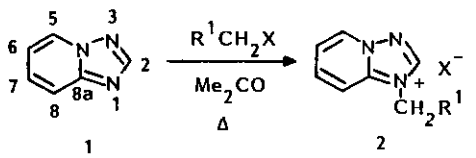
YLIDE-INDUCED YLIDE FORMATION: A THERMAL REACTION AND A DOUBLE CYCLOADDITION REACTION OF [1,2,4]TRIAZOLO[1,5-a]PYRIDINIUM YLIDES

Mikio Hori*, Tadashi Kataoka, Hiroshi Shimizu, Eiji Imai, and Masaharu Yokomoto
Gifu Pharmaceutical University, 6-1, Mitahora-higashi 5-chome, Gifu 502, Japan
Kiyomi Tanaka, Kazuhiko Kimura, and Yoshinobu Hashimoto
Kaken Pharmaceutical Co., Ltd., 2-28-8, Honkomagome, Bunkyo-ku, Tokyo 113, Japan

Abstract — 1-Alkyl[1,2,4]triazolo[1,5-a]pyridinium salts (2) were synthesized by the reaction of [1,2,4]triazolo[1,5-a]pyridine (1) with alkyl halides in dry acetone under reflux. The thermal reaction of ylides (3) gave 2-cyanamidopyridines (4) or 2-oxazolylpyridine (5). The reaction of ylides (3) with methyl propiolate or dimethyl acetylenedicarboxylate resulted in the formation of pyrazolo[1,5-a]pyridine derivatives via a double 1,3-dipolar cycloaddition reaction.

In the preceding papers, we reported the thermal reaction of [1,2,4]triazolo[1,5-a]pyrimidinium ylides[1] and the reaction with methyl propiolate (MP) or dimethyl acetylenedicarboxylate (DMAD) to give 1:2 adducts by a double 1,3-dipolar cycloaddition reaction which includes "ylide-induced ylide".[2] This paper describes the thermal reactions and double 1,3-dipolar cycloaddition of [1,2,4]triazolo[1,5-a]pyridinium ylides.

Synthesis of 1-Alkyl[1,2,4]triazolo[1,5-a]pyridinium Salts (2) --- Alkylation of [1,2,4]triazolo-[1,5-a]pyridine[3] (1) was carried out with alkyl halides in refluxing acetone to afford the iminium salts (2) in 43-96% yields (Scheme 1) (Table 1.).



1 2

Scheme 1

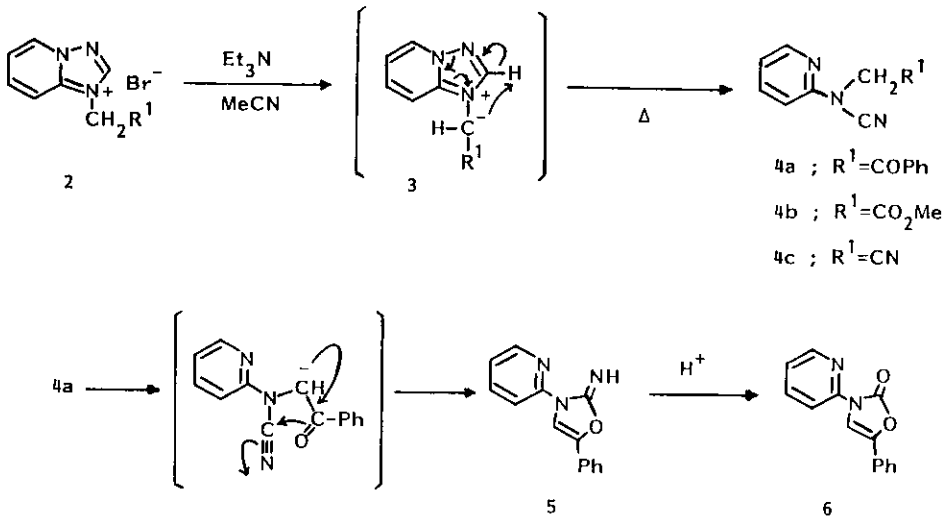
Table 1. Preparation of 1-Alkyl[1,2,4]triazolo[1,5-a]pyridinium Salts (2)

Compound No.	R^1	X	Time (h)	eq. of alkyl halide	Yield (%)	mp (decomp) (°C)
2a	COPh	Br	9	1.1	96	212-213.5
2b	CO_2Me	Br	22	11	76	165-167.5
2c	CN	Br	24	5	43	226-228
2d	CN	Cl	23	11	1.0	oil

There are no reports on alkylation of 1 or its derivatives.[4] Considering the fact that 2-Methyl-[1,2,4]triazolo[1,5-a]pyridine is protonated at N_1-position,[5] alkylation of 1 would occur at N_1-position. This assumption was confirmed by thermolysis of the ylides (3) described below.

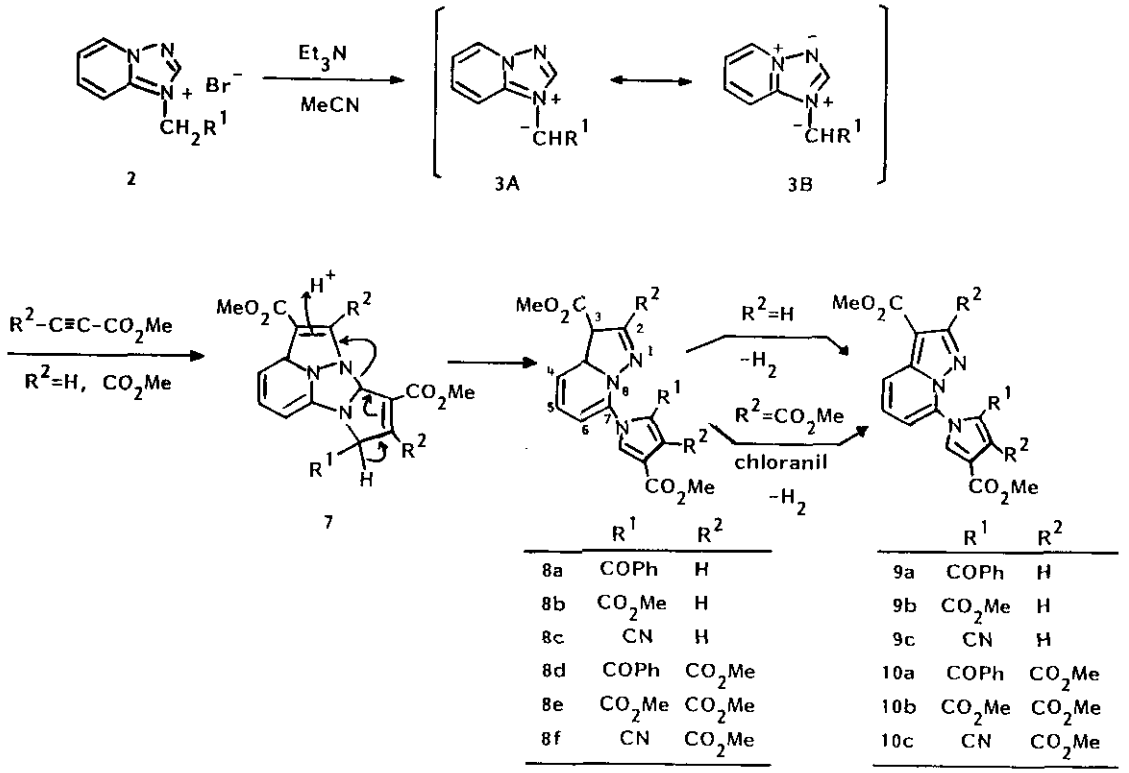
Thermal Reaction of [1,2,4]Triazolo[1,5-a]pyridinium Ylides (3) --- The iminium salts (2) were treated with triethylamine in dry acetonitrile under a nitrogen atmosphere at room temperature to afford a red solution of the ylides (3) which were too unstable to be isolated. Refluxing the red solution of ylides (3b,c) gave 2-cyanamidopyridines (4b,c). The cyanamidopyridines (4b,c) showed an absorption at 2240cm^{-1} (CN) in their ir spectra and multiplet signals at δ 6.94-8.34 arising from the four pyridine protons in their ^{1}H-nmr spectra. The plausible reaction mechanism for the thermolysis is shown in Scheme 2.

On the other hand, thermolysis product of benzoyl derivative (3a) was not 2-cyanamidopyridine (4a) but 2-(2-imino-5-phenyl-2,3-dihydrooxazol-3-yl)pyridine (5). The compound 5 exhibited absorptions of NH at 3270cm^{-1} and an imino group at 1680cm^{-1} in the ir spectrum and showed an olefinic proton signal at δ 7.88 in the ^{1}H-nmr spectrum. The oxazoline ring of 5 might be derived from the N-cyano-N-phenacylamino moiety of primarily formed 2-(N-cyano-N-phenacylamino)pyridine (4a). The ring-opened intermediate (4a) is deprotonated by triethylamine to produce an enolate anion, which attacks the carbon atom of the cyano group to cyclize to the oxazoline (5). The intermediate (4a) was not obtained even by the reaction of 2a with 0.9 eq. of triethylamine, while 2-(N-cyano-N-phenacylamino)pyrimidine has been obtained from the reaction of [1,2,4]triazolo-[1,5-a]pyrimidinium ylides.[1] The oxazoline (5) was easily hydrolyzed by the treatment with silica gel in chloroform to give 2-(2-oxo-5-phenyl-2,3-dihydrooxazol-3-yl)pyridine (6) in 56% yield. The oxazolone (6) showed an absorption of ketone at 1735cm^{-1} in the ir spectrum and the signal of oxazoline ring proton at δ 8.00 in the ^{1}H-nmr spectrum.



Scheme 2

Reaction of Ylides (3) with MP or DMAD --- Iminium salts (2) were treated with triethylamine in the presence of MP at room temperature in dry acetonitrile under a nitrogen atmosphere to give pyrazolo[1,5-a]pyridine derivatives (9) in addition to thermolysis products (4b-c, 5) (Scheme 3). The ^{1}H-nmr spectra of 9 showed two doublets at δ 7.5 and 7.8 (J=1.5 Hz) due to 2,4-disubstituted pyrrole ring and a singlet at δ 8.0 due to C_2-H of pyrazolo[1,5-a]pyridine moiety. In the reaction with DMAD, the mixtures of 3,3a-dihydropyrazolo[1,5-a]pyridines (8d-f) and their 3,3a-dehydrogenated derivatives (10) were obtained. Mass spectra of the mixtures showed molecular ion peaks of 1:2 adduct(8d-f) and 10. Moreover, the ^{1}H-nmr spectra exhibited complicated multiplets assigned to diastereomeric C_3-H and C_{3a}-H of 8d-f in the region of δ 5-6. 3,3a-Dihydropyrazolopyridines (8d-f) were very easily dehydrogenated to pyrazolopyridines (10) during purification by preparative TLC and we could not isolate 8d-f in pure forms. The mixtures of 8d-f and 10 were treated with chloranil in benzene under reflux to afford 10 (Scheme 3). The 1:1 adduct were not obtained even from the reaction with 1 eq. of MP or DMAD. The plausible mechanism for the formation of 9 and 10 involves the double 1,3-dipolar cycloaddition of ylide (3B), named "ylide-induced ylide", which is one of resonance structures of azomethine ylide (3A), with 2 moles of MP. The cycloadducts (7) would readily afford ring-opened products (8). Dihydropyrazolopyridines (8) are aromatized with dehydrogenation to give pyrazolo[1,5-a]pyridines (9, 10) (Scheme 3).



	R^1	R^2
8a	COPh	H
8b	CO_2Me	H
8c	CN	H
8d	COPh	CO_2Me
8e	CO_2Me	CO_2Me
8f	CN	CO_2Me

	R^1	R^2
9a	COPh	H
9b	CO_2Me	H
9c	CN	H
10a	COPh	CO_2Me
10b	CO_2Me	CO_2Me
10c	CN	CO_2Me

Scheme 3

In conclusion, 1-alkyl[1,2,4]triazolo[1,5-a]pyridinium ylides provided a number of pyridine derivatives by thermal reaction and pyrazolo[1,5-a]pyridine derivatives by double 1,3-dipolar cycloaddition reaction with active acetylenic compounds. Further investigation in this area is under way.

EXPERIMENTAL

Melting points were determined with a Yanagimoto micro melting point apparatus and are uncorrected. TLC was performed on silica gel (Kiesel gel 60 PF_{254}, Merck). Column chromatography was performed on silica gel (Fujigel BW-820MH). Solvent combinations for elution are given as v/v. The ir spectra were recorded with a JASCO A-1 spectrometer and the mass spectra were recorded with a JEOL JMS-D300 spectrometer. ^{1}H-nmr spectra were recorded at 60 MHz with a HITACHI R 20-B spectrometer. Chemical shifts are given on the δ scale and tetramethylsilane was used as an internal standard.

1-Alkyl[1,2,4]triazolo[1,5-a]pyridinium Salts (2a-d), General Procedure --- A solution of [1,2,4]-triazolo[1,5-a]pyridine[3] (1) and alkylating agent in dry acetone was refluxed under a nitrogen atmosphere. The precipitated solid was collected, washed with dry ether, and recrystallized from ethanol or methanol. Reaction time, eq. of alkylating agent, yield (%) and melting point are shown in Table 1. Mass, ir and ^{1}H-nmr spectra are summarized in Table 2. Appearance, recrystallizing solvent and analytical data are listed in Table 3.

Table 2. Spectral Data of 1-Alkyl[1,2,4]triazolo[1,5-a]pyridinium Salts (2)

Compound No.	ir cm^{-1} (KBr)	^{1}H-nmr δ (DMSO-d_6-$CDCl_3$)
2a	1685 (CO)	6.68 (2H, s, CH_2), 7.50-8.88 (8H, m, ArH), 9.42-9.62 (1H, m, ArH), 9.74 (1H, s, C_2-H)
2b	1745 (CO)	3.79 (3H, s, OCH_3), 5.76 (2H, s, CH_2), 7.82-8.08 (1H, m, ArH), 8.50-8.76 (2H, m, ArH), 9.49-9.67 (1H, m, ArH), 9.85 (1H, s, C_2-H)
2c	a	6.19 (2H, s, CH_2), 7.86-8.08 (1H, m, ArH), 8.33-8.90 (2H, m, ArH), 9.44-9.66 (1H, m, ArH), 9.94 (1H, s, C_2-H)

a) An absorption of the cyano group was so weak that it was not observed by the KBr disc method. And ir spectrum in solution was not measured because of low solubility in chloroform, dichloromethane and acetone.

Table 3. Analytical Data of 1-Alkyl[1,2,4]triazolo[1,5-a]pyridinium Salts (2)

Compound No.	Appearance (Recrystn. Solvt.)	Formula	Analysis (%) Calcd (Found) C	H	N
2a	colorless prisms (EtOH)	$C_{14}H_{12}BrN_3O\ H_2O$	50.02 (50.05	4.20 4.13	12.50 12.26)
2b	colorless prisms (MeOH)	$C_9H_{10}BrN_3O_2$	39.73 (39.49	3.70 3.74	15.44 15.41)
2c	pale yellow prisms (EtOH)	$C_8H_7BrN_4$	40.19 (40.00	2.95 3.05	23.44 23.39)

Thermal Reaction of 3b --- Triethylamine (0.14 ml, 1 mmol) was added to a solution of 1-(methoxycarbonyl)methyl[1,2,4]triazolo[1,5-a]pyridinium bromide (2b)(272 mg, 1 mmol) in dry acetonitrile (10 ml) under a nitrogen atmosphere and the mixture was heated under reflux for 2h. After cooling to room temperature, the solvent was evaporated under reduced pressure. The residue was ex-

tracted several times with chloroform, and the extracts were washed with saturated aqueous NaCl solution and dried over $MgSO_4$. The solvent was removed under reduced pressure to afford 2-[N-cyano-N-(methoxycarbonyl)amino]pyridine (4b)(117 mg, 61%). Recrystallization from AcOEt-petroleum ether gave colorless prisms, mp 63-65°C; ir (KBr) cm^{-1} : 1760 (CO), 2240 (CN); ^{1}H-nmr ($CDCl_3$) δ : 3.80 (3H, s, OCH_3), 4.62 (2H, s, CH_2), 6.94-8.36 (4H, m, ArH); ms m/z: 191 (M^+). Anal. Calcd for $C_9H_9N_3O_2$: C, 56.54; H, 4.75; N, 21.98. Found: C, 56.39; H, 4.73; N, 21.74.

Thermal Reaction of 3c --- 2-[N-Cyano-N-(cyanomethyl)amino]pyridine (4c) was obtained in quantitative yield by the similar procedure as for 4b. Recrystallization from benzene-petroleum ether gave pale brown prisms, mp 72-73.5°C; ir (KBr) cm^{-1} : 2240 (CN); ^{1}H-nmr ($CDCl_3$) δ : 4.82 (2H, s, CH_2), 7.05-8.48 (4H, m, ArH); ms m/z: 158 (M^+). Anal. Calcd for $C_8H_6N_4$: C, 60.75; H, 3.82; N, 35.42. Found: C, 60.96; H, 3.79; N, 35.22.

Thermal Reaction of 3a --- 2-(2-Imino-5-phenyl-2,3-dihydrooxazol-3-yl)pyridine (5) was obtained by the similar mehtod as above and purified by preparative TLC (AcOEt:hexane=1:2) as an oil (yield 29%); ir (KBr) cm^{-1} :1680 (O-C=N), 3270 (NH); ^{1}H-nmr ($CDCl_3$) δ : 4.88 (1H, br s, NH), 7.88 (1H, s, oxazoline H), 6.98-8.64 (9H, m, ArH); ms m/z: 237 (M^+). The product 5 was coverted to 2-(2-oxo-5-phenyl-2,3-dihydrooxazol-3-yl)pyridine (6) by stirring with silica gel in chloroform. The compound 6 was purified by preparative TLC (AcOEt:hexane=1:2). Recrystallization from hexane gave colorless needles (yield 56%), mp 119-121.5°C; ir (KBr) cm^{-1} : 1735 (CO); ^{1}H-nmr ($CDCl_3$) δ : 8.00 (1H, s, oxazoline H), 7.98-8.58 (9H, m, ArH); ms m/z: 238 (M^+). Anal. Calcd for $C_{14}H_{10}N_2O_2$: C, 70.58; H, 4.23; N, 11.76. Found: C, 70.72; H, 4.33; N, 11.63.

Reaction of 3a with MP --- Triethylamine (0.14 ml, 1 mmol) was added slowly to a solution of 2a (477 mg, 1.5 mmol) and MP (252 mg, 3 mmol) in dry acetonitrile (20 ml) under a nitrogen atmosphere at room temperature. After the mixture was stirred for 6h at room temperature, the solvent was evaporated under reduced pressure. The residue was extracted with chloroform and the extracts were dried over $MgSO_4$. The solvent was removed under reduced pressure to give an oily product which was separated by preparative TLC (AcOEt:hexane=1:3) to afford 7-[2-benzoyl-4-(methoxycarbonyl)pyrrol-1-yl]-3-(methoxycarbonyl)pyrazolo[1,5-a]pyridine (9a) (137 mg, 23%) in addition to a trace amount of 5. Compound 9a was recrystallized from benzene-petroleum ether to give yellow prisms, mp 145-147°C; ir (KBr) cm^{-1} : 1635, 1710 (CO); ^{1}H-nmr ($CDCl_3$) δ :3.87, 3.90 (each 3H, each s, OCH_3X2), 7.55, 7.80 (each 1H, each d, J=1.5Hz, pyrrole H), 8.28 (1H, s, C_2-H), 7.05-8.41 (8H, m, ArH); ms m/z: 403 (M^+). Anal. Calcd for $C_{22}H_{17}N_3O_5$: C, 65.50; H, 4.25; N, 10.42. Found: C, 65.71; H, 4.23; N, 10.36.

Reaction of 3b with MP --- The crude products were obtained from 2b (432 mg, 1.58 mmol), triethylamine (0.55 ml, 3.95 mmol) and MP (332 mg, 3.95 mmol) by the similar reaction as for 3a,

and separated by preparative TLC (AcOEt:hexane=1:3) to give 7-[2,4-di(methoxycarbonyl)pyrrol-1-yl]-3-(methoxycarbonyl)pyrazolo[1,5-a]pyridine (9b) (67 mg, 19%) and 4b (174 mg, 58%). Compound (9b) was recrystallized from benzene-petroleum ether to give colorless needles, mp 202.5-203.5°C; ir (KBr) cm^{-1} : 1730 (CO); ^{1}H-nmr ($CDCl_3$) δ : 3.65, 3.87, 3.94 (each 3H, each s, OCH_3X3), 7.60, 7.68 (each 1H, each d, J=1.5Hz, pyrrole H), 8.37 (1H, s, C_2-H), 7.00-8.45 (3H, m, ArH); ms m/z: 357 (M^+). Anal. Calcd for $C_{17}H_{15}N_3O_6$: C, 57.14; H, 4.23; N, 11.76. Found: C, 57.40; H, 4.20; N, 11.75.

Reaction of 3c with MP --- The crude products were obtained from 2c (239 mg, 1 mmol), triethylamine and MP (168 mg, 2 mmol) by the similar reaction as above and separated by preparative TLC (AcOEt:hexane=1:3) to give 7-[2-cyano-4-(methoxycarbonyl)pyrrol-1-yl]-3-(methoxycarbonyl)pyrazolo-[1,5-a]pyridine (9c) (8 mg, 2.5%) and 4c (89 mg, 56%). Compound 9c (oil): ^{1}H-nmr ($CDCl_3$) δ : 3.87, 3.97 (each 3H, each s, OCH_3X2), 7.45, 7.58 (each 1H, each d, J=1.5Hz, pyrrole H), 8.48 (1H, s, C_2-H), 7.15-8.35 (3H, m, ArH); ms m/z: 324 (M^+).

Reaction of 3a with DMAD --- A mixture of 2a (278 mg, 0.87 mmol), triethylamine and DMAD (247 mg, 1.74 mmol) in dry acetonitrile (20 ml) was stirred for 3.5 h at room temperature and the solvent was evaporated. The oily product was separated by preparative TLC (ether:hexane=2:1) to afford 7-[2-benzoyl-3,4-di(methoxycarbonyl)pyrrol-1-yl]-2,3-di(methoxycarbonyl)pyrazolo[1,5-a]pyridine (10a) (47 mg) and a mixture of 8d and 10a (190 mg). The mixture was treated with chloranil (106 mg, 0.43 mmol) in benzene (10 ml) under reflux for 2 h to give 10a (164 mg, total 36%). Compound 10a was recrystallized from benzene-petroleum ether to give yellow prisms, mp 141.5-143°C: ir (KBr) cm^{-1} : 1640, 1720, 1740 (CO); ^{1}H-nmr ($CDCl_3$) δ:3.29, 3.75, 3.85, 3.86 (each 3H, each s, OCH_3X4), 7.71 (1H, s, pyrrole H), 7.17-7.94 (7H, m, ArH), 8.24 (1H, dd, J=9.6, 1.5 Hz, C_4 or C_6-H); ms m/z: 519 (M^+). Anal. Calcd for $C_{26}H_{21}N_3O_4$: C, 60.12; H, 4.07; N, 8.09. Found. C, 59.97; H, 4.10; N, 8.03.

Reaction of 3b with DMAD --- A crude product was obtained from the reaction of 2b (761 mg, 2.8 mmol), DMAD (796 mg, 5.6 mmol) and triethylamine (0.78 ml, 5.6 mmol) in dry acetonitorile (30 ml) at room temperature for 3.5 h and separated by column chromatography (AcOEt:hexane=1:2) to give 4b (53 mg, 9.9%) and a mixture of 8e and 10b (686 mg). The mixture of 8e and 10b was heated with chloranil (426 mg, 1.73 mmol) in benzene (30 ml) under reflux for 2 h. The solvent was removed under reduced pressure to afford 2,3-di(methoxycarbonyl)-7-[2,3,4-tri(methoxycarbonyl)pyrrol-1-yl]pyrazolo[1,5-a]pyrididine (10b) (516 mg, 39%), which was purified by column chromatography (AcOEt:hexane=1:2) and recrystallized from AcOEt to give a colorless powder, mp 222.5-224°C; ir (KBr) cm^{-1} : 1720, 1740 (CO); ^{1}H-nmr ($CDCl_3$) δ:3.61, 3.84, 3.93, 3.97, 3.99 (each 3H, each s, OCH_3X5), 7.12 (1H, dd, J=7.2, 1.5Hz, C_4 or C_6-H), 7.59 (1H, dd, J=9.0, 7.2Hz, C_5-H), 7.61 (1H, s, pyrrole H), 8.35 (1H, dd, J=9.0, 1.5Hz, C_4 or C_6-H); ms m/z: 473 (M^+). Anal. Calcd for $C_{21}H_{19}N_3O_{10}$:

C, 53.28; H, 4.05; N, 8.88. Found: C, 53.09; H, 4.02; N, 8.90.

Reaction of 3c with DMAD --- A crude product was obtained from the reaction of dry triethylamine (0.28 ml, 2 mmol), 2c (195 mg, 0.82 mmol) and DMAD (284 mg, 2 mmol) in dry acetonitrile (10 ml) and separated by column chromatography (AcOEt:hexane=1:1) to give 4c (18 mg, 14%) and a mixture of 8f and 10c. The mixture of 8f and 10c was heated with chloranil (400 mg, 1.6 mmol) in benzene (10 ml) under reflux for 12 h and purified by column chromatography (AcOEt:hexane=1:1) to afford 7-[2-cyano-3,4-di(methoxycarbonyl)pyrrol-1-yl]-2,3-di(methoxycarbonyl)pyrazolo[1,5-a]pyridine (10c). Compound (10c) was recrystallized from benzene-petroleum ether to give colorless prisms, mp 185-187°C; ir (KBr) cm^{-1} : 1720, 1740 (CO), 2240 (CN); ^{1}H-nmr ($CDCl_3$) δ : 3.89, 3.97, 4.00, 4.02 (each 3H, each s, OCH_3X4), 7.31 (1H, dd, J=7.2, 1.5Hz, C_4 or C_6-H), 7.67 (1H, dd, J=9.0, 7.2Hz, C_5-H), 7.91 (1H, s, pyrrole H), 8.41 (1H, dd, J=9.0, 1.5Hz, C_4 or C_6-H); ms m/z:440 (M^+). Anal. Calcd for $C_{20}H_{16}N_4O_8$: C, 54.55; H, 3.66; N, 12.72. Found: C, 54.49; H, 3.57; N, 12.64.

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