STUDIES ON PYRAZOLO[3,4-*d*]PYRIMIDINE DERIVATIVES. XVIII.[1] FACILE PREPARATION OF 1*H*-PYRAZOLO[3,4-*d*]PYRIMIDIN-4(5*H*)-ONES

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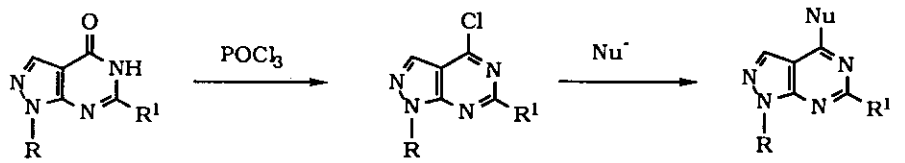
Abstract——Reaction of 5-amino-1-phenyl-1*H*-pyrazole-4-carboxamide (**4**) with the esters (**3a-h**) in the presence of sodium ethoxide in ethanol gave 1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4(5*H*)-one (**1a**) and its 6-substituted derivatives (**1b-h**). Similar treatment of 5-amino-1-methyl-1*H*-pyrazole-4-carboxamide (**5**) with **3a-h** gave the 1-methyl-1*H*-pyrazolo[3,4-*d*]-pyrimidin-4(5*H*)-ones (**2a-h**).

The 1*H*-pyrazolo[3,4-*d*]pyrimidin-4(5*H*)-ones are key compounds for preparation of the 4-substituted 1*H*-pyrazolo[3,4-*d*]pyrimidine derivatives,[2,3] as shown in Scheme 1. Although the 1*H*-pyrazolo[3,4-*d*]pyrimidin-4(5*H*)-ones having no substituent at 6-position such as 1-phenyl- (**1a**) or 1-methyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4(5*H*)-one (**2a**) are easily obtained by the reaction of 5-amino-1*H*-pyrazole-4-carboxamide with formamide,[3] the ready synthetic methods of the 6-substituted 1*H*-pyrazolo[3,4-*d*]pyrimidin-4(5*H*)-ones are little known. Therefore, the purpose of our study was focused on a facile preparation of the 6-substituted 1*H*-pyrazolo[3,4-*d*]pyrimidin-4(5*H*)-ones.



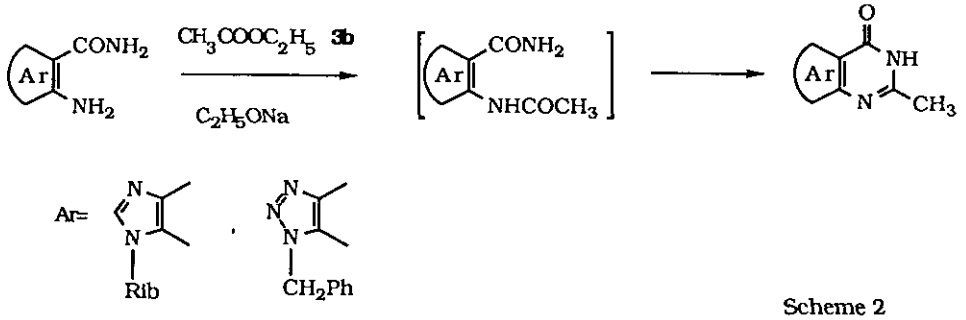
1 (R=Ph, **1a**: R^1=H)
2 (R=CH_3, **2a**: R^1=H)

Nu⁻ = nucleophile

Scheme 1

It has been reported that the aromatic compounds possessing amino group and carboxamide group in vicinity with each other reacted with ethyl acetate (**3b**) in the presence of sodium ethoxide to afford condensed pyrimidinones[4,5] through the *N*-acetyl inter-

mediates. We then applied the above method to the preparation of the pyrazolopyrimidinones (**1**, **2**).



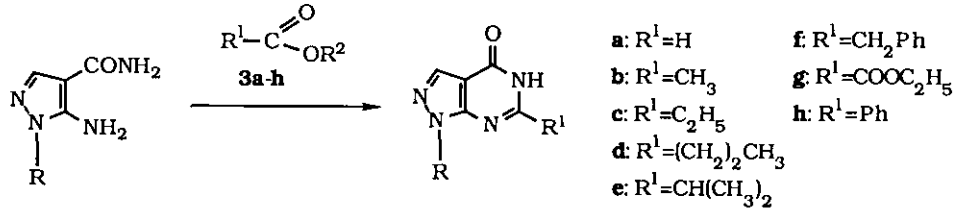
Scheme 2

The basic compounds, 5-amino-1-phenyl-1*H*-pyrazole-4-carboxamide (**4**) and 5-amino-1-methyl-1*H*-pyrazole-4-carboxamide (**5**), were prepared from the corresponding carbonitriles by hydrolysis according to the procedure of Cheng and Robins.[3]

When the mixture of **4** and ethyl formate (**3a**) in ethanolic sodium ethoxide solution was refluxed for 14 h, 1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4(5*H*)-one (**1a**) was only obtained in 82% yield. The similar treatment of **4** with ethyl acetate (**3b**), methyl propionate (**3c**), ethyl butyrate (**3d**), ethyl isobutyrate (**3e**), ethyl phenylacetate (**3f**), and methyl benzoate (**3h**) in the presence of sodium ethoxide in C_2H_5OH gave the corresponding 1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4(5*H*)-ones (**1b-f**, **h**) in satisfactory yields. The reaction of **4** with diethyl oxalate (**3g**) gave ethyl 4,5-dihydro-4-oxo-1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidine-6-carboxylate (**1g**), even if the yield was low (44%). Similarly, **5** reacted with the esters (**3a-h**) in the presence of sodium ethoxide to give the 1-methyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4(5*H*)-ones (**2a-h**) in 50 to 89% yields. The results are summarized in Table I.

The structures of **1a**, **1b**, and **2a** were identified by comparison with the authentic specimens prepared from **4**, **5**, and 5-acetamido-1-phenyl-1*H*-pyrazole-4-carbonitrile by the procedure of Cheng and Robins.[3,6] The structures of the other 1*H*-pyrazolo[3,4-*d*]pyrimidin-4(5*H*)-ones (**1c-h**, **2b-h**) were supported by the elemental analyses and confirmed by analyses of ir and ^{1}H-nmr spectra, as shown in Tables II and III.

This procedure is simple and useful method for preparation of the 6-substituted 1*H*-pyrazolo[3,4-*d*]pyrimidin-4(5*H*)-ones.



a: R^1=H **f**: R^1=CH_2Ph
b: R^1=CH_3 **g**: R^1=$COOC_2H_5$
c: R^1=C_2H_5 **h**: R^1=Ph
d: R^1=$(CH_2)_2CH_3$
e: R^1=$CH(CH_3)_2$

4 (R=Ph)
5 (R=CH_3)

1a-h (R=Ph)
2a-h (R=CH_3)

Scheme 3

Table I. Reactions of **4** and **5** with **3** in the Presence of Sodium Ethoxide.

4, 5		ester	(R^1- $R^1C(=O)OR^2$	R^2-)	Reaction Time (h)	Products	Yields (%)
4	(R=Ph)	**3a**	H	C_2H_5	14	**1a**	82
4	(R=Ph)	**3b**	CH_3	C_2H_5	6	**1b**	81
4	(R=Ph)	**3c**	C_2H_5	CH_3	7	**1c**	70
4	(R=Ph)	**3d**	$(CH_2)_2CH_3$	C_2H_5	6	**1d**	56
4	(R=Ph)	**3e**	$CH(CH_3)_2$	C_2H_5	7	**1e**	57
4	(R=Ph)	**3f**	CH_2Ph	C_2H_5	14	**1f**	93
4	(R=Ph)	**3g**	$COOC_2H_5$	C_2H_5	14	**1g**	44
4	(R=Ph)	**3h**	Ph	CH_3	14	**1h**	97
5	($R=CH_3$)	**3a**	H	C_2H_5	6	**2a**	83
5	($R=CH_3$)	**3b**	CH_3	C_2H_5	10	**2b**	88
5	($R=CH_3$)	**3c**	C_2H_5	CH_3	9	**2c**	89
5	($R=CH_3$)	**3d**	$(CH_2)_2CH_3$	C_2H_5	8	**2d**	68
5	($R=CH_3$)	**3e**	$CH(CH_3)_2$	C_2H_5	6	**2e**	57
5	($R=CH_3$)	**3f**	CH_2Ph	C_2H_5	13	**2f**	73
5	($R=CH_3$)	**3g**	$COOC_2H_5$	C_2H_5	14	**2g**	50
5	($R=CH_3$)	**3h**	Ph	CH_3	10	**2h**	58

EXPERIMENTAL

All melting points are uncorrected. The ir spectra were recorded on a JASCO A-102 diffraction grating IR spectrophotometer. The ^{1}H-nmr spectra were obtained with Hitachi R-24B high resolution NMR spectrometer. Chemical shifts are quoted in parts per million (ppm) with tetramethylsilane as an internal standard and coupling constants (*J*) are given in Herts (Hz). The following abbreviations are used: s=singlet, d=doublet, t=triplet, q=quartet, and m=multiplet.

General procedure—Ester (**3**, 0.4 *mol*) was added to a mixture of 5-amino-1*H*-pyrazole-4-carboxamide (**4**, **5**, 0.2 mol) and sodium ethoxide (prepared from 9.2 g of Na and 500 ml of C_2H_5OH), and the mixture was refluxed in an oil bath with stir (reaction time is listed in Table I). The resulting solution was concentrated under reduced pressure to dryness, and the residue was dissolved in 500 ml of H_2O. The insoluble impurities were removed by filtration, the filtrate was neutralized with conc. HCl, the separated solid was collected, and recrystallization from CH_3OH gave the 1*H*-pyrazolo[3,4-*d*]pyrimidin-4(5*H*)-ones (**1**, **2**) as white needles.

The results are summarized in Table I. Melting points, elemental analyses, and ^{1}H-nmr spectra are listed in Tables II and III.

Table II. Melting Points, Elemental Analyses, and Ir Spectrum for **1** and **2**.

Compd.	mp (℃)	Formula	Calcd (Found) C	H	N	Ir ν_{KBr}^{max} cm^{-1}
1a	297-298	$C_{11}H_8N_4O$	62.26	3.80	26.40	2900-3200 (NH)
	(lit.[3] 299)		(62.14)	(3.81)	(26.40)	1720 (CO)
1b	298-299	$C_{12}H_{10}N_4O$	63.70	4.46	24.77	2700-3100 (NH)
	(lit.[6] 301-302)		(63.41)	(4.46)	(24.54)	1680 (CO)
1c	294-295	$C_{13}H_{12}N_4O$	64.98	5.03	23.32	2700-3100 (NH)
			(64.77)	(5.04)	(23.15)	1675 (CO)
1d	249-251	$C_{14}H_{14}N_4O$	66.12	5.55	22.04	2700-3100 (NH)
			(66.24)	(5.62)	(22.12)	1680 (CO)
1e	270-271	$C_{14}H_{14}N_4O$	66.13	5.55	22.03	2800-3100 (NH)
			(65.94)	(5.53)	(22.01)	1670 (CO)
1f	265-266	$C_{18}H_{14}N_4O$	71.51	4.67	18.53	2800-3100 (NH)
			(71.29)	(4.68)	(18.57)	1680 (CO)
1g	201-203	$C_{14}H_{12}N_4O_3$	59.15	4.26	19.71	2900-3100 (NH)
			(58.83)	(4.22)	(19.71)	1750, 1680 (CO)
1h	289-291	$C_{17}H_{12}N_4O$	70.82	4.20	19.44	2900-3200 (NH)
			(70.55)	(4.21)	(19.27)	1680 (CO)
2a	296-298	$C_6H_6N_4O$	48.00	4.03	37.32	2900-3100 (NH)
	(lit.[3] 300>)		(48.09)	(4.04)	(37.39)	1665 (CO)
2b	276-277	$C_7H_8N_4O$	51.21	4.91	34.13	2800-3200 (NH)
			(51.26)	(4.97)	(34.07)	1660 (CO)
2c	224-225	$C_8H_{10}N_4O$	53.92	5.66	31.45	2700-3200 (NH)
			(53.69)	(5.73)	(31.50)	1690 (CO)
2d	197-199	$C_9H_{12}N_4O$	56.24	6.29	29.15	2700-3100 (NH)
			(56.18)	(6.31)	(29.31)	1660 (CO)
2e	288-290	$C_9H_{12}N_4O$	56.24	6.29	29.15	2800-3200 (NH)
			(56.25)	(6.29)	(29.07)	1665 (CO)
2f	234-235	$C_{13}H_{12}N_4O$	64.99	5.03	23.32	2700-3100 (NH)
			(64.94)	(5.04)	(23.48)	1680 (CO)
2g	216-217	$C_9H_{10}N_4O_3$	48.65	4.54	25.21	2800-3200 (NH)
			(48.41)	(4.44)	(25.49)	1760, 1680 (CO)
2h	240-243	$C_{12}H_{10}N_4O$	63.70	4.46	24.77	2900-3200 (NH)
			(63.69)	(4.59)	(25.07)	1680 (CO)

Table III. ^{1}H-Nmr Spectrum for **1** and **2**.

Compd.	^{1}H-Nmr ($CF_3COOD + CDCl_3$) δ (ppm)
1a	8.47 (1H, s, C^3-H), 8.40 (1H, s, C^6-H), 7.50 (5H, s, Ph)
1b	8.48 (1H, s, C^3-H), 7.55 (5H, s, Ph), 2.68 (3H, s, CH_3)
1c	8.50 (1H, s, C^3-H), 7.55 (5H, s, Ph), 2.95 (2H, q, J=8 Hz, $C\underline{H}_2CH_3$), 1.46 (3H, t, J=8 Hz, $CH_2C\underline{H}_3$)
1d	8.46 (1H, s, C^3-H), 7.55 (5H, s, Ph), 2.88 (2H, t, J=8 Hz, $C\underline{H}_2CH_2CH_3$), 1.92 (2H, m, $CH_2C\underline{H}_2CH_3$), 1.08 (3H, t, J=8 Hz, $CH_2CH_2C\underline{H}_3$)
1e	8.51 (1H, s, C^3-H), 7.45-7.80 (5H, m, Ph), 3.21 (1H, m, $C\underline{H}(CH_3)_2$), 1.54 (6H, d, J=7 Hz, $CH(C\underline{H}_3)_2$)
1f	8.42 (1H, s, C^3-H), 7.50 (5H, s, Ph), 7.25 (5H, s, Ph), 4.15 (2H, s, $C\underline{H}_2$)
1g	8.45 (1H, s, C^3-H), 7.22-7.72 (5H, m, Ph), 4.50 (2H, q, J=8 Hz, $OC\underline{H}_2CH_3$), 1.47 (3H, t, J=8 Hz, $OCH_2C\underline{H}_3$)
1h	8.64 (1H, s, C^3-H), 7.40-8.20 (10H, m, Ph)
2a	8.39 (1H, s, C^3-H), 8.28 (1H, s, C^6-H), 4.12 (3H, s, NCH_3)
2b	8.36 (1H, s, C^3-H), 4.12 (3H, s, NCH_3), 2.70 (3H, s, CH_3)
2c	8.38 (1H, s, C^3-H), 4.14 (3H, s, NCH_3), 2.97 (2H, q, J=8 Hz, $C\underline{H}_2CH_3$), 1.48 (3H, t, J=8 Hz, $CH_2C\underline{H}_3$).
2d	8.31 (1H, s, C^3-H), 4.12 (3H, s, NCH_3), 2.90 (2H, t, J=8 Hz, $C\underline{H}_2CH_2CH_3$), 1.93 (2H, m, $CH_2C\underline{H}_2CH_3$), 1.09 (3H, t, J=8 Hz, $CH_2CH_2C\underline{H}_3$)
2e	8.40 (1H, s, C^3-H), 4.15 (3H, s, NCH_3), 3.15 (1H, m, $C\underline{H}(CH_3)_2$), 1.45 (6H, d, J=6 Hz, $CH(C\underline{H}_3)_2$)
2f	8.20 (1H, s, C^3-H), 7.23 (5H, s, Ph), 4.14 (2H, s, CH_2), 4.08 (3H, s, NCH_3)
2g	8.30 (1H, s, C^3-H), 4.58 (2H, q, J=8 Hz, $OC\underline{H}_2CH_3$), 4.15 (3H, s, NCH_3), 1.55 (3H, t, J=8 Hz, $OCH_2C\underline{H}_3$)
2h	8.40 (1H, s, C^3-H), 7.45-8.28 (5H, m, Ph), 4.22 (3H, s, NCH_3)

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