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A GREEN, HIGHLY EFFICIENT SYNTHESIS OF 1,5-BENZOTHIAZEPINES USING 2-METHOXYETHANOL UNDER MICROWAVE IRRADIATION

Sainath Zangade, Avinash Shinde, Shivshankar Sundge and Yeshwant Vibhute *

abstract: A simple, rapid and highly efficient synthesis of 1,5-benzothiazepines by condensation of 2'-hydroxychalcones and *o*-aminophenol using 2-methoxyethanol as an alternative and environmentally benign solvent under microwave irradiation. The clean reaction conditions, shorter reaction time and high yields and purity of product are notable advantages of method.

key words: 2'-hydroxychalcones; 1,5-benzothiazepines; *o*-aminophenol, 2-methoxyethanol; microwave irradiation.

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Introduction

Benzothiazepines have attracted as an important class of heterocyclic compounds in the field of drug and pharmaceutical research. These compounds are widely used as anticonvulsant, analgesic, sedative, antidepressive, antibacterial, hypnotic agents as well as anti-inflammatory agents [1]. The 2,3-dihydro-1,5-benzothiazepines-4-(5*H*)-ones substituted with alkyl, alkoxythio, hydroxyl of amino group on the fused benzene ring of 1,5-benzothiazepine have demonstrated to posses platelet aggregation inhibitory properties [2].

1,5-benzothiazepines were commonly synthesized by the reaction of *o*-aminophenol with α,β-unsaturated carbonyl compounds, β-haloketones. There are various methods have reported for the preparation of 1,5-benzothiazepines using inorganic solid support such as silica gel [3], pyridine [4], ethanol-acetic acid mixture [5], aluminium oxide [6], EtoH/Hcl [7], magnesium perchlorate/1,2-dichloroethane [8], DMF/MWI [9], CH_3COOH [10], KSF/MWI [11], Zeolite [12]. However, many of these reported procedures have one or more disadvantages such as use of expensive catalyst, low selectivity, harsh reaction conditions, low yield, relatively long reaction time and environmental concern. In recent years replacement of hazardous-solvent with environmentally benign solvents is one of the major focus areas of green chemistry. The use of alternative reaction solvents such as water [13], ionic liquid [14], flourous [15], supercritical media [16], polyethylene glycol (PEG) [17] is rapidly growing.

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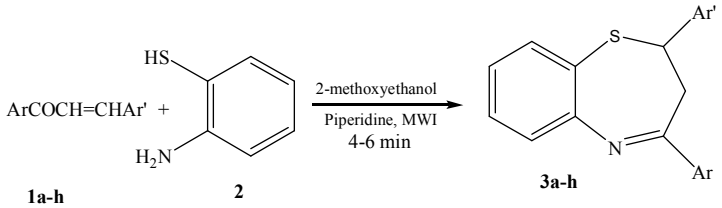
The application of microwave (MW) irradiation as a nonconventional energy source for activation of reactions has now become a very popular and useful technology in organic chemistry [18]. Many researchers have described accelerated organic reactions towards proving the synthetic utility of MW irradiation in routine organic synthesis [19]. Due to the wide range of pharmacological activity and application of microwave technique in organic synthesis, promoted us towards the synthesis of 1,5-benzothiazepines using piperidine in 2-methoxyethanol as an alternative and environmentally begin reaction solvent under microwave irradiation.

Experimental

Melting points were uncorrected and determined in an open capillary tube. IR spectra were recorded on FTIR Shimadzu spectrometer. ^{1}H NMR spectra were recorded in $CDCl_3$ on Avance 300 MH_Z spectrometer using TMS as an internal standard. The mass spectra were recorded on EI-Shimadzu-GC-MS spectrometer. Elemental analysis was performed on a Carlo Erba 106 Perkin-Elmer model 240 analyzer.

Typical procedure for Synthesis of 1,5-benzothiazepines

In a round-bottomed flask, substituted 2'-hydroxychalcones **1a-h** (0.01 mol), *o*-aminophenol **2** (0.012 mol) and piperidine (3-4 drops) in 2-methoxyethanol (10 ml) was irradiated in microwave oven for 4-6 minutes (TLC), with short interval of time for 10 sec. to avoid evaporation of excessive solvent. Then reaction mixture was cooled to room temperature. Solid separated was isolated by simple Buchner filteration; final purification was achieved by recrystallization from mixture of ethanol:dioxane to give corresponding 1,5-benzothiazepines **3a-h**. The purity of product checked by Thin Layer Chromatography.



Scheme 1 *Synthesis of 1,5-benzothiazepines.*

2-[2-(3,4-Dimethoxy-phenyl)-2,3-dihydro-benzo[b][1,4]thiazepin-4-yl]-4-iodo-naphthalen-1-ol. 3a: IR (KBr): 1560 (C=N), 1450 (C=C) cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MH_Z): δ 3.37 (s, 6H, OCH_3), 2.85 (dd, J_{AB}= 12 Hz, J_{AX}= 11.2Hz, 1H, H_A), 3.81 (dd, J_{BA}= 12Hz, J_{BX}= 3.1 Hz, 1H, H_B), 5.43 (dd, J_{XA}= 11.2 Hz, J_{XB}= 3 Hz, 1H, H_X), 7.58-8.20 (m, 12H, Ar-H) 12.0 (s, 1H, OH). ^{13}C NMR 40.65 (-CH_2), 41.38 (-CH), 55.34 (C *of two methoxy group*), 90.86 (C *of* Ar-I), 116.43-156.71 (C *of Aromatic ring*), 165.89 (C *of* C=N). MS (m/z): 567 (M^+); Anal.Calcd. for $C_{27}H_{22}O_3NSI$: C,57.14; H, 3.88; X (I), 22.39. Found: C,57.11; H, 3.85; X (I), 22.37.

4-Iodo-2-[2-(4-methoxy-phenyl)-2,3-dihydro-benzo[b][1,4]thiazepin-4-yl]-naphthalen-1-ol. 3b: IR (KBr): 1565 (C=N), 1452 (C=C) cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MH_Z): δ 3.37 (s, 3H, OCH_3), 2.88 (dd, J_{AB}= 12 Hz, J_{AX}= 11 Hz, 1H, H_A), 3.79 (dd, J_{BA}= 12Hz, J_{BX}= 3.1 Hz, 1H, H_B), 5.52 (dd, J_{XA}= 11Hz, J_{XB}= 3Hz, 1H, H_X), 7.42-8.22 (m, 13H, Ar-H) 12.0 (s, 1H,

OH). ^{13}C NMR 40.52 (-CH_2), 41.26 (-CH), 55.31 (C *of methoxy group*), 90.92 (C *of* Ar-I), 116.37-156.62 (C *of Aromatic ring*), 165.83 (C *of* C=N). MS (m/z): 536 (M^+); Anal.Calcd. for $C_{26}H_{20}O_2NSI$: C, 58.20; H, 3.73; X (I), 23.69. Found: C, 58.28; H, 3.76; X (I), 23.74.

2-[2-(4-Chloro-phenyl)-2,3-dihydro-benzo[b][1,4]thiazepin-4-yl]-naphthalen-1-ol. 3c: IR (KBr): 1562 (C=N), 1454 (C=C) cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MH_Z): 3.10 (dd, J_{AB}= 12.2 Hz, J_{AX}= 11.1 Hz, 1H, H_A), 3.86 (dd, J_{BA}= 12.2 Hz, J_{BX}= 3.1 Hz, 1H, H_B), 5.56 (dd, J_{XA}= 11.2 Hz, J_{XB}= 3.1Hz, 1H, H_X), 7.42-8.22 (m, 14H, Ar-H) 12.0 (s, 1H, OH). ^{13}C NMR 40.72 (-CH_2), 41.46 (-CH), 112.43-158.41 (C *of Aromatic ring*), 165.86 (C *of* C=N). MS (m/z):416 (M^+); Anal.Calcd. for $C_{25}H_{18}ONSCl$: C, 72.11; H, 4.32; X (Cl), 8.53. Found: C, 72.15; H, 4.36; X (Cl), 8.58.

2-[2-(3,4,5-Trimethoxy-phenyl)-2,3-dihydro-benzo[b][1,4]thiazepin-4-yl]-naphthalen-1-ol. 3d: IR (KBr): 1560 (C=N), 1450 (C=C) cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MH_Z): δ 3.37 (s, 9H, OCH_3), 2.90 (dd, J_{AB}= 12 Hz, J_{AX}= 11.2 Hz, 1H, H_A), 3.84 (dd, J_{BA}= 12 Hz, J_{BX}= 3.1 Hz, 1H, H_B), 5.48 (dd, J_{XA}= 11.2 Hz, J_{XB}= 3.1 Hz, 1H, H_X), 7.42-8.15 (m, 12H, Ar-H) 12.0 (s, 1H, OH). ^{13}C NMR 40.78 (-CH_2), 41.45 (-CH), 55.42 (C *of three methoxy group*), 112.43-156.14 (C *of Aromatic ring*), 165.91 (C *of* C=N). MS (m/z): 471 (M^+); Anal.Calcd. for $C_{28}H_{25}O_4NS$: C, 71.33; H, 5.30. Found: C, 71.37; H, 5.33.

2-[2-(3,4-Dimethoxy-phenyl)-2,3-dihydro-benzo[b][1,4]thiazepin-4-yl]-naphthalen-1-ol. 3e: IR (KBr): 1562 (C=N), 1448 (C=C) cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MH_Z): δ 3.37 (s, 6H, OCH_3), 2.88 (dd, J_{AB}= 12 Hz, J_{AX}= 11.2 Hz, 1H, H_A), 3.83 (dd, J_{BA}= 12Hz, J_{BX}= 3.1 Hz, 1H, H_B), 5.45 (dd, J_{XA}= 11.2 Hz, J_{XB}= 3 Hz, 1H, H_X), 7.55-8.20 (m, 13H, Ar-H) 12.0 (s, 1H, OH). ^{13}C NMR 40.63 (-CH_2), 41.47 (-CH), 55.54 (C *of two methoxy group*), 112.35-157.25 (C *of Aromatic ring*), 165.90 (C *of* C=N). MS (m/z): 441 (M^+); Anal.Calcd. for $C_{27}H_{23}O_3NS$: C, 73.46; H, 5.21. Found: C, 73.51; H, 5.24.

2-[2-(4-Fluoro-phenyl)-2,3-dihydro-benzo[b][1,4]thiazepin-4-yl]-naphthalen-1-ol. 3f: IR (KBr): 1561 (C=N), 1453 (C=C) cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MH_Z): 3.10 (dd, J_{AB}= 12.2 Hz, J_{AX}= 11.1 Hz, 1H, H_A), 3.88 (dd, J_{BA}= 12.2 Hz, J_{BX}= 3.1 Hz, 1H, H_B), 5.58 (dd, J_{XA}= 11.2 Hz, J_{XB}= 3.1 Hz, 1H, H_X), 7.42-8.22 (m, 14H, Ar-H) 12.0 (s, 1H, OH). ^{13}C NMR 40.79 (-CH_2), 41.52 (-CH), 112.43-160.41 (C *of Aromatic ring*), 165.93 (C *of* C=N). MS (m/z): 399 (M^+); Anal.Calcd. for $C_{25}H_{18}ONSF$: C, 75.18; H, 4.51; X (F), 4.76. Found: C, 75.23; H, 4.54; X (F), 4.81.

4-Bromo-2-[2-(4-methoxy-phenyl)-2,3-dihydro-benzo[b][1,4]thiazepin-4-yl]-naphthalen-1-ol. 3g: IR (KBr): 1562 (C=N), 1454 (C=C) cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MH_Z): δ 3.39 (s, 3H, OCH_3), 2.88 (dd, J_{AB}= 12 Hz, J_{AX}= 11 Hz, 1H, H_A), 3.77 (dd, J_{BA}= 12Hz, J_{BX}= 3.1 Hz, 1H, H_B), 5.52 (dd, J_{XA}= 11Hz, J_{XB}= 3Hz, 1H, H_X), 7.48-8.18 (m, 13H, Ar-H) 12.0 (s, 1H, OH). ^{13}C NMR 40.57 (-CH_2), 41.37 (-CH), 55.34 (C *of methoxy group*), 91.87 (C *of* Ar-Br), 116.56-157.48 (C *of Aromatic ring*), 165.87 (C *of* C=N). MS (m/z): 570 (M^+), 572 (M+2); Anal.Calcd. for $C_{26}H_{20}O_2NSBr$: C, 54.73; H, 3.50; X (Br), 14.0. Found: C, 54.76; H, 3.53; X (Br), 14.06.

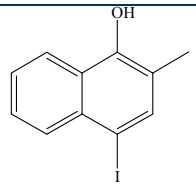
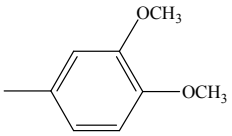
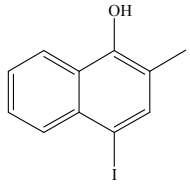
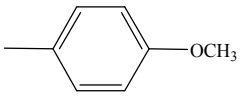
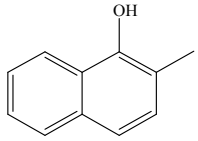
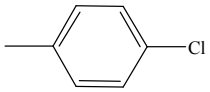
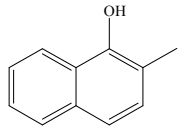
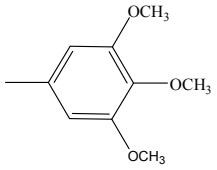
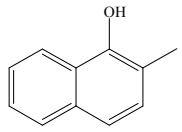
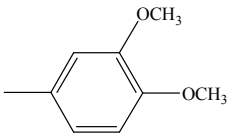
4-Bromo-2-[2-(3,4-dimethoxy-phenyl)-2,3-dihydro-benzo[b][1,4]thiazepin-4-yl]-naphthalen-1-ol. **3h**: IR (KBr): 1560 (C=N), 1450 (C=C) cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MH_Z): δ 3.39 (s, 6H, OCH_3), 2.88 (dd, J_{AB}= 12 Hz, J_{AX}= 11.2Hz, 1H, H_A), 3.83 (dd, J_{BA}= 12Hz, J_{BX}= 3.1 Hz, 1H, H_B), 5.43 (dd, J_{XA}= 11.2 Hz, J_{XB}= 3 Hz, 1H, H_X), 7.58-8.20 (m, 12H, Ar-H) 12.0 (s, 1H, OH). ^{13}C NMR 40.71 (-CH_2), 41.48 (-CH), 55.39 (C *of two methoxy group*), 91.24 (C *of* Ar-Br), 115.27-155.86 (C *of Aromatic ring*), 165.92 (C *of*

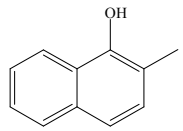
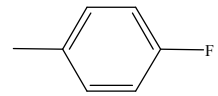
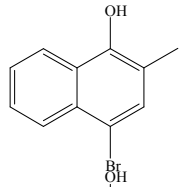
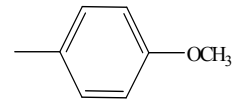
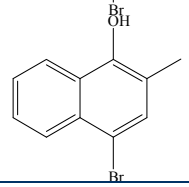
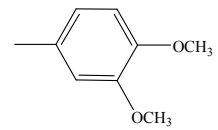
C=N). MS (m/z): 504 (M^+), 506 (M+2); Anal.Calcd. for $C_{27}H_{22}O_2NSBr$: C, 64.28; H, 4.36; X (Br): 15.87. Found: C, 64.26; H, 4.34; X (Br), 15.84.

Results and discussion

With our recent success on the development of new selective environmentally friendly methodologies in synthetic organic chemistry [20]. Herein, we wish to report typical condensation reaction between 2'-hydroxychalcones **1a-h** with *o*-aminophenol using piperidine in 2-methoxyethanol as an alternative reaction solvent. The chalcones were prepared by well-known Claisen-Schmidt condensation under solvent-free condition [21]. Synthesis of 1,5-benzothiazepines using 2-methoxyethanol under microwave irradiation was completed in 4-6 minutes giving 88-96 % yield of desired product Table 1. Microwave irradiation has been used to accelerate organic reaction because of is high heating efficiency, providing remarkable rate enhancement, dramatic reduction in reaction times with improvement in yield and quality of products.

Table 1 Synthesis of some 1,5-benzothiazepines using 2-methoxyethanol under microwave irradiation.

Entry	Ar	Ar'	Time (min)	Yield (%)	M.P. (^{0}C)
1			4	96	142
2			5	88	126
3			4.5	90	138
4			5	92	128
5			6	90	139

6			4.5	88	154
7			5	90	148
8			6	91	123

An initial examination was carried out for condensation of 3-(3,4-Dimethoxy-phenyl)-1-(1-hydroxy-4-iodo-naphthalen-2-yl)-propenone with *o*-aminophenol using piperidine in 2-methoxyethanol as reaction solvent. The reaction went to completion with 4 min and corresponding product **3a** was obtained in 96 % yield. In order to optimize the reaction conditions, we carried out the above reaction in different reaction medium such as ethanol, acetic acid, THF, dioxane, DMF and 2-methoxyethanol (Table 2). We conclude that 2-methoxyethanol as an efficient reaction medium in terms of clean reaction conditions, not expensive, yields and environmentally ecofriendly. In view of these results, we carried out condensation reaction between substituted 2'-hydroxychalcones with *o*-aminophenol in 2-methoxyethanol. In all cases reaction proceed smoothly in high yields and purity of desired product. Formation of 1,5-benzothiazepines were assumed to proceed through the Micheal-type addition of sulpher in *o*-aminophenol to activated double bond followed by intramolecular cyclization [22,23] with the elimination of water molecule.

Table 2 Effect of solvent on the condensation reaction of 1-(1-Hydroxy-4-iodo-naphthalen-2-yl)-3-(3,4,5-trimethoxy-phenyl)-propenone with *o*-aminophenol under microwave irradiation.

Entry	Solvent	Time (min)	Yield (%)
1.	EtOH	15	70
2.	CH_3COOH	18	68
3.	THF	20	66
4.	Dioxane	26	62
5.	DMF	22	60
6.	2-methoxyethanol	04	96

Structures of compounds **3a-h** have been elucidated by IR, ^{1}H NMR, ^{13}C NMR, MS and elemental analysis. In the IR spectra the disappearance of characteristic absorption corresponding to C=O at 1635 cm^{-1} of α,β-unsaturated carbonyl of chalcones and the appearance of bands at 3320 and 1560 cm^{-1} proved the formation of cyclic product. Further proof came from NMR spectrum where in the typical ABX pattern caused by the newly

formed chiral center showed three double doublets at δ 2.85-3.10, 3.78-3.88 and 5.43-5.58 with coupling constants 12 (J_{AB}), 11.2 (J_{AX}) and 3 (J_{BX}) H_Z, respectively.

Conclusion

In summary, present methodology described a simple and highly efficient condensation reaction between substituted 2'-hydroxychalcones with *o*-aminophenol using piperidine in 2-methoxyethanol as an efficient and environmentally friendly reaction solvent is described. The advantages of present protocol are simplicity of operation, time saving, high yields of products and avoidance of expensive catalyst and usage of volatile organic solvent.

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