Triazolo[4,5-*d*]pyrimidines. X.[1] Halogen–Metal Exchange Reaction of 7-Halo-3-phenyl-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidines with Butyllithium

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The amino group at the 7-position on the 3*H*-1,2,3-triazolo[4,5-*d*]pyrimidine ring was converted into halogen atoms by treatment with isopentyl nitrite in halomethanes, in satisfactory yields. The halogen–metal exchange reaction between 7-iodo-3-phenyl-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidine (2) and butyllithium in the presence of *N,N,N′,N′*-tetramethylethylenediamine proceeded, giving the 7-lithio compound (9). The lithio compound (9) reacted smoothly with electrophiles to give the corresponding 7-substituted compounds (15—18). On the other hand, the reaction of 7-chloro-3-phenyl-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidine (1) with butyllithium gave the ring fission product, 5-amino-1-phenyl-1*H*-1,2,3-triazole-4-carbonitrile (14).

Keywords 7-halo-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidine; halogen–metal exchange reaction; butyllithium; electrophile; ring fission

We reported that the substitution of a methylsulfonyl group at the 5-[1] and 7-positions[2] on the 3*H*-1,2,3-triazolo[4,5-*d*]pyrimidine (triazolopyrimidine) ring with Grignard reagents as carbanions gave the corresponding 5- and 7-alkylated derivatives, while the addition[1] of Grignard reagents across the C^7,N^6-double bond on the triazolopyrimidine ring proceeded when 5-chloro-3-pyenyl-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidine reacted with Grignard reagents. It is well known[3] that lithio compounds of heteroarenes react smoothly with electrophiles, and this is a useful method for introduction of functionalized carbon chains into heteroarenes. However, only a few studies[4] have been reported on the reaction of fused pyrimidine rings with organo lithium compounds. In this paper, we describe the reaction of the 7-halotriazolopyrimidines (**1**—**5**) with butyllithium (BuLi).

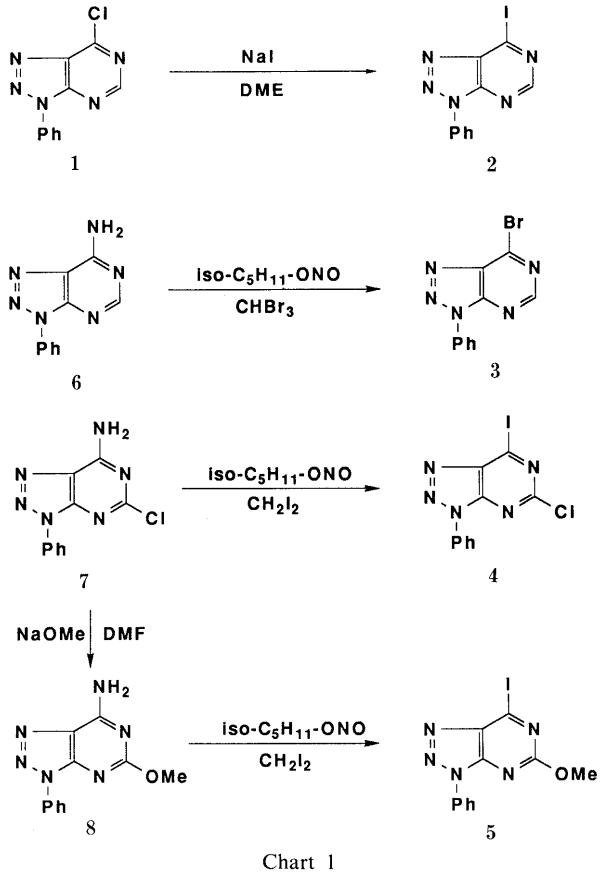

Chart 1

Two methods, A and B, have been reported for the preparation of iodonated condensed pyrimidines. Method A[5] is substitution of a chlorine atom on the condensed pyrimidine ring with sodium iodide in dimethoxyethane (DME), and method B[6] is conversion of the amino group into a halogen atom by treatment with pentyl nitrite in halomethanes, such as tetrachloromethane, tribromomethane and diiodomethane, in good yields.

Firstly, we examined the preparation of 7-iodo- (**2**, **4** and **5**) and 7-bromo-3-phenyl-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidines (**3**) by methods A and B. 7-Chloro-3-phenyl-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidine (**1**) reacted with sodium iodide to give 7-iodo-3-phenyl-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidine (**2**) in 87% yield by method A. The conversion of the amino group at the 7-position on the triazolopyrimidine ring into a bromo or an iodo atom by method B proceeded and the corresponding 7-halo derivatives (**3**—**5**) were obtained in satisfactory yields, as shown in Table I.

Next, we investigated the reaction of the 7-halotriazolopyrimidines (**1**—**3**) with BuLi. When a solution of **2** and BuLi in the presence of *N,N,N′,N′*-tetramethylethylenediamine (TMEDA) in tetrahydrofuran (THF) was stirred at −100 °C for 1 min and quenched with aqueous ammonium chloride, 3-phenyl-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidine (**10**) was obtained in 41% yield, together with 7,7′-bis[3-phenyl-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidine] (**11**). This result indicates that the lithio compound (**9**) was initially formed as

TABLE I. Yields, Melting Points and Elemental Analysis Data for **2**—**5**

Compd.	Yield (%)	mp (°C)	Formula	Analysis (%) Calcd (Found)		
				C	H	N
2	87	143—144	$C_{10}H_6IN_5$	37.17 (37.45)	1.87 (1.87)	21.68 (21.59)
3	69	134—136	$C_{10}H_6BrN_5$	43.50 (43.67)	2.19 (2.22)	25.37 (25.35)
4	66	186—188	$C_{10}H_5ClIN_5$	33.59 (33.70)	1.41 (1.47)	19.59 (19.59)
5	41	165—167	$C_{11}H_8IN_5O$	37.42 (37.40)	2.28 (2.26)	19.83 (19.85)

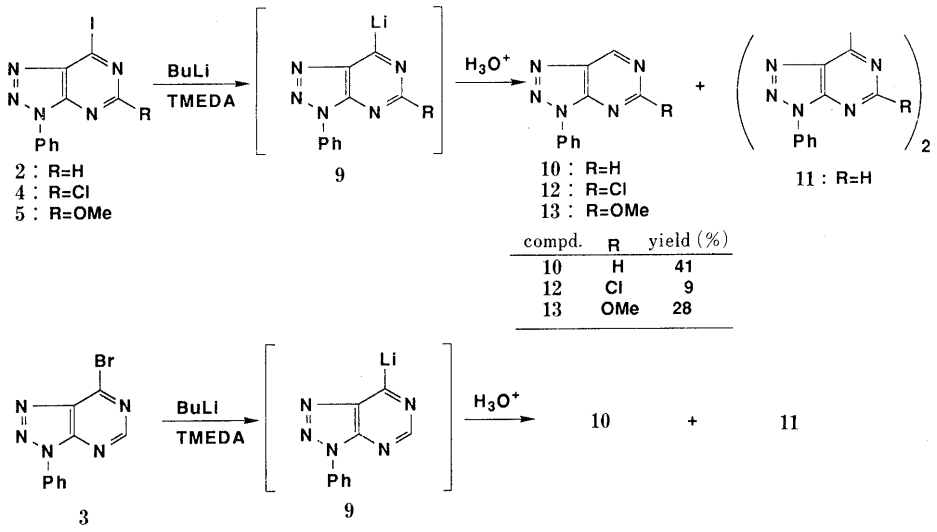

Chart 2

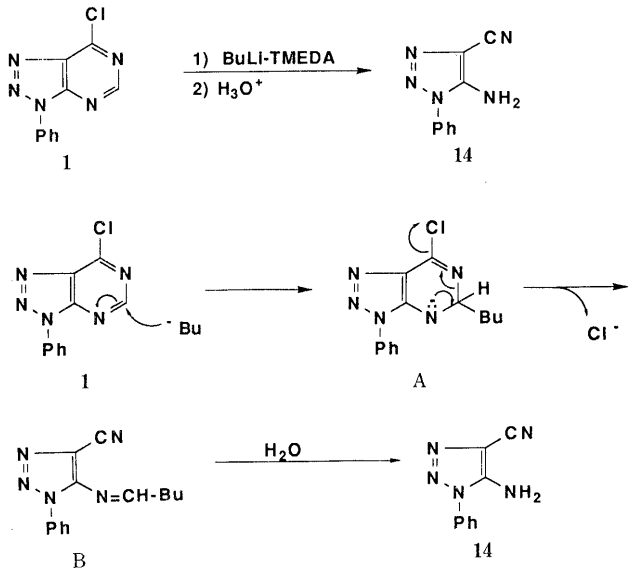

Chart 3

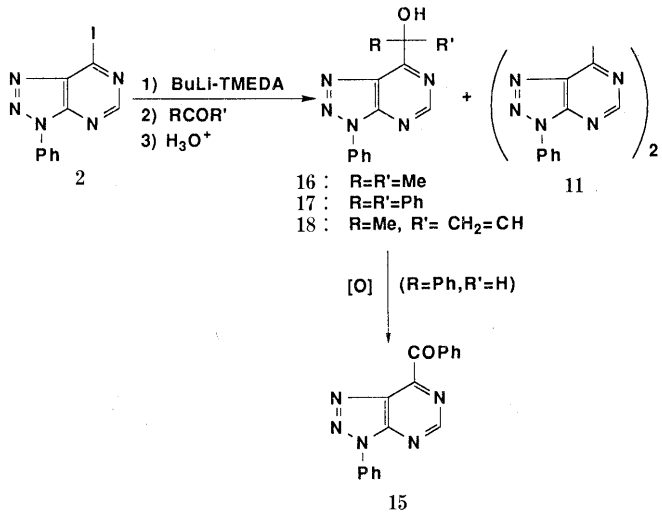

Chart 4

an intermediate. Similarly, the halogen–metal exchange reaction of **3** with BuLi under the same conditions proceeded to give **10**, though the yield was low. On the other hand, in the case of the 7-chloro compound (**1**), ring fission between the C^5 and N^6-positions occurred, resulting in the formation of 5-amino-1-phenyl-1*H*-1,2,3-triazole-4-carbonitrile (**14**) in 62% yield.

The formation of **14** may be explained by the process shown in Chart 3. The first step is nucleophilic addition of BuLi across the C^5,N^4-double bond to form the intermediate A, followed by ring fission between the C^5 and N^6-positions to give the intermediate B, which then gives **14** with loss of valeraldehyde. Moreover, the halogen–metal exchange reaction of the 5-substituted 7-iodo-3-phenyltriazolopyrimidines (**4** and **5**) proceeded under the same conditions to give the desired products (**12** and **13**), but in low yields, as shown in Chart 2.

Finally, we investigated the reaction of the lithio compound (**9**) with electrophiles such as benzaldehyde and ketones. When a solution of **9**, prepared from **2** with BuLi and TMEDA, and benzaldehyde in THF was stirred at −100——10 °C for 1 h, 7-benzoyl-3-phenyl-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidine (**15**) was obtained in 36% yield, together with **11**. Similarly, the lithio compound (**9**) reacted smoothly with ketones such as acetone and benzophenone under the same conditions, giving 7-(2-hydroxy-2-propyl)- (**16**) and 7-(hydroxydiphenylmethyl)-3-phenyl-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidines (**17**), together with **11**. In the case of methyl vinyl ketone, the nucleophilic addition of the

TABLE II. Yields, Melting Points and Elemental Analysis Data for **15**—**18**

Compd.	Yield (%)	mp (°C)	Formula	Analysis (%) Calcd (Found)		
				C	H	N
15	36	141—142[a]				
16	39	115—116	$C_{13}H_{13}N_5O$	61.16	5.13	27.44
				(61.37	5.12	27.44)
17	25	209—210	$C_{23}H_{17}N_5O$	72.81	4.52	18.46
				(73.07	4.54	18.23)
18	18	86—88	$C_{14}H_{13}N_5O$	62.91	4.90	26.20
				(62.93	4.94	26.17)

a) Lit.[10] mp 141 °C.

lithio compound (**9**) to the carbonyl group proceeded, giving 7-(2-hydroxy-3-buten-2-yl)-3-phenyl-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidine (**18**).

The experimental results may be summarized as follows. i) The 7-iodo- and 7-bromotriazolopyrimidines were easily prepared from the 7-aminotriazolopyrimidines by treatment with isopentyl nitrite in halomethanes. ii) The halogen–metal exchange reaction between the 7-iodo derivative and BuLi proceeded and the 7-lithio compound reacted smoothly with electrophiles. iii) The reaction of the lithio compound with electrophiles provides a method for the introduction of functionalized carbon chains into the 7-position of the triazolopyrimidine ring.

Experimental

All melting points are uncorrected. Infrared (IR) spectra were measured with a JASCO IR-700 diffraction grating IR spectrophotometer. Proton nuclear magnetic resonance (^{1}H-NMR) spectra were taken at 60 MHz and 23 °C with a Hitachi R-24B high resolution ^{1}H-NMR spectrometer. Chemical shifts are expressed in parts per million (ppm) downfield from tetramethylsilane as an internal standard. The following abbreviations are used: s = singlet, dd = double doublet, m = multiplet, br = broad.

7-Iodo-3-phenyl-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidine (2) A solution of **1**[7] (2.3 g, 10 mmol) and NaI (10 g, 66 mmol) in DME (200 ml) was refluxed for 3 d. The generated NaCl was filtered off, and the filtrate was evaporated under reduced pressure. The residue was diluted with H_2O and extracted with benzene. The crude product was purified by SiO_2 column chromatography with benzene and recrystallized from petroleum benzin–benzene to give colorless needles (**2**), mp 143—144 °C. Yield 2.8 g (87%).

7-Bromo-3-phenyl-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidine (3) Isopentyl nitrite (15 ml, 112 mmol) was added to a suspension of **6**[2] (2 g, 9.4 mmol) in tribromomethane (45 ml) under a nitrogen atmosphere and the mixture was stirred at 80 °C for 30 min. The solvent was removed under reduced pressure. The crude product was purified by SiO_2 column chromatography with petroleum benzin–benzene (1 : 1) and recrystallized from petroleum benzin–benzene to give colorless prisms (**3**), mp 134—136 °C. Yield 1.8 g (69%).

7-Amino-5-chloro-3-phenyl-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidine (7) A solution of 5,7-dichloro-3-phenyl-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidine[8] (4 g, 15 mmol) and 28% aqueous NH_4OH (7 ml) in dimethylformamide (DMF) (55 ml) was stirred at room temperature for 5 min. The reaction mixture was poured onto ice-water. The generated solids were filtered off to give colorless solids (**7**), mp > 300 °C (lit.[8] mp > 300 °C). Yield 3.4 g (93%).

5-Chloro-7-iodo-3-phenyl-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidine (4) Isopentyl nitrite (30 ml, 233 mmol) was added to a suspension of **7**[8] (2 g, 8.1 mmol) in diiodomethane (60 ml) under a nitrogen atmosphere and the mixture was stirred at 85 °C for 4 d. The solvent was removed under reduced pressure. The crude product was purified by SiO_2 column chromatography with petroleum benzin–benzene (1 : 1) and recrystallized from MeOH to give colorless needles (**4**), mp 186—188 °C. Yield 1.9 g (66%).

7-Amino-5-methoxy-3-phenyl-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidine (8) A solution of NaOMe (4.4 g, 83 mmol) in MeOH (40 ml) was added to a solution of **7** (1 g, 4.1 mmol) in DMF (20 ml). The mixture was stirred at 60 °C for 1 h. The generated NaCl was filtered off and the filtrate was evaporated under reduced pressure. The residue was diluted with H_2O and neutralized with concentrated HCl. The generated solids were filtered off and recrystallized from MeOH to give colorless powders (**8**), mp 233—236 °C (dec.). Yield 0.85 g (85%). MS *m/z*: 242 (M^+). IR ν_{max}^{KBr} cm^{-1}: 3176, 3320 (NH_2). ^{1}H-NMR (DMSO-d_6): 3.94 (3H, s, OCH_3), 7.25—7.79 (3H, m, N^3-Ph), 7.80—8.81 (4H, m, N^3-Ph, NH_2).

7-Iodo-5-methoxy-3-phenyl-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidine (5) Isopentyl nitrite (30 ml, 224 mmol) was added to a suspension of **8** (2 g, 8.3 mmol) in diiodomethane (60 ml) under a nitrogen atmosphere. The mixture was stirred at 85 °C for 2.5 h. The solvent was removed under reduced pressure. The crude product was purified by SiO_2 column chromatography with petroleum benzin–benzene (1 : 1) and recrystallized from petroleum benzin–benzene to give colorless needles (**5**), mp 165—167 °C. Yield 1.2 g (41%).

Reaction of 2 with BuLi A solution of TMEDA (235 mg, 2 mmol) in THF (15 ml) was cooled to −100 °C under a nitrogen atmosphere and treated with BuLi (1.62 M in hexane, 1.4 ml, 2.2 mmol). After 5 min, a solution of **2** (323 mg, 1 mmol) in THF (10 ml) was added dropwise to the solution for 10 min at −100 °C. After 30 s, aqueous NH_4Cl was added to the mixture, and the whole was extracted with $CHCl_3$. The crude product was purified by SiO_2 column chromatography. The fraction eluted with petroleum benzin–benzene (1 : 1) gave 3-phenyl-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidine (**10**) as pale yellow needles, mp 112—114 °C (lit.[9] mp 114—115 °C). Yield 80 mg (41%). ^{1}H-NMR ($CDCl_3$): 7.39—7.82 (3H, m, N^3-Ph), 8.00—8.39 (2H, m, N^3-Ph), 9.20 (1H, s, C^5-H), 9.55 (1H, s, C^7-H). The fraction eluted with benzene–$CHCl_3$ (1 : 1) gave 7,7′-bis[3-phenyl-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidine] (**11**) as pale yellow needles, mp 264—268 °C (dec.) (lit.[9] mp 266—270 °C). Yield 54 mg (28%). ^{1}H-NMR ($CDCl_3$): 7.40—8.60 (10H, m, N^3-Ph), 9.70 (2H, s, C^5-H).

Reaction of 3 with BuLi A solution of **3** (276 mg, 1 mmol) in THF (10 ml) was treated with BuLi and TMEDA as described for the reaction of **2** with BuLi. Work-up as described above gave **10** (40 mg) in 20% yield and **11** (25 mg) in 13% yield.

Reaction of 1 with BuLi A solution of **1** (232 mg, 1 mmol) in THF (10 ml) was treated with BuLi and TMEDA as described for the reaction of **2** with BuLi, and the reaction mixture was worked up in the same way. The eluate from benzene was recrystallized from petroleum benzin–benzene to give 5-amino-1-phenyl-1*H*-1,2,3-triazole-4-carbonitrile (**14**) as colorless needles, mp 126—129 °C (lit.[10] mp 127 °C). IR ν_{max}^{KBr} cm^{-1}: 3320, 3196 (NH_2), 2238 (CN). ^{1}H-NMR ($CDCl_3$): 4.42—4.95 (2H, br, NH_2), 7.41 (5H, s, N^1-Ph).

Reaction of 4 with BuLi A soluton of TMEDA (120 mg, 1 mmol) in THF (15 ml) was cooled to −100 °C under a nitrogen atmosphere and treated with BuLi (1.62 M in hexane, 0.7 ml, 1.1 mmol). After 5 min, a solution of **4** (358 mg, 1 mmol) in THF (10 ml) was added dropwise to the solution for 10 min at −100 °C. After 30 s, aqueous NH_4Cl was added to the mixture, and the whole was extracted with $CHCl_3$. The crude product was purified by SiO_2 column chromatography with benzene and recrystallized from petroleum benzin–benzene to give 5-chloro-3-phenyl-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidine (**12**) as colorless needles mp 137—138 °C (lit.[8] mp 137—138 °C). Yield 20 mg (9%). ^{1}H-NMR ($CDCl_3$): 7.27—7.83 (3H, m, N^3-Ph), 7.85—8.32 (2H, m, N^3-Ph), 8.88 (1H, s, C^7-H).

Reaction of 5 with BuLi A solution of **5** (353 mg, 1 mmol) in THF (10 ml) was treated with BuLi and TMEDA as described for the reaction of **2** with BuLi. A similar work-up gave 5-methoxy-3-phenyl-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidine (**13**) as colorless needles, mp 93—94 °C (lit.[8] mp 94—95 °C). Yield 36 mg (28%). ^{1}H-NMR ($CDCl_3$): 4.14 (3H, s, OCH_3), 7.38—7.65 (3H, m, N^3-Ph), 8.10—8.28 (2H, m, N^3-Ph), 9.41 (1H, s, C^7-H).

7-Benzoyl-3-phenyl-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidine (15) A solution of TMEDA (235 mg, 2 mmol) in THF (15 ml) was cooled to −100 °C under a nitrogen atmosphere and treated with BuLi (1.62 M in hexane, 1.4 ml, 2.2 mmol). After 5 min, a solution of **2** (323 mg, 1 mmol) in THF (10 ml) was added dropwise to the solution for 10 min at −100 °C. After 30 s, a solution of benzaldehyde (1.1 g, 10 mmol) in THF (10 ml) was dropped into the mixture at −100 °C and the whole was stirred at −100—−10 °C for 1.5 h. Aqueous NH_4Cl was added, and the mixture was extracted with $CHCl_3$. The crude product was purified by SiO_2 column chromatography. The fraction eluted with petroleum benzin–benzene (1 : 1) gave pale yellow needles (**15**) from petroleum benzin–benzene, mp 141—142 °C (lit.[11] mp 141 °C). Yield 109 mg (36%). The fraction eluted with benzene–$CHCl_3$ (1 : 1) gave **11**. Yield 42 mg (22%).

7-(2-Hydroxy-2-propyl)-3-phenyl-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidine (16) A solution of **2** (323 mg, 1 mmol) in THF (15 ml) and acetone (580 mg, 10 mmol) was treated with BuLi and TMEDA as described for **15**. A similar work-up gave **16** (100 mg) as colorless needles from petroleum benzin–benzene, mp 115—116 °C, in 39% yield and **11** (40 mg) in 21% yield.

7-(Hydroxydiphenylmethyl)-3-phenyl-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidine (17) A solution of **2** (323 mg, 1 mmol) in THF (15 ml) and benzophenone (1.8 g, 10 mmol) in THF (10 ml) was treated with BuLi and

TABLE III. ^{1}H-NMR Spectral Data for **2**—**5**

Compd.	^{1}H-NMR ($CDCl_3$) δ
2	7.31—7.80 (3H, m, N^3-Ph), 7.89—8.30 (2H, m, N^3-Ph), 8.75 (1H, s, C^5-H)
3	7.21—7.65 (3H, m, N^3-Ph), 7.89—8.20 (2H, m, N^3-Ph), 8.71 (1H, s, C^5-H)
4	7.25—7.78 (3H, m, N^3-Ph), 7.85—8.20 (2H, m, N^3-Ph)
5	4.10 (3H, s, OCH_3), 7.29—7.71 (3H, m, N^3-Ph), 7.85—8.22 (2H, m, N^3-Ph)

TABLE IV. IR and ^{1}H-NMR Spectral Data for **15**—**18**

Compd.	IR ν_{max}^{KBr} (cm^{-1})	^{1}H-NMR ($CDCl_3$) δ
15	1665 (C=O)	7.32—7.79 (6H, m, N^3-Ph, COPh), 7.80—8.36 (4H, m, N^3-Ph, COPh), 9.23 (1H, s, C^5-H)
16	3442 (OH)	1.91 (6H, s, $C(CH_3)_2$), 4.95 (1H, br, OH), 7.31—7.78 (3H, m, N^3-Ph), 8.04—8.32 (2H, m, N^3-Ph), 9.08 (1H, s, C^5-H)
17	3396 (OH)	6.26 (1H, s, OH), 7.15—7.96 (13H, m, N^3-Ph, $C(Ph)_2$), 8.05—8.46 (2H, m, N^3-Ph)
18	3410 (OH)	2.01 (3H, s, CH_3), 5.13 (1H, s, OH), 5.14 (1H, dd, $J_{AB}=2.0$ Hz, $J_{AX}=18.0$ Hz, $CH_X=C\underline{H}_AH_B$), 5.52 (1H, dd, $J_{AB}=2.0$ Hz, $J_{BX}=12.0$ Hz, $CH_X=CH_A\underline{H}_B$), 6.49 (1H, dd, $J_{AX}=18.0$ Hz, $J_{BX}=12.0$ Hz, $C\underline{H}_X=CH_AH_B$), 7.24—7.71 (3H, m, N^3-Ph), 7.90—8.27 (2H, m, N^3-Ph), 8.98 (1H, s, C^5-H)

TMEDA as described for **15**. A similar work-up gave **17** (93 mg) as colorless prisms from benzene–MeOH, mp 209—210 °C, in 25% yield and **11** (30 mg) in 15% yield.

7-(2-Hydroxy-3-buten-2-yl)-3-phenyl-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidine (18) A solution of **2** (323 mg, 1 mmol) in THF (15 ml) and methyl vinyl ketone was treated with BuLi and TMEDA as described for **15**. A similar work-up gave **18** (47 mg) as pale yellow needles from petroleum benzin, mp 86—88 °C, in 20% yield and **11** (45 mg) in 23% yield.

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