Synthesis of 5,7-Disubstituted 7H-Pyrrolo[2,3-d]Pyrimidin-4(3H)-ones and Their *N*-Alkylation's under Phase Transfer Conditions

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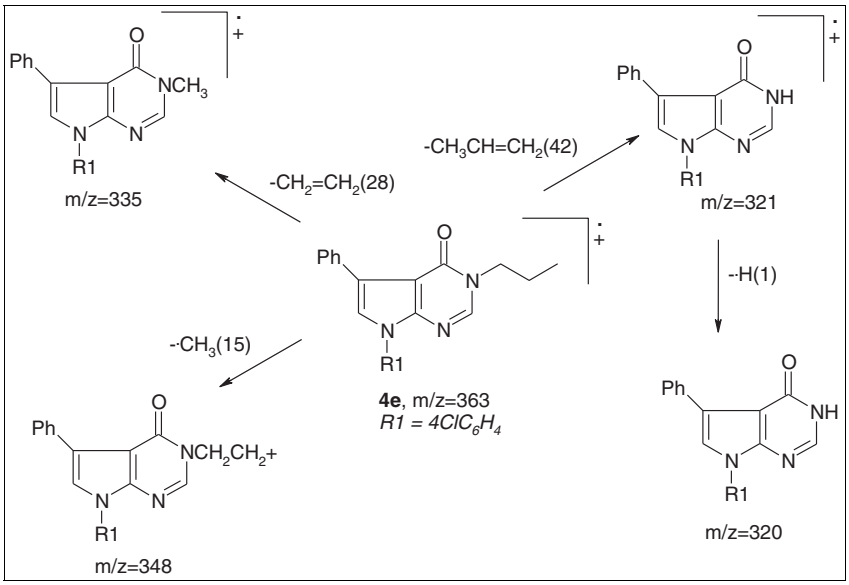

5,7-disubstituted 7H-pyrrolo[2,3-d]pyrimidin-4(3H)-ones **2** were synthesized by the cyclocondensation of 1,4-disubstituted 2-amino-3-cyanopyrrole **1** with formic acid. When comparative study of *N* versus *O* alkylation of ambident 5,7-disubstituted 7H-pyrrolo[2,3-d]pyrimidin-4(3H)-ones **2** was carried out under liquid–liquid PTC, solid–liquid PTC, and solid–liquid solvent free conditions using various alkylating agents **3**, the *N*-alkylated product **4** were obtained selectively and exclusively.

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INTRODUCTION

Pyrrolo[2,3-d]pyrimidines and their 4-oxoderivatives deserve interest because of the presence of this moiety in important antibiotics tubercidin [1], toyocamycin [1], and sangivamycin [2,3], as well as for their potential antitumor activity [4–6]. Various 6-substituted pyrrolo[2,3-d]pyrimidin-3, 4-ones were tested *in vitro* for mammalian xanthine oxidase inhibitory activity; among them, 5-methyl-6-phenylpyrrolo [2,3-d]pyrimidin-2,4-dione [7] was found to be the most active compound. Hypoxenthine isoster pyrrolo[2,3-d] pyrimidin-4(3H)ones have found to occur as heterocyclic bases in a number of antibiotics [8,9]. Thus, there have been ample precedents for the synthesis of pyrrolo[2,3-d] pyrimidin-4(3H)ones derivatives [10,11].

A study of *N* versus *O* alkylation in various ambident heterocyclic compounds under phase transfer conditions [12–15] has been reported. However, there is no report of such study in 5,7-disubstituted 7H-pyrrolo[2,3-d]pyrimidin-4(3H)-ones **2**. Therefore, in continuation of our interest in fused pyrimidines and phase transfer catalyzed alkylation of ambident heterocyclic system [16], it was of interest to select compound **2**, which is an ambident system. Therefore, we wish to report herein the *N* versus *O* alkylation in ambident 5,7-disubstituted 7H-pyrrolo[2,3-d]pyrimidin-4(3H)-ones **2** under phase transfer condition in order to obtain compound of biological interest, which were investigated for antibacterial, CNS depressant, and anti-tubercular activities.

RESULTS AND DISCUSSION

5,7-Disubstituted 7H-pyrrolo[2,3-d]pyrimidin-4(3H)-ones **2** [11] required for *N* versus *O* alkylation study under phase transfer condition were synthesized by cyclocondensation of 1,4-disubstituted 2-amino-3-cyanopyrrole **1** with formic acid. During the process, the cyano group of compound **1** was supposed to be partially hydrolyzed

because of the acidic nature of formic acid to give 1,4-disubstituted 2-amino-3-carboxamidopyrrroles, which subsequently cyclised on prolonged heating with formic acid to give the 5,7-disubstituted 7H-pyrrolo[2,3-d]pyrimidin-4(3H)-ones **2** (Scheme 1).

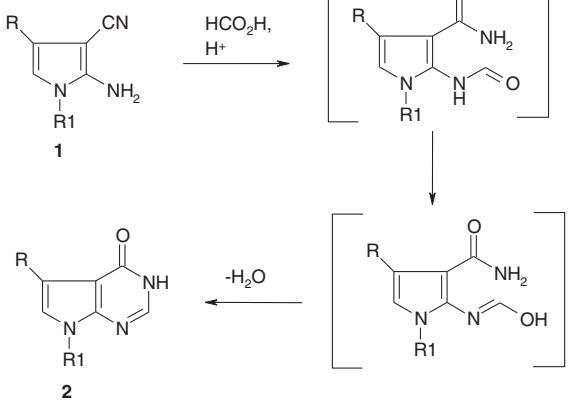
Alkylation of 5,7-disubstituted 7H-pyrrolo[2,3-d]pyrimidin-4(3H)-ones **2** (Scheme 2) was studied under different phase transfer conditions: (i) liquid–liquid phase transfer condition (PTC) (50% KOH, chlorobenzene); (ii) solid–liquid PTC (solid KOH, chlorobenzene); and (iii) solid–liquid PTC (solid KOH, solvent free condition). Ethylation of 5-phenyl-7-(4-chlorophenyl)-7H-pyrrolo[2,3-d]pyrimidin-4(3H)-one **2b** was selected as a case study under different phase transfer conditions. All studies provided selectively *N*-alkylated product, and in no case, *O*-alkylated product was obtained during the reaction. However, the comparison between these phase transfer conditions revealed that the highest product yield was found when solid–liquid solvent free phase transfer condition employed (Table 1).

A study of the reaction between 5-phenyl-7-(4-chlorophenyl)-7H-pyrrolo[2,3-d]pyrimidin-4(3H)-one **2b** and ethyl bromide was also undertaken using solid–liquid solvent free condition with different phase transfer catalysts: triethylbenzyl ammonium chloride (TEBA), tetrabutylammonium bromide (TBAB), and cetyltrimethylammonium bromide (Table 2). Ethylation of 5-phenyl-7-(4-chlorophenyl)-7H-pyrrolo[2,3-d]pyrimidin-4(3H)-one **2b** with different phase transfer catalysts provided exclusively *N*-alkylated product. *O*-alkylated product was not found during the experimental conditions employed. The highest yield was found when TEBA was used as phase transfer catalyst. In the absences of phase transfer catalyst, the reaction was found to proceed very slowly; after several hours, the majority of the starting material **2b** remained in the reaction mixture (TLC).

In conclusion, the solid–liquid solvent free phase transfer condition using TEBA as catalyst was the best choice and therefore, it was utilized for the *N* versus *O* alkylation of 5,7-disubstituted 7H-pyrrolo[2,3-d]pyrimidin-4(3H)-ones **2**. *N* versus *O* alkylation of compound **2** with different alkylating agents such as ethyl bromide, n-propyl bromide, isopropyl bromide, 1-bromo-3-chloropropane, and benzyl chloride provide exclusively *N*-alkylated products. During the alkylation reaction under solid–liquid solvent free phase transfer condition, the excess of alkylating agent itself worked as a solvent, and TEBA was used as a phase transfer catalyst. At the end of reaction, alkylating agent was recovered by distillation under vacuum to obtain the solid alkylated product (Scheme 2).

The IR (potassium bromide) spectra of 5,7-disubstituted 3-alkyl-7H-pyrrolo[2,3-d]pyrimidin-4(3H)-ones **4** exhibited a strong absorption band in the region 1700–1650 cm^{-1} indicated the presence of cyclic ketone structure. The absence

Scheme 1

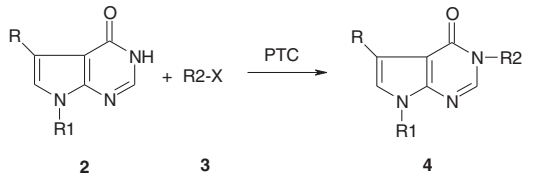


1

2

1, 2	R	R1
a	C_6H_5	4-$OCH_3C_6H_4$
b	C_6H_5	4-ClC_6H_4
c	C_6H_5	4-BrC_6H_4
d	C_6H_5	3-Cl-4-FC_6H_3
e	4-ClC_6H_4	C_6H_5
f	4-ClC_6H_4	4-$CH_3C_6H_4$
g	4-ClC_6H_4	4-$OCH_3C_6H_4$
h	4-ClC_6H_4	4-FC_6H_4
i	4-ClC_6H_4	4-ClC_6H_4
j	4-ClC_6H_4	4-BrC_6H_4
k	4-ClC_6H_4	4-IC_6H_4
l	4-ClC_6H_4	3-Cl-4-FC_6H_3

Scheme 2



2 **3** **4**

4	R	R1	R2
a	C_6H_5	4-$OCH_3C_6H_4$	C_2H_5
b	C_6H_5	4-$OCH_3C_6H_4$	$CH_2CH_2CH_2Cl$
c	C_6H_5	4-$OCH_3C_6H_4$	$CH_2C_6H_5$
d	C_6H_5	4-ClC_6H_4	C_2H_5
e	C_6H_5	4-ClC_6H_4	*n*-C_3H_7
f	C_6H_5	4-ClC_6H_4	*iso*-C_3H_7
g	C_6H_5	4-ClC_6H_4	$CH_2CH_2CH_2Cl$
h	C_6H_5	3-Cl-4-FC_6H_3	C_2H_5
i	C_6H_5	3-Cl-4-FC_6H_3	*n*-C_3H_7
j	C_6H_5	3-Cl-4-FC_6H_3	$CH_2CH_2CH_2Cl$
k	4-ClC_6H_4	C_6H_5	C_2H_5
l	4-ClC_6H_4	C_6H_5	*iso*-C_3H_7
m	4-ClC_6H_4	C_6H_5	$CH_2CH_2CH_2Cl$
n	4-ClC_6H_4	4-$OCH_3C_6H_4$	*iso*-C_3H_7
o	4-ClC_6H_4	4-FC_6H_4	C_2H_5
p	4-ClC_6H_4	4-FC_6H_4	*iso*-C_3H_7
q	4-ClC_6H_4	4-FC_6H_4	$CH_2CH_2CH_2Cl$
r	4-ClC_6H_4	4-ClC_6H_4	$CH_2CH_2CH_2Cl$
s	4-ClC_6H_4	3-Cl-4-FC_6H_3	C_2H_5
t	4-ClC_6H_4	3-Cl-4-FC_6H_3	*iso*-C_3H_7
u	4-ClC_6H_4	3-Cl-4-FC_6H_3	$CH_2CH_2CH_2Cl$
V	4-ClC_6H_4	3-Cl-4-FC_6H_3	$CH_2C_6H_5$

Table 1

Comparison of various phase transfer conditions for ethylation of compound **2b**.

Reaction condition	Phase transfer catalyst	Yield %	Time (hours)	Temperature °C
Liquid–liquid PTC (50% KOH, chlorobenzene),	TEBA 10 mole %	68	2.5	50–60
Solid–liquid PTC (solid KOH, chlorobenzene	TEBA 10 mole %	73	1.5	50–60
Solid–liquid PTC (solid KOH, solvent free condition)	TEBA 10 mole %	89	0.75	Reflux

Table 2

Comparison of various phase transfer catalysts for ethylation of compound **2b**.

Phase transfer catalyst	Mole % of catalyst	Yield (%)	Time (minutes)
TEBA	10	89	45
TBAB	10	83	45
Cetyl trimethylammonium bromide	10	75	60

of characteristic bands for NH around 3250–3100 cm^{-1} confirmed *N*-alkylation of 5,7-disubstituted 7H-pyrrolo[2,3-d] pyrimidin-4(3H)-ones. The absorption band because of C=C, C=N (ring) stretching vibrations were found near 1600–1500 cm^{-1}.

^{1}H NMR (deuteriochloroform) spectral data of 5,7-di-substituted 3-alkyl-7H-pyrrolo[2,3-d]pyrimidin-4(3H)-ones **4** are also mentioned in Table 3. The aromatic protons are found to be resonated at δ 7.0–8.2 in the form of multiplet. Proton shift for other aliphatic protons are described in Table 3.

The mass spectra of 3-n-propyl-5-phenyl-7-(4-chloro-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-4(3H)-ones **4e** exhibited a molecular ion peak at *m/z* = 363. Hydrogen from γ position migrates to ketone functionality as a result fragment obtained at *m/z* = 321, showed McLafferty rearrangement [17,18]. Important fragments of compound **4e** are depicted in Scheme 3.

EXPERIMENTAL

Melting points were determined by the electrothermal method in an open capillary tube and are uncorrected. The IR spectra

Table 3

IR and ^{1}H NMR spectral data for compound **4a–v**.

No.	IR (potassium bromide) cm^{-1}	^{1}H NMR (δ ppm)
4a	1677, 1602, 1576,1518	1.37–1.42 (t, *J* = 7.2, 3H, CH_3), 3.86 (s, 3H, OCH_3), 4.04–4.11(q, *J* = 7.2, 2H, CH_2), 7.02–7.90(m, 11H, Ar-H)
4b	1678, 1578, 1540,1520	2.24–2.39 (m, 2H, CH_2), 3.38–3.56 (m, 2H, CH_2Cl),3.88 (s, 3H, OCH_3), 4.14–4.20 (m, 2H, NCH_2), 7.10–7.93(m, 11H, Ar-H)
4c	1685, 1595, 1550, 1505	3.87 (s, 3H, OCH_3), 5.34 (s, 2H, CH_2), 7.23–8.13 (m, 16H, Ar-H)
4d	1685, 1580, 1515, 1505	1.38–1.43 (t, *J* = 7.2, 3H, CH_3), 4.05–4.12 (q, *J* = 7.2, 2H, CH_2), 7.22–7.92(m, 11H, Ar-H)
4e	1680, 1590, 1530, 1510	0.94–0.99 (t, *J* = 7.5, 3H, CH_3), 1.75–1.87 (sextet, *J* = 7.2, 2H, CH_2), 3.95–3.99 (t, *J* = 7.2, 2H, NCH_2), 7.21–7.88 (m, 11H, Ar-H)
4f	1665, 1600, 1575, 1515	1.46–1.48 (d, *J* = 6.7, 6H, $2CH_3$), 5.25–5.34 (heptet, *J* = 7.0, 1H, CH), 7.23–7.94 (m, 11H, Ar-H)
4g	1660, 1600, 1580, 1510	2.25–2.40 (m, 2H, CH_2), 3.37–3.57 (m, 2H, CH_2Cl), 4.16–4.22 (m, 2H, NCH_2), 7.28–7.98(m, 11H, Ar-H)
4h	1681, 1603, 1577, 1513	1.39–1.45 (t, *J* = 7.3, 3H, CH_3), 4.06–4.13 (q, *J* = 7.4, 2H, CH_2), 7.20–8.05 (m, 10H, Ar-H)
4i	1670, 1600, 1578, 1551	0.95–0.99 (t, *J* = 7.4, 3H, CH_3), 1.78–1.89 (sextet, *J* = 7.3, 2H, CH_2), 3.96–4.02 (t, *J* = 7.5, 2H, NCH_2), 7.19–8.03 (m, 10H, Ar-H)
4j	1656, 1600, 1577, 1512	2.30–2.40 (m, 2H, CH_2), 3.39–3.57 (m, 2H, CH_2Cl), 4.17–4.23 (m, 2H, NCH_2), 7.21–8.00 (m, 10H, Ar-H)
4k	1679, 1597, 1549, 1511	1.36–1.41 (t, *J* = 7.2, 3H, CH_3), 4.03–4.09 (q, *J* = 7.3, 2H, CH_2), 7.21–7.97(m, 11H, Ar-H)
4l	1660, 1599, 1555, 1535	1.45–1.47 (d, *J* = 6.9, 6H, $2CH_3$), 5.22–5.32 (heptet, *J* = 6.9, 1H, CH), 7.26–7.95 (m, 11H, Ar-H)
4m	1678, 1578, 1552, 1513	2.27–2.42 (m, 2H, CH_2), 3.38–3.59 (m, 2H, CH_2Cl), 4.15–4.21 (m, 2H, NCH_2), 7.18–8.02 (m, 11H, Ar-H)
4n	1659, 1574, 1552, 1528	1.47–1.49 (d, *J* = 6.8, 6H, $2CH_3$), 3.87 (s, 3H, OCH_3), 5.26–5.34 (heptet, *J* = 7.0, 1H, CH), 7.15–7.93 (m, 10H, Ar-H)
4o	1681, 1575, 1551, 1519	1.37–1.43 (t, *J* = 7.1, 3H, CH_3), 4.05–4.11 (q, *J* = 7.2, 2H, CH_2), 7.20–8.0 (m, 10 H, Ar-H)
4p	1663, 1573, 1555, 1517	1.46–1.48 (d, *J* = 6.6, 6H, $2CH_3$), 5.24–5.33 (heptet, *J* = 6.9, 1H, CH), 7.19–7.98 (m, 10H, Ar-H)
4q	1663, 1581, 1551, 1509	2.28–2.43 (m, 2H, CH_2), 341–3.60 (m, 2H, CH_2Cl), 4.19–4.25 (m, 2H, NCH_2), 7.22–8.04 (m, 10H, Ar-H)
4r	1678, 1578, 1552, 1512	2.27–2.44 (m, 2H, CH_2), 3.40–3.61 (m, 2H, CH_2Cl), 4.18–4.24 (m, 2H, NCH_2), 7.19–8.01 (m, 10H, Ar-H)
4s	1693, 1583, 1555, 1515	1.38–1.44 (t, *J* = 7.4, 3H, CH_3), 4.06–4.12 (q, *J* = 7.5, 2H, CH_2), 7.23–8.03 (m, 9H, Ar-H)
4t	1678, 1580, 1555, 1537	1.48–1.50 (d, *J* = 7.0, 6H, $2CH_3$), 5.26–5.35 (heptet, *J* = 7.2, 1H, CH), 7.24–8.06 (m, 9H, Ar-H)
4u	1676, 1598, 1580, 1555	2.28–2.44 (m, 2H, CH_2), 3.41–3.61 (m, 2H, CH_2Cl), 4.20–4.25 (m, 2H, NCH_2), 7.26–8.08 (m, 9H, Ar-H)
4v	1682, 1582, 1547, 1514	5.36 (s, 2H, CH_2), 7.30–8.16 (m, 14H, Ar-H)

Scheme 3

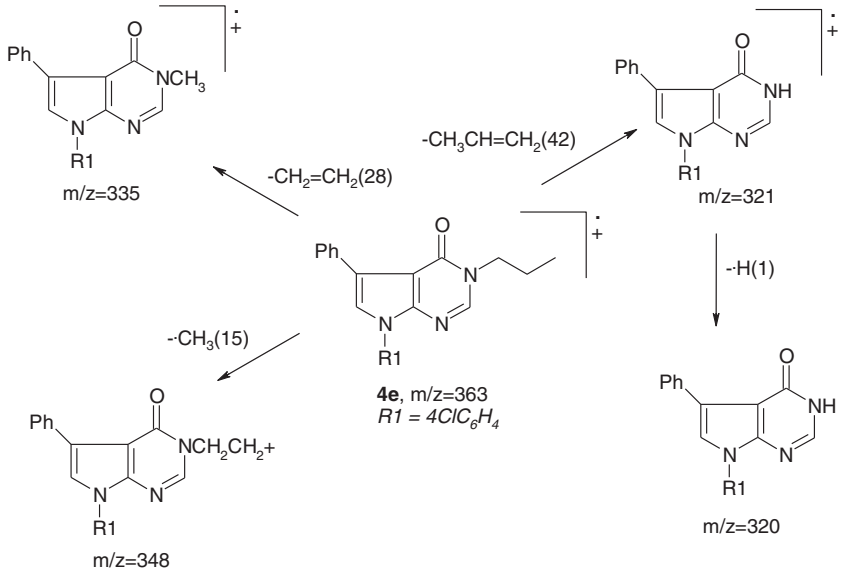


Table 4

Physical and analytical data for compounds **4a–v**.

Compound no.	Time (hours)	Temperature °C	Yield %	mp °C	Molecular formula	Analysis% calcd./found		
						C	H	N
4a	0.75	35-40	87	122–123	$C_{21}H_{19}N_3O_2$	73.02	5.54	12.16
						73.17	5.29	12.21
4b	1.5	65–70	88	112–113	$C_{22}H_{20}ClN_3O_2$	67.08	5.11	10.66
						67.12	5.23	10.57
4c	1.0	75–80	79	138–139	$C_{26}H_{21}N_3O_2$	76.63	5.19	10.31
						76.83	5.13	10.47
4d	0.75	35–40	89	200–201	$C_{20}H_{16}ClN_3O$	68.61	4.57	12.01
						68.89	4.71	12.16
4e	1.0	65–70	84	143–144	$C_{21}H_{18}ClN_3O$	69.32	4.98	11.54
						69.42	4.91	11.65
4f	1.0	55–60	82	174–175	$C_{21}H_{18}ClN_3O$	69.32	4.98	11.54
						69.21	4.89	11.42
4g	1.5	65–70	82	117–118	$C_{21}H_{17}Cl_2N_3O$	63.32	4.30	10.55
						63.26	4.41	10.36
4h	1.0	35–40	83	162–163	$C_{20}H_{15}ClFN_3O$	65.30	4.11	11.42
						65.59	4.37	11.09
4i	1.0	65–70	82	119–120	$C_{21}H_{17}ClFN_3O$	66.05	4.48	11.00
						66.31	4.37	11.15
4j	1.5	65–70	81	148–149	$C_{21}H_{16}Cl_2FN_3O$	60.53	3.84	10.09
						60.77	3.92	10.23
4k	0.75	35–40	88	150–151	$C_{20}H_{16}ClN_3O$	68.66	4.61	12.01
						68.49	4.72	12.23
4l	1.0	55–60	83	181–182	$C_{21}H_{18}ClN_3O$	69.32	4.98	11.54
						69.45	4.87	11.73
4m	1.5	65–70	91	88–89	$C_{21}H_{17}Cl_2N_3O$	63.32	4.30	10.55
						63.12	4.25	10.62
4n	1.5	55–60	82	134–135	$C_{22}H_{20}ClN_3O_2$	67.08	5.11	10.66
						67.19	5.31	10.57
4o	1.0	35–40	90	153–154	$C_{20}H_{15}ClFN_3O$	65.30	4.11	11.42
						65.22	4.25	11.58
4p	1.5	55–60	88	115–116	$C_{21}H_{17}ClFN_3O$	66.05	4.48	11.00

(Continued)

Table 4

(*Continued*)

Compound no.	Time (hours)	Temperature °C	Yield %	mp °C	Molecular formula	Analysis% calcd./found		
						66.16	4.31	11.06
4q	2.0	65–70	82	145–146	$C_{21}H_{16}Cl_2FN_3O$	60.58	3.87	10.09
						60.72	3.66	10.27
4r	2.0	65–70	88	106–107	$C_{21}H_{16}Cl_3N_3O$	58.23	3.69	9.71
						58.48	3.81	9.84
4s	1.0	35–40	82	160–161	$C_{20}H_{14}Cl_2FN_3O$	59.71	3.50	10.44
						59.60	3.62	10.32
4t	1.5	55–60	87	129–130	$C_{21}H_{16}Cl_2FN_3O$	60.58	3.87	10.09
						60.78	3.66	10.23
4u	2.0	65–70	83	140–141	$C_{21}H_{15}Cl_3FN_3O$	55.95	3.35	9.32
						55.64	3.57	9.11
4v	1.5	75–80	76	156–157	$C_{25}H_{16}Cl_2FN_3O$	64.66	3.47	9.04
						64.45	3.70	9.13

are recorded in cm^{-1} and were acquire as potassium bromide pellets on a Buck scientific spectrophotometer. The ^1H NMR spectra were recorded on Bruker AC 300 F NMR spectrometer using tetramethylsilane as internal standard and chemical shift are expressed in ppm (δ). The mass spectra were recorded on LKB 9000 mass spectrometer. The purity of the compound was routinely checked by thin-layer chromotography (TLC) using silica gel G, and the spots were exposed to iodine vapor.

General procedure for the synthesis of 5,7-disubstituted 3-alkyl-7H-pyrrolo[2,3-d]pyrimidin-4(3H)-ones 4a–v. A mixture of 5,7-disubstituted 7H-pyrrolo[2,3-d]pyrimidin-4(3H)-ones **2** (0.005 mole), potassium hydroxide (0.01 mole), TEBA (0.0005 mole), and alkylating agent **3** (15 mL) were placed in a 100-ml three-neck round bottom flask equipped with reflux condenser and stirrer. The reaction mixture was heated at appropriate temperature with stirring and time given in Table 4. After completion of reaction (TLC), the excess of alkylating agent was removed *in vacuo* to obtain the crude product. The solid separated on cooling was filtered, washed with water, cold methanol, dried, and crystallized from ethanol.

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