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Green synthesis of imidazo[1,2-a]pyridines in aqueous medium

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Abstract: *A simple and economic way of synthesis of imidazo[1,2-a]pyridines using 2-aminopyridine and phenacylbromide derivatives in aqueous medium by microwave irradiation has resulted in bridged azaheterocycles in good to excellent yields. The synthesised derivatives were found to be fluorescent in nature and show antibacterial activity also.*

Keywords*: Antibacterial activity, Azaheterocycles, Fluorescence,Green chemistry,*

Introduction

Imidazo[1,2-a]pyridines due to their interesting biological activities are important structural part in many natural and synthetic bioactive molecules. In several drug formulations imidazo[1,2-a]pyridines are widely used. Imidazo[1,2-a]pyridines have received a significant attention in pharmaceutical industry owing to their interesting biological activities including antibacterial[1],antifungal[2],antiviral[3-5] and anti-inflammatory[6] activity.

Reactions in aqueous medium in organic synthesis plays a major role for a clean synthetic procedure. A number of reactions in water medium has been reported earlier[7,8]. This involves a clean procedure that avoid usage of harmful organic solvents. Several investigations were conducted on the synthesis of the imidazo[1,2-a]pyridine ring systems[9-16].

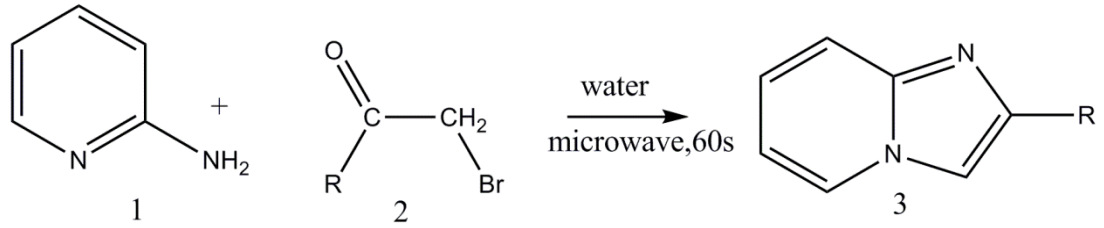
Several imidazo[1,2-a]pyridine derivatives were reported to be fluorescent in nature[17].Further studies were conducted on the fluorescence behaviour of imidazo[1,2-a]pyridine derivatives. In the present study a mixture of 2-aminopyridine and phenacylbromide derivatives were subjected to microwave irradiation in aqueous medium to give imidazo[1,2-a]pyridines in good to excellent yields.

Experimental

Melting points were determined with a Metler melting point apparatus and are uncorrected. All reactions were carried out in a commercially available microwave oven (Samsung M183DN) operating at 300W. IR spectra were recorded on a Jasco FT/IR -4100 spectrometer using KBr. Mass spectra were recorded with a Waters-3100 spectrometer. ^{1}H NMR spectra were measured in DMSO at room temperature on BruckerAvance III 400MHz spectrometer. All fluorescence measurements were recorded on Jaz Ocean Optics spectrofluorometer. UV-Visible absorption spectra were performed using Spectro UV-Visible double beam UVD-3500 spectrophotometer Thin layer chromatography was carried out on aluminium foil coated with silica gel60 F254 (Merck) and column chromatography on silica gel; 70-230mesh (Merck). All reagents were obtained from commercial sources and used without further purification.

Materials and methods

The synthetic method adopted here is a microwave technique as reported earlier in the synthesis of cycl[3,2,2]azine derivatives[18]. A mixture of phenacyl bromide(1mmole)(0.199gm) and 2-aminopyridine (1mmole)(0.094gm)was mixed with 1ml of water in an Erlenmeyer flask and is fitted with a bent tube. The other end of the bent tube is connected to a receiver. The reaction mixture was irradiated for 60 seconds at 300W with intermittent irradiation for 30 seconds (reaction monitored by TLC). The viscous mass obtained was cooled to room temperature(Scheme 1). After completion of the reaction the crude products were purified by column chromatographic technique using dichloromethane as solvent. The products were recrystallized from methanol.



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R=a)C_6H_5,b)$C_6H_5NO_2$,c)C_6H_5Cl,d)$C_6H_5OCH_3$,e)$C_6H_5CH_3$,f)C_6H_5OH,g)C_6H_5Br,h)C_6H_5F

Scheme 1 Synthesis of 1-azaindolizines,3(a-h)

Finally, the structure of 4-bromoazaindolizine **3g** was proven by X-ray analysis (Fig. 1).

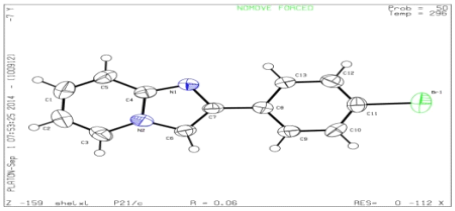

Fig.1 Crystal structure of 4- bromoazaindolizine

The analytical parameters of the synthesised compounds are presented in TABLE 1.

Table 1 Analytical parameters of the synthesised compounds

Compound	Yield (%)	M.P (^{0}C)	M^+ from mass spectra	Molecular formula
3a	62	126-127	193	$C_{13}H_{10}N_2$
3b	88	304-305	239	$C_{13}H_9N_2O_2$
3c	92	207-208	228.5	$C_{13}H_9N_2Cl$
3d	58	109-110	224	$C_{14}H_{12}N_2O$
3e	65	115-116	208	$C_{14}H_{12}N_2$
3f	66	143-144	210	$C_{13}H_{10}N_2O$
3g	96	200-202	271	$C_{13}H_9N_2Br$
3h	61	139-140	211	$C_{13}H_9N_2F$

Results and discussion

The method of synthesis describes an easy and convenient route for the synthesis of azaindolizines. Early methods needed tedious route of synthetic procedure, but this new method is quite simple and the products were obtained within a few minutes. The progress of reactions was monitored by TLC and imidazo[1,2-a]pyridine 3(a-h) were synthesised in good to excellent yield. The structures of all the synthesised fused imidazo[1,2-a]pyridine derivatives were confirmed by spectroscopic data. The physical and spectroscopic data of the reported compounds were comparable with literature. The method is a simple route for the preparation of bridgehead N heterocycles in water. This green chemistry approach is easy to handle, economic, nontoxic and thus makes it environment friendly.

The basic strength of azaindolizines depends both on the number and position of ring nitrogens. IR spectra of these compounds exhibit the characteristic NH absorption bands at about 3400 cm^{-1} and 3100 cm^{-1}. The ^{1}H-NMR spectra of these compounds reveal characteristic NH signals in the range of δ 8.71-8.89 and the signals of H-2 protons from pyrrolo ring at δ 6.8-7.1. The aromatic ring proton gave a doublet at 8.17 δ ppm it shows in spectrum due to the effect of nitrogen atom. The aromatic ring of the phenyl ring protons are on same atmosphere so these protons gave a multiplet at 7.63 δ ppm-7.97 δ ppm in spectra.

The ^{13}C values for methylene (-CH_2) carbon is observed between 40-60 δ ppm. Aromatic carban shows peaks between 110-150 δ ppm.

Further studies revealed the antibacterial activity of these derivatives. The antibacterial activity of the compounds were studied against Escherichia coli (NCIM 2343), Klebsiella pneumonia (NCIM 2707) and Staphylococcus aureus (NCIM 2127) which were chosen based on their clinical and pharmacological importance[19-23].

The bacterial strains obtained from Institute of Microbial Technology, Chandigarh, were used for evaluating antimicrobial activity. The sensitivities of the bacterial species to azaindolizines were determined by measuring the sizes of inhibitory zones (including the diameter of disc) on the agar surface around the discs, and values < 8 mm were considered as not active against microorganisms(Fig.2). The MIC values of the derivatives were also noted(TABLE 2).

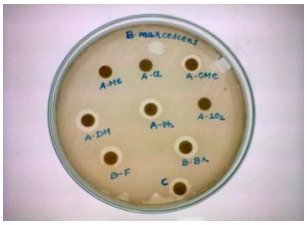

Fig.2 Zone of inhibition of bacteria against 2-azaindolizine derivative

Table 2. Minimum inhibitory concentration of bacteria against azaindolizine derivatives

Compound	Bacteria	Standard antibiotic (ampicillin) μg/ml	Control (Methanol) mg/ml	MIC(M)
3d	Klebsiella pneumoniae	1.0	Resistant	0.5
3e	Staphyllococcus aureus	0.01	25	0.125
3f	Escherchia coli	0.1	Resistant	0.125

The MIC of the sample was detected by serial dilution method[24]. The procedure was also repeated using the reference antibiotic ampicillin (5mg mL^{-1}). After incubation, the bacterial growth was determined as optical density (OD) at 600 nm in a UV visible spectrophotometer. The lowest concentrations without visible growth (OD600=0) were defined as concentrations that completely inhibited bacterial growth (MICs).

Several reports revealed the fluorescent nature of indolizine and similar compounds[25]. Fluorescence behaviour of the imidazo[1,2-a]pyridine derivatives were investigated and the compounds showed a fluorescence quenching behaviour in presence of metal ions. Selectivity of azaindolizine derivative was investigated against solutions of K^+,Ca^{2+}, $Mg^{2+,}$ Li^+, V^{2+}, $Pb^{2+,}$, $Fe^{2+}$and Fe^{3+} A drastic quenching in fluorescence intensity was observed by the addition of Fe^{3+} while not much change is observed by the addition of other metal ions(Fig.3).

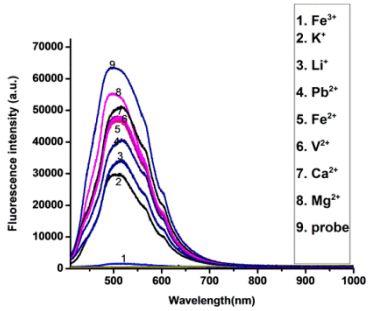

Fig.3 Quenching effect of imidazo[1,2-a]pyridine derivative in presence of various metal ions

The structure of imidazo[1,2-a]pyridine derivatives were further confirmed by spectral studies[26].

2-Phenylimidazo[1,2a]pyridine,3a $C_{13}H_{10}N_2$; Yield 62%; M^+193;Elemental Anal C-71.04,H-4.29,N-18.41 FoundC71.32,H5.09,N18.22;IR(KBr)cm^1:3055,1598,1285;^{1}HNMR400MHz((DMSO)7.17.5(m,4H),7.88(s,1H), 8.05(d,1H);^{13}CNMR400MHz(DMSO)108.3,113.2,114.5,115.2,122.3,123.3,128.7,128.8,129.0,143.5,144.2,145.1 .

2-(4-Nitrophenyl)-imidazo[1,2a]pyridine,3b $C_{13}H_9N_3O_2$; Yield 88%; M^+239; Elemental Anal C-72.10,H-4.24,N14.74FoundC72.76,H4.98,N14.34;IR(KBr)cm^1:2954,1598,1509,1333,1254;^{1}HNMR400MHz((DMSO)7. 2(d,1H),8.4(d,1H),5.0(s,1H);^{13}CNMR400MHz(DMSO)108.0,111.2,112.7,115.9,122.7,122.9,126.7,128.2,128.5, 140.1,142.2,144.4.

2-(4-Chlorophenyl)-imidazo[1,2a]pyridine,3c $C_{13}H_9N_2Cl$; Yield 92%; M^+228; Elemental Anal C-68.22,H-6.34,N20,32FoundC69,07,H5.78,N20.16;IR(KBr)cm^1:2990,1629,1253,737;^{1}HNMR400MHz((DMSO)8.2(d,1H) ,8.4(d,1H),δ6.676.82(m,1H),7.067.11(m,1H),7.65(d,1H),7.84(s,1H);^{13}CNMR400MHz(DMSO)109.3,112.8,112. 4,113.3,114.3,121.8,122,1,122.9,126.7,128.2,142.7,143.3,146.0.

2-(4-Methoxyphenyl)-imidazo[1,2a]pyridine,3d $C_{14}H_{12}N_2O$; Yield 58%; M^+224; Elemental Anal C-68.83,H-6.29,N15.5FoundC67.77,H5.68,N14.89;IR(KBr)cm^1:2982,1598,1115,1069;^{1}HNMR400MHz((DMSO)7.1(d,1H) ,7.88(d,1H),8.65(d,2H,J=8.34Hz);^{13}CNMR400MHz(DMSO)109.2,111.6,112.4,112.8,113.5,121.3,122.7,126.8,1 28.8,128.9,141.5,143.6,146.1.

2-(4-Methylphenyl)-imidazo[1,2a]pyridine,3e $C_{14}H_{12}N_2$; Yield 65%; M^+208; Elemental Anal C-71.68,H-4.75,N17.52FoundC70.54,H4.13,N16.73;IR(KBr)cm^1:3052,2872,1523,1444,1254;^{1}HNMR400MHz((DMSO)2. 35(s,3H),6.65(s,1H),6.797.62(m,4H);^{13}CNMR400MHz(DMSO)108.1,111.5,111.7,112.3,112.6,122.4,122.8,124. 9,126.1,127.6,142.6,143.1,154.4,154.9

2-(4-Hydroxyphenyl)-imidazo[1,2a]pyridine,3f $C_{13}H_{10}N_2O$; Yield 66%; M^+210; Elemental Anal C-68.64,H-5.75,N-14.73FoundC-69.54,H-5.12,N-13.97;IR(KBr)cm^{-1}: 3346,2976,1345,1258;^{1}HNMR400MHz((DMSO)6.2-6.78(m,4H),7.41(d,1H),7.79(d,1H);^{13}CNMR400MHz(DMSO)113.5,114.1,114.7,114.9,122.8,122.9,127.6,128.3, 128.6,142.5,143.2,144.7,157.3

2-(4-Bromophenyl)-imidazo[1,2a]pyridine3g $C_{13}H_9N_2Br$; Yield 96%; M^+271; Elemental Anal C-78.34,H-5.76,N14.78FoundC78.79,H5.13,N13.38;IR(KBr)cm^1:,3056,15721268,740;^{1}HNMR400MHz((DMSO)6.88(d,1

H),7.32(s,1H),7.41(d,1H);^{13}CNMR400MHz(DMSO)112.3,112.6,113.7,121.5,121.7,122.3,124.8,128.2,128.7,142.5,142.6,145.7,155.8

2-(4-Fluorophenyl)-imidazo[1,2a]pyridine3h $C_{13}H_9N_2F$; Yield 61%; M^+211; Elemental AnalC56.54,H-3.16,N17.62FoundC55.34,H3.46,N16.75;IR(KBr)cm^1:3047,1485,1315,1273;^{1}HNMR400MHz((DMSO)7.4(d,1H),7.79(s,1H),8.0`(d,1H),^{13}CNMR400MHz(DMSO)109.6,112.1,112.6,112.9,122.1,122.5,124.8,126.8,128.2,140.5,142.6,145.1,154.7

Conclusion

Eight derivatives of azaindolizines were synthesised by a simple microwave synthesis. Within this context we have developed a green chemistry approach to synthesize fused imidazoles under aqueous reaction condition. Herein, we described a convenient way of synthesis of some azaindolizines **3a-h** and the present method seems to overcome all the drawbacks of synthesising the same compounds commercially which involves long reaction times, unsatisfactory yields, and the use of expensive and hazardous reagents. Since water is a cheap and non-toxic solvent the use of water as a medium for organic reactions is a very important footstep. Thus this is an efficient synthetic method to prepare 1-azaindolizines that have high fluorescence emission efficiencies and biological activities. The synthesized derivatives were screened for antibacterial activity against Escherichia coli, Klebsiella pneumoniae and Staphylococcus aureus and the MIC values were also measured.

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References

[1] Y. Rival, G. Grassy, G. Michel, Synthesis and antibacterial activity of some imidazo[1,2-a]pyrimidine, Chemical and Pharmaceutical Bullettin, 40(5),1992,1170–1176.

[2] M. H. Fisher, A. Lusi, Imidazo[1,2-a]pyridine anthelmintic and antifungal agents, Journal of Medicinal Chemistry, 15(9),1972, 982–985.

[3] C. Hamdouchi, J. Blas, M. Prado, J. Gruber, B.A. Heinz, L. Vance, 2-Amino-3 substituted-6-[(E)-1-phenyl-2-(N-methylcarbamoyl)vinyl]imidazo-[1,2-a] pyridines as a novel class of inhibitors of human rhinovirus: Stereospecific synthesis and antiviral activity, Journal of Medicinal Chemistry, 42(1), 1999, 50–59.

[4] M. Lhassani, O. Chavignon, J. M. Chezal, J. C. Teulade, J.P. Chapat, R. Snoeck, G. Andrei, J. Balzarini, E. Clercq, A. Gueiffier : Synthesis and antiviral activity of imidazo[1,2-a]pyridines, European Journal of Medicinal Chemistry, 34(3), 1999, 271–274.

[5] A. Gueiffier, M. Lhassani, A. Elhakmaoui, R. Snoeck, G. Andrei, O. Chavignon, J.C. Teulade, A. Kerbal, E. M. Essassi, J.C. Debouzy, M. Witvrouw, Y. Blache, J. Balzarini, E. Clercq, J.P. Chapat, Synthesis of acyclo-C-nucleosides in the imidazo[1,2-a]pyridine and pyrimidine series as antiviral agents, Journal of Medicinal Chemistry, 39(14), 1996, 2856–2859.

[6] K. C. Rupert, J. R. Henry, J. H. Dodd, S. A. Wadsworth, D. E. Cavender, G. C. Olini, B. Fahmy and J. J. Siekierka, Imidazopyrimidines, potent inhibitors of p38 MAP kinase, Bioorganic and Medicinal Chemistry Letters, 13(3), 2003, 347-350.

[7] S. Kumar and D. P. Sahu, Aqueous phase synthesis of bridgehead azaheterocycles in the presence of β-cyclodextrin, ARKIVOC, (xv), 2008, 88-98.

[8] M. S.Gopal, I. Anitha, Aqueous phase microwave synthesis of some bisindolizines, International Journal of Chemical Studies, 2(4), 2014, 35-38.

[9] A. Gueiffier, S. Mavel, M. Lhassani, A. Elhakmaoui, R. Snoeck, G. Andrei, O. Chavignon, J.C. Teulade, M. Witvrouw, J. Balzarini, E. Clercq, J. P. Chapat, Synthesis of imidazo[1,2-a]pyridines as antiviral agents, Journal of Medicinal Chemistry, 41(25), 1998, 5108–5112.

[10] C. Enguehead, J. N. Renou, H. Allouchi, J. M. Leger, A. Gueiffier, Synthesis of diaryl-substituted imidazo[1,2-a]pyridines designed as potential aromatase inhibitors, Chemical and Pharmaceutical Bullettin, 48(7), 2000, 935–940.

[11] N. Donora, V. Laquintana, M. G.Pisu, R. Dore, L. Murru, A. Latrofa, G. Trapani, E. Sanna, 2-Phenyl-imidazo[1,2-a]pyridine compounds containing hydrophilic groups as potent and selective ligands for peripheral benzodiazepine receptors: synthesis, binding affinity and electrophysiological studies, Journal of Medicinal Chemistry, 51(21), 2008, 6876–6888.

[12] R. B. Lacerda, C.K.F.de Lima, L.L.da Silva, N. C. Romeiro, A.N.P.Miranda, E.J. Barreiro, C.A.M. Fraga, Discovery of novel analgesic and anti-inflammatory 3-arylamine-imidazo[1,2-a]pyridine symbiotic prototypes, Bioorganic and Medicinal Chemistry Letters, 17(1), 2009, 74–84.

[13] A .Kamal, J. S. Reddy, M. J. Ramaiah, D. Dastagiri, E. V. Bharathi, M.V. P. Sagar, C.V.L.S. N. Pushpavalli, P. Ray, M. P. Bhadra, Design, synthesis and biological evaluation of imidazopyridine/pyrimidine-chalcone derivatives as potential anticancer agents, Medicinal Chemical Communications, 1(5), 2010, 355–360.

[14] S. Ide, K. Katou, T. Itou, C. Motokawa, Y. Chiyomaru, Y. Matsuda, Synthesis of imidazo[1,2-a]pyridine derivatives and their reactions, Yakugaku Zasshi, 113(12), 1993, 861–869.

[15] J. Wang, R. Mason, D. VanDerveer, K. Feng, X. R. Bu, Convenient preparation of a novel class of imidazo[1,5-a]pyridines: decisive role by ammonium acetate in chemoselectivity, Journal of Organic Chemistry, 68(13), 2003, 5415–5418.

[16] M. Adib, E. Sheibani, L.G. Zhu, P. Mirzaei, An efficient synthesis of 3-amino-2-arylimidazo[1,2-a]pyridines, Tetrahedron Letters, 49(34), 2008, 5108–5110.

[17] J. Wright, T. Heffner, T. Pugsley, R. MacKenzie, L. Wise, Discovery of selective dopamine D3 ligands: II. 2-[4-[3-(4-aryl-1 piperazinyl)propoxy]phenyl]benzimidazole partial agonists, Bioorganic and Medicinal Chemistry Letters, 5(21), 1995, 2547-2550.

[18] M. S.Gopal, I. Anitha, Microwave synthesis and characterisation of some cycl[3,2,2]azine derivatives, International journal of science and research, 5(2), 2016, 960-963.

[19] M. Alebouyeh**,** P. G. Orimi, M. Azimi-rad, M. Tajbakhsh, E. Tajeddin, S. J. Sherafat, E N. Mojarad, M.R. Zali, Fatal sepsis by Bacillus circulansin an immunocompromised patient, Iranian Journal of Microbiology, 3(3), 2011**,**156-158.

[20] G. L.Archer, Staphylococcus aureus: a well-armed pathogen. Clinical infectious diseases, 26(5), 1998,1179-81.
[21] E. J.Bottone, Bacillus cereus, a volatile human pathogen. Clinical Microbiology Reviews, 23(2), 2010, 382-98.
[22] J. A.Driscoll, S. L.Brody, M. H. Kollef, The epidemiology, pathogenesis and treatment of Pseudomonas aeruginosa infections, Drugs, 67(3), 2007, 351-68.
[23] R. Podschun, U. Ullmann, Klebsiella spp. as Nosocomial Pathogens: Epidemiology, Taxonomy, Typing Methods, and Pathogenicity Factors, Clinical Microbiology Reviews, 11(4), 1998, 589-603.
[25] D. R. Stalons and C. Thornsberry, Broth-dilution method for determining the antibiotic susceptibility of anaerobic bacteria, Antimicrobial agents and chemotherapy, 7(1), 1975, 15-21.
[26] I. Anitha, M. S. Gopal, D. Thomas, A new fluorescent sensor based on bisindolizine derivative, Journal of fluorescence, 26(2),2016,725-729.
[27] V. V. Kumbhar, S. P. Hangirgekar and N. B. Wadwale, Aqueous phase synthesis of substituted imidazo[1,2-a]pyridine in the presence of β-cyclodextrin, Der Pharma Chemica, 5(5),2013, 274-279.