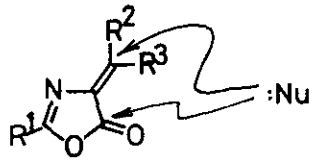
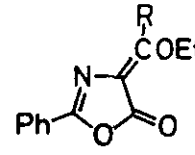
# REACTIONS OF 4-ETHOXYALKYLIDENE-2-PHENYL-2-OXAZOLIN-5-ONES WITH 1,3-BINUCLEOPHILIC HETEROAROMATIC SYSTEMS

Otohiko Tsuge* and Michihiko Noguchi
Research Institute of Industrial Science, Kyushu University 86,
Hakozaki, Higashi-ku, Fukuoka 812, Japan

Abstract — One-pot syntheses of pyrido[1,2-b]pyrimidine and thiazolo[2,3-b]pyrimidine derivatives were achieved by the reactions of 4-ethoxyalkylidene-2-phenyl-2-oxazolin-5-ones with 2-aminopyridines and 2-aminothiazole in refluxing ethanol, respectively. In the reaction of the oxazolinone with 2-aminopyrimidine under similar conditions, however, the expected pyrimido-pyrimidine derivative was not formed, but instead (2-pyrimidylaminomethylene)-oxazolinone and its ethanolysis product were obtained.

Since 4-methylene-2-oxazolin-5-ones have two reactive sites towards nucleophiles, their ring opening reactions are complicated[1]. Among 4-methylene-2-oxazolin-5-ones, however, 4-ethoxymethylene-2-phenyl-2-oxazolin-5-one (1)[1] is not only a useful intermediate for the synthesis of amino acids[2-4], but also an effective reagent reacting with binucleophiles such as diethyl 3-oxoglutarate[4], acetylacetone[5], o-phenylenediamine[6], and o-aminophenol[7], because the ethoxymethylene group of 1 is very reactive towards nucleophiles.




1 R=H
2 R=Me

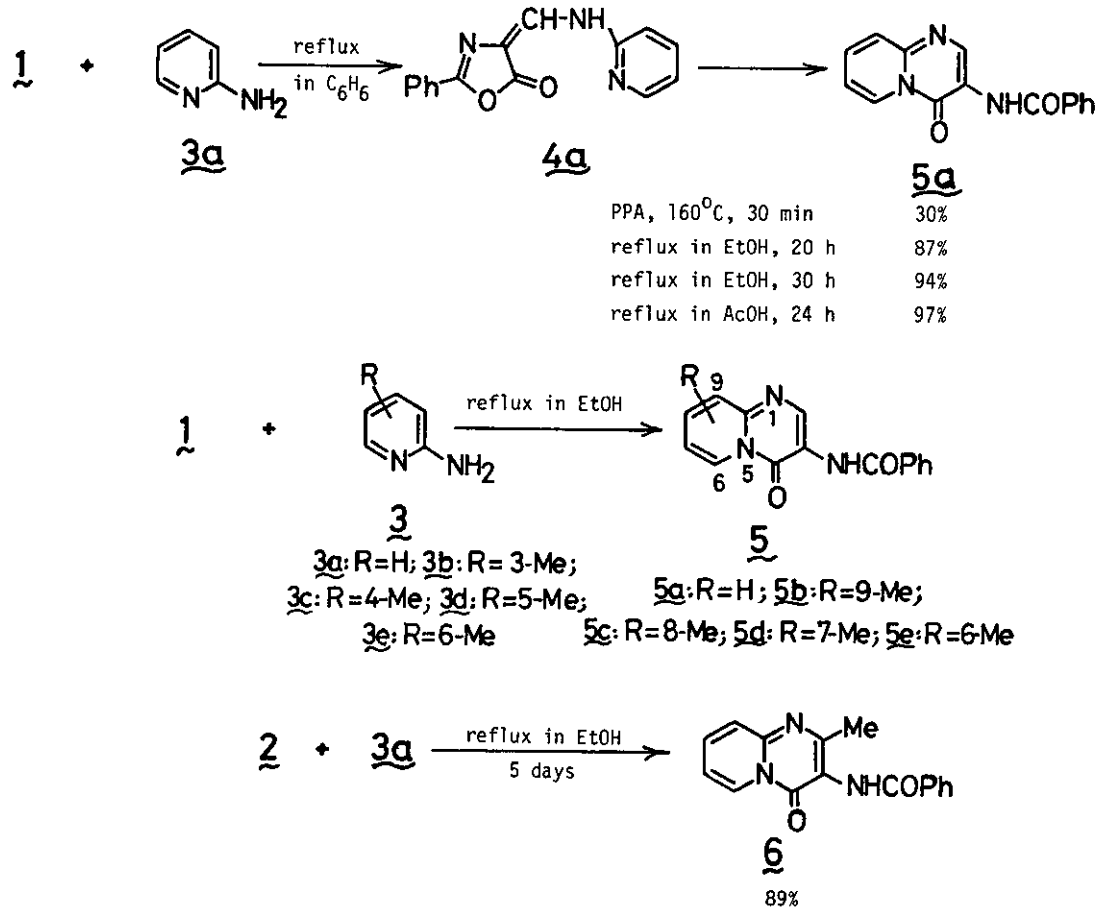
*In this paper we wish to report the reactions of* 1 *and* 4-ethoxyethylidene-2-phenyl-2-oxazolin-5-one (2)[8] with 1,3-binucleophiles such as 2-aminopyridines, 2-aminothiazole, and 2-aminopyrimidine.

Reaction with 2-Aminopyridines. Oxazolinone 1 reacted with an equimolar amount of 2-aminopyridine (3a) *in refluxing benzene for 2 h to give* 2-phenyl-4-(2-pyridylaminomethylene)-2-oxazolin-5-one (4a) in 98% yield [4a: yellow needles; mp 168-169°C; IR (KBr) 3250, 1760, 1730, 1660 $cm^{-1}$; $^1H$ NMR ($CDCl_3$)

δ 8.47 (1H, broad s, =CH), 8.55 (1H, broad, NH, exchanged with $D_2O$); MS m/e 265 ($M^+$)][9].

Next, cyclization of 4a by nucleophilic attack of the nitrogen of pyridine ring at the oxazolinone moiety has been investigated under various conditions; it has been found that upon only heating in ethanol or acetic acid 4a was transformed into the expected 4-oxopyrido[1,2-b]pyrimidine 5a in a good yield[10] (Scheme 1). This fact suggested the possibility of one-pot synthesis of 5a from the reaction of 1 with 3a in refluxing ethanol. In fact, 1 reacted with 3a in refluxing ethanol to afford 5a in a good yield.

Similarly, the reaction of 1 with four methyl-substituted 2-aminopyridines, 3b, 3c, 3d, and 3e, in refluxing ethanol afforded the corresponding pyridopyrimidines, 5b, 5c, 5d, and 5e, in good yields




Scheme 1

except for 5e. The results are shown in Table 1.

Also, oxazolinone 2 reacted with 3a under similar conditions to give the pyridopyrimidine 6.

Structural elucidation of pyridopyrimidines 5 and 6 was accomplished on the basis of spectral data (Table 2).

Table 1. Reactions of Oxazolinone 1 with 2-Aminopyridines 3 in Refluxing Ethanol

| 2-Aminopyridine | Reaction time h | Pyridopyrimidine | Yield, % |
|---|---|---|---|
| 3a (R=H) | 30 | 5a (R=H) | 88 |
| 3b (R=3-Me) | 72 | 5b (R=9-Me) | 89 |
| 3c (R=4-Me) | 30 | 5c (R=8-Me) | 93 |
| 3d (R=5-Me) | 30 | 5d (R=7-Me) | 91 |
| 3e (R=6-Me) | 120 | 5e (R=6-Me) | 38[a] |

[a] 4-(6-Methyl-2-pyridylaminomethylene)-2-phenyl-2-oxazolin-5-one (4e)[11] was isolated in 51% yield.

Table 2. Physical and Spectral Data of Pyridopyrimidines 5 and 6[a]

5a: mp 196.5-198°C[10]; colorless spears; IR 3300, 1665, 1640 $cm^{-1}$; $^1H$ NMR δ 7.17 (1H, ddd, 7-H, J= 6.5, 5.5, 2.5 Hz), 7.40-7.85 (5H, m), 7.90-8.15 (2H, m), 8.85 (1H, broad, NH), 8.98 (1H, pseudo double t, 6-H, J=6.5, 1.0, 1.0 Hz), 9.77 (1H, s, 2-H); MS m/e 265 ($M^+$).[b]

5b: mp 171.5-173°C; colorless needles; IR 3410, 1665 $cm^{-1}$; $^1H$ NMR δ 2.61 (3H, s), 7.04 (1H, pseudo triple d, 7-H), 7.40-7.70 (4H, m), 7.90-8.10 (2H, m), 8.86 (2H, dd and broad, 6-H and NH), 9.72 (1H, s, 2-H); MS m/e 279 ($M^+$).

5c: mp 217.5-218.5°C; pale yellow prisms; IR 3400, 1650 $cm^{-1}$; $^1H$ NMR δ 2.49 (3H, s), 7.00 (1H, dd, 7-H, J=8.0, 1.0 Hz), 7.40-8.20 (6H, m), 8.78 (1H, broad, NH), 8.88 (1H, dd, 6-H, J=8.0, < 1 Hz), 9.69 (1H, s, 2-H); MS m/e 279 ($M^+$).

5d: mp 206-207°C; colorless spears; IR 3300, 1650, 1635 $cm^{-1}$; $^1H$ NMR δ 2.44 (3H, s), 7.30-7.80 (5H, m), 7.90-8.20 (2H, m), 8.86 (1H, broad, NH), 9.71 (1H, s, 2-H); MS m/e 279 ($M^+$).

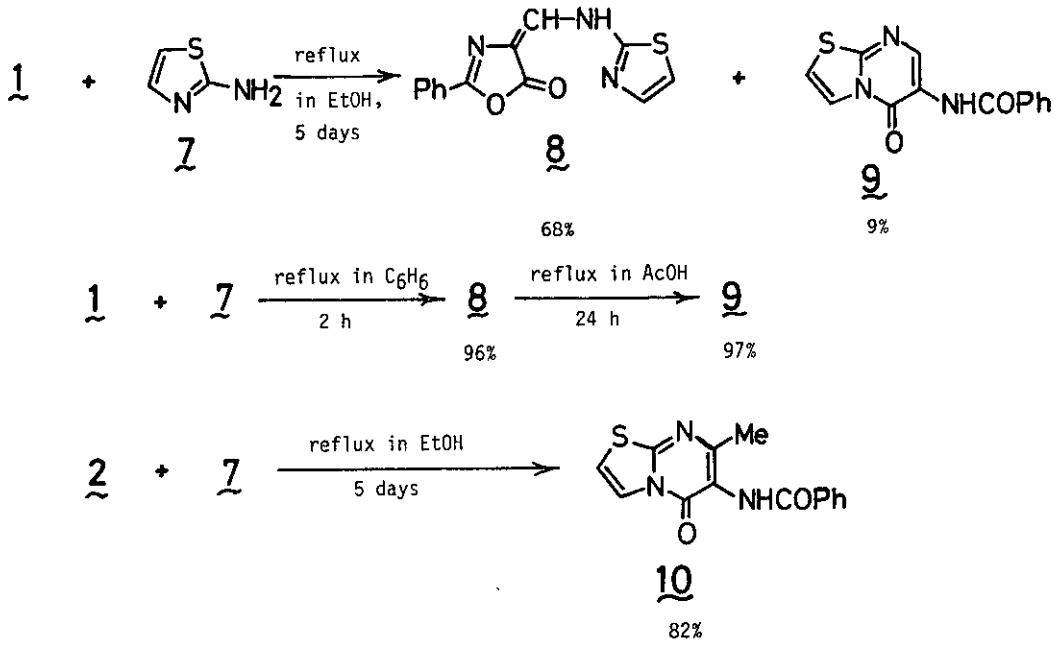
5e: mp 159-160°C; pale yellow needles; IR 3400, 1680, 1650 $cm^{-1}$; $^1H$ NMR δ 3.08 (3H, s), 6.40 (1H, dd, 7-H), 7.20-8.0 (7H, m), 8.70 (1H, broad, NH), 9.43 (1H, s, 2-H); MS m/e 279 ($M^+$).

6: mp 201-202°C; colorless spears; IR 3310, 1675 $cm^{-1}$; $^1H$ NMR δ 2.54 (3H, s), 7.12 (1H, m, 7-H), 7.40-7.60 (3H, m), 7.60-7.80 (2H, m), 7.80-8.0 (2H, m), 8.55 (1H, broad, NH), 8.94 (1H, m, 6-H); MS m/e 279 ($M^+$).

[a] IR and $^1H$ NMR spectra were taken in KBr disks and $CDCl_3$ solutions, respectively.

[b] $^{13}C$ NMR ($CDCl_3$) δ 115.7, 119.4, 126.5, 126.8, 127.2, 128.8, 132.1, 133.1, 133.9, 141.4, 145.9, 153.5, 165.6.

Reaction with 2-Aminothiazole. Next, the reaction of oxazolinones 1 and 2 with 2-aminothiazole (7) has been investigated. Even when oxazolinone 1 was heated with 7 in ethanol for 5 days, the major product was 2-phenyl-4-(2-thiazolylaminomethylene)-2-oxazolin-5-one (8), and the expected thiazolo[2,3-b]pyrimidine 9 was formed in a low yield. When 8 which was easily formed from the reaction of 1 with 7 in refluxing benzene was heated in acetic acid, however, 9 was obtained in a good yield. On the other hand, oxazolinone 2 reacted with 7 in refluxing ethanol to afford the corresponding thiazolopyrimidine 10 (Scheme 2).




Scheme 2

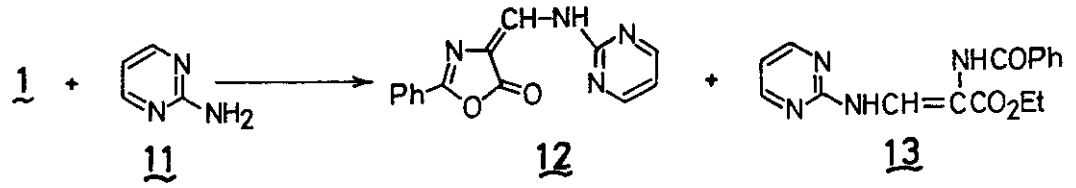
Structural elucidation of 8, 9, and 10 was again accomplished on the basis of spectral data.

8: mp 188-189°C; yellow needles; IR (KBr) 3100-2400, 1775 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 7.20, 7.41 (each 1H, d, J=3.5 Hz), 7.40-7.70 (3H included dd at δ 7,41, m), 7.90-8.10 (2H, m), 7.99 (1H, s, =CH), 11.90 (1H, broad, NH); MS m/e 271 ($M^+$).

9: mp 187-188°C; pale yellow needles; IR (KBr) 3400, 1660 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 7.32 (1H, d, J= 5.0 Hz), 7.40-7.70, 7.90-8.10 (each 3H, m), 8.67 (1H, broad, NH), 9.43 (1H, s); MS m/e 271 ($M^+$).

10: mp 206-208°C; colorless spears; IR (KBr) 3300, 1655 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 2.42 (3H, s), 6.96, 7.86 (each 1H, d, J=5.0 Hz), 7.30-7.60 (3H, m), 6.80-7.10 (4H (1H was exchanged with $D_2O$), m, aromatic protons + NH); MS m/e 285 ($M^+$).

Reaction with 2-Aminopyrimidine. When oxazolinone 1 was heated with 2-aminopyrimidine (11) in ethanol for 30 h, 2-phenyl-4-(2-pyrimidinylaminomethylene)-2-oxazolin-5-one (12) and its ethanolysis product 13 were formed in 38 and 31% yields, respectively. The compound 12 was obtained in 81% yield from the same reaction in refluxing dioxan for 1 h. Even when 12 was heated in acetic acid for 24 h, however, 12 was unchanged.




12: mp 243-244°C (dec); yellow needles; IR (KBr) 3300-2400, 1795 $cm^{-1}$; MS m/e 266 ($M^+$).

13: mp 181-182°C, colorless needles; IR (KBr) 3310, 1695, 1660 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 1.37 (3H, t, J=7.0 Hz), 4.29 (2H, q, J=7.0 Hz), 6.78 (1H, t, J=5.0 Hz), 7.30-7.60 (3H, m), 7.80-8.00 (2H, m), 8.29 (1H, d, =CH, J=11.5 Hz, changed to a singlet when treated with $D_2O$), 8.30 (1H, broad, NH, exchanged with $D_2O$), 8.42 (2H, d, J=5.0 Hz), 9.72 (1H, broad d, NH, J=11.5 Hz, exchanged with $D_2O$); MS m/e 312 ($M^+$).

References and Notes

1. H. T. Clarke, J. R. Johnson, and R. Robinson, 'Chemistry of Penicillin', Princeton Univ. Press, Princeton N. J., 1949.
2. T. Kaneko and Y. Nakayama, Nippon Kagaku Zasshi, 1956, 77, 1054.
3. T. Kaneko, K. Oizumi, and H. Katsura, ibid., 1958, 79, 91.
4. T. Hiraoka and Y. Kishida, Chem. Pharm. Bull., 1968, 16, 1576.
5. H. Behringer and K. Falkenberg, Chem. Ber., 1963, 96, 1428.
6. H. Kristen, K. Peseke, C. Vogel, and H. Braeuniger, Ger. (East) 116,827; Chem. Abstr., 1976, 85, 5704x.
7. H. Kristen, K. Peseke, C. Vogel, and H. Braeuniger, Ger. (East) 117,678; Chem. Abstr., 1976, 85, 177510x.
8. P. Tripathy and M. K. Rout, J. Indian Chem. Soc., 1959, 96, 625; Chem. Abstr., 1962, 56, 17369g.
9. Although compound 4a is recorded in Ref. 1, its synthetic method and physical properties are not described. All new compounds in this paper gave satisfactory elemental analyses.
10. It has been reported that the treatment of 4a with sodium ethoxide in ethanol, followed by decomposition of the formed lemon-yellow compound with water afforded 5a, mp 168°C[1]. However,

5a obtained here melted at 196.5-198°C.

11. 4e: mp 194-195°C; IR (KBr) 3300, 1775, 1730 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 2.50 (3H, s), 6.72 (1H, dd, J=8.0, 1.0 Hz), 6.88 (1H, dd, J=7.5, 1.0 Hz), 7.40-7.70 (4H, m), 7.90-8.10 (2H, m), 8.45 (1H, broad, NH), 8.48 (1H, s, =CH); MS m/e 279 ($M^+$).

Received, 1st September, 1981