 with O-methyl derivatives (9a—c) of 2 yielded the corresponding bicyclic heterocycles (10a—c).

Keywords—4H-1,3-oxazin-4-one; 2,3-dihydro-4H-1,3-oxazin-4-one; lithium diisopropylamide; butyllithium; ring transformation; lactam; lactim ether; N-trimethylsilylactam

It has been reported that 4H-1,3-oxazin-4-ones readily react with several nucleophiles and undergo ring transformations into a variety of heterocyclic compounds; pyridines, pyrimidines, triazoles, pyrazoles, oxadiazoles, and isoxazoles.2) Thus, they have considerable synthetic importance as intermediates in heterocyclic chemistry. The ring transformation reactions involve the attack of the nucleophiles on the carbon at the 2- or 6-position of the 1,3-oxazine ring in the initial step. This paper presents two novel reaction modes of 6-methyl-2-phenyl-4H-1,3-oxazin-4-one (1) with lactams (2) and N-trimethylsilyl derivatives (3) of 2. The lactams 2 used were ε-caprolactam (2a), δ-valerolactam (2b), and γ-butyrolactam (2c). In addition, the reaction of 1 with O-methyl derivatives (9) of 2 to provide bicyclic heterocycles (10) is described.

First, reaction of 1 with lactams 2 was investigated. Treatment of 1 with 2a in tetrahydrofuran (THF) at −70°C in the presence of 2 eq each of butyllithium (BuLi) and N,N,N',N'-tetramethylethenediamine (TMEDA), followed by quenching with 10% HCl at the same temperature, gave rise to a ring-opened compound 3a in 66% yield. The structure 3a was determined on the basis of the following chemical evidence as well as analytical and spectroscopic data such as infrared (IR), proton nuclear magnetic resonance (1H-NMR), and mass spectra (MS) (Table I). Product 3a was hydrolyzed with 10% HCl at room temperature to give the acetoacetylated derivative 4, which showed no depression of melting point on admixture with an authentic sample prepared from 2a and 2,2,6-trimethyl-1,3-dioxin-4-one (5) (Chart 1). δ-Valerolactam (2b) and γ-butyrolactam (2c) similarly reacted with 1 to give the corresponding ring-opened 3b and 3c in 74% and 42% yields, respectively.

In the 1H-NMR spectra of 3a and 3c, distinctive singlet signals due to the olefinic protons of the structures 3a and 3c (Chart 1) were observed at δ 5.86 and 5.81, respectively. In contrast, 3b gave a characteristic singlet signal due to two protons of the –COCH₂– moiety of the structure 3b at δ 4.16.

Formation of 3 suggests that the reaction was initiated by attack of the anion from 2 on the carbon atom at the 4-position of the 1,3-oxazine ring. This ring-opening mode of the 4H-1,3-oxazin-4-one has never previously been observed.

In these reactions, the use of lithium diisopropylamide (LDA) as a metallating agent was
Table 1. Ring-Opened Compounds $3a$–$c$ from $1$ and $2a$–$c$

| Product No. | Yield (%) | mp ($^\circ$C) (Recrystn. solvent) | Formula ($m/e$ M$^+$) | Analysis (%$\delta$) Calc (Found) | IR (KBr cm$^{-1}$) | NMR (CDCl$_3$-CF$_3$COOH) $\delta$
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<tr>
<td>$3a$</td>
<td>66</td>
<td>204–206 (MeOH)</td>
<td>C$_4$H$_9$N$_2$O$_3$</td>
<td>67.98 (68.05) 6.71 (6.63) 9.33 (9.25)</td>
<td>3330 1.42–2.53 (6H, m), 2.44 (3H, s), 1710 3.35–3.74 (2H, m), 4.87–5.16 (6H, m)</td>
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<td></td>
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<td>(300)</td>
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<td>1680 5.86 (1H, s), 7.41–8.16 (6H, m)</td>
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<td>$3b$</td>
<td>74</td>
<td>203.5–205 (MeOH)</td>
<td>C$_3$H$_5$N$_2$O$_3$</td>
<td>67.11 (67.13) 6.34 (6.42) 9.78 (9.55)</td>
<td>3260 1.61–2.15 (2H, m), 2.44 (3H, s), 3180 2.23–2.62 (2H, m), 3.12–3.43 (6H, m)</td>
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<td>(286)</td>
<td></td>
<td>1710 4.16 (2H, s), 7.23–7.90 (6H, m)</td>
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<td>$3c$</td>
<td>42</td>
<td>174–176 (C$_3$H$_4$O)</td>
<td>C$_2$H$_5$N$_2$O$_3$</td>
<td>66.16 (66.21) 5.92 (5.96) 10.22 (9.92)</td>
<td>3200 2.26–3.28 (2H, m), 2.35 (3H, s), 1710 3.46–3.81 (2H, m), 4.70 (1H, m), 1680 5.81 (1H, s), 7.43–8.25 (6H, m)</td>
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The reactions of $2a$ and $2c$ gave resinous substances which could not be purified, and the reaction of $2b$ gave only a trace amount of $3b$.

Next, reactions of $1$ with the $N$-trimethylsilyl derivatives ($6a$–$c$) of $2$ were carried out. Treatment of $1$ with $6a$ in the presence of 2 eq each of BuLi and TMEDA in the same manner as described above yielded a trace of $7a$. The use of LDA instead of the BuLi–TMEDA system increased the yield of $7a$. Thus, $1$ was treated with $6a$ in the presence of 2 eq of LDA at $-70^\circ$C, followed by quenching with 10% HCl at the same temperature, to give $7a$ in good yield. The structure $7a$ was confirmed by various analytical and spectral data, such as IR, $^1$H-NMR, and mass spectra. Hydrolysis of $7a$ afforded $3$-benzoyl- $\varepsilon$-caprolactam ($8$) in good yield, providing additional evidence for the structure $7a$. $N$-Trimethylsilyl derivatives $6b$ and $6c$ reacted analogously with $1$ to yield the corresponding dihydro derivatives $7b$ and $7c$, but the yields were low. Formation of $7$ evidently resulted from the addition reaction of $6$ across the
C = N double bond of the 1,3-oxazine ring.

Finally, our attention was directed to the reaction of 1 with lactim ethers 9. When 1 was allowed to react with the lactim ether 9a in the presence of 1 eq of LDA, the bicyclic compound 10a was obtained in 62% yield. The structural assignment of 10a was carried out on the basis of analytical and spectroscopic evidence (Table III). Similar treatment of 9b and 9c furnished the corresponding 10b and 10c in fair yields.

The ring transformation of 1 into 10 can be explained by a pathway (Chart 3) in which the initial attack of the anion of 9 took place preferentially on the 2-position of the 1,3-oxazine ring. This reaction mode is essentially the same as the conventional one.

In summary, new reaction modes of 1 were demonstrated: a) the attack of the nucleophile took place predominantly at the 4-position on the 1,3-oxazine ring, leading to the ring-opened
3, b) the nucleophile added across the C = N double bond in the 1,3-oxazine ring to give the adduct 7. In contrast, reaction of 1 with 9 was initiated by attack at the 2-position of the ring, giving the bicyclic compound 10.

Further work on these different reaction modes is under way.

Experimental

Melting points were obtained in a Mel-Temp melting point apparatus with an open capillary tube, and are uncorrected. IR spectra were obtained on a Shimadzu IR-400 or IR-430 spectrometer. 1H-NMR spectra were measured on a JEOL JNM-PMX 60 instrument. Chemical shifts are reported in δ values downfield relative to internal tetradeuterosilane or sodium 2,2,2-dimethyl-2-silapentane-5-sulfonate. The following abbreviations are used: s = singlet, d = doublet, t = triplet, m = multiplet, and br = broad. Diisopropylamine and TMEDA were freshly distilled from CaH2. THF was distilled from LiAlH4 directly before use. A 10% BuLi hexane solution (Nakarai Chemicals, Ltd.) was used as received.

Reaction of 1 with Lactam 2a–c: General Procedure—A 10% BuLi hexane solution (20 mmol) was added dropwise to an ice-salt-cooled solution of 2 (10 mmol) and TMEDA (2.32 g, 20 mmol) in THF (20 ml) with stirring for a period of 1 h. After completion of the addition, stirring was continued for a further 1.5 h at the same temperature. The resulting solution was added dropwise to a solution of 1 (10 mmol) in THF (30 ml) with stirring over a period of 1 h at −70 °C. Stirring was continued for another 2 h at the same temperature. A 10% HCl solution was added at −70 °C. The reaction mixture was concentrated under reduced pressure, followed by extraction with CHCl3. The CHCl3 layer was dried over MgSO4, filtered, and concentrated under reduced pressure. The remaining crude product 3 was purified by recrystallization from the solvent indicated in Table I.

Hydrolysis of 3a to 4—A solution of 3a (500 mg) in THF (20 ml) and 10% HCl (10 ml) was stirred for 48 h at room temperature. The reaction mixture was concentrated under reduced pressure, followed by extraction with CHCl3. The CHCl3 layer was dried over MgSO4, filtered, and concentrated under reduced pressure. The residue was washed with ether. The ether-insoluble material was recrystallized from benzene to give 4 (210 mg, 64%), mp 133–134 °C, which showed no depression of melting point on admixture with an authentic sample prepared by the
procedure described below. IR ν max cm⁻¹: 3200, 1710, 1680. ¹H-NMR (CDCl₃) δ: 1.33—2.20 (6H, m), 2.06 (3H × 3/5, s), 2.33 (3H × 2/5, s), 3.00—3.66 (3H, m), 3.73 (2H × 2/5, s), 5.60 (1H × 3/5, s), 6.86 (1H, br), 15.14 (1H × 3/5, br). Anal. Calcd for C₁₂H₁₄NO₄: C, 60.89; H, 7.67; N, 7.10. Found: C, 60.85; H, 7.22; N, 6.90. The ether washings were concentrated. The residue was purified by recrystallization from ether to give benzamide (110 mg, 54%).

Synthesis of 4 — A 10% BuLi hexane solution (20 mmol) was added dropwise to an ice-salt-cooled solution of 2a (1.13 g, 10 mmol) and TMEDA (2.32 g, 20 mmol) in THF (20 ml) with stirring over a period of 1 h. After completion of the addition, stirring was continued for a further 1.5 h at the same temperature. A solution of 5 (1.42 g, 10 mmol) in THF (20 ml) was added dropwise to the resulting solution at −70 °C. The reaction mixture was allowed to warm to 0 °C then neutralized with 10% HCl, concentrated under reduced pressure, followed by extraction with CHCl₃. The CHCl₃ layer was dried over MgSO₄, filtered, and concentrated under reduced pressure. The residual solid was washed with ether. The ether-insoluble solid was recrystallized from benzene to give 4 in 30% yield. The IR spectrum of the product was identical with that of the sample obtained above.

Reaction of 1 with N-Tritylthiobenzylactam 6a—c: General Procedure —A 10% BuLi hexane solution (20 mmol) was added dropwise to a solution of disopropylamine (20 mmol) in THF (20 ml) with stirring over a period of 10 min, and then a solution of 6 (10 mmol) in THF (20 ml) was added dropwise. The whole was stirred for 1 h, then a solution of 1 (1.87 g, 10 mmol) in THF (30 ml) was added dropwise to the resulting solution with stirring over a period of 1 h. The reaction mixture was stirred for a further 1 h and neutralized with 10% HCl. During these procedures, the temperature was kept at −70 °C. The reaction mixture was concentrated under reduced pressure and extracted with CHCl₃. The CHCl₃ layer was dried over MgSO₄, filtered, and concentrated under reduced pressure. The remaining crude product 7 was purified by recrystallization from the solvent indicated in Table II.

Hydrolysis of 7c to 8 — A solution of 7c (300 mg) in conc. H₂SO₄ (2 ml) was allowed to stand at room temperature for 15 min, and then poured onto ice. The resulting mixture was made alkaline with 10% Na₂CO₃ solution. The precipitate formed was collected by filtration and recrystallized from 95% EtOH to give 8 (180 mg, 83%). mp 203 °C (lit. mp 186—188 °C), as colorless needles, which showed no depression of melting point on admixture with an authentic sample prepared by the procedure described below. IR ν max cm⁻¹: 3210, 1690, 1660. ¹H-NMR (CDCl₃) δ 1.50—2.43 (6H, m), 3.33—3.73 (2H, m), 4.50—4.80 (1H, m), 7.33—8.03 (5H, m), 8.50 (1H, br).

Synthesis of 8 — A 10% BuLi hexane solution (20 mmol) was added dropwise to a solution of an ice-salt-cooled solution of 2a (1.13 g, 10 mmol) and TMEDA (2.32 g, 20 mmol) in THF (20 ml) over a period of 1 h. Stirring was continued for a further 1.5 h. A solution of ethyl benzolate (1.5 g, 10 mmol) in THF (20 ml) was added dropwise at −70 °C. The reaction solution was allowed to warm to 0 °C, neutralized with 10% HCl, and then concentrated under reduced pressure, followed by extraction with CHCl₃. The CHCl₃ layer was dried over MgSO₄, filtered, and concentrated under reduced pressure. The residual solid was washed with ether and then purified by recrystallization from 95% EtOH to give 8. The IR spectrum of this product was identical with that of the sample obtained above.

Reaction of 1 with Lactim Ether 9a—c — A 10% BuLi hexane solution (10 mmol) was added dropwise to a solution of disopropylamine (10 mmol) in THF (20 ml) with stirring over a period of 10 min, and then a solution of 9 (10 mmol) in THF (20 ml) was added dropwise. The whole was stirred for 1 h, then a solution of 1 (1.87 g, 10 mmol) in THF (30 ml) was added dropwise with stirring over a period of 1 h. Stirring was continued for a further 1 h. During these procedures, the temperature was kept at −70 °C. The reaction solution was allowed to warm to 0 °C. Finely powdered triethylamine hydrochloride (1.37 g, 10 mmol) was added, and the mixture was concentrated under reduced pressure. The residual solid was washed successively with water and ether. The remaining crude product 10 was purified by recrystallization from the solvent indicated in Table III.

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References