Facile One Pot Microwave Induced Solvent-Free Synthesis and Antifungal, Antitubercular Screening of Spiro [1,5]-Benzothiazepin-2,3′[3′*H*]indol-2[1′*H*]-ones

Anshu DANDIA,*[a] Meha SATI,[a] Kapil ARYA,[a] Rekha SHARMA,[a] and André LOUPY[b]

[a] *Department of Chemistry, University of Rajasthan; Jaipur 302 004, India: and* [b] *Laboratoire des Réactions Sélectives Sur Supports, ICMMO, UMR 8615, Building 410, Université Paris-Sud, 91405 Orsay cedex, France.*

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Microwave activation coupled with dry media technique as a green chemistry procedure has been applied to synthesis of a series of some new title compounds. They have been obtained by the reaction of *in situ* synthesized 1,3-dihydro-3-[2-(phenyl/4-fluorophenyl)-2-oxoethylidene)-indol-2(1*H*)-one (4a, b) with substituted aminobenzenethiols (5a—d). The key intermediates 4a, b were also prepared in one step by this improved technique by reacting isatin and substituted acetophenones (2a, b). The results obtained under microwave irradiation when compared with that following conventional method demonstrate the versatility of the process. The title compounds 7a—e have also been screened for their antifungal and antitubercular activity, 7a and 7e showing maximum inhibition of growth of *Alternaria alternata* and *Fusarium oxysporium* and 7b, c, e revealing significant antitubercular activity.

Key words spiro[benzothiazepin-indol]-2-one; microwave induced synthesis; dry media technique; biological activity; 3-aroylmethylene-2*H*-indol-2-one; *o*-aminobenzenethiol

Studies on chemistry and pharmacology of 1,5-benzothiazepines have provided the famous cardiovascular drugs *Diltiazem*, *Clentiazem*, *etc.* to the mankind and those in which the fused benzene ring is substituted at various positions have been found to be more potent.[1)] The research on the chemistry of indoles has continued unabated due to their wide spread occurrence in nature and biological activities[2—4)] and the compounds in which the bio-active indole nucleus is spiro fused with another heterocycle at the C-3 position shows immense pharmaceutical applications.[5—7)] Further, spiro-3-indole derivatives, incorporating five and six membered heterocycles have been extensively reviewed[8—12)] but few reports are available regarding those incorporating a seven membered thiazepine moiety. Also, 3-aroyl-2*H*-indol-2-ones (**4a**, **b**) have been found as the essential synthetic building block[13—15)] for the synthesis of a wide variety of 3-spiro indolines and condensed indole derivatives. The investigation of their reaction with substituted aminobenzenethiols to form the title products was found interesting in view of the fact that different reaction sites are available in the key intermediates which may lead to a mixture of products as observed earlier in reactions with several other nitrogen containing nucleophiles.[16—20)]

The use of microwave (MW) for assisting different organic reactions has become very popular in the last few years and recently the use of supported reagents coupled with MW irradiation has gained special attention[21—23)] due to its eco-friendliness and safety. Many review articles[24—30)] have been published in this field. Due to timeliness, ease of workability, dramatic rate enhancement and increased selectivity, microwave technology provides a promising alternative to environmentally unacceptable conventional procedures that may be time consuming or using toxic, expensive, problematic *versus* pollution and often flammable solvents in large amounts.

Hence, we were encouraged by the vast potential of rapid and efficient solvent-less MW induced method that have manipulative advantages over heterogeneous reactions and in continuation to our earlier interest on the synthesis of various biodynamic spiro-3-indole derivatives[31—38)] under MW irradiation. So, we report here in a facile and enviro-economic synthesis of the title compounds **7a**—**e** incorporating two biologically important heterocycles (1,5-benzothiazepine and indole) with the assumption that the combination of these moieties may enhance the biological profile of the compound many fold versus its parent nuclei.

Results and Discussion

The usual thermal procedure for the synthesis of **4a**, **b** requires a two steps procedure[39)] which involves reaction of isatin (**1**) with substituted acetophenones (**2a**, **b**) in refluxing ethanol and Et_2NH as basic catalyst (3 or 4 drops) to afford 1,3-dihydro-3-hydroxy-3-[2-phenyl/4-fluorophenyl-2-oxoethylidene]-indol-2(1*H*)-ones (**3a**, **b**) followed by dehydration in the presence of a mixture of refluxing glacial AcOH and concentrated HCl afforded 1,3-dihydro-3-[2-(phenyl/4-fluorophenyl)-2-oxoethylidene]-indol-2(1*H*)-one (**4a**, **b**).

However, when the same reaction was studied under MW irradiation using basic alumina as the inorganic solid support, the compounds **4a**, **b** were obtained in quantitative yields with reasonable purity in 5—6 min without formation of the expected products **3a**, **b**. The usage of basic alumina as the mineral support therefore eliminates the necessity of an external base for the synthesis of required intermediate **4** which was formed in reasonable purity (TLC) hence used as such for further reaction with 5-substituted-2-aminobenzenethiols **5a**—**d** to afford the title products **7a**—**e** in a one step procedure whereas a tedious three steps procedure was required for the same reaction under classical conditions (Chart 1).

The MW assisted reactions were tried in various mediums such as basic alumina or montmorillonite KSF as solid supports, ethanol+conc. HCl, toluene+TFA, ethylene glycol+conc. HCl, ethylene glycol+piperidine to check the most ef-

* To whom correspondence should be addressed. e-mail: dranshudandia@eth.net

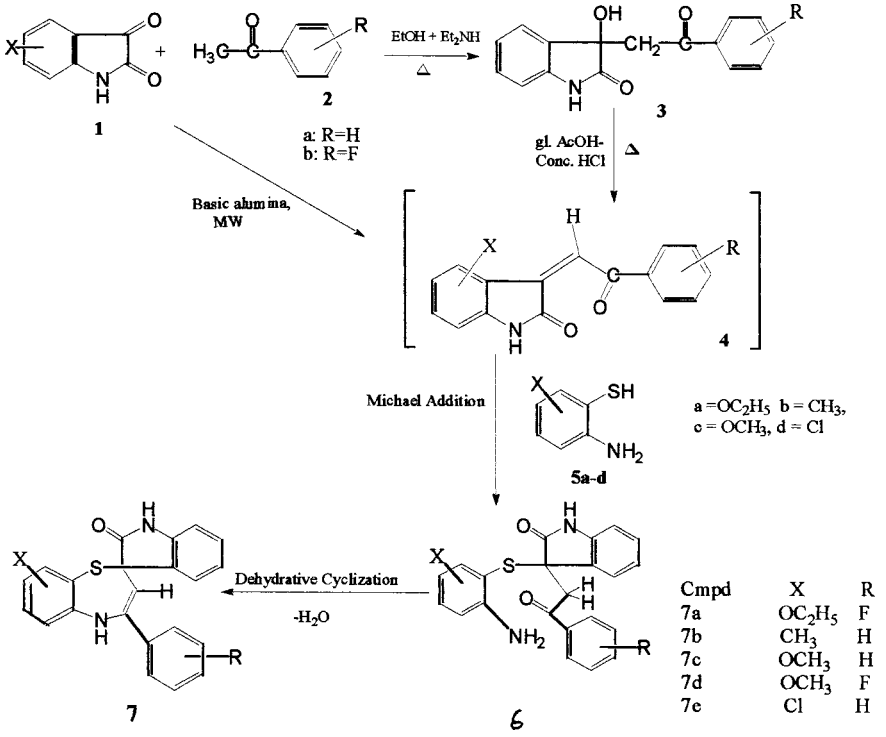

Chart 1

fective condition for the above synthesis. For sake of comparison, the reaction was also carried out conventionally in neutral, basic and acidic medium. Positive results were only obtained in acidic medium with lower yields due to the formation of side products and hence required further purification and crystallization, while, the reaction in basic medium gave an intractable mixture which could not be separated into identifiable pure compounds and reaction did not occur in neutral medium even on prolonged reflux. From the results of Table 1, it can be concluded that basic alumina used as the dry support is the simplest and the most effective catalyst for the synthesis of **7a** and consequently we extended same conditions to synthesize a new series of spiro-fused 1,5-benzothiazepines **7b**—**e** (Table 2).

Finally, in order to check the possible intervention of specific (non-thermal) MW effects, the results obtained under MW were compared to conventional heating. The reaction, in the case of compound **7a**, has been carried out using preheated oil bath, under the same conditions as under MW (time, temperature, vessel) (Table 3).

In all cases it has been found that reactions proceed with considerable lower yields under similar thermal conditions demonstrating that the effect of MW is evidently not purely thermal.[40,41] These specific non-thermal effects remain noticeable even by extended reaction times up to 6 h, are consistent with the consideration of mechanisms[42] and with the assumption that MW effects are increased when the polarity of a system is enhanced. The rate-determining step consists in the Michael addition of thiophenol moiety on carbon–carbon double bond of α,β-unsaturated carbonyl compound. One can expect important specific MW effects due to the enhancement of polarity of the system during the reaction progress which is provided by ionic dissociation of the ion pairs from the ground state of the reaction towards the transition state, which is more polar due to the negative charge delocalization. The more important stabilization of the transition state by dipole–dipole electrostatic interactions with the electric field is therefore responsible for an enhancement of reactivity by a decrease of the activation energy (Chart 2).

Table 1. Comparative Results Obtained for the Synthesis of **4a**, **b** by Reacting **1** and **2a**, **b**

Compd.	Method	Temperature[a] (°C)	Reaction time (min)	Yield[b] (%)	
				MW	Δ
4a	Δ (EtOH+Et_2NH)	Reflux	300	—	72
	MW (basic alumina)	130	4	96	0[c]
	Δ (basic alumina)	130	300	—	Traces[d]
4b	Δ (EtOH+Et_2NH)	Reflux	300	—	67
	MW (basic alumina)	128	6	98	0[c]
	Δ (basic alumina)	128	300	—	17[d]

a) Final temperature is measured at the end of microwave irradiation by introducing a glass thermometer in the reaction mixture in the beaker. *b*) Yield of the isolated products. *c*) Yield under identical thermal conditions of time and temperature as under microwaves. *d*) Yield under identical thermal conditions of temperature, after extended time.

This step is followed by intramolecular nucleophilic addition to the carbonyl group involving the formation of a dipolar transition state, which is stabilized by microwaves (Chart 3). Hence, the formation of (**7**) is substantially accelerated by MW under solvent-free conditions.

IR spectra of the final products displayed characteristic absorptions in the region 3405—3138 (N–H), 1695—1680 (–NHCO) and 1180—1159 cm^{-1} (C–N). The ^{1}H-NMR spectra showed a singlet at 6.79—6.91 (=C–H) and two broad signals in the region 8.08—8.4 ppm (NH thiazepine, NH indole, exchangeable with deuterium) and at 6.54—7.85 (m, aromatic protons). Disappearance of exocyclic C=C at 1620,

Table 2. Analytical and Physical Data of **7a**—**e**

Compd.	R	X	mp (°C)	Time[a] (min) $\Delta^{b)}/MW^{c)}$	Yield[a] (%) $\Delta^{b)}/MW^{c)}$	Molecular formula	Nitrogen (%) Found (Calcd.)
7a	F	OC_2H_5	174—176	360/*15*	47/*72*	$C_{24}H_{19}FN_2O_2S$	6.9 (7.1)
7b	H	CH_3	145—146	360/*11*	65/*66*	$C_{23}H_{18}N_2OS$	7.4 (7.6)
7c	H	OCH_3	160—162	420/*18*	58/*68*	$C_{23}H_{18}N_2O_2S$	7.4 (7.2)
7d	F	OCH_3	150—152	300/*14*	48/*68*	$C_{23}H_{17}FN_2O_2S$	7.0 (6.8)
7e	H	Cl	155—157	420/*26*	65/*73*	$C_{22}H_{15}ClN_2OS$	7.5 (7.3)

a) Time and yield for the compounds isolated from. *b*) Conventional method, using EtOH+dry HCl gas. *c*) in italics, microwave-assisted method using basic alumina as solid support.

Table 3. Comparative Results Obtained for the Synthesis of **7a** by Reacting **4b** and **5a**

Conditions	Temperature[a] (°C)	Reaction time (min)	Yield[b] (%) MW	Yield[b] (%) Δ
EtOH+HCl	78	17	58	Nil[c] (47)[d]
Toluene+glacial AcOH	108	17	48	Nil[c] (19)[d]
Ethylene glycol+piperidine	117	12	55	30[c]
Basic alumina	158	15	72	18[c] (34)[d]
Montmorillonite KSF	110	18	67	Nil[c] (21)[d]
	138	30	70	—

a) Final temperature is measured at the end of microwave irradiation by introducing a glass thermometer in the reaction mixture in the beaker. *b*) Yield of the isolated products. *c*) Yield under identical thermal conditions of time and temperature as under microwaves. *d*) Yields obtained after extension of reaction time up to 360 min at similar temperature (under MWs).

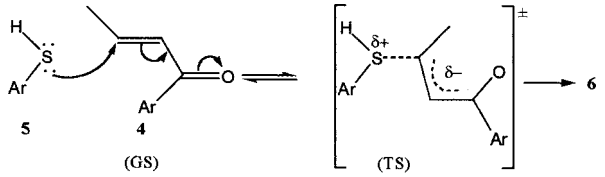

Chart 2

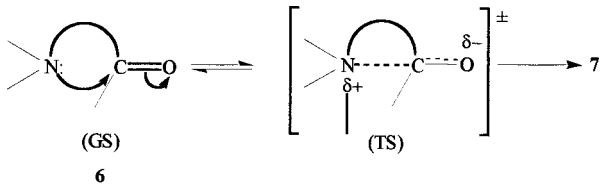

Chart 3

Table 4. IR and ^{1}H-NMR Spectral Data of Compounds **7a**—**e**

Compd.	IR (cm^{-1})				^{1}H-NMR δ (ppm), J in Hz			
	NH	C=O	C–N	=CH	X	ArH	NH[a]	NH[a]
7a	3400—3145	1685	1159	6.79 (s, 1H)	1.33 (t, J=7, 3H) 3.96 (q, J=7, 2H)	6.73—7.65 (m, 11H)	8.11	8.4
7b	3395—3138	1690	1165	6.80 (s, 1H)	2.25 (s, 3H)	6.9—7.85 (m, 12H)	8.08	8.3
7c	3405—3155	1680	1182	6.83 (s, 1H)	3.83 (s, 3H)	6.54—7.70 (m, 12H)	8.09	8.36
7d	3390—3140	1685	1180	6.91 (s, 1H)	3.77 (s, 3H)	6.85—7.74 (m, 11H)	8.2	8.33
7e	3400—3150	1695	1160	6.86 (s, 1H)	—	6.75—7.52 (m, 12H)	8.19	8.38

a) Exchangeable with deuterium.

C=O absorption at 1670 cm^{-1} and retention of NHCO peak at 1680—1695 cm^{-1} indicated the participation of α,β-unsaturated carbonyl system of side chain of **4** resulting in the formation of spiro heterocycle at position 3 of 2-indolinone. Further, the absence of primary amino group absorption at 3450 and 3350 cm^{-1} confirmed the formation of 1,5-benzothiazepine ring system ruling out the possibility of **6** (Table 4).

^{13}C-NMR spectrum of **7a** showed signals at δ [$CDCl_3$+$(CD_3)_2SO$] 14.1, $OCH_2\underline{CH_3}$, 56.8, spiro carbon; 61.6, $O\underline{CH_2}CH_3$; 94.2, C-3; 138.9, C-4; 155.3, C-8; 165.4, C=O; 111.1—149.0, 18 aromatic ring carbon atoms. The presence of fluorine was confirmed by[40,41] F-NMR spectra of **7d** and **7a** where the C–F signal was observed at δ [$CDCl_3$+$(CD_3)_2SO$] −119.05 and −118.73 ppm respectively. In the mass spectra of **7b** and **7a**, molecular ion peaks were observed at *m*/*z* 370 (3.7%) and 418 (2.2%) corresponding to the molecular formula $C_{23}H_{18}N_2OS$ and $C_{24}H_{19}FN_2O_2S$ respectively.

Table 5. *In Vitro* Evaluation of Antitubercular Activity against Mycobacterium Tuberculum

Compd.	X	MIC (μg/ml)	% Inhibition
7a	OC_2H_5	>12.5	97 +
7b	CH_3	>12.5	99 +
7c	OCH_3	>12.5	99 +
7d	OCH_3	>12.5	92 +
7e	Cl	>12.5	100 +

MIC RMP=0.25 μg/ml, 98% inhibition *vs. M. tuberculosis*. + Inhibition greater than 90%, % inhibition=activity of each compound at the 12.5 μg/ml level. Final column lists the minimum inhibitory concentration of a control drug for comparison. MIC=minimum inhibitory concentration in μg/ml.

Evaluation of Antitubercular Activity The antitubercular evaluation of the compounds was carried out by the "Tuberculosis Antimicrobial Acquisition and Coordinating facility" (TAACF) in U.S.A. Primary screening of the compounds have been conducted at 12.5 μg/ml against Mycobac-

Table 6. Effect of Synthesized Compounds **7a**—**e** on the Radial Growth of Different Fungi

Cmpd.	Radial growth (in cm) and percent inhibition of *Alternaria alternata*					Radial growth (in cm) and percent inhibition of *Fusarium oxysporium*				
	Check 0 ppm	500 ppm	% Inhibition	1000 ppm	% Inhibition	Check 0 ppm	500 ppm	% Inhibition	1000 ppm	% Inhibition
7a	5.10	2.40	52.94	1.50	70.58	4.50	1.80	60.00	1.50	48.57
7b	3.30	1.50	54.54	1.00	69.69	3.50	2.50	28.57	1.30	62.85
7c	3.30	1.30	60.60	1.00	69.69	3.50	2.10	40.00	1.10	68.57
7d	5.10	3.10	39.21	0.70	86.27	4.50	2.80	37.77	2.00	55.55
7e	3.30	1.30	60.60	0.80	75.75	3.50	1.30	62.85	1.80	66.66

Each observation on average of three replications. Percent growth=[radial growth in check (cm)−radial growth in treatment (cm)]/[radial growth in check (cm)]×100.

terium tuberculum H37 RV, in BACTEC 12 B medium using BACTEC 460 radiometric system.[43] Antitubercular activity data were compared with standard drug Rifamipin at 0.25 μg/ml concentration which showed 98% inhibition. Compounds **7a**—**e** showed 97, 99, 97, 92 and 100% activity respectively (Table 5), which were further screened for level-2 screening.

Evaluation of Antifungal Activity The synthesized compounds **7a**—**e** were screened for antifungal activity against *Alternaria alternata* and *Fusarium oxysporium* in three replications by 'Food poision technique.[44] Each of the compound was dissolved in 20% acetone at 1000 and 500 ppm concentrations, which was then added, in required quantities, to Potato Dextrose Agar (PDA) medium, in three replicates before dispersing into petriplates. Standard checks were also prepared by inoculating fungi in PDA media for comparison. After 7 d of incubation at 25 °C, radial growth of the colony was measured. The data obtained were statistically analyzed using completely randomized design and averages compared using critical difference at 0.05% probability.

These compounds **7a**—**e** are more effective against *Alternaria alternata* than *Fusarium oxysporium*. The concentrations of the compounds greatly influence their efficiency in reducing fungus growth (Table 6).

Experimental

Melting points were determined in open glass capillaries and were uncorrected. Thin layer chromatography on silica gel 'G' coated glass plates using benzene, ethanol and ammonia (7 : 2 : 1) as eluent was used for monitoring progress of the reactions. IR spectra (KBr) were recorded on a Magna FT IR-550 spectrophotometer, ^{1}H- and ^{19}F- and ^{13}C-NMR spectra [$CDCl_3$+$(CD_3)_2SO$] were taken on a Jeol FX 90Q spectrometer at 89.55, 84.25 and 22.49 MHz respectively, using TMS as an internal standard for PMR and hexafluorobenzene as external standard for ^{19}F-NMR and mass spectra were recorded on Jeol D-300 spectrometer at an ionisation potential of 70 e.v. Microwave assisted reactions were carried out on a BPL BMO model, operating at 700 W, generating 2450 MHz frequency.

5-Chloro/methyl/methoxy/ethoxy-2-aminobenzenethiols (**5a**—**d**) were synthesized according to literature reported methods.[45]

1,3-Dihydro-3-[2-(4-fluorophenyl)-2-oxoethylidene]indol-2(1*H*)-one (**4b**) was prepared by two different ways:

Conventional Synthesis Involving a Two Steps Procedure: 1,3-Dihydro-3-hydroxy-3-(4-fluorophenyl-2-oxoethylidene)-indol-2(1*H*)-ones (**3b**)

Step 1. An equimolar mixture of indole 2,3-dione (**1**) (10 mmol, 1.47 g) and 4-fluoroacetophenone (**2b**) (10 mmol, 1.38 g) was refluxed on a water bath for 4—5 h in absolute ethanol (15 ml) containing 3—5 drops of diethylamine. On cooling, yellow coloured crystals separated out which were filtered and recrystallized from methanol to give white needles. mp=172 °C (Lit.[46] 170 °C); yield=74%.

Step 2. The compound **3b** (10 mmol, 1.47 g) was refluxed with a mixture of glacial acetic acid (15 ml) and conc. hydrochloric acid (5 ml) on a water bath for 1 h. The reaction mixture was cooled to room temperature. A red colored compound separated out which was filtered and recrystallized from ethanol to give red needles of **4b**. mp=185—187 °C (Lit.[46] 187 °C); yield, 67%.

Microwave Mediated Synthesis: An equimolar mixture of indole 2,3-dione (**1**) (10 mmol, 1.47 g) and 4-fluoroacetophenone (**2b**) (10 mmol, 1.38 g) was adsorbed separately on basic alumina (20% by weight of the reactants) *via* a solution in acetone, mixed thoroughly and irradiated in a domestic MW oven (700 W, generating 2450 MHz frequency) at an emitted power of 640 W for 5—6 min at 128 °C (monitored by T.L.C.). The product was extracted by eluting with ethanol. Excess solvent was evaporated on water bath to give red crystals of the chalcone. mp 186 °C, yield=98%.

Likewise **4a** was prepared by the same procedure. mp 195 °C (Lit.[46] 196 °C), yield, 96%.

8-Ethoxy-2,5-dihydro-(4-fluorophenyl)-spiro[[1,5]-benzothiazepin-2,3′[3′*H*]-indol]-2′(1′*H*)-one **7a** was also synthesized by two different ways: (i) a conventional method, (ii) a MW assisted method.

Conventional Method: The reactions of **4b** and **5a** were tried in three different reaction media, *viz.* neutral (dry toluene), basic (dry toluene+piperidine) and acidic (dry ethanol saturated with hydrogen chloride gas). No significant results were obtained in neutral and basic media and spiro compound was obtained exclusively in acidic medium using EtOH+dry HCl gas as follows:

A solution of **4b** (1 mmol, 267 mg) in absolute ethanol (15 ml) was saturated with hydrogen chloride gas when the red colored solution turned brown. To this, a solution of 5-ethoxy-2-aminobenzenethiol (**5a**) (1 mmol, 169 mg) in absolute ethanol (5 ml) was added slowly with continuous stirring when the solution darkened further. It was refluxed for 4—6 h till the completion of reaction, as monitored by T.L.C. The reaction mixture was cooled and kept in refrigerator for 12 to 48 h. Solid thus obtained was filtered, washed with saturated $NaHCO_3$, dried and crystallized from dry methanol to obtain the title compound **7a**. The reaction was also tried in toluene+TFA and the results are summarized in Table 1.

Microwave Assisted Synthesis: (1) Using various solvents. An equimolar mixture of **4b** and **5a** was dissolved in the minimum amount of an appropriate solvent required to form slurry, for *e.g.* (a) ethanol+conc. HCl, (b) toluene+TFA, (c) ethylene glycol+conc. HCl, (d) ethylene glycol+piperidine *etc.* in an open borosil vessel. It was irradiated inside a MW oven at an appropriate power output for an adequate time (Table 1) till the reaction was found to complete as indicated by T. L. C. Reaction mixture was cooled and poured over crushed ice in the last two cases (c) and (d). The crystalline product separated out immediately on cooling in case of (a) and (b). The crystals thus obtained were filtered, dried and recrystallized from methanol to obtain the title compounds **7a** (Table 1).

(2) Using various inorganic solid supports in dry media. Equimolar quantities of **4b** and **5a** were adsorbed separately on montmorillonite KSF or basic alumina (20% by weight of the reactants) *via* a solution in ethyl acetate, mixed thoroughly and irradiated for an appropriate time at 640 W until the completion of the reaction (monitored by T. L. C.). The recyclable inorganic solid support was separated by filtration after eluting the product with ethanol. The solvent was evaporated to give the crystalline product **7a** of reasonable purity. (Table 3).

Comparison of the results obtained by the conventional and MW methods proved basic alumina to be the most effective support. Likewise, following the same procedure compounds **7b**—**e** were prepared and their structural characterization was done on the basis of IR, ^{1}H-NMR and spectral and elemental analysis (Tables 2, 4).

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