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RESEARCH ARTICLE

An efficient and green synthesis of 3- phenyl-1H-pyrazolo [3, 4-d] pyrimidine derivatives

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Abstract

An efficient and green method for the preparation of 3- phenyl-1H-pyrazolo [3, 4-d] pyrimidine derivatives (3a-r) in minutes of time with high yields is accomplished by the mixture of 3-iodo-1H-pyrazolo[3,4-d]pyrimidine pyrazole (1) and various aryl boronic acids (2a-m) at 100°C under microwave irradiation in the presence of Pyridine-Pyrazole/ Pd (II) complex and aqueous medium. The catalyst recovered, reused several times and air-stable.

Introduction:-

Pyrazolo pyrimidine and their derivatives are widely used in the field of medicinal chemistry. They are biologically active isomeric purine analogues and have useful properties as anti metabolites in purine biochemical reactions [1]. They show wide pharmacological activities like antihypertensive [2], tuberculostatic [3] antitumor [4], antimicrobial [5], neuroleptic [6], and antileishmanial activities [7].The great biological activity of pyrazolo pyrimidine derivatives attracted many researchers. Hence, different methods have been reported for pyrimidine derivatives [8-13] However; some of these methods still suffer from certain demerits, such as recycle of catalyst, long reaction times, low yields, air sensitive catalysts, multistep and low selectivity's. Thus, the development of simple and environmentally protocal is still in demand.

Therefore, to develop a rapid and efficient method for the synthesis of 3- subphenyl-1H-pyrazolo [3, 4-d] pyrimidine derivatives, we have sought to speed up Suzuki coupling using Pyridine-Pyrazole/ Pd (II) complex and aqueous medium under microwave sources. In this paper, we report carboxylated water-soluble pyridine-pyrazole ligands as supporting ligands for the Suzuki reaction

Results and discussion:-

Suzuki coupling of 3 - iodio 1H-pyrazolo [3, 4-d] pyrimidine (1), phenylboronic acid (2) and NaOH in the presence of Pyridine-Pyrazole/ Pd (II) complex and TBAB in water, under microwave irradiation 100 °C as shown in the **Scheme1.** The reaction was completed 5 min to afford the corresponding product, 3- phenyl-1H-pyrazolo [3, 4-d] pyrimidine (**3a**) in excellent yields. The product was confirmed by ^{1}H NMR and Mass spectroscopy.

Scheme 1: 3- phenyl-1H-pyrazolo [3, 4-d] pyrimidine (**3a**)
We first investigated the effect of the base on the reaction out come. Numerous bases were successfully employed to promote the transformation Carbonates afford the desired product in good yields. Potassium phosphate afforded the desired product in very good yields. Both KOH and NaOH were found to give in excellent yields. Finally NaOH was found to be suitable for this transformation under microwave condition.

We observed that the concentration of the catalyst played a major role in this Suzuki reaction, hence varying the concentration of Pyridine-Pyrazole/ Pd (II) complex from just 2 mol% to 10 mol%, the yield of product was varied from 75% to 95%. It shows that 5 mol% of Pyridine-Pyrazole/ Pd (II) suitable and sufficient for the synthesis of titled compounds.

In order to investigate the recyclability and reusability of the catalyst, it was recovered by simple aqueous phase separated. This was reused as such for subsequent experiments at least five consecutive cycles without much appreciable loss in its catalytic activity This data demonstrate that high stability of the catalyst (**Figure 2**) under microwave irradiation conditions

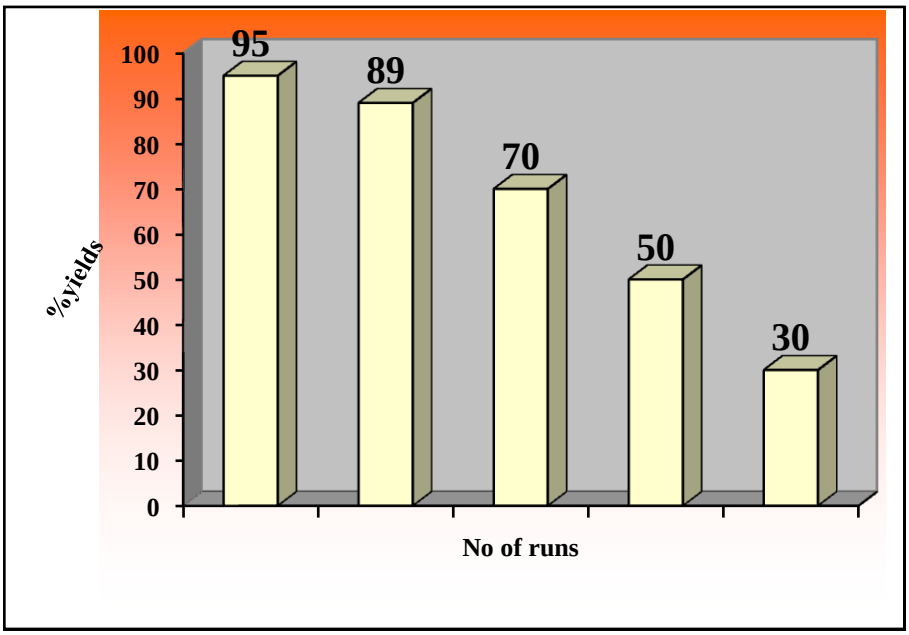

Figure 2: Reusability of the Pyridine-Pyrazole/ Pd (II) complex catalyst in Suzuki coupling

Having optimized reaction conditions in hand carried out the coupling of 3 - iodio 1H-pyrazolo [3, 4-d] pyrimidine (1) various aryl boronic acids (**2a-r**), NaOH, TBAB and using Pyridine-Pyrazole/Pd(II) complex 5 mol% to obtained the titled compounds (**3a-r**) with good to excellent product yields without formation of any side products under MWI with 100 W power at 100 °C in aqueous medium (**Table1**). All aryl boronic acids participated effectively in reaction and gave excellent product yields (**Table 1**, entries 1-18). All the products were confirmed by their ^{1}H NMR, IR and Mass spectral analysis.

Tabele1: synthesis of 3- phenyl-1H-pyrazolo [3, 4-d] pyrimidine derivatives.

Entry	Aryl boronic acids	Products	Time (min)	Yield (%)
01		3a	5	96
02		3b	10	92
03		3c	9	94
04		3d	8	94
05		3e	8	92
06		3f	10	94
07		3g	10	89
08		3h	8	93
09		3i	8	95
10		3j	8	91
11		3k	12	84

12		3l	9	90
13		3m	8	94
14		3n	7	93
15		3o	7	94
16		3p	8	94
17		3q	8	92
18		3r	7	94

[a]Reaction of 3 - iodio 1H-pyrazolo [3, 4-d] pyrimidine (1) (1.0 equiv) , aryl boronic acids (1.1 equiv), Pyridine-Pyrazole/ Pd (II) complex (5 mol %) , TBAB (2 mol%) and NaOH (3.0 equiv); [b]all the reactants irradiated with 100 W microwaves; [c]Isolatedyields with >95% purity as determined by ^{1}H NMR and Mass analysis.

Conclusion:-

3- phenyl-1H-pyrazolo [3, 4-d] pyrimidine derivatives were synthesized by the coupling with 3 - iodio 1H-pyrazolo [3, 4-d] pyrimidine and variety of aryl boronic acids in the presence of Pyridine-Pyrazole/ Pd (II) as catalyst and aqueous medium under microwave condition process is proved to be an excellent method.

Experimental section:-

All the chemicals and reagents procured from Sigma-Aldrich (Hyderabad, India), Merck (Mumbai, India), Lancaster Chemical (Mumbai, India) and SD fine chemicals were used as such without further purification. All the NMR spectra were recorded on Bruker 400 MHz spectrometer operating at 400 MHz for ^{1}H NMR. The compounds were dissolved in $CDCl_3$ and the chemical shifts were referenced to TMS. Coupling constants were calculated in hertz (Hz). The mass spectra were recorded on Agilent LC/MSD SL 1100 instrument. All the microwave reactions were carried out in CEM Focused microwave reactor.

General procedure for the preparation of 3-phenyl-1H-pyrazolo [3, 4-d] pyrimidine (3a):
A dry Pyrex tube fitted with an air-tight rubber cap was charged with 3 - iodio 1H-pyrazolo [3, 4-d] pyrimidine (1, 200 mg, 0.81 mmol), phenyl boronic acid (2a, 100 mg, 0.81 mmol , NaOH (97 mg, 2.43 mmol), Pyridine-Pyrazole/Pd(II) (16 mg, 0.04 mmol), TBAB (5.2mg, 0.016 mmol) and water (2 mL) were added. The resulting mixture was placed in a CEM Microwave reactor at 100 °C for 5min. Then the reaction mixturewas cooled, and diluted withethylacetate and water. The organic phase was separated and dried over anhydrous sodiumsulfate. The organic solution was filtered and the filtrate concentrated prior to silicagel chromatography using hexane-ethyl acetate. The fractions were concentrated and dried invacuum to get 142 mg (yield, 96%) of 3-phenyl-1H-pyrazolo [3, 4-d] pyrimidine. Aqueous phase was reused for further reaction.

3-phenyl-1H-pyrazolo [3, 4-d] pyrimidine (3a):
^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.65 (s, 1 H, NCHN), 9.02 (s, 1H, CHN), 8.1 (d, 2H, Ar-H), 7.76 (t, J = 8.0 Hz, 2 H, Ar-H), 7.50 (d, 1 H, Ar-H). MS: m/z 196 (M), 197 (M+1).

3-(4-methoxyphenyl)-1H-pyrazolo [3, 4-d] pyrimidine (3b):
^{1}H NMR (400 MHz, CDCl3) δ: 9.65 (s, 1 H, NCHN), 9.03 (s, 1H, CHN), 8.05 (d, 2H, Ar-H), 7.6 0 (s, 1 H, NH), 7.21(d, 2 H, Ar-H), 3.87(s, 3H, OCH_3). MS: m/z 226(M), 227 (M+1).

3-(3-methoxyphenyl)-1H-pyrazolo [3, 4-d] pyrimidine (3c)
^{1}H NMR (400 MHz, dmso-d6) δ: 9.65 (s, 1 H, NCHN), 9.02 (s, 1H, CHN), 7.70 (d, 1H, Ar-H), 7.58 (s, 1 H, Ar-H), 7.46(t, 1 H, Ar-H), 7.06 (d, 1H, Ar- H), 3.90 (s, 3H, OCH_3). MS: m/z 226(M), 227 (M+1).

3-(2-methoxyphenyl)-1H-pyrazolo [3,4-d]pyrimidine(3d)
^{1}H NMR (300 MHz, $CDCl_3$) δ: 9.65 (s, 1H, NCHN), 9.02 (s, 1H, CHN), 7.70 (d, 1H, Ar-H), 7.38-7.21 (t, 2H, Ar-H), 6.90 (d, 1 H), 3.90(s, 3H, OCH_3). MS: m/z 226 (M), 227 (M+1).

3-(naphthalen-1-yl)-1H-pyrazolo [3, 4-d] pyrimidine (3e)
^{1}H NMR (300 MHz, $CDCl_3$) δ: 9.69 (s, 1H, NCHN), 9.02 (s, 1H, CHN), 7.95-7.82 (m, 4H, Ar-H), 7.61 (dd, 1H, Ar-H), 7.50-7.43 (m, 2 H). MS: m/z 246 (M), 247 (M+1).

3-o-tolyl-1H-pyrazolo [3, 4-d] pyrimidine(3f)
^{1}H NMR (300 MHz, $CDCl_3$) δ: 9.65 (s, 1H, NCHN), 9.02 (s, 1H, CHN) 7.76 (d, 1 H, Ar-H), 7.34-7.21 (m, 3 H, Ar-H), 2.39 (s, 3 H, CH_3). MS: m/z 182 (M), 183 (M+1).

3-(5-fluoro-2-methylphenyl)-1H-pyrazolo [3, 4-d] pyrimidine (3g)
^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.65 (s, 1H,), 9.02 (s, 1H, CHN), 7.23-7.18 (m, 1H), 7.61 (dd, 1H, Ar-H), 6.92 (m, 1H, Ar-H), 2.92 (s, 3H, CH_3). m/z 228 (M), 229 (M+1).

3-(furan-3-yl)-1H-pyrazolo [3, 4-d] pyrimidine (3h)
^{1}H NMR (400 MHz, $CDMSO-d_6$) δ: 11.2 (b s, 1H, NH), 9.67 (s, 1H,), 9.02 (s, 1H, CHN), 8.64 (s, 1H, OCH), 7.88 (d, 1H, OCH), 7.10 (d, 1H). m/z 186 (M), 187(M+1).

3-(thiophen-3-yl)-1H-pyrazolo [3, 4-d] pyrimidine (3i)
^{1}H NMR (400 MHz, $CDMSO-d_6$) δ: 11.2 (br s, 1H, NH), 9.74 (s, 1H,), 9.02 (s, 1H, CHN), 8.40 (s, 1H, SCH), 7.78 (d, 2H), 7.10 (d, 1H). m/z 202 (M), 203 (M+1).

3-(2,3-dihydrobenzofuran-5-yl)-1H-pyrazolo[3,4-d]pyrimidine(3j)
^{1}H NMR (300 MHz, $CDCl_3$) δ: 9.70 (s, 1 H, NCHN), 9.02 (s, 1H, NCH), 7.61 (s, 1 H, Ar-H), 7.46 (d, 1H, Ar-H). 6.52 (d, 1 H, Ar-H), 4.60 (t, 2 H, OCH_2), 3.23 (t, 2 H, Ar-CH_2). m/z 238 (M), 239 (M+1).

3-(2-(cyclopropylmethoxy) phenyl)-1H-pyrazolo[3,4-d]pyrimidine(3k)
^{1}H NMR (300 MHz, $CDCl_3$) δ: 9.70 (s, 1H), 9.02 (s, 1H), 7.53 (d, 1H, Ar-H), 7.25-7.18 (m, 1H, Ar-H), 6.97 - 6.90 (m, 2H), 3.90 (d, 2H, OCH_2), 1.38-1.33(m, 1H, CH-cycloprapane), 0.72-0.65 (m, 2H, CH_2),0.40 - 0.35(m, 2H, CH_2). m/z 266 (M), 267 (M+1).

3-(2-chlorophenyl)-1H-pyrazolo [3,4-d]pyrimidine(3l)
^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.70 (s, 1 H, NCHN), 9.02 (s, 1H, NCH), 7.47 (d, 1 H, Ar-H), 7.45 (d, 1 H, Ar-H), 7.31- 7.24-7.23 (m, 3H, Ar-H). m/z 230(M), 231 (M+1).

3-(4-fluorophenyl)-1H-pyrazolo [3, 4-d] pyrimidine (3m)
^{1}H NMR (400 MHz, dmso-d6) δ: 9.65 (s, 1 H, NCHN), 9.02 (s, 1H, CHN), 8.23 (d, 2H, Ar-H), 7.41(d, 2 H, Ar-H), MS: m/z 214 (M), 215 (M+1).

3-(3-fluorophenyl)-1H-pyrazolo [3,4-d]pyrimidine(3n)
^{1}H NMR (400 MHz, dmso-d6) δ: 9.65 (s, 1 H, NCHN), 9.02 (s, 1H, CHN), 8.0 (d, 1H, Ar-H), 7.8(d, 1 H, Ar-H), 7.61(t, 1H, Ar-H), 7.40 (, 1H, Ar-H). MS: m/z 214 (M), 215 (M+1).

3-(3, 4-dimethoxyphenyl)-1H-pyrazolo [3,4-d]pyrimidine(3o)
^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.67 (s, 1 H, NCHN), 9.02 (s, 1H, CHN), 6.98 (d, 1 H, Ar-H), 6.90 (d, 1 H, Ar-H), 3.94 (s, 3H, OCH3), 3.90 (s, 3H, OCH_3). MS: m/z 256 (M), 257 (M+1).

3-(2-ethoxy-5-fluorophenyl)-1H-pyrazolo [3,4-d]pyrimidine(3p)
^{1}H NMR (300 MHz, $CDCl_3$) δ: 9.67 (s, 1 H, NCHN), 9.02 (s, 1H, CHN), 7.26-7.21 (m, 1 H, Ar-H), 6.91-6.86 (m, 2H, Ar-H), 4.13 (t, 2 H, OCH_2), 2.89 1.53-1.47(m, 2H, CH_3). MS: m/z 258 (M), 259 (M+1).

3-(3-ethoxy-5-fluorophenyl)-1H-pyrazolo [3,4-d]pyrimidine(3q)
^{1}H NMR (300 MHz, $CDCl_3$) δ: 9.68 (s, 1 H, NCHN), 9.02 (s, 1H, CHN), 7.11-6.97 (m, 3 H, Ar-H), 4.11 (m, 2 H, OCH_2), 1.54-1.45 (m, 2 H, CH_3). MS: m/z 258 (M), 259 (M+1).

3-(3,5-difluorophenyl)-1H-pyrazolo[3,4-d]pyrimidine(3r)
^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.68 (s, 1 H, NHCN), 9.02(s, 1H, CHN), 7.0 (d, 2 H, Ar-H), 6.67 (t, 1H, Ar-H). MS: m/z 232 (M), 233(M+1).

References:-

1. M.B.Tollefson, B.A.Acker, E.J. Jacobsen, R.O.Hughes, J.K. Walker, Bioorg. Med. Chem. Lett, 20, (**2010**), 3120. b. A.A, Aly, I.A.G. El-Karim, Journal of the Korean Chemical Society, 05, (**2011**), 05.
2. A.V. Ivachtchenko, D.E. Dmitriev, E.S. Golovina, E.S. Dubrovskaya, M.G. Kadieva, A.G, Koryakova V.M. Kysil, O.D.Mitkin, O.D., S.E. Tkachenko, I.M.Okun , , A.A. Vorobiov, Bioorg. Med. Chem. Lett, 20, (**2010**) 2133.
3. M. Bakavoli , G. Bagherzadeh , M. Vaseghifar, A.Shiri, M.Pordel, M. Mashreghi,
4. P.Pordeli, . M. Araghi, Bioorg. Med. Chem. Lett, 4, (**2010**) 647.
5. K.J. Curran, J.C. Verheijen, Joshua Kaplan, D.J. Richard, L.Toral-Barza,I.J. Hollander, J.Lucas, S. Ayral-Kaloustian, K.YU. Arie Zask, Bioorg. Med. Chem. Lett, 20, (**2010**) 1440.
6. kyon Kim, Jong Hwan Song, Chang Min Park, Joon Won Jeong, Hyung Rae Kim, Jin Ryul Ha, Zaesung No, Young-Lan Hyun, Young Sik Cho, Nam Sook Kang, Dong Ju Jeon, Bioorg. Med. Chem. Lett, 20, (**2010**) 922.
7. L.Yuan, C.W. Song, L. Ying, L. Dong, S. Yin, European Journal of Medicinal Chemistry, 67, (**2013**) ,152 .
8. S. Schenone, C. Brullo, O. Bruno, F. Bondavalli, L. Mosti, G. Maga, E. Crespan, F.Carraro, F.Manetti, C. Tin- tori, European Journal of Medicinal Chemistry, 43, (**2008**), 2665.
9. Asma Agrebi1, Fatma Allouche, Hamadi Fetoui and Fakher Chabchoub, Mediterranean Journal of Chemistry, 3, (**2014**), 864-876
10. Ana M. F. Oliveira-Campos, Abdellatif M. Salaheldin, and Lígia M. Rodrigues, ARKIVOC , (**2007**), 92-100.
11. Xiaohong Zhang, Qiulian Lin and Ping Zhong, Molecules, 15, (2010), 3079-3086
12. Phoebe, F. Lamie, Int. J. Pharm. Sci. Rev. Res, 24, (2014), 208-214.
13. Arun Goyal, Harvinder Singh Sohal, Sanjay Kumar, Rajshree Khare, IOSR Journal of Applied Chemistry, 7 (**2014**), 63-66.
14. Mehdi Bakavoli, Ghodsieh Bagherzadeh, Maryam Vaseghifar, Ali Shiri, Mehdi Pordel,
15. Mansour Mashreghi, Parvaneh Pordeli, Maryam Araghi, European Journal of Medicinal Chemistry, 45, (**2010**), 647–650