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Note

Novel clay-catalysed expeditious cyclization to bis-benzothiazepine

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A microwave-expediated, high yielding synthesis of 4,4′-bis(2″-aryl-2″,3″-dihydro-1″,5″-benzothiazepin-4"-yl)bibenzyls **3a-j** involving Claisen-Schmidt condensation of 4,4′-diacetylbibenzyl with aromatic aldehyde at room temperature followed by cyclocondensation with 2-aminothiophenol on montmorillonite K 10 clay in solvent-free condition under microwave is reported. All compounds show promising antifungal activity against *Fusarium oxysporum* and *Penicillium citrinum*. Structure-activity relationships for the screened compounds are discussed.

Keywords: Benzothiazepine, clay-catalyzed, Claisen-Schmidt condensation, microwave irradiation, fungicide

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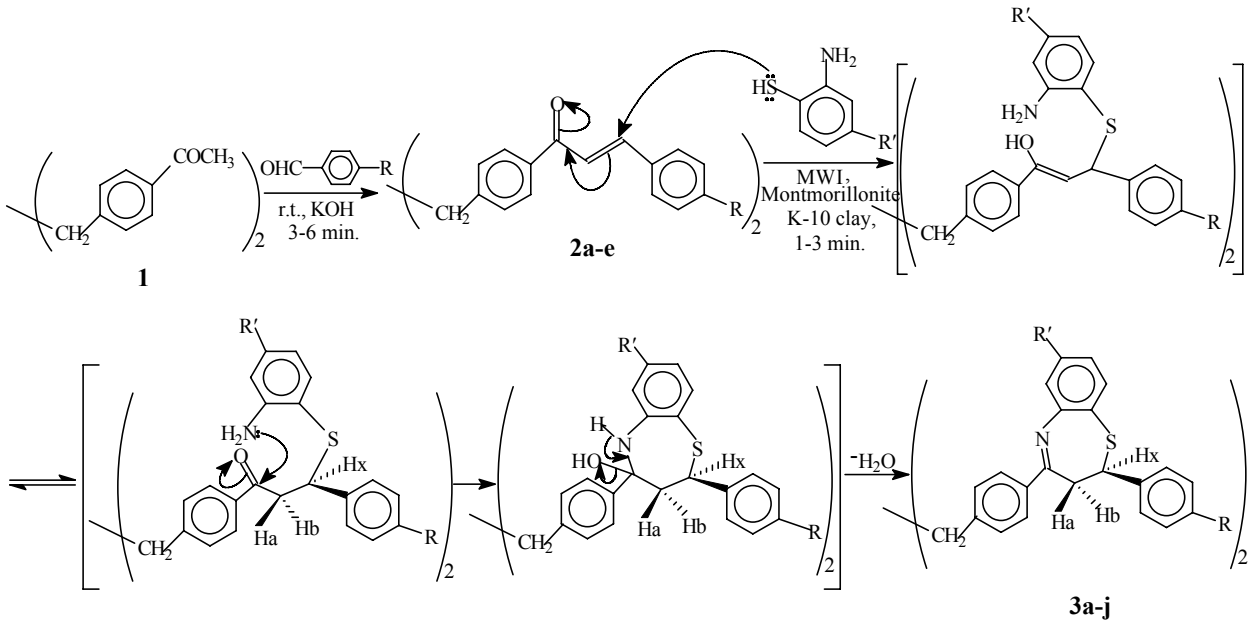
The chemistry of seven-membered heterocycles have been for less extensively studied than that of other heterocycles such as five and six membered ones. 1,5-Benzothiazepines are gaining more attention due to their chemotherapeutic applications such as coronary vasodilation[1], antihypertention[2], antiulcer[3,4], anti-feedant[5], antimicrobial[6,7], maintenance of Ca^{++} ion concentration etc. In recent report of other bioactive 1,5-benzothiazepines, has enthused great interest in the detailed study of 1,5-benzothiazepine class of compounds. It has also prompted us to search for improved synthetic routes and the study of substituents at different positions in benzothiazepine nucleus.

Clay-catalyzed organic transformations have generated considerable interest because of their inexpensive nature and special catalytic attribute under heterogeneous conditions[8,9]. The use of solid supports[10] as well as microwave[11] is well established pollution free technique currently under investigation by synthetic organic chemists and has attracted much attention in recent years because it offers several advantages, such as rapid reaction rates and higher yields of pure products[12,13] as a consequence of the selective absorption of microwave energy by polar molecules or polar intermediates formed during the course of the reaction[13]. Furthermore with increasing environmentally benign synthetic method has become desirable. The solvent-free reactions are especially used as they provide an opportunity to work with open vessels, thus avoiding the risk of high-pressure development and with a possibility of carrying out the reaction to the associated selectivity. In this respect organic syntheses under solvent-free[14,15] conditions are basic protocols because solvents are often toxic and are agents that pollute the environment.

In view of this observation and in continuation of our earlier efforts[16-18], on synthesis of potentially bio-active compounds, herein we report the synthesis of bis-1,5-benzothiazepines. For the synthesis of target bis-1,5-benzothiazepines, the reaction sequences were followed as outlined in the **Scheme I**. The title compounds were synthesized by using Claisen-Schmidt condensation of 4,4′-diacetylbibenzyl with aromatic aldehyde at room temperature followed by Michael addition of 2-aminobenzenethiol to α,β-unsaturated ketone through –SH group under microwave irradiation, leading to dehydrative cyclisation to form 2,3-dihydro-1,5-benzothiazepine. In the proposed mechanism (**Scheme I**; **2a-e → 3a-j**) initially Michael addition of 2-aminothiophenol to α,β-unsaturated ketone takes place through -SH group and not -NH_2 group. This is due to greater polarizability of -SH group in comparison to -NH_2 group (in aminothiol) initial nucleophilic attack by -SH group occurs at β-position and not at α-position in the α,β-unsaturated ketonic system, so other analogues of benzothiazepine have not been obtained[19]. Purity of title compound was confirmed by TLC (silica gel, benzene-MeOH; 7:3, v/v). The structure was assigned by ^{1}H NMR and mass spectra and elemental analysis.

The J_{ab} value of 17 Hz indicates that both the hydrogens of methylene are sterically different; H_a is axial and H_b is equatorial. The axial proton, most often, resonates at higher field than the geminal equatorial proton. The chemical inequivalence of H_a (δ 3.08) and H_b (δ 2.00) distinguishes H_a as axial protron and H_b as equatorial proton.



Compd	R	Compd	R	R′	Compd	R	R′
2a	H	**3a**	H	H	**3f**	H	OCH_3
2b	OCH_3	**3b**	OCH_3	H	**3g**	OCH_3	OCH_3
2c	Cl	**3c**	Cl	H	**3h**	Cl	OCH_3
2d	CH_3	**3d**	CH_3	H	**3i**	CH_3	OCH_3
2e	NO_2	**3e**	NO_2	H	**3j**	NO_2	OCH_3

Scheme I - Novel clay-catalysed expeditious cyclization to bis-benzothiazepine

Further H_a couples with H_b to give a doublet with J_{ab} = 17 Hz but the presence of double doublet is due to its coupling with methine proton at C_2 (J_{ax} = 13.5 Hz). Similarly, the H_b proton, which resonates at δ 2.00, on coupling with geminal proton, gives a doublet (J_{ab} = 17 Hz) and on coupling with methine proton produces a double doublet (J_{bx} = 2.5 Hz). The difference in J values of J_{ax} and J_{bx} is due to the different conformations of H_a and H_b.

After some preliminary experimentation, it was found that the envisaged cyclization (**1→3**) was effective with montmorillonite K 10 clay under microwave irradiation for the time specified in **Table I**, to afford bis-1,5-benzothiazepines **3a-j** in 87-95% yield (**Table I**). However, the use of other mineral supports, viz. silica gel, neutral or basic alumina was less effective resulting in either no cyclization (in basic alumina) or very low yields (13-33%) (in the case of silica gel and neutral alumina). That the effect of microwaves may not be purely thermal[21] but may have some non-thermal effect viz. frequency charge-space polarization[22,23] (specific MW effect). This is supported by the fact that the reaction could not be completed, that is only 59% conversion over 9 hr at the same bulk temperature (90°C) employing conventional heating in an oil-bath.

Most of the conventional methods[19,20] suffer from one or more drawbacks such as extended reaction time, use of large amount of solvent and with lesser yields. Herein we describe a new method for the synthesis of 1,5-benzothiazepines under microwave irradiation in solvent-free conditions in which considerable reduction in reaction time and enhancement of yield of the product was observed. In conclusion we have developed an environmentally benign, expeditious method for the synthesis of bis-1,5-benzothiazepines on a clay surface under solvent-free conditions. It is noteworthy that all the bibenzyl based bis-1,5-benzothiazepines **3a-j** are new. The application of this method to the synthesis of aglycon-modified potentially antiviral nucleoside is at present ongoing in our laboratory.

Antifungal screening. *In vitro* antifungal activity of compounds **2a-e** and **3a-j** were evaluated against *Fusarium oxysporium* and *Penicillium citrinum* by poisoned food technique[24] at 1000, 100 and 10 ppm concentrations using Czapek′s agar medium as described in the literature[25,26]. The number of replicate

Table I – Physical and spectral data of compounds **2a-e** and **3a-j**

Compd	Time (min.)	Yield[a] (%)	mp °C	Mol. formula[b] (Mol. wt.)	^{1}H NMR (δ, ppm)	MS m/z (M^+)
2a	4.0	88	199	$C_{32}H_{26}O_2$ (442.54)	2.88 (s, 4H, acyclic CH_2CH_2), 7.14-7.76 (m, 18H, ArH), 7.85 (d, 2H, *J*=15 Hz, *α*-CH), 7.95 (d, 2H, *J*=15 Hz, *β*-CH)	442
2b	6.0	87	205	$C_{34}H_{30}O_4$ (502.59)	2.88 (s, 4H, acyclic CH_2CH_2), 3.73 (s, 6H, OCH_3), 6.72-7.76 (m, 16H, ArH), 7.85 (d, 2H, *J*=15 Hz, *α*-CH), 7.95 (d, 2H, *J*=15 Hz, *β*-CH)	502
2c	3.0	90	213	$C_{32}H_{24}O_2Cl_2$ (511.43)	2.88 (s, 4H, acyclic CH_2CH_2), 7.22-7.76 (m, 16H, ArH), 7.85 (d, 2H, *J*=15 Hz, *α*-CH), 7.95 (d, 2H, *J*=15 Hz, *β*-CH)	510
2d	5.0	87	198	$C_{34}H_{30}O_2$ (470.60)	2.88 (s, 4H, acyclic CH_2CH_2), 2.35 (s, 6H, CH_3), 7.01-7.76 (m, 16H, ArH), 7.85 (d, 2H, *J*=15 Hz, *α*-CH), 7.95 (d, 2H, *J*=15 Hz, *β*-CH)	470
2e	6.0	89	201	$C_{32}H_{24}N_2O_6$ (532.54)	2.88 (s, 4H, acyclic CH_2CH_2), 7.31-7.90 (m, 16H, ArH), 8.01 (d, 2H, *J*=15 Hz, *α*-CH), 8.23 (d, 2H, *J*=15 Hz, *β*-CH)	532
3a	2.5	90	230	$C_{44}H_{36}N_2S_2$ (656.90)	2.00 (dd, 2H, *J* = 17 Hz, *J* = 2.5 Hz, H_b), 2.88 (s, 4H, acyclic CH_2CH_2), 3.08 (dd, 2H, *J* = 17 Hz, *J* = 13.5 Hz, H_a), 4.54 (dd, 2H, *J* = 13.5 Hz, *J* = 2.5 Hz, H_x), 7.00-7.57 (m, 26H, ArH)	656
3b	3.0	91	233	$C_{46}H_{40}N_2O_2S_2$ (716.95)	2.00 (dd, 2H, *J* = 17 Hz, *J* = 2.5 Hz, H_b), 2.88 (s, 4H, acyclic CH_2CH_2), 3.08 (dd, 2H, *J* = 17 Hz, *J* = 13.5 Hz, H_a), 3.37 (s, 6H, 2xOCH_3), 4.54 (dd, 2H, *J* = 13.5 Hz, *J* = 2.5 Hz, H_x), 6.72-7.20 (m, 24H, ArH)	716
3c	1.0	93	240	$C_{44}H_{34}N_2S_2Cl_2$ (725.79)	2.00 (dd, 2H, *J* = 17 Hz, *J* = 2.5 Hz, H_b), 2.88 (s, 4H, acyclic CH_2CH_2), 3.08 (dd, 2H, *J* = 17 Hz, *J* = 13.5 Hz, H_a), 4.54 (dd, 2H, *J* = 13.5 Hz, *J* = 2.5 Hz, H_x), 7.00-7.22 (m, 24H, ArH)	724
3d	2.5	89	212	$C_{46}H_{40}N_2S_2$ (684.95)	1.23 (s, 6H, CH_3), 2.00 (dd, 2H, *J* = 17 Hz, *J* = 2.5 Hz, H_b), 2.88 (s, 4H, acyclic CH_2CH_2), 3.08 (dd, 2H, *J* = 17 Hz, *J* = 13.5 Hz, H_a), 4.54 (dd, 2H, *J* = 13.5 Hz, *J* = 2.5 Hz, H_x), 7.00-7.20 (m, 24H, ArH)	684
3e	3.0	87	210	$C_{44}H_{34}N_4O_4S_2$ (746.89)	2.00 (dd, 2H, *J* = 17 Hz, *J* = 2.5 Hz, H_b), 2.88 (s, 4H, acyclic CH_2CH_2), 3.08 (dd, 2H, *J* = 17 Hz, *J* = 13.5 Hz, H_a), 4.54 (dd, 2H, *J* = 13.5 Hz, *J* = 2.5 Hz, H_x), 7.00-8.14 (m, 24H, ArH)	746
3f	2.0	94	218	$C_{46}H_{40}N_2O_2S_2$ (716.95)	2.00 (dd, 2H, *J* = 17 Hz, *J* = 2.5 Hz, H_b), 2.88 (s, 4H, acyclic CH_2CH_2), 3.08 (dd, 2H, *J* = 17 Hz, *J* = 13.5 Hz, H_a), 3.73 (s, 6H, 2xOCH_3), 4.54 (dd, 2H, *J* = 13.5 Hz, *J* = 2.5 Hz, H_x), 6.70-7.21 (m, 24H, ArH)	716
3g	2.0	93	225	$C_{48}H_{44}N_2O_4S_2$ (777.00)	2.00 (dd, 2H, *J* = 17 Hz, *J* = 2.5 Hz, H_b), 2.88 (s, 4H, acyclic CH_2CH_2), 3.08 (dd, 2H, *J* = 17 Hz, *J* = 13.5 Hz, H_a), 3.73 (s, 12H, OCH_3), 4.54 (dd, 2H, *J* = 13.5 Hz, *J* = 2.5 Hz, H_x), 6.70-7.57 (m, 22H, ArH)	776
3h	2.5	95	230	$C_{46}H_{38}N_2O_2S_2Cl_2$ (785.84)	2.00 (dd, 2H, *J* = 17 Hz, *J* = 2.5 Hz, H_b), 2.88 (s, 4H, acyclic CH_2CH_2), 3.08 (dd, 2H, *J* = 17 Hz, *J* = 13.5 Hz, H_a), 3.73 (s, 6H, 2xOCH_3), 4.54 (dd, 2H, *J* = 13.5 Hz, *J* = 2.5 Hz, H_x), 6.70-7.22 (m, 22H, ArH)	784
3i	1.5	90	237	$C_{48}H_{44}N_2O_2S_2$ (745.00)	1.23 (s, 6H, CH_3), 2.00 (dd, 2H, *J* = 17 Hz, *J* = 2.5 Hz, H_b), 2.88 (s, 4H, acyclic CH_2CH_2), 3.08 (dd, 2H, *J* = 17 Hz, *J* = 13.5 Hz, H_a), 3.73 (s, 6H, 2xOCH_3), 4.54 (dd, 2H, *J* = 13.5 Hz, *J* = 2.5 Hz, H_x), 6.70-7.57 (m, 22H, ArH)	744
3j	2.5	89	222	$C_{46}H_{38}N_4O_6S_2$ (806.94)	2.00 (dd, 2H, *J* = 17 Hz, *J* = 2.5 Hz, H_b), 2.88 (s, 4H, acyclic CH_2CH_2), 3.08 (dd, 2H, *J* = 17 Hz, *J* = 13.5 Hz, H_a), 3.73 (s, 6H, 2xOCH_3), 4.54 (dd, 2H, *J* = 13.5 Hz, *J* = 2.5 Hz, H_x), 6.70-8.14 (m, 22H, ArH)	806

[a] Yield of purified and isolated products

[b] All compounds gave C, H and N analyses with ±0.30%.

assays in each were three, and six replicate controls were used. A standard commercial fungicide, Dithane M-45 and Griseofulvin were also tested under similar conditions for comparison. No remarkable morphological change was observed in the developing fungi. The antifungal screening results are summarized in **Table II**.

For the most active compounds **2c**, **3b**, **3c**, **3g** and **3h** it was ascertained whether they are fungistatic or fungicidal. Thus, following the procedure of Garber *et al*.[27], compounds **2c**, **3b**, **3c**, **3g** and **3h** were added separately to Czapek′s agar medium in different petridishes to maintain the final concentrations at their respective lethal dose (1000, 800 and 700 ppm). The test fungi were inoculated in the centre of these petridishes and incubated at 28 ± 1°C for 96 hr, after which time, the percent inhibition of mycelial growth compared with that in control dishes was recorded. Then the fungal disks were taken from the treated and control dishes, washed with sterilized double-distilled water, and reinoculated in fresh petridishes containing Czapek′s agar medium only. The plates were incubated for 96 hr at 28 ± 1°C and the percent inhibition was recorded. The number of replicate assays in each case was three, and six replicate controls were used. It was found that compounds **2c**, **3b**, **3c**, **3g** and **3h** caused complete inhibition of mycelial growth of the test fungi in treated as well as reinoculated dishes and hence were fungicidal.

Experimental Section

Melting point were determined by open glass capillary method and are uncorrected. An unmodified domestic household microwave (Padmini Essentia, Model Brownie) operating at 2450 MHz was used at a power output of 600W for all experiments. Completion of the reaction was monitored by TLC (silica gel, benzene-MeOH; 7:3, v/v). The final products were purified by flash chromatography using silica gel with increasing percentage of MeOH in benzene. ^{1}H NMR spectra were recorded on a Bruker 40°C (400 MHz) FT spectrometer in $CDCl_3$, using TMS as internal reference (chemical shifts in δ, ppm); and mass spectra on a Jeol D-300 mass spectrometer at 70 eV. Elemental analyses were carried out by using Coleman automatic C, H, N analyzer.

4,4′-Bis(1′′-oxo-3′′-aryl-2′′-propen-1′′-yl)bibenzyls 2a-e. A mixture of 4,4′-diacetylbibenzyl **1** (5.0 mmoles), aromatic aldehyde (benzaldehyde/*p*-methoxybenzaldehyde/*p*-chlorobenzaldehyde/*p*-methylbenzaldehyde/*p*-nitrobenzaldehyde) (10 mmoles) and KOH (10 mmoles) were ground by pestle and mortar at room temperature for the time specified in **Table I** and treated with water. The resultant yellow product

Table II — Antifungal screening results of compounds **2a-e** and **3a-j**

Compd	Average % inhibition after 96 hr against					
	F. oxysporium			*P. citrinum*		
	1000 ppm	100 ppm	10 ppm	1000 ppm	100 ppm	10 ppm
2a	48	20	10	50	22	12
2b	50	36	30	55	40	20
2c	88	50	22	84	37	25
2d	55	47	35	52	20	16
2e	40	27	10	41	30	15
3a	61	50	24	46	32	17
3b	98	73	65	100	73	68
3c	100	86	74	97	80	56
3d	61	56	49	69	47	35
3e	59	45	40	53	46	28
3f	60	42	30	67	53	42
3g	97	89	68	100	85	64
3h	100	81	59	100	79	63
3i	80	77	69	94	84	55
3j	76	64	55	75	66	45
Dithane M-45	100	95	92	100	98	96
Griseofulvin	100	98	94	100	97	95

was filtered, washed with ice-cold water and recrystallized from MeOH to obtained analytically pure **2a-e**.

4,4′-Bis(2″-aryl-2″,3″-dihydro-1″,5″-benzothiazepin-4″-yl)bibenzyls 3a-j. Compound **2a** (2.5 mmoles) and 2-aminothiophenol (unsubstituted/ substituted) (5.0 mmoles) were taken in 100 mL pyrex beaker and adsorbed on montmorillonite K 10 clay. This was subjected to microwave irradiation for the time specified in **Table I**. On completion of reaction, monitored by TLC silica gel (benzene-MeOH; 7:3, v/v), the reaction mixture was cooled to room temperature and eluted with acetone (3×20 mL). The elute was evaporated under reduced pressure to obtain crude product. The residue on purification with flash chromatography gave analytically pure **3a**.

Similarly, compounds **3b-j** were prepared.

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