IOSR Journal of Applied Chemistry (IOSR-JAC)
e-ISSN: 2278-5736.Volume 10, Issue 8 Ver. II (August. 2017), PP 51-54
www.iosrjournals.org

Phase Transfer Catalysis Aided Synthesis of Pyrazolopyrimidineamines by Chemoselective Reductive Ring Opening

*Shah Rina D, Shah Nirmal M.
Chemistry Department, M. G. Science Institute, Ahmedabad, India,
Corresponding Author: Shah Rina D

Abstract: *Chemoselective tetrazole ring opening of pyrazolotetrazolopyrimidines **2**, obtained from 4-chloropyrazolopyrimidines **1**, by reduction with Sodium borohydride under solid-liquid and liquid-liquid phase transfer catalysis has been carried out to form pyrazolopyrimidineamines **3.** A comparative study of conventional as well as phase transfer catalysis for synthesis of pyrazolopyrimidineamines **3** has also been reported. One pot synthesis of **3** directly form **1** under liquid-liquid PTC has also been conducted with insitu generation of **2**.*

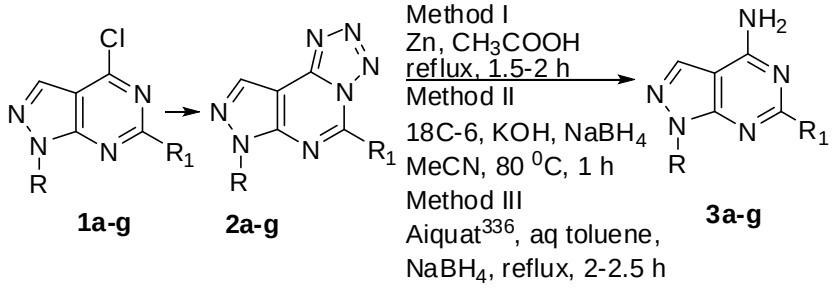
Keywords: *Chemiselective reaction, Pyrazolopyrimidines, PTC, 18-C-6, Aliquat^{336}*

Date of Submission: 24-08-2017 Date of acceptance: 05-09-2017

I. Introduction:

Fused tetrazole serves as latent amino functionality[1-3] and Pyrazolopyrimidines have been identified as potent bioactive compounds[4-16]. Some pyrazolo[3,4-*d*]pyrimidineamines have been reported as inhibitors of tyrosine kinase enzymes and found to be useful for immune regulation and for the treatment of cancer, angiogenesis and atherosclerosis[7-16]. A variety of pharmaceutically important heterocycles such as imidazole, triazole and pyrimidine can be annulated on pyrimidine ring[17-25]. Phase Transfer Catalysis(PTC) technique has been an efficient procedure that offers many advantages providing safer, rapid, cleaner, step reducing and yield increasing reaction with milder operational conditions with simple work up, and can easily be scalable[26-33]. Despite these great benefits and wide scope of applicability, yet PTC technique hasn't received much attention due to lack of awareness. Incorporation of environmental friendly phase transfer catalysis with reductive ring cleavage of tetrazole is always interesting to study. Therefore, a comparative studies of chemoselective reductive ring cleavage of 7,9-disubstituted 7*H*-pyrazolo[4,3-*e*]tetrazolo[1,5-*c*]pyrimidines **2** has been attempted conventionally with zinc and acetic acid and also under different PT conditions such as solid-liquid and liquid-liquid PTC. Pyrazolotetrazolopyrimidines **2** prepared from 4-chloropyrazolo[3,4-*d*]pyrimidines **1**, underwent tetrazole ring opening under reduction afforded pyrazolo[3,4-*d*]pyrimidineamines **3**. Reduction by classical method was carried out by reacting pyrazolotetrazolopyrimidines **2** with zinc dust and acetic acid under reflux for 1.5-2.0 h (method I, yield 58-64%). PTC aided reduction included the comparative studies of solid-liquid and liquid-liquid PTC using chemoselective milder reducing agent such as sodium borohydride. In case of solid-liquid PTC, compound **2** were treated with sodium borohydride in acetonitrile using 18-C-6 as PT catalyst and KOH as base under stirring at 80 ^{0}C for 1 h (method II, yield 75-81%). Reduction of **2** under Liquid-liquid PTC included the use of Aliquat^{336} (methyltrioctyl ammonium chloride)as PT catalyst and an aqueous toluene as solvent under reflux for 2-2.5 h (method III, yield 70-79%) to form corresponding **3** (scheme 1)

Scheme 1

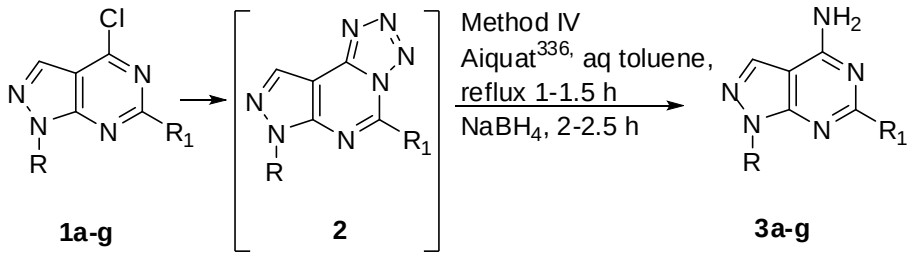


1,3	R	R_1
a	CH_3	H
b	C_6H_5	H
c	4-$CH_3C_6H_4$	H
d	4-$OCH_3C_6H_4$	H
e	4-ClC_6H_4	H
f	C_6H_5	CH_3
g	2-pyridyl	H

Usually direct formation of chloro to amines in azines operated under harsh conditions[34-37]. Alternatively one pot indirect amination was fascinated by azidolysis followed by reductive ring cleavage of

tetrazole ring. One pot synthesis of **3** has been attempted directly from 4-chloropyrazolopyrimidines **1** using liquid- liquid PT condition (method IV) through *in situ* formation of tetrazoles **2** using sodium azide, Aliquat[336] as a catalyst and aqueous toluene as a solvent (checked by TLC), followed by the reduction with sodium borohydride under reflux(scheme 2).

Scheme 2



II. Result And Discussion:

Identity of compounds **3** prepared by conventional as well as PTC was proved by TLC and mixed melting point. The structure elucidation of all the compounds has been done on the basis of spectral analysis. The IR spectra of compound **3** displayed absorption bands near 3427-3286 cm^{-1} and the ^1H NMR spectra showed a broad singlet in the region δ 7.3-8.06 supported the reduction of tetrazole ring to form pyazolopyrimidineamines **3**. Among PTC and convention procedures, PTC was found to be more advantageous, in addition solid-liquid PTC assisted reduction of **2**, found to occur at lower temperature with reduced reaction time, less molar concentration of PTC and high yield. Although the use of higher concentration of catalyst, liquid-liquid PT condition remain the only choice for the direct synthesis of **3** from **1**. The yield and time comparison of all the employed methods for compound **3** has been shown in table 1.

Table 1: Yield and time comparison of MI-MIV for compound 3a-g

Compound 3	Time h				Yield %			
	Conv.	PTC	PTC	Overall (two steps) One Pot MIV	Conv.	PTC	PTC	Overall (two steps) One pot MIV
	MI	MII	MIII		MI	MII	MIII	
a	2.0	1	2.25	3.75	58	75	70	55
b	1.5	1	2	3.5	62	76	71	60
c	1.5	1	2.5	3.75	61	76	71	51
d	2.0	1	2	3.5	62	77	73	59
e	1.5	1	2.25	3.75	64	80	74	60
f	1.5	1	2	3.5	58	79	75	58
g	1.5	1	2	3.5	59	81	79	60

Experimental:

Melting points were determined by electrothermal method in an open capillary tube and are uncorrected. The IR spectra were recorded in cm^{-1} for KBr pellets on Brucker spectrophotometer. ^1H NMR spectra were recorded on Varian 400 MHz spectrometer using DMSO d^6 as a solvent and TMS as the internal reference standard. The chemical shifts are expressed in δppm. Mass spectra were taken on LC-MS-Agilent 1100 series. The purity of the compounds were routinely checked by TLC using Silica G and the spots were visulized in iodine vapour or UV light.

Synthesis of 1,6-disubstituted 4-amino 1*H*-pyrazolo[3,4-*d*]pyrimidines 3 a-f: General Procedure

Method I: To a solution of **2** (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, neutralized with ammonia solution (6N), extracted with chloroform (2 X 30 mL), the combined chloroform layer was dried over anhydrous magnesium sulphate and concentrated *in vacuo*. The solid obtained was filtered, dried, and crystallized from ethanol.

Method II: Solid-liquid PT catalysis condition: To a mixture of **2** (2 mmol), acetonitrile (25 mL), 18-C-6 (0.132 g., 0.5 mmol) and potassium hydroxide (0.841 g, 15 mmol) was added sodium borohydride (0.302 g) portion wise under stirring condition at 80 ^{0}C. The reaction mixture was heated for 1 h. The excess of solvent was distilled under vacuum. Thus obtained solid was filtered, washed with chilled methanol, fltered, dried, and crystallized from ethanol..

Method III: Liquid-liquid PT catalysis condition: Sodium borohydride (0.302g, 6 mmol) was added in portions over a period of 0.5 h to a well stirred mixture of **2** (2 mmol), toluene (20 mL), Aliquat^{336} (0.202 g., 0.5 mmol) and water (5 mL) under stirring and the reaction mixture was refluxed for 1 h. After, the separation of two phases, the aqueous phase was extracted with toluene (10 mL) and collected organic layers were washed with water and dried over anhydrous sodium sulphate. The excess of solvent was distilled under vacuum. To the oily residue was added cold n-hexane and thus the obtained solid was filtered, dried, and crystallized from ethanol.

Method IV: One pot Synthesis of **3** from **1** by liquid-liquid PT catalysis condition: To a mixture of **1**[15,38] (2 mmol), toluene (20 mL), Aliquat^{336} (0.323 g., 0.8 mmol) was added sodium azide (0.390 g, 6mmol) in water (5 mL) under stirring in portions and refluxed for 1-1.5 h to get formation of **2** (TLC). Then sodium borohydride (0.302g, 6 mmol) was added in portions and was refluxed for 2-2.5 h. The separation of two phases was done same as method III to get the identical compounds **3**.

1-Methyl 1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine 3a: mp: 266-68 ^{0}C[15], IR (KBr): 3405,3290,1644(NH_2), 1616,1504 (C=C, C=N ring) cm^{-1}, ^{1}H NMR (DMSO d^6): δ 8.35(s,1H,Ar-H at C6), 8.22(s,1H,Ar-H at C3), 7.89(s,2H,NH_2,d_2O exchangeable), 3.01(s,1H, CH_3), MS: 149 (M^+). Anal. Calcd for $C_6H_7N_5$: C 48.32, H 4.73, N 46.95 %. Found: C 48.67, H 4.92, N 47.19 %.

1-Phenyl 1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine 3b: mp: 209-210 ^{0}C[15], IR (KBr): 3400,3315,1650(NH_2),1590, 1505(C=C, C=N ring) cm^{-1}, ^{1}H NMR (DMSO d^6): δ 8.36(s,1H,Ar-H at C6), 8.22(s,1H,Ar-H at C3), 8.05(s,2H,NH_2,d_2O exchangeable), 7.56-7.6(m,4H,Ar-H), 7.4-44(t,1H,Ar-H). MS: 211 (M^+). Anal. Calcd for $C_{11}H_9N_5$: C 62.55, H 4.29, N 33.16 %. Found: C 62.67, H 4.62, N 32.98 %.

1-(4-Methylphenyl) 1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine 3c:
mp: **223-24** ^{0}C[12]. IR (KBr): 3427,3370,1660(NH_2), 1586, 1514(C=C, C=N ring) cm^{-1}, ^{1}H NMR (DMSO d^6): δ 8.37(s,1H,Ar-H at C6), 8.33(s,1H,Ar-H at C3), 8.21(d,2H, Ar-H), 7.36(d,2H,Ar-H), 7.25(bs,2H,NH_2, d_2O exchangeable), 2.41(s, 3H,CH_3). MS: 225 (M^+). Anal. Calcd for $C_{12}H_{11}N_5$: C 63.99, H 4.92, N 31.09 %. Found: C 63.67, H 4.62, N 30.98 %.

1-(4-Methoxyphenyl) 1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine 3d: mp: 218-19 ^{0}C[12], IR (KBr): 3419,3386, 1669(NH_2), 1658, 1522(C=C, C=N ring) cm^{-1}, ^{1}H NMR (DMSO d^6): δ 8.34 (s,1H,H at C6), 8.32(s,1H,H at C3), 8.19(d,2H,Ar-H), 7.31(bs,2H,NH_2, d_2O exchangeable), 7.15(d,2H,Ar-H), 3.9(s,3H,OCH_3). MS: 241 (M^+). Anal. Calcd for $C_{12}H_{11}N_5O$: C 59.74, H 4.60, N 29.03 %. Found: C 60.01, H 4.62, N 29.36%.

1-(4-Chlorophenyl) 1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine 3e: mp: 280-281 ^{0}C[15], IR (KBr): 3380,3396, 1666(NH_2), 1592, 1554(C=C, C=N ring) cm^{-1}, ^{1}H NMR (DMSO d^6): δ 8.38(s,1H,Ar-H at C6), 8.33(s,1H,Ar-H at C3), 7.4-8.25(m,4H,Ar-H), 7.3(bs,2H,NH_2,D_2O exchangeable). MS: 245 (M^+). Anal. Calcd for $C_{11}H_8N_5Cl$: C 53.78, H 3.28, N 28.51 %. Found: C 53.55, H 3.54, N 28.78 %.

1-Phenyl-6-methyl 1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine 3f: mp: 240-42 ^{0}C, reported 160 ^{0}C[19], IR (KBr): 3420,3286(NH_2),1630, 1605, 1530(C=C, C=N ring) cm^{-1}, ^{1}H NMR (DMSO d^6): δ 7.4-8.3(m,6H,Ar-H), 8.09(s,2H,NH_2,d_2O exchangeable), 1.86(s,3H, CH_3). MS: 241 (M^+). Anal. Calcd for $C_{12}H_{11}N_5O$: C 59.74, H 4.60, N 29.03 %. Found: C 60.01, H 4.62, N 29.36%.

1-(2-Pyridyl) 1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine 3g: mp: 239-40^{0}C[11], IR (KBr): 3480,3370,1655(NH_2), 1600,1512(C=C, C=N ring) cm^{-1}, ^{1}H NMR (DMSO d^6): δ 8.6-7.4(m,6H,ArH), 7.88(d,2H,NH_2,d_2O exchangeable). MS: 212 (M^+). Anal. Calcd for $C_{10}H_8N_6$: C 56.60; H 3.80; N 39.60; Found: C 56.88; H 3.45; N 39.72%.

III. Conclusion

A comparative study of conventional and PTC methodologies has been attempted for tetrazole reductive ring opening to form pyrazolopyrimidin-4-amines, among PTC aided reduction was employed using solid-liquid and liquid PTC, where solid-liquid method was found to be more efficient. In case of indirect amination of 4-chloropyrazolopyrimidines, azidolysis followed by amination have been carried out with liquid-liquid PTC in one pot. The formation of synthetically and biologically important pyrazolopyrimidin-4-amines was fascinated by PTC.

Acknowledgement

We are thankful to Centre of Excellence, National Facility for Drug Discovery Centre(NFDD) Rajkot, India for the ^{1}H NMR and mass spectral analysis, University Grant Commission for funding and M. G. Science Institute for research facility.

References

[1]. N. S. Habib, S. M. Rida, E. A. M. Badawey, and H. T. Y. Fahmy; Condensed Thiazoles, II: Synthesis of 7-Substituted Thiazolo[4,5-d]pyrimidines as Possible Anti-HIV, Anticancer, and Antimicrobial Agents, Monatshefte fiir Chemie 127, 1209-1214, 1996

[2]. C. J. Shishoo and S. K. Jain, Synthesis of some novel azido/tetrazolothienopyrimidines and their reduction to 2,4-diaminothieno[2,3-d]pyrimidines, J Heterocycl. Chem., **29**, 883, 1992

[3]. C. G. Dave, R. D. Shah, Synthesis of 7H-Tetrazolopyrrolopyrimidines and their reductive ring cleavage to 4-aminopyrrolopyrimidines: J. Heterocycl. Chem., **31**, 1800, 1999.

[4]. D. K. Kim, D. H. Ryu, N. Lee, J. Y. Lee, J. S. Kim, S. Lee , J. Y. Choi, , J. H. Ru, N. H. Kim, , G. J. Im, W. S.Choi and T. K. Kim, Synthesis and Phosphodiesterase 5 Inhibitory Activity of New 5-Phenyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one Derivatives Containing an N-Acylamido Group on a Phenyl Ring. Bioorg. Med. Chem., 9, 1895–1899, 2001

[5]. E. R. Aymn, I. H. Mohamed, E. A. M. Randa, F. Nahed and M. E. A. M Farouk, Synthesis and anti-HSV-1 evaluation of some pyrazoles and fused pyrazolopyrimidines. Eur. J. Med. Chem., 44, 3285–3292, 2009

[6]. J. Quiroga, J., J. Trilleras, B. Insuasty, R. Abonia, M. Nogueras, A. Marchal and J. Cobo, Microwave-assisted synthesis of pyrazolo[3,4-d]pyrimidines from 2-amino-4,6-dichloropyrimidine-5-carbaldehyde under solvent-free conditions. Tetrahedron Lett., 49, 3257–3259, 2008

[7]. R. L. Dow, K. Koch and G. R. Schulte, 4-aminopyrazolo(3-,4-d)pyrimidine and 4-aminopyrazolo(3,4-d)pyridine tyrosine kinase inhibitors, US 5593997 A, 1998**.**

[8]. A. Rahmouni, A. Romdhane, A. B. Said, K. Majouli, H. B. Jannet, Synthesis of new pyrazole and antibacterial pyrazolopyrimidine derivatives, Turk J. Chem., 38, 210–221, 2014

[9]. A. M. F. Oliveira-Campos, A. M. Salaheldin, L. M. Rodrigues, Synthesis of some novel pyrazolo[3,4-d]pyrimidine derivatives, ARKIVOC (xvi) 92-100, 2007

[10]. A. Kreutzberger and K. Burgwitz, K., 1-Carbocyclisch und heterocyclisch substituierte 4-Aminopyrazolo[3 ,4-d]pyrimidine, Arch. Pharm. (Weinheim) 314, 394-398, 1981

[11]. A. E. Abd El Razik and A. E. Abdel Wahab**,** Synthesis and Biological Evaluation of Some Novel Fused Pyrazolopyrimidines as Potential Anticancer and Antimicrobial Agents, Arch. Pharm. Chem. Life Sci. 2011, 11, 184–196.

[12]. S. Gupta, L. M. Rodrigues, A. P. Esteves, A. F. Oliveira-Campos, M. S. J. Nascimento, N. N. H. Cidade, M. P. Neves, E. Fernandes, P. Madalena , P. N. M. Cerqueira, N. Bra´s, Synthesis of N-aryl-5-amino-4-cyanopyrazole derivatives as potent xanthine oxidase inhibitors**,** Eur. J. Med. Chem., 43, 771-80, 2008

[13]. A. H. Abdelazeem, S. A. Abdelatef, M. T. El-Saadi, H. A. Omar, S. I. Khan, C. R. McCurdy, Novel pyrazolopyrimidine derivatives targeting COXs and iNOS enzymes; design, synthesis and biological evaluation as potential anti-inflammatory agents, Eur. J. Pharma. Sci., 62, 197-211, 2014

[14]. J. Roger, I. A. Gillespie, C. Claire, E. Dawson T. Colin, Bioorganic Medicinal Chemistry Letters Volume 18 (9), 2008 doi 10.1016 2Fj.bmcl.2008.03.072

[15]. Cheng C. C. and Robins, R. K, Potential Purine Antagonists. VI. Synthesis of 1-Alkyl- and 1-Aryl-4-substituted Pyrazolo[3,4-d]pyrimidines.., J. Org. Chem., **21**, 1240–1256, 1956

[16]. Eur. Pat. 1 746 099 A1, 2007

[17]. A. Thurkauf and P. Albaugh, Certain aryl fused imidazopyrimidines; a new class of GABA brain receptor ligands. US Patent 5,212,310, 1993

[18]. L. Siegfried, V. Helmut and G. Michael, Ger. (East), DD258,233, **1988**, Chem Abstr, 110, 114858, 1989

[19]. A. Karoui, F. Allouche, M. Deghrigue, A. Agrebi, A. Bouraoui and F. Chabchoub, Synthesis and pharmacological evaluation of pyrazolopyrimidopyrimidine derivatives: anti-inflammatory agents with gastroprotective effect in rats, Med. Chem. Res., 23, 1591–1598, 2014

[20]. L. Martarello, C. D. Kilts, T. M. Owens, C. B. Nemeroff and M. M. Goodman, Synthesis and characterization of fluorinated and iodinated pyrrolopyrimidines as PET/SPECT ligands for the CRF1 receptor, Nucl. Med. Biol., 28, 187, 2001

[21]. Y. L. Zhang, L. R. Zhang, Z. J. Yang, J. M. Min, L. H.Zhang, L. U. Yang, N. B. Gong and Q. T. Zheng, Coupling Reaction of 4-Chloro-7H-Pyrrolo[2,3-d]Pyrimidine with 2,3,5-Tri-O-Acetyl-b-D-Ribofuranosyl Chloride. Chinese Chem. Lett, 12, 391-94, 2001

[22]. A. Gangjee, H. D., Jain, R. L. Kisliuk, Novel 2-amino-4-oxo-5-arylthio-substitutedpyrrolo[2,3-d]pyrimidines as nonclassical antifolate inhibitors of thymidylate synthase, Bioorg. Med. Chem. Lett., 15, 2225-30, 2005

[23]. N. D. Desai, The Gould-Jacob Type of Reaction for the Synthesis of Novel Pyrimidopyrrolopyrimidines : A Comparison of Classical heating vs Solvent Free Microwave Irradiation, J. Heterocycl. Chem., 43, 1343-48, 2008

[24]. C. G. Dave and M. C. Shukla, Diethyl ethoxymethylenemalonate in triheterocycles: A new synthesis of pyrido[3,2-e]pyrimido[1,2-c]pyrimidines. Heterocycles, 34, 1805-08, 1997

[25]. C. G. Dave and R. D. Shah, Gould-jacob type of reaction in the synthesis of thieno[3,2-e]pyrimido[1,2-c]pyrimidines: A comparison of classical heating vs solvent-free microwave irradiation, Heterocycles, 51,1819–1826, 1999

[26]. M. Halpern, Increasing Plant Profits by Phase-Transfer Catalysis Retrofit,Phase-Transfer Catalysis Communications, 2, 1, 1996

[27]. E. D'Incan**,** P. Viout and R. Gallo**,** Phase Transfer Catalysis and Selectivity in Organic Synthesis, Isr. J**.** Chem**.,** 26**,** 277–281, 1985

[28]. Y. Goldberg, Phase-Transfer Catalysis, Selected Problems and Application, Amsterdam: Gordon and Breach Sci Publ., 1992

[29]. E. V. Dehmlow and S. S. Dehmlow, Phase-Transfer Catalysis. 2nd ed, Weinheim: Verlag Chemie, 1983

[30]. C. M. Starks, C. L. Liotta and M. Halpern M., Phase-Transfer Catalysis: Fundamentals, Applications and Industrial Perspectives, NY: Chapman and Hall, 1994

[31]. W.(Ed). Hoyle, Pilot Plants and Scale-Up of Chemicals, Royal Society of Chemistry (Great Britain), Cambridge, 1999

[32]. M. Sabahi and R. Irwin, (Albemarle); Process for preparing Michael addition products, U. S. Patent 5,347,043, 1994

[33]. A. Malik, G. Manser, R. Carson and G. Archibald, Solvent-free process for the synthesis of energetic oxetane monomers. US Patent 5,523,424, 1996

[34]. J. F. Hartwig, Palladium-Catalyzed Amination of Aryl Halides: Mechanism and Rational Catalyst, Synlett, 329, 1997

[35]. J. F. Hartwig, Mechanism for aryl halide amination catalyzed by palladium complexes, Angew. Chem., Int. Ed., 1998, 37, 2046.

[36]. C. G. Frost and P. Mendoncua, Recent developments in aromatic heteroatom coupling reactions**,** J. Chem. Soc., Perkin Trans., 1, 2615, 1998

[37]. S. Jaime-Figueroa, Y. Liu, J. Muchowski and D. Putman, Tetrahedron Lett., 39, 1313, 1998

[38]. C. Monril, S. Babu, N. G. Almstead and Y. Moon, Synthesis of 1,4-Disubstituted pyrazolo[3,4-d]pyrimidines from 4,6-Dichloropyrimidine-5-carboxaldehyde: Insights into Selectivity and Reactivity, Synthesis, 45, 1791-1806, 2013

IOSR Journal of Applied Chemistry (IOSR-JAC) is UGC approved Journal with Sl. No. 4031, Journal no. 44190.

Shah Rina D. "Phase Transfer Catalysis Aided Synthesis of Pyrazolopyrimidineamines by Chemoselective Reductive Ring Opening." IOSR Journal of Applied Chemistry (IOSR-JAC), vol. 10, no. 8, 2017, pp. 51–54.