Research article Available online www.ijsrr.org ISSN: 2279–0543

International Journal of Scientific Research and Reviews

Imidazole mediated facile synthesis of 2-thiopyridines using non-conventional method

Mohsin Abdul Aziz*and Maqdoom Farooqui

Post Graduate and Research Centre, Dr. Rafiq Zakaria Campus, Maulana Azad College, Rouza Baugh, Aurangabad-431001 (M.S.) India
*E-mail: maaziz114@rediffmail.com

ABSTRACT:

This work describes a four component reaction of aldehydes, acetophenones, thiophenols and malononitrile under microwave conditionfor the synthesis of 2-thiopyridines in presence of imidazole as an organocatalyst. This process involves an almost neutral reaction medium and provides product 2-thiopyridinesin high yields with short reaction time.

KEYWORDS: Chalcone, Thiophenol, Malononitrile, Imidazole, Pyridine.

***Corresponding author**

Mohsin Abdul Aziz

Post Graduate and Research Centre,

Dr. Rafiq Zakaria Campus, Maulana Azad College,

Rouza Baugh, Aurangabad-431001 (M.S.) India

*E-mail: maaziz114@rediffmail.com

INTRODUCTION:

The pyridine nucleus is of a great interest because the ring is major member component in a series of biological privileged compounds both for naturally occurring as well as synthetic scaffolds with measurable complexity[1]. A thiopeptide antibiotic cyclothiazomycin has a considerable attention due to their intriguing structure and bacterial protein inhibition potentially preventing the growth of gram positive bacteria *S-aureus*[2]. The antibiotic bears a central 2, 3, 6-tri-substituted pyridine ring as structural motif shown in figure-1, which is structurally similar to berninamycin, eninthiocin, promothiocins, radamycin, and thioxamycin[3-4].

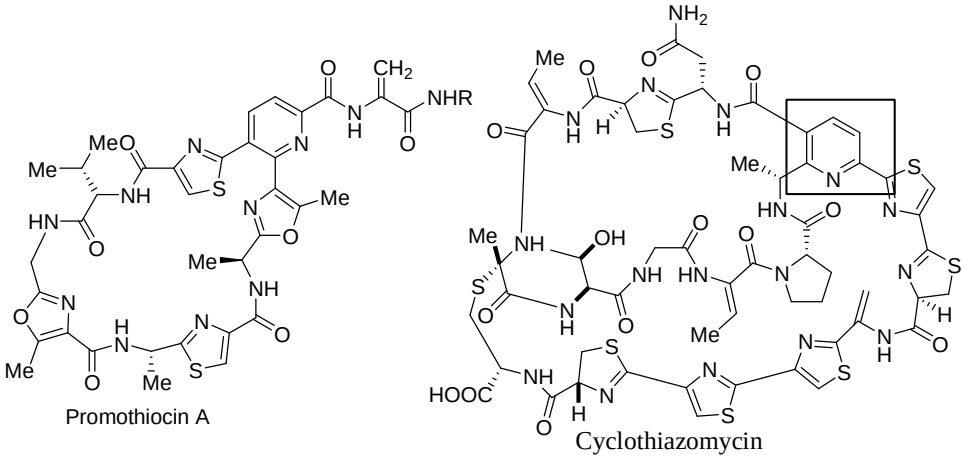


Figure-1: Structures of pyridine thiopeptide antibiotic

Pyridine scaffolds are important class of nitrogen containing heterocycles isolated from many natural product and found in active pharmaceuticals and functional compounds[5-8], Diploclidine[9], Nakinadine[10] are structurally diverse natural product having pyridine as core structural moiety, pyridine containing active pharmaceutical ingredient Atazanavir[11] act as HIV drug chronic myelogenous leukemia, camptothecin is a cytotoxic pyridine structure based alkaloid which inhibits the DNA enzyme topoisomerase-I (topo-I) and can act as anticancer drugs its different analogues like Irinotecan can also be used as cancer therapeutics[12] depicted in figure-2.

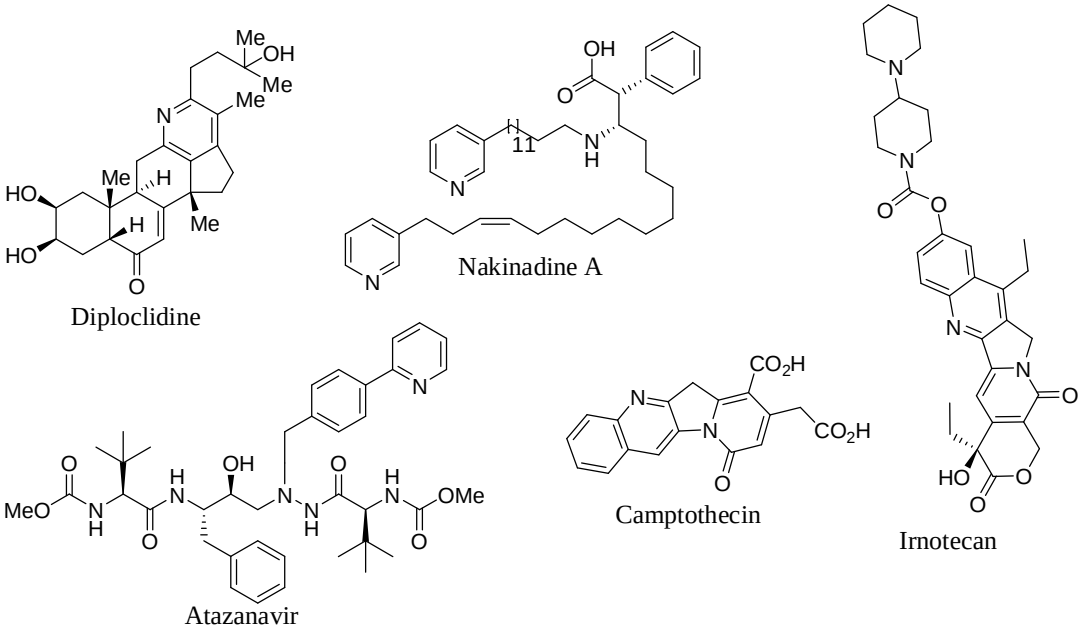


Figure-2: Pyridine containing natural products

Pyridine and cyanopyridine scaffolds are privileged intermediates in nicotinamide, nicotinic acid, and isonicotinic acid[13], and also exhibits in many synthetic organic entities[14] with wide spectrum of biological activities[15-16].The pharmacological and physiological active non glycosidic cardiotonic agent Milrinone[17-18], and substituted pyridines active against herpes virus, and human immune deficiency virus[19-20], the alkaloid structure Ricinine, pyridine structure based anti-tubercular[21], anti-cancer[22-23], Adenosine receptor antagonists[24], antihypertensive[25], antihistaminic[26], anti-inflammatory[27], analgesic and anti-pyretic[28-29]properties based motifs are exemplified in figure-3.

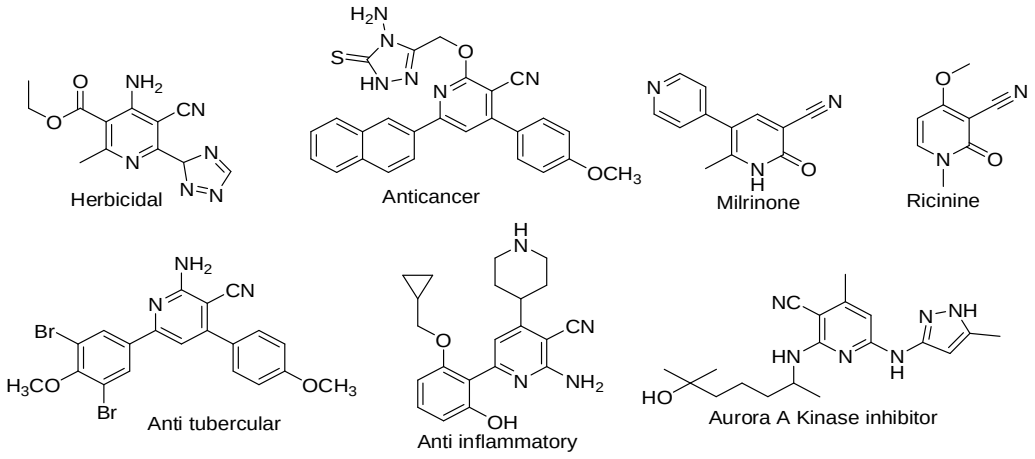


Figure-3:Cyanopyridine motif containing medicinal scaffolds

Among several cycnopyridines, synthesis of 2-thiopyridines tethered with cyano functionality is very limited. X. H. Wang and *et al* has reported an efficient and direct synthesis of 2-thiopyridines by three component coupling under microwave irradiation[30], the synthesis concludes a series of 2-p-tolylthiopyridines scaffolds via three component direct condensation of chalcones, malononitrile, and 4-methylthiophenol catalyzed by trimethylamine and DMF as solvent under microwave irradiation. The synthetic strategy claims promising methodology with comparable results in terms of reaction time, yield and operational simplicity. Similarly, M.R.P Heravi and Amir Soufi has reported a four component condensation of substituted acetophenones, substituted aldehydes malononitrile and arylthiol by employing a non-ionic surfactant (Triton X-100)[31] with good to moderate yield.

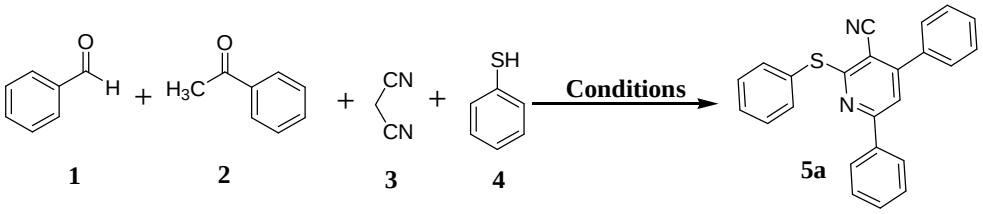
In multicomponent reactions imidazole has been explored as an efficient organocatalyst.[32]In light of green and sustainable chemistry we have developed an efficient method using imidazole as an organocatalyst employing environmentally benign PEG-400 as a solvent under microwave irradiation.

RESULTS AND DISCUSSIONS

For our initial study benzaldehyde (0.5 mmol), acetophenone (0.5 mmol), malononitrile (0.5 mmol) and thiophenol (0.5 mmol) was chosen as a reaction model. Under catalyst-free conditions with PEG-400 as a solvent and at room temperature the above combinations provided the desired product **5a** only in trace amount after 24h. (Table 1, entry1). With the same substrates combination and at the same reaction condition when imidazole 10 mol% as a catalyst was added; 15% yield of the desired product was obtained (Table 1, entry2). Increase in yield 60% was observed in heating condition (Table1, entry3) that also reduced the reaction time. Increase in loading of imidazole increases the yield and reduces the reaction time (Table1, entry 4). Interestingly a trial reaction of this model substrates in PEG-400 medium and with imidazole catalyst in presence of microwave irradiation showed very significant increase in yield (92%) within 15 min (Table1, entry5). The effect of catalyst loading was also checked. Lowering the amount of imidazole from 20 mol% to 10 mol% simultaneously lowers the yield of the desired product (Table1, entry6). Similarly effect of temperature on yield of the product was also checked and it was found that lowering the temperature lowed the yield of the product (Table1, entry 7). Further we have checked the reaction model with various organic/inorganic and acid/base catalysts such as TEA, DABCO, Benzoic acid, KOH, HCl (Table1, entries 8-13) but were not so efficient compared to imidazole. Finally, we have also screened the model reaction with polar protic solvents such as acetic acid, H_2O, and ethanol (Table 1,

entries 14-16) and polar aprotic solvents such as DMF, THF, DMSO and acetonitrile respectively (Table1, entries 17-20) but no significant impact on yield was observed. Non-polar solvent such as toluene (table1, entry 21) was tested in this reaction but yields was discouraging.

Table1:Optimization of reaction conditions[a]



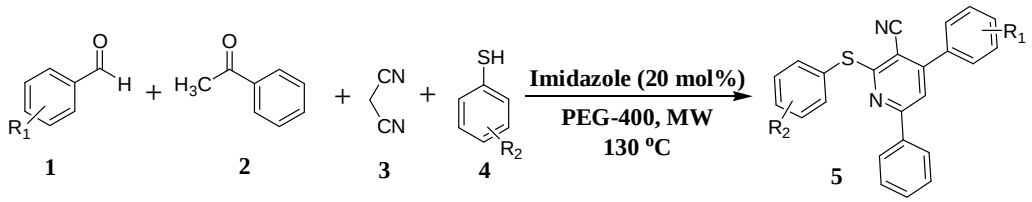
Entry	Catalyst	Reaction conditions[a]	Yield[b](%)
1	---	PEG-400 rt 24h	trace
2	Imidazole (10 mol%)	PEG-400 rt 24h	15
3	Imidazole (10 mol%)	PEG-400, 130°C, 12h	60
4	Imidazole (20 mol%)	PEG-400, 130°C, 8h	75
5	**Imidazole (20 mol%)**	**PEG-400, MW, 130°C, 15 min**	**92**
6	Imidazole (10 mol%)	PEG-400, MW, 130°C, 15 min	80
7	Imidazole (20 mol%)	PEG-400, MW, 100°C, 15 min	75
8	L-Proline (20 mol%)	PEG-400, MW, 130°C, 15 min	55
9	TEA (20 mol%)	PEG-400, MW, 130°C, 15 min	80
10	DABCO (20 mol%)	PEG-400, MW, 130°C, 15 min	70
11	Benzoic acid (20 mol%)	PEG-400, MW, 130°C, 15 min	trace
12	KOH (20 mol%)	PEG-400, MW, 130°C, 15 min	65
13	HCl (20 mol%)	PEG-400, MW, 130°C, 15 min	trace
14	Imidazole (20 mol%)	Acetic acid, MW, 130°C, 15 min	35
15	Imidazole (20 mol%)	H_2O, MW, 130°C, 15 min	69
16	Imidazole (20 mol%)	Ethanol, MW, 130°C, 15 min	70
17	Imidazole (20 mol%)	DMF, MW, 130°C, 15 min	30
18	Imidazole (20 mol%)	THF, MW, 130°C, 15 min	62
19	Imidazole (20 mol%)	DMSO, MW, 130°C, 15 min	43
20	Imidazole (20 mol%)	Acetonitrile, MW, 130°C, 15 min	65
21	Imidazole (20 mol%)	Toluene, MW, 130°C, 15 min	15

[a]Reaction of benzaldehyde (0.5 mmol), acetophenone (0.5 mmol), malononitrile (0.5 mmol) and thiophenol (0.5 mmol) at different reaction conditions.[b] Isolated yield

From the optimization table-1 imidazole as a catalyst and PEG-400 as a solvent was observed to be the most suitable for this type of reactions under microwave heating.

With the optimized conditions in hand we turned our attention toinvestigatethescopeandgeneralapplicabilityofthismethodologybycarryingoutthesynthesisof 2-thiopyridinesusingdifferentaldehydesandthiols (Table2).

Table2: Synthesis of substituted 2-thiopyridines[a]



1 2 3 4 5

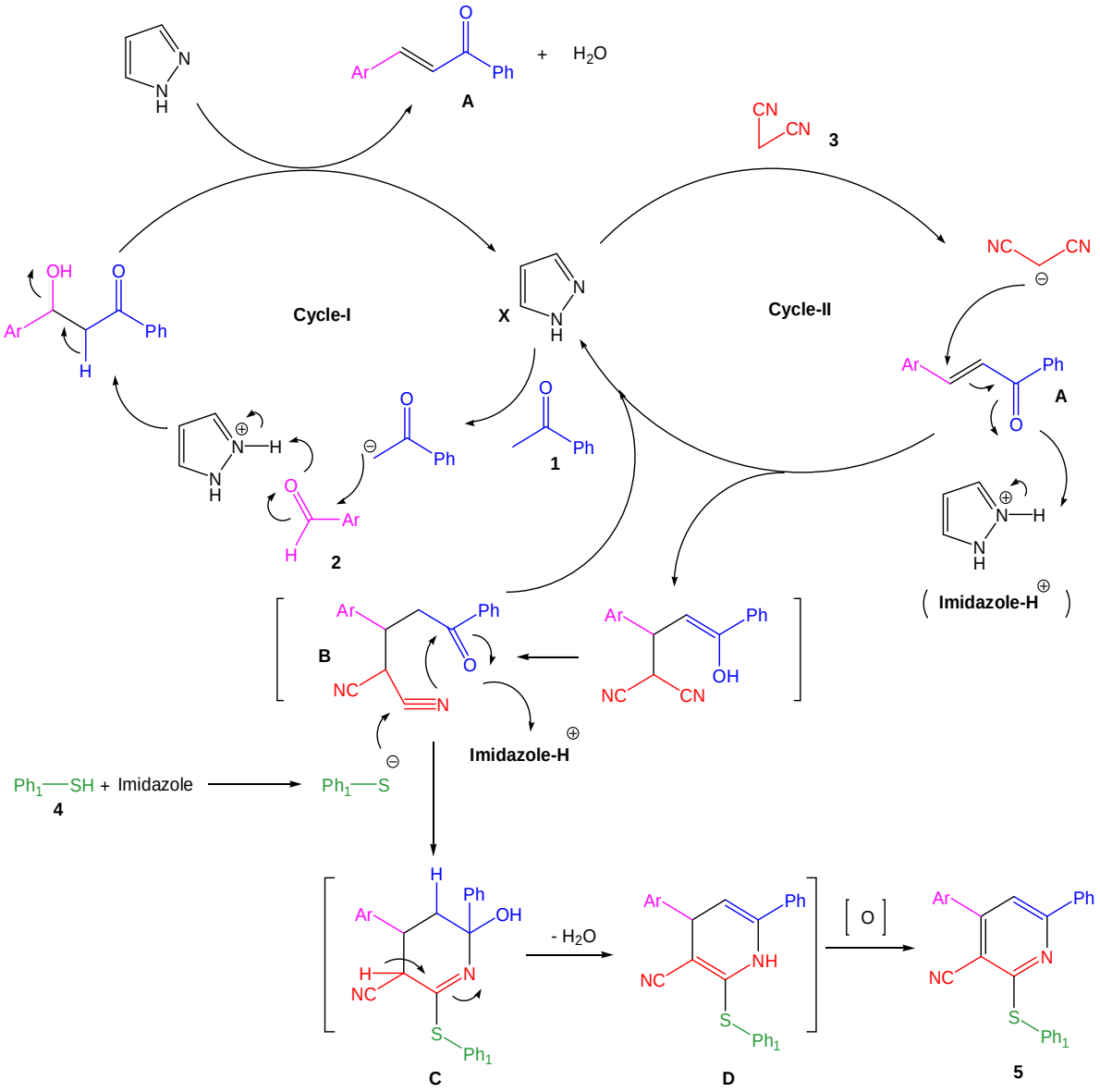
Entry	R_1	R_2	Product	Time (min)	Yield (%)[b]	Melting Point (°C)
1	H	H	5a	15	90	234-236^0 C
2	4-Cl	H	5b	15	92	191-193^{0}C
3	2-Cl	H	5c	15	91	187-189^{0}C
4	4-CH_3	H	5d	15	90	241-243^{0}C
5	2-CH_3	H	5e	15	89	236-238^{0}C
6	4-NO_2	H	5f	15	92	247-249^{0}C
7	4-Cl	4-CH_3	5f	15	92	194-196^{0}C
8	4-NO_2	4-CH_3	5h	15	91	264-266^{0}C
9	4-OMe	4-CH_3	5i	15	91	251-253^{0}C

[a] Reaction of aldehydes (0.5 mmol), acetophenone (0.5 mmol), malononitrile (0.5 mmol), thiols (0.5 mmol), imidazole (20 mol%), PEG-400 (1.0 ml) in MW at 130 °C for 15 min. [b] Isolated yield

A wide range of aromatic aldehydes such as unsubstituted as well as tethered with either electron-withdrawing or electron-donating groups were tested and was found to be suitable in this reaction (Table 2, entries 1-9) and corresponding 2-thiopyridine were obtained in good yields. Aliphatic aldehyde such as formaldehyde was also tested in this reaction but resulted in inseparable mixtures. Apart from simple thiophenol (Table 2, entries 1-6) that resulted in good yields 4-methyl thiophenols were aslo tested and produced the desired product substituted 2-thiopyridines in good yield (Table2, entries 7-9). It is to mention that in all the cases except in case of aliphatic aldehydes the reactions were found remarkably clean and isolation of the products was easy. All products were characterized by IR, ^{1}H NMR, ^{13}C NMR and by elemental analysis.

PROPOSED MECHANISM

In the first catalytic cycle-I, we believed that imidazole promotes to condense acetophenone (**1**) and aldehyde (**2**) to form the intermediate **A** as shown in the mechanism (scheme-1). In the next catalytic cycle-II malononitrile undergoes Michael addition with the in situ generated intermediate A. and forms an another intermediate **B**. Thiophenol subsequently attacks to the nitrile functionality of the intermediate B and forms a cyclic intermediate C which further on dehydration and tautomerization forms the an another intermediate D a 1,4-dihydropyridine. In the final step this intermediate 1,4-dihydropyridine forms the desired pyridine molecule upon aerial oxidation.



Scheme-1: Imidazole catalyzed 2-thiopyridine

EXPERIMENTAL

GENERAL

All reagents were used without further purification and were procured from commercial sources. Microwave irradiation was carried out with Initiator 2.5 microwave synthesizers from Biotage (Uppsala, Sweden). A Shimadzu FTIR spectro-photometer was used for recording IR spectra. ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker 400MHz spectrometers in DMSO-d6 using TMS asan internal reference. Elemental analysis was carried out in a Perkin Elmer 2400

automatic CHN analyzer or Elementer Vario ELIII. All compounds were characterized by the ir meltingpoints, ^{1H} NMR and ^{13}C NMR spectra and elemental analysis.

General procedure for the synthesis of 2-amino-4-(aryl/alkyl)-4H-benzo[h]chromene-3 carbonitrile (5a-5i)

A mixture of aldehyde (0.5mmol), acetophenone (0.5 mmol), malononitrile (0.5mmol), thiols (0.5 mmol) and imidazole (20 mol%) in PEG-400 (1.0 mL) was taken in a sealed 0.5-2.0 mL vial containing aTeflon-coated magnetic stirring bar and irradiated at 130 ^{o}C at 120W power for the appropriate time (Table 2) using a microwave reactor. The resulting mixture was cooled to 50 ^{o}C by an air flow. After completion of the reaction, 2.0 ml ethanol was added for the precipitation of the product. The product was separated by filtration and ethanol was removed from the filtrate using rotary evaporator. Finally recovered PEG-400 was washed with diethyl ether to obtain clean PEG-400. This recovered PEG-400 was further used for the next cycle and the same procedure was repeated two more times without significant loss of activity. The%ofyieldobtainedindifferentrunswas90(1st),90(2nd)and85%(3rd)respectively.

4,6-Diphenyl-2-(phenylthio)nicotinonitrile (5a): White solid; 90% yield; mp 234-236^{o}C; IR (KBr): 3110, 2216, 1572, 1527, 1454, 1387, 1090, 978, 865, 748, 732 cm^{-1}; ^{1}H NMR (DMSO-d$_6$, 400 MHz): δ = 8.68 (d, 2H, *J* = 7.4 Hz, ArH), 7.94 (d, 2H, *J* = 8.1 Hz, ArH), 7.85-7.63 (m, 3H, ArH), 7.52-7.45 (m, 3H, ArH), 7.41-7.30 (m, 2H, ArH), 7.31-7.27 (m, 4H, ArH); ^{13}C NMR (DMSO-d$_6$, 100 MHz): δ = 180.1, 160.3, 159.4, 139.7, 138.3, 137.9, 136.8, 135.7, 134.8, 133.5, 132.3, 131.0, 130.4, 129.6, 128.3, 126.3, 125.4, 124.3, 123.1, 122.5, 121.4, 117.2, 112.8, 101.6; Anal. Calcd. for $C_{24}H_{16}N_2S$: C, 79.09; H, 4.42; N, 7.69; Found: C, 79.11; H, 4.37; N, 7.66.

2-(p-Tolylthio)-6-(4-methoxyphenyl)-4-phenylpyridine-3-carbonitrile (5i): IR (KBr): 3019, 2974,2218, 1611, 1571, 1530, 1494, 1408, 1371, 1317, 1171,1021, 837,809,772,756,699 cm^{-1};^{1}HNMR(DMSO-d$_6$): δ = 7.89-7.87 (m,3H,ArH),7.76-7.75 (m,2H,ArH),7.62-7.58 (m,5H,ArH), 7.38 (d,*J* = 8.1 Hz,2H,ArH), 6.91 (d,*J* = 8.7 Hz,2H,ArH), 3.80 (s,3H,OCH_3), 2.47 (s,3H,CH_3).Anal.Calcd.for$C_{26}H_{20}N_2OS$:C,76.44;H,4.93;N,6.86;Found:C,76.48;H,4.89;N, 6.81.

ACKNOWLEDGEMENT:

Authors are grateful to Postgraduate and Research Centre-Maulana Azad College for providing basic research facilities to carry out this work. Authors are also grateful to Wockhardt Ltd and SAIF Punjab University Chandigarh for the IR, NMR and CHN analysis of the synthesized molecules.

CONCLUSIONS:

In summary, the present work describes imidazole-mediated multicomponent reaction sinvolving in situ-generated chalcone of aldehydes and acetophenone intermediates for easy access to a wide range of highly substituted 2-thiopyridines. This protocol has the advantages of a wide scope of substrates, ready availability, lower cost of the catalyst, operational simplicity, short reaction time and no need for column chromatographic separation with good to high isolated yields.

REFERENCES:

1. (a) Boger, D. L.; Nakahara, S. *J. Org. Chem.***1991**, 56, 880-884. (b) Boger, D. L.; Kasper, A. M. *J. Am. Chem. Soc.***1989**, 111, 1515-1517. (c) Zhang, T. Y.; Stout, J. R.; Keay, J. G.; Scriven, E. F. V.; Toomey, J. E.; Goe, G. L. *Tetrahedron*. **1995**, 51, 13177-13184. (d) Ma, X.; Gang, D. R. *Nat. Prod. Rep.* **2004**, 21, 752-772. (e). Altaf, A. A.; Shahzad, A.; Gul, Z.; Rasool, N.; Badshah, A.; Lal, B.; Khan, E. *J. Drug Des. Med. Chem*. **2015**, 1, 1-11. (f). Bull, J. A.; Mousseau, J. J.; Pelletier, G.; Charette, A. B. *Chem. Rev.***2012**, 112, 2642-2713. (G). Guo, Z. *Acta Pharm Sin B.* **2017**, 7, 119-136.
2. Bagley, M. C.; Dale, J. W.; Merritt, E. A.; Xiong, X. *Chem. Rev.* **2005,** 105, 685-714.
3. Zou, Y.; Liu, Q.; Deiters, A. *Org. Lett.* **2011**, 13, 4352-4355.
4. (a). Bagley, M.C.; Bashford, K.E.; Hesketh, C.L.; Moody, C.J.*J. Am. Chem. Soc.* **2000**,122, 3301-3313. (b). Zou, Y.; Liu, Q.; Deiters, A. *Org. Lett.***2011**, 13, 4352-4355.
5. Jones,G. Katritzky,A.R.; Rees,C.W.; Scriven, E.F.V.; McKillop, A. *Comprehensive Heterocyclic Chemistry II, Pergamon, Oxford*,**1996,**Vol. 5, 167-243.
6. (a). Henry, G.D. *Tetrahedron*.**2004,** 60, 6043–6060. (b). Ye, H.; Chen, D.; Liu, M.; Su, S.-J.; Wang, Y.-F.; Lo, C.-C.; Lien, A.; Kido, J. *Adv. Funct. Mater*. **2014**, 24, 3268-3275,
7. Joule, J.A.;Mills, K. *Heterocyclic Chemistry, Blackwell Science, Cambridge,***2000**, 63-120.
8. Michael, J.P. *Nat. Prod. Rep.***2005,** 22, 627-646.
9. Jayasinghe, L.; Jayasooriya, C.P.; Hara, N.; Fujimoto, Y. *Tetrahedron Lett.***2003**, 44, 8769-8771. (b). Hill, M. D. *Chem. Eur. J*. **2010**, 16 , 12052-12062
10. (a). Kubota,T. Nishi,T. Fukushi, E. Kawabata,J. Fromont, J. Kobayashi, J. *Tetrahedron Lett.* **2007**, 48, 4983-4985. (b). Garg, Y.; Pandey, S. K.*RSC Adv*. **2016**, 6, 25913-25917.
11. Harrison,T. S.; Scott, L.J. *Drugs*. **2005**, 65, 2309-2336.
12. Takimoto, C.H.; Calvo, E.; Pazdur, R.; Wagman L.D.; Camphausen, K.A.; Hoskins, W.J.*Cancer Management: A Multidisciplinary Approach.* 11 ed. **2008**.

13. (a). Shishoo, C. J.; Devani, M. B.; Bhadti, V. S.; Ananthan, S.; Ullas, G. V. *Tetrahedron Lett.***1983**, 24, 4611. (b). Gouda, M. A.; Berghot, M. A.;Ghani, G. E. A.; Khalil, A. E.-G. *Synth. Commun*. **2013**, 297-330.
14. Aly, A. A. *Phosphorus, Sulfur, and Silicon.***2006,** 181, 2395-2409.
15. Alice Bernardino, M. R.; Pinheiro, L. C. S.; Rodrigues, C. R.; Loureiro, N. I.; Castro, H. C.; Rangel, A. L.; Lopes, J. S.; Borges, J. C.; Carvalho, J. M.; Romeiro, A. G.; Ferreira, V. F.; Frugulhetti, I. C.P.P.; Vannier-Santosv, M. A. *Bioorg. Med. Chem.***2006,** 14, 5429-5770.
16. (a). Boschelli, D. H.; Wu, B.; Barrios, S. A. C.; Durutlic, H.; Ye, F.; Raifeld, Y.; Golas, J. M.; Boschelli, F. *J Med Chem.***2004,** 47, 6666-6668. (b). Manna, K.; Ghosh, P. S.; Das, M.; Banik, U.; Das, A. *Int. J. Pharm. Sci. Res*. **2014**, 5, 2158-2163.
17. Shiae, M. J.; Shyu, L. M.; Chen, C.F. *Heterocycles.***1990,** 31, 523.
18. (a). Hopkins, S. J. *Drugs of Today*.**1990,** 26, 295. (b). Koster, G.; Bekema, H. J.; Wetterslev, J.; Gluud, C.; Keus, F.; Horst, I. C. C. *Intensive Care Med*. **2016**, 42, 1322-1335.
19. Saad, H. A.; Mokbil, M. N.; El-Gendy, A. M.; Haikal, A. Z. *Synth. Commun*.**2002,** 32, 1189.
20. Dolle, V.; Fan, E.; Nguyen, C. H.; Bisagni, E. *J. Med. Chem.***1995,** 38, 4679.
21. Hoefling, W. L.; Elhaner, D.; Reckling, E. *Chem. Abstr.*,**1965,** 63, 6979. (b). Tang, X.; Liu, P.; Li, R.; Jing, Q.; Lv, J.; Liu, L.; Liu, Y. *BCPT*, **2015**, 117, 186-194.
22. Toyota, K.; Shinkai, H.; Etou, H.; Kamimura, A.; Eguchi, C.; Oosumi, K.;Turuo, T. Eur. Pat. Appl. EP 330,470 (Cl. C07D211/90) 30 Aug. **1989**. (b). Salib, J. Y.; Kassem, M. E. S.; Raslan, M. *J. Pharm. Res*. **2014**, 8, 764-1767.
23. Wang, G. T; Wang, X.; Wang, W.; Hasvold, L. A.; Sullivan, G.; Hutchins, C. W.;O'Conner, S.; Gentiles, R.; Sowin, T.; Cohen, J.; Gu, W. Z.; Zhang, H.;Rosenberg, S. H.; Sham, H. L. *Bioorg. Med. Chem. Lett.***2005,** 15, 153-158.
24. Mantri, M.; de Graaf, O.; van Veldhoven, J.; Goblyos, A.; von Frijtag Drabbe Kunzel, J. K.; Mulder-Krieger, T.; Link, R.; de Vries, H.; Beukers, M. W.; Brussee, J.; Ijzerman, A. P. *J Med Chem.***2008**, 51, 4449-4455.
25. Baldwin, J. J.; Engelhardt, E. L.; Hirschmann, R.; Ponticello, G. S.; Atkinson,J. G.; Wasson, B. K.; Sweet, C. S.; Scriabine, A. *J. Med. Chem.***1980**, 23, 65-70.
26. Krauze, A.; Vitolina, R.; Zarins, G.; Pelcers, J.; Kalme, Z.; Kimenis, A.;Duburs, G. *Khim. Farm. Zh.* **1985**, 19, 540-545.
27. (a). Quintela J. M, Peinador, C.; Botana, L.; Estevez, M.; Riguera, R. *Bioorg Med Chem.***1997**, 5, 1543-1553. (b). Kumar. N.; Chauhan, A.; Drabu, S. *Biomed Pharmacother*. **2011**, 65, 375-380.

28. (a). Manna, F.; Chimenti, F.; Bolasco, A.; Filippelli, A.; Palla, A.; Filippelli,W.; Lampa, E.; Mercantini, R. *Eur. J. Med. Chem.***1992,** 27, 627-632. (b). Ayvaz, S.; Cankaya, M.; Atasever, A.; Altuntas, A. *J. Enzyme Inhib. Med. Chem*. **2013**, 28, 305-310.
29. (a). Manna, F.; Chimenti, F.; Bolasco, A.; Bizzarri, B.; Filippelli, W.; Filippelli,A.; Gagliardi, L. *Eur. J. Med. Chem.***1999,** 34, 245-254. (b). Patoliya, P. U.; Gohel, V. P.; Purohit, D. M.; Patolia, V. N. *J. Chem. Pharm.Res*. **2015**, 7, 182-186.
30. Wang, X. H.; Cao, X. D.; Tu, S. J.; Zhang, X. H.; Hao, W. J.; Yan, S.; Wu, S. S.; Han, Z. G.; Shi, F. *J. Heterocyclic Chem.***2009**, 46, 886-889.
31. Heravi, M. R. P.; Soufi, A. *Chinese Chemical Letter*. **2015,** 26, 263-266.
32. Khan, M. N.; Pal, S.; Karamthulla, S.; Choudhury, L. H. *RSC Adv.***2014**, 4, 3732-3741.