Condensation Reaction of 3,4-Dibenzoyl-1-methyl-2,5-diphenylpyrrole and -1-phenylpyrazole with Methylamine Derivatives Affording Pyrrolo [3,4-*c*]pyridine and 2*H*-Pyrazolo[3,4-*c*]- and [4,3-*c*]pyridines

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The reaction of 3,4-dibenzoyl-1-methyl-2,5-diphenylpyrrole (**1**) and -1-phenylpyrazole (**2**) with methylamines (**3a-c**) afforded pyrrolo[3,4-*c*]pyridine (**4**), and isomeric 2*H*-pyrazolo[3,4-*c*]pyridines (**5a-c**) and [4,3-*c*]pyridines (**6a-c**), respectively.

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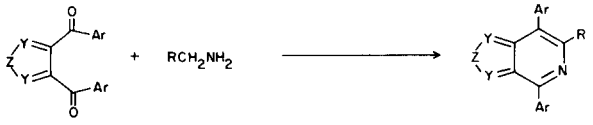
We have previously reported that the reaction of 3,4-diaroyl-1,2,5-thia- and 1,2,5-oxadiazoles and *o*-dibenzoylbenzene with methylamine derivatives gave 1,2,5-thia- and 1,2,5-oxadiazolo[3,4-*c*]pyridines (1,2) and 3-substituted 1,4-diphenylisoquinolines (3), respectively.

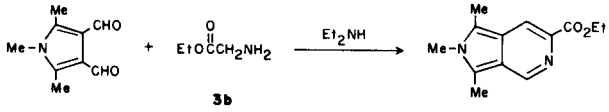


Ar = C_6H_5-, p-ClC_6H_4-, p-$CH_3C_6H_4$-

R = Alkyl, aryl, $-CH=CH_2$, $-CH_2OH$, $-CN$, $-CO_2Et$, $-COC_6H_5$

Y = N, Z = O; Y = N, Z = S; Y = CH, Z = -CH=CH-

To our knowledge, the reaction of 3,4-diformyl-1,2,5-trimethylpyrrole with ethylglycinate (**3b**) (6) is the only known example of the base-catalyzed condensation reaction of vicinally dicarbonyl-substituted heterocycles to alkylamine affording pyridine fused heterocycles except for our studies (1-3).

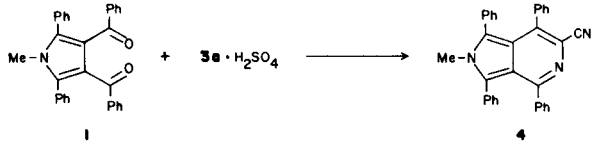


3b

As an extenstion of the above reaction, we now report the condensation reaction of 3,4-dibenzoyl-2,5-diphenyl-1-methylpyrrole (**1**) (4) and 3,4-dibenzoyl-1-phenylpyrazole (**2**) (5) with aminoacetonitrile (**3a**), ethyl glycinate (**3b**), and benzylamine (**3c**).

Results and Discussions

In the reaction of **1** with cyanomethylammonium hydrogen sulfate (**3a**·H_2SO_4) in refluxing butanol for 24 hours, expected cyano-substituted pyrrolo[3,4-*c*]pyridine (**4**) was obtained in 62% yield, accompanied with recovery of **1** in 12% yield.



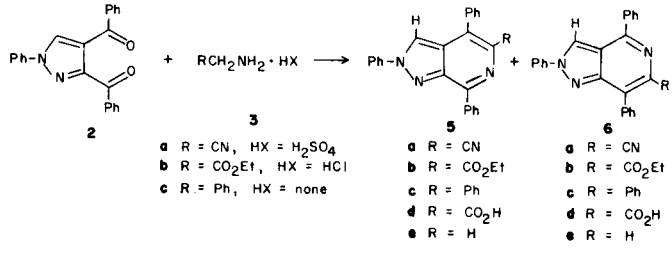
1 **4**

The reaction of **1** with **3b** in the presence of potassium *t*-butoxide or potassium hydroxide did not give the expected pyrrolo[3,4-*c*]pyridine and unreacted **1** was recovered. The reaction of **1** with ethyl glycinate hydrogen chloride (**3b**·HCl) in refluxing butanol also resulted in the recovery of **1** in 56% yield.

The reaction of **1** with **3c** in the presence of strong base such as DBU or potassium *t*-butoxide did not proceed in refluxing toluene or *t*-butyl alcohol, and **1** was recovered quantitatively. When **1** was heated in an excess of **3c** at 140-150° for 4 days, 19% yield of **1** was recovered with a large amount of tarry materials.

Next, we investigated the condensation reaction of dibenzoylpyrazole (**2**) with **3**, expecting the formation of two isomeric pyrazolopyridines.

The reaction of **2** with the mineral acid salts of amines bearing an electron-withdrawing group afforded the corresponding two isomeric pyrazolopyridines, **5a** and **6a**, and **5b** and **6b**, in the yields shown in Table I



2 **3** **5** **6**

a R = CN, HX = H_2SO_4
b R = CO_2Et, HX = HCl
c R = Ph, HX = none

Table I

The Reaction of Pyrazole (**2**) with Methylamines (**3**)

Run	3	Base	Products (% Yield)
1	**3a**·H_2SO_4		**5a** (8), **6a** (32)
2	**3b**·HCl		**5b** (8), **6b** (37)
3	**3c**		**5c** (1), **6c** (5)
4	**3c**	DBU	**5c** (7), **6c** (19)

When **2** was heated in a large excess of **3c** at 140-150° for 15 hours, the expected tetraphenylpyrazolopyridines, **5c** and **6c**, were formed in 1 and 5% yields, respectively. Addition of a small amount of DBU raised the yields of **5c** and **6c** up to 7 and 19%, respectively.

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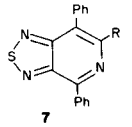
The structural assignment of the isomers, **5** and **6**, were done on the basis of ^{1}H-nmr spectral study, as is described below.

The two *ortho*-protons of the phenyl group on the 7-position of **5a-e** appeared in the region of 8.6-8.9 ppm, while such a down field shift was not observed in the ^{1}H-nmr spectra of **6a-e**. In the ^{1}H-nmr spectra of **7** (1-2) and **8** (1-2), two *ortho*-protons of the phenyl group on the 4-position appeared in the region of 8.5-8.8 ppm, respectively (1, 2).



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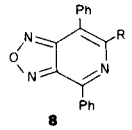
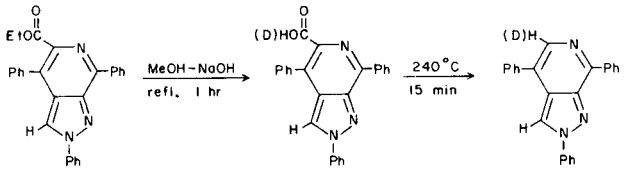
(R = NC, EtO_2C, C_6H_5)



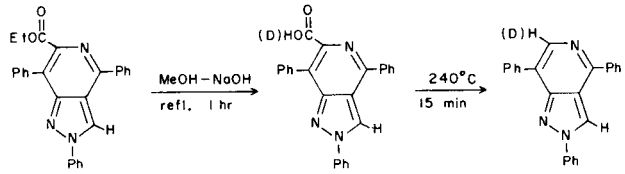
8

(R = NC, EtO_2C, C_6H_5)

Furthermore, the pyrazole ring protons of **6a-c** were observed in a lower region than those of **5a-c**. We assume that such a shift may be due to the magnetic anisotropy caused by the restricted rotation of the phenyl group on the 4-position in **5a-c**. Thus, the esters, **5b** and **6b**, were hydrolyzed in refluxing methanolic sodium hydroxide and the obtained carboxylic acids were decarboxylated to afford the corresponding triphenylpyrazolopyridines **5e** and **6e**, respectively. In the ^{1}H-nmr spectrum of **5e**, the pyrazole ring proton appeared at δ 8.62 ppm, which is *ca.* 0.4 ppm lower than that of **5b**.



5b **5d** **5e**



6b **6d** **6e**

On the other hand, the difference between the pyrazole ring proton of **6b** and that of **6e** is *ca.* 0.1 ppm. Assignment of the pyrazole ring protons of **5e** and **6e** was based upon the preparation of deuterated **5e** and **6e** (isotopic purities determined based on mass spectra, were 58 and 33%, respectively) by the pyrolysis of the deuterated carboxylic acids, which were obtained by the treatment of the corresponding carboxylic acids with deuterium oxide in dueteriochloroform.

From the above, we assigned the structure of **5** and **6** as 2,4,7-triphenyl-2*H*-pyrazolo[3,4-*c*]pyridine, and 2,4,7-triphenyl-2*H*-pyrazolo[4,3-*c*]pyridine, respectively.

EXPERIMENTAL

All melting points are uncorrected. Ir spectra were measured on a Nippon Bunko A-102 spectrophotometer as potassium bromide pellets. ^{1}H-nmr were determined at 100 MHz on a Nippon Denshi JEOL FT-100 in deuteriochloroform using TMS as an internal standard. Mass spectra were obtained on a Nippon Denshi JMS-01SG-2 mass spectrometer at 75 eV using a direct inlet system. Column chromatography was carried out using Wako gel C-300.

Reaction of **1** with **3a**·H_2SO_4.

A mixture of **1** (300 mg) and **3a**·H_2SO_4 (1070 mg) in 30 ml of butanol was refluxed for 24 hours and was cooled to room temperature. The precipitate was filtered off and the filtrate was evaporated *in vacuo* to leave the residue which was triturated with ethanol affording 196 mg of 6-cyano-2-methyl-1,3,4,7-tetraphenylpyrrolo[3,4-*c*]pyridine (**4**). From the ethanol filtrate, 35 mg of **1** was recovered.

Compound **4** was obtained as yellow needles (hexane), mp 232-234°; ms: m/e (relative intensity) 461 (M^+ 100); ^{1}H-nmr: δ 3.60 (s, 3H), 6.90 – 7.43 ppm (m, 20H).

Anal. Calcd. $C_{33}H_{23}N_3$: C, 85.87; H, 5.02; N, 9.10. Found: C, 85.76; H, 5.09; N, 8.97.

Reaction of **2** with **3a**·H_2SO_4.

A mixture of **2** (300 mg) and **3a**·H_2SO_4 (1312 mg) in 30 ml of butanol was refluxed for 24 hours and was cooled to room temperature. Precipitates were filtered and washed with benzene. The combined filtrate and washings were evaporated *in vacuo* to leave the residue, which was dissolved in 3 ml of benzene and subjected to column chromatography. Compound **5a** (25 mg) was eluted with a 1:2 mixture of hexane and benzene, and **6a** (100 mg) was eluted with benzene and chloroform.

5-Cyano-2,4,7-triphenylpyrazolo[3,4-*c*]pyridine (**5a**).

This compound was obtained as colorless needles (1:1 mixture of hexane and benzene), mp 231-232°; ir: ν CN 2215 cm^{-1}; ms: m/e (relative intensity) 372 (M^+ 60), 344 (M^+ – CN 34); ^{1}H-nmr: δ 7.46-7.61 (m, 9H), 7.66-7.78 (m, 2H), 7.86-7.98 (m, 2H), 8.49 (s, 1H), 8.73-8.83 ppm (m, 2H). *Anal.* Calcd. for $C_{25}H_{16}N_4$: C, 80.63; H, 4.33; N, 15.04. Found: C, 80.36; H, 4.50; N, 15.10.

6-Cyano-2,4,7-triphenylpyrazolo[4,3-*c*]pyridine (**6a**).

This compound was obtained as colorless needles (1:1 mixture of hexane and benzene), mp 243-244°; ir: ν CN 2215 cm^{-1}; ms: m/e (relative intensity) 372 (M^+ 100), 77 (Ph 22); ^{1}H-nmr: δ 7.43-7.62 (m, 9H), 7.83-8.14 (m, 6H), 8.82 ppm (s, 1H).

*Anal.*Calcd. for $C_{25}H_{16}N_4$: C, 80.63; H, 4.33; N, 15.04. Found: C, 80.56; H, 4.55; N, 14.94.

Reaction of **2** with **3b**·HCl.

A mixture of **2** (300 mg) and **3b**·HCl (1188 mg) in 30 ml of butanol was refluxed for 96 hours. Solvent was evaporated *in vacuo* and the residue was dissolved into 3 ml of benzene, which was subjected to column chromatography.

The fraction eluted with a 1:1 mixture of hexane and benzene afforded oily materials which, on trituration with hexane, gave 28 mg of **5b**. The compound **6b** (132 mg) was eluted with benzene and chloroform.

Ethyl 2,4,7-Triphenyl-2*H*-pyrazolo[3,4-*c*]pyridine-5-carboxylate (**5b**).

This compound was obtained as colorless needles (hexane), mp 109-111°; ir: ν CO, 1722 cm^{-1}; ms: m/e (relative intensity) 419 (M^+ 52), 346 (M^+-$CO_2C_2H_5$ 100); ^{1}H-nmr: δ 0.98 (t, 3H), 4.10 (q, 2H), 7.26-7.48 (m, 11H), 7.75-7.87 (m, 2H), 8.23 (s, 1H), 8.67-8.77 ppm (m, 2H).

Anal. Calcd. for $C_{27}H_{21}N_3O_2$: C, 77.31; H, 5.05; N, 10.02. Found: C, 77.49; H, 5.29; N, 9.91.

Ethyl 2,4,7-Triphenyl-2*H*-pyrazolo[4,3-*c*]pyridine-6-carboxylate (**6b**).

This compounds was obtained as colorless prisms (hexane), mp 116-118°; ir: ν CO 1735 cm^{-1}; ms: m/e (relative intensity) 419 (M^+ 32), 347 (M^+-$CO_2C_2H_5$ 50), 77 (Ph 100); ^{1}H-nmr: δ 1.04 (t, 3H), 4.17 (q, 2H), 7.35-7.50 (m, 9H), 7.60-7.73 (m, 2H), 7.76-7.88 (m, 2H), 7.97-8.12 (m, 2H), 8.72 ppm (s, 1H).

Anal. Calcd. for $C_{27}H_{21}N_3O_2$: C, 77.31; H, 5.05; N, 10.02. Found: C, 77.20; H, 5.49; N, 9.57

Reaction of **2** with **3c**.

(i) In the Absence of DBU

A mixture of **2** (300 mg) in 6 ml of **3c** was stirred at 140-150° for 15 hours. It was cooled to room temperature and subjected to column chromatography using a 1:2 mixture of hexane and benzene to afford 24 mg of 1:4 mixture (determined by ^{1}H-nmr) of **5c** and **6c**.

(ii) In the Presence of DBU

A mixture of **2** (300 mg) and DBU (0.8 ml) in 20 ml of **3c** was stirred at 140-150° for 15 hours and treated as described above. Compound **5c** (27 mg) was eluted with a 1:2 mixture of hexane and benzene, and then **6c** (67 mg) was eluted with benzene.

2,4,5,7-Tetraphenyl-2*H*-pyrazolo[3,4-*c*]pyridine (**5c**).

This compound was obtained as colorless needles (hexane), mp 273-275°; ms: m/e (relative intensity) 423 (M^+ 100), 422 (86), 77 (Ph 17); ^{1}H-nmr: δ 7.17-7.58 (m, 16H), 7.83-7.96 (m, 2H), 8.29 (s, 1H), 8.78-8.90 ppm (m, 2H).

Anal. Calcd. for $C_{30}H_{21}N_3$: C, 85.08; H, 5.00; N, 9.92. Found: C, 84.90; H, 5.05; N, 9.68.

2,4,6,7-Tetraphenyl-2*H*-pyrazolo[4,3-*c*]pyridine (**6c**).

This compound was obtained as colorless needles (hexane), mp 270-271°; ms: m/e (relative intensity) 423 (M^+ 100), 422 (95), 77 (Ph 9); ^{1}H-nmr: δ 7.17-7.57 (m, 16H), 7.78-7.91 (m, 2H), 8.05-8.17 (m, 2H), 8.71 ppm (s, 1H).

Anal. Calcd. for $C_{30}H_{21}N_3$: C, 85.08; H, 5.00; N, 9.92. Found: C, 84.97; H, 5.07; N, 9.73.

Hydrolysis of **5b**.

After a mixture of **5b** (25 mg) and sodium hydroxide (1.0 g) in 10 ml of methanol was refluxed for 1 hour, it was poured into 10% hydrogen chloride solution (30 ml) and extracted with benzene (20 ml × 2). The benzene solution was dried over sodium sulfate and evaporated to afford **5d** in 31% yield.

2,4,7-Triphenyl-2*H*-pyrazolo[3,4-*c*]pyridine-5-carboxylic acid (**5d**).

This compound was obtained as colorless needles (acetone), mp 225-227° dec; ir: ν CO 1755 cm^{-1}; ms: m/e (relative intensity) 391 (35), 347 (100), 346 (51), 319 (24), 270 (23), 242 (25); ^{1}H-nmr: δ 7.48-7.66 (m, 11H), 7.86-7.98 (m, 2H), 8.32 (s, 1H), 8.63-8.75 (m, 2H), 11.52 ppm (s, 1H).

Anal. Calcd. for $C_{25}H_{17}N_3O_2$: C, 76.71; H, 4.38; N, 10.73. Found: C, 76.46; H, 4.36; N, 10.85.

Hydrolysis of **6b**.

Hydrolysis of **6b** was carried out as described above to give **6d** in 55% yield.

2,4,7-Triphenyl-2*H*-pyrazolo[4,3-*c*]pyridine-6-carboxylic acid (**6d**).

This compound was obtained as colorless needles (methanol), mp 215-216° dec; ir: ν CO 1770 cm^{-1}; ms: m/e (relative intensity) 391 (15), 347 (81), 270 (35), 215 (19), 76 (100); ^{1}H-nmr: δ 7.43-7.68 (m, 11H), 7.80-7.95 (m, 2H), 7.98-8.13 (m, 2H), 8.83 ppm (s, 1H).

Anal. Calcd. for $C_{25}H_{17}N_3O_2$: C, 76.71; H, 4.38; N, 10.73. Found: C, 76.36; H, 4.61; N, 10.68.

Decarboxylation of **5d**.

After **5d** (230 mg) was heated at 240-260° for 15 minutes in a silicon bath, it was cooled to room temperature. Trituration with a mixture of hexane and benzene afforded **5e** in 57% yield.

2,4,7-Triphenyl-2*H*-pyrazolo[3,4-*c*]pyridine (**5e**).

This compound was obtained as colorless prisms (hexane), mp 148-151°; ms: m/e (relative intensity) 347 (100), 319 (41), 270 (28); ^{1}H-nmr: δ 7.30-7.64 (m, 9H), 7.69-7.83 (m, 2H), 7.92-8.06 (m, 2H), 8.39 (s, 1H), 8.62 (s, 1H), 8.68-8.81 ppm (m, 2H).

Anal. Calcd. for $C_{24}H_{17}N_3$: C, 82.97; H, 4.93; N, 12.09. Found: 82.72; H, 4.96; N, 11.66.

Decarboxylation of **6d**.

The compound **6d** was treated as described above to give **6e** in 76% yield.

2,4,7-Triphenyl-2*H*-pyrazolo[4,3-*c*]pyridine (**6e**).

This compound was obtained as colorless prisms (hexane), mp 133-134°; ms: m/e (relative intensity) 347 (100), 270 (36), 215 (49), 77 (76); ^{1}H-nmr: δ 7.48-7.73 (m, 9H), 7.93-8.32 (m, 6H), 8.68 (s, 1H), 8.81 ppm (s, 1H).

Anal. Calcd. for $C_{24}H_{17}N_3$: C, 82.97; H, 4.93; N, 12.09. Found: C, 82.65; H, 4.96; N, 12.28.

REFERENCES AND NOTES

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