Catalytic Action of Azolium Salts. I. Aroylation of 4-Chloro-1*H*-pyrazolo[3,4-*d*]pyrimidines with Aromatic Aldehydes Catalyzed by 1,3-Dimethylbenzimidazolium Iodide[1)]

Akira MIYASHITA,*,[a] Hideaki MATSUDA,[b] Chihoko IIJIMA,[a] and Takeo HIGASHINO[a]

School of Pharmaceutical Sciences, University of Shizuoka,[a] 395 Yada, Shizuoka 422, Japan and Central Research Laboratories, S S Pharmaceutical Co., Ltd.,[b] 1143 Nanpeidai, Narita 286, Japan.

Received September 28, 1989

When a mixture of 4-chloro-1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidine (9), aromatic aldehyde (5), sodium hydride, and a catalytic amount of 1,3-dimethylbenzimidazolium iodide (4) in tetrahydrofuran was refluxed, the nucleophilic aroylation occurred, resulting in the formation of the aryl 1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl ketones (11).

Similar reaction of 4-chloro-1-methyl-1*H*-pyrazolo[3,4-*d*]pyrimidine (10) gave the corresponding aryl 1-methyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl ketones (12) in moderate yields. Use of dimethylformamide or dimethyl sulfoxide in the above reaction reduced the necessary reaction time and reaction temperature. A plausible reaction pathway for the formation of the ketones 11 and 12 involving the catalytic action of 4 is proposed.

Keywords benzimidazolium salt; nucleophilic aroylation; 4-aroyl-1*H*-pyrazolo[3,4-*d*]pyrimidine; 4-chloro-1*H*-pyrazolo[3,4-*d*]pyrimidine; catalytic action; aromatic aldehyde; benzoin condensation

It is well known that the cyanide ion (1)[2)] is an effective catalyst for benzoin condensation. Moreover, it has also been reported that some azolium salts such as thiazolium salts (2)[3a)] and benzimidazolium salts (3)[3b)] are also effective catalysts for the condensation.

The mechanism of benzoin formation catalyzed by cyanide ion was extensively investigated by Lapworth,[4)] and the condensation may be considered to proceed through the formation of a cyanohydrin *O*-anion (B-1: Z=CN) with a subsequent prototropic shift to afford an acyl anion equivalent (cyanohydrin carbanion, B-2: Z=CN), as shown in Chart 1. Breslow and McNelis reported[5)] that the similar intermediate B-2 (Z=2-thiazolium or 2-benzimidazolium) corresponding to the cyanohydrin carbanion (B-2: Z=CN) was formed by the reaction of benzaldehyde (**5f**) with the above azolium salts (**2, 3**) in the presence of a base. In connection with the benzoin condensation, our interest was focussed on the utilization of the intermediate B-2 (Z=2-

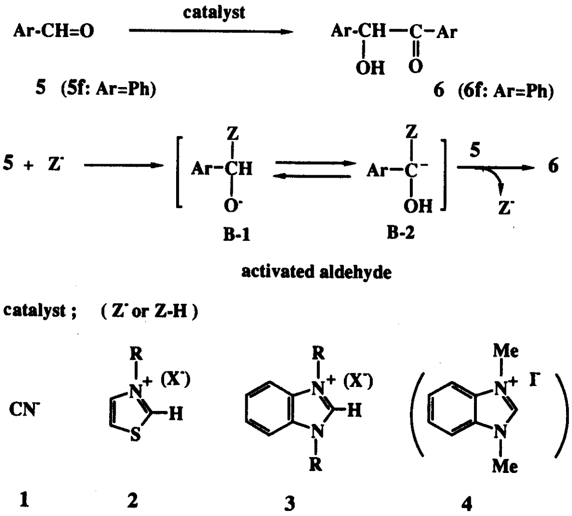

Chart 1

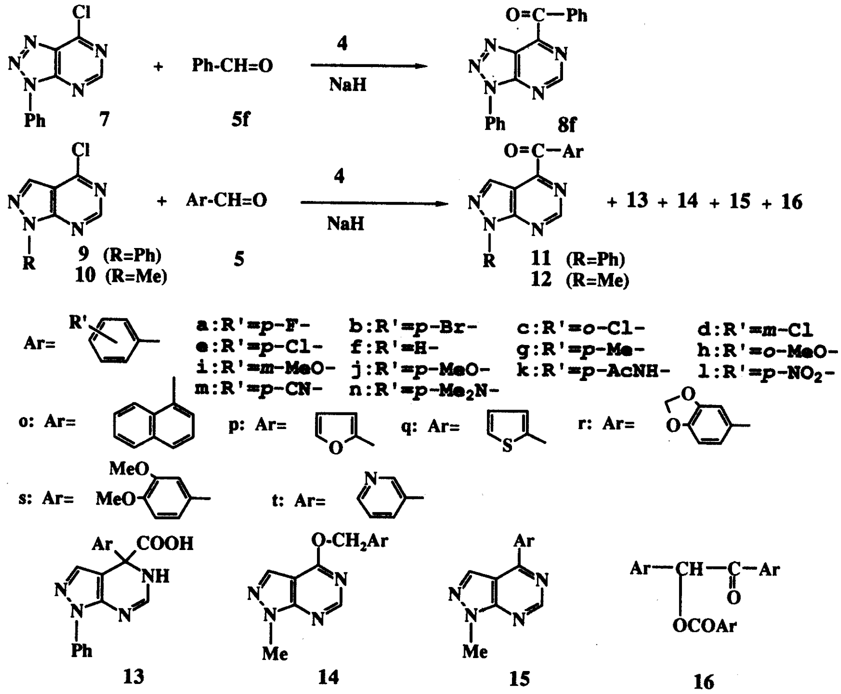

Chart 2

benzimidazolium) for introducing aroyl groups at the α-position to the ring nitrogen for aromatic heterocycles.

We reported that 7-chloro-3-phenyl-3*H*-triazolo[4,5-*d*]pyrimidine (**7**) reacted with benzaldehyde (**5f**) in the presence of sodium hydride (NaH) and a catalytic amount of 1,3-dimethylbenzimidazolium iodide (**4**) in tetrahydrofuran (THF) to give phenyl 3-phenyl-3*H*-triazolo[4,5-*d*]pyrimidin-7-yl ketone (**8f**),[6a] as shown in Chart 2. Since the 4-chloro-1*H*-pyrazolo[3,4-*d*]pyrimidines (**9**, **10**)[7] are considered to be analogues of **7**, it was expected that the aroylation of **9** or **10** to the 4-aroyl-1*H*-pyrazolo[3,4-*d*]pyrimidines (**11**, **12**) might proceed. Hence we carried out the reactions of **9** and **10** with aromatic aldehydes (**5**) in the presence of NaH and **4**, and found that the expected aroylation took place. In the present paper, we describe our detailed investigation of the aroylations of **9** and **10**.

When a mixture of 4-chloro-1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidine (**9**), benzaldehyde (**5f**), and NaH was refluxed in THF for 30 min in the presence of a catalytic amount of **4**, the chlorine atom at the 4-position of **9** was replaced with a benzoyl group, and phenyl 1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl ketone (**11f**) was obtained in 57% yield. In order to examine the generality of this nucleophilic aroylation, we carried out the reactions of **9** and **10** with various aromatic aldehydes (**5**) in the presence of **4**.

Aromatic aldehydes used in this reaction were as follows: *p*-fluorobenzaldehyde (**5a**), *p*-bromobenzaldehyde (**5b**), *o*-chlorobenzaldehyde (**5c**), *m*-chlorobenzaldehyde (**5d**), *p*-chlorobenzaldehyde (**5e**), benzaldehyde (**5f**), *p*-tolualdehyde (**5g**), *o*-methoxybenzaldehyde (**5h**), *m*-methoxybenzaldehyde (**5i**), *p*-methoxybenzaldehyde (**5j**), *p*-acetamidobenzaldehyde (**5k**), *p*-nitrobenzaldehyde (**5l**), *p*-cyanobenzaldehyde (**5m**), *p*-(*N*,*N*-dimethylamino)benzaldehyde (**5n**), 1-naphthalenecarbaldehyde (**5o**), 2-furancarbaldehyde (**5p**), 2-thiophenecarbaldehyde (**5q**), 3,4-methylenedioxybenzaldehyde (**5r**), 3,4-dimethoxybenzaldehyde (**5s**), and 3-pyridinecarbaldehyde (**5t**).

The reaction of **9** with aromatic aldehydes (**5a**—**f**, **g**—**j**, **o**, **q**) in the presence of **4** in refluxing THF (method A) gave the corresponding ketones (**11a**—**f**, **g**—**j**, **o**, **q**) in satisfactory yields. The reactions of **5k** and **5m** afforded the desired ketones (**11k**, **m**), but the yields were poor. In the case of **5l**, **5n**, and **5t**, the nucleophilic aroylation of **9** failed, resulting in the quantitative recovery of the starting material **9**. But use of dioxane instead of THF in the reaction of **9** with **5t** gave the ketone **11t** in poor yield (12%).

TABLE I. Reactions of **9** and **10** with **5** in the Presence of **4**

9, 10	5	Solv.	Reaction conditions Time (min)	Temp.[a] (°C)	Products 11, 12	Yield (%)	Others	
9	**5a**	THF	60	refl.	**11a**[6b]	54		
9	**5b**	THF	30	refl.	**11b**[6b]	76		
9	**5c**	THF	30	refl.	**11c**[10]	64		
9	**5d**	THF	40	refl.	**11d**[10]	53		
9	**5e**	THF	40	refl.	**11e**[10]	96		
9	**5e**	DMF	20	r.t.	**11e**	78		
9	**5f**	THF	20	refl.	**11f**[10]	57		
9	**5f**	DMF	30	r.t.	**11f**	57	**13f**	7
9	**5g**	THF	50	refl.	**11g**[10]	69		
9	**5h**	THF	20	refl.	**11h**[10]	72		
9	**5h**	DMF	30	r.t.	**11h**	2	**13h**	42
9	**5i**	THF	20	refl.	**11i**[10]	65		
9	**5j**	THF	60	refl.	**11j**[10]	78		
9	**5j**	DMF	15	r.t.	**11j**	54		
9	**5k**	THF	60	refl.	**11k**	17		
9	**5k**	DMF	35	r.t.	**11k**	93		
9	**5l**	THF	30	refl.	**11l**	—[b]		
9	**5l**	DMF	40	r.t.	**11l**	—[c]		
9	**5m**	THF	30	50	**11m**[6b]	8		
9	**5n**	THF	60	refl.	**11n**	—[d]		
9	**5n**	DMF	40	r.t.	**11n**	—[e]		
9	**5o**	THF	40	refl.	**11o**	52		
9	**5p**	THF	60	refl.	**11p**[10]	15		
9	**5q**	THF	30	refl.	**11q**	66		
9	**5q**	DMSO	20	r.t.	**11q**	56		
9	**5r**	DMSO	20	r.t.	**11r**	57		
9	**5s**	DMF	60	r.t.	**11s**	47		
9	**5t**	THF	60	refl.	**11t**	—[f]		
9	**5t**	Dioxane	50	refl.	**11t**	12		
9	**5t**	DMF	60	r.t.	**11t**	62		
10	**5a**	THF	20	refl.	**12a**	82		
10	**5a**	DMF	10	r.t.	**12a**	54		
10	**5b**	THF	20	refl.	**12b**	98		
10	**5c**	THF	40	refl.	**12c**	40	**14c**	27[g]
10	**5d**	THF	40	refl.	**12d**	54	**14d**	29
10	**5e**	THF	20	refl.	**12e**[10]	88	**14e**	1[h]
10	**5e**	DMSO	15	r.t.	**12e**	52	**15e**	6
10	**5f**	THF	30	refl.	**12f**[10]	54		
10	**5g**	THF	40	refl.	**12g**[10]	58		
10	**5g**	DMF	20	r.t.	**12g**	53		
10	**5h**	THF	30	refl.	**12h**	67		
10	**5i**	THF	20	refl.	**12i**[10]	41		
10	**5j**	THF	30	refl.	**12j**[10]	75		
10	**5j**	DMF	15	r.t.	**12j**	64		
10	**5l**	Dioxane	60	refl.	**12l**	—[i]		
10	**5l**	DMF	30	r.t.	**12l**	—[j]		
10	**5o**	THF	60	refl.	**12o**	40		
10	**5p**	THF	20	refl.	**12p**[10]	11		
10	**5q**	THF	20	refl.	**12q**	48		
10	**5s**	DMF	15	r.t.	**12s**	57		
10	**5t**	DMF	10	r.t.	**12t**	18		

a) r.t. = room temperature. refl. = reflux. *b*) Compound **11l** was not isolated, and **9** was recovered in 54% yield. *c*) Compound **9** was recovered in 24% yield. *d*) Compound **11n** was not isolated, and **9** was recovered in 65% yield. *e*) Compound **9** was recovered in 68% yield. *f*) Compound **9** was recovered in 62% yield. *g*) **16c**, 6%. *h*) **16e**, 4%. *i*) Compound **10** was recovered in 67% yield. *j*) Compound **10** was recovered in 25% yield.

Use of dimethylformamide (DMF) or dimethyl sulfoxide (DMSO) instead of THF or dioxane (method B) reduced the reaction temperature required to achive the aroylation. That is to say, the reactions of **5e**, **5j**, and **5k** in DMF at room temperature gave the ketones (**11e**, **j**, **k**) in moderate yields. The same treatment of **9** with **5f** and **5h** gave the ketones (**11f**, **h**) together with the corresponding 4-aryl-3,4-dihydropyrazolopyrimidine-4-carboxylic acids (**13f**, **h**). The yield of the ketone **11h** was low (2%), because the additional reaction of the resulting ketone **11h** with hydroxide ion in DMF and subsequent aryl migration proceeded, resulting in the formation of **13h**. Both **5l**, possessing a strongly electron-withdrawing group, and **5n**, possessing a strongly electron-donating group, failed to give the corresponding ketones (**11l**, **n**) under similar conditions, and the starting material **9** was recovered in 24% and 68% yields, respectively. However, the same treatment of **9** with **5t** in DMF gave the ketone **11t** in 62% yield. The reactions of **5q** and **5r** in DMSO gave the corresponding ketones (**11q**, **r**).

The aroylation of **9** was extended to 4-chloro-1-methyl-1*H*-pyrazolo[3,4-*d*]pyrimidine (**10**). Namely, **10** reacted with aromatic aldehydes (**5a**—**b**, **f**—**j**, **o**, **q**) in the presence of **4** in THF (method C) to afford the desired ketones

(**12a**—**b**, **f**—**j**, **o**, **q**) in moderate yields. In the case of the reaction with **5p**, the ketone **12p** was obtained in only poor yield (11%). The reactions with **5c**, **5d**, and **5e** under similar conditions gave the corresponding ketones (**12c**, **d**, **e**) as the main product together with the 4-benzyloxypyrazolopyrimidines (**14c**, **d**, **e**) and the aroylaroins (**16c**, **e**) as by-products.

Use of DMF or DMSO (method D) instead of THF in the aroylation of **10** produced the similar effects, that is the required reaction time and temperature were reduced, to those seen in the aroylation of **9**. The reaction with **5a**, **5g**, **5j**, and **5s** in DMF at room temperature gave the desired ketones (**12a**, **g**, **j**, **s**) in moderate yields. Similarly, **10** reacted with **5t** in DMF to give the ketone **12t**, but the yield was low (18%). In the case of **5e**, the ketone **12e** was obtained together with 4-(4-chlorophenyl)-1-methyl-1*H*-pyrazolo[3,4-*d*]pyrimidine (**15e**). Compound **15e** may be formed by aryl migration of the resulting ketone **12e**, followed by decarboxylation and oxidation. The reaction of **10** with **5l** in dioxane or DMF did not afford the desired ketone **12l**, and the starting material **10** was recovered in 67% or 25% yield, as in the reaction of **9** and **5l**. The results are summarized in Table I.

The structures of the new ketones **11** and **12** were supported by the elemental analyses and molecular ion (M$^+$) peaks in the mass spectra (MS), and confirmed by analyses of infrared (IR) absorption, proton nuclear magnetic resonance (^{1}H-NMR), and carbon nuclear magnetic resonance (^{13}C-NMR) spectra, as shown in Tables II, III, and IV. Compounds **13f** and **13h** showed undepressed melting points on admixture with the corresponding authentic samples.[6b)] The 4-benzyloxypyrazolopyrimidines (**14c**—**e**) were identified by comparison with authentic specimens prepared from **10** by treatment with the chlorobenzyl alcohols (**17c**—**e**) and NaH in THF. Similarly, the aroylaroins (**16c**, **e**) were identified by comparison with authentic specimens prepared from the aroins (**6c**, **e**) (mixture melting point test).

Table II. Melting Points, Mass Spectral Data, and Elemental Analyses for **11** and **12**

Compd.	mp (°C)	Formula	Analysis (%) Calcd C	Calcd H	Calcd N	Found C	Found H	Found N	MS *m/z* M$^+$
11k	213—214[d,g)]	$C_{20}H_{15}N_5O_2$	67.22	4.23	19.60	66.90	4.22	19.47	357
11o	198—199[a,f)]	$C_{22}H_{14}N_4O$	75.42	4.03	15.99	75.26	4.15	15.97	350
11q	170.5—171[a,f)]	$C_{16}H_{10}N_4OS$	62.73	3.29	18.29	62.65	3.38	18.26	306
11r	159—159.5[b,f)]	$C_{19}H_{12}N_4O_3$	66.28	3.51	16.27	66.30	3.44	16.16	344
11s	180[a,f)]	$C_{20}H_{16}N_4O_3$	66.66	4.48	15.55	66.35	4.48	15.51	360
11t	139—140[a,f)]	$C_{17}H_{11}N_5O$	67.77	3.68	23.25	67.75	3.61	23.46	301
12a	116—118[a,f)]	$C_{13}H_9FN_4O$	60.94	3.54	21.87	60.72	3.64	21.65	256
12b	146—147[a,f)]	$C_{13}H_9BrN_4O$	49.23	2.86	17.67	49.25	2.82	17.67	316, 318
12c	106—107.5[e,f)]	$C_{13}H_9ClN_4O$	57.26	3.33	20.55	57.29	3.26	20.53	272
12d	142—143[c,f)]	$C_{13}H_9ClN_4O$	57.26	3.33	20.55	57.12	3.33	20.48	272
12h	117—118[d,f)]	$C_{14}H_{12}N_4O_2$	62.68	4.51	20.89	62.78	4.50	20.73	268
12o	148.5—150[a,f)]	$C_{17}H_{12}N_4O$	70.82	4.20	19.43	70.95	4.25	19.66	288
12q	129[a,f)]	$C_{11}H_8N_4OS$	54.09	3.30	22.94	53.80	3.37	22.80	244
12s	171—171.5[a,f)]	$C_{15}H_{14}N_4O_3$	60.40	4.73	18.78	60.34	4.70	18.67	298
12t	154—155[a,f)]	$C_{12}H_9N_5O$	60.25	3.79	29.27	60.15	3.74	29.13	239

a) Yellow needles. *b*) Pale yellow needles. *c*) Colorless needles. *d*) Yellow granules. *e*) Slightly yellow prisms. *f*) Recrystallized from MeOH. *g*) Recrystallized from benzene.

Table III. IR and ^{1}H-NMR Spectral Data for **11** and **12**

Compd.	IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}	^{1}H-NMR ($CDCl_3$) ppm
11k	3350 (NH) 1640, 1690 (CO)	9.30 (1H, s, C^6-H), 8.51 (1H, s, C^3-H), 7.45—8.10 (9H, m), 2.30 (3H, s, –COMe)
11o	1660 (CO)	9.06 (1H, s, C^6-H), 8.53 (1H, s, C^3-H), 7.05—8.43 (12H, m)
11q	1640 (CO)	9.15 (1H, s, C^6-H), 8.14 (1H, s, C^3-H), 7.05—8.28 (6H, m), 8.47 (1H, dd, J=4, 2 Hz), 7.45 (1H, dd, J=5, 2 Hz)
11r	1650 (CO)	9.12 (1H, s, C^6-H), 8.51 (1H, s, C^3-H), 6.75—8.25 (8H, m), 6.00 (2H, s, –O$C\underline{H}_2$O–)
11s	1640 (CO)	9.10 (1H, s, C^6-H), 8.46 (1H, s, C^3-H), 6.80—8.23 (8H, m), 3.90 (6H, s, –OMe)
11t	1675 (CO)	9.20 (1H, s, C^6-H), 8.69 (1H, s, C^3-H), 9.47 (1H, d, J=3 Hz), 7.30—8.80 (8H, m)
12a	1665 (CO)	8.97 (1H, s, C^6-H), 8.30 (1H, s, C^3-H), 8.05—8.18 (2H, m), 6.88—7.17 (2H, m), 4.10 (3H, s, –NMe)
12b	1650 (CO)	9.01 (1H, s, C^6-H), 8.39 (1H, s, C^3-H), 8.05 (2H, d, J=8 Hz), 7.55 (2H, d, J=8 Hz), 4.15 (3H, s, –NMe)
12c	1680 (CO)	8.95 (1H, s, C^6-H), 8.41 (1H, s, C^3-H), 7.25—7.60 (4H, m), 4.11 (3H, s, –NMe)
12d	1660 (CO)	9.10 (1H, s, C^6-H), 8.40 (1H, s, C^3-H), 7.20—8.40 (4H, m), 4.17 (3H, s, –NMe)
12h	1665 (CO)	8.92 (1H, s, C^6-H), 8.26 (1H, s, C^3-H), 6.80—7.70 (4H, m), 4.12 (3H, s, –NMe), 3.52 (3H, s, –OMe)
12o	1660 (CO)	9.89 (1H, s, C^6-H), 8.39 (1H, s, C^3-H), 7.25—8.30 (7H, m), 4.16 (3H, s, –NMe)
12q	1640 (CO)	9.10 (1H, s, C^6-H), 8.56 (1H, s, C^3-H), 8.45 (1H, dd, J=4, 2 Hz), 7.75 (1H, dd, J=4, 2 Hz), 7.08—7.25 (1H, m), 4.16 (3H, s, –NMe)
12s	1655 (CO)	9.01 (1H, s, C^6-H), 8.30 (1H, s, C^3-H), 7.68—7.95 (2H, m), 6.80 (1H, d, J=9 Hz), 4.13 (3H, s, –NMe), 3.92 (6H, s, –OMe)
12t	1660 (CO)	9.42 (1H, d, J=2 Hz), 9.10 (1H, s, C^6-H), 8.48 (1H, s, C^3-H), 8.75 (1H, dd, J=4, 2 Hz), 8.40—8.60 (1H, m), 7.40 (1H, dd, J=8, 4 Hz), 4.18 (3H, s, –NMe)

TABLE IV. ^{13}C-NMR Spectral Data for **11** and **12**

Compd.	^{13}C-NMR ($CDCl_3$) ppm
11o	113.9 (s), 121.6 (d), 122.8 (s), 124.1 (d), 125.5 (d), 126.7 (d), 127.2 (d), 128.2 (d), 128.7 (d), 129.3 (d), 130.7 (s), 131.3 (s), 132.0 (d), 132.5 (s), 133.8 (d), 133.9 (s), 135.0 (d), 138.4 (s), 155.1 (d), 194.7 (s, CO)
11q	113.3 (s), 121.5 (d), 127.1 (d), 128.1 (d), 129.2 (d), 135.5 (d), 137.5 (d), 138.3 (s), 139.4 (s), 154.1 (s), 154.6 (d), 184.8 (s, CO)
11r	102.1 (t, $-\underset{\cdot}{C}H_2-$), 108.1 (d), 110.4 (d), 114.0 (s), 121.6 (d), 127.2 (d), 128.8 (d), 129.3 (d), 129.6 (s), 135.1 (d), 138.4 (s), 148.2 (s), 152.9 (s), 153.9 (s), 154.7 (d), 156.6 (s), 189.3 (s, CO)
11s	56.1 (q, –OMe), 110.1 (d), 112.4 (d), 114.0 (s), 121.5 (d), 127.1 (d), 127.3 (d), 128.0 (s), 129.2 (d), 135.0 (d), 138.4 (s), 149.2 (s), 154.5 (s), 154.6 (d), 156.8 (s), 189.5 (s, CO)
12a[a)]	33.9 (q, –NMe), 112.1 (d), 116.0, 133.8, 133.9, 134.2, 153.7 (d), 154.1 (d), 155.0 (s), 160.4 (s), 171.8 (s), 189.9 (s, CO)
12b	34.0 (q, –NMe), 112.2 (s), 129.3 (s), 129.9 (s), 131.7 (d), 132.5 (d), 133.5 (d), 133.9 (s), 154.0 (d), 154.7 (s), 190.6 (s, CO)
12c	34.0 (q, –NMe), 111.1 (d), 126.7 (d), 130.1 (d), 130.5 (d), 132.4 (d), 133.3 (d), 136.8 (s), 153.8 (s), 154.4 (s), 154.7 (d), 194.6 (s, CO)
12d	34.0 (q, –NMe), 112.2 (s), 129.2 (d), 129.7 (d), 131.0 (d), 133.5 (d), 133.6 (d), 134.6 (s), 136.7 (s), 154.1 (d), 154.6 (s), 190.4 (s, CO)
12h	34.0 (q, –NMe), 55.6 (q, –OMe), 110.9 (s), 111.9 (d), 120.9 (d), 126.8 (s), 130.7 (d), 133.2 (d), 134.1 (d), 154.2 (s), 154.6 (d), 156.5 (s), 159.0 (s), 194.7 (s, CO)
12o	34.0 (q, –NMe), 112.2 (s), 124.1 (d), 125.4 (d), 126.6 (d), 128.1 (d), 128.6 (d), 131.2 (s), 131.8 (d), 132.6 (s), 133.6 (d), 133.9 (s), 154.4 (s), 154.5 (d), 156.1 (s), 194.8 (s, CO)
12q	34.0 (q, –NMe), 111.6 (s), 128.0 (d), 134.0 (d), 137.3 (d), 139.5 (s), 154.0 (d), 154.3 (s), 162.2 (s), 182.6 (s, CO)
12s	34.0 (q, –NMe), 56.0 (q, –OMe), 56.1 (q, –OMe), 110.0 (d), 112.4 (d), 127.2 (d), 128.1 (s), 133.5 (d), 149.2 (s), 154.1 (d), 154.4 (s), 156.5 (s), 189.7 (s, CO)
12t	34.0 (q, –NMe), 111.9 (s), 123.2 (d), 131.0 (s), 133.6 (d), 138.2 (d), 152.2 (d), 153.6 (d), 153.9 (s), 154.1 (d), 154.3 (s), 190.8 (s, CO)

a) The spectrum was observed with ^{13}C–^{19}F coupling.

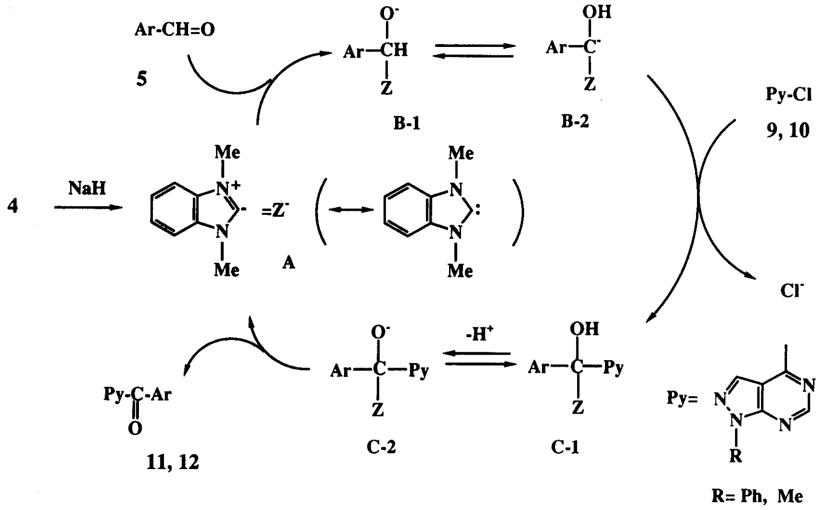

Chart 3

In connection with benzoin condensation, the mechanism of the aroylation of **9** to **11** or **10** to **12** was considered as follows. The initial step is the formation of the benzimidazolium ylide A. The subsequent addition of the ylide A to aromatic aldehydes (**5**) affords the *O*-anion B-1 (Z = 2-benzimidazolium) which rearranges to the carbanion B-2 (Z = 2-benzimidazolium) through a prototropic shift. The nucleophilic attack of the carbanion B-2 on the 4-chloropyrazolopyrimidines (**9**, **10**) at the 4-position gives the tetrahedral intermediates (C-1, C-2). Finally, loss of the benzimidazolium ylide A from the intermediate C-2 affords the ketones (**11**, **12**) as shown in Chart 3. The benzimidazolium salt (**4**) is recycled in the reaction system as a catalyst.

When the reaction of **10** with **5e** and NaH in the absence of **4** was attempted, neither the ketone **12e** nor the 4-benzyloxypyrazolopyrimidine (**14e**) was formed, and there was a quantitative recovery of the starting material **10**. This result suggested that the benzimidazolium salt (**4**) is involved in the formation of **14**. Since it was reported by Castells *et al.*[8)] that the type B-2 intermediate (Z = CN or 2-thiazolium) acts as a reducing agent, redox reaction presumably proceeds between the intermediate B-2 (Z = 2-benzimidazolium) and aromatic aldehyde (**5**) to afford the intermediate **19** together with the benzyl alcohol (**17**). The benzyl alcholate anion (E) attacks the C^4 carbon of the 4-chloropyrazolopyrimidines (**9**, **10**), resulting in the formation of **14**. The intermediate **19**, whose acyl group is active to the nucleophile,[9)] reacts with the aroin *O*-anion (F) to give the intermediate D. The subsequent elimination of the benzimidazolium ylide A from the intermediate D affords **16**. The mechanisms of formation of **14** and **16** are shown in Chart 4.

The aryl migration of the ketones (**11**, **12**) to the 4-aryl-3,4-dihydropyrazolopyrimidine-4-carboxylic acids (I, **13**: R = Ph) involving the benzilic acid rearrangement mechanism was reported by Higashino *et al.*[6b)] A similar migration of the ketones (**11**, **12**) may proceed with hydroxide ion to give I (**13**: R = Ph) *via* intermediate G, as shown in Chart 5. Furthermore, compound I undergoes

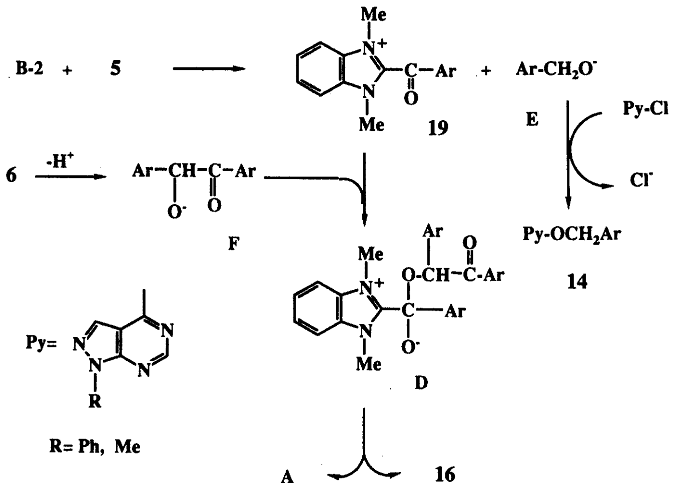

Chart 4

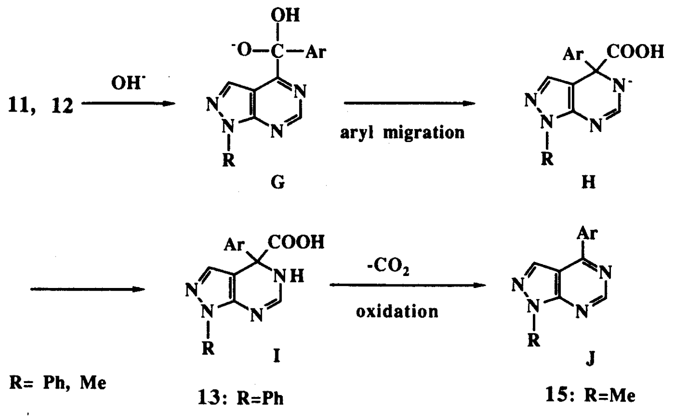

Chart 5

sequential decarboxylation and oxidation, resulting in the formation of the 4-arylpyrazolopyrimidines (J, **15**: R = Me). The oxidizing reagent may be oxygen in air.

In conclusion, the nucleophilic aroylation of the 4-chloro-1*H*-pyrazolo[3,4-*d*]pyrimidines (**9**, **10**) with aromatic aldehydes (**5**) catalyzed by 1,3-dimethylbenzimidazolium iodide (**4**) is a very useful method for preparation of the 4-aroyl-1*H*-pyrazolo[3,4-*d*]pyrimidines (**11**, **12**).

Experimental

All melting points are uncorrected. IR spectra were recorded on a Jasco A-102 diffraction grating IR spectrometer. ^{1}H-NMR spectra were measured at 60 MHz on a Hitachi R-24B high-resolution NMR spectrometer, and ^{13}C-NMR spectra were obtained with a JEOL JNM-FX90Q FT-NMR spectrometer operating at 22.5 MHz. Chemical shifts are quoted in parts per million (ppm) with tetramethylsilane as an internal standard, and coupling constants (*J*) are given in hertz (Hz). The following abbreviations are used: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, and dd = double doublet. 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).

1,3-Dimethylbenzimidazolium Iodide (4) (a) Methylation of Benzimidazole: In following the reported procedure,[11] a mixture of benzimidazole (7.0 g, 0.06 mol), methyl iodide (25.6 g, 0.18 mol), and sodium methoxide (prepared from 1.4 g Na and 50 ml of MeOH) was placed in a sealed tube, and heated at 100 °C for 3 h. The resulting solution was concentrated under reduced pressure to give **4** (10.7 g, 66%, recrystallized from MeOH). (b) Methylation of 1-Methylbenzimidazole: A solution of 1-methylbenzimidazole (13.2 g, 0.1 mol) and methyl iodide (21.3 g, 0.15 mol) in 100 ml of MeOH was placed in a sealed tube, and heated at 100 °C for 3 h. After the reaction, the solution was concentrated under reduced pressure, and the residue was recrystallized from acetone to afford **4** in 89% (24.5 g) yield. Slightly yellow columns, mp 139—140 °C (lit.[1] 137—139 °C). ^{1}H-NMR (DMSO-d^6) ppm: 4.09 (6H, s, –NMe), 7.50—8.10 (4H, m, aromatic-H), 9.65 (1H, s, C^2-H). ^{13}C-NMR (DMSO-d^6) ppm: 33.3 (q, –NMe), 113.2 (d), 126.2 (d), 131.5 (s), 142.9 (d).

4-Chloro-1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidine (9) and 4-Chloro-1-methyl-1*H*-pyrazolo[3,4-*d*]pyrimidine (10) Compounds **9** and **10** were prepared by chlorination of the corresponding 1*H*-pyrazolo[3,4-*d*]pyrimidin-4-(5*H*)-ones with POCl$_3$ according to the procedure reported by Cheng and Robins.[12]

Reaction of 4-Chloro-1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidine (9) with Aromatic Aldehydes (5) in the Presence of NaH and 1,3-Dimethylbenzimidazolium Iodide (4): General Procedure for Method A Sodium hydride (216 mg, 50% in oil, 4.5 mmol) was added to a stirred solution of **9** (692 mg, 3 mmol), **5** (4.5 mmol), and **4** (274 mg, 1 mmol) in THF or dioxane (20 ml), and the mixture was refluxed (reaction time and reaction solvent are listed in Table I). The reaction mixture was poured into an excess of ice-H$_2$O, and extracted with CHCl$_3$. The extract was washed with H$_2$O, dried over Na$_2$SO$_4$, and concentrated under reduced pressure to dryness. The residue was chromatographed on a column of SiO$_2$ with benzene as the eluent. The first fraction gave the aryl 1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl ketones (**11**).

Yields, melting points, analytical and spectral data are listed in Tables I—IV.

General Procedure for Method B Sodium hydride (216 mg, 50% in oil, 4.5 mmol) was added to a stirred solution of **9** (692 mg, 3 mmol), **5** (4.5 mmol), and **4** (274 mg, 1 mmol) in DMF or DMSO (20 ml) at room temperature, and the mixture was stirred at room temperature (reaction conditions are shown in Table I). The reaction mixture was poured into an excess of ice-H$_2$O, and extracted with AcOEt. The extract was washed with H$_2$O, and dried over Na$_2$SO$_4$. The Na$_2$SO$_4$ was filtered off, and the filtrate was concentrated under reduced pressure to give a yellow solid. The solid was passed through a column of SiO$_2$ with benzene as the eluent to remove impurities. The first fraction gave the ketones (**11**).

In the case of **5f**, the H$_2$O layer was neutralized with acetic acid, and left overnight at room temperature. The separated crystals were filtered off. Recrystallization from MeOH gave 4,5-dihydro-1,4-diphenyl-1*H*-pyrazolo[3,4-*d*]pyrimidine-4-carboxylic acid (**13f**, 67 mg, 7%), colorless powder, mp 220—221 °C (lit.[6b] 219—220 °C).

In the case of **5h**, 4,5-dihydro-4-(2-methoxyphenyl)-1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidine-4-carboxylic acid (**13h**, 440 mg, 42%) was similarly afforded. Recrystallization from MeOH gave colorless prisms, mp 229-230 °C (lit.[6b] 231 °C).

Reaction of 4-Chloro-1-methyl-1*H*-pyrazolo[3,4-*d*]pyrimidine (10) with Aromatic Aldehydes (5) in the Presence of NaH and 1,3-Dimethylbenzimidazolium Iodide (4): General Procedure for Method C Sodium hydride (288 mg, 50% in oil, 6 mmol) was added to a stirred solution of **10** (674 mg, 4 mmol), **5** (6 mmol), and **4** (274 mg, 1 mmol) in THF or dioxane (30 ml). The mixture was refluxed in an oil bath under stirring (reaction conditions are shown in Table I). The reaction mixture was poured into an excess of ice-H$_2$O mixture, and extracted with CHCl$_3$. The extract was washed with H$_2$O, and dried over anhydrous Na$_2$SO$_4$. The Na$_2$SO$_4$ was filtered off, and the filtrate was concentrated under reduced pressure to give a yellow oil. The residue was chromatographed on a column of SiO$_2$ with benzene and CHCl$_3$ as the eluent, and the fraction eluted with CHCl$_3$ afforded the aryl 1-methyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl ketones (**12**). Yields, recrystallization solvent, appearance, elemental analysis, IR, ^{1}H-NMR, and ^{13}C-NMR spectral data are listed in Tables I—IV.

In the case of **5c**, the first and second fractions eluted with benzene gave *O*-(2-chlorobenzoyl)-2,2′-dichlorobenzoin (**16c**, 50 mg, 6%) and 4-(2-chlorobenzyloxy)-1-methyl-1*H*-pyrazolo[3,4-*d*]pyrimidine (**14c**, 444 mg, 40%), respectively. The fraction subsequently eluted with CHCl$_3$ gave the ketone (**12c**). **14c**, recrystallization from petroleum benzin gave colorless needles, mp 95—96 °C. **16c**, recrystallization from petroleum benzin gave colorless needles, mp 95—96 °C.

In the reaction of **5d**, the reaction mixture was worked up as described above for the reaction of **5c**, giving **14d** (592 mg, 54%) and **12d**. Compound **14d** was recrystallized from petroleum benzin to give colorless needles, mp 90—91 °C.

In the case of **5e**, the first and second fractions eluted with benzene gave **16e** (34 mg, 4%) and **14e** (10 mg, 1%), respectively. The fraction subsequently eluted with CHCl$_3$ gave the ketone (**12e**). **14e**, recrystallization from petroleum benzin gave colorless needles, mp 123—125 °C.

General Procedure for Method D Sodium hydride (288 mg, 50% in oil, 6 mmol) was added to a stirred mixture of **10** (674 mg, 4 mmol), **5**

(6 mmol), and **4** (274 mg, 1 mmol) in DMF or DMSO (30 ml), and the mixture was stirred at room temperature (reaction conditions are shown in Table I). The resulting solution was poured into an excess of ice-H_2O, and extracted with AcOEt. The extract was washed with H_2O, and dried over Na_2SO_4. The Na_2SO_4 was filtered off, and the filtrate was evaporated under reduced pressure to give a yellow oily liquid. The residue was chromatographed on a column of SiO_2 eluted with $CHCl_3$. The first fraction gave the ketones (**12**).

In the case of **5e**, the second fraction eluted with $CHCl_3$ gave 4-(4-chlorophenyl)-1-methyl-1*H*-pyrazolo[3,4-*d*]pyrimidine (**15e**) in 6% (59 mg) yield. Recrystallization from MeOH gave colorless needles, mp 145—146 °C. *Anal.* Calcd for $C_{12}H_9ClN_4$: C, 58.91; H, 3.71; N, 22.90. Found: C, 58.96; H, 3.71; N, 22.83. ^{1}H-NMR ($CDCl_3$) ppm: 8.98 (1H, s, C^6-H), 8.25 (1H, s, C^3-H), 8.08 (2H, d, aromatic-H, $J=8$ Hz), 7.45 (2H, d, aromatic-H, $J=8$ Hz), 4.12 (3H, s, –NMe). MS *m/z*: 244 (M^+).

Reaction of 10 with 5e and NaH Sodium hydride (216 mg, 50% in oil, 4.5 mmol) was added to a stirred solution of **10** (506 mg, 3 mmol) and **5e** (632 mg, 4.5 mmol) in THF (20 ml), and the mixture was refluxed in an oil bath with stirring for 30 min. The reaction mixture was poured into an excess of ice-H_2O, and extracted with $CHCl_3$. The extract was washed with H_2O, dried over Na_2SO_4, and concentrated to dryness under reduced pressure. The residue was purified by recrystallization from petroleum benzin to recover the starting material **10** (425 mg, 84%).

4-Chlorobenzyloxy-1-methyl-1*H*-pyrazolo[3,4-*d*]pyrimidines (14): General Procedure Sodium hydride (216 mg, 50% in oil, 4.5 mmol) was added to a stirred solution of **10** (506 mg, 3 mmol) and chlorobenzyl alcohol (**17**, 513 mg, 3.6 mmol) in THF (20 ml) at room temperature, and the mixture was refluxed in an oil bath under stirring for 30 min. The reaction mixture was poured into an excess of ice-H_2O, and extracted with $CHCl_3$. The extract was washed with H_2O, dried over Na_2SO_4, and concentrated to dryness under reduced pressure. The residue was purified by recrystallization from petroleum benzin to give **14**.

4-(2-Chlorobenzyloxy)-1-methyl-1*H*-pyrazolo[3,4-*d*]pyrimidine (**14c**, 645 mg, 78%), colorless needles, mp 97—98 °C. *Anal.* Calcd for $C_{13}H_{11}ClN_4O$: C, 56.84; H, 4.04; N, 20.40. Found: C, 56.81; H, 4.02; N, 20.27. MS *m/z*: 274 (M^+). ^{1}H-NMR ($CDCl_3$) ppm: 8.40 (1H, s, C^6-H), 7.91 (1H, s, C^3-H), 7.10—7.55 (4H, m, aromatic-H), 5.67 (2H, s, $-OC\underline{H}_2-$), 4.00 (3H, s, –NMe). ^{13}C-NMR ($CDCl_3$) ppm: 34.1 (q, –NMe), 65.7 (t, $-O\underline{C}H_2-$), 102.6 (s), 126.8 (d), 129.5 (d), 129.7 (d), 131.0 (d), 133.7 (s), 152.4 (s), 155.0 (d), 163.2 (s).

4-(3-Chlorobenzyloxy)-1-methyl-1*H*-pyrazolo[3,4-*d*]pyrimidine (**14d**, 715 mg, 87%), colorless needles, mp 90—92 °C. *Anal.* Calcd for $C_{13}H_{11}ClN_4O$: C, 56.84; H, 4.04; N, 20.40. Found: C, 57.21; H, 4.19; N, 20.13. MS *m/z*: 274 (M^+). ^{1}H-NMR ($CDCl_3$) ppm: 8.39 (1H, s, C^6-H), 7.89 (1H, s, C^3-H), 7.10—7.35 (4H, m, aromatic-H), 5.46 (2H, s, $-OC\underline{H}_2-$), 3.98 (3H, s, –NMe). ^{13}C-NMR ($CDCl_3$) ppm: 34.1 (q, –NMe), 67.5 (t, $-O\underline{C}H_2-$), 102.6 (s), 124.7 (s), 126.2 (d), 128.2 (d), 128.4 (d), 129.8 (d), 130.9 (d), 134.5 (s), 137.9 (s), 154.8 (d), 163.1 (s).

4-(4-Chlorobenzyloxy)-1-methyl-1*H*-pyrazolo[3,4-*d*]pyrimidine (**14e**, 780 mg, 95%), colorless needles, mp 123—125 °C. *Anal.* Calcd for $C_{13}H_{11}ClN_4O$: C, 56.84; H, 4.04; N, 20.40. Found: C, 57.13; H, 4.10; N, 20.42. MS *m/z*: 274 (M^+). ^{1}H-NMR ($CDCl_3$) ppm: 8.46 (1H, s, C^6-H), 7.92 (1H, s, C^3-H), 7.30 (4H, s, aromatic-H), 5.50 (2H, s, $-OC\underline{H}_2-$), 4.02 (3H, s, –NMe). ^{13}C-NMR ($CDCl_3$) ppm: 34.1 (q, –NMe), 67.6 (t, $-O\underline{C}H_2-$), 102.7 (s), 128.1 (s), 128.5 (s), 128.8 (s), 129.7 (s), 131.0 (d), 134.4 (s), 154.9 (d), 163.2 (s).

***O*-(2-Chlorobenzoyl)-2,2′-dichlorobenzoin (16c)** A mixture of 2,2′-dichlorobenzoin (2370 mg, 8.43 mmol),[13] 2-chlorobenzoyl chloride (**18c**, 1476 mg, 8.43 mmol), and Et_3N (1703 mg, 16.9 mmol) was stirred at room temperature for 2 h. The reaction mixture was poured into an excess of ice-H_2O mixture, and extracted with $CHCl_3$. The extracts was washed with H_2O, dried over Na_2SO_4, and concentrated to dryness under reduced pressure. The residue was purified by column chromatography eluted with benzene to give **16c** in 73% (2574 mg) yield. Recrystallization from petroleum benzin gave colorless prisms, mp 95—97 °C. *Anal.* Calcd for $C_{21}H_{13}Cl_3O_3$: C, 60.10; H, 3.12. Found: C, 60.19; H, 3.09. IR ν_{max}^{KBr} cm^{-1}: 1712, 1694 (C=O). ^{1}H-NMR ($CDCl_3$) ppm: 7.05—8.05 (aromatic-H, $-C\underline{H}-$).

***O*-(4-Chlorobenzoyl)-4,4′-dichlorobenzoin (16e)** A mixture of 4,4′-dichlorobenzoin (1405 mg, 5 mmol)[14] 4-chlorobenzoyl chloride (**18e**, 875 mg, 5 mmol), and Et_3N (1010 mg, 10 mmol) was stirred at room temperature for 2 h. The reaction mixture was worked up as described above for the reaction of **16c**, giving **16e** in 78% (1610 mg) yield, mp 127—128 °C as colorless needles from petroleun benzin. *Anal.* Calcd for $C_{21}H_{13}Cl_3O_3$: C, 60.10; H, 3.12. Found: C, 59.81; H, 3.02. IR ν_{max}^{KBr} cm^{-1}: 1728, 1715 (C=O). ^{1}H-NMR ($CDCl_3$) ppm: 7.16—7.98 (12H, m, aromatic-H), 6.90 (1H, s, $-C\underline{H}-$).

Acknowledgement The authors are greatly indebted to the staff of the central analysis room of the University of Shizuoka for elemental analysis and mass spectral measurement.

References

1) A part of this work was presented at Abstract of Papers, the 9th International Congress of Heterocyclic Chemistry, Tokyo, August 1983, p. 303.
2) W. S. Ide and J. S. Buck, *Org. React.*, **4**, 269 (1948).
3) *a*) T. Ugai, T. Tanaka, and S. Dokawa, *Yakugaku Zasshi*, **63**, 296 (1943); *b*) T. Ugai, T. Dokawa, and S. Tsubokawa, *ibid.*, **64**, A7, 3 (1944).
4) *a*) A. Lapworth, *J. Chem. Soc.*, **83**, 995 (1903); *b*) *Idem, ibid.*, **85**, 1206 (1904).
5) *a*) R. Breslow, *Chem. Ind.* (London), **1957**, 893; *b*) *Idem, J. Am. Chem. Soc.*, **80**, 3719 (1958); *c*) R. Breslow and E. McNelis, *ibid.*, **81**, 3080 (1959); *d*) *Idem, ibid.*, **82**, 2394 (1960).
6) *a*) T. Higashino, M. Takemoto, A. Miyashita, and E. Hayashi, *Chem. Pharm. Bull.*, **33**, 1395 (1985); *b*) T. Higashino, Y. Matsushita, M. Takemoto, and E. Hayashi, *ibid.*, **31**, 3951 (1983).
7) *a*) T. Higashino, Y. Iwai, and E. Hayashi, *Yakugaku Zasshi*, **94**, 1191 (1974); *b*) *Idem, ibid.*, **96**, 1352 (1976).
8) *a*) J. Castells, H. Llitjos, and M. Moreno-Mañas, *Tetrahedron Lett.*, **1977**, 205; *b*) J. Castells, M. Moreno-Mañas, and F. Pujol, *ibid.*, **1978**, 385; *c*) J. Castells and F. Pujol, *Tetrahedron*, **38**, 337 (1982); *d*) H. Inoue and K. Higashiura, *J. Chem. Soc., Chem. Commun.*, **1980**, 549.
9) S. Ohta, S. Hayakawa, H. Moriwaki, S. Tsuboi, and M. Okamoto, *Heterocycles*, **23**, 1759 (1985).
10) T. Higashino, M. Goi, and E. Hayashi, *Chem. Pharm. Bull.*, **22**, 2493 (1974).
11) E. Hayashi, T. Ishikawa, and M. Inaoka, *Yakugaku Zasshi*, **80**, 838 (1960).
12) C. C. Cheng and R. K. Robins, *J. Org. Chem.*, **23**, 191 (1958).
13) H. H. Hodgson and W. Rosenberg, *J. Chem. Soc.*, **1930**, 14.
14) M. Gomberg and J. V. Natta, *J. Am. Chem. Soc.*, **51**, 2238 (1929).