Notes

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Synthesis of Furan Derivatives. LXXXV.[1] Condensation of Heteroaromatic Aldehydes with Tosylmethyl Isocyanide[2]

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Reaction of tosylmethyl isocyanide (**2**) with heteroaromatic aldehydes, *i.e.*, 2-furaldehyde (**1a**), 5-nitro-2-furaldehyde (**1b**) and 5-methoxycarbonyl-2-furaldehyde (**1c**); thiophene-2-carbaldehyde (**1d**) and 5-nitrothiophene-2-carbaldehyde (**1e**); 1-methylpyrrole-2-carbaldehyde (**1f**); 2-, 3- and 4-pyridinemonocarbaldehyde (**1g**, **1h** and **1i**) in the presence of an equimolar amount of potassium carbonate in refluxing methanol afforded the corresponding 5-substituted oxazoles (**3a**—**i**). However, a similar treatment of pyrrole-2-carbaldehyde (**4**) with **2** gave 3-tosylpyrrolo[1, 2-*c*]pyrimidine (**6**) instead; a mechanism for this reaction is proposed.

Keywords——heteroaromatic aldehydes; tosylmethyl isocyanide; 5-substituted oxazoles; pyrrolo[1,2-*c*]pyrimidines; dehydration; N-hydrogen in pyrrole ring; isocyano-carbon

A.M. van Leusen and his co-workers[4] have indicated that tosylmethyl isocyanide[5] (TosMIC (**2**)) is a useful synthon to lead to five-membered heterocyclic compounds (oxazoles,[6a] imidazoles,[5,6b] pyrroles,[6b,6c] 1,2,4-triazoles,[6d] and 1,3-thiazoles,[6e,f]) with unsaturated substrates such as aldehydes, imines, Michael acceptors, diazonium salts, carboxymethyl dithioates or carbon disulfide in base-induced reactions.[6b]

In this communication, we wish to report the reaction of heteroaromatic aldehydes (**1a**—**i**) with TosMIC (**2**) in the presence of an equimolar amount of potassium carbonate in refluxing methanol in order to obtain the corresponding 5-substituted oxazoles (**3a**—**i**), respectively (Chart 1).

First of all, the reaction of 2-furaldehyde (**1a**) or thiophene-2-carbaldehyde (**1d**) with **2** readily gave the furyl- and thienyl-substituted oxazoles (**3a** and **3d**), respectively. Secondly, the corresponding nitro-substituted oxazoles (**3b** and **3e**) also were prepared successfully from **2** and 5-nitro-2-furaldehyde (**1b**) or 5-nitrothiophene-2-carbaldehyde (**1e**), although these aldehydes are relatively susceptible to potassium carbonate as a base.

1) Part LXXXIV: H. Saikachi and T. Kitagawa, *Chem. Pharm. Bull.* (Tokyo), **26**, 1054 (1978).
2) Some parts of this work presented at the 98th Annual Meeting of Pharmaceutical Society of Japan at Okayama, April 1978.
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4) Leading references: *a*) O.H. Oldenziel, D.van Leusen, and A.M. van Leusen, *J. Org. Chem.*, **42**, 3114 (1977); *b*) O. Possel and A.M. van Leusen, *Tetrahedron Lett.*, **1977**, 4229; *c*) D. van Leusen and A.M. van Leusen, *ibid.*, **1977**, 4233; *d*) J. Wildeman, P.C. Borgen, H. Pluim, P.H.F.M. Rouwette, and A.M. van Leusen, *ibid.*, **1978**, 2213; see further ref. 5 and 6.
5) A.M. van Leusen, J. Wildeman, and O.H. Oldenziel, *J. Org. Chem.*, **42**, 1153 (1977).
6) *a*) A.M. van Leusen, B.E. Hoogenboom, and H. Siderius, *Tetrahedron Lett.*, **1972**, 2369; *b*) O. Possel and A.M. van Leusen, *Heterocycles*, **7**, 77 (1977); *c*) A.M. van Leusen, H. Siderius, B.E. Hoogenboom, and D.van Leusen, *Tetrahedron Lett.*, **1972**, 5337; *d*) A.M. van Lsusen, B.E. Hoogenboom, and H.A. Houwing, *J. Org. Chem.*, **41**, 711 (1976); *e*) O.H. Oldenziel and A.M. van Leusen, *Tetrahedron Lett.*, **1972**, 2777; *f*) A.M. van Leusen and J. Wildeman, *Synthesis*, **1977**, 501.

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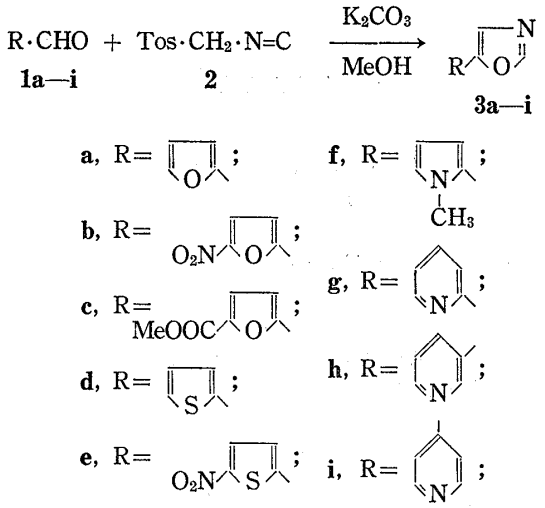
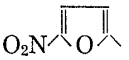
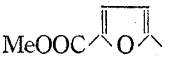
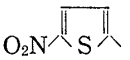
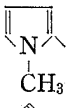


Chart 1

In a similar manner, the reaction of each 2-, 3- and 4-pyridinemonocarbaldehyde (**1g**, **1h** and **1i**) with **2** gave the corresponding oxazoles (**3g**, **3h** and **3i**) in good yields (Tables I and II).

However, in the course of these studies, it was found that the reaction of pyrrole-2-carbaldehyde (**4**) with **2** under similar conditions led unexpectedly to the formation of 3-tosylpyrrolo[1,2-*c*]pyrimidine (**6**) (mp 208—209°) in *ca.* 20% yield (Chart 2). Recently an analogous formation of pyrrolo[1, 2-*c*]pyrimidine-3-carboxylic acid esters by condensation of pyrrole-2-carbaldehydes with methyl isocyanoacetate was reported.[7] The structural assignment of **6** was corroborated on the basis of elemental analyses, infrared (IR), nuclear magnetic resonance (NMR) and mass spectral (MS) data. For reference, in order to establish the essential role of a hydrogen at the pyrrole-nitrogen, the reaction of 1-methylpyrrole-2-carbaldehyde (**1f**) with **2** in a similar manner resulted in 5-(1-methyl-2-pyrroyl)oxazole (**3f**) in 47% yield as shown in Chart 1. It thus appears that a N-hydrogen in pyrrole-2-carbaldehyde (**4**) is

Table I. 5-Substituted Oxazoles

Compd. No. 3a—i	R	bp[c]/mmHg (mp) [°C]	Yield[d] (%)	Recrystn. solvent[e]	Reaction time (hr)	Formula	Analysis (%) Found (Calcd.) C	H	N
a		61—63/0.3[a]	81.5	—	2	$C_7H_5NO_2$	62.10 (62.22)	3.65 (3.73)	10.26 (10.37)
b		(117—118)[b]	83.3	B	0.5	$C_7H_4N_2O_4$	46.71 (46.67)	1.95 (2.24)	15.31 (15.55)
c		(157—158)[b]	88.1	B	3	$C_9H_7NO_4$	55.97 (55.96)	3.35 (3.65)	7.29 (7.25)
d		81—84/0.3[a]	79.5	—	2	C_7H_5NOS	55.39 (55.63)	3.38 (3.34)	8.97 (9.27)
e		(112—113)[b]	68.4	B	1	$C_7H_4N_2O_3S$	43.07 (42.87)	2.01 (2.06)	14.09 (14.29)
f		82—84/0.15[a]	47.3	—	3	$C_8H_8N_2O$	64.91 (64.85)	5.23 (5.44)	19.07 (18.91)
g		95—98/0.15[a]	82.0	—	2	$C_8H_6N_2O$	65.82 (65.75)	4.06 (4.14)	19.14 (19.17)
h		(64—65)[b]	80.1	C	3	$C_8H_6N_2O$	65.74 (65.75)	4.00 (4.14)	18.79 (19.17)
i		(128—129)[b]	66.6	C	3	$C_8H_6N_2O$	65.77 (65.75)	3.99 (4.14)	19.31 (19.17)

a) Pale yellow oil. *b*) Pale yellow needles. *c*) The temperature in oil-bath. *d*) Calcd. on the basis of the aldehyde.
e) B=benzene, C=cyclohexane-petroleum ether (4:1).

7) M. Suzuki and N. Yoneda, *J. Org. Chem.*, **41**, 1482 (1976).

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TABLE II. UV and NMR Spectra of 5-Substituted Oxazoles

Compound No. 3a—i	UV λ_{max}^{EtOH} nm (log ε)	NMR ($CDCl_3$) δ[a] H-2	H-4	Aromatic substituent's and the other signals
a	275 (4.03)	7.84 (s)	7.24 (s)	6.46 (1H, q, H-4′), 6.65 (1H, q, H-5′), 7.46 (1H, q, H-3′)
b	238 (4.05) 351 (4.16)	7.98 (s)	7.60 (s)	8.86 and 7.42 (each H, d, d, J=4 Hz, H-3′ and H-4′)
c	297 (4.36)	7.92 (s)	7.54 (s)	7.04 and 7.40 (each H, d, d, J=4 Hz, H-3′ and H-4′), 3.86 (3H, s, $-CH_3$)
d	286 (4.16)	7.84 (s)	7.20 (s)	7.08 (1H, q, H-4′), 7.30 (1H, q, H-5′), 7.36 (1H, q, H-3′)
e	250 (3.88)	7.96 (s)	7.48 (s)	7.20 and 7.98 (each H, d, d, J=4 Hz, H-3′ and H-4′)
f	282 (4.12)	7.86 (s)	7.06 (s)	6.20 (1H, q, J=2 Hz, H-4′), 6.50 (1H, q, J=2 Hz, H-3′), 6.72 (1H, q, J=2 Hz, H-5′), 7.70 (3H, s, $-N(-CH_3)$)
g	256 (4.14) 289 (4.00)	7.96 (s)	7.70 (s)	7.12—8.66 (4H, m, H-3′, H-4′, H-5′ and H-6′)
h	261 (4.88)	8.00 (s)	7.46 (s)	7.26—8.96 (4H, m, H-2′, H-4′, H-5′ and H-6′)
i	271 (4.60)	8.00 (s)	7.56 (s)	8.68 and 7.50 (each 2H, q, q, H-2′, H-3′, H-5′ and H-6′)

a) ppm from tetramethylsilane as an internal reference; s, singlet, d, doublet, q, quartet and J in Hz.

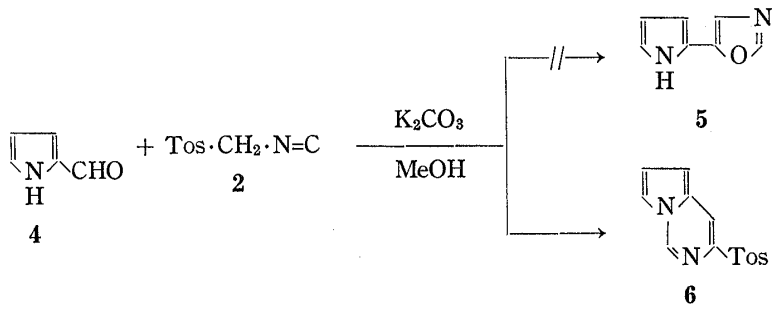
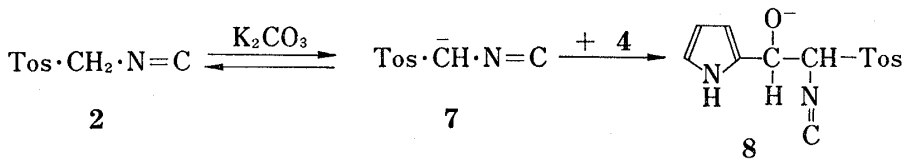


Chart 2



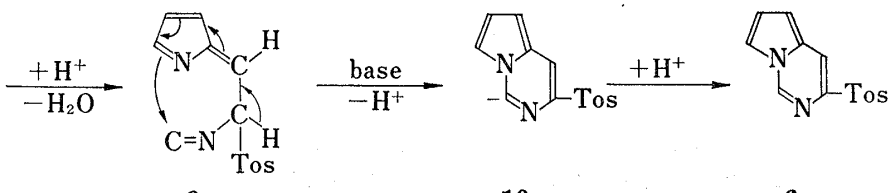


Chart 3

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prerequisite for cyclization to a pyrimidine ring rather than to an oxazole. With this mind we suggest the following rationale for the reaction of **4** with **2** (Chart 3). Finally, the crucial step seems to be dehydration of the primarily formed adduct (**8**) to give **9**, before ring closure to an oxazole can take place. Cyclization of **9** then occurs by nucleophilic attack of the pyrrole-nitrogen on the isocyano-carbon as indicated.

Experimental[8)]

Preparation of 5-Substituted Oxazoles (3a—i)——General Procedure: To a methanol solution (30 ml) of each aldehyde (**1a—i**) (0.01 mol) and **2** (1.95 g, 0.01 mol) was added anhydrous potassium carbonate (1.38 g, 0.01 mol) with stirring. The resulting mixture was gently refluxed on a water-bath for the time indicated in Table I, and then the solvent was evaporated under reduced pressure. The resulting residue was poured into ice-water, and extracted with ether. The extract was washed with 2% hydrochloric acid, and water, and then dried over anhydrous sodium sulfate. After the organic solvent was evaporated, the residue was distilled, or crystallized from the solvents listed in Table I. The yield, bp (or mp), the values of the elementary analyses, UV λ_{max}^{EtOH} nm (log ε) and NMR ($CDCl_3$) δ of **3a—i** are also given in the Tables I and II.

3-Tosylpyrrolo[1, 2-c]pyrimidine (6)——To a methanol solution (30 ml) of pyrrole-2-carbaldehyde (**4**) (0.96 g, 0.01 mol) and **2** (1.95 g, 0.01 mol) was added anhydrous potassium carbonate (1.38 g, 0.01 mol) with stirring. The resulting mixture was gently refluxed on a water-bath for 2 hr, and then the solvent was evaporated under reduced pressure. The resulting residue was poured into ice-water, and extracted with ethyl acetate. The extract was washed with water, and dried over anhydrous sodium sulfate, and then the organic solvent was evaporated under reduced pressure. The crystalline mass obtained was recrystallized from a mixture of ethanol and cyclohexane (4: 1); pale yellow needles, yield, 0.5 g (20%), mp 208—209.° Anal. Calcd. for $C_{14}H_{12}N_2O_2S$: C, 61.76; H, 4.44; N, 10.29. Found: C, 61.54; H, 4.23; N, 10.18. IR ν_{max}^{KBr} cm^{-1}: 1320 and 1140 (SO_2). UV λ_{max}^{EtOH} nm (log ε): 228 (4.30), 253 (4.21) and 298 (3.89). NMR (DMSO-d_6) δ: 9.20 (1H, d, J=2 Hz, H-1), 8.38 (1H, d, J=2 Hz, H-4), 7.90 (1H, m, H-7), 7.44 and 7.88 (each 2H, d, d, each J=8 Hz, phenyl-H), 2.36 (3H, s, $-CH_3$) and 7.10 (1H, m, H-6). MS (*m/e*): 272 (M^+).

8) All melting points are uncorrected. IR spectra were measured on a Hitachi 215 Infrared Spectrophotometer. The ultraviolet (UV) spectra were measured on a Hitachi 323 Recording Spectrophotometer. NMR spectra were measured on a Nihondenshi Model C-100H NMR Spectrometer (100 MHz, TMS as an internal reference). MS was measured on a Hitachi Mass Spectrometer, Model RMU-6MG.

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