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MONTMORILLONITE KSF CATALYZED FACILE SYNTHESIS OF NOVEL SPIRO HETEROCYCLES UNDER MICROWAVE IRRADIATION

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The arylidienes of spiro thiazolidines (**5**) containing ~~α,β~~-unsaturated function have been used as component of Micheal addition with equimolar amount of 2-aminopyridine (**6a**) to give novel spiro [indole-3,2′-pyrido[1,2-a]thiazolo[5,4-e]pyrimidines] (**7**) in a single step under microwaves in presence of montmorillonite KSF as solid support. The new improved synthetic method for spiro [indole-3, 2′-thiazolo[4,5-d]pyrimidines] **(8)** has also been developed involving the reaction of (**5**) with thiourea under microwaves. Comparison with conventional synthesis indicated the enhanced yield with faster reactions under microwaves.

Bridgehead thiazolopyrimidines occupy a unique place in medicinal chemistry due to their wide applications as drugs and drug intermediates. Synthesis of thiazolo[4,5-d]pyrimidines is extensively studied by various workers and are patented as arteriosclerosis,[1] immunomodulator,[2] antirheumatic,[3] antidepressant,[4] cardiotonic,[5] antihypertensive[6], and antiinflammatery agents[7]; with no synthetic details.

A perusal of the literature has revealed manifold implications of pyrido [2,3-d] pyrimidines , viz.antibacterial[8] , antifungal[9] and antiallergic,[10] etc. The nucleosides of pyrido [2,3-d] pyrimidines have also been reported as potent antileukemic,[11] anti HIV, [12]anti cancer[13] and dihydrofolate reductase inhibitors.[14]

The chemistry of spiro indoles in which an indole ring is joined to sulfur and nitrogen containing heterocycles at the C-3 position through a spiro carbon atom is of great interest due to their physiological and biological activities.[15,16] Spiro [indole-thiazolidines] are known to possess various biological activity e.g. anti-inflammatory,[17] fungistatic,[18] bacteriostatic,[19] anticonvulsant activities[20] and used as dyes.[21] The significance of these compounds can be judged from the fact that most of the references of spiro-indoles in the literature are patents.[22] Arylidene derivatives of condensed 4-thiazolidinones have been found to be better fungistatic agents than the parent 4-thiazolidinones. Besides, condensed 4-thiazolidinones are better antibacterial agents than their thiazole counterparts.[23-25]

Therefore, it was though of interest to construct a system, which may combine these biolabile rings together in a single molecular framework to see the additive effect towards their biological activities.

Recent years have witnessed the importance of microwaves in mediating organic reactions[26-28] because of their advantages with respect to classical organic chemistry in terms of shorter reaction times, minimum waste, generally higher yields, possibility of

carrying out reactions in the absence of solvents and in safe conditions. In view of this, more interest has now been focused on dry media synthesis, involving the coupling of MWI with solid supported reagents. The method provides unique chemical process with special attribute to enhanced reaction time, higher yield, greater selectivity and ease of manipulation.

Literature survey reveals that there is no report on the synthesis of title novel nucleus yet so far. Therefore, it was thought that it would be desirable to develop a facile, efficient, environeconomic, microwave induced method for preparation of novel spiro indolines **7** and **8** by the reaction of arylidiens derivative (**5**) with 2-aminopyridine (**6a**) and thiourea (**6b)** using montmorillonte KSF as solid support under microwaves.

Hence, in continuation of our earlier interest on molecular diversity and search for new leads in drug designing programme in the synthesis of molecules,[29] which are novel yet resemble known biologically active molecules by virtue of the presence of some critical structural features, we wish to report our results on the use of microwave technique in a multistep synthesis of a novel spiro [indole-3,2′-pyrido[1,2-a]thiazolo[5,4-e]pyrimidines](**7**) and 5′-thioxo-4,5,6,7-tetrahydro-2H, 3′H-spiro [indole-3, 2′-thiazolo[4,5-d]pyrimidines] (**8**) (**Scheme-1**) by combining 2-3 steps as a one pot reaction to reduce the pollution at source as important green chemical theme. [30]

The required spiro[indole-thiazolidines] (**1**) were prepared by the multicomponent condensation between indole-2,3-dione,amines and marcaptoacetic acid[31] using montmorillonite KSF as solid support. These on reaction with araldehyde “in situ” by Knoevengal condensation yielded 3′aryl-5′-benzylidene-4′*H*-spiro-[indole-3,2'-thiazolidine]-2,4'(1*H*)-dione (**5**) in 85-90% yield in 4-5 min under same reaction conditions in one pot. These arylidenes with an ~~α, β~~-unsaturated ketonic fuction (-CH=CH-CO-) in their structure have been used as a component of Micheal adition with 2-aminopyridine and yielded the novel compound spiro [indole-3,2′-pyrido[1,2-a]thiazolo[5,4-e]pyrimidines]-2 (1H)-one (**7**) in a single step in presence of montmorillonite KSF as solid support in 87-90% yield in 6-8 min. A non-isolated intermediate has been presumed to be formed during such condensation (**Scheme-2**). Further 5′-thioxo-4,5,6,7-tetrahydro-spiro [indole-3, 2′-thiazolo[4,5-d]pyrimidine]-2(1H)-one (**8a-d**) were also synthesized by improved enviro economic green chemical procedure by the reaction of arylidenes derivatives (**5**) with thiourea in 86-95% yield in 6-9 min.

Scheme-2

Conventionally **5**, **7** and **8** were synthesized by long refluxing in gl. AcOH and fused

sodium acetate in volatile solvents such as dioxane, dry toluene using Dean Strak apparatus with tedious work up process and purification by chromatographic technique with further need of solvent yielding the desired compounds in lower yield.

RESULTS AND DISCUSSION

The structure assigned to arylidiene derivatives (**5**) was confirmed by spectral studies. ^{1}H NMR spectrum of **5a** showed characteristic signals at δ 2.49(s, 1H, CH_3), 2.79 (s, 1H, CH_3),5.1 (s, 1H, CH) and 7.13-7.64 (m, 13H, Ar-H) and 9.23 (s, 1H, NH). Absence of CH_2 signal(dd) in ^{1}H NMR at δ 3.80-4.22 ppm further confirmed the formation of **5.** In ^{13}C NMR spectrum of **5** signals were observed at δ 81.6 (spiro carbon), 113.2-147.3 (olefinic carbon and aromatic carbons), 162.8, 169.2 (both C=O).

The formation of **7**and **8** from arylidene derivatives (**5**) was confirmed by IR and ^{1}H NMR data. In IR spectrum of **7a** and **8a** disappearance of C=O absorption band at 1680-1695cm-^{1} which was present in **5** confirmed the cyclization or involvement of α,β-unsaturated carbonyl system. ^{1}H NMR spectrum of **7a** showed characteristic signals at δ 3.71 (s, 1H, C-10′H), 5.91 (m, 1H, C-8′H), 7.02 (m, 1H, C-6'H), 7.23-8.02 (m, 17H, Ar-H) and 9.01 (s, 1H, NH). Formation of **7a** was further confirmed by ^{13}C NMR and Mass spectra. ^{13} C NMR spectrum of **7a** showed signals at δ 58.9 (C-10′), 84.9 (spiro carbon), 107.6-142.6 (aromatic carbons), 165.2 (C=N) and 168.5 (NH-C=O). Mass spectrum of **7a** showed molecular ion peak m/z at 505 ($[M]^+$, 14.6%) corresponding to its molecular weight along with base peak at 385 ($[M^+-C_8H_{10}N]$, 100%) and other peaks at 281 (12.3), 188 (13), 160 (20.8), 121 (58.2), 78 (19.3).

^{1}H NMR spectrum of **8a** showed characteristic signals at δ 4.82 (s, 1H, C-7′H), 6.98-7.62 (m, 13H, Ar-H), 9.13 (s, 1H, NH) and 10.25 (bs, 2H, pyridine NH). ^{13} C NMR spectrum of **8a** showed signals at δ 52.6 (C-7′), 92.8 (spiro carbon), 112.9-139.6 (aromatic carbons), 169.4 (C=O) and 176.5 (C=S). Mass spectrum of **8a** showed molecular ion peak m/z at 487 ($[M]^+$, 17.4%) corresponding to its molecular weight along with base peak at 443 ($[M^+-CS]$, 100) and other peaks at 367 ($[M^+-C_8H_{10}]$, 25.5), 281(42), 185(25), 165 (28.5), 131(63.7), 78(50.4).

EXPERIMENTAL

Melting points were determined in open glass capillaries and were uncorrected. Thin layer chromatography on silica gel 'G' coated glass plates using benzene, ethyl acetate (8: 2)

as eluent was used for monitoring the progress of the reactions. IR spectra (KBr) were recorded on a Magna FT IR–550 spectrophotometer, ^{1}H and ^{13}C NMR spectra [$CDCl_3$ + $(CD_3)_2SO$] were taken on a Bruker-300DX spectrometer at 300 and 200 MHz respectively, using TMS as an internal standard for PMR and mass spectra were recorded on Jeol D–300 spectrometer at an ionization potential of 70 e.v. Microwave assisted reactions were carried out on a National panasonic oven with inverter technology operating at fixed frequency 2450 MHz with power out put range 1000w.

Spiro [indole-3,2′-thiazolidine]-2,4′ (1H)-dione (5) :

These compounds were synthesized in one pot by multicomponent cyclocondensation of equimolar mixture(0.01 mol) of indol-2.3-dione, amines and marcaptoacetic acid using montmorillonite KSF as solid support as reported by us.[31] Since tlc studies showed 100% conversion with formation of single product hence it is used as such for further conversion without isolating them.For structure confirmation some products are isolated by desorption with methanol and compared with authentic samples prepared by literature methods.[32]

5'-(4-N,

N-dimethylbenzylidene)-3'-phenyl-2'*H*-spiro[indole-3,2'-thiazolidine]-2,4'(1*H*)-dione (7a): It was synthesized by following different ways

(a)Conventional method:

An equimolar mixture of **4a** (2.75 g, 0.01 mol)**,** N, N-dimethylbenzaldehyde (1.75 g, 0.01 mol) and anhyd sodium acetate in gl acetic acid (40 ml) was refluxed for 5 hrs. On cooling, the reaction mixture was poured into ice cold water. The solid thus obtained was filtered, washed with water, dried and crystallized from benzene. m.p.=240°C, Yield =58 %

(b)Microwave mediated synthesis:

N, N-dimethylbenzaldehyde (1.75 g, 0.01 mol) was adsorbed on montmorillonite KSF (70% weight of reactants) and mixed with spiro thiazolidinone (**4a**) (synthesized “in situ”) and irradiated inside microwave oven at 640 watt till completion of reaction (TLC). The product was obtained by desorption with methanol and further recrystallization with ethylacetate gave pure product. m.p =240°C, Yield =95 %

10′-(4-N,N-dimethylphenyl)-3′phenyl-spiro[indole-3,2′-pyrido[1,2-a]thiazolo[5,4-e] pyrimidines] (7a): It was synthesized by following methods

(a) Conventional method:

(i)A equimolar mixture of **5a** (4.27 g, 0.01 mol), 2-amino pyridine **(6a)** (.94 g, 0.01 mol**)** and fused anhyd sodium acetate (2 g) in dioxane (40 ml) was refluxed for 8 hrs. The solvent was removed by distillation in vacuo and residue poured into cold water. The solid thus obtained was washed with water and crystallized from ethanol to gave **7a**.

m.p. = 132°C, Yield =54 %

(ii)A equimolar mixture of **5a** (4.27 g, 0.01 mol), 2-amino pyridine **(6a)** (.94 g, 0.01 mol**)** in ethanol (30 ml) containing 6-8 drops of gl. acetic acid was refluxed for 7 hrs. A crude product appeared on cooling the reaction mixture, which was filtered, washed with water and recrystallized form ethanol to give desired product **7a.**. m.p = 132°C, Yield =57 %

(b) Microwave mediated synthesis:

An equimolar mixture (0.01mol) of **5a** and **6a** was adsorbed on montmorillonite KSF (80% weight of reactants). The reaction mixture was irradiated for 7 min. The recyclable montmorillonite KSF separated by eluting the product with methanol and excess solvent was evaporated on rotaevaporator to give pure product (TLC), with no need of further purification. m.p. = 132°C, Yield=88%

7′-(4-N,N-dimethylphenyl)-3′-phenyl-5′-thioxo-4,5,6,7-tetrahydro-spiro[indole-3,2′-thiazolo [4,5-d]pyrimidine] (8a): it was synthesized by following different way

(c)Conventional method:

A equimolar mixture of **5a** (2.75 g, 0.01 mol)**,** thiourea (**6b**) (.78g, 0.01 mol) in absolute ethanol (25 ml)/anhyd pyridine (25 ml) was refluxed for 9 hrs. On cooling, the crude solid appeared which was filtered, washed with ice cold water containing dil. HCl with constant stirring. The solid mass thus obtained was filtered and crystallized from ethanol. m.p =212°C , Yield = 62%

(d)Microwave mediated synthesis:

It was synthesized by reaction of **5a** and **6b** using montmorillonite KSF as solid support under microwaves. m.p = 212°C, Yield =89 %

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5a: X=H, Y=H, Z= 4-$N(CH_3)_2$

5b: X=5-Cl, Y=H, Z= 4-OCH_3

5c: X=5-CH_3, Y=H, Z= 3-OCH_3

5d: X=H, Y=4-OCH_3, Z= 4-CH_3

Scheme-1

Table-2: ^{1}H NMR spectral & analytical data of 5, 7,8 a-d

! rdrbCmpd	X	Y	Z	Yield (%)	M. P. (°C)	IR (cm-^{1})	1H NMR (δ, ppm)*	Elemental analysis (found/ calculated)		
								C	H	N
! vertalt **5a**	H	H	4-N(CH_3)$_2$	85	240	3380-3290 (bs, NH), 1720, 1680 (both C=O)	2.49(s, 1H, CH_3), 2.79(s, 1H, CH_3) 5.10 (s, 1H, CH) ,7.13-7.64 (m, 13H, Ar-H), 9.23 (s, 1H, NH).	70.39 (70.23)	4.89 (4.95)	9.78 (9.83)
! drcf1**5b**	5-Cl	H	4-OCH_3	88	205[33]	3370-3250 (bs, NH), 1715, 1690 (both C=O), 1150 (C-O-C), 760(C-Cl)	3.62 (s, 3H, OCH_3) 5.21(s, 1H, CH) ,7.05-7.68 (m,12H, Ar-H), 9.28 (s, 1H, NH).	64.15 (64.21)	3.92 (3.82)	6.35 (6.24)
! vertalt **5c**	5-CH_3	H	3-OCH_3	90	215	3360-3290 (bs, NH), 1720, 1695 (both C=O), 1150 (C-O-C)	2.24 (s, 3H, CH_3), 3.57 (s, 3H, OCH_3) 5..4 (s, 1H, CH) ,7.10-7.85 (m,12H, Ar-H) , 9.36 (s, 1H, NH).	70.15 (70.07)	4.62 (4.70)	6.45 (6.54)
! vertalt **5d**	H	4-OCH 3	CH_3	87	192	3390-3280 (bs, NH), 1710, 1690 (both C=O), 1140 (C-O-C)	2.28 (s, 3H, CH_3), 3.58(s, 3H, OCH_3) 5.18 (s, 1H, CH) , 7.15-7.89 (m,12H , Ar-H) , 9.23 (s, 1H, NH).	70.18 (70.07)	4.62 (4.70)	6.48 (6.54)
! vertalt **7a**	H	H	4-N(CH_3)$_2$	88	132	3380-3270 (bs, NH), 1710(C=O), 1620 (C=N)	2.45, (s, 1H, CH_3) 2.73 (s, 1H, CH_3), 3.71 (s, 1H, C-10′H), 5.91 (m, 1H, C-8′H), 7.02 (m, 1H, C-6′H), 7.23-8.02 (m, 17H,Ar-H) , 9.01 (s, 1H, NH)	71.19 (71.26)	5.31 (5.38)	13.92 (13.85)
! vertalt **7b**	5-Cl	H	4-OCH_3	90	139	3360-3290 (bs, NH), 1720(C=O), 1610 (C=N), 1150 (C-O-C)	3.62 (s, 3H, OCH_3), 3.81 (s, 1H, C-10′H), 5.87 (m, 1H, C-8′H), 7.05 (m, 1H, C-6′H), 7.18-8.09 (m,16H, Ar-H) , 9.15 (s, 1H, NH)	66.21 (66.09)	4.51 (4.40)	10.71 (10.63)
! vertalt **7c**	5-CH_3	H	3-OCH_3	90	148	3375-3290 (bs, NH), 1715(C=O), 1620 (C=N), 1160 (C-O-C)	2.36 (s, 3H, CH_3), 3.56 (s, 3H, OCH_3), 3.79 (s, 1H, C-10′H), 5.86 (m, 1H, C-8′H), 7.01 (m, 1H, C-6′H), 7.15-8.12 (m,16H, Ar-H) , 9.28 (s, 1H, NH)	71.26 (71.12)	5.02 (5.17)	11.23 (11.06)
! vertalt **7d**	H	4-OCH 3	CH_3	87	120	3360-3250 (bs, NH), 1710(C=O), 1610 (C=N), 1145 (C-O-C)	2.28 (s, 3H, CH_3), 3.58 (s, 3H, OCH_3), 3.79 (s, 1H, C-10′H), 5.95 (m, 1H, C-8′H), 6.95 (m, 1H, C-6′H), 7.10-8.02 (m,16H, Ar-H) , 9.26 (s, 1H, NH)	71.02 (71.12)	5.07 (5.17)	11.11 (11.06)
! drcf1**8a**	H	H	4-N(CH_3)$_2$	89	212	3380-3280 (bs, NH), 1710(C=O), 1220 (C=S)	2.43, (s, 1H, CH_3) 2.85(s, 1H, CH_3),4.82 (s, 1H, C-7′H), 6.98-7.62 (m,13H,Ar-H),	64.15 (64.04)	5.29 (5.17)	14.42 (14.36)

							9.13 (s, 1H, NH) ,10.25 (bs, 2H, pyridine NH)			
! vertalt **8b**	5-Cl	H	4-OCH_3	86	172	3380-3250 (bs, NH), 1720(C=O), 1230 (C=S) ,1145 (C-O-C)	3.58 (s, 3H, OCH_3),4.87 (s, 1H, C-7ⁱ-H), 7.01-7.85 (m,12H, Ar-H), 9.19 (s, 1H, NH),10.32 (bs, 2H, pyridine NH)	58.78 (58.99)	4.08 (4.16)	11.09 (11.01)
! vertalt **8c**	5-CH_3	H	3-OCH_3	90	134	3390-3260 (bs, NH), 1720(C=O), 1225 (C=S), 1145 (C-O-C)	2.43 (s, 3H, CH_3), 3.65 (s, 3H, OCH_3), 4.76 (s, 1H, C-7ⁱ-H), 7.05-7.89 (m,12H, Ar-H), 9.25 (s, 1H, NH), 10.18 (bs, 2H, pyridine NH)	63.75 (63.91)	4.89 (4.95)	11.56 (11.47)
! vertalt **8d**	H	4-OCH 3	CH_3	88	185	3395-3260 (bs, NH), 1715(C=O), 1235(C=S), 1145 (C-O-C)	2.35 (s, 3H, CH_3), 3.54 (s, 3H, OCH_3), 4.81 (s, 1H, C-7ⁱ-H), 6.96-7.89 (m,12H Ar-H), 9.26 (s, 1H, NH), 10.23 (bs, 2H, pyridine NH)	63.84 (63.91)	4.86 (4.95)	11.41 (11.47)