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ONE-POT DRY MEDIA SYNTHESIS OF NEW TETRACYCLIC 1,5-BENZOTHIAZEPINES UNDER MICROWAVE ACTIVATION

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Abstract- Green chemical approaches to the condensation reaction of substituted benzenethiols and 2-arylidene-1-tetralone as synthons for the syntheses of a series of new 7-phenyl-5,6,6a,7-tetrahydrobenzo[*b*]naphtho[1,2-*e*][1,4]thiazepines (**4a-e**) of biological importance are described. The reaction using montmorillonite KSF as an inorganic solid is accelerated under microwave irradiation. Details and advantages of this new, efficient, solvent-free protocol along with non-thermal specific microwave effects are underlined.

INTRODUCTION

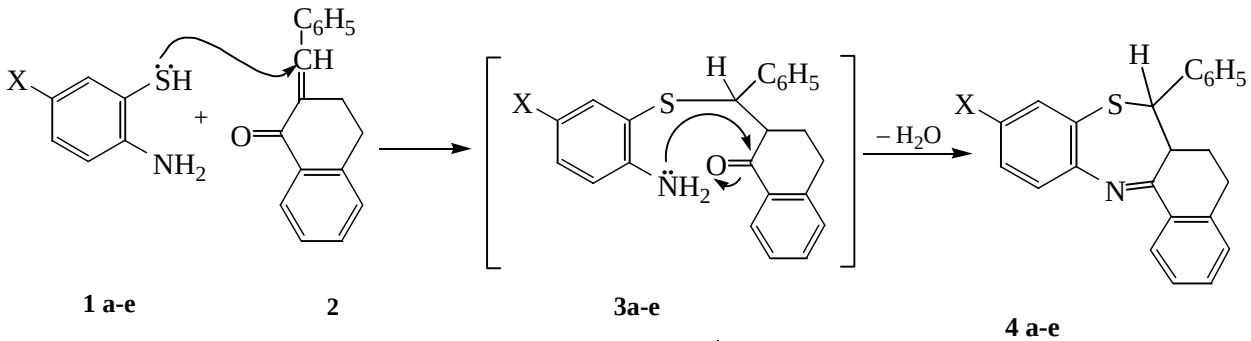
The synthesis of compounds belonging to 1,5-benzothiazepine series constitutes an important area of research due to their use as known cardiovascular drugs acting as calcium channel blockers[1-3] for e.g. *Diltiazem.* Literature survey reveals the importance of substituents on the aromatic ring fused with the 1,5-benzothiazepine nucleus as potential pharmacophores.[4, 5] Knowing the pharmacological activities of naphthyl group[6] and arylidene tetralones, [7-9] we planned to synthesize tetracyclic 1,5-benzothiazepines bearing essentially a substituent in the fused phenyl ring. Furthermore it became obvious that solvent-free conditions are especially adapted to microwave activation for successful syntheses of various compounds leading to increased efficiencies, better conversions within shorter reactions times.[10] This technique was widely applied to several condensation reactions involving 2-aminobenzenethiols[11] but, to the best of our knowledge no attention has been focused on the reactions of benzylidenetetralones (important synthons for the synthesis of several heterocycles) with substituted 2-aminobenzenethiols under microwave irradiation.

Hence, encouraged by our earlier success in the synthesis of biodynamic heterocycles under microwave irradiation[12] and in continuation to our work on searching for the better choice of cardiovascular drugs possessing the benzothiazepine moeity[13] by introducing biolabile pharmacophores, we report therein the

dry media synthesis of the title compounds (**4a-e**) under microwave irradiation. For the sake of comparison, conventionally, they were synthesized by refluxing in ethanol + conc. HCl/toluene + TFA.

RESULTS AND DISCUSSION

The usual reaction of 5-methoxy-2-aminobenzenethiol (**1d**) and 2-arylidene-1-tetralone (**2**) involved reflux in dry toluene for 4 h and gave a mixture of the Michael adduct (**3d**) and tetracyclic benzothiazepine (**4d**), as indicated by TLC. The intermediate **(3d)** was subsequently cyclized to **4d** by extended reflux in ethanol / acetic acid mixture for 1 h. On another hands, **4d** was obtained directly when
1d and **2** were refluxed in toluene with strong acids such as TFA or conc. HCl for 3-7 h (Scheme 1).



1 a-e **2** **3a-e** **4 a-e**

Scheme-1

1,3 and 4	**a**	**b**	**c**	**d**	**e**
X	Cl	Br	Me	OMe	OEt

The standard method involves the use of strong and corrosive acids and extended reflux time in high boiling solvents, tedious work-up procedures with the formation of corresponding disulfides.[14] So, we studied the reaction of **1a-e** with **2** in solvent-free conditions under microwave irradiation, using mineral oxides as solid support (Table 1).

The reaction of **1d** with **2** was also considered under neat conditions, i.e. without using any support or solvent. Unfortunately, no reaction occurred even if a few drops of DMF were added as homogenizing and energy transfer agent able to raise the reaction temperature. This behavior is in contrast with our previous study of reaction of β-aroylacrylic acids with substituted aminotbenzenethiols.[13e] This experiment is therefore clearly indicative for the need of a catalyst provided here by the support.

Table 1: Comparative study for the synthesis of **4d** (X = OMe),
(A) Under microwave irradiation.

Experiment	Power (Watts)	Time (min)	Temp[a] (°C)	Yield[b] (%)
Montmorillonite KSF	**640**	**17**	**116**	**77**
Montmorillonite K10	640	20	124	68
Silica Gel	640	22	90	Nil
Silica Gel + AcOH	640	18	138	63
Basic Alumina	640	21	110	69
Neat + DMF (few drops)	640	24	118	Nil
Ethanol + HCl (conc.)	275	15	78	65

(B) Under conventional heating.

Experiment	Time (min)	Temp[a] (°C)	Yield[b] (%)
Montmorillonite KSF	**17**	**116**	**12**
Montmorillonite KSF	**120**	**116**	**36**
Montmorillonite KSF	**150**	**116**	**28**
Ethanol + Conc. HCl	420	Reflux	68
Dry Toluene	240	Reflux	40
Toluene + TFA	280	Reflux	65

[a] The final temperature is measured at the end of microwave irradiation by introducing a glass thermometer in the reaction mixture.
[b] Yield of the isolated products.

From the observations of Table 1, we draw the conclusion that **4d** was obtained in higher yields (77%) with high purity within very short time (17 min) in dry-media synthesis using preferentially montmorillonite KSF as the acidic solid support under microwave irradiation. The microwave induced method proved to be by far more efficient, clean, safe and economical since the recyclable inorganic supports used are inexpensive and non-pollutant.

Consequently, the reaction conditions were extended to synthesize a series of products **(4a-e)** in satisfying yields (69-81%) (Table 2). Analytical data are indicated in Table 3.

Table 2: Synthetic data for **4a-e.**

	Conventional heating (Δ)			Microwave activation (MW)		
compd	temp.[a] (^oC)	time (min)	yield[c] (%)	temp.[b] (^oC)	time (min)	yield[c] (%)
4a	Reflux	280	67	119	19	81
4b	Reflux	480	58	129	15	69
4c	Reflux	390	64	102	21	73
4d	Reflux	420	66	116	17	77
4e	Reflux	300	67	118	15	73

a: Reflux in EtOH + conc. HCl (76-78 ^oC)
b: The final temperature is measured at the end of MW irradiation by introducing a glass thermometer in the reaction mixture.
c: Yield of the isolated products.

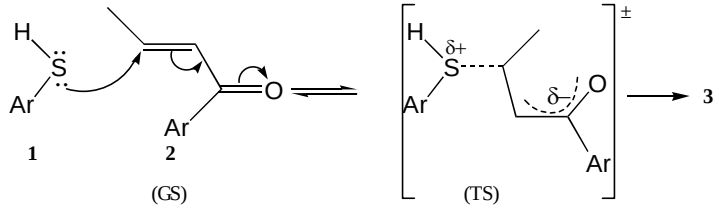
Table 3: Analytical data of **4a-e.**

compd	m.p. (°C)	Rf [a]	Molecular formula	Analysis found (Calcd)			
				C	H	N	S
4a	125	0.68	$C_{23}H_{18}NClS$	73.57 (73.49)	4.79 (4.83)	4.71 (4.43)	8.67 (8.53)
4b	154	0.72	$C_{23}H_{18}NBrS$	65.83 (65.72)	4.42 (4.32)	3.31 (3.57)	7.58 (7.63)
4c	138	0.67	$C_{24}H_{21}NS$	80.85 (81.09)	6.07 (5.95)	4.05 (3.94)	8.95 (9.02)
4d	160	0.70	$C_{24}H_{21}NOS$	77.68 (77.59)	5.63 (5.70)	3.76 (3.54)	8.71 (8.63)
4e	142	0.74	$C_{25}H_{23}NOS$	78.01 (77.89)	5.95 (6.01)	3.32 (3.49)	8.26 (8.32)

a: Using solvent system benzene : petroleum ether (6 : 2).

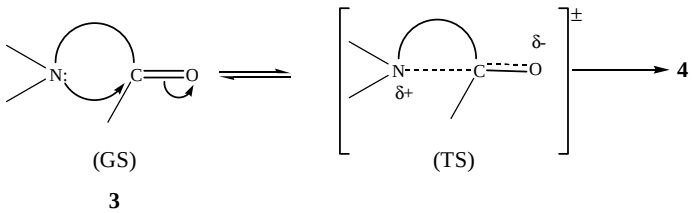
Finally, in order to check the possible intervention of specific (non-thermal) microwave effect, the best results under microwaves were compared with those obtained from conventional heating. The reaction, in

the case of compound (**4d)**, has been carried out using thermostated oil-bath under the same conditions as under microwaves (time, temperature, and vessel) for 17 min at 116°C using montmorillonite KSF. Only 12% of the product when compared to 77% under microwave was obtained and most of the reactant remained unchanged as determined by chromatographic analysis, demonstrating thus that the effect of microwaves is not purely thermal. The results reveal a very strong specific microwave effect. The reaction time was then extended up to 2 hours, yield obtained was no more than 36% and the remaining part contained an intractable mixture consisting of at least three compounds. The specific non-thermal microwave effects observed here can be possibly explained by considering the mechanism concerned.[15] The rate-determining step consists in the Michael addition of benzenethiomoiety on carbon-carbon double bond of α,β-unsaturated carbonyl compound. One can expect an important specific microwave effect due to the evolution of polarity of the system during the reaction progress, as the transition state (TS) is more polar than the ground state (GS) in this reaction. The more important stabilization of the transition state is therefore responsible for an enhancement of reactivity by a decrease of the activation energy (Scheme 2).



Scheme 2

This first step is followed by an intramolecular nucleophilic addition of amino group to the carbonyl moiety, which also involves a dipolar transition state. That one can be stabilized by dipole-dipole electrostatic interactions with electromagnetic field connected to an increase in the polarity of reaction medium (Scheme 3). Hence, microwave substantially accelerates formation of **4** under solvent-free conditions.



Scheme 3

IR spectra of the final products (**4a-e**) did not reveal characteristic ketocarbonyl absorption peak in the range 1690-1710 cm^{-1} and also, absorption of primary amino group, as the bands in the region 1710-1690 and 3445-3200 cm^{-1} were absent. However, a strong absorption band at 1600-1618 cm^{-1} appeared indicative of C=N stretching. Absorptions at around 3100-3000, 1600-1590, 1550 and 1460-1440 cm^{-1} could be assigned to aromatic skeletal vibrations (Table 3).

^{1}H NMR spectra of the final cyclized product (**4d**) showed signals at δ 4.76 (d, J= 12.3 Hz, 1H, H-7), δ 3.39 (dd, J= 5.0 and 2.4 Hz, 1H, H-6a), δ 1.40 and δ 1.87 (ddd, J= 2.4, 5.0; 2.4, 5.0; 5.0, 12.3; and J (gem)= 13.8 Hz, 2H, H-6), δ 2.65 and δ 3.07 (ddd, J= 5.0, 12.3; 2.4, 5.0; J (gem)= 17.7 Hz, 2H, H-5), δ 8.52 (dd, J= 1.8 and 8.2 Hz, 1H, H-1), δ 3.8 (s, OCH_3, 3H) and δ 6.9-7.6 (m, 12H, Ar-H). MS spectrum of **4d** showed peaks at m/z, $[M + H]^+$ at 372 and others at 370, 341, 338, 279, 265 etc. Formation of the final compound **(4d)** was further confirmed on the basis of ^{13}C NMR spectrum. Sharp signals at δ 56.12 ($O\underline{C}H_3$), δ 164.6 ($\underline{C}$=N), δ 24.90 (C_6), δ 25.3 (C_5), δ 43.2 (C_7-S), δ 113.5, 111.8, 114.4, 123.2, 143.6, 130.1, 160.7, 131, 139.9, 128.4, 129.3, 128.8, 130.6, 140.03, 132.6, 129.3 for 12 aromatic carbons were observed (Table 4).

Table 4: ^{1}H NMR Chemical shifts (δ TMS=0), multiplicities, coupling constants and IR spectral data of **4a-e**.

Compd	H-10	H-7 (d) J (Hz) 12.3-12.5	H-6a (dd) J (Hz) 5.2-5.0 2.5-2.4	H-6 (ddd) J (Hz) 2.5-2.4 5.2-5.0 2.5-2.4 5.2-5.0 5.2-5.0 12.5-12.3 J (gem) = 14.1-13.8	H-5 (ddd) J (Hz) 5.2-5.0 12.5-12.3 2.5-2.4 5.2-5.0 J (gem) = 17.7-17.5	H-1 (dd) J (Hz) 2.0-1.8 8.2-8.1	Ar-H (m) J (Hz)	*v* C=N (cm^{-1})
4a	-	4.79	3.38	1.40, 1.88	2.68, 3.08	8.57	7.1-7.8	1608
4b	-	4.74	3.35	1.38, 1.88	2.66, 3.06	8.62	7.0-7.5	1600
4c	2.67 (s, CH_3)	4.68	3.37	1.42, 1.85	2.68, 3.07	8.55	7.2-7.9	1615
4d	3.84 (s, O CH_3)	4.76	3.39	1.40, 1.87	2.65, 3.07	8.52	6.9-7.6	1618
4e	4.12 (q, J =6 Hz $OC\underline{H}_2$), 1.38 (t, J=6 Hz $-C\underline{H}_3$)	4.81	3.39	1.39, 1.89	2.63, 4.01	8.57	7.0-7.7	1610

EXPERIMENTAL

The melting points were determined in open glass capillaries on a Toshniwal melting point apparatus and were uncorrected. IR spectra (*v* max in cm^{-1}) were recorded on a Perkin-Elmer infracord spectrophotometer (Model-577) in KBr pellets. ^{1}H NMR and ^{13}C NMR spectra were recorded on dpx 200 spectrophotometer at 200.13 MHz and 50.33 MHz respectively using $CDCl_3$ as the solvent and TMS as an internal reference. MS spectra were recorded on Kratos-30 mass spectrometer. Reaction progress was monitored by TLC using silica gel 'G' coated glass plates and benzene: petroleum ether as an eluent. The microwave assisted procedures were carried out using a BPL BMO domestic oven operating at 700W generating 2450 MHz frequency.

5-Substituted 2-aminobenzenethiols[16] **(1a-e)** and *2-arylidene-1-tetralone*[17] **(2)** were prepared according to literature reported methods.

10-Methoxy-7-phenyl-5,6,6a,7-tetrahydrobenzo[b]naphtho[1,2-e][1,4]thiazepine **(4d)** was prepared following two routes: (1) a conventional one, (2) a microwave- assisted procedure.

Conventional synthesis

An equimolar mixture of **1d** (155 mg, 1 mmol) and **2** (234 mg, 1 mmol) was solubilized in ethanol (20 mL) with 1 mL of conc .HCl/ toluene (25 mL) with catalytic amounts of TFA and refluxed for an appropriate time till the reactants disappeared as followed by TLC. The excess of solvent was removed under reduced pressure and the residue left was recrystallized from ethanol to give the respective product (**4d**) (Tables 1 and 2).

Microwave assisted synthesis

(a) Ethanol containing catalytic amount of conc. HCl

An equimolar mixture of **1d** and **2** in ethanol (10 mL) containing catalytic amount of conc.HCl (1 mL) was placed in the microwave oven (using 30% power, i.e. 275 W) and irradiated for 10 min. The irradiation was completed with a short interruption of 1 min after every 3 min to avoid overheating of the solvent. Progress of the reaction was monitored by TLC. Reaction mixture was cooled down and the so-obtained residue on crystallization from ethanol gave light yellow flakes of **4d**.

(b) Using various inorganic solid supports

An equimolar mixture of **1d** and **2** was introduced in a beaker and dissolved in acetone (5 mL). Inorganic solid support such as montmorillonite KSF, basic alumina or silica gel (20% by weight of the reactants) was then added and swirled for a while followed by removal of the solvent under gentle vacuum. The dry free flowing powder thus obtained was irradiated in the microwave oven at a power output of 90% (640 watts), for an appropriate time (monitored by TLC).The recyclable inorganic solid support was separated by filtration after eluting the product with methanol. The solvent was evaporated to give crystals of **4d**, which were found to be pure (TLC) and do not require further recrystallization in the case of montmorillonite KSF, whereas with basic alumina and silica gel, the product obtained was crystallized from methanol.

It can be concluded that montmorillonite KSF under MW irradiation is the simplest and most effective system for the synthesis of **4a**. Other compounds **(4a-c)** and **(4e)** were similarly prepared by this method and results were compared with those following conventional thermal method (ethanol + conc. HCl). The structure of the compounds **(4a-f)** were confirmed by IR, ^{1}H NMR spectra and elemental analyses for nitrogen (Tables 3 and 4).

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