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Microwave promoted synthesis of pharmacologically active Schiff bases of indolo [2, 3-*b*] quinoxaline

Nandini R. Pai*and Krishnakant T. Waghmode

Department of Chemistry, D. G. Ruparel College, University of Mumbai, India

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ABSTRACT

Microwave promoted synthesis of pharmacologically active Schiff bases of indolo [2, 3-b] quinoxaline is described. Microwave assisted synthesis not only reduced the reaction time drastically but also gave excellent yields of Schiff bases of indolo [2, 3-b] quinoxaline derivatives. The synthesized compounds are characterized by FTIR, 1H NMR and Mass spectral data.

Key words: Indolo [2, 3-b] quinoxaline, Microwave irradiations.

INTRODUCTION

Nitrogen containing heterocyclic compounds are in dispensable structural units for both the chemist and the biochemist. Among the various classes of heterocyclic compounds, quinoxalines form an important component of pharmacologically active compounds. The literature survey revealed that substituted quinoxaline derivatives exhibit a wide variety of biological activities. It has been reported that some quinoxalines demonstrated antibacterial [1], antifungal [2], antiviral [3], antineoplastic [4], antidepressant [5], anti-inflammatory [6] and anti HIV-1 [7] activities, some indolo quinoxaline derivatives substituted at nitrogen of indole moiety had been described as antibacterial and anti-inflammatory agents [6].

Synthesis of 6-substituted indophenazines as possible psychotropic and anti-inflammatory agent has been described [8].

The development of simple general and efficient synthetic methods for widely used organic compounds from readily available reagents is one of the major challenges in organic synthesis. Microwave-induced Organic Reaction Enhancement (MORE) is used for carrying out chemical transformations e.g. organic reactions and their uses in ecofriendly manners [9-11]. The microwave assisted organic reactions occur more safely and in an environmentally friendly manner with enhanced product purity and chemical yields [12]. Shorter reaction time periods, simple reaction conditions and higher yields render the microwave method superior [13].

MATERIALS AND METHODS

Experimental Section:
All air reactions were carried out in oven dried (120 ^{0}C) or flame dried glassware. Microwave reactions were carried out in domestic microwave oven (Samsung model) Analytical thin layer chromatography was performed with Merck silica gel plates (0.25mm thickness) with PF_{254} indicator. Compounds were visualized under UV lamp. Column chromatography was carried out using 60-120 mesh silica gel and technical grade solvents. ^{1}H-NMR spectra were

recorded on at 200,300 and 400 MHz instruments with tetramethylene silane as an internal standard. IR spectra were recorded on Shimadzu Hyper IR instrument.

Experimental Procedure:-
2-(5, 8-dihydro quinoxalino [2, 3-b] indol-5-yl) acetohydrazide was prepared by the reported method [8]. Indolo [2, 3-b] quinoxaline was treated with ethyl chloroacetate in K_2CO_3 and DMF to afford Ethyl 5,8-dihydro quinoxalino[2,3-b]indol-5-yl acetate. Further this ester was refluxed with hydrazine hydrate in ethanol to get 2-(5, 8-dihydro quinoxalino [2, 3-b] indol-5-yl) acetohydrazide.

Synthesis of 3.a-j:
Conventional heating[8]: In a round bottom flask, 2-(5, 8-dihydro quinoxalino [2, 3-b] indol-5-yl) acetohydrazide (0.01 mol) 1 and Substituted aromatic aldehydes (0.01mol), few drops of acetic acid were taken in ethyl alcohol and stirred with heating for four hours till the completion of the reaction. Progress of the reaction was checked with TLC (hexane-ethyl acetate 8:2). Then it was cooled and added with ice-cold water. It was filtered, washed with water and purified by recrystallization through glacial acetic acid. Time and yield are mentioned in table-I.

Table I: Synthesis of Schiff bases 3a-j under conventional and microwave heating

Entry	R	Conventional heating		Microwave heating			mp. Obs. (lit.)** ^{0}C
		Time in Hours	% Yields*	Microwave power in Watt	Time in min.	% yield*	
3a	H	4	81	450	2.5	85	220-223(222)
3b	3-NO_2	4	61	450	3.5	78	>250
3c	Furfural	4	74	450	2	86	>250
3d	4-CH_3	4	70	450	2	85	>250 (>270)
3e	4-OH	4	75	450	2.5	80	>250 (>270)
3f	4-$N(CH_3)_2$	4	70	450	3	75	>250
3g	2-Cl	4	66	450	2.5	80	>250
3h	4-OH,3-OCH_3	4	79	450	3	85	>250 (>270)
3i	4-OCH_3	4	82	450	3	85	>250(268)
3j	2-OH	4	68	450	2.5	82	>250

**Yields refer to pure products.*
*** Compounds whose melting points are shown in bracket are known compounds; they were characterized by comparison of their physical and spectral data with that of literature data [8].*

Microwave heating: In a hard glass tube, 2-(5, 8-dihydro quinoxalino [2, 3-b] indol-5-yl) acetohydrazide (0.01 mol) 1 and Substituted aromatic aldehyde (0.01mol), few drops of acetic acid were taken and mixed well to prepare a paste. This mixture was irradiated in microwave till the completion of the reaction. Progress of the reaction was checked with TLC (hexane-ethyl acetate 8:2). After the completion of reaction, reaction mixture was cooled to room temperature and ice-cold water was added to it. It was filtered, washed with water and purified by recrystallization through glacial acetic acid. Same procedure was followed for the synthesis of compound 3a to 3j. Microwave power, irradiation time and time and yield are mentioned in table-I.

3a. N'-benzylidene-2-(6H-indolo [2,3-b] quinoxalin-6-yl) acetohydrazide: mp.-220-223 ^{0}C; IR (KBr): 3332, 3062 (NH), 1681,1581 (C=C), 1498m(C-N), 1334 (CH), 1242,833 (C-C), 1133, 756 (CH), 694 (CH), cm^{-1}; 1H NMR (300 MHz, DMSO-d^6) δ(ppm): 11.84(1H,s, NH), 8.43-8.40(1H,d, Ar-CH) 8.32-8.27(1H,d, Ar-CH),8.12-8.10(1H,d,Ar-CH),8.10(1H,s,CH),7.86-7.80(6H,m,Ar-CH),7.74-7.42(4H,m, Ar-CH),5.75(2H,s,CH2), MS:- m/z = 379(m^+)

3b. N'-3-nitro benzylidene-2-(6H-indolo [2,3-b]quinoxalin-6-yl) acetohydrazide: mp.>250 ^{0}C; IR (KBr): 3332, 3186 (NH), 1681,1581 (C=C), 1488 (C-N), 1334 (CH), 1280,1203,1010 (C-C), 941, 748 (CH), 694 (CH), cm^{-1}; 1H NMR (200 MHz, DMSO-d^6) δ(ppm): 12.024 (1H,s, NH), 8.61(1H,d,Ar-CH)8.41-8.37(1H,d, Ar-CH),8.29-8.22(1H,d,Ar-CH),8.10(1H,s,CH),8.06(1H,s,Ar-CH),7.81-7.69(5H,m,Ar-CH),7.41(1H,t, Ar-CH),5.79(2H,s,CH2), MS:- m/z = 424(m^+)

3c. N'-furfurylidene-2-(6H-indolo [2,3-b]quinoxalin-6-yl) acetohydrazide: mp.>250 ^{0}C; IR (KBr): 3332, 3201,3062 ,1681 1581 (C=C), 1498 (C-N), 1334 (CH), 1288,1203,763, cm^{-1}; 1H NMR (200 MHz, DMSO-d^6) δ(ppm): 11.75 (1H,s, NH), 8.40-8.38(1H,d, Ar-CH) 8.29-8.26(1H,d,Ar-CH),8..12-8.10(1H,d,Ar-CH),8.06(1H,s,CH),7.98-7.69(5H,m,Ar-CH),7.44-7.41(1H,t, Ar-CH),6.99-6.97(1H,dd,Ar-H),6.66-6.64(1H,dd,Ar-H)5.66(2H,s,CH2), MS:- m/z = 369(m^+)

3d: N'-4-methyl benzylidene-2-(6H-indolo [2,3-b]quinoxalin-6-yl) acetohydrazide: mp.>250 ^{0}C; IR (KBr): 3186 (NH), 3039,1681,1581 (C=C), 1496 (C-N), 1280,1203,1118 (C-C), 948, 748, cm^{-1}; ^{1}H NMR (200 MHz,

DMSO-d^6) δ(ppm): 11.56 (1H,s, NH), 8.40-8.36(1H,d, Ar-CH) 8.29-8.26(1H,d, Ar-CH),8.18-8.08(1H,d,Ar-CH),7.94(1H,s,CH),7.84-7.69(4H,mAr-CH),7.57-7.41(4H,m,Ar-CH),7.21-7.19(2H,m,Ar-CH),5.68(2H,s,CH2),2.22(3H,s,Ar-CH_3) MS:- m/z = 393(m^+)

3e: N'- 4-hydroxybenzylidene-2-(6H-indolo[2,3-b]quinoxalin-6-yl) acetohydrazide: mp.>250 ^{0}C; IR (KBr): 3332, 3201,3062 ,1681 1581, 1498, 1334 , 1288,1203,763, cm^{-1}; 1H NMR (400 MHz, DMSO-d^6) δ(ppm): 11.59 (1H,s, NH), 9.92(1H,s, Ar-OH), 8.40-8.37(1H,d, Ar-CH) 8.30-8.29(1H,d, Ar-CH),8..26-8.25(1H,d,Ar-CH),8.07(1H,s,CH), 7.98-7.81(4H,m,Ar-CH),7.75-7.61(1H,t, Ar-CH), 7.57-7.38(2H,m, Ar-CH),6.83-6.76(2H,m,Ar-H), 5.69(2H,s,CH2), MS:- m/z = 395(m^+)

3f. N'-N,N-dimethyl benzylidene-2-(6H-indolo[2,3-b]quinoxalin-6-yl) acetohydrazide: mp.>250 ^{0}C; IR (KBr): 3332, 3178, 3062,1681,1612,1527,1488, 1288 , 1280,1203,1010, 948, 748 cm^{-1}; 1H NMR (200 MHz, DMSO-d^6) δ(ppm): 11.56 (1H,s, NH), 8.40-8.36(1H,d, Ar-CH) 8.29-8.26(1H,d, Ar-CH),8.18-8.08(1H,d,Ar-CH),7.94(1H,s,CH),7.84-7.69(4H,mAr-CH),7.57-7.41(4H,m,Ar-CH),6.74-6.69(2H,m,Ar-CH),5.68(2H,s,CH2),2.97-2.94(6H,s,$N(CH_3)_2$) MS:- m/z = 422(m^+)

3g.N'-2-chloro benzylidene-2-(6H-indolo[2,3-b]quinoxalin-6-yl) acetohydrazide: mp.>250 ^{0}C; IR (KBr): 3332, 3186 (NH), 1681,1581 (C=C), 1488 (C-N), 1334 (CH), 1280,1203,1010 (C-C), 941, 748 (CH), 694 (CH), cm^{-1}; 1H NMR (200 MHz, DMSO-d^6) δ(ppm): 10.45(1H,s, NH), 8.42-8.41(1H,d, Ar-CH) 8.31-8.29(1H,d, Ar-CH),8.11-8.09(1H,d,Ar-CH),8.00(1H,s,CH),7.82-7.76(3H,mAr-CH),7.75-7.57(2H,m,Ar-CH),7.56-7.54(1H,t,Ar-H),7.43-7.39(1H,t,Ar-CH), 7.17-7.13(1H,t,Ar-CH),5.76(2H,s,CH2), MS:- m/z = 416(m^{+2})

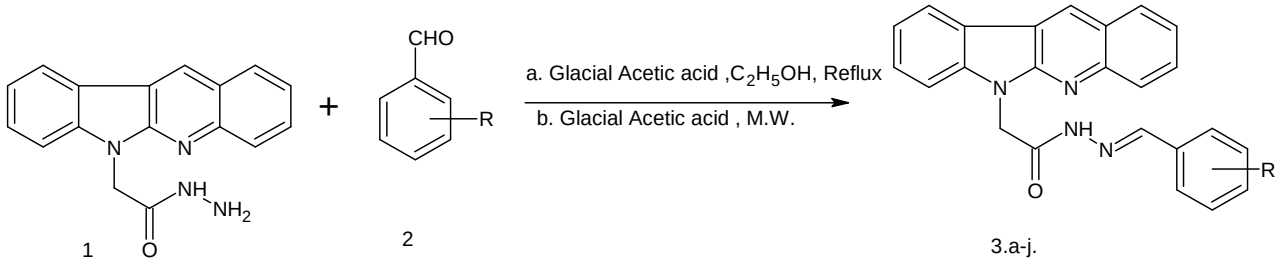
3h. N'-4-hydroxy 3-methoxy benzylidene-2-(6H-indolo[2,3-b]quinoxalin-6-yl) acetohydrazide: mp.>250 ^{0}C; IR (KBr): 3170 ,3062, 1681,1589, 1427, 1288, 1203,1126,1041, 941, 748 , 663 cm^{-1}; 1H NMR (200 MHz, DMSO-d^6) δ(ppm): 11.62(1H,s, NH), 9.50(1H,s, Ar-OH), 8.41-8.37(1H,d,Ar-CH)8.30-8.25(1H,d,Ar-CH),8.07(1H,d,Ar-CH),7.97(1H,s,CH), 7.81-7.69(5H,mAr-CH), 7.45-7.39(2H,m,Ar-CH), 7.22-7.17(1H,mAr-H), 6.85-6.81(1H,t,Ar-H), 5.72 (2H,s,CH2),3.83-3.72(3H,s,OCH_3) MS:- m/z = 425(m^+)

3i:N'-4-methoxy benzylidene-2-(6H-indolo [2,3-b]quinoxalin-6-yl) acetohydrazide: mp.>250 ^{0}C; IR (KBr): 3178,3062 1681,1589,1488, 1280,1234,1049, 948, 748 cm^{-1}; 1H NMR (200 MHz, DMSO-d^6) δ(ppm): 10.45(1H,s, NH), 8.42-8.41(1H,d, Ar-CH) 8.31-8.29(1H,d, Ar-CH),8.11-8.09(1H,d,Ar-CH),7.98(1H,s,CH),7.82-7.76(3H,mAr-CH),7.75-7.57(2H,m,Ar-CH),7.44(2H,mAr-H),7.30(2H,m,Ar-CH),5.76(2H,s,CH2),3.85 (3H,s,OCH_3) MS:- m/z = 409(m^+)

3j.N'-2-hydroxy benzylidene-2-(6H-indolo [2,3-b]quinoxalin-6-yl) acetohydrazide: mp.>250 ^{0}C; IR (KBr): 3186, 1681,1589, 1473 , 1296 ,1203,1111, 948, 736, 671 cm^{-1}; 1H NMR (400 MHz, DMSO-d^6) δ(ppm): 10.45 (1H,s, NH), 9.57(1H,s,Ar-OH) 8.42-8.41(1H,d, Ar-CH) 8.31-8.29(1H,d, Ar-CH),8.11-8.09 (1H,d,Ar-CH),8.02 (1H,s,CH), 7.80-7.76(3H,mAr-CH),7.59-7.57(2H,m,Ar-CH),7.45-7.43(2H,m,Ar-CH),7.42-7.41(1H,d,Ar- H). 6.95-6.91(1H,t,AR-H)5.76(2H,s,CH2), MS:- m/z = 395(m^+)

RESULTS AND DISCUSSION

The condensation of substituted aromatic aldehydes with 2-(5, 8-dihydro quinoxalino [2, 3-b] indol-5-yl) acetohydrazide has been carried out by both conventional and microwave heating methods to give compounds **(3a-j)**. In conventional heating method reaction is carried out in ethanol and it takes about 4 hr, while under microwave irradiation it takes only 2-3 min. In conventional heating method the yield is lower as compared to microwave irradiation. Microwave irradiation facilitates the polarization of the molecule under irradiation causing rapid reaction to occur. A comparative study in terms of yield and reaction period is shown in **Table-I.**



CONCLUSION

Researchers across the globe have developed green resolution to design synthesis in the organic chemistry. The microwave assisted greener chemical transformation affords excellent product yield, reduced reaction time and minimization or elimination of by product. The result obtained confirms superiority of microwave irradiation over the conventional heating method **(Table-I).**

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