RING OPENING OF 4-CHLOROQUINAZOLINE INTO 2-ARYLMETHYLENEAMINOBENZONITRILE BY GRIGNARD REACTION

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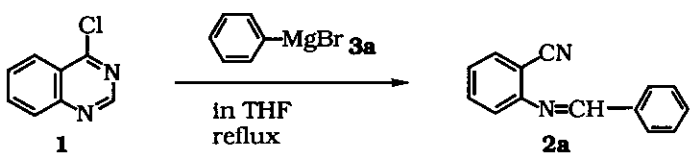
Abstract——The treatment of 4-chloroquinazoline (**1**) with arylmagnesium bromide (**3**) in tetrahydrofuran (THF) resulted in the formation of 2-arylmethyleneaminobenzonitrile (**2**). Continued reaction of ring opening of **1** and subsequent hydrolysis of the products (**2**) afforded the corresponding arenecarbaldehydes (**4**).

In the course of the study of fused pyrimidines,[1] the reaction of 4-chloroquinazoline (**1**) with Grignard reagents was examined in order to prepare the 4-alkyl- or 4-arylquinazolines.[2] The expected product, 4-phenylquinazoline was not given, when the compound (**1**) was treated with phenylmagnesium bromide in refluxing THF for 3 h, and only one product (**2a**) was obtained. The product (**2a**) in the above reaction, yellow prisms and mp 106-108 °C, whose formula was assigned to $C_{14}H_{10}N_2$ by elemental analysis and ms spectral measurement, was given in 75% yield. The ir spectrum of **2a** exhibits the characteristic band of 2220 cm^{-1} due to cyano group (CN) together with 1620 cm^{-1} assigned to the carbon-nitrogen double bond. In the ^{1}H-nmr spectrum, the characteristic signal at 8.40 ppm shows a singlet due to a hydrogen of benzylideneamino group (Ph-CH=N-). From these spectral data the structure could be assigned to 2-benzylideneaminobenzonitrile (**2a**).

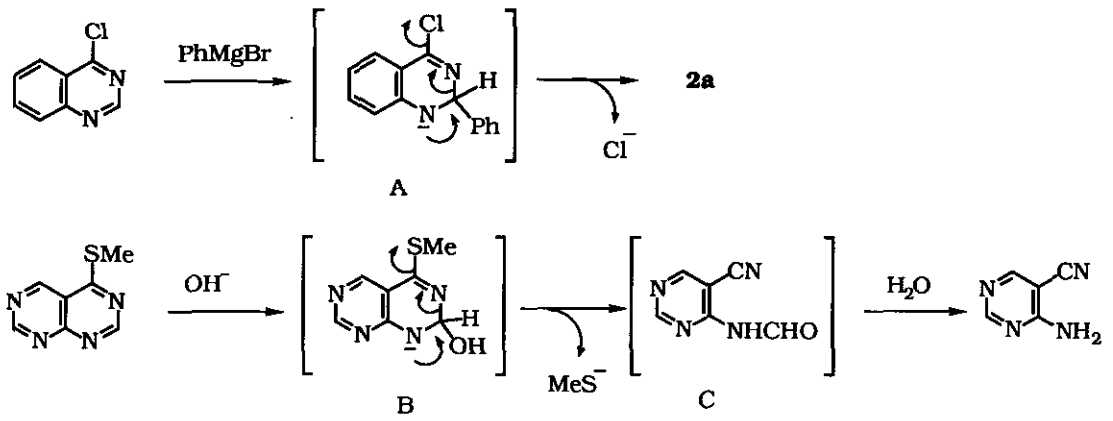


1 **2a** 75 %

Scheme 1

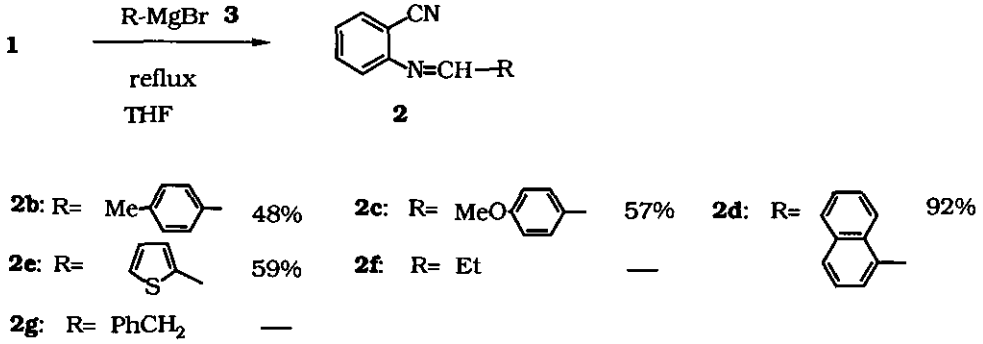
The formation process may be considered that the phenylmagnesium bromide attached across N^1/C^2 double bond of **1** to give an intermediate A, and subsequent ring-cleavage of the intermediate A with expulsion of chlorine anion afforded **2a**. The formation process is similar to that of the ring cleavage of fused pyrimidines with alkali, which was reported by Taylor *et al.*[3] That is to say, in the literature, it was reported that when 4-methylthiopyrimido[2,3-*d*]pyrimidine was treated with sodium hydroxide in MeOH, ring

cleavage proceeded through the similar intermediate B.



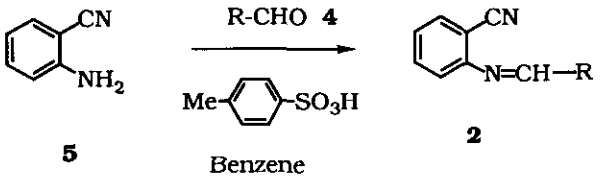
Scheme 2

In order to extend the ring-opening reaction, the reaction of **1** with various arylmagnesium bromides (**3**) was examined. As shown in Scheme 3, when the compound (**1**) was treated with the arylmagnesium bromide (**3**), such as *p*-methylphenylmagnesium bromide (**3b**), *p*-methoxyphenylmagnesium bromide (**3c**), 1-naphthylmagnesium bromide (**3d**), and 2-thienylmagnesium bromide (**3e**), in refluxing THF, the corresponding ring-opening products, such as 2-(*p*-methylphenylmethyleneamino)benzonitrile (**2b**), 2-(*p*-methoxyphenylmethyleneamino)benzonitrile (**2c**), 2-(1-naphtylmethyleneamino)benzonitrile (**2d**), and 2-(2-thienylmethyleneamino)benzonitrile (**2e**), were given in moderate yield. In contrast, though the reaction of **1** with alkylmagnesium bromides, such as ethylmagnesium bromide (**3f**) and benzyl magnesium bromide (**3g**) under same conditions described in the reaction with arylmagnesium bromide was carried out, neither the corresponding ring-cleavage products nor the substituted products were given, and a large amount of oily liquid which could not be purified, was afforded.

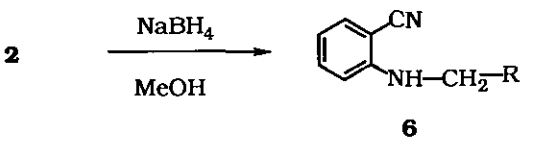


Scheme 3

For the purpose of the determination of the structure of the ring-opening products (**2**), the compounds (**2**) were synthesized by another route starting 2-aminobenzonitrile (**5**). The condensation of **5** with arenecarbaldehydes (**4**) in the presence of catalytic amount of *p*-toluenesulfonic acid in benzene gave the corresponding 2-arylmethyleneaminobenzonitrile (**2**). The results are shown in Scheme 4. To establish the elemental analyses, a few of the products (**2**) were reduced by sodium borohydride ($NaBH_4$) in MeOH.



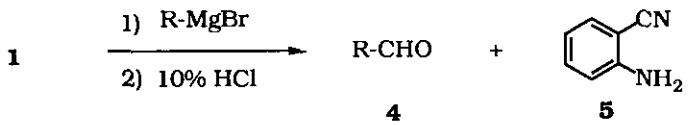
2a: 82%
2b: 76%
2c: 81%
2d: 93%
2e: 92%



6b: 30%
6c 65%
6d: 23%

Scheme 4

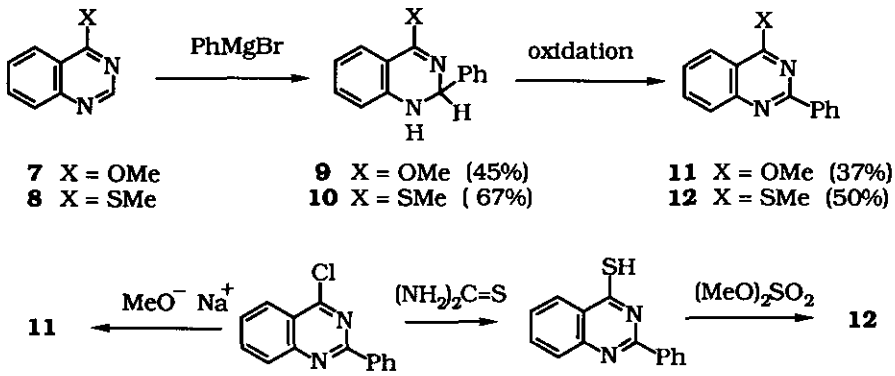
These results prompted us to examine the preparation of arenecarbaldehyde (**4**) through the formation of ring-opening product. Namely, continued reaction of ring cleavage and hydrolysis of the products (**2**) gave the arenecarbaldehydes (**4**) together with 2-aminobenzonitrile (**5**). For example, the ring-opening product obtained in the reaction of **1** with phenylmagnesium bromide (**3a**) was hydrolyzed by 10% HCl for 1 h without purification. The resultant solution was steam distilled to give benzaldehyde (**4a**) in 89% yield together with **5** in 56% yield. Similarly, preparation of the arenecarbaldehydes (**4**) was accomplished by continued reaction of **1** with arylmagnesium bromides (**3**) and hydrolysis of the products, as illustrated in Scheme 5.



R-	Product Yield (%) 4		5
a	**4a**	89	56
b	**4b**	89	52
c	**4c**	79	48
e	**4e**	66	45

Scheme 5

For extension of the reaction, the Grignard reaction of 4-methoxyquinazoline (**7**) or 4-methylthioquinazoline (**8**) was carried out, but the ring opening was failed to proceed. In the above reaction 2-phenyl-4-methoxy-1,2-dihydroquinazoline (**9**) and 2-phenyl-4-methylthio-1,2-dihydroquinazoline (**10**) were given and next oxidation of the dihydro compounds (**9**) and (**10**) by potassium ferricyanide or 1,2-dichloro-4,5-dicyano-*p*-benzoquinone (DDQ) yielded aromatized compounds (**11**) and (**12**). The structures of **11** and **12** were determined by mixed melting point test with authentic specimens prepared by another route. The above results are shown in Scheme 6.



7 X = OMe
8 X = SMe

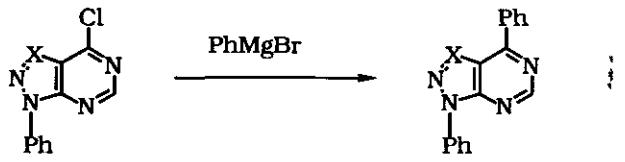
9 X = OMe (45%)
10 X = SMe (67%)

11 X = OMe (37%)
12 X = SMe (50%)

11 **12**

Scheme 6

Next, we examined the reaction with arylmagnesium bromides to other fused pyrimidines, expecting ring-opening reaction. The treatment of 4-chloro-1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidine (**13**)[4] and 7-chloro-3-phenyl-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidine (**14**)[5] with phenylmagnesium bromide (**3a**) was failed to produce the expected ring-opening product. And substituted products, 1,4-diphenyl-1*H*-pyrazolo[3,4-*d*]pyrimidine (**15**)[6] and 3,7-diphenyl-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidine (**16**)[7] were obtained in 40% and 12% yields together with recovery of the starting chloropyrimidines (**13**) and (**14**), respectively.



13 X = CH
14 X = N

15 X = CH (40%)
16 X = N (12%)

Scheme 7

In conclusion, a new ring-opening reaction of 4-chloroquinazoline (**1**) into 2-arylmethyleneaminobenzonitrile (**2**) was found by reaction of **1** with arylmagnesium bromide. Moreover, synthesis of arenecarbaldehydes (**4**) was succeeded by Grignard reaction of **1**, followed by hydrolysis in excellent yields.

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 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).

Grignard Reaction of 4-Chloroquinazoline: General Procedure ——— Grignard reagents (prepared from bromoarene (15 mmol) and Mg (480 mg, 20 mmol) in 30 ml of ether) was added to a solution of 4-chloroquinazoline (1645 mg, 10 mmol) in 20 ml of THF, and the mixture was refluxed on an oil bath for 3 h. The resultant mixture was poured onto ice-NH_4Cl solution (10 g of NH_4Cl was dissolved in 100 ml of H_2O and to the solution was added 5 ml of 30% NH_4OH), and extracted with AcOEt (100 ml x 2). The organic layer was dried over Na_2SO_4, and concentrated to dryness. The residue was chromatographed on a column of SiO_2 with benzene. The first fraction gave the 2- arylmethyleneaminobenzonitrile (**2**).

Preparation of 2-Arylmethyleneaminobenzonitrile (2): General Procedure ——— In a 200 ml of round-bottomed flask fitted with a water separator, 2-aminobenzonitrile (**5**, 2360 mg, 20 mmol), arenecarbaldehydes (**4**, 22 mmol), and *p*-toluenesulfonic acid (344 mg, 2 mmol) were dissolved in 50 ml of benzene. The mixture was refluxed on an oil bath for 5 h. The solution was concentrated to dryness, and the residue was passed through a column of SiO_2 with benzene. The first fraction gave the 2-arylmethyleneaminobenzonitrile (**2**).

Reduction of 2-Arylmethyleneaminobenzonitrile with $NaBH_4$: General Procedure ——— To a solution of 2-arylmethyleneaminobenzonitrile (**2**, 6 mmol) in 30 ml of MeOH was added $NaBH_4$ (228 mg, 6 mmol), and the mixture was stirred at room temperature for 1 h. The mixture was concentrated under reduced pressure, and extracted with $CHCl_3$. The organic layer was dried over Na_2SO_4, evaporated to dryness, and the residue was passed through a column chromatography of SiO_2 with benzene to give 2-arylmethylaminobenzonitrile (**6**).

Synthesis of Arenecarbaldehyde by Ring Opening of 4-Chloroquinazoline with Arylmagnesium Bromide: General Procedure ——— Arylmagnesium bromide (prepared from bromoarene (15 mmol) and Mg (480 mg, 20 mmol) in 30 ml of ether) was added to a solution of 4-chloroquinazoline (1645 mg, 10 mmol) in 20 ml of THF, and the mixture was refluxed on an oil bath for 1 h. The resultant mixture was poured into ice-NH_4Cl solution (10 g of NH_4Cl was disolved in 100 ml of H_2O and to the solution was added 5 ml of 30% NH_4OH), and extracted with benzene (100 ml x 2). The organic layer was dried over Na_2SO_4 and concentrated to dryness. The residue was dissolved in 30 ml of THF, to the solution was added 30 ml of 10% HCl, and the whole was refluxed for 1 h. The resultant solution was concentrated and the

residue was steam distilled to give arenecarbaldehyde (**4**). After steam distillation, the residual solution was extracted with $CHCl_3$ and the organic layer was dried over Na_2SO_4. The solvent was evaporated and the residue was passed through a column chromatography of SiO_2 with benzene to give 2-aminobenzonitrile (**5**).

Reaction of 4-Methoxyquinazoline with Phenylmagnesium Bromide ——— To a solution of 4-methoxyquinazoline (1600 mg, 10 mmol) in THF (30 ml) was added phenylmagnesium bromide (prepared from bromobenzene (3140 mg, 20 mmol) and Mg (720 mg, 30 mmol) in 30 ml of ether). The mixture was refluxed on an oil bath with stirring for 3 h. After cooling, the mixture was poured onto a 100 ml of NH_4Cl solution (prepared from 10 g of NH_4Cl in 100 ml of H_2O and 5 ml of 30% NH_4OH), extracted with benzene, and the organic layer was dried over Na_2SO_4. The solvent was evaporated, and the residue was passed through a column of SiO_2 eluted with benzene then $CHCl_3$. The fraction eluted with $CHCl_3$ gave 2-phenyl-4-methoxy-2,3-dihydroquinazoline (**9**, 1060 mg, 45%), recrystallization from MeOH (slightly yellow needles), mp 117-118 °C.

Reaction of 4-Methylthioquinazoline with Phenylmagnesium Bromide ——— To a solution of 4-methylthioquinazoline (1760 mg, 10 mmol) in THF (30 ml) was added phenylmagnesium bromide (prepared from bromobenzene (3140 mg, 20 mmol) and Mg (720 mg, 30 mmol) in 30 ml of ether). The mixture was refluxed on an oil bath with stirring for 3 hr. After cooling, the mixture was poured onto a 100 ml of NH_4Cl solution (prepared from 10 g of NH_4Cl in 100 ml of H_2O and 5 ml of 30% NH_4OH), extracted with benzene, and the organic layer was dried over Na_2SO_4. The solvent was evaporated, and the residue was passed through a column of SiO_2 eluted with benzene then $CHCl_4$. The fraction eluted with $CHCl_3$ gave 2-phenyl-4-methylthio-1,2-dihydroquinazoline (**10**, 1700 mg, 67%) as yellow oil.

Oxidation of 2-Phenyl-4-methoxy-1,2-dihydroquinazoline with DDQ ——— A solution of 2-phenyl-4-methoxy-1,2-dihydroquinazoline (**9**, 340 mg, 1.43 mmol) and DDQ (390 mg, 1.72 mmol) in benzene (10 ml) was refluxed on an oil bath for 2 h. After cooling, the solvent was evaporated to dryness, and the residue was passed through a column of SiO_2 with benzene then $CHCl_3$. The fraction eluted with $CHCl_3$ gave 2-phenyl-4-methoxyquinazoline (**11**) in 37% yield (124 mg). Recrystallization from MeOH gave colorless needles, mp 59-62 °C.

Oxidation of 2-Phenyl-4-methylthio-1,2-dihydroquinazoline with $K_3Fe(CN)_6$ ——— To a solution of 2-phenyl-4-methylthio-1,2-dihydroquinazoline (**10**, 500 mg) in 20 ml of benzene was added 2*N* NaOH (10 ml) and 10 ml of $K_3Fe(CN)_6$ solution (1 g in 5 ml of H_2O). The mixture was continued to stir at room temperature for 1 h. The whole was extracted with benzene, the organic layer was dried over Na_2SO_4, and concentrated to dryness. The residue was passed through a column chromatography of SiO_2. The fraction eluted with benzene gave 2-phenyl-4-methylthioquinazoline (**12**, 248 mg, 50%). Recrystallization from petroleum benzin gave yellow needles, mp 88-90 °C.

Preparation of 2-Phenyl-4-methylthioquinazoline ——— To a solution of thiourea (1 g, 13 mmol)

Table I. Melting Points, Elemental Analyses, and Ms Measurements for Products (**2** and **6**).

Compd.	mp (°C)	Formula	Calcd (Found) C	H	N	Ms (m/z) M^+
2a	106-108	$C_{14}H_{10}N_2$	81.53	4.89	13.58	206
			(81.23)	(4.89)	(13.25)	
2b	74-76	$C_{15}H_{12}N_2$	81.79	5.49	12.73	220
			(81.61)	(5.49)	(12.73)	
2c	yellow oil	$C_{15}H_{12}N_2O$				236
2d	111-113	$C_{18}H_{12}N_2$	84.35	4.72	10.93	256
			(84.03)	(4.72)	(10.72)	
2e	106-107	$C_{12}H_8N_2S$	67.90	3.80	13.20	212
			(67.59)	(3.81)	(13.19)	
6b	122-123	$C_{15}H_{14}N_2$	81.05	6.35	12.60	222
			(80.88)	(6.37)	(12.53)	
6c	88-89	$C_{15}H_{14}N_2O$	5.61	5.92	11.76	238
			(75.49)	(5.92)	(11.73)	
6d	122-123	$C_{18}H_{14}N_2$	83.69	5.46	10.84	258
			(83.53)	(5.51)	(10.71)	

Table II. Ir and ^{1}H-Nmr Spectral Data for Products (**2** and **6**).

Compd.	Ir ν_{max}^{KBr} cm^{-1}	^{1}H-NMR (ppm)
2a	2220 (CN)	8.40 (1H, s, -N=C<u>H</u>-), 7.00 - 8.10 (9H, m, aromatic H)
	1620 (-C=N-)	
2b	2220 (CN)	7.38 (1H, s, -N=C<u>H</u>-), 7.02 -8.85 (8H, m, aromatic H)
	1620 (-C=N-)	2.40 (3H, s, CH_3)
2c	2210 (CN)	8.31 (1H, s, -N=C<u>H</u>-), 6.80 - 8.00 (8H, m, aromatic H)
	1620 (-C=N-)	3.80 (3H, s, OCH_3)
2d	2220 (CN)	9.10 - 9.25 (1H, m, ), 8.95 (1H, s, -N=C<u>H</u>-)
	1620 (-C=N-)	7.10 - 8.15 (10H, m, aromatic H)
2e	2220 (CN)	8.58 (1H, s, -N=C<u>H</u>-), 7.05 - 7.70 (7H, m, aromatic H)
	1620 (-C=N-)	
6b	2210 (CN)	6.50 - 7.40 (8H, m, aromatic H), 4.90 (1H, br s, NH),
	3380 (NH)	4.40 (2H, s, $-CH_2-$), 2.30 (3H, s, CH_3)
6c	2210 (CN)	6.50 - 7.40 (8H, m, aromatic H), 4.90 (1H, br s, NH),
	3400 (NH)	4.35 (2H, s, $-CH_2-$), 3.75 (3H, s, OCH_3)
6d	2210 (CN)	6.50 - 8.05 (11H, m, aromatic H), 4.90 (1H, br s, NH),
	3350 (NH)	4.80 (2H, s, $-CH_2-$)

in MeOH (20 ml) was slowly added 4-chloro-2-phenylquinazoline (1000 mg, 4.2 mmol),[8] and then the mixture was refluxed with stirring for 1 h. The separated crystalline solid was collected, dissolved in 2*N* NaOH (20 ml), the resultant solution was heated on a water bath for 30 min, and the insoluble solid was filtered off. The filtrate was acidified with acetic acid and the separated solid was collected by suction. Recrystallization from MeOH gave yellow needles in 73% yield (720 mg), mp 218-220 °C. Dimethylsulfonate (0.5 ml) was added to a solution of 2-phenyl-4-mercaptoquinazoline (720 mg) in 2*N* NaOH (10 ml) with stirring. The mixture was vigorously stirred at room temperature for 30 min. The separated crystalline solid was collected by suction, washed with H_2O and dried. Recrystallization from MeOH gave colorless needles in 47% yield (**12**, 360 mg), mp 89-91 °C.

Reaction of 4-Chloro-1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidine with Phenylmagnesium Bromide——— Phenylmagnesium bromide (prepared from bromobenzene (3140 mg, 20 mmol) and Mg (720 mg, 30 mmol) in 30 ml of ether) was added to a solution of 4-chloro-1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidine (**13**, 2300 mg, 10 mmol) in 50 ml of THF, and then the mixture was refluxed for 3 h. The resulting solution was poured into a NH_4Cl solution (prepared from 10 g of NH_4Cl in 100ml of H_2O and 5 ml of 30% NH_4OH), extracted with benzene, dried over Na_2SO_4, and the solvent was concentrated to dryness. The residue was chromatographed on a column of SiO_2 with benzene then $CHCl_3$. The fraction eluted with benzene recovered the starting **13** (16%, 370 mg). The fraction eluted with $CHCl_3$ gave 1,4-diphenylquinazoline in 40% yield (1080 mg). Recrystallization from benzene-petroleum benzin gave slightly yellow needles, mp 127-129 °C.

Reaction of 7-Chloro-3-phenyl-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidine with Phenylmagnesium Bromide——— Phenylmagnesium bromide (prepared from 820 mg of bromobenzene and 190 mg of Mg in 10 ml of ether) was added to a solution of 7-chloro-3-phenyl-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidine (**14**, 600 mg, 2.6 mmol) in 20 ml of THF, and then the resulting mixture was refluxed on a water bath for 3 h. The solution was poured into NH_4Cl solution (prepared from 10 g of NH_4Cl in 100 ml of H_2O and 5 ml of 30% NH_4OH), extracted with benzene, dried over Na_2SO_4, and the solvent was concentrated to dryness. The residue was chromatographed on a column of SiO_2 with benzene. The first fraction recovered starting **14** in 75% yield (450 mg). The second fraction gave 3,7-diphenyl-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidine (**16**) in 12% yield (85 mg). Recrystallization from petroleum benzin gave slightly yellow needles, mp 126-128 °C.

ACKNOWLEDGEMENT

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