PYRAZOLOPYRIDINES. 1. FORMYLATION AND ACYLATION OF PYRAZOLO[1,5-a]PYRIDINES

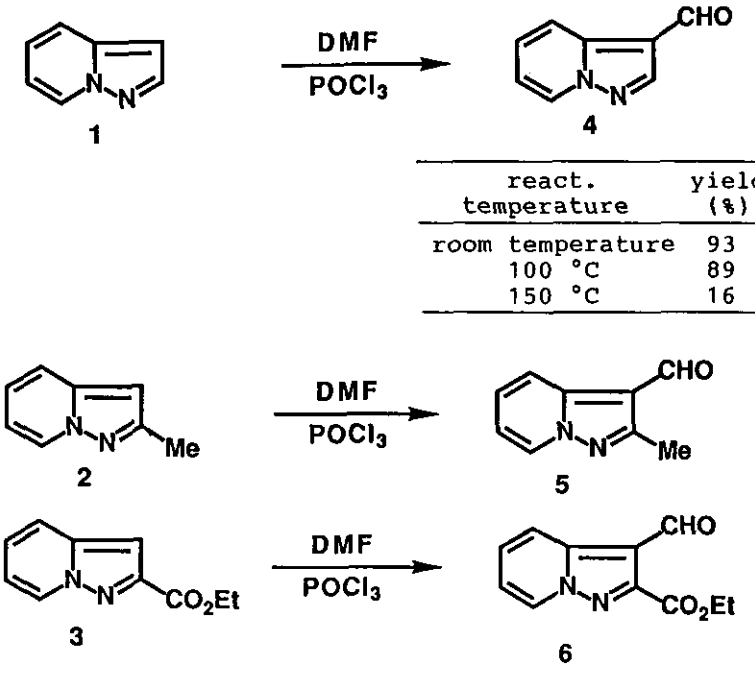
Ken-ichi Tanji*, Takehiko Sasahara, Junko Suzuki, and Takeo Higashino

School of Pharmaceutical Sciences, University of Shizuoka, 52-1 Yada, Shizuoka 422, Japan

Abstract——In the treatment of pyrazolo[1,5-a]pyridines with dimethylformamide and phosphorus oxychloride, Vilsmeier-Haack formylation proceeded at the 3-position, giving 3-pyrazolo[1,5-a]pyridinecarboxaldehydes. Reaction of the pyrazolo[1,5-a]pyridine with acyl halide gave 3-acylpyrazolo[1,5-a]pyridines. Conversion of the formyl group into the alkenyl group was achieved easily by Wittig reaction.

It is well known that Vilsmeier-Haack formylation[1] and Friedel-Crafts acylation[2] are useful methods for introduction of carbon chains into π-excess heteroarenes. However, only a few studies[3] have been reported on introducing electrophiles into pyrazolo[1,5-a]pyridine (the pyrazolopyridine) ring. We investigated Vilsmeier-Haack formylation and Friedel-Crafts acylation of the pyrazolopyridines (1-3) to introduce formyl and acyl groups. In the present paper, we describe the results obtained from the above reactions. First, the pyrazolopyridines (1-3) were subjected to the reaction with di-

Dedicated to Prof. Edward C. Taylor on the occasion of his 70th birthday.



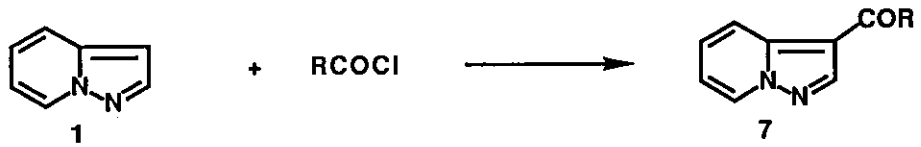
react. temperature	yield (%)
room temperature	93
100 °C	89
150 °C	16

Scheme 1

methylformamide (DMF) and phosphorus oxychloride ($POCl_3$) by means of Vilsmeier-Haack formylation. When a mixture of 1, DMF, and $POCl_3$ was stirred at room temperature for 1 h, 3-pyrazolo[1,5-a]pyridinecarboxaldehyde (4) was obtained in 93 % yield, selectively. When the same reaction was carried out at 150°C, the yield of 4 was decreased by polymerization and so this reaction prefers the rather low reaction temperature. Moreover, no significant effects of the substituent at the 2-position on Vilsmeier-Haack reaction were observed. Namely, under the same conditions, 2-methylpyrazolo[1,5-a]pyridine (2) having an electron-donating substituent and ethyl 2-pyrazolo[1,5-a]pyridinecarboxylate (3) having an electron-withdrawing substituent afforded 2-methyl-3-pyrazolo[1,5-a]pyridinecarboxaldehyde (5) and ethyl 3-formyl-2-pyrazolo[1,5-a]pyridinecarboxylate (6), respectively, in considerable yields.

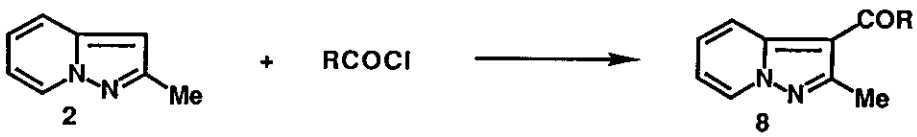
Awano already reported[4] that the aroylation of the pyrazolopyridines with

aroyl chlorides to synthesize the compounds possessing inhibitory activity on Platelet aggregation and declared the aroylation proceeds at the 3-position of the pyrazolopyridine ring. But, the reaction of the pyrazolopyridine (1) not having substituent with benzoyl chloride and aliphatic acyl chloride has not been reported. Next, we examined the reaction of pyrazolo[1,5-a]pyridine (1) with benzoyl chloride and aliphatic acyl chlorides such as acetyl, propionyl, and cyclohexanecarbonyl chlorides, to introduce acyl groups.



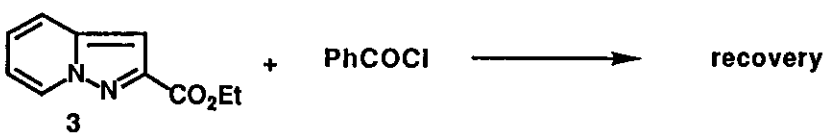
1 7

	R	react. temperature	time (h)	catalyst	yield(%) 7	1
a	Ph	50 °C	24	-	0	80
a	Ph	100 °C	24	-	20	30
a	Ph	100 °C	24	$BF_3 \cdot Et_2O$	21	35
a	Ph	150 °C	3	-	50	0
b	cyclohexyl	150 °C	3	-	47	0
c	Et	reflux	24	-	50	0
d	Me	reflux	24	-	17	45



2 8

	R	react. temperature	time (h)	yield(%) 8	1
a	Ph	150 °C	3	85	0
b	cyclohexyl	150 °C	3	41	0
c	Et	reflux	24	54	0
d	Me	reflux	24	47	33

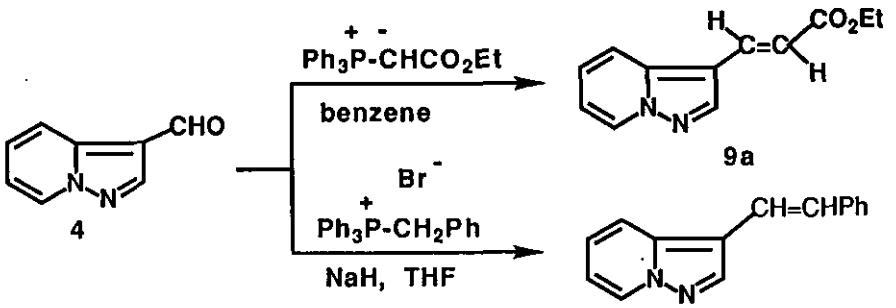


3

Scheme 2

The reaction of 1 with benzoyl chloride at 50-100°C resulted in the recovery of the starting pyrazolopyridine (1), but the reaction at 150°C

afforded 3-benzoylpyrazolo[1,5-a]pyridine (7a) in 50 % yield without the recovery of 1. These results show that this reaction seems to require a rather high reaction temperature. Boron trifluoride etherate as one of Lewis acid is an effective catalyst[2] on Friedel-Crafts reaction, but in this case the acylation was not catalyzed by the addition of boron trifluoride etherate as shown in scheme 2. Similarly, compound (1) reacted with cyclohexanecarbonyl, propionyl and acetyl chlorides to give the corresponding 3-acylpyrazolopyridines (7b-d) at 150 °C or refluxing conditions. Moreover, the 2-methylpyrazolopyridine (2) having an electron-donating substituent at the 2-position reacted with acyl chloride to give the 3-acyl-2-methylpyrazolopyridine (8a-d), but in the case of ethyl 2-pyrazolopyridinecarboxylate (3) having an electron-withdrawing substituent at the 2-position, acylation failed to give the expected product.



Scheme 3

Finally, in order to convert a formyl group into an alkenyl group, 3-formylpyrazolo[1,5-a]pyridine (4) was subjected to the reaction with Wittig reagents. When 4 was heated with (triphenylphosphonio)ethoxycarbonylmethanide in benzene under reflux, ethyl 3-pyrazolo[1,5-a]pyridineacrylate (9a) was obtained in 72 % yield. Similarly, in the treatment of 4 with benzyltriphenylphosphonium bromide in the presence of sodium hydride in tetrahydrofuran, Wittig reaction proceeded to give 3-styrylpyrazolo[1,5-a]pyridine (9b). In the ^{1}H-nmr spectrum of 9a, the signal due to one of the olefinic protons on the side chain appears at 7.78 (1H, d) with a coupling

constant of 16 Hz, indicating that the stereochemistry of the double bond of 9a is trans. The alkenylpyrazolopyridine (9b) was a mixture of the trans- and cis-isomers, but the relative ratio of the trans-cis isomers could not be calculated owing to the overlapping of the two olefinic protons with aromatic protons.

In summary this study revealed that the Vilsmeier-Haack formylation and Friedel-Crafts acylation with aliphatic acyl chloride proceed at 3-position of the pyrazolopyridine ring selectively and the formyl group at the 3-position can be converted easily to the alkenyl group.

EXPERIMENTAL

All melting points are uncorrected. Ir spectra were measured with a Jasco A-102 diffraction grating ir spectrophotometer. ^{1}H-Nmr spectra were taken at 60 MHz and 23 °C with a JEOL JNM-PMX60SI ^{1}H-nmr spectrometer. Chemical shifts are expressed in ppm downfield from tetramethylsilane as an internal standard.

General Procedure for the Vilsmeier-Haack Reaction of the Pyrazolopyridine (1-3)

To a solution of phosphorus oxychloride ($POCl_3$) (0.8 g, 5.2 mmol) in dimethylformamide (DMF) (2 ml), a pyrazolopyridine (1-3)[5-7] (1.7 mmol) was added. The mixture was stirred at room temperature for 1 h. The solvent was removed under reduced pressure. The residue was diluted with H_2O, made alkaline with 2N NaOH, and extracted with $CHCl_3$. After drying over sodium sulfate, the solvent was removed under reduced pressure. The crude product was purified by SiO_2 column chromatography with benzene to give the 3-pyrazolo[1,5-a]pyridinecarboxaldehydes (4-6) as colorless needles.

General Procedure for Reaction of the Pyrazolopyridine (1 and 2) with Acyl Chlorides

A mixture of a pyrazolopyridine (1 and 2) (1.7 mmol) and an acyl chloride (2 ml) was heated at 150, °C for 3 h or refluxed for 24 h. The mixture was

Table I. Ir Spectral Data, Melting Points and Elemental Analysis for 4-6

Compd.	$Ir\nu_{max}^{KBr}$ (cm^{-1}) (C=O)	mp(°C)	Formula	Analysis(%) Calcd(Found) C	H	N
4	1659	89-91	$C_8H_6N_2O$	65.74 (65.47)	4.14 (4.12)	19.17 (19.18)
5	1661	74-76	$C_9H_8N_2O$	67.48 (67.10)	5.03 (4.82)	17.49 (17.41)
6	1740 1660	132-134	$C_{11}H_{10}N_2O_3$	60.55 (60.52)	4.52 (4.40)	12.84 (12.88)

Table II. ^{1}H-Nmr Spectral Data for 4-6

Compd.	^{1}H-Nmr ($CDCl_3$)ppm
4	6.98(1H,dd,$J_{5,6}$=6 Hz,$J_{6,7}$=7 Hz,C^6-H),7.43(1H,dd,$J_{5,6}$=6 Hz, $J_{4,5}$=9 Hz,C^5-H),8.20(1H,d,$J_{4,5}$=9 Hz,C^4-H),8.30(1H,s,C^2-H), 8.50(1H,d,$J_{6,7}$=7 Hz,C^7-H),9.97(1H,s,CHO)
5	2.65(3H,s,CH_3),6.87(1H,dd,$J_{5,6}$=7 Hz,$J_{6,7}$=8 Hz,C^6-H),7.35 (1H,dd,$J_{5,6}$=7 Hz,$J_{4,5}$=9 Hz,C^5-H),8.08(1H,d,$J_{4,5}$=9 Hz,C^4-H), 8.32(1H,d,$J_{6,7}$=8 Hz,C^7-H),9.92(1H,s,CHO)
6	1.48(3H,t,J=7 Hz,$CH_2\underline{CH_3}$),4.54(2H,q,J=7 Hz,$\underline{CH_2}CH_3$),7.10(1H, dd,$J_{5,6}$=6 Hz,$J_{6,7}$=7 Hz,C^6-H),7.53(1H,dd,$J_{5,6}$=6 Hz,$J_{4,5}$=8 Hz,C^5-H),8.08(1H,d,$J_{4,5}$=8 Hz,C^4-H),8.57(1H,d,$J_{6,7}$=7 Hz, C^7-H),10.58(1H,s,CHO)

poured into 2N NaOH, stirred for 1 h, and extracted with $CHCl_3$. After drying over sodium sulfate, the solvent was removed under reduced pressure. The crude product was purified by SiO_2 column chromatography with benzene or petroleum benzin-benzene (1:1) and recrystallized from petroleum benzin to give 3-acylpyrazolo[1,5-a]pyridine (7a-d and 8a-d).

Reaction of 1 with Benzoyl Chloride in the presence of Boron Trifluoride Etherate (BF_3·Et_2O)

A mixture of benzoyl chloride (2 ml) and boron trifluoride etherate (0.24 g, 1.7 mmol) was stirred at room temperature for 10 min and then 1 (0.2 g, 1.7 mmol) was added to the mixture. The mixture was heated at 150 °C for

Table III. Ir Spectral Data, Melting Points and Elemental Analysis for 7a-d and 8a-d

Compd.	Irν_{max}^{KBr} (cm^{-1}) (C=O)	mp(°C)	Formula	Analysis(%) Calcd(Found) C	H	N
7a	1635	98-100	$C_{14}H_{10}N_2O$	75.65 (75.56)	4.54 (4.52)	12.61 (12.58)
7b	1644	99-101	$C_{14}H_{16}N_2O$	73.66 (73.74)	7.06 (6.84)	12.27 (12.15)
7c	1646	128-129	$C_{10}H_{10}N_2O$	68.95 (68.88)	5.79 (5.74)	16.08 (15.95)
7d	1645	99-100	$C_9H_8N_2O$	67.48 (67.30)	5.03 (5.04)	17.49 (17.23)
8a	1614	59-60	$C_{15}H_{12}N_2O$	76.25 (76.19)	5.12 (5.16)	11.86 (11.61)
8b	1628	60-61	$C_{15}H_{18}N_2O$	74.35 (74.43)	7.49 (7.40)	11.56 (11.63)
8c	1644	82-83	$C_{11}H_{12}N_2O$	70.18 (70.13)	6.43 (6.47)	14.88 (14.75)
8d	1637	87-88[a]				

a) Lit.,[8] mp 90 °C.

24 h. The mixture was poured into 2N NaOH, stirred for 1 h, and extracted with $CHCl_3$. After drying over sodium sulfate, the solvent was removed under reduced pressure. The crude product was purified by SiO_2 column chromatography. The fraction eluted with petroleum benzin-benzene (1:1) gave 1. Recovery 70 mg (35 %). The fraction eluted with benzene gave 3-benzoylpyrazolo[1,5-a]pyridine (7a). Yield 80 mg (21 %).

Reaction of 4 with (Triphenylphosphonio)ethoxycarbonylmethanide

A solution of 4 (0.3 g, 2.1 mmol) and (triphenylphosphonio)ethoxycarbonylmethanide (1.2 g, 2.8 mmol) in benzene (10 ml) was refluxed for 3 h. The solvent was removed under reduced pressure. The residue was diluted with H_2O and extracted with $CHCl_3$. After drying over sodium sulfate, the solvent was removed under reduced pressure. The crude product was purified by SiO_2 column chromatography with benzene and recrystallized from petroleum benzin to give ethyl 3-pyrazolo[1,5-a]pyridineacrylate (9a) as colorless needles, mp 65-66 °C. Yield 0.32 g (72 %). Anal. Calcd for $C_{12}H_{12}N_2O_2$: C, 66.65; H, 5.59; N, 12.95. Found: C, 66.52; H, 5.62; N, 12.69. Irν_{max}^{KBr} cm^{-1}: 1712 (C=O). ^{1}H-Nmr ($CDCl_3$)δ: 1.32 (3H, t, J=7 Hz, $OCH_2C\underline{H}_3$), 4.22 (2H, q,

J=7 Hz, $OC\underline{H}_2CH_3$), 6.22 (1H, d, J=16 Hz, $CH=C\underline{H}CO_2Et$), 6.79 (1H, dd, $J_{5,6}$=6 Hz, $J_{6,7}$=7 Hz, C^6-H), 7.22 (1H, dd, $J_{4,5}$=9 Hz, $J_{5,6}$=6 Hz, C^5-H), 7.69 (1H, d, $J_{4,5}$9 Hz, C^4-H), 7.78 (1H, d, J=16 Hz, $C\underline{H}=CHCO_2Et$), 8.40 (1H, d, $J_{6,7}$= 7 Hz, C^7-H).

Table IV. ^{1}H-Nmr Spectral Data for 7a-d and 8a-d

Compd.	^{1}H-Nmr ($CDCl_3$)ppm
7a	6.87(1H,dd,J=6 Hz,J=8 Hz,C^6-H),7.15-7.80(6H,m,C^5-H and COPh), 8.12(1H,s,C^2-H),8.22-8.47(2H,m,C^4-H and C^7-H)
7b	1.05-2.20(10H,m,cyclohexyl),2.80-3.28(1H,br,cyclohexyl),6.85 (1H,dd,$J_{5,6}$=6 Hz,$J_{6,7}$=7 Hz,C^6-H),7.33(1H,dd,$J_{5,6}$=6 Hz,$J_{4,5}$=9 Hz,C^5-H),8.15-8.47(3H,m,C^4-H,C^2-H and C^7-H)
7c	1.23(3H,t,J=7 Hz,$CH_2C\underline{H}_3$),2.88(2H,q,J=7 Hz,$C\underline{H}_2CH_3$),6.85(1H,dd, $J_{5,6}$=6 Hz,$J_{6,7}$=7 Hz,C^6-H),7.35(1H,ddJ$_{5,6}$=6 Hz,$J_{4,5}$=9 Hz,C^5-H) 8.17-8.48(3H,m,C^4-H,C^2-H and C^7-H)
7d	2.50(3H,s,CH_3),6.92(1H,dd,$J_{5,6}$=7 Hz,$J_{6,7}$=8 Hz,C^6-H),7.37(1H, dd,$J_{5,6}$=7 Hz,$J_{4,5}$=10 Hz,C^5-H),8.28-8.55(3H,m,C^4-H,C^2-H and C^7-H)
8a	2.42(3H,s,CH_3),6.77(1H,dd,J=6 Hz,J=8 Hz,C^6-H),7.02-7.68(7H,m, C^5-H,C^4-H and COPh),8.35(1H,d,J=7 Hz,C^7-H)
8b	0.75-2.17(10H,m,cyclohexyl),2.68(3H,s,CH_3),2.70-3.20(1H,br, cyclohexyl),6.75(1H,dd,$J_{5,6}$=6 Hz,$J_{6,7}$=7 Hz,C^6-H),7.25(1H,dd, $J_{5,6}$=6 Hz,$J_{4,5}$=9 Hz,C^5-H),8.02(1H,d,J=9 Hz,C^4-H),8.27(1H,d,J= 7 Hz,C^7-H)
8c	1.23(3H,t,J=7 Hz,$CH_2C\underline{H}_3$),2.65(3H,s,CH_3),2.83(2H,q,J=7 Hz,$C\underline{H}_2CH_3$) 6.77(1H,dd,$J_{5,6}$=6 Hz,$J_{6,7}$=7 Hz,C^6-H),7.27(1H,dd,$J_{5,6}$=6 Hz,$J_{4,5}$= 9 Hz,C^5-H),8.07(1H,d,J=9 Hz,C^4-H),8.25(1H,d,J=7 Hz,C^7-H)
8d	2.53(3H,s,CH_3),2.67(3H,s,CH_3),6.80(1H,dd,$J_{5,6}$=6Hz,$J_{6,7}$=7 Hz, C^6-H),7.30(1H,dd,$J_{5,6}$=6 Hz,$J_{4,5}$=9 Hz,C^5-H),8.15(1H,d,J=9 Hz,C^4-H),8.32(1H,d,J=7 Hz,C^7-H)

Reaction of 6 with Benzyltriphenylphosphonium Bromide

A mixture of benzyltriphenylphosphonium bromide (2.15 g, 4.9 mmol) and NaH (0.2 g, 60 % in oil, 4.9 mmol) in THF (10 ml) was stirred at room temperature for 30 min. To the mixture 4(0.24 g, 1.6 mmol) was added and the mixture was refluxed for 3 h. the same work-up of the reaction mixture as described for the reaction of 4 with (triphenylphosphonio)ethoxycarbonylmethanide gave 3-styrylpyrazolo[1,5-a]pyridine (9b) as pale yellow needles, mp 135-137 °C. Yield 0.27 g (73 %). Anal. Calcd for $C_{15}H_{12}N_2$: C, 81.79; H, 5.49; N, 12.72. Found: C, 81.68; H, 5.49; N, 12.74. ^{1}H-Nmr ($CDCl_3$)δ: 6.69 (1H, dd, $J_{5,6}$=5 Hz, $J_{6,7}$=7 Hz, C^6-H), 6.94-7.52 (8H, m, C^5-H and CH=CHPh), 7.68 (1H, d, $J_{4,5}$=8 Hz, C^4-H), 8.09 (1H, s, C^2-H), 8.38 (1H, d, $J_{6,7}$=7 Hz, C^7-H).

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