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A convenient synthesis of derivatives of the pyrido[1′,2′:1,5]pyrazolo[3,4-*d*]pyrimidine ring system from readily available 2-amino-3-cyano-5,7-diphenylpyrazolo[1,5-*a*]pyridine I and carbon disulfide, aryl isothiocyanates or nitriles is described. Derivatives of compound I undergo cyclization to the titled ring system by action of dimethylformamide dimethylacetal or hydrogen sulfide followed by treatment with triethylamine.

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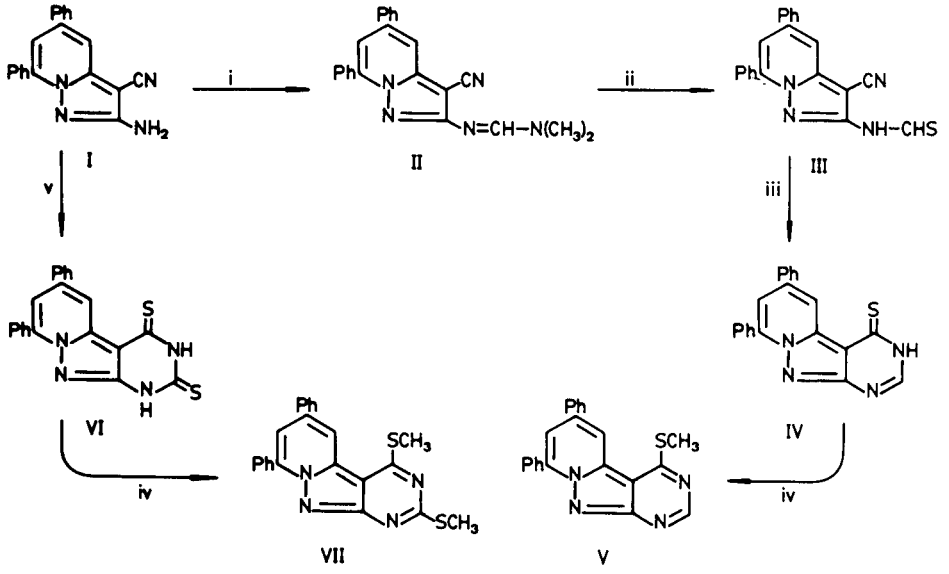
Derivatives of the pyrazolo[3,4-*d*]pyrimidine ring system are known to possess potent biological and pharmacological properties [3]. As a part of our continuing study on the synthesis of pharmacologically interesting fused heterocycles such as *s*-triazolo[1,5-*a*]pyridine [4] or 1,3,4-thiadiazolo[3,4-*a*]pyridine derivatives [5,6], we became interested in the synthesis of new heterocyclic systems derived from pyrazolo[3,4-*d*]pyrimidine and incorporating potential pharmacologically active molecules such as pyridine. In this context, we now wish to report the conversion of 2-amino-3-cyano-5,7-diphenylpyrazolo[1,5-*a*]pyridine (I) into derivatives of the new heterocyclic system incorporating the pyrimidine moiety, namely, pyrido[1′,2′:1,5]pyrazolo-[3,4-*d*]pyrimidine.

Compound I, readily available from 1-amino-4,6-diphenyl-2-methylthiopyridinium iodide and malononitrile [7], reacts with dimethylformamide dimethylacetal in benzene solution to give the *N,N*-dimethylaminomethyleneamino derivative II as crystalline solid in high yield (82%). Compound II, reacts smoothly in acetone solution with hydrogen sulfide to give the desired thioformylamine derivative III in high yield (84%). It is known that *o*-cyanothioformylamines undergo cyclization and further rearrangement in the presence of bases to give derivatives of the pyrimidine-4-thione ring system [8].

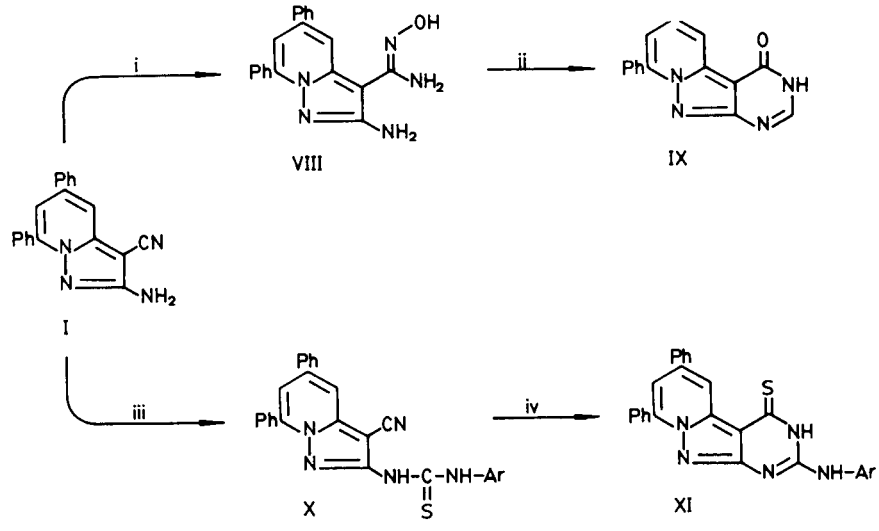
When treated with bases, compound III is directly converted to the corresponding pyrimidine-4-thione derivative IV. The best result is obtained when the reaction is carried out in the presence of triethylamine with pyridine as solvent (95%). Compound IV, undergoes *S*-methylation by reaction with methyl iodide in the presence of sodium methoxide, yielding the methylthio derivative V, which shows in the ^{1}H-nmr spectrum a singlet at δ 2.85 ppm attributable to S-CH_3 group (Table II).

On the other hand, compound I reacts with carbon disulfide in pyridine solution at reflux temperature to give the pyrimidine-1,3-dithione derivative VI as crystalline solid in near quantitative yield, which undergoes *S*-meth-



Reagents; i: $HC(OCH_3)_2N(CH_3)_2$; ii: SH_2/acetone; iii: Et_3N/pyridine; iv: $ICH_3/NaOCH_3$; v: CS_2

Scheme 1



Reagents; i: H_2N-OH; ii: $HC(OCH_3)_2N(CH_3)_2$; iii: Ar-NCS/DMF/Et_3N/RT; iv: Et_3N/∇

Scheme 2

ylation to give the corresponding bis(methylthio) derivative VII. The ^{1}H-nmr spectrum of VII shows two singlets at δ 2.72 and δ 2.86 ppm attributable to the S-CH_3 groups.

When compound I is treated with hydroxylamine, it is converted into the derivative VIII, which undergoes cyclization by reaction with dimethylformamide dimethylacetal to give the pyrimidone derivative IX. An alternative route to IX involves the reaction of 2-amino-3-carbamoyl-5,7-diphenylpyrazolo[1,5-*a*]pyridine, readily available from 1-amino-4,6-diphenyl-2-methylthiopyridinium iodide and cyanoacetamide [7], with dimethylformamide dimethylacetal.

The reaction of compound I with aryl isothiocyanates at room temperature in dimethylformamide in the presence of triethylamine leads to the corresponding *N,N'*-disubstituted thioureas X, isolable as crystalline solids in high yields (78-84%) (Table I). When compounds X are treated with triethylamine in pyridine solution at reflux tempera-

Table I

Pyrido[1',2':1,5]pyrazolo[3,4-*d*]pyrimidine Derivatives Prepared

Compound No.	Ar	Yield (%)	Mp (°C)	Molecular Formula	Analyses (%) Calcd. C	H	N	Found C	H	N
IV		95	330	$C_{21}H_{14}N_4S$ (354.4)	71.16	3.98	15.80	71.25	3.90	15.72
V		89	340	$C_{22}H_{16}N_4S$ (368.5)	71.73	4.34	15.21	71.58	4.25	15.36
VI		95	>350	$C_{21}H_{14}N_4S_2$ (386.5)	65.26	3.65	14.49	65.08	3.65	14.25
VII		80	>350	$C_{23}H_{18}N_4S_2$ (414.5)	66.66	4.35	13.51	66.78	4.31	13.40
IX		79	336	$C_{21}H_{14}N_4O$ (338.4)	74.54	4.17	16.56	74.77	4.03	16.58
XIa	4-BrC_6H_4	85	295	$C_{27}H_{18}BrN_5S$ (524.4)	61.84	3.46	13.35	61.75	3.42	13.40
XIb	4-ClC_6H_4	84	272	$C_{27}H_{18}ClN_5S$ (479.9)	67.64	3.75	14.61	67.56	3.70	14.53
XIc	4-$H_3CC_6H_4$	90	235	$C_{28}H_{21}N_5S$ (459.6)	73.20	4.57	15.25	73.31	4.51	15.18
XIIa	CH_3	90	>350	$C_{22}H_{17}N_5$ (351.4)	75.19	4.88	19.93	74.93	4.62	20.12
XIIb	C_6H_5	57	>350	$C_{27}H_{19}N_5$ (413.5)	78.43	4.63	16.93	78.61	4.52	17.17

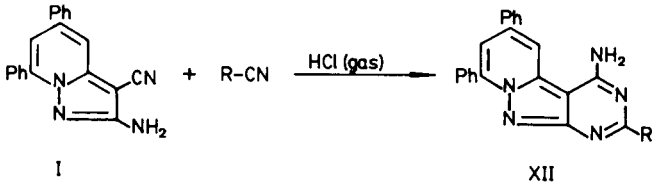
Table II

Spectral Data of Pyrido[1′,2′:1,5]pyrazolo[3,4-*d*]pyrimidine Derivatives

Compound No.	IR (cm^{-1}, Nujol)	^{1}H-NMR (ppm)	MS, m/e (%)
IV	3180, 3040, 1645, 1600, 1550, 1500, 1470, 1190, 1160, 1025, 765, 750, 700	12.2 (1H, s), 8.25-7.63 (13H, m)	354 (M^+, 83), 353 (100), 326 (16), 295 (7), 294 (11), 203 (5), 202 (7), 77 (12)
V	3060, 1640, 1620, 1600, 1570, 1450, 1380, 1160, 1150, 1020, 770, 700	8.7-7.3 (13H, m), 2.85 (3H, s)	368 (M^+, 94), 367 (100), 353 (6), 352 (6), 321 (14), 296 (31), 202 (15), 77 (16)
VI	3380, 3040, 1640, 1600, 1500, 1450, 1430, 1230, 1180, 1150, 1130, 750, 710, 690	8.86 (1H, s), 8.62 (1H, s), 8.2-7.25 (12H, m)	386 (M^+, 92), 354 (34), 353 (100), 327 (7), 326 (15), 295 (10), 202 (7), 77 (7)
VII	3040, 1635, 1580, 1560, 1500, 1480, 1380, 1170, 1020, 780, 750, 700, 680	8.4-7.42 (12H, m) 2.86 (3H, s) 2.72 (3H, s)	414 (M^+, 100), 399 (45), 367 (15), 353 (29), 351 (16), 77 (15)
IX	3220, 1730, 1675, 1620, 1550, 1500, 1475, 1390, 1220, 1125, 860, 785, 770, 700	9.33 (1H, s), 8.08-7.25 (13H, m)	338 (M^+, 99), 337 (100), 310 (7), 282 (23), 255 (20), 227 (23), 226 (23), 203 (19), 115 (11), 77 (40)
XIa	3400, 3160, 1650, 1640, 1600, 1570, 1525, 1485, 1340, 1300, 1265, 1180, 1110, 1075, 960, 860, 830, 760, 700	9.1 (1H, s), 8.5-7.25 (16H, m), 6.75 (1H, s)	
XIb	3410, 3150, 3060, 1660, 1640, 1605, 1585, 1540, 1490, 1410, 1380, 1160, 1090, 1010, 850, 760, 700	9.1 (1H, s) 8.6-7.3 (16H, m), 6.8 (1H, s)	
XIc	3420, 3160, 3060, 1660, 1650, 1610, 1600, 1550, 1500, 1470, 1430, 1380, 1170, 1120, 1040, 820, 770, 710	9.2 (1H, s) 9.35-7.05 (16H, m), 6.7 (1H, s), 2.25 (3H, s)	459 (M^+, 33), 458 (47), 426 (10), 425 (11), 416 (16), 415 (19), 402 (12), 400 (15), 352 (75), 351 (55), 310 (95), 309 (93), 105 (100), 77 (98)
XIIa	3390, 3340, 3160, 1670, 1640, 1500, 1310, 1215, 1170, 800, 760, 690	8.0-7.36 (12H, m), 6.7 (2H, s), 2.63 (3H, s)	351 (M^+, 6), 310 (3), 282 (5), 203 (4), 155 (87), 127 (100), 77 (41)
XIIb	3345, 3140, 3060, 1670, 1650, 1610, 1580, 1550, 1530, 1410, 1290, 1150, 870, 780, 770, 760, 745, 720, 695	8.2-7.38 (17H, m), 6.6 (2H, s)	413 (M^+, 6), 412 (7), 308 (11), 281 (14), 280 (14), 218 (37), 175 (55), 157 (44), 111 (100), 99 (88), 84 (93) 77 (48)

ture, undergo cyclization and rearrangement to give the fused pyrimidine-4-thione derivatives XI.

Dave, *et al.* have reported the reaction of *o*-aminocarbonyl compounds with nitriles to yield condensed pyrimidines [9]. In our hands, compound I reacts with aliphatic and aromatic nitriles in the presence of dry hydrogen chloride gas to give the condensed pyrimidines XII in fair to good yields (Table I).



I XII

Scheme 3

EXPERIMENTAL

The melting points were determined with a Kofler hot stage microscope and were uncorrected. The ir spectra were recorded of mineral oil mulls with a Perkin-Elmer 457 instrument. The ^{1}H-nmr spectra were obtained on solutions in DMSO-d_6 with TMS as internal standard using a Varian FT-80 instrument. Mass spectra were obtained with a Hewlett-Packard 5980 A GC/MS system; compounds were introduced through the direct insertion probe. The electron beam energy was 70 eV and the ion source was at *ca* 300°. Microanalysis were performed with a Perkin-Elmer 240 instrument.

2-(*N,N*-Dimethylaminomethyleneamino)-3-cyano-5,7-diphenylpyrazolo-[1,5-*a*]pyridine (II).

To a solution of 2-amino-3-cyano-5,7-diphenylpyrazolo[1,5-*a*]pyridine (I) (0.31 g, 1 mmole) in dry benzene (20 ml), dimethylformamide dimethylacetal (0.2 g, 1 mmole) was added and the reaction mixture was heated at reflux temperature for 24 hours. After cooling, the solvent was removed off under reduced pressure and the resultant crude product was recrystallized from methanol to give II as yellow prisms in 82% yield, mp 257°; ir (Nujol): 3070, 2220, 1630, 1550, 1530, 1505, 1440, 1400, 1340, 1190, 1120, 860, 780, 770, 735, 705 cm^{-1}; ms (70 eV) m/e 365 (M^+, 100), 350 (36), 322 (50), 308 (48), 294 (42), 202 (16), 164 (22), 115 (6), 102 (15), 77 (25); ^{1}H-nmr: δ ppm 8.57 (1H, s), 8.1-7.05 (12H, m), 3.1 (6H, s).

Anal. Calcd. for $C_{23}H_{19}N_5$: C, 75.62; H, 5.20; N, 19.18. Found: C, 75.41; H, 5.32; N, 19.02.

2-Thioformylamino-3-cyano-5,7-diphenylpyrazolo[1,5-*a*]pyridine (III).

A stream of hydrogen sulfide was passed through a solution of II (0.365 g, 1 mmole) in acetone (40 ml) at room temperature for 3 hours. Then, the solvent was removed off under reduced pressure and the resultant solid was recrystallized from ethanol-chloroform (1:1) to give III as yellow prisms in 84% yield, mp 320°; ir (Nujol): 3300, 2220, 1625, 1540, 1520, 1500, 1420, 1395, 1110, 935, 870, 860, 775, 760, 705 cm^{-1}; ms (70 eV) m/e, 354 (M^+, 80), 353 (100), 327 (23), 322 (11), 308 (12), 294 (15), 202 (17), 164 (20), 102 (17), 77 (37).

Anal. Calcd. for $C_{21}H_{14}N_4S$: C, 71.18; H, 3.95; N, 15.82. Found: C, 71.32; H, 3.90; N, 16.00.

7,9-Diphenylpyrido[1',2':1,5]pyrazolo[3,4-*d*]-1(2*H*)-pyrimidinethione (IV).

To a solution of III (0.354 g, 1 mmole) in pyridine (15 ml), triethylamine (1 mmole) was added and the resultant solution was heated at reflux temperature for 22 hours. After cooling the solution was poured into ice-water and the precipitated solid recrystallized from methanol-benzene (2:1) to produce IV as yellow prisms in 95% yield, mp 330° (Table I).

7,9-Diphenyl-1-methylthiopyrido[1',2':1,5]pyrazolo[3,4-*d*]pyrimidine (V).

To a solution of IV (0.354 g, 1 mmole) in dry methanol (35 ml), sodium methoxide (0.054 g, 1 mmole) was added and the mixture was heated at reflux temperature for 2 hours. After cooling, methyl iodide (0.710 g, 5 mmoles) was added and the resultant solution was stirred at room temperature for 5 hours. Finally, the solvent was removed off under reduced pressure and the crude was recrystallized from methanol to give V as yellowish-green prisms in 89% yield, mp 340° (Table I).

7,9-Diphenyl-1,2,3,4-tetrahydropyrido[1',2':1,5]pyrazolo[3,4-*d*]pyrimidine-1,3-dithione (VI).

To a solution of I (0.310 g, 1 mmole) in pyridine (10 ml), carbon disulfide (10 ml) was added and the resultant solution was heated at reflux temperature for 8 hours. After cooling, methanol (30 ml) was added and the precipitated solid was collected and recrystallized from methanol-benzene (1:1) to produce VI as yellow crystals in 95% yield (Table I).

1,3-Bis(methylthio)-7,9-diphenylpyrido[1',2':1,5]pyrazolo[3,4-*d*]pyrimidine (VII).

To a solution of VI (0.054 g, 1 mmole) in dry methanol (20 ml), sodium methoxide (0.267 g, 1 mmole) was added and the mixture was heated at reflux temperature for 2 hours. After cooling, methyl iodide (0.710 g, 5 mmoles) was added and the solution was stirred at room temperature for 5 hours. Then, the solvent was removed off under reduced pressure and the residual product was recrystallized from methanol to give VII as yellow prisms in 80% yield (Table I).

Preparation of Compound VIII.

To a solution of hydroxylamine chlorhydrate (0.139 g, 2 mmoles) in dry methanol (40 ml), sodium methoxide (0.108 g, 2 mmoles) was added and the solution was heated at reflux temperature for 1 hour. After cooling, the precipitated inorganic salt was separated by filtration and to the filtrate, compound I (0.310 g, 1 mmole) was added. The reaction mixture was heated at reflux temperature for 18 hours. After cooling, the solvent was removed off under reduced pressure and the residue was recrystallized from benzene to give VIII as yellow crystals in 70% yield, mp 240°; ir (Nujol): 3450, 3400, 3300, 3180, 3040, 1650, 1610, 1550, 1400, 1220, 1160, 1100, 770, 760, 700 cm^{-1}; ms (70 eV) m/e: 343 (M^+, 28), 327 (48), 326 (36), 310 (100), 309 (48), 230 (44), 203 (22), 202 (32), 102 (20), 77 (41); ^{1}H-nmr: δ ppm 9.4 (1H, broad), 8.05-7.09 (12H, m), 6.21 (2H, s), 5.78 (2H, s).

Anal. Calcd. for $C_{20}H_{17}N_5O$: C, 69.97; H, 4.95; N, 20.41. Found: C, 69.75; H, 4.80; N, 20.25.

7,9-Diphenylpyrido[1',2':1,5]pyrazolo[3,4-*d*]-1(2*H*)-pyrimidinone (IX).

To a solution of VIII (0.343 g, 1 mmole) in dry benzene (30 ml), dimethylformamide dimethylacetal (0.119 g, 1 mmole) was added and the resultant solution was heated at reflux temperature for 20 hours. After cooling, the solvent was removed off under reduced pressure and the crude product was recrystallized from ethanol to give IX as yellow crystals in 79% yield, mp 336° (Table I).

N,N-Disubstituted Thioureas X. General Procedure.

To a solution of I (0.310 g, 1 mmole) in dry dimethylformamide (20 ml), triethylamine (1 mmole) and the appropriate aryl isothiocyanate were added and the resultant solution was stirred at room temperature for 18 hours. Then, was poured into water (30 ml) and the precipitated solid was recrystallized from the appropriate solvent to give X. The following compounds have been prepared by the above method.

This compound where Ar = 4-BrC_6H_4 was obtained in 78% yield, mp 200° from methanol; ir (Nujol): 3280, 3200, 3060, 2220, 1640, 1600, 1560, 1530, 1480, 1460, 1420, 1380, 1220, 1190, 860, 830, 775, 760, 700 cm^{-1}; ^{1}H-nmr: δ ppm 8.25-7.1 (16H, m), 6.4 (1H, s).

Anal. Calcd. for $C_{27}H_{18}BrN_5S$: C, 61.84; H, 3.46; N, 13.35. Found: C, 61.91; H, 3.50; N, 13.28.

This compound where Ar = 4-ClC_6H_4 was obtained in 84% yield, mp 308° from methanol-benzene (1:1); ir (Nujol): 3240, 3160, 3060, 2220, 1640, 1600, 1560, 1540, 1480, 1400, 1150, 850, 770, 760, 700 cm^{-1}; ^{1}H-nmr: δ ppm 8.2-7.1 (16H, m), 6.35 (1H, s).

Anal. Calcd. for $C_{27}H_{18}ClN_5S$: C, 67.64; H, 3.75; N, 14.61. Found: C, 67.49; H, 3.66; N, 14.48.

This compound where Ar = 4-$H_3CC_6H_4$ was obtained in 82% yield, mp 215° from methanol-benzene (1:1); ir (Nujol): 3300, 3150, 3060, 2220, 1640, 1610, 1580, 1530, 1460, 1400, 1380, 1220, 1200, 1110, 810, 770, 700 cm^{-1}; ^{1}H-nmr: δ ppm 8.3-7.25 (16H, m), 6.3 (1H, s), 2.25 (3H, s).

Anal. Calcd. for $C_{28}H_{21}N_5S$: C, 73.20; H, 4.57; N, 15.25. Found: C, 73.31; H, 4.48; N, 15.30.

7,9-Diphenyl-3-arylaminopyrido[1',2':1,5]pyrazolo[3,4-*d*]-1(2*H*)-pyrimidinethiones XI. General Procedure.

To a solution of the appropriate pyrazolo[1,5-*a*]pyridine X (1 mmole) in pyridine (20 ml), triethylamine (1 mmole) was added and the resultant solution was heated at reflux temperature for 10 hours. After cooling, the solution was poured into water (40 ml) and the precipitated solid was separated by filtration and recrystallized from the appropriate solvent to give XI (Table I).

1-Amino-7,9-diphenylpyrido[1',2':1,5]pyrazolo[3,4-*d*]pyrimidines 3-Substituted XII. General Procedure.

A stream of dry hydrogen chloride gas was passed through a mixture of compound I (2 mmoles) and the appropriate nitrile (2.5 mmoles) in dioxan (100 ml) for 3 hours. The resultant solution was heated at reflux temperature for 2 hours. After cooling, the solution was concentrated under reduced pressure, the precipitate obtained was filtered off, and recrystallized from ethanol to give XII (Table I).

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