PREPARATION OF HETEROARENECARBONITRILES BY REACTION OF HALOHETEROARENES WITH POTASSIUM CYANIDE CATALYZED BY SODIUM *p*-TOLUENESULFINATE

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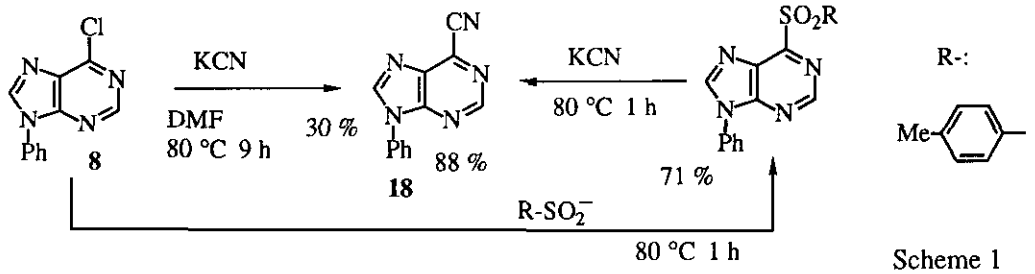
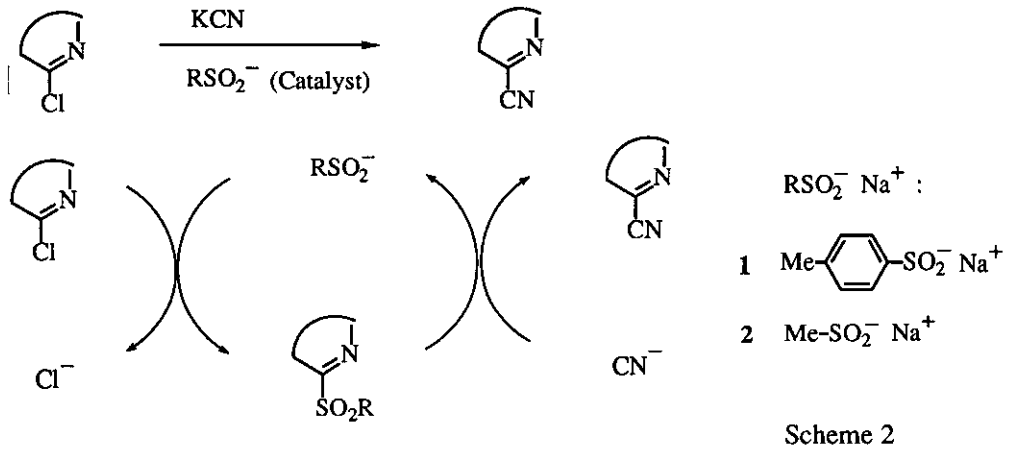
Abstract——— Several heteroarenecarbonitriles were prepared by reaction of haloheteroarenes with potassium cyanide catalyzed by sodium *p*-toluenesulfinate (**1**) or sodium methanesulfinate (**2**). In the reaction pathway, the cyanation proceeds through the formation of the sulfonylheteroarenes.

Heteroarenecarbonitriles are key compounds as a starting material for preparation of heteroarene derivatives containing a functionalized carbon substituent.[1] Preparative methods of the heteroarenecarbonitriles reported in literature can be classified as follows: a) nucleophilic substitution of haloheteroarenes with cyanide ion,[2] b) the reaction of heteroarene *N*-oxide with cyanide ion in the presence of acylating reagent (Reissert-Henze reaction),[3] and c) dehydration of heteroarenealdoxime or heteroarenecarboxamide.[4] The method a) is most easy and simple procedure for preparation of heteroarenecarbonitriles. But the substitution of chloroheteroarenes with cyanide ion often failed to proceed or proceeded in the low formation of the heteroarenecarbonitriles. In the above reaction, it is well known[5-7] that the sulfonyl group attached onto the heteroarenes at π-electron-deficient position has higher reactivity than that of the chloro group for the nucleophilic substitution with cyanide ion and the sulfonylheteroarenes can be produced from the chloroheteroarenes.[6] For example, the reaction of 6-chloro-9-phenyl-9*H*-purine (**8**)[7] with potassium cyanide at 80 °C for 9 h gave 9-phenyl-9*H*-purine-6-carbonitrile (**18**) in 30% yield with the unchanged chloropurine (**8**), but treatment of 6-(*p*-tolylsulfonyl)-9-phenyl-9*H*-purine with potassium cyanide at 80 °C for only 1 h led to cyanation to give the carbonitrile (**18**) in 88% yield.



Scheme 1

In order to develop a simple procedure for the preparation of heteroarenecarbonitriles from the corresponding chloro derivatives, we investigated a catalytic action of sodium sulfinates (**1** and **2**) for the substitution of chloroheteroarenes with potassium cyanide. Our idea can be outlined as illustrated in Scheme 2. That is to say, we could considered that in the presence of catalytic amount of sulfinate (**1** and **2**) the cyanation of chloroheteroarenes with potassium cyanide proceeds through the formation of sulfonylheteroarenes.



Scheme 2

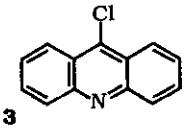
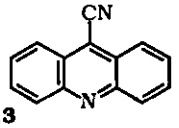
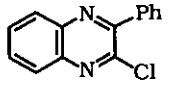
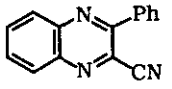
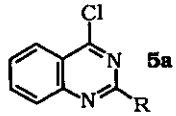
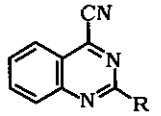
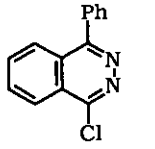
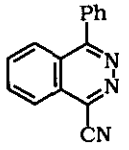
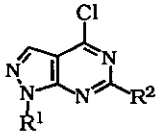
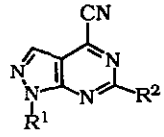
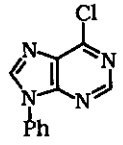
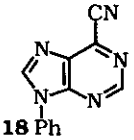
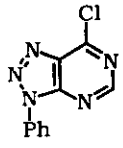
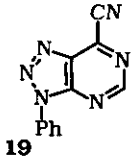
Treatment of 4-chloroquinazoline (**5a**)[8a] with potassium cyanide in *N,N*-dimethylformamide (DMF) at room temperature for 3 h gave 4-quinazolinecarbonitrile (**15a**)[8b] in 42% yield together with recovery of the starting **5a** in 43% yield. In contrast, in the presence of sodium *p*-toluenesulfinate (**1**), the above reaction gave only the carbonitrile (**15a**) in 71% yield. In the presence of **1** the cyanation was achieved by the reaction at 50 °C for only 0.5 h and the carbonitrile (**15a**) was given in 83% yield, while the reaction in absence of **1** at 70 °C for 3.5 h gave the carbonitrile (**15a**) in 75% yield. Similar result was given in the reaction of 4-chloro- (**10a**), 4-chloro-2-methyl- (**10b**), 4-chloro-2-ethyl-5,6-dimethyl-7-phenyl-7*H*-pyrrolo[2,3-*d*]pyrimidine (**10c**), and 4-bromo-5,6-dimethylfuro[2,3-*d*]pyrimidine (**11**). Namely, in the absence of **1**, the cyanation failed to proceed or proceeded in the low formation of the heteroarenecarbonitriles, but in the presence of **1** the cyanation proceeded to give the corresponding carbonitriles in good yields. As illustrated in Table I, the preparations of several heteroarenecarbonitriles were accomplished in good yield by the reaction of haloheteroarenes with potassium cyanide catalyzed by sodium *p*-toluenesulfinate (**1**).

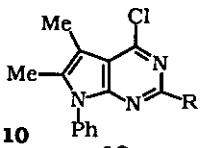
We examined the scope and limitations of the catalytic effect of sodium *p*-toluenesulfinate (**1**) for the cyanation. In isoquinoline area, the catalytic effect of the sodium *p*-toluenesulfinate (**1**) could not be observed. The cyanation of 1-chloroisoquinoline (**12**) catalyzed by **1** gave the 1-isoquinolinecarbonitrile (**22**) in 19% yield, though the cyanation in the absence of **1** afforded the carbonitrile in 6% yield. The difference of the yields of the carbonitrile (**22**) for the both reaction was not observed.

Next, we compaired the catalytic effect of sodium methanesulfinate (**2**) with that of **1**. In the pyrrolo[2,3-*d*]pyrimidine area, the cyanation of **10a** under similar conditions gave the carbonitrile (**20a**) in 98% yield for 0.5 h. Similarly, the reaction of **10c** afforded the corresponding carbonitrile in 83% yield.

Moreover, the reaction of 1-chloroisoquinoline (**12**) with potassium cyanide catalyzed by **2** gave the carbonitrile in 42% yield. The catalytic effect of **2** was higher than that of **1**. We considered that key reaction

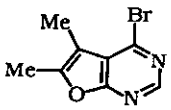
TABLE I. Preparation of Heteroarenecarbonitriles by Treatment of Haloheteroarenes with Potassium Cyanide Catalyzed by Sodium *p*-Toluenesulfinate (**1**)

Chloroheteroarenes	Reaction Conditions Temp. (°C)	Time (h)	Catalyst	Product, Yield (%) Heteroarenecarbonitriles		Recovery
 **3**	60	1	+	 **13**	99.5	
 **4**	80	1	+	 **14**	96	
 **5**	**5a** R = H r.t. r.t. 50 70	3 3 0.5 3.5	+ − + −	 **15**	**15a** R = H 71 42 83 75	 43
 **6**	**5b** R = Ph 70 90 90	1 1 1	+ + −		**15b** R = Ph 73 90 44	
 **7**				 **17**		
7a Me H	80	0.5	+	**17a** Me H	83	
7b Me Et	80	0.5	+	**17b** Me Et	57	
7c Me Ph	80	0.5	+	**17c** Me Ph	93	
7d Ph H	60	0.5	+	**17d** Ph H	92	
7e Ph Me	80	0.5	+	**17e** Ph Me	62	
 **8**	80	1	+	 **18**	83	
 **9**	r.t.	1	+	 **19**	68	



10

10a R = H			**20a** R = H		
150	2	+	95		
150	2	–	43		25
150	8	–	60		
10b R = Me			**20b** R = Me		
150	5	+	86		
150	5	–	19		74
10c R = Et			**20c** R = Et		
150	5	+	63		
150	5	–	–		85



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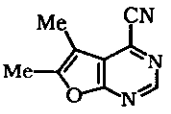

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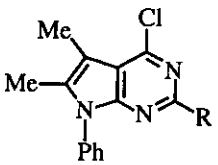
120	1	+	86	
120	1	–	–	88

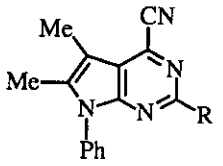


10a , c

KCN

$MeSO_2^- Na^+$ (**2**)

DMF 150 °C



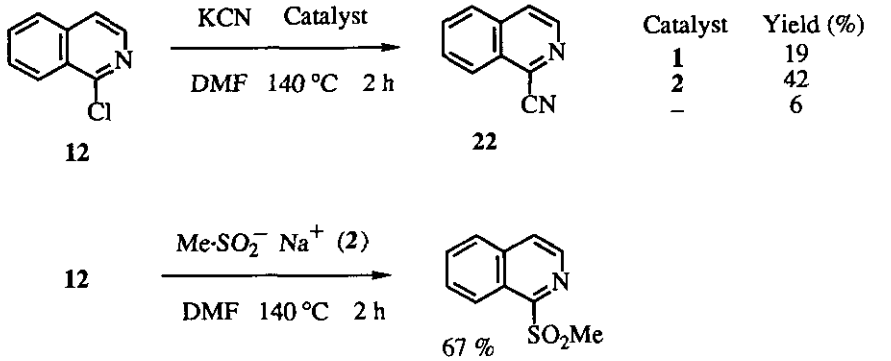
20a , c

Time (h)	Yield (%)
0.5	**20a** (R = H) 98 %
5.0	**20c** (R = Et) 83 %

Scheme 3

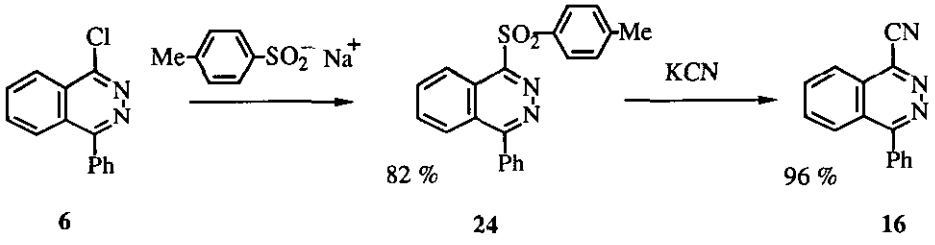
of the cyanation is formation of the sulfonylheteroarenes and in spite of the low activity of the isoquinoline ring, 1-methylsulfonylisoquinoline (**23**) may be produced under the conditions because methylsulfonyl anion has higher nucleophilic activity than *p*-tolylsulfonyl anion. In fact, treatment of 1-chloroisoquinoline (**12**) with sodium methanesulfinate (**2**) at 140 °C for 2 h resulted in the formation of 67% of **23**.

The cyanation process involving two steps which were considered by us is reasonable to explain the experimental results. Initial step is formation of the *p*-tolylsulfonylheteroarene by exchange between chloro group and *p*-tolylsulfonyl group. It is well known that cyanide ion prefer to react with *p*-tolylsulfonylheteroarene rather than chloroheteroarene, resulting in the formation of heteroarenecarbonitriles.[6,9] In the above reaction system, sodium *p*-toluenesulfinate acts as a catalyst.



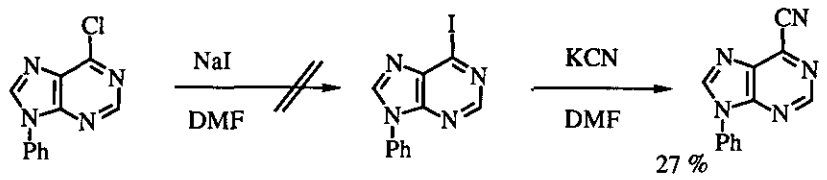
Scheme 4

Indeed, in the 4-chloro-1-phenylphthalazine (**6**),[10] as the cyanation with potassium cyanide in the presence of sodium *p*-toluenesulfinate (**1**) proceeded to give 1-phenyl-4-phthalazinecarbonitrile (**16**)[10] in 90 % yield, in absence of the sulfinate (**1**), the carbonitrile (**16**) was obtained in only 44% yield together with recovery of the starting chlorophthalazine (**6**) in 39% yield under same conditions. 1-Phenyl-4-(*p*-tolylsulfonyl)phthalazine(**24**) underwent the cyanation by reaction with potassium cyanide to give the corresponding carbonitrile (**16**) in 96% yield. The sulfonylation of the chlorophthalazine (**6**) with sodium *p*-toluenesulfinate (**1**) gave the sulfonylphthalazine (**24**) in 82% yield.



Scheme 5

In addition to the above, we examined another catalyst for the cyanation. In similar consideration, it prompted us that sodium iodide acts as a catalyst because the iodoheteroarene was produced through chloroheteroarene and the iodoheteroarene reacts with cyanide ion easily.[11] 6-Iodo-9-phenyl-9*H*-purine (**25**)[12] underwent the cyanation to give the carbonitrile (**18**), but the yield was low (27%). Moreover, the iodination of 6-chloro-9-phenyl-9*H*-purine (**8**) by sodium iodide under similar conditions failed to proceed and recovered the starting chloropurine (**8**) in quantitative yield (92%).



8 **25** **18**

Scheme 6

In conclusion, we found that sodium *p*-toluenesulfinate (**1**) and sodium methanesulfinate (**2**) are effective catalyst for the cyanation of haloheteroarenes with potassium cyanide. And a formation process of the heteroarenecarbonitriles involving a catalytic action of sulfinates (**1** or **2**) is proposed in Scheme 2.

EXPERIMENTAL

All melting points were uncorrected. Ir spectra were recorded on a JASCO A-102 diffraction grating IR spectrophotometer. Proton magnetic resonance (^{1}H-nmr) spectra were measured at 60 MHz on a HITACHI High Resolution NMR R-1100 Spectrometer. Chemical shifts are quoted in parts per million (ppm) with tetramethylsilane (TMS) as an internal standard, and coupling constants (*J*) are given in hertz (Hz). Column chromatography were carried out on SiO_2, Wakogel C-200 (200 mesh), or on Al_2O_3, Sumitomo KCG-30.

Reaction of 6-chloro-9-phenyl-9*H*-purine (8) with Potassium Cyanide ———— A mixture of 6-chloro-9-phenyl-9*H*-purine (692 mg, 3 mmol), potassium cyanide (390 mg, 6 mmol), and 20 ml of DMF was heated at 80 °C for 9 h with stirring. The resultant mixture was poured into ice-H_2O, extracted with AcOEt, the extract was dried over Na_2SO_4, and concentrated. The residue was chlomatographed on a column of SiO_2 with benzene. The first fraction gave 9-phenyl-9*H*-purine-6-carbonitrile (**18**) in 30% (199 mg) yield. The second fraction recovery the chloropurine (**8**) in 20% (138 mg) yield.

Reaction of 6-(*p*-tolylsulfonyl)-9-phenyl-9*H*-purine with Potassium Cyanide ———— A mixture of 6-(*p*-tolylsulfonyl)-9-phenyl-9*H*-purine (1050 mg, 3 mmol), potasium cyanide (390 mg, 6 mmol), and 20 ml of DMF was heated at 60 °C for 1 h with stirring. The resultant mixture was poured into ice-H_2O, extracted with AcOEt, the extract was dried over Na_2SO_4, and concentrated. The residue was passed through a column chromatography of SiO_2. The fraction eluted with benzene gave 9-phenyl-9*H*-purine-6-carbonitrile (**18**) in 88% (584 mg) yield.

General Procedure for the Preparation of Heteroarenecarbonitriles by Reaction of Chloroheteroarenes with Potassium Cyanide in the Presence of Sodium Sulfinate (1 or 2) ————A mixture of haloheteroarene (3 mmol), potassium cyanide (293 mg, 4.5 mmol), and sodium *p*-toluenesulfinate (178 mg, 1 mmol) or sodium methanesulfinate (102 mg, 1 mmol) in 20 ml of DMF was heated on an oil bath with stirring The resultant mixture was poured into ice-H_2O mixture and extracted with AcOEt (100 ml x 2). The organic layer was washed with water and dried over Na_2SO_4. After removal of AcOEt to dryness, the residue was dissolved in a small portion of benzene, and chromatographed on a column of SiO_2 with benzene. The first fraction gave the heteroarenecarbonitrile. The reaction conditions and yields are shown in Table I.

2-Phenyl-4-quinazolinecarbonitrile (15b)
Pale yellow needles (benzene-petr.benzin), mp 171-172 °C (lit.,[13] 166-167 °C).

1-Methyl-1*H*-pyrazolo[3,4-*d*]pyrimidine-4-carbonitrile (17a)
Pale yellow prisms (petr. benzin), mp 115-116 °C. *Anal.* Calcd for $C_7H_5N_5$: C; 52.83, H; 3.17, N; 44.01. Found: C; 52.85, H; 3.04, N; 44.16. ^{1}H-Nmr ($CDCl_3$) ppm: 8.97 (1H, s, C^6-H), 8.19 (1H, s, C^3-H),. 4.13 (3H, s, Me).

1-Methyl-6-ethyl-1*H*-pyrazolo[3,4-*d*]pyrimidine-4-carbonitrile (17b)
Colorless needles (petr. benzin), mp 78-79 °C. *Anal.* Calcd for $C_9H_9N_5$: C; 57.74, H; 4.85, N; 37.41. Found: C; 57.82, H; 4.63, N; 37.68. ^{1}H-Nmr ($CDCl_3$) ppm: 8.11 (1H, s, C^3-H), 4.12 (3H, s, Me), 3.10 (2H, q, J = 9, $C\underline{H}_2CH_3$), 1.43 (3H, t, J = 9, $CH_2C\underline{H}_3$).

1-Methyl-6-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidine-4-carbonitrile (17c)
Colorless needles (petr. benzin), mp 151-152 °C. *Anal.* Calcd for $C_{13}H_9N_5$: C; 66.37, H; 3.86, N; 29.77. Found: C; 66.47, H; 3.86, N; 29.73. ^{1}H-Nmr ($CDCl_3$) ppm: 8.03 (1H, s, C^3-H), 8.10 - 8.50 (2H, m, aromatic H), 7.16 (3H, m aromatic H), 4.09 (3H, s, Me).

1-Phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidine-4-carbonitrile (17d)
Pale yellow needles (MeOH), mp 189-191 °C (lit.,[9a] 190.5-191.5 °C).

1-Phenyl-6-methyl-1*H*-pyrazolo[3,4-*d*]pyrimidine-4-carbonitrile (17e)
Colorless needles (MeOH), mp 141-142 °C. *Anal.* Calcd for $C_{13}H_9N_5$: C; 66.37, H; 3.86, N; 29.77. Found: C; 66.62, H; 3.89, N; 29.65. ^{1}H-Nmr ($CDCl_3$) ppm: 8.38 (1H, s, C^3-H), 8.10 - 8.30 (2H, m, aromatic H), 7.30 - 7.74 (3H, m aromatic H), 2.90 (3H, s, Me).

5,6-Dimethyl-7-phenyl-7*H*-pyrrolo[2,3-*d*]pyrimidine-4-carbonitrile (20a)
Yellow needles (benzene-petr. benzin), mp 168-169 °C. *Anal.* Calcd for $C_{15}H_{12}N_4$: C; 72.56, H; 4.87, N; 22.57. Found: C; 72.49, H; 4.81, N; 22.57. ^{1}H-Nmr ($CDCl_3$) ppm: 8.72 (1H, s, C^2-H), 7.20 -7.60 (5H, m, aromatic H), 2.50 (3H, s, Me), 2.30 (3H, s, Me). Ir (KBr) cm^{-1}: 2250 (CN).

2,5,6-Trimethyl-7-phenyl-7*H*-pyrrolo[2,3-*d*]pyrimidine-4-carbonitrile (20b)

Pale yellow needles (MeOH), mp 211-213 °C. *Anal.* Calcd for $C_{16}H_{14}N_4$: C; 73.26, H; 5.38, N; 21.36. Found: C; 73.18, H; 5.42, N; 21.43. ^{1}H-Nmr ($CDCl_3$) ppm: 7.10 -7.60 (5H, m, aromatic H), 2.67 (3H, s, C^2-Me), 2.47 (3H, s, Me), 2.25 (3H, s, Me). Ir (KBr) cm^{-1}: 2220 (CN).

5,6-Dimethyl-2-ethyl-7-phenyl-7*H*-pyrrolo[2,3-*d*]pyrimidine-4-carbonitrile (20c)
Pale yellow needles (MeOH), mp 150 °C. *Anal.* Calcd for $C_{17}H_{16}N_4$: C; 73.89, H; 5.84, N; 20.28. Found: C; 73.30, H; 5.78, N; 19.89. ^{1}H-Nmr ($CDCl_3$) ppm: 7.16 -7.50 (5H, m, aromatic H), 2.90 (2H, q, J = 7, $C\underline{H}_2CH_3$), 2.47 (3H, s, Me), 2.27 (3H, s, Me), 1.21 (3H, t, J = 7, $CH_2C\underline{H}_3$). Ir (KBr) cm^{-1}: 2220 (CN).

1-Phenyl-4-phthalazinecarbonitrile (16)
Colorless needles (benzene-petr. benzin), mp 183-184 °C (lit.,[10] 180 - 182 °C).

2-Phenyl-3-quinoxalinecarbonitrile (14)
Colorless needles (benzene-petr.benzin), mp 163-165 °C (lit.,[14] 163 °C).

5,6-Dimethylfuro[2,3-*d*]pyrimidine-4-carbonitrile (21)
Pale yellow needles (petr. benzin), mp 97-98 °C. *Anal.* Calcd for $C_9H_7N_3O$: C; 62.42, H;4.07, N;24.26. Found: C; 62.15, H; 4.07, N; 24.19. ^{1}H-Nmr ($CDCl_3$) ppm: 8.87 (1H, s, C^6-H), 2.50 (3H, s, Me), 2.40 (3H, s, Me) . Ir (KBr) cm^{-1}: 2220 cm^{-1} (CN).

Preparation of Sodium Methanesulfinate (2) ——A mixture of 2-methylsulfonylquinoxaline[5b] (10.4 g, 50 mmol) and sodium ethoxide (prepared from 50 ml of EtOH and 1.4 g (60 mmol) of Na) was refluxed for 1 h. The solvent was removed under reduced pressure to dryness, to the residue was added benzene (30 ml), and the insoluble solid was collected to give sodium methanesulfinate. Colorless powder, 4.8 g (94%).

General Procedure for the Preparation of 4-Chloro-1*H*-pyrazolo[3,4-*d*]pyrimidines —— A mixture of 1*H*-pyrazolo[3,4-*d*]pyrimidin-4(5*H*)-one[17,18] (0.05 mol) in 50 ml (0.54 mol) of $POCl_3$ was refluxed in an oil bath with stirring for 2 h. The resultant solution was concentrated under reduced pressure, the residue was dissolved in small portion of $CHCl_3$, and the solution was poured into ice-30% NH_4OH (50 ml). The mixture was extracted with $CHCl_3$, the organic layer was dried over Na_2SO_4, and concentrated. The residue was chromatographed on a short column of Al_2O_3. The fraction eluted with $CHCl_3$ gave 4-chloro-1*H*-pyrazolo[3,4-*d*]pyrimidine.

4-Chloro-1-methyl-1*H*-pyrazolo[3,4-*d*]pyrimidine (7a)
Colorless needles (petr. benzin), mp 96 -97 °C (lit.,[18a] 98 - 99 °C). Yield 93%.

4-Chloro-1-methyl-6-ethyl-1*H*-pyrazolo[3,4-*d*]pyrimidine (7b)
Pale yellow oil. Yield 85 %. *Anal.* Calcd for $C_8H_9N_4Cl$: C, 48.86; H, 4.61; N: 28.49. Found: C, 48.75; H, 4.57; N, 28.46. ^{1}H-Nmr ($CDCl_3$) ppm: 7.95 (1H, s, C^3-H), 4.05 (3H, s, Me), 3.08 (2H, q, J = 8, $C\underline{H}_2CH_3$), 1.40 (3H, t, J = 8, $CH_2C\underline{H}_3$).

4-Chloro-1-methyl-6-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidine (7c)

Pale yellow prisms (petr. benzin), mp 115 -117 °C. Yield 80%. *Anal.* Calcd for $C_{12}H_9N_4Cl$: C, 58.91; H, 3.71; N: 22.90. Found: C, 59.04; H, 3.71; N, 23.02. ^{1}H-Nmr ($CDCl_3$) ppm: 8.30-8.50 (2H, m, aromatic H), 7.86 (1H, s, C^3-H), 7.30 - 7.45 (3H, m, aromatic H), 4.05 (3H, s, Me).

4-Chloro-1-phenyl-6-methyl-1*H*-pyrazolo[3,4-*d*]pyrimidine (7e)
Colorless powder (petr. benzin), mp 93 -94 °C (lit.,[18b] 85 -86 °C). Yield 72%.

5,6-Dimethyl-3,7-dihydro-7-phenyl-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one———— A mixture of 2-amino-4,5-dimthyl-1-phenyl-3-pyrrolecarboxamide[15] (20 g, 0.087 mol), ethyl formate (60 ml, 0.76 mol), and sodium ethoxide(prepared from 400 ml of EtOH and 8 g (0.35 mol) of Na) was refluxed for 5 h with stirring. The solvent was evaporated under reduced pressure and the residue was dissolved in 200 ml of H_2O. The resultant solution was acidified with AcOH, the separated solid was collected, and dried. Recrystallization from MeOH gave pale yellow needles, mp 298-299 °C. Yield 78% (16.3 g). *Anal.* Calcd for $C_{14}H_{13}N_3O$: C, 70.28; H, 5.48; N, 17.56. Found: C, 69.63; H, 5.50; N: 17.70. ^{1}H-Nmr (d^6-DMSO) ppm: 11.65 (1H, br s, NH or OH), 7.66 (1H, s, C^2-H), 7.20-7.70 (5H, m, aromatic H), 2.32 (3H, s, CH_3), 2.07 (3H, s, CH_3). Ir (KBr) cm^{-1}; 1660 (CO).

2,5,6-Trimethyl-3,7-dihydro-7-phenyl-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one———— A mixture of 2-amino-4,5-dimthyl-1-phenyl-3-pyrrolecarboxamide (10 g, 0.044 mol), ethyl acetate (30 ml, 0.31 mol), and sodium ethoxide(prepared from 200 ml of EtOH and 4 g (0.17 mol) of Na) was refluxed for 6 h with stirring. The solvent was evaporated under reduced pressure and the residue was solved in 500 ml of H_2O. The resultant solution was acidified with AcOH, the separated solid was collected, and dried. Recrystallization from MeOH gave purple needles, mp > 300 °C. Yield 99% (11.0 g). *Anal.* Calcd for $C_{15}H_{15}N_3O$: C, 71.12; H, 5.97; N: 16.59. Found: C, 71.18; H, 6.21; N, 16.30. ^{1}H-Nmr (d^6-DMSO) ppm: 7.20-7.70 (5H, m, aromatic H), 2.75 (3H, s, CH_3), 2.43 (3H, s, CH_3), 2.13 (3H, s, CH_3), 3.05 (2H, q, $C\underline{H}_2CH_3$). Ir (KBr) cm^{-1}; 1675 (CO).

2-*Ethyl*-5,6-dimethyl-3,7-dihydro-7-phenyl-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one———— A mixture of 2-amino-4,5-dimthyl-1-phenyl-3-pyrrolecarboxamide (10 g, 0.044 mol) , ethyl propionate (30 ml, 0.26 mol), and sodium ethoxide (prepared from 200 ml of EtOH and 4 g (0.17 mol) of Na) was refluxed for 6 h with stirring. The solvent was evaporated under reduced pressure and the residue was solved in 500 ml of H_2O. The resultant solution was acidified with AcOH, the separated solid was collected, and dried. Recrystallization from MeOH gave gray needles, mp 247 - 249 °C. Yield 96 % (11.2 g). *Anal.* Calcd for $C_{16}H_{17}N_3O$: C, 71.88; H, 6.41; N: 15.72. Found: C,71.79; H, 6.53; N, 15.79. ^{1}H-Nmr (d^6-$DMSO_3$) ppm: 7.20 -7.70 (5H, m, aromatic H), 3.05 (2H, q, J = 7, $C\underline{H}_2CH_3$), 2.45 (3H, s, CH_3), 2.13 (3H, s, CH_3), 1.43 (3H, t, J = 7, $CH_2C\underline{H}_3$). IR (KBr) cm^{-1}; 1675 (CO).

General Procedure for the Preparation of 4-Chloro-5,6-dimethyl-7-phenyl-7*H*-pyrrolo[2,3-*d*]pyrimidines
————A mixture of 5,6-dimethyl-3,7-dihydro-7-phenyl-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one (0.05 mol) in $POCl_3$ (50 ml, 0.54 mol) was refluxed for 2 h. Excess $POCl_3$ was concentrated, the residue was dissolved in small portion of $CHCl_3$, and the solution was poured onto ice-30% NH_4OH (50 ml). The mixture was extracted with $CHCl_3$, the extract was dried over Na_2SO_4 and concentrated. The residue was solved in $CHCl_3$ and chromatographed on a column of Al_2O_3. The fraction eluted with $CHCl_3$ gave 4-chloro-5,6-dimethyl-7-phenyl-7*H*-pyrrolo[2,3-*d*]pyrimidine.

4-Chloro-5,6-dimethyl-7-phenyl-7*H*-pyrrolo[2,3-*d*]pyrimidine (10a)
Colorless needles (MeOH), mp 166.5 - 167 °C. Yield 77%. *Anal.* Calcd for $C_{14}H_{12}N_3Cl$: C, 65.25; H, 4.69; N, 16.30. Found: C, 64.71; H, 4.68; N: 16.33. ^{1}H-Nmr ($CDCl_3$) ppm: 8.50 (1H, s, C^2-H), 7.30-7.70 (5H, m, aromatic H), 2.50 (3H, s, CH_3), 2.30 (3H, s, CH_3).

4-Chloro-2,5,6-trimethyl-7-phenyl-7*H*-pyrrolo[2,3-*d*]pyrimidine (10b)
Colorless needles (petr. benzin), mp 127 °C. Yield 99%. *Anal.* Calcd for $C_{15}H_{14}N_3Cl$: C, 66.30; H, 5.19; N: 15.46. Found: C, 66.32; H, 5.25; N, 15.49. ^{1}H-Nmr ($CDCl_3$) ppm: 7.10-7.57 (5H, m, aromatic H), 2.60 (3H, s, CH_3), 2.43 (3H, s, CH_3), 2.17 (3H, s, CH_3).

4-Chloro-5,6-dimethyl-2-ethyl-7-phenyl-7*H*-pyrrolo[2,3-d]pyrimidine (10c)
Colorless needles (petr. benzin), mp 109 °C. Yield 88%. *Anal.* Calcd for $C_{16}H_{16}N_3Cl$: C, 67.25; H, 5.64; N: 14.70. Found: C, 67.03; H, 5.58; N, 14.53. ^{1}H-Nmr ($CDCl_3$) ppm: 7.15-7.53 (5H, m, aromatic H), 2.85 (2H, q, J = 8, $C\underline{H}_2CH_3$), 2.43 (3H, s, CH_3), 2.20 (3H, s, CH_3), 1.25 (3H, t, J = 8, $CH_2C\underline{H}_3$).

4-Amino-5,6-dimethylfuro[2,3-*d*]pyrimidine———— A mixture of 2-amino-3-cyano-4,5-dimethylfuran[16] (20 g, 0.15 mol), formamide (150 ml, 3.8 mol), and acetic anhydride (1 ml, 0.014 mol) was refluxed for 2 h. The reaction mixture was cooled to room temperature, the separated yellow crystalline was collected, washed with H_2O then MeOH, and dried to give pure 4-amino-5,6-dimethylfuro[2,3-*d*]pyrimidine[16] in 58% (14 g) yield as yellow scales.

4-Bromo-5,6-dimethylfuro[2,3-*d*]pyrimidine (11)————To a mixture of 4-amino-5,6-dimethylfuro[2,3-*d*]pyrimidine (7.5 g, 46 mmol) in 45 ml (0.40 mol) of dibromomethane (CH_2Br_2) was added slowly isoamyl nitrite (11 ml, 0.13 mol). The resultant mixture was gradually heated until 85 °C and the solution was stirred for 1 h at 85 °C. Excess dibromomethane was evaporated under reduced pressure and the residue was chromatographed on a column of SiO_2 with benzene. The first fraction gave 4-bromo-5,6-dimethylfuro[2,3-*d*]pyrimidine in 47% (4.9 g) yield, and recrystallization from petr. benzin gave slightly yellow needles, mp 115-117 °C. *Anal.* Calcd for $C_8H_7N_2OBr$: C, 42.32; H, 3.11; N: 12.34. Found: C,42.28; H, 3.07; N, 12.40. ^{1}H-Nmr ($CDCl_3$) ppm: 8.50 (1H, s, C^6-H), 2.41 (3H, s, Me), 2.31 (3H, s, Me).

Reaction of 1-Chloroisoquinoline (12) with Sodum methanesulfinate (2) ———— A mixture of 1-chloroisoquinoline (**12**, 491 mg, 3 mmol) and sodium methanesulfinate (**2**, 612 mg, 6 mmol) in DMF (20 ml) was heated at 140 ° C for 2 h with stirring. The resultant mixture was poured onto ice-H_2O, extracted with AcOEt, and the extract was dried over Na_2SO_4. The organic layer was concentrated, the residue was dissolved in a small portion of benzene, and the solution was passed through a column of SiO_2 with benzene. The first fraction gave 1-methylsulfonylisoquinoline (**23**)[19] in 67% (416 mg) yield. The second fraction recovered 1-chloroisoquinoline (**12**, 113 mg, 23%).

Reaction of 4-Chloro-1-phenylphthalazine (6) with Sodum *p*-Toluenesulfinate (1) ———— A mixture of 4-chloro-1-phenylphthalazine (722 mg, 3 mmol) and sodium *p*-toluenesulfinate (**1**, 1069 mg, 6 mmol) in DMF (20 ml) was heated at 90 ° C for 1 h with stirring. The reaction mixture was poured onto ice-H_2O, extracted with AcOEt, and the extract was dried over Na_2SO_4. The organic layer was concentrated, the residue was solved in

a small portion of benzene, and the solution was passed through a column of SiO_2 with benzene. The first fraction gave 4-(*p*-tolylsulfonyl)-1-phenylphthalazine (**24**). Recrystallization from benzene-petr. benzin gave colorless needles (886 mg, 82%), mp 192 -194 °C. *Anal.* Calcd for $C_{21}H_{16}N_2O_2S$: C, 69.98; H, 4.47; N: 7.77. Found: C, 69.73; H, 4.55; N, 7.68. ^{1}H-Nmr ($CDCl_3$) ppm: 9.03-9.26 (1H, m, C^8-H), 7.24 - 8.18 (12H, m, aromatic H), 2.44 (3H, s, CH_3). Ir (KBr) cm^{-1} : 1140, 1315 (SO_2).

Reaction of 6-Chloro-9-phenyl-9*H*-purine (8) with Potassium Cyanide ———A mixture of 6-chloro-9-phenyl-9*H*-purine (692 mg, 3 mmol) and potassium cyanide (293 mg, 4.5 mmol) in DMF (20 ml) was heated at 80 °C for 9 h with stirring. The reaction mixture was poured onto ice-H_2O, extracted with AcOEt, and the organic layer was dried over Na_2SO_4. The organic layer was concentrated and the residue was passed through a column of SiO_2 with benzene. The first fraction gave the carbonitrile (**18**, 199 mg, 30%) and the second fraction recovered the chloropurine (138 mg, 20%). 9-Phenyl-9*H*-purine-6-carbonitrile (**18**) : colorless needles (MeOH), mp 182 °C (lit.,[6] 181-182 °C).

Reaction of 6-Iodo-9-phenyl-9*H*-purine (24) with Potassium Cyanide ——— A mixture of 6-iodo-9-phenyl-9*H*-purine (**25**, 322 mg, 1 mmol) and potassium cyanide (130 mg, 2 mmol) in DMF (10 ml) was heated at 80 °C for 1 h with stirring. The reaction mixture was poured onto ice-H_2O, extracted with AcOEt, and the organic layer was dried over Na_2SO_4. The organic layer was concentrated and the residue was passed through a column of SiO_2 with benzene. The first fraction gave the carbonitrile (**18**, 60 mg, 27%) and the second fraction recovered the iodopurine (**8**, 216 mg, 67%).

Reaction of 6-Chloro-9-phenyl-9*H*-purine (8) with Sodium Iodide ——— A mixture of 6-chloro-9-phenyl-9*H*-purine (231 mg, 1 mmol) and sodium iodide (302 mg, 2 mmol) in DMF (10 ml) was heated at 140 °C for 2 h with stirring. The reaction mixture was poured onto ice-H_2O and extracted with AcOEt. The organic layer was dried over Na_2SO_4, concentrated, the residue was solved in small portion of benzene and the solution was passed through a column of SiO_2 with benzene. The first fraction recovered the chloropurine (**8**, 212 mg, 92%).

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