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Studies on Pyrimidine Derivatives. XIX.[1] Synthesis of Isoxazolo[5,4-*d*]pyrimidines[2]

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5-Amino-3-phenylisoxazole-4-carbaldehyde (III) was synthesized by the Vilsmeier reaction of 5-amino-3-phenylisoxazole (I) *via* N,N-dimethyl-N′-(4-formyl-3-phenylisoxazol-5-yl)formamidine (II). Reaction of III with formamidine and ethyl imidates afforded 3-phenylisoxazolo[5,4-*d*]pyrimidine (IVa) and its 6-substituted derivatives (IVb—e), respectively.

Condensation of the oxime (V) of III with ethyl orthoformate gave 3-phenylisoxazolo-[5,4-*d*]pyrimidine 5-oxide, which was readily deoxygenated with PCl_3 to give IVa. Treatment of IVa with Grignard reagents gave 4-substituted 4,5-dihydro derivatives (VIIa, b) which were aromatized with $K_3Fe(CN)_6$ to yield 4-substituted isoxazolo[5,4-*d*]pyrimidines (VIIIa, b).

Keywords——Vilsmeier reaction; 5-aminoisoxazoles; ring closure reaction; isoxazolo-[5,4-*d*]pyrimidines; deoxygenation with PCl_3; oxidation with $K_3Fe(CN)_6$

A substantial difference of chemical properties between unfused pyrimidines and isoxazolopyrimidines is to be expected, because isoxazole derivatives usually show the smallest basicity among corresponding 1,2- and 1,3-azoles. In order to investigate the reactivity of isoxazolopyrimidines in comparison with that of monocyclic pyrimidines, it is necessary to develop an efficient procedure for the synthesis of such fused pyrimidines. The present paper deals with the synthesis of 5-amino-3-phenylisoxazole-4-carbaldehyde and its conversion to isoxazolo[5,4-*d*]pyrimidine derivatives.

Treatment of 5-amino-3-phenylisoxazole (I)[4] with phosphoryl chloride and dimethylformamide at 55—60° for 20 hr afforded pale yellow needles, mp 120—121°, in 82% yield. This compound was identified as N,N-dimethyl-N′-(4-formyl-3-phenylisoxazol-5-yl)formamidine (II) on the basis of its elemental analysis ($C_{13}H_{13}N_3O_2$) and nuclear magnetic resonance (NMR) spectrum. In the latter, signals due to an aldehyde and an azomethine, as well as two N-methyl groups were observed, and the signal (5.40 ppm) due to the proton at the 4-position of I was absent. Removal of the dimethylaminomethylene group from II was successfully achieved by hydrolysis with 6N hydrochloric acid at room temperature, to afford 5-amino-3-phenylisoxazole-4-carbaldehyde (III) in almost quantitative yield. Vilsmeier reaction of 5-amino-3-methylisoxazole, however, failed to give the corresponding formyl derivative.

Ring closure reactions of III, to afford isoxazolo[5,4-*d*]pyrimidines, were then investigated. When III was heated with two mole equivalents of formamidine acetate in ethanol in the presence of sodium methoxide, colorless needles, mp 132—133°, were obtained in 62% yield. Elemental analysis ($C_{11}H_7N_3O$) and the NMR spectrum, in which no signals were observed other than those of aromatic ring protons, established the structure of this product as 3-phenyl-

1) Part XVIII: H. Yamanaka, S. Ogawa, and S. Konno, *Chem. Pharm. Bull.*, **28**, 1526 (1980).
2) A part of this work was reported as a communication [H. Yamanaka, T. Sakamoto, and A. Shiozawa, *Heterocycles*, **7**, 51 (1977)].
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isoxazolo[5,4-*d*]pyrimidine (IVa). It is well known[5] that condensation of *o*-aminobenzaldehyde oxime with ethyl orthoformate affords quinazoline 3-oxide. Using the same procedure, 5-amino-3-phenylisoxazole-4-carbaldehyde oxime (V), prepared from III in the usual manner, was heated with excess ethyl orthoformate without any solvent to give yellow leaflets, mp 223—224°, $C_{11}H_7N_3O_2$, in 45% yield. Treatment of this product with phosphorus trichloride gave rise to a deoxygenated compound which was identical with IVa. Evidence for the assignment of the structure 3-phenylisoxazolo[5,4-*d*]pyrimidine 5-oxide (VI) to the condensation product, in addition to the above results, was obtained from the infrared (IR) spectrum (KBr) in which an absorption band at 1246 cm^{-1} appeared.

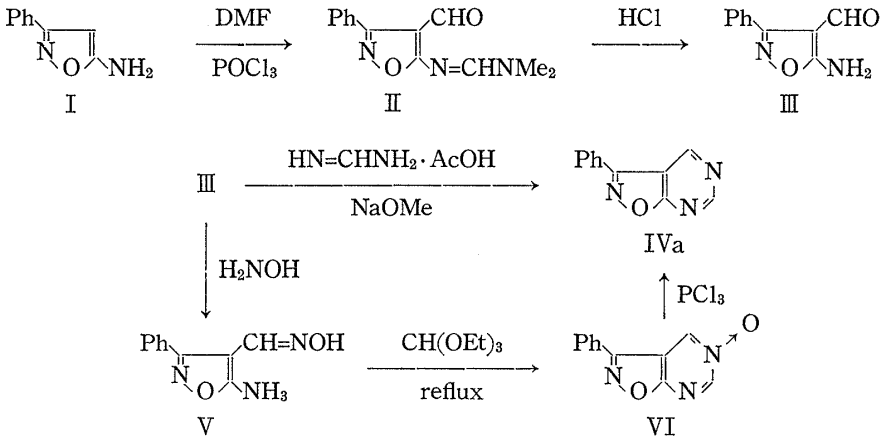
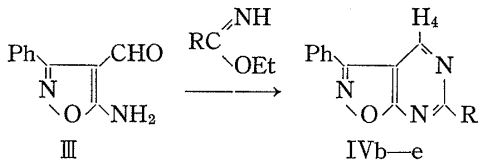


Chart 1

In place of formamidine, various imidates could be employed in the condensation. Namely, ethyl acetimidate, propionimidate, phenylacetimidate, and benzimidate reacted with III to give 6-methyl-3-phenyl- (IVb), 6-ethyl-3-phenyl- (IVc), 6-benzyl-3-phenyl- (IVd), and 3,6-diphenyl-isoxazolo[5,4-*d*]pyrimidine (IVe), respectively.

Table I. Reaction of III with Ethyl Imidates

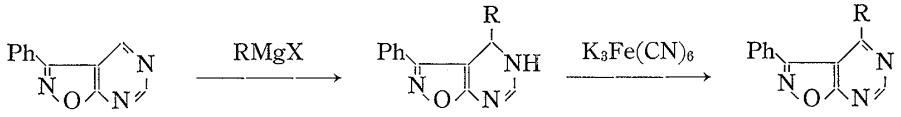


No.	R	Yield (%)	mp (°C)	H_4	NMR		
					Phenyl protons	Other protons	(Solvent)
IVb	Me	82	147—148	9.80	7.55—7.86(3H, m) 7.86—8.15(2H, m)	3.23(3H, s)	(CF_3COOH)
IVc	Et	52	84 — 86	9.30	7.40—7.74(3H, m) 7.76—8.15(2H, m)	1.48(3H, t, J=7.8 Hz) 3.16(2H, q, J=7.8 Hz)	($CDCl_3$)
IVd	$PhCH_2$	75	130.0—131.5	9.30	7.05—7.70(8H, m) 7.70—8.30(2H, m)	4.45(2H, s)	($CDCl_3$)
IVe	Ph	46	162—163	9.86	7.46—8.12(6H, m) 8.30—8.60(4H, m)		(CF_3COOH)

Compounds containing a substituent at the 4-position were prepared from IVa by treatment with Grignard reagents as follows. Treatment of IVa with methylmagnesium iodide

5) P.S. Burns, *J. Prakt. Chem.*, [2], **47**, 124 (1893).

followed by neutralization with NH_4Cl gave colorless needles, mp 154.5—155.5°, in 87% yield. Based on the spectral data, the 4-methyl-4,5-dihydro structure (VIIa) was assigned to this product. Thus, in the NMR spectrum ($CDCl_3$), a doublet due to a secondary methyl group was observed at 1.35 ppm (J=6.2 Hz), together with a quartet due to a methine group (5.31 ppm, J=6.2 Hz). In the IR spectrum (KBr), an absorption band due to NH appeared at 3200 cm^{-1}. Potassium ferricyanide oxidation of VIIa in an alkaline medium afforded the corresponding aromatic compound, 4-methyl-3-phenylisoxazolo[5,4-*d*]pyrimidine (VIIIa). Although this compound and IVb are not identical, a great similarity is apparent in their NMR spectra. Similar results were obtained in the reaction of IVa with phenylmagnesium bromide, as shown in Chart 2.



IVa R=Me, X=I R=Ph, X=Br VIIa VIIb VIIIa VIIIb

Chart 2

Although our experiments have been carried out only with the 3-phenyl derivatives so far, a combination of the ring closure reactions of III and the Grignard reactions of IVa may provide a simple preparative route to 4,6-dialkyl(or aryl)isoxazolo[5,4-*d*]pyrimidine derivatives.

Experimental

All melting points are uncorrected. IR spectra were measured with a JASCO IRA-1 spectrometer. NMR spectra were taken at 60 MHz with a Hitachi-Perkin-Elmer R-20 spectrometer. Chemical shifts are expressed as ppm downfield from tetramethylsilane (TMS) as an internal standard. The following abbreviations are used: s=singlet, d=doublet, t=triplet, q=quartet, and m=multiplet.

N,N-Dimethyl-N′-(4-formyl-3-phenylisoxazol-5-yl)formamidine (II)——5-Amino-3-phenylisoxazole (4.80 g, 0.03 mol) was added with stirring to a mixture of DMF (15.36 g, 0.21 mol) and $POCl_3$ (13.80 g, 0.09 mol) at room temperature. The mixture was heated at 55—60° with stirring for 20 hr and was then added to 3 N Na_2CO_3 under ice-cooling and stirring. The resulting precipitate was filtered, dissolved in C_6H_6 and the solution was dried over Na_2SO_4. The crude product obtained by concentration was recrystallized from C_6H_6 to give pale yellow needles, mp 120—121°. Yield 5.96 g (82%). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1675, 1635. NMR ($CDCl_3$) ppm: 3.11 (6H, s), 7.25—7.57 (3H, m), 7.65—7.93 (2H, m), 8.57 (1H, s), 9.82 (1H, s). *Anal.* Calcd for $C_{13}H_{13}N_3O_2$: C, 64.18; H, 5.39; N, 17.28. Found: C, 64.22; H, 5.41; N, 17.40.

5-Amino-3-phenylisoxazole-4-carbaldehyde (III)——A 6 N HCl solution (25 ml) of II (3.03 g, 0.0125 mol) was stirred at room temperature for 20 hr. The resulting yellow precipitate was filtered, washed with H_2O, and dried. The crude product was recrystallized from ether to give pale yellow needles, mp 125—126°. Yield 2.25 g (96%). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3550, 3360, 1668. NMR ($CDCl_3$) ppm: 6.60—7.32 (2H, broad), 7.32—8.00 (5H, m), 9.66 (1H, s). *Anal.* Calcd for $C_{10}H_8N_2O_2$: C, 63.82; H, 4.29; N, 14.89. Found: C, 63.72; H, 4.32; N, 15.21.

3-Phenylisoxazolo[5,4-*d*]pyrimidine (IVa)——A mixture of III (1.88 g, 0.01 mol), formamidine acetate (2.08 g, 0.02 mol), NaOMe (1.08 g, 0.02 mol), and abs. EtOH (60 ml) was refluxed for 7 hr. The reaction mixture was evaporated to dryness under reduced pressure, the residue was dissolved in H_2O, and the aqueous solution was extracted with ether. The crude product obtained on concentration of the extract was purified by Al_2O_3 column chromatography using ether as an eluant. Recrystallization from ether gave colorless needles, mp 132—133°. Yield 1.18 g (62%). NMR ($CDCl_3$) ppm: 7.36—7.73 (3H, m), 7.73—8.13 (2H, m), 9.16 (1H, s), 9.40 (1H, s). *Anal.* Calcd for $C_{11}H_7N_3O$: C, 67.01; H, 3.55; N, 21.32. Found: C, 67.22; H, 3.51; N, 21.24.

5-Amino-3-phenylisoxazole-4-carbaldehyde Oxime (V)——An aqueous solution (50 ml) of $H_2NOH \cdot HCl$ (3.5 g, 0.05 mol) and AcONa (4.1 g, 0.05 mol) was added to an EtOH solution(50 ml) of III (4.7 g, 0.025 mol). The mixture was heated at 80° for 3 hr and worked-up in the usual way. The crude product was recrystallized from acetone to give colorless needles, mp 188—189°. Yield 4.63 g (91%). IR ν_{max}^{KBr} cm^{-1}: 3435, 3120, 1645. NMR (CF_3COOH) ppm: 7.40—7.75 (5H, m), 7.77 (1H, s). *Anal.* Calcd for $C_{10}H_9N_3O_2$: C, 59.10; H, 4.46; N, 20.68. Found: C, 59.08; H, 4.59; N, 20.75.

3-Phenylisoxazolo[5,4-*d*]pyrimidine 5-Oxide (VI)——A mixture of V (2 g, 0.01 mol) and ethyl orthoformate (10 ml) was refluxed for 3 hr. The resulting EtOH and excess ethyl orthoformate were removed under reduced pressure and the precipitate was filtered. This crude product was recrystallized from MeOH as yellow leaflets, mp 223—224°. Yield 0.95 g (45%). IR ν_{max}^{KBr} cm^{-1}: 1246. NMR (CF_3COOH) ppm: 7.55—7.85 (3H, m), 7.85—8.12 (2H, m), 9.51 (1H, d, $J=1.5$ Hz), 9.92 (1H, d, $J=1.5$ Hz). *Anal.* Calcd for $C_{11}H_7N_3O_2$: C, 61.97; H, 3.31; N, 19.71. Found: C, 62.07; H, 3.49; N, 19.80.

Deoxygenation of VI with PCl_3——Phosphorus trichloride (1.37 g, 0.01 mol) was added to a suspension of VI (1.065 g, 0.005 mol) in $CHCl_3$ (40 ml) under ice-cooling and stirring. The mixture was refluxed for 30 min and poured into ice-water. After making the mixture alkaline with K_2CO_3, it was extracted with $CHCl_3$. The crude product obtained on concentration of the extract was recrystallized from $CHCl_3$–C_6H_6 to give colorless needles (IVa), mp 131—132°. Yield 0.72 g (73%).

6-Methyl-3-phenylisoxazolo[5,4-*d*]pyrimidine (IVb)——A mixture of III (1.88 g, 0.01 mol) and ethyl acetimidate (2.6 g, 0.03 mol) was heated at 50° overnight. After removal of excess ethyl acetimidate under reduced pressure, the residue was recrystallized from C_6H_6 to give colorless prisms. Yield 1.72 g. *Anal.* Calcd for $C_{12}H_9N_3O$: C, 68.23; H, 4.30; N, 19.90. Found: C, 68.40; H, 4.40; N, 19.99.

6-Ethyl-3-phenylisoxazolo[5,4-*d*]pyrimidine (IVc)——A mixture of III (1.88 g, 0.01 mol) and ethyl propionimidate (3.03 g, 0.03 mol) was heated at 40—50° for 48 hr. After removal of excess ethyl propionimidate under reduced pressure, the residue was recrystallized from ether to give colorless prisms. Yield 1.18 g. *Anal.* Calcd for $C_{13}H_{11}N_3O$: C, 69.32; H, 4.92; N, 18.66. Found: C, 69.43; H, 4.80; N, 18.88.

6-Benzyl-3-phenylisoxazolo[5,4-*d*]pyrimidine (IVd)——A mixture of III (1.88 g, 0.01 mol) and ethyl phenylacetimidate (4.89 g, 0.03 mol) was heated at 40—50° for 35 hr. The resulting solid was recrystallized from ether to give colorless plates. Yield 2.14 g. *Anal.* Calcd for $C_{18}H_{13}N_3O$: C, 75.24; H, 4.56; N, 14.63. Found: C, 75.43; H, 4.50; N, 14.68.

3,6-Diphenylisozxazolo[5,4-*d*]pyrimidine (IVe)——A mixture of III (1.88 g, 0.01 mol) and ethyl benzimidate (3.5 g, 0.0235 mol) was heated at 60° overnight and then at 120° for 2 hr. The resulting solid was purified by Al_2O_3 column chromatography using petr. benzin and C_6H_6 as eluants. The C_6H_6 eluate gave colorless needles which were recrystallized from C_6H_6. Yield 1.26 g. *Anal.* Calcd for $C_{17}H_{11}N_3O$: C, 74.71; H, 4.06; N, 15.38. Found: C, 74.67; H, 4.02; N, 15.40.

4-Methyl-3-phenyl-4,5-dihydroisoxazolo[5,4-*d*]pyrimidine (VIIa)——An anhydrous THF (60 ml) solution of IVa (3.94 g, 0.02 mol) was added to an anhydrous ether (70 ml) solution of methylmagnesium iodide [prepared from magnesium (1.22 g, 0.05 g atom) and methyl iodide (7.1 g, 0.05 mol)] and the mixture was refluxed for 2 hr. After quenching with sat. aq. NH_4Cl, the mixture was extracted with $CHCl_3$. The crude product obtained by concentration of the extract was recrystallized from $CHCl_3$–hexane to give colorless needles, mp 154.5—155.5°. Yield 3.7 g (87%). IR ν_{max}^{KBr} cm^{-1}: 3200, 1625. NMR ($CDCl_3$) ppm: 1.35 (3H, d, $J=6.2$ Hz), 5.31 (1H, q, $J=6.2$ Hz), 7.25 (1H, s), 6.98—7.73 (6H, m). *Anal.* Calcd for $C_{12}H_{11}N_3O$: C, 67.59; H, 5.20; N, 19.71. Found: C, 67.52; H, 5.16; N, 19.68.

4-Methyl-3-phenylisoxazolo[5,4-*d*]pyrimidine (VIIIa)——An aq. solution (60 ml) of $K_3Fe(CN)_6$ (19.8 g, 0.06 mol) was added with stirring to a suspension of VIIa (2.13 g, 0.01 mol) in an aq. solution (80 ml) of KOH (4.5 g, 0.08 mol) at room temperature. After stirring for 1hr at room temperature, the mixture was extracted with $CHCl_3$ and the crude product obtained by concentration was purified by Al_2O_3 column chromatography using hexane and ether as eluants. The ether eluate gave colorless prisms which were recrystallized from ether, mp 84—85°. Yield 0.76 g (36%). NMR ($CDCl_3$) ppm: 2.68 (3H, s), 7.62 (5H, s), 9.03 (1H, s). *Anal.* Calcd for $C_{12}H_9N_3O$: C, 68.23; H, 4.30; N, 19.90. Found: C, 68.37; H, 4.37; N, 19.97.

3,4-Diphenyl-4,5-dihydroisoxazolo[5,4-*d*]pyrimidine (VIIb)——An anhydrous THF (20 ml) solution of IVa (1 g, 0.005 mol) was added to an anhydrous ether (20 ml) solution of phenylmagnesium bromide [prepared from magnesium (0.62 g, 0.0255 g atom) and bromobenzene (4 g, 0.0255 mol)] and the mixture was refluxed for 3.5 hr. After quenching with sat. aq. NH_4Cl, the mixture was extracted with $CHCl_3$. The crude product obtained on concentration of the extract was recrystallized from $CHCl_3$–C_6H_6 to give colorless needles, mp 200—201°. Yield 1.20 g (86%). IR ν_{max}^{KBr} cm^{-1}: 3180, 1632. NMR (DMSO-d_6) ppm: 6.32 (1H, s), 7.06—7.70 (11H, m), 8.78—9.17 (1H, broad). *Anal.* Calcd for $C_{17}H_{13}N_3O$: C, 74.16; H, 4.76; N, 15.26. Found: C, 74.22; H, 4.86; N, 14.97.

3,4-Diphenylisoxazolo[5,4-*d*]pyrimidine (VIIIb)——An aq. solution (60 ml) of $K_3Fe(CN)_6$ (19.8 g, 0.06 mol) was added with stirring to a suspension of VIIb (2.75 g, 0.01 mol) in an aq. solution (80 ml) of KOH (4.5 g, 0.08 mol) at room temperature. After stirring for 2 hr at room temperature, the mixture was extracted with $CHCl_3$. The crude product obtained on concentration of the extract was recrystallized from ether–hexane to give colorless prisms, mp 108—109°. Yield 2.48 g (91%). NMR ($CDCl_3$) ppm: 7.10—7.75 (10H, m), 9.31 (1H, s). *Anal.* Calcd for $C_{17}H_{11}N_3O$: C, 74.71; H, 4.06; N, 15.38. Found: C, 74.98; H, 4.07; N, 15.40.

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