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Studies on Pyrazolo[3,4-*d*]pyrimidine Derivatives. XVI.¹⁾ Preparation of Reissert Compounds from Condensed Pyrimidine Systems Catalyzed by Lewis Acids

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Among various Lewis acids, aluminium chloride (AlCl_3) was the most effective catalyst for the formation of the Reissert compound (**2_{1a}**, 5-benzoyl-4,5-dihydro-1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidine-4-carbonitrile) of 1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidine (**1₁**) by using benzoyl chloride and trimethylsilyl cyanide (TMSCN) in anhydrous methylene chloride (CH_2Cl_2).

Application of this method to derivatives of the following condensed pyrimidines, 1*H*-pyrazolo[3,4-*d*]pyrimidine (**1**), 9*H*-purine (**3**), 3*H*-1,2,3-triazolo[4,5-*d*]pyrimidine (**5**), and quinoxaline (**7**), gave the corresponding new series of Reissert compounds (**2**, **4**, **6**, **8**, and **9**), which could not be prepared by the standard method using potassium cyanide and acid chloride in aqueous media.

Keywords—catalyst; aluminium chloride; Reissert compound; condensed pyrimidine; trimethylsilyl cyanide; acid chloride

It would appear that Reissert compounds^{1,2a)} derived from condensed pyrimidine systems are potentially useful as synthetic intermediates. In the pyrazolo[3,4-*d*]pyrimidine area, it was also reported that when attempts were made to form 5-benzoyl-4,5-dihydro-1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidine-4-carbonitrile (**2_{1a}**), one of the Reissert compounds of the pyrazolo[3,4-*d*]pyrimidine system, by the standard method³⁾ using benzoyl chloride and potassium cyanide in a chloroform–water solvent system, 1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidine (**1₁**)^{2b)} underwent ring fission, resulting in the formation of 5-amino-1-phenyl-1*H*-pyrazole-4-carbaldehyde (**10**) and *N*-formylbenzamide (**11**).^{2c)} In 1977, Ruchirawat *et al.* obtained the Reissert compound of isoquinoline (2-benzoyl-1,2-dihydro-1-isoquinoline-carbonitrile) in anhydrous media using benzoyl chloride, trimethylsilyl cyanide (TMSCN), and a catalytic amount of aluminium chloride, which was an effective catalyst, in methylene chloride.¹³⁾ Recently, we reported that application of this method to **1₁** yielded the anticipated Reissert compound **2_{1a}**.^{2d)}

Firstly, in order to select the most effective catalyst, the effects of various Lewis acids on the Reissert formation of **1₁** in anhydrous media was examined, and the results were compared with that in the absence of Lewis acid. Thus, **1₁** in methylene chloride was stirred under the reaction conditions shown in Table I with equimolar amounts of TMSCN and benzoyl chloride, and a catalytic amount of a Lewis acid (1/5–1/10 mol). Lewis acids used in the reaction were as follows: aluminium chloride, zinc chloride, titanium(IV) chloride, and boron trifluoride etherate. As shown in Table I, the presence of each Lewis acid increased the yield of the Reissert compound **2_{1a}** and reduced the reaction time as compared with those in the absence of Lewis acid. Moreover, it became clear that, among the Lewis acids used, aluminium chloride was the most effective catalyst with regard to the yield of the Reissert

Chart 1

TABLE I. Reissert Compound Formation of 1_1 using PhCOCl and TMSCN in the Presence of Lewis Acids in CH_2Cl_2 to 2_{1a}

Lewis acid	Mol. ratio (PhCOCl/Lewis acid)	Reaction time (h)	Yield of 2_{1a} (%)
—	—	96	12
AlCl_3	10/1	13	95
ZnCl_2	10/1	22	66
TiCl_4	10/1	22	78
$\text{BF}_3 \cdot \text{Et}_2\text{O}$	5/1	72	52

compound 2_{1a} and reaction time. Therefore, this method using aluminium chloride as a catalyst in anhydrous media was applied to the Reissert compound formation of derivatives of the following condensed pyrimidine rings; 1*H*-pyrazolo[3,4-*d*]pyrimidine (**1**), 9*H*-purine (**3**), 3*H*-1,2,3-triazolo[4,5-*d*]pyrimidine (**5**), and quinazoline (**7**).

In the pyrazolo[3,4-*d*]pyrimidine area, application of Reissert compound formation in the presence of aluminum chloride to 1-phenyl- (1_1),^{2b} 6-methyl-1-phenyl- (1_2), and 1-methyl-1*H*-pyrazolo[3,4-*d*]pyrimidines (1_3)^{2e} gave the corresponding Reissert compounds (2_{1a} , 2_{2a} , and 2_{3a}) in satisfactory yields. In addition to benzoyl chloride, use of ethyl chloroformate, acetyl chloride, benzenesulfonyl chloride, and *p*-substituted benzoyl chlorides provided the corresponding Reissert compounds (2_{1b} — 2_{1g} , 2_{2c} , and 2_{3b}) in good yields, as shown in Chart 2.

The experimental results shown in Chart 2 demonstrate that, in the pyrazolo[3,4-*d*]pyrimidine system, selective mono-Reissert formation across the 4,5-double bond rather than the 6,7-double bond proceeds, indicating that phenyl and methyl groups at the 1-position prevent the formation of Reissert compounds across the 6,7-double bond. In fact, even when a blocking group was present at the 4-position, the Reissert compound formation of 4-methyl- (1_4)^{2b} and 4-ethoxy-1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidines (1_5)^{4a} with benzoyl chloride and TMSCN in the presence of aluminium chloride did not proceed, giving none of the corresponding Reissert compounds across the 6,7-double bond.

In the 9*H*-purine area, no work on Reissert compound formation has been reported in the literature. When Reissert compound formation of 9-phenyl-9*H*-purine (3_1)^{5a} was attempted by the standard method³) using benzoyl chloride and potassium cyanide in a chloroform–water solvent system, 3_1 underwent ring fission of the imidazole ring, giving 4-benzamido-5-(*N*-phenylformamido)pyrimidine (**12**) in 23% yield, which was easily converted

1	R ¹	R ²	R	Reaction time (h)	2	Yield (%)
1 ₁	H	Ph	PhCO	13	2 _{1a}	95
1 ₁	H	Ph	EtOCO	25	2 _{1b}	88
1 ₁	H	Ph	Ac	36	2 _{1c}	63
1 ₁	H	Ph	PhSO ₂	336	2 _{1d}	41
1 ₁	H	Ph	<i>p</i> -MeC ₆ H ₄ CO	8	2 _{1e}	84
1 ₁	H	Ph	<i>p</i> -MeOC ₆ H ₄ CO	18	2 _{1f}	73
1 ₁	H	Ph	<i>p</i> -NO ₂ C ₆ H ₄ CO	18	2 _{1g}	65
1 ₂	Me	Ph	PhCO	17	2 _{2a}	76
1 ₂	Me	Ph	<i>p</i> -MeC ₆ H ₄ CO	21	2 _{2e}	41
1 ₃	H	Me	PhCO	51	2 _{3a}	73
1 ₃	H	Me	EtOCO	31	2 _{3b}	83

Chart 2

3	R ¹	R	Reaction time (h)	4	Yield (%)
3 ₁	H	Ph	16	4 _{1a}	48
3 ₁	H	EtO	72	4 _{1b}	51
3 ₂	Me	Ph	8	4 _{2a}	50
3 ₂	Me	EtO	20	4 _{2b}	46

Chart 3

into 4-anilino-5-benzamidopyrimidine (13) by alkaline hydrolysis for structure determination.

The treatment of 3₁ and 8-methyl-9-phenyl-9*H*-purine (3₂)^{5b)} with equimolar quantities of benzoyl chloride and TMSCN, and a catalytic amount of aluminium chloride in methylene

5	R ¹	R	Reaction time (h)	6	Yield (%)
5 ₁	H	Ph	48	6 _{1a}	74
5 ₁	H	EtO	19	6 _{1b}	84
5 ₂	Me	Ph	98	6 _{2a}	65
5 ₃	MeO	Ph	7 (d)	6 _{3a}	—

Chart 4

chloride, gave the corresponding Reissert compounds 1-benzoyl-1,6-dihydro-9-phenyl-9H-purine-6-carbonitrile (4_{1a}) and the 8-methyl derivative of 4_{1a} (4_{2a}), respectively. Use of ethyl chloroformate in the cases of 3₁ and 3₂ provided the Reissert compounds 4_{1b} and 4_{2b}, respectively. The results are summarized in Chart 3.

In the 3H-1,2,3-triazolo[4,5-d]pyrimidine area, it was reported that when attempts were made to form 6-benzoyl-6,7-dihydro-3-phenyl-3H-1,2,3-triazolo[4,5-d]pyrimidine-7-carbonitrile (6_{1a}), one of the Reissert compounds of the 3H-1,2,3-triazolo[4,5-d]pyrimidine, by the standard method³⁾ using benzoyl chloride and aqueous potassium cyanide, 3-phenyl-3H-1,2,3-triazolo[4,5-d]pyrimidine (5₁)^{2f)} underwent ring fission, resulting in the formation of 5-amino-1-phenyl-1H-1,2,3-triazole-4-carboxaldehyde (14₁) and 11.^{2c)} However, in the same Reissert formation as described for 2 and 4, use of benzoyl chloride and ethyl chloroformate in the case of 5₁ resulted in the formation of the corresponding selective mono-Reissert compounds across the 6,7-double bond, such as 6-benzoyl- (6_{1a}) and 6-ethoxycarbonyl-6,7-dihydro-3-phenyl-3H-1,2,3-triazolo[4,5-d]pyrimidine-7-carbonitriles (6_{1b}). Similarly, use of benzoyl chloride in the case of 5-methyl-3-phenyl-3H-1,2,3-triazolo[4,5-d]pyrimidine (5₂) gave 6-benzoyl-6,7-dihydro-5-methyl-3-phenyl-3H-1,2,3-triazolo[4,5-d]pyrimidine-7-carbo-

Chart 5

Chart 6

nitrite (6_{2a}). The results are summarized in Chart 4.

Application of this Reissert compound formation to 5-methoxy-1-phenyl-1*H*-1,2,3-triazolo[4,5-*d*]pyrimidine (5₃) did not give the anticipated Reissert compound (6_{3a}) and the starting material was recovered. This indicates that steric hindrance caused by an alkoxy group at the 5-position prevents the formation of the mono-Reissert compound across the 6,7-double bond.

Compound 5₂ was prepared starting from 5-amino-1-phenyl-1*H*-1,2,3-triazole-4-carboxamide (14₂).⁶⁾ The process in Chart 4, involving successive condensation of 14₂ with ethyl acetate, chlorination, and finally dechlorination with catalytic reduction over Pd-MgO, gave 5₂ with an overall yield of almost 40% based on the starting 14₂. Compound 5₃ was also prepared from 5-amino-2,4-dichloropyrimidine (19₁)⁷⁾ by way of 19₂ and the chloro compound (5₆) as shown in Chart 4.⁸⁾

In the quinazoline area, it was reported by Popp and coworkers⁹⁾ that the Reissert

TABLE II. Melting Points, Elemental Analytical, and MS Data for 2, 4, 6, 8, and 9

Compd.	mp (°C)	Formula	Analysis (%)			MS <i>m/z</i> M ⁺
			Calcd (Found)			
			C	H	N	
2_{1a} ^{2d)}	175—176 ^{a,f)}	C ₁₉ H ₁₃ N ₅ O	69.71	4.00	21.40	
2_{1b}	115—116 ^{a,g)}	C ₁₅ H ₁₃ N ₅ O ₂	61.01 (60.68)	4.44 4.52	23.72 23.28)	295
2_{1c}	184—185 ^{a,g)}	C ₁₄ H ₁₁ N ₅ O	63.38 (63.31)	4.18 4.20	26.40 26.40)	265
2_{1d}	109—110 ^{a,h)}	C ₁₈ H ₁₃ N ₅ O ₂ S	59.49 (59.26)	3.61 3.61	19.27 19.02)	363
2_{1e}	197—198 ^{a,g)}	C ₂₀ H ₁₅ N ₅ O	70.37 (70.37)	4.43 4.46	20.52 20.32)	341
2_{1f}	188—189 ^{a,g)}	C ₂₀ H ₁₅ N ₅ O ₂	67.22 (67.13)	4.23 4.26	19.60 19.46)	357
2_{1g}	202—203 ^{b,g)}	C ₁₉ H ₁₂ N ₆ O ₃	61.29 (61.34)	3.25 3.24	22.57 22.51)	372
2_{2a}	155—156 ^{b,g)}	C ₂₀ H ₁₅ N ₅ O	70.37 (70.18)	4.43 4.48	20.52 20.25)	341
2_{2c}	194—195 ^{b,g)}	C ₂₁ H ₁₇ N ₅ O	70.96 (70.86)	4.82 4.87	19.71 19.50)	355
2_{3a}	107—108 ^{c,g)}	C ₁₄ H ₁₁ N ₅ O	63.38 (63.55)	4.18 4.20	26.40 26.42)	265
2_{3b}	123—124 ^{c,g)}	C ₁₀ H ₁₁ N ₅ O ₂	51.49 (51.55)	4.75 4.76	30.03 29.51)	233
4_{1a}	192—193 ^{b,g)}	C ₁₉ H ₁₃ N ₅ O	69.71 (69.55)	4.00 4.02	21.40 21.51)	327
4_{1b}	119—120 ^{a,g)}	C ₁₅ H ₁₃ N ₅ O ₂	61.01 (60.97)	4.44 4.43	23.72 23.76)	295
4_{2a}	166—167 ^{a,g)}	C ₂₀ H ₁₅ N ₅ O	70.37 (70.37)	4.43 4.42	20.52 20.61)	341
4_{2b}	141—142 ^{d,g)}	C ₁₆ H ₁₅ N ₅ O ₂	62.12 (62.16)	4.89 4.88	22.64 22.49)	309
6_{1a}	160—161 ^{a,f)}	C ₁₈ H ₁₂ N ₆ O	65.84 (65.58)	3.68 3.72	25.59 25.37)	328
6_{1b}	131—132 ^{d,i)}	C ₁₄ H ₁₂ N ₆ O ₂	56.75 (56.76)	4.08 4.08	28.37 28.35)	296
6_{2a}	164—166 ^{c,g)}	C ₁₉ H ₁₄ N ₆ O	66.65 (66.60)	4.12 4.15	24.55 24.67)	342
8_{1a} ^{2g)}	171—172 ^{a,h)}	C ₁₆ H ₁₁ N ₃ O	73.55	4.24	16.08	
8_{2a}	121 ^{e,h)}	C ₁₇ H ₁₃ N ₃ O	74.16 (73.85)	4.76 4.71	15.26 15.19)	
9_{3a}	88 ^{a,h)}	C ₁₈ H ₁₅ N ₃ O ₂	70.80 (70.80)	4.95 4.89	13.76 13.75)	305

a) Colorless needles. b) Colorless prisms. c) Colorless plates. d) Pale yellow needles. e) Orange needles. f) Recrystallized from benzene. g) Recrystallized from AcOEt. h) Recrystallized from benzene-petroleum ether. i) Recrystallized from MeOH.

compound formation of quinazoline (7₁) using Ruchirawat's method selectively gave the mono-Reissert compound (8_{1a}, 3-benzoyl-3,4-dihydro-4-quinazolinecarbonitrile) in 67% yield. They also reported⁹⁾ that application of this Reissert compound formation to 4-methylquinazoline (7₄) provided the mono-Reissert compound (9_{4a}, 1-benzoyl-1,2-dihydro-4-methyl-2-quinazolinecarbonitrile) and selectively functionalized the 1,2-double bond.

TABLE III. IR and ¹H-NMR Spectral Data for **2**, **4**, **6**, **8**, and **9**

Compd.	IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} ¹²⁾	¹ H-NMR (CDCl ₃) ppm
2_{1b}	1740 (CO)	8.00—7.70 (2H, m, Ph-H), 7.89 (1H, s, C ⁶ -H), 7.60—7.20 (3H, m, Ph-H), 7.50 (1H, s, C ³ -H), 6.18 (1H, s, C ⁴ -H), 4.40 (2H, q, $J=6.5$ Hz, OCH ₂ CH ₃), 1.38 (3H, t, $J=6.5$ Hz, CH ₂ CH ₃)
2_{1c}	1694 (CO)	8.00—7.70 (2H, m, Ph-H), 7.73 (1H, s, C ⁶ -H), 7.60—7.05 (3H, m, Ph-H), 7.57 (1H, s, C ³ -H), 6.30 (1H, s, C ⁴ -H), 2.47 (3H, s, COCH ₃)
2_{1d}	1370, 1170 (SO ₂)	8.15—7.10 (12H, m, Ph-H, C ⁶ -H, and C ³ -H), 6.22 (1H, s, C ⁴ -H)
2_{1e}	1680 (CO)	8.00—7.00 (11H, m, Ph-H, C ⁶ -H, and C ³ -H), 6.30 (1H, s, C ⁴ -H), 2.40 (3H, s, CH ₃)
2_{1f}	1680 (CO)	8.00—7.00 (9H, m, Ph-H, C ⁶ -H, and C ³ -H), 6.92 (2H, d, $J=9.0$ Hz, Ph-H), 6.25 (1H, s, C ⁴ -H), 3.80 (3H, s, OCH ₃)
2_{1g} ^{a)}	1310, 1520 (NO ₂), 1700	8.36 (2H, d, $J=8.0$ Hz, Ph-H), 8.75—7.20 (7H, m, Ph-H, C ⁶ -H, and C ³ -H), 7.95 (2H, d, $J=8.0$ Hz, Ph-H), 6.70 (1H, s, C ⁴ -H)
2_{2a}	1672 (CO)	8.10—7.80 (2H, m, Ph-H), 7.70—7.10 (9H, m, Ph-H and C ³ -H), 6.20 (1H, s, C ⁴ -H), 2.05 (3H, s, CH ₃)
2_{2c}	1662 (CO)	8.10—7.80 (2H, m, Ph-H), 7.70—7.10 (8H, m, Ph-H and C ³ -H), 6.20 (1H, s, C ⁴ -H), 2.43 (3H, s, CH ₃), 2.08 (3H, s, CH ₃)
2_{3a}	1680 (CO)	7.80—7.10 (7H, m, Ph-H, C ⁶ -H, and C ³ -H), 6.23 (1H, s, C ⁴ -H), 3.80 (3H, s, CH ₃)
2_{3b}	1740 (CO)	7.88 (1H, s, C ⁶ -H), 7.40 (1H, s, C ³ -H), 6.20 (1H, s, C ⁴ -H), 4.40 (2H, q, $J=6.5$ Hz, OCH ₂ CH ₃), 3.80 (3H, s, CH ₃), 1.41 (3H, t, $J=6.5$ Hz, CH ₂ CH ₃)
4_{1a} ^{b)}	1690 (CO)	7.88 (1H, s, C ² -H), 7.80—7.20 (11H, m, Ph-H and C ⁸ -H), 6.47 (1H, s, C ⁶ -H)
4_{1b}	1740 (CO)	7.77 (1H, s, C ² -H), 7.70—7.20 (5H, m, Ph-H), 7.54 (1H, s, C ⁸ -H), 6.22 (1H, s, C ⁶ -H), 4.40 (2H, q, $J=6.5$ Hz, OCH ₂ CH ₃), 1.37 (3H, t, $J=6.5$ Hz, CH ₂ CH ₃)
4_{2a}	1680 (CO)	7.80—7.15 (11H, m, Ph-H and C ² -H), 6.39 (1H, s, C ⁶ -H), 2.37 (3H, s, CH ₃)
4_{2b}	1730 (CO)	7.83 (1H, s, C ² -H), 7.80—7.10 (5H, m, Ph-H), 6.30 (1H, s, C ⁶ -H), 4.40 (2H, q, $J=6.5$ Hz, OCH ₂ CH ₃), 2.31 (3H, s, CH ₃), 1.39 (3H, t, $J=6.5$ Hz, CH ₂ CH ₃)
6_{1a}	1690 (CO)	8.05—7.25 (11H, m, Ph-H and C ⁵ -H), 6.51 (1H, s, C ⁷ -H)
6_{1b}	1765 (CO)	8.07 (1H, s, C ⁵ -H), 8.00—7.80 (2H, m, Ph-H), 7.63—7.30 (3H, m, Ph-H), 6.44 (1H, s, C ⁷ -H), 4.48 (2H, q, $J=6.5$ Hz, OCH ₂ CH ₃), 1.44 (3H, t, $J=6.5$ Hz, CH ₂ CH ₃)
6_{2a}	1680 (CO)	8.35—7.80 (4H, m, Ph-H), 7.70—7.30 (6H, m, Ph-H), 6.41 (1H, s, C ⁷ -H), 2.12 (3H, s, CH ₃)
8_{2a}	1680 (CO)	7.80—7.18 (9H, m, Ph-H and aromatic H), 6.17 (1H, s, C ⁴ -H), 2.04 (3H, s, CH ₃)
9_{3a}	1660 (CO)	7.90—6.60 (9H, m, Ph-H and aromatic H), 6.80 (1H, s, C ² -H), 4.32 (2H, q, $J=7.0$ Hz, OCH ₂ CH ₃), 1.42 (3H, t, $J=7.0$ Hz, CH ₂ CH ₃)

a) ¹H-NMR in (CD₃)₂SO. b) ¹H-NMR in a mixture of CDCl₃ and (CD₃)₂SO.

The same selective mono-Reissert compound formation was found to occur with 2-methyl- (**7₂**)¹⁰⁾ and 4-ethoxyquinazolines (**7₃**).¹¹⁾ Thus, application of the Reissert compound formation as described for **2** to **7₂** resulted in the formation of the anticipated mono-Reissert compound (**8_{2a}**, 3-benzoyl-3,4-dihydro-2-methyl-4-quinazolinecarbonitrile). The reaction of **7₃** yielded the mono-Reissert compound (**9_{3a}**, 1-benzoyl-1,2-dihydro-4-ethoxy-2-quinazolinecarbonitrile) across the 1,2-double bond.

Structural determination of the new series of Reissert compounds was accomplished on the basis of analytical and spectral data (Tables II, III, and IV) and the results obtained from the following experiments (shown in Chart 6). Thus, **2_{1a}**, **2_{2a}**, **4_{1a}**, **6_{1a}**, **6_{2a}**, **8_{2a}** in an acid medium underwent ring fission, resulting in the formation of the α -benzamido-1*H*-pyrazole-4-acetonitrile (**15**),^{2d)} 4-(4-pyrazolyl)oxazole (**15₂**),⁸⁾ α -benzamido-1*H*-imidazole-4-acetonitrile (**16**),⁸⁾ α -benzamido-1*H*-1,2,3-triazole-4-acetonitriles (**17₁** and **17₂**),⁸⁾ 4-aryl-2-phenyloxazole (**18**),⁸⁾ respectively, confirming the positions bonded with cyano and benzoyl groups in the new series of Reissert compounds.

The above observations provide a useful synthetic method for the Reissert compounds from condensed pyrimidines. Studies on the reactivity of the new series of Reissert

TABLE IV. ^{13}C -NMR Spectral Data for **2**, **4**, **6**, **8** and **9**

Compd.	^{13}C -NMR (CDCl_3) ppm
2_{1b}	14.1 (q, CH_3), 42.9 (d, C^4), 65.1 (t, CH_2), 96.7 (s), 115.8 (s, CN), 122.5 (d), 127.3 (d), 129.0 (d), 135.1 (d), 138.3 (s), 140.7 (s), 142.1 (d), 151.4 (s, CO)
2_{1c}	22.0 (q, CH_3), 41.0 (d, C^4), 97.8 (s), 116.8 (s, CN), 122.0 (d), 127.1 (d), 129.0 (d), 136.2 (d), 138.2 (s), 140.7 (s), 145.1 (d), 170.3 (s, CO)
2_{1d}	43.2 (d, C^4), 96.3 (s), 114.9 (s, CN), 122.6 (d), 127.5 (d), 127.9 (d), 129.0 (d), 130.0 (d), 134.8 (d), 135.3 (d), 136.3 (s), 138.0 (s), 140.1 (s), 141.3 (d)
2_{1e}^{a)}	21.1 (q, CH_3), 41.6 (d, C^4), 98.5 (s), 116.8 (s, CN), 122.0 (d), 127.1 (s), 128.8 (d), 129.0 (d), 129.4 (d), 129.7 (d), 136.0 (d), 138.1 (s), 141.0 (s), 143.3 (s), 145.5 (d), 169.6 (s, CO)
2_{1f}^{a)}	41.6 (d, C^4), 55.5 (q, CH_3), 98.6 (s), 114.2 (d), 116.9 (s, CN), 122.0 (d), 123.5 (s), 127.1 (d), 129.0 (d), 132.1 (d), 135.9 (d), 138.2 (s), 141.1 (s), 145.7 (d), 162.9 (s), 169.1 (s, CO)
2_{1g}^{a)}	41.7 (d, C^4), 98.3 (s), 116.5 (s, CN), 122.1 (d), 123.9 (d), 127.2 (d), 129.1 (d), 130.9 (d), 136.2 (d), 137.6 (s), 138.1 (s), 140.7 (s), 144.9 (d), 149.5 (s), 168.4 (s, CO)
2_{2a}^{a)}	26.2 (q, CH_3), 42.2 (d, C^4), 99.9 (s), 117.0 (s, CN), 121.7 (d), 126.9 (d), 129.0 (d), 133.2 (d), 134.3 (s), 135.1 (d), 138.3 (s), 142.0 (s), 153.4 (s), 170.8 (s, CO)
2_{2c}^{a)}	21.1 (q, CH_3), 26.2 (q, CH_3), 42.2 (d, C^4), 99.9 (s), 117.1 (s, CN), 121.7 (d), 126.9 (d), 129.1 (d), 129.6 (d), 131.4 (s), 135.1 (d), 138.3 (s), 142.1 (s), 144.0 (s), 153.6 (s), 170.7 (s, CO)
2_{3a}	34.4 (q, CH_3), 42.0 (d, C^4), 95.8 (s), 115.9 (s, CN), 129.1 (d), 129.2 (d), 131.4 (s), 132.9 (d), 133.9 (d), 140.9 (s), 143.2 (d), 169.6 (s, CO)
2_{3b}^{a)}	14.0 (q, CH_3), 34.0 (q, CH_3), 43.0 (d, C^4), 64.6 (t, CH_2), 95.4 (s), 117.1 (s, CN), 134.1 (d), 140.4 (s), 142.5 (d), 151.7 (s, CO)
4_{1a}^{a)}	44.4 (d, C^6), 115.9 (s, CN), ^{b)} 116.9 (s), ^{b)} 123.6 (d), 127.9 (d), 128.8 (d), 129.3 (d), 129.4 (d), 131.7 (s), 131.9 (d), 132.5 (s), 134.4 (s), 136.3 (d), 142.1 (d), 169.8 (s, CO)
4_{1b}	14.1 (q, CH_3), 45.9 (d, C^6), 65.0 (t, CH_2), 115.4 (s, CN), ^{b)} 116.2 (s), ^{b)} 123.7 (d), 128.2 (d), 129.5 (d), 132.2 (s), 134.4 (s), 135.8 (d), 139.9 (d), 151.8 (s, CO)
4_{2a}^{a)}	13.7 (q, CH_3), 44.3 (d, C^6), 114.4 (s), ^{b)} 115.9 (s, CN), ^{b)} 127.0 (d), 128.2 (d), 128.8 (d), 129.2 (d), 132.0 (s), 132.4 (d), 133.8 (s), 140.9 (d), 144.3 (s), 169.8 (s, CO)
4_{2b}^{a)}	13.7 (q, CH_3), 13.9 (q, CH_3), 45.7 (d, C^6), 64.4 (t, CH_2), 113.6 (s), ^{b)} 116.2 (s, CN), ^{b)} 127.1 (d), 128.7 (d), 129.3 (d), 132.3 (s), 133.9 (s), 139.1 (d), 144.3 (s), 151.8 (s, CO)
6_{1a}	43.2 (d, C^7), 114.6 (s, CN), 122.5 (d), 124.3 (s), 129.6 (d), 129.7 (d), 129.8 (d), 131.1 (s), 133.7 (d), 135.7 (s), 137.1 (s), 146.2 (d), 169.6 (s, CO)
6_{1b}	14.1 (q, CH_3), 44.1 (d, C^7), 65.8 (t, CH_2), 114.6 (s, CN), 122.2 (d), 123.2 (s), 129.1 (d), 129.4 (d), 135.4 (s), 136.9 (s), 144.4 (d), 151.1 (s, CO)
6_{2a}	26.2 (q, CH_3), 42.9 (d, C^7), 114.6 (s, CN), 121.6 (d), 125.1 (s), 128.0 (d), 128.7 (d), 129.1 (d), 129.2 (d), 133.5 (d), 135.3 (s), 137.4 (s), 155.6 (s), 170.4 (s, CO)
8_{2a}	25.8 (q, CH_3), 43.9 (d, C^4), 115.7 (s, CN), 119.7 (s), 125.3 (d), 125.6 (d), 127.7 (d), 128.7 (d), 129.0 (d), 130.8 (d), 133.1 (d), 134.1 (s), 140.2 (s), 151.3 (s), 169.5 (s, CO)
9_{3a}	13.9 (q, CH_3), 60.1 (d, C^2), 62.9 (t, CH_2), 115.7 (s, CN), ^{b)} 117.8 (s), ^{b)} 123.6 (d), 125.5 (d), 128.6 (d), 128.7 (d), 131.7 (d), 132.2 (d), 133.4 (s), 137.7 (s), 162.6 (s), 168.5 (s, CO)

a) ^{13}C -NMR in $(\text{CD}_3)_2\text{SO}$. b) Assignments may be interchanged.

compounds are now in progress and will shortly be reported in a separate paper.

Experimental

All melting points are uncorrected. Infrared absorption (IR) spectra were recorded on a Jasco A-102 diffraction grating IR spectrometer. Proton nuclear magnetic resonance (^1H -NMR) spectra were measured at 60 MHz on a Hitachi R-24B high-resolution NMR spectrometer, and ^{13}C -NMR spectra were taken at 90 MHz on a JEOL JNM-FX90Q FTNMR spectrometer. Chemical shifts are quoted in parts per million (ppm) with tetramethylsilane as an internal standard, and coupling constants (J) are given in Hz. The following abbreviations are used: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, and br s = broad singlet. Mass spectra (MS) were recorded on a JEOL JMS D-100 mass spectrometer. Samples were vaporized in a direct inlet system. Column chromatography was carried out on SiO_2 , Wakogel C-200 (200 mesh). Thin-layer chromatography (TLC) was performed on precoated Kieselgel 60 F_{254} plates (Merck) with CHCl_3 .

Reisert Compound Formation of Condensed Pyrimidines (1, 3, 5 and 7) Catalyzed by Lewis Acids—The procedure for the Reisert compound 5-carbethoxy-4,5-dihydro-1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidine-4-carbonitrile (**2**_{1b}) is described as a typical example. Ethyl chloroformate (570 mg, 5.2 mmol) was added to a well stirred solution of 1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidine (**1**₁, 980 mg, 5.0 mmol) in freshly distilled CH₂Cl₂ (25 ml), then TMSCN (532 mg, 5.2 mmol) was added. After 5 min, AlCl₃ (66.7 mg, 0.5 mmol) was added at once, and the whole was stirred at room temperature until the starting material **1**₁ had disappeared (25 h), as monitored by TLC. The solution was washed with H₂O, 5% HCl, H₂O, 5% NaOH, and H₂O. The CH₂Cl₂ solution was dried over Na₂SO₄ and concentrated. The residue was passed through a column of SiO₂ with CHCl₃ to remove impurities. Recrystallization from AcOEt gave **2**_{1b} as colorless needles, mp 115–116 °C, in 88% yield (1300 mg).

Yields, melting points, analytical and spectral data for the new Reisert compounds (**2**, **4**, **6**, **8**, and **9**) are listed in Charts 2–5 and Tables II–IV.*

6-Methyl-1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidine (1**₂)**—A solution of 4-chloro-6-methyl-1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidine^{4b} (33.5 g, 136.8 mmol) in a mixture of benzene (280 ml) and MeOH (140 ml) was added to a catalyst prepared from 1% PdCl₂ (100 ml) and MgO (2.7 g), and the mixture was shaken in an H₂ stream. The reaction was stopped when 136 mmol of H₂ had been absorbed. The catalyst was filtered off and the filtrate was concentrated under reduced pressure. The residue was decomposed with diluted aqueous NH₃ and extracted with CHCl₃. The extract was washed with H₂O, dried over Na₂SO₄, and concentrated to dryness under reduced pressure. The residue was recrystallized from petroleum benzin to give **1**₂ as colorless needles, mp 99–100 °C, in 90% yield (25.8 g). *Anal.* Calcd for C₁₂H₁₀N₄: C, 68.55; H, 4.79; N, 26.65. Found: C, 68.65; H, 4.87; N, 26.93. MS *m/z*: 210 (M⁺). ¹H-NMR (CDCl₃): 9.08 (1H, s, C⁴-H), 8.13 (1H, s, C³-H), 8.40–8.10 (2H, m, Ph-H), 7.70–7.10 (3H, m, Ph-H), 2.85 (3H, s, CH₃). ¹³C-NMR (CDCl₃): 26.4 (q), 113.6 (s), 120.9 (d), 126.3 (d), 129.0 (d), 133.6 (d), 138.8 (s), 152.0 (d), 153.0 (s), 165.7 (s).

Reaction of 9-Phenyl-9*H*-purine (3**₁) with Benzoyl Chloride in the Presence of KCN**—A solution of KCN (260 mg, 4 mmol) in H₂O (1 ml) was added dropwise to a stirred solution of **3**₁ (392 mg, 2 mmol) and benzoyl chloride (281 mg, 2 mmol) in CHCl₃ (4 ml), and the mixture was stirred for 1 h. The reaction mixture was poured into a large amount of H₂O and extracted with CHCl₃. The extract was washed with H₂O, dried over Na₂SO₄, and concentrated under reduced pressure. The residue was chromatographed on a column of SiO₂ with CHCl₃. The first fraction gave 5-benzamido-4-(*N*-phenylformamido)pyrimidine (**12**) as colorless needles from benzene, mp 144–145 °C, in 23% yield (146 mg). The second fraction gave the starting **3**₁ in 24% yield (94 mg).

12: *Anal.* Calcd for C₁₈H₁₄N₄O₂: C, 67.91; H, 4.43; N, 17.60. Found: C, 67.65; H, 4.44; N, 17.65. MS *m/z*: 318 (M⁺). IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 3250 (NH), 1720, 1650 (C=O). ¹H-NMR (CDCl₃): 9.40 (1H, s, CH=O), 8.85 (1H, s, pyrimidine H), 8.78 (1H, s, pyrimidine H), 8.50–7.00 (11H, m, Ph-H and NH). ¹³C-NMR ((CD₃)₂SO): 125.3 (d), 126.4 (s), 126.9 (d), 127.5 (d), 128.1 (d), 128.9 (d), 131.9 (d), 133.0 (s), 137.1 (s), 153.9 (s), 155.0 (d), 156.6 (d), 165.1 (s).

Alkaline Hydrolysis of 12—A mixture of **12** (50 mg) and 2*N* NaOH (1 ml) was heated for 5 min on a steam bath. The reaction mixture was poured into a large amount of H₂O and extracted with CHCl₃. The extract was dried over Na₂SO₄, and concentrated under reduced pressure, and the residue was chromatographed on a column of SiO₂ with CHCl₃. The first fraction gave 4-anilino-5-benzamidopyrimidine (**13**) as colorless needles from MeOH, mp 193.5–194.5 °C, in 57% yield (26 mg). MS *m/z* Calcd for C₁₇H₁₄N₄O: 290.1167 (M⁺). Observed: 290.1182. IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 3250 (NH), 1658 (C=O). ¹H-NMR (CDCl₃–((CD₃)₂SO): 9.70 (1H, br s, exchangeable with D₂O, NH), 8.52 (1H, s, pyrimidine H), 8.49 (1H, s, pyrimidine H), 8.40 (1H, br s, exchangeable with D₂O, NH), 8.20–7.00 (10H, m, Ph-H).

Benzoylation of 5-Amino-4-anilinopyrimidine^{5a)}—Benzoyl chloride (140 mg, 1 mmol) was added to a solution of 5-amino-4-anilinopyrimidine (186 mg, 1 mmol) in pyridine (1 ml) and the mixture was stirred overnight at room temperature. The separated crystals were collected by suction, washed with H₂O, and recrystallized from MeOH–benzene to give **13** as colorless needles in 80% yield (232 mg).

3,6-Dihydro-5-methyl-3-phenyl-7*H*-1,2,3-triazolo[4,5-*d*]pyrimidin-7-one (5**₄)**—A mixture of 5-amino-1-phenyl-1*H*-1,2,3-triazole-4-carboxamide (**14**₂, 40.6 g, 0.2 mol) and AcOEt (40 ml) in EtONa solution prepared by dissolving Na (9.2 g, 0.4 mol) in an EtOH (400 ml) was refluxed under stirring for 20 h. The EtOH was removed under reduced pressure, and H₂O (1 : 1) was added to the residue. After the insoluble crystals had been filtered off, the filtrate was neutralized with AcOH and the separated crystals were recrystallized from MeOH to give **5**₄ as slightly yellow needles, mp 267–268 °C (dec.), in 78% yield (35.5 g). *Anal.* Calcd for C₁₁H₉N₅O: C, 58.14; H, 3.99; N, 30.82. Found: C, 58.20; H, 4.04; N, 31.08. IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 1695 (C=O). ¹H-NMR (CDCl₃): 8.2–6.9 (5H, m, Ph-H), 6.2–4.7 (1H, br, NH), 2.4 (3H, s, CH₃).

7-Chloro-5-methyl-3-phenyl-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidine (5**₅)**—*N,N*-Dimethylaniline (3.5 g) was added dropwise to a stirred mixture of **5**₄ (5.0 g) and POCl₃ (40 ml), and the mixture was refluxed for 30 min in an oil bath. The POCl₃ was removed under reduced pressure and a large amount of H₂O was added to the residue. The reaction mixture was stirred for 5 min, and extracted with benzene. The extract was dried over Na₂SO₄, concentrated, and chromatographed on a column of SiO₂ with benzene. The first fraction gave **5**₅ as yellow needles from benzene, mp 114–116 °C, in 76% yield (4.1 g). *Anal.* Calcd for C₁₁H₈ClN₅: C, 53.78; H, 3.28; N, 28.51. Found: C, 53.76; H, 3.26; N, 28.54. ¹H-NMR (CDCl₃): 8.40–7.45 (5H, m, Ph-H), 2.89 (3H, s, CH₃).

5-Methyl-3-phenyl-3H-1,2,3-triazolo[4,5-d]pyrimidine (5₂)—A solution of 5₁ (3.6 g, 14 mmol) in benzene (50 ml) was added to a catalyst prepared from 1% PdCl₂ (10 ml) and MgO (2.7 g) in H₂O (10 ml), and the mixture was shaken in an H₂ stream. The reaction was stopped when 313 ml (14 mmol) of H₂ had been absorbed. The same work-up as described for 1₂ gave 5₂ as colorless plates from benzene, mp 158–159 °C, in 72% yield (2.2 g). *Anal.* Calcd for C₁₁H₉N₅: C, 62.55; H, 4.30; N, 33.16. Found: C, 62.69; H, 4.36; N, 33.11. ¹H-NMR (CDCl₃): 9.50 (1H, s, C⁷-H), 8.50–7.40 (5H, m, Ph-H), 2.93 (3H, s, CH₃).

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References and Notes

- 1) Part XV: T. Higashino, S. Sato, A. Miyashita, and T. Katori, *Chem. Pharm. Bull.*, **35**, 4078 (1987).
- 2) a) T. Higashino, H. Kokubo, and E. Hayashi, *Chem. Pharm. Bull.*, **33**, 950 (1985); b) T. Higashino, Y. Iwai, and E. Hayashi, *Yakugaku Zasshi*, **94**, 666 (1974); c) T. Higashino, H. Kokubo, A. Goto, M. Takemoto, and E. Hayashi, *Chem. Pharm. Bull.*, **32**, 3690 (1984); d) T. Higashino, S. Sato, A. Miyashita, and T. Katori, *ibid.*, **34**, 4569 (1986); e) T. Higashino, Y. Iwai, and E. Hayashi, *ibid.*, **24**, 3120 (1976); f) T. Higashino, T. Katori, and E. Hayashi, *ibid.*, **27**, 2431 (1979); g) T. Higashino, H. Kokubo, and E. Hayashi, *ibid.*, **32**, 3900 (1984).
- 3) a) W. E. McEwen and R. L. Cobb, *Chem. Rev.*, **55**, 511 (1955); b) F. D. Popp, "Advances in Heterocyclic Chemistry," Vol. 9, ed. by A. R. Katoritzky and A. J. Boulton, Academic Press, Inc., New York, 1968, p. 1; c) *Idem*, *ibid.*, Vol. 24, 1979, p. 187.
- 4) a) C. C. Cheng and R. K. Robins, *J. Org. Chem.*, **21**, 1240 (1956); b) *Idem*, *ibid.*, **23**, 191 (1958).
- 5) a) E. Hayashi, N. Shimada, and Y. Matsuoka, *Yakugaku Zasshi*, **99**, 114 (1979); b) E. Hayashi, N. Shimada, Y. Matsuoka, and Y. Miwa, *ibid.*, **99**, 207 (1979).
- 6) A. Dornow and J. Helberg, *Chem. Ber.*, **93**, 2001 (1960).
- 7) N. Whittaker, *J. Chem. Soc.*, **1951**, 1565.
- 8) Unpublished data. The results obtained from acid hydrolysis will be reported in detail in a separate paper.
- 9) J. Kant, F. D. Popp, B. L. Joshi, and B. C. Uff, *Chem. Ind. (London)*, **1984**, 415.
- 10) A. Bischler, *Ber.*, **24**, 506 (1891).
- 11) M. T. Bogert and C. E. May, *J. Am. Chem. Soc.*, **31**, 509 (1909).
- 12) No absorption due to the cyano group was seen in the IR spectra. This is compatible with the reported absence of the cyano group absorption of 2_{1a} and 8_{1a}.^{3d, g)}
- 13) S. Ruchirawat, N. Phadungkul, M. Chuankamnerdkarn, and C. Thebtaranonth, *Heterocycles*, **6**, 43 (1977).