Phase Transfer Catalysis Assisted Nucleophilic Displacements in Pyrrolopyrimidines

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Abstract

Strategy to involve eco friendly phase transfer catalysis (PTC) with nucleophilic displacements has always been of great interest to study. Therefore, comparative studies of chlorination, azidolysis and indirect amination for synthesis of novel 7,9-disubstituted 5-methyl-7H-tetrazolo[1,5-*c*]pyrrolo[3,2-*e*]pyrimidines **4** and their ring cleavage to 5,7-disubstituted 2-methyl-4-amino-7H-pyrrolo[2,3-*d*]pyrimidines **5** have been undertaken with and without PTC. Chlorination of 5,7-disubstituted 2-methyl-7H-pyrrolo[2,3-*d*]pyrimidin-4(3H)-ones **2** obtained from 1,4-disubstituted 2-amino-3-pyanopyrroles **1**, followed by azidolysis of 5,7-disubstituted 2-methyl-4-chloro-7H-pyrrolo[2,3-*d*]pyrimidines **3** forming **4** and their chemoselective tetrazole ring cleavage to **5** have been carried out with and without PTC. PTC assisted one pot synthesis of **5** directly from **3** have also been reported.

Keywords: nucleophilic displacements, phase transfer catalysis, tetraethyl benzyl ammonium bromide, 18-crown-6, aliquat, pyrrolopyrimidines
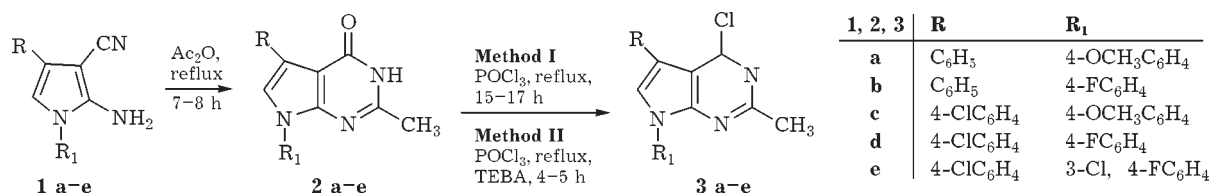
INTRODUCTION

Nucleophilic displacements are the key reactions in the field of synthetic chemistry and those in fused pyrimidines have been extensively reviewed for annellation of various pharmaceutically important nitrogen heterocycles such as imidazole, triazole, pyrimidine and tetrazole ring systems [1–13]. For instance, 4-chloropyrimidines achieved by chlorination of 4-pyrimidones have further capacity to undergo nucleophilic displacements with varieties of reagents like amines, hydrazines, azides, thiourea to construct imidazole, pyrimidine, triazole and tetrazole rings onto pyrimidine ring [1–8]. Amongst, study of azidolysis resulting into tetrazolopyrimidines was found to be attractive which in turn reduced to 4-aminopyrimidines [6]. Pyrrolo[2,3-*d*]pyrimidines have proved to be the land marks of pharmaceutics [9–14]. Moreover, a number of biological activities attributed to fused tetrazolopyrimidines and 4-aminopyrrolopyrimidines [6, 15–22]. Synergism of eco friendly phase transfer catalysis (PTC) with nucleophilic displacements such as chlorination, azidolysis and indirect amination has always been interesting to study. PTC has been a well known technique providing cleaner, faster, step reducing and yield improving path with milder operational conditions and easy work up, and can easily be scaled up [23–27]. Therefore, comparative studies of chlorination, azidolysis and amination for synthesis and ring cleavage of novel 7,9-disubstituted 5-methyl-7H-tetrazolo[1,5-*c*]pyrrolo[3,2-*e*]pyrimidines **4** have been undertaken with and without PTC. Conventional method to convert chloro functionality of azines into amino functionality was reported under high pressure condition [28–32]. PTC was proved to be efficient to give facile one pot synthesis of some new 5,7-disubstituted 2-methyl-4-amino-7H-pyrrolo[2,3-*d*]pyrimidines **5** directly from 5,7-disubstituted 2-methyl-4-chloro-7H-pyrrolo[2,3-*d*]pyrimidines **3** through *in situ* generation of **4**.

EXPERIMENTAL

Melting points were determined by electro thermal method in open capillary tube and are

Scheme 1.

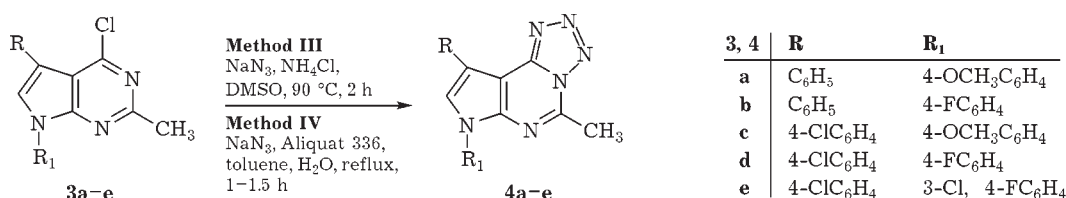| 1, 2, 3	R	R_1
a	C_6H_5	$4\text{-}OCH_3C_6H_4$
b	C_6H_5	$4\text{-}FC_6H_4$
c	$4\text{-}ClC_6H_4$	$4\text{-}OCH_3C_6H_4$
d	$4\text{-}ClC_6H_4$	$4\text{-}FC_6H_4$
e	$4\text{-}ClC_6H_4$	$3\text{-}Cl, \ 4\text{-}FC_6H_4$

uncorrected. The IR spectra for potassium bromide pellets were recorded on Buck-500 spectrophotometer. The ^1H NMR spectra were recorded on a Bruker 300 MHz spectrophotometer in DMSO-d^6 using TMS as internal standard and the chemical shifts are expressed in δ ppm. MS spectra were recorded on JEOL/SX-102 mass spectrophotometer under electron-impact (EI) ionization. Elemental analyses were performed on a Carlo Erba 1108 microanalyser or Elementar's Vario EL III microanalyser. The purity of the compounds was routinely checked by TLC using silica gel G and spots were exposed in iodine vapour.
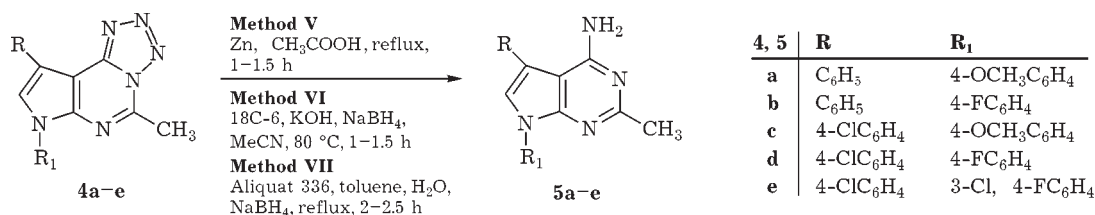
RESULTS AND DISCUSSION

To exploit nucleophilic substitution reactions in newly synthesized 5,7-disubstituted 2-methyl-7H-pyrrolo[2,3-d]pyrimidin-4(3H)-ones **2**, prepared from 1,4-disubstituted 2-amino-3-pyano-pyrroles **1** on treatment with boiling acetic anhydride, were reacted with refluxing phosphorous oxychloride for 15−17 h to give 5,7-disubstituted 2-methyl-4-chloro-7H-pyrrolo[2,3-d]-pyrimidines **3** (yield: 60−70 %) (Method I). With a view to reduce prolonged heating time the same reaction has been attended in the presence of TEBA (tetraethylbenzylammonium bromide) as PT catalyst (Method II) which interestingly enhanced the rate of reaction with improved reaction time (4−5 h) and the yield of reaction products (yield: 70−78 %) (Scheme 1).

Chloro functionality in position 4 of pyrrolo[2,3-d]-pyrimidines was found to be labile towards nucleophilic substitution reactions. To construct tetrazole ring onto pyrrolo[2,3-d]pyrimidines, 2-methyl-4-chloro-7H-pyrrolo[2,3-d]pyrimidines **3** were stirred with sodium azide and ammonium chloride in dimethyl sulphoxide for 1−1.5 h and for 1 h at RT (Method III). Association of liquid-liquid PTC with azidolysis of **3** by using toluene and water as solvents and Aliquat 336 (methyltrioctylammonium chloride) as a catalyst (Method IV) proved to be cleaner, rate enhancing and yield improving as compared to conventional methodology (Scheme 2). Replacement of polar solvent such as DMSO by non-polar solvent such as toluene solved the problem of recovery of DMSO which was often found yield lowering.
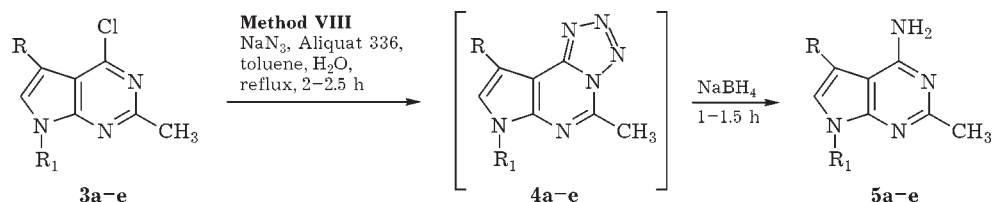
Direct conversion of chloro to amino functionality in azines operated under harsh conditions [28−32]. In contrast azidolysis followed by reduction facilitated the indirect amination. Thus azides and tetrazoles can be viewed as latent amino functionalities. Therefore, tetrazolopyrrolopyrimidines **4**, obtained from **3** have been reduced conventionally (Method V) with zinc powder and acetic acid under reflux condition as well as under different PT conditions. Two different solid-liquid (Method VI) and liquid-liquid PT conditions (Method VII) have been employed. Solid-liquid PT condition included the reduction with sodium borohydride in the presence of 18-crown-6, powdered KOH and acetonitrile under stirring condition at 80 °C, where

Scheme 2.

3, 4	R	R_1
a	C_6H_5	$4\text{-}OCH_3C_6H_4$
b	C_6H_5	$4\text{-}FC_6H_4$
c	$4\text{-}ClC_6H_4$	$4\text{-}OCH_3C_6H_4$
d	$4\text{-}ClC_6H_4$	$4\text{-}FC_6H_4$
e	$4\text{-}ClC_6H_4$	$3\text{-}Cl, \ 4\text{-}FC_6H_4$

Scheme 3.

4, 5	R	R_1
a	C_6H_5	$4\text{-}OCH_3C_6H_4$
b	C_6H_5	$4\text{-}FC_6H_4$
c	$4\text{-}ClC_6H_4$	$4\text{-}OCH_3C_6H_4$
d	$4\text{-}ClC_6H_4$	$4\text{-}FC_6H_4$
e	$4\text{-}ClC_6H_4$	$3\text{-}Cl, \ 4\text{-}FC_6H_4$

Scheme 4.

as liquid-liquid PT condition involved the use of sodium borohydride, Aliquat 336, toluene and water under reflux condition (Scheme 3). This improved protocol was found to be efficient over conventional method (yield: 60−62 %) and solid-liquid PTC (yield: 70−75 %) proved to be advantageous over liquid-liquid PT condition (yield: 64−68 %) using less molar concentration of catalyst forming products in good yields.

One pot synthesis of **4** has also been obtained directly from 4-chloropyrrolopyrimidines **3** using liquid-liquid PT condition (Method VIII) through *in situ* generation of tetrazoles **4** using sodium azide, Aliquat 336 as catalyst and toluene and water as solvents under reflux condition (checked by TLC) followed by reduction with

sodium borohydride (Scheme 4). Although the use of higher concentration of catalyst, liquid-liquid PT condition, it became the only choice of method for the direct synthesis of **5** from **4**.

Identity of compounds **2−4** and **5** prepared by conventional as well as PTC was proved by TLC and mixed melting point. The physicochemical constants of **2−4** and **5** are recorded in Tables 1−3. The structure elucidation of all the compounds has been done on the basis of spectral analysis. The IR and ^{1}H NMR data of all the compounds has been recorded in Table 4.

The mass fragmentation pattern of compound **4a** was found similar to that of regular pattern of fused tetrazolopyrimidines giving molecular ion peak at 356. The peaks at m/z

TABLE 1

Physicochemical constants of compounds **2a−e**

Compounds	T, °C	Yield, %	Molecular formula (MW)	Analysis, % Calculated/Found		
				C	H	N
2a	240−242	65	$C_{20}H_{17}N_3O_2$	72.49	5.17	13.68
			(331.37)	72.52	5.20	12.77
2b	235−237	67	$C_{19}H_{14}FN_3O$	71.46	4.42	13.96
			(319.33)	72.51	4.50	13.83
2c	246−248	70	$C_{20}H_{15}ClN_3O_2$	65.65	4.14	11.52
			(364.81)	65.61	4.10	11.63
2d	250−252	69	$C_{19}H_{13}ClFN_3O$	64.50	3.70	11.88
			(353.78)	64.61	3.60	11.61
2e	256−258	71	$C_{19}H_{12}Cl_2FN_3O$	58.78	3.12	10.82
			(388.22)	58.65	3.30	10.61

TABLE 2

Physicochemical constants of compounds **3** and **4a–e**

Compounds	T, °C	Yield, %		Molecular formula (MW)	Analysis, %		
		Method			Calculated/Found		
		Conventional	PTC		C	H	N
3a	130–132	65	72	$C_{20}H_{16}N_3$	68.67	4.61	12.01
				(349.81)	68.52	4.30	12.27
3b	150–151	63	78	$C_{19}H_{13}ClFN_3$	67.56	4.52	11.09
				(337.78)	67.52	4.30	11.27
3c	141–142	69	78	$C_{20}H_{15}Cl_2N_3O$	62.51	3.93	10.94
				(384.26)	62.61	3.80	10.73
3d	168–169	67	77	$C_{19}H_{12}Cl_2FN_3$	61.31	3.25	11.19
				(372.22)	61.21	3.40	11.31
3e	171–172	70	78	$C_{19}H_{11}Cl_3FN_3$	56.12	2.73	10.33
				(406.67)	56.21	2.60	10.41
4a	224–226	65	73	$C_{20}H_{16}N_6O$	67.40	4.53	23.58
				(356.38)	67.52	4.30	23.37
4b	237–239	60	70	$C_{19}H_{13}FN_6$	66.27	3.81	24.41
				(344.35)	66.51	3.70	24.38
4c	208–210	65	76	$C_{20}H_{15}ClN_6O$	61.46	3.87	21.50
				(390.83)	61.53	3.70	21.36
4d	235–237	61	71	$C_{19}H_{13}ClFN_6$	60.09	3.45	22.13
				(379.80)	60.23	3.65	22.26
4e	254–256	65	71	$C_{19}H_{12}Cl_2FN_6$	55.09	2.92	20.29
				(414.24)	55.21	2.75	20.56

TABLE 3

Physicochemical constants of compounds **5a–e**

Compounds	T, °C	Yield, %				Molecular formula (MW)	Analysis, %		
		Method					Calculated/Found		
		Conventional	Solid-liquid PTC	Liquid-liquid PTC	One pot PTC		C	H	N
5a	185–186	61	64	70	51	$C_{20}H_{18}N_4O$	72.71	5.49	16.96
						(330.38)	72.52	5.30	16.77
5b	187–189	60	65	71	50	$C_{19}H_{15}FN_4$	71.68	4.75	17.60
						(318.35)	71.53	4.50	17.78
5c	224–226	61	66	75	51	$C_{20}H_{17}ClN_4O$	65.84	4.70	15.36
						(364.83)	65.63	4.50	15.75
5d	238–239	62	68	72	52	$C_{19}H_{15}ClFN_4$	64.50	4.27	15.84
						(353.80)	64.63	4.51	15.72
5e	238–240	60	67	74	50	$C_{19}H_{14}Cl_2FN_4$	58.78	3.63	14.43
						(388.25)	58.61	3.50	14.52

TABLE 4

IR and 1H NMR spectral data for compounds **2–4** and **5a–e**

Compounds	Ir (KBr), cm^{-1}	^{1}H NMR δ, ppm
2a	3242 (NH), 1681 (C=O), 1586, 1508 (C=C, C=N ring)	3.0 (s, 3H, CH$_3$), 3.72 (s, 3H, OCH$_3$), 7.2–8.1 (m, 10H, Ar-H), 10.65 (s, 1H, NH)
2b	3240 (NH), 1678 (C=O), 1587, 1509 (C=C, C=N ring)	3.01 (s, 3H, CH$_3$), 7.25–8.15 (m, 10H, Ar-H), 10.68 (s, 1H, NH)
2c	3242 (NH), 1675 (C=O), 1588, 1512 (C=C, C=N ring)	3.03 (s, 3H, CH$_3$), 3.74 (s, 3H, OCH$_3$), 7.23–8.1 (m, 9H, Ar-H), 10.69 (s, 1H, NH)
2d	3249 (NH), 1678 (C=O), 1588, 1515 (C=C, C=N ring)	3.0 (s, 3H, CH$_3$), 7.25–8.13 (m, 9H, Ar-H), 10.71 (s, 1H, NH)
2e	3250 (NH), 1680 (C=O), 1590, 1520 (C=C, C=N ring)	3.02 (s, 3H, CH$_3$), 7.25–8.13 (m, 8H, Ar-H), 10.72 (s, 1H, NH)
3a	1580, 1515 (C=C, C=N ring)	3.02 (s, 3H, CH$_3$), 3.85 (s, 3H, OCH$_3$), 7.18–8.08 (m, 10H, Ar-H)
3b	1586, 1508 (C=C, C=N ring)	3.01 (s, 3H, CH$_3$), 7.2–8.1 (m, 10H, Ar-H)
3c	3242 (NH), 1675 (C=O), 1588, 1512 (C=C, C=N ring)	3.03 (s, 3H, CH$_3$), 3.74 (s, 3H, OCH$_3$), 7.23–8.1 (m, 9H, Ar-H), 10.69 (s, 1H, NH)
3d	3249 (NH), 1678 (C=O), 1588, 1515 (C=C, C=N ring)	3.0 (s, 3H, CH$_3$), 7.25–8.13 (m, 9H, Ar-H), 10.71 (s, 1H, NH)
3e	3250 (NH), 1680 (C=O), 1590, 1520 (C=C, C=N ring)	3.02 (s, 3H, CH$_3$), 7.25–8.13 (m, 8H, Ar-H), 10.72 (s, 1H, NH)
4a	1610, 1515 (C=C, C=N ring)	3.03 (s, 3H, CH$_3$), 3.86, (s, 3H, OCH$_3$), 7.18–8.38 (m, 10H, Ar-H)
4b	1615, 1520 (C=C, C=N ring)	3.01 (s, 3H, CH$_3$), 7.15–8.2 (m, 10H, Ar-H)
4c	1608, 1505 (C=C, C=N ring)	3.02 (s, 3H, CH$_3$), 3.9 (s, 3H, OCH$_3$), 7.1–8.05 (m, 9H, Ar-H)
4d	1610, 1515 (C=C, C=N ring)	3.03 (s, 3H, CH$_3$), 7.2–8.2 (m, 9H, Ar-H)
4e	1608, 1505 (C=C, C=N ring)	3.02 (s, 3H, CH$_3$), 7.2–8.22 (m, 8H, Ar-H)
5a	3465, 3290, 1650 (NH), 1580, 1515 (C=C, C=N ring)	3.01 (s, 3H, CH$_3$), 3.9 (s, 3H, OCH$_3$), 5.34 (d, 2H, NH$_2$), 7.20–8.1 (m, 10H, Ar-H)
5b	3472, 3293, 1645 (NH), 1604, 1520 (C=C, C=N ring)	3.03 (s, 3H, CH$_3$), 5.25 (d, 2H, NH$_2$), 7.25–8.15 (m, 10H, Ar-H)
5c	3465, 3275, 1644 (NH), 1595, 1517 (C=C, C=N ring)	3.02 (s, 3H, CH$_3$), 3.88 (s, 3H, OCH$_3$), 5.25 (d, 2H, NH$_2$), 7.3–8.4 (m, 9H, Ar-H)
5d	3475, 3273, 1646 (NH), 1604, 1520 (C=C, C=N ring)	3.03 (s, 3H, CH$_3$), 5.36 (d, 2H, NH$_2$), 7.3–8.2 (m, 9H, Ar-H)
5e	3483, 3291, 1648 (NH), 1605, 1521 (C=C, C=N ring)	3.03 (s, 3H, CH$_3$), 5.38 (d, 2H, NH$_2$), 7.32–8.34 (m, 8H, Ar-H)

328, 301 and 300 resulted due to successive nitrogen and methyl cyanide elimination or due to subsequent removal of two nitrogen molecules [14, 33].

The X-ray crystallography study [34] of compound **4a** also proved the tetrazole ring formation giving following ortep diagram (Fig. 1).

General procedure for the synthesis of 5,7-disubstituted 2-methyl-7H-pyrrolo-[2,3-d]pyrimidin-4(3H)-ones 2a–e

1,4-Disubstituted 2-amino-3-cyanopyrroles **1** [35, 36] (0.01 mol) were refluxed with acetic anhydride (20 mL) for 7–8 h. The reaction mixture was then allowed to cool, poured onto crushed ice (50 g), neutralized with sodium hydroxide solution (5 N), filtered, dried, and crystallized from a mixture of DMF and ethanol (6 : 4 v/v).

General procedure for the synthesis of 5,7-disubstituted 2-methyl-4-chloro-7H-pyrrolo[2,3-d]-pyrimidines 3a–e

Method I. 5,7-Disubstituted 2-methyl-4-chloro-7H-pyrrolo[2,3-*d*]pyrimidin-4(3H)-ones **2** (0.01 mol) and phosphorous oxychloride (25 mL)
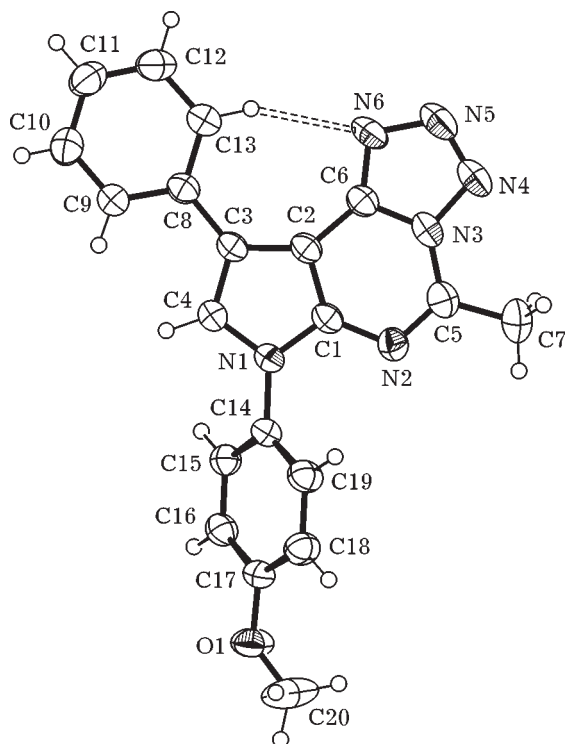
Fig. 1.

were refluxed for 15−17 h. The excess of reagent was distilled under reduced pressure. Then the reaction mixture was allowed to cool, poured onto crushed ice (50 g), neutralized with sodium hydroxide solution (5 N), filtered, dried, and crystallized from ethanol.

Method II. A mixture of 2 (0.01 mol), phosphorous oxychloride (20 mL) and TEBA (10 mmol) was refluxed for 4−5 h. The excess of regent was distilled under reduced pressure. The reaction mixture was then allowed to cool, poured onto crushed ice (50 g), neutralized with sodium hydroxide solution (5 N), filtered, dried, and crystallized from ethanol.

General procedure for the synthesis of 7,9-disubstituted 5-methyl-7H-tetrazolo-[1,2-c]pyrrolo[3,2-e]pyrimidines 4a−e

Method III. To a well stirred mixture of sodium azide (5 mmol) and ammonium chloride (6 mmol) in DMSO (15 mL) was added 5,7-disubstituted 2-methyl-4-chloro-7H-pyrrolo[2,3-*d*]-pyrimidines 3 (5 mmol) portion wise with constant stirring. The reaction mixture was stirred for 2 h at 90 °C and for 1 h at RT. Then the cold reaction mixture was poured onto crushed ice

(25 g) and the solid obtained was filtered washed with water, dried, and crystallized from dioxane.

Method IV. To a well stirred mixture of 3 (5 mmol) and Aliquat 336 (0.202 g, 0.5 mmol) in toluene (25 mL) was added sodium azide (0.390 g, 6 mmol) in water (5 mL). The reaction mixture was stirred under reflux condition for 1−1.5 h. Thereafter, the two phases were separated, the aqueous phase was extracted with toluene (15 mL) and combined organic layers were washed with water (2 mL × 10) and passed through anhydrous sodium sulphate. The excess of solvent was distilled under reduced pressure. The oily residue was treated with cold methanol. The obtained solid was filtered, dried, and crystallized from dioxane.

General procedure for the synthesis of 5,7-disubstituted 2-methyl-4-amino-7H-pyrrolo[2,3-d]pyrimidines 5a−e

Method V. To a solution of 4 (2 mmol) in acetic acid (5 mL) was added zinc dust (0.2 g) in portions over a period of 0.5 h and the reaction mixture was refluxed for 1−1.5 h. Then the cold reaction mixture poured onto crushed ice (25 g), neutralized with ammonia solution (6 N), and extracted with chloroform (30 mL × 2), the combined chloroform layer was dried over anhydrous magnesium sulphate and concentrated *in vacuo*. The solid obtained was filtered, dried, and crystallized from a mixture of ethanol : chloroform (8 : 2 v\v).

Method VI. Solid-liquid PTC condition: to a mixture of 4 (2 mmol), acetonitrile (25 mL), 18-C-6 (0.132 g, 0.5 mmol) and powdered KOH (0.841 g, 15 mmol) was added sodium borohydride (0.302 g) portion wise over a period of 2−2.5 h under stirring condition at 80 °C. The excess of solvent was distilled under vacuum. Thus obtained solid was filtered, washed with chilled methanol, dried, and crystallized from a mixture of ethanol : chloroform (8 : 2 v\v).

Method VII. Liquid-liquid PTC condition: to a mixture of 4 (2 mmol), toluene (20 mL), Aliquat 336 (0.202 g, 0.5 mmol) and water (5 mL) was added sodium borohydride (0.302 g, 6 mmol) in portions over a period of 0.5 h under stirring condition at 60 °C. The reaction mixture was refluxed for 1 h. Thereafter, the two phases were separated, the aqueous phase was extracted with tol-

uene (15 mL) and combined organic layers were washed with water (2 mL × 2) and dried over anhydrous sodium sulphate. The excess of solvent was distilled under vacuum. The oily residue was treated with cold *n*-hexane and obtained solid was filtered, washed with chilled methanol, dried, and crystallized from a mixture of ethanol : chloroform (8 : 2 v/v).

Method VIII. One pot synthesis of **5a−e** by liquid-liquid PTC condition: to a mixture of **3** (2 mmol), toluene (20 mL), Aliquat 336 (0.323 g, 0.8 mmol) was added sodium azide (0.390 g, 6 mmol) in water (5 mL) under stirring in portions and refluxed for 2−2.5 h to get formation of **4** (TLC). Then sodium borohydride (0.302 g, 6 mmol) was added in portions and was refluxed 3 h. The separation of two phases was done same as Method VI to get the identical compounds **5**.

CONCLUSION

A cleaner, faster, environmental friendly and economic PTC technique for the greatly studied nucleophilic substitution reactions like chlorination, azidolysis and indirect amination providing the formation of synthetically and biologically important novel 5-methyltetrazolo-pyrrolopyrimidines and 2-methyl-4-aminopyrrolopyrimidines has been established.

Acknowledgements

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