SYNTHESIS OF 3-SUBSTITUTED PYRAZOLO[1,5-*a*]-PYRIDINES BY ELECTROPHILIC REACTIONS†

Yasuyoshi Miki,*[a] Sanae Yagi,[a] Hiroko Hachiken,[a] and Masazumi Ikeda[b]

[a]*Faculty of Pharmaceutical Sciences, Kinki University, 3-4-1, Kowakae, Higashi-Osaka 577, Japan, and* [b]*Kyoto Pharmaceutical University, Misasagi, Yamashina, Kyoto 607, Japan*

Abstract —— Reactions of pyrazolo[1,5-*a*]pyridines with Eschenmoser's salt, activated alkenes and alkynes, and chlorosulfonyl isocyanate provided general routes to 3-substituted pyrazolo[1,5-*a*]pyridines such as 3-dimethylaminomethyl- and 3-(2-nitroethyl)pyrazolo[1,5-*a*]pyridines, 1-phenyl-3-(pyrazolo[1,5-*a*]pyrid-3-yl)-2-propen-1-ones, 4-(pyrazolo[1,5-*a*]pyrid-3-yl)-3-buten-2-one, pyrazolo[1,5-*a*]pyridine-3-carboxamide, and pyrazolo[1,5-*a*]pyridine-3-carbonitrile.

The previously investigated electrophilic reactions of the pyrazolo[1,5-*a*]pyridines (**1**) include bromination,[1] nitration,[2] nitrosation,[2] Friedel-Crafts acylation,[3-5] Vilsmeier-Haack reaction,[5] and the acid-catalyzed reaction with aldehydes.[6] All of these reactions always occur at the 3-position of **1**, as predicted by the frontier electron density calculations.[1,2,7] As our contribution to this relatively unexplored area, we have now examined the electrophilic reactions of **1** with Eschenmoser's salt,[8] activated alkenes and alkynes, and chlorosulfonyl isocyanate (CSI),[9] in the hope of developing general and convenient routes to the 3-substituted pyrazolo[1,5-*a*]pyridines.

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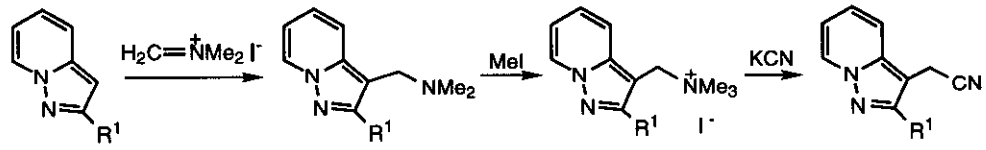
† This paper is dedicated to Professor Emeritus Yasumitsu Tamura of Osaka University on the occasion of his 70th birthday.

Reaction with Eschenmoser's Salt

Treatment of 2-phenylpyrazolo[1,5-*a*]pyridine (**1a**)[10] with Eschenmoser's salt ($H_2C{=}N^+Me_2\ I^-$) in dichloromethane in the presence of trifluoroacetic acid at room temperature for 4 h gave the Mannich base (**2a**) in 95% yield. Similarly, pyrazolo[1,5-*a*]pyridine (**1b**)[11] reacted with the Eschenmoser's salt to afford the Mannich base (**2b**) in 89% yield. Evidence that the substitution occurred at the 3-position was given by an examination of the ^{1}H-nmr spectra of **2a,b**, in which the signal due to the H-3 (δ 6.76 for **1a**[10] and δ 6.33 for **1b**[11]) disappeared. The compounds (**2a,b**) were converted to the acetonitriles (**4a**)[12] and (**4b**) *via* the trimethylammonium iodides (**3a,b**) in 91 and 78% yields, respectively.

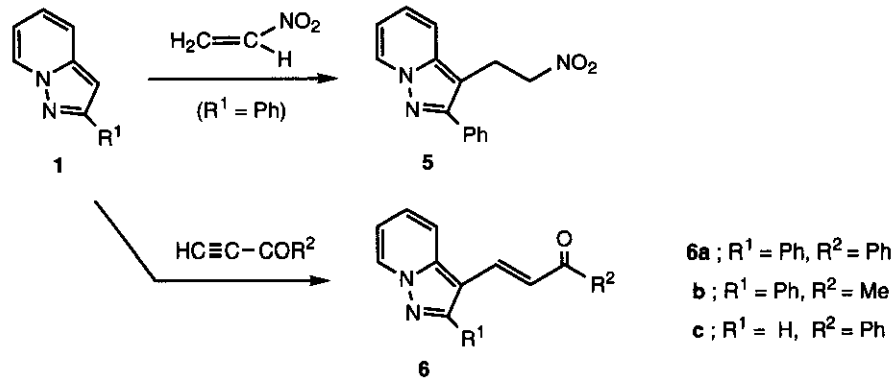


1 **2** **3** **4**

a; R^1 = Ph, b; R^1 = H

Reaction with Activated Alkenes and Alkynes

Although the pyrazolo[1,5-*a*]pyridine (**1a**) failed to react with ethyl acrylate or methyl vinyl ketone in the presence of trifluoroacetic acid, **1a** reacted with more reactive nitroethene in refluxing dichloroethane containing trifluoroacetic acid to give the Michael adduct (**5**) in 58% yield. However, **1b** did not react with nitroethene under the reaction conditions we used. When **1a** or **1b** was treated with benzoylacetylene under similar conditions, the corresponding Michael adducts (**6a,c**) were obtained in 63 and 19% yields, respectively.



1 **5** **6**

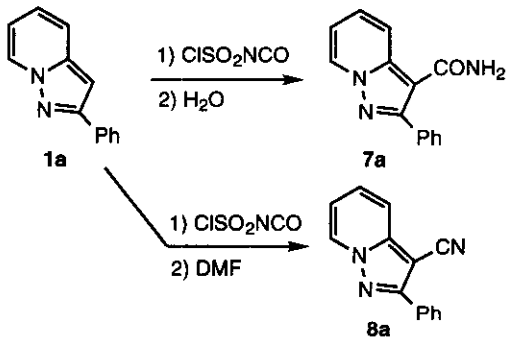
6a ; R^1 = Ph, R^2 = Ph
b ; R^1 = Ph, R^2 = Me
c ; R^1 = H, R^2 = Ph

Similarly, the reaction of **1a** with acetylacetylene afforded **6b** in 97% yield. The (*E*)-stereochemistry about the carbon-carbon double bond in **6** was assigned on the basis of the large coupling constants (16 Hz) between the olefinic protons.

Reaction with Chlorosulfonyl Isocyanate

Upon treatment with chlorosulfonyl isocyanate (CSI)[9] in acetonitrile at room temperature for 3 h followed by quenching with water, **1a** gave the pyrazolo[1,5-*a*]pyridine-3-carboxamide (**7a**) in 73% yield. When the reaction mixture obtained from the reaction of **1a** with CSI in acetonitrile was stirred with *N*,*N*-dimethylformamide at room temperature for 2 h, the pyrazolo[1,5-*a*]pyridine-3-carbonitrile (**8a**) was obtained in 36% yield. However, **1b** failed to react with CSI under the reaction conditions we employed.

In summary, the present study revealed that the electrophilic reactions towards **1** provide efficient routes to various 3-substituted pyrazolo[1,5-*a*]pyridines.



EXPERIMENTAL

All mps are uncorrected. The ^{1}H-nmr spectra were determined on a JEOL FX200 spectrometer using tetramethylsilane as an internal standard. The ir spectra were recorded with a Hitachi EPI-G2 spectrophotometer.

3-Dimethylaminomethyl-2-phenylpyrazolo[1,5-*a*]pyridine (2a)

To a solution of 2-phenylpyrazolo[1,5-*a*]pyridine (**1a**) (291 mg, 1.5 mmol) and Eschenmoser's salt (278 mg, 1.5 mmol) in dichloromethane (10 ml) was added trifluoroacetic acid (2.5 mmol) and the mixture was stirred at room temperature for 4 h. After the reaction mixture was neutralized with a 5% sodium bicarbonate solution,

the organic layer was separated and the aqueous layer was extracted with dichloromethane. The combined organic extracts were washed with water, dried over Na_2SO_4, and concentrated. The residue was chromatographed on silica gel ($CHCl_3$: MeOH = 10 : 1) to give **2a** (358 mg, 95%), mp 63-64°C (from hexane); ^{1}H-nmr ($CDCl_3$) δ: 2.26 (6H, s, 2xNCH$_3$), 3.60 (2H, s, CH_2N), 6.72 (1H, dt, *J*=7, 1.5 Hz, H-6), 7.09 (1H, ddd, *J*=9, 7, 1 Hz, H-5), 7.3-7.5 (3H, m, Ph), 7.60 (1H, ddd, *J*=9, 1.5, 1 Hz, H-4), 7.9-8.0 (2H, m, Ph), and 8.43 (1H, dt, *J*=7, 1 Hz, H-7). *Anal.* Calcd for $C_{16}H_{17}N_3$: C, 76.46; H, 6.82; N, 16.72. Found: C, 76.59; H, 6.93; N, 16.81.

3-Dimethylaminomethylpyrazolo[1,5-*a*]pyridine (2b)

Following a procedure similar to that described for the preparation of **2a**, **2b** (469 mg, 89%) was obtained from **1b** (354 mg, 3.0 mmol) and Eschenmoser's salt (666 mg, 3.6 mmol) as an oil; ^{1}H-nmr ($CDCl_3$) δ: 2.26 (6H, s, 2xNCH$_3$), 3.62 (2H, s, CH_2N), 6.69 (1H, dt, *J*=7, 1 Hz, H-6), 7.06 (1H, ddd, *J*=9, 7, 1 Hz, H-5), 7.55 (1H, dt, *J*=9, 1 Hz, H-4), 7.85 (1H, s, H-2), and 8.39 (1H, dt, *J*=7, 1 Hz, H-7).

(2-Phenylpyrazolo[1,5-*a*]pyrid-3-ylmethyl)trimethylammonium Iodide (3a)

To a solution of **2a** (100 mg, 0.4 mmol) in methanol (0.4 ml) was added methyl iodide (75 ml, 1.2 mmol) and the reaction mixture was allowed to stand for 1 h. Ether was added to the reaction mixture and the precipitated solid was collected to give **3a** (155 mg, 98%), which was used without purification for the next step.

(Pyrazolo[1,5-*a*]pyrid-3-ylmethyl)trimethylammonium Iodide (3b)

Following a procedure similar to that described for the preparation of **3a**, **3b** (573 mg, 90%) was obtained from **2b** (350 mg, 2.0 mmol), mp 193-194°C (from EtOH); ^{1}H-nmr (DMSO-d_6) δ: 3.05 (9H, s, 3xNCH$_3$), 4.74 (2H, s, CH_2N), 7.00 (1H, dt, *J*=7, 1 Hz, H-6), 7.40 (1H, ddd, *J*=9, 7, 1 Hz, H-5), 7.96 (1H, dt, *J*=9, 1 Hz, H-4), 8.18 (1H, s, H-2), and 8.72 (1H, dt, *J*=7, 1 Hz, H-7). *Anal.* Calcd for $C_{11}H_{16}N_3I$: C, 41.66; H, 5.08; N, 13.25. Found: C, 41.68; H, 4.80; N, 13.28.

2-Phenylpyrazolo[1,5-*a*]pyridine-3-acetonitrile (4a)

To a solution of **3a** (1.38 g, 3.5 mmol) in dry acetonitrile (35 ml) was added dicyclohexyl-18-crown-6 (0.13 g, 0.35 mmol) and potassium cyanide (0.91 g, 14 mmol) and the mixture was refluxed for 24 h. Water was added to the reaction mixture and the mixture was extracted with dichloromethane. The extracts were washed

with brine, dried over Na_2SO_4, and evaporated off. The residue was purified by column chromatography on silica gel (CH_2Cl_2) to give **4a** (0.76 g, 93%), mp 120-121°C (from hexane-AcOEt); ir (nujol): 2250 cm^{-1}; ^{1}H-nmr ($CDCl_3$) δ: 3.92 (2H, s, CH_2), 6.87 (1H, dt, *J*=7, 1 Hz, H-6), 7.26 (1H, ddd, *J*=9, 7, 1 Hz, H-5), 7.4-7.7 (6H, m, H-4 and Ph), and 8.51 (1H, dt, *J*=7, 1 Hz, H-7). *Anal.* Calcd for $C_{15}H_{11}N_3$: C, 77.23; H, 4.75; N, 18.01. Found: C, 77.31; H, 4.96; N, 18.02.

Pyrazolo[1,5-*a*]pyridine-3-acetonitrile (4b)

To a solution of **3b** (1.11 g, 3.5 mmol) in dry acetonitrile (35 ml) was added dicyclohexyl-18-crown-6 (0.13 g, 0.35 mmol) and potassium cyanide (0.91 g, 14 mmol) and the mixture was refluxed for 3 days. After workup similar to that described for the preparation of **4a**, the residue was purified by column chromatography on silica gel ($CHCl_3$) to give **4b** (0.48 g, 87%), mp 69-71°C (hexane)(lit.,[12] mp 72°C); ir (neat): 2200 cm^{-1}; ^{1}H-nmr ($CDCl_3$) δ: 3.84 (2H, s, CH_2), 6.81 (1H, dt, *J*=7, 1 Hz, H-6), 7.19 (1H, ddd, *J*=9, 7, 1 Hz, H-5), 7.53 (1H, dt, *J*=9, 1 Hz, H-4), 7.90 (1H, s, H-2), and 8.45 (1H, dt, *J*=7, 1 Hz, H-7).

3-(2-Nitroethyl)-2-phenylpyrazolo[1,5-*a*]pyridine (5)

A solution of **1a** (388 mg, 2.0 mmol), nitroethene (222 mg, 3.0 mmol), and trifluoroacetic acid (390 ml, 5 mmol) in dichloroethane (20 ml) was heated under reflux for 14 h. After the reaction mixture was neutralized with a 5% sodium bicarbonate solution, the organic layer was separated and the aqueous layer was extracted with dichloromethane. The combined extracts were washed with water, dried over Na_2SO_4, and concentrated. The crude product was chromatographed on silica gel (hexane : AcOEt = 10 : 1) to give **5** (308 mg, 58%), mp 117-118°C (from hexane-AcOEt); ir (neat): 1550 and 1380 cm^{-1}; ^{1}H-nmr ($CDCl_3$) δ: 3.62 (2H, t, *J*=7 Hz, $CH_2CH_2NO_2$), 4.47 (2H, t, *J*=7 Hz, $CH_2CH_2NO_2$), 6.75 (1H, dt, *J*=7, 1 Hz, H-6), 7.13 (1H, ddd, *J*=9, 7, 1 Hz, H-5), 7.4-7.7 (6H, m, H-4 and Ph), and 8.42 (1H, dt, *J*=7, 1 Hz, H-7). *Anal.* Calcd for $C_{15}H_{13}N_3O_2$: C, 67.40; H, 4.90; N, 15.72. Found: C, 67.36; H, 5.06; N, 15.56.

(*E*)-1-Phenyl-3-(2-phenylpyrazolo[1,5-*a*]pyrid-3-yl)-2-propen-1-one (6a)

Using a procedure similar to that described for the preparation of **5**, **6a** (62 mg, 63%) was obtained from **1a** (58 mg, 0.3 mmol) and benzoylacetylene (39 mg, 0.3 mmol), mp 142-143°C (from EtOH); ir (nujol): 1645 cm^{-1}; ^{1}H-nmr ($CDCl_3$) δ: 6.94 (1H, dt, *J*=7, 1 Hz, H-6), 7.36 (1H, d, *J*=16 Hz, PhCO-C*H*=CH-), 7.3-8.0 (12H, m, H-4, H-5, and Ph), 8.09 (1H, d, *J*=16 Hz, PhCO-CH=C*H*-), and 8.52 (1H, dt, *J*=7, 1 Hz, H-7). *Anal.*

Calcd for $C_{22}H_{16}N_2O$: C, 81.46; H, 4.97; N, 8.64. Found: C, 81.56; H, 4.96; N, 8.61.

(*E*)-4-(Pyrazolo[1,5-*a*]pyrid-3-yl)-3-buten-2-one (6b)

Using a procedure similar to that described for the preparation of **5**, **6b** (228 mg, 97%) was obtained from **1a** (174 mg, 0.9 mmol) and acetylacetylene (212 ml, 2.7 mmol), mp 140-141°C (from MeOH); ir (nujol): 1655 cm^{-1}; ^{1}H-nmr ($CDCl_3$) δ: 2.31 (3H, s, CH_3), 6.61 (1H, d, *J*=16 Hz, CH_3CO-C*H*=CH-), 6.93 (1H, dt, *J*=7, 1 Hz, H-6), 7.34 (1H, ddd, *J*=9, 7, 1 Hz, H-5), 7.4-7.7 (5H, m, Ph), 7.76 (1H, d, *J*=16 Hz, CH_3CO-CH=C*H*-), 7.84 (1H, br d, *J*=9 Hz, H-4), and 8.52 (1H, dt, *J*=7, 1 Hz, H-7). *Anal.* Calcd for $C_{17}H_{14}N_2O$: C, 77.84; H, 5.38; N, 10.68. Found: 77.83; H, 5.63; N, 10.52.

(*E*)-1-Phenyl-3-(pyrazolo[1,5-*a*]pyrid-3-yl)-2-propen-1-one (6c)

Using a procedure similar to that described for the preparation of **5**, **6c** (23 mg, 19%) was obtained from **1b** (59 mg, 0.5 mmol) and benzoylacetylene (65 mg, 0.5 mmol), mp 178-179°C (from MeOH); ir (nujol): 1650 cm^{-1}; ^{1}H-nmr ($CDCl_3$) δ: 6.89 (1H, dt, *J*=7, 1 Hz, H-6), 7.3-7.6 (4H, m, H-5 and Ph), 7.40 (1H, d, *J*=16 Hz, PhCO-C*H*=CH-), 7.79 (1H, br d, *J*=9 Hz, H-4), 7.95-8.1 (2H, m, Ph), 8.04 (1H, d, *J*=16 Hz, PhCO-CH=C*H*-), 8.30 (1H, s, H-2), and 8.48 (1H, dt, *J*=7, 1 Hz, H-7). *Anal.* Calcd for $C_{16}H_{12}N_2O$: C, 77.40; H, 4.87; N, 11.28. Found: C, 77.34; H, 4.97; N, 11.19. Compound (**1b**)(40 mg, 68%) was also recovered.

2-Phenylpyrazolo[1,5-*a*]pyridine-3-carboxamide (7a)

To a solution of **1a** (58 mg, 0.3 mmol) in acetonitrile (3 ml) was added CSI (26 ml, 0.3 mmol) and the mixture was stirred at room temperature for 3 h. Water was added to the reaction mixture and the mixture was washed with dichloromethane. The aqueous layer was concentrated *in vacuo* and the residual solid was recrystallized from methanol to give **7a** (52 mg, 73%), mp 244-245°C (from MeOH); ir (nujol): 3200 and 1655 cm^{-1}; ^{1}H-nmr ($CDCl_3$) δ: 5.36 (2H, br s, NH_2), 6.91 (1H, dt, *J*=7, 1 Hz, H-6), 7.35 (1H, ddd, *J*=9, 7, 1 Hz, H-5), 7.4-7.7 (5H, m, Ph), 8.38 (1H, dt, *J*=9, 1 Hz, H-4), and 8.44 (1H, dt, *J*=7, 1 Hz, H-7). *Anal.* Calcd for $C_{14}H_{11}N_3O$: C, 70.87; H, 4.67; N, 17.71. Found: C, 70.85; H, 4.80; N, 17.46.

2-Phenylpyrazolo[1,5-*a*]pyridine-3-carbonitrile (8a)

To a solution of **1a** (58 mg, 0.3 mmol) in acetonitrile (3 ml) was added CSI (26 ml, 0.3 mmol) and the mixture

was stirred at room temperature for 3 h. *N,N*-Dimethylformamide (26 ml, 0.3 mmol) was added to the reaction mixture and the mixture was stirred at room temperature for 2 h. After water was added to the reaction mixture, the whole mixture was extracted with dichloromethane. The extracts were washed with water, dried over Na_2SO_4, and concentrated. The residue was chromatographed on silica gel (hexane : AcOEt = 10:1). The first fraction gave **1a** (20 mg, 34%). The second fraction gave **8a** (24 mg, 36%); mp 147-148°C (from MeOH); ir (nujol): 2150 cm^{-1}; ^{1}H-nmr ($CDCl_3$) δ: 6.99 (1H, dt, *J*=7, 1 Hz, H-6), 7.35-7.55 (4H, m, H-5 and Ph), 7.73 (1H, dt, *J*=9, 1 Hz, H-4), 8.05-8.15 (2H, m, Ph), and 8.52 (1H, dt, *J*=7, 1 Hz, H-7). *Anal.* Calcd for $C_{14}H_9N_3$: C, 76.69; H, 4.14; N, 19.17. Found: C, 76.64; H, 4.36; N, 19.22.

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