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A Recyclable and Highly Effective Sulfamic Acid/EtOH Catalytic System in Synthesis and Natural Product Chemistry of Lignan Compounds

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The utilization of green chemistry techniques is dramatically reducing chemical waste and reaction times and has recently been proven in several organic syntheses and chemical transformations. To illustrate these advantages sulphamic acid is used as a novel recyclable heterogeneous catalyst in the cyclization of Perkin condensation product α-arylidine-β-benzoyl propionic acid to achieve biologically potent 1-phenylnaphthalene system and pericarbonyl lactone lignans under two experimental conditions *i.e.*, conventional and microwave irradiation. The generality of this protocol has been demonstrated by synthesizing a variety of substituted 1-phenyl-naphthalene systems in excellent yields, short reaction time and with good purity.

Key Words: Sulphamic acid/Ethanol system, Lignans, Cyclization, Recyclable system.

INTRODUCTION

1-Phenylnaphthalene system attracted special attention of organic chemists because these are biologically active with potential applications as antiinflammatory[1], antibacterial[2], antioxidant[3], anticancer[4] and CNS depressants[5]. 1-Phenyl-naphthalenes are versatile moieties in that their pendant like skeleton exists in a number of pharmaceuticals and natural products. As a result of their importance from industrial, biological and synthetic point of view, it is desirable to choose an efficient and versatile protocol for their easy and clean synthesis.

The catalytic activity of sulphamic acid (SA) has emerged as a useful acid imparting high region and chemo selectivity in various chemical transformations[6-9]. It is a dry, nonvolatile, non hygroscopic, odorless and white crystalline solid Bronsted acid with outstanding physical properties. It is inexpensive, insoluble in common organic solvents, highly stable and its zwitterionic property makes its recycling and reuse very convenient[10,11].

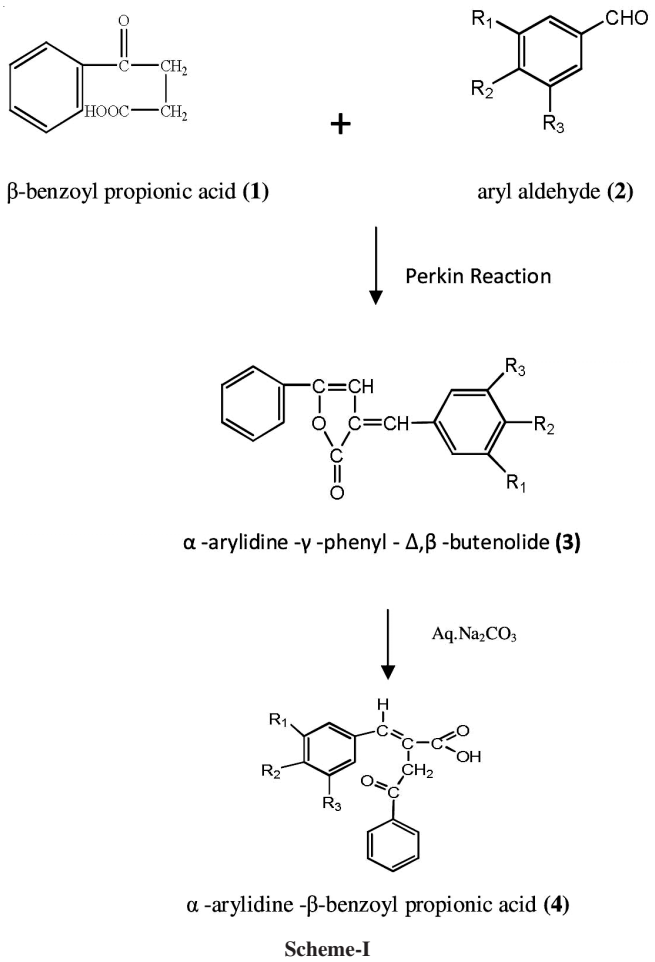
We report herein a highly efficient procedure for the synthesis of various substituted 1-phenylnaphthalene systems and pericarbonyl lactones using sulphamic acid as an efficient and versatile catalyst under both methods-conventional and microwave irradiation.

By the use of microwave in combination with sulphamic acid, the term "green chemistry" ideally disappears as all chemistry becomes green.

EXPERIMENTAL

All the chemicals and reagents were of LR or AR grade and procured from S.D. Fine Chem. Limited, (Mumbai), LOBA Chemie, Mumbai, E. Merck (India) Ltd. and used as received. IR spectra were recorded on Perkin-Elmer FT spectrophotometer in KBr disc. ^{1}H NMR were recorded on Varian 300 MHz spectrophotometer in $CDCl_3$ as a solvent and TMS as an internal standard. Melting points were recorded on a melting point apparatus with capillary tubes and are uncorrected. Analytical TLC was performed on glass slides coated of silica gel G/UV-254 of 0.2 mm thickness. Elemental analysis data were recorded using Thermo Finnegan FLASH EA 1112 CHN analyzer. For the microwave irradiation experiments described below, a conventional (unmodified) house hold microwave oven equipped with a turn able was used (LG Smart Chef MS-255r operating at 2450 MHz having maximum output of 800 W).

Conversion of β-benzoyl propionic acid to α-arylidine-β-benzoyl propionic acid: For the synthesis of 1-phenyl-naphthalene system, β-benzoyl propionic acid was taken as a starting moiety. Perkin condensation of β-benzoyl propionic acid with aryl aldehyde yields butenolide[12] which on cleavage by methanolic solution of Na_2CO_3 leads to α-arylidine-β-benzoyl propionic acid[13] (**Scheme-I**). The system (**4**) thus contains the required skeleton to prepare 1-phenylnaphthalene system and pericarbonyl lactone lignans[14,15] (**Scheme-II**).



Scheme-I

Path-A

Cyclization of α-arylidine-β-benzoyl propionic acid (4) to 1-phenylnaphthoic acid (7)

Conventional method: A mixture of 1 mmol of α-arylidine-β-benzoyl propionic acid, 0.2 mmol (20 mmol %) sulphamic acid and ethanol (taken in excess: 10 mL) was taken as a reaction solvent in 250 mL round bottom flask. Stir the mixture vigorously by keeping in reflux at 118-120 ºC for an appropriate time as mentioned in Table-1. After completion of reaction as indicated by TLC, the reaction mixture was cooled at room temperature and diluted with diethyl ether [3 × 10 mL] to precipitate sulphamic acid. Thus sulphamic acid could be separated easily. The combined organic layers were dried over anhydrous Na_2SO_4. The solvent was removed and the residue was column chromatographed using petroleum ether:ethyl acetate (2:3) as the eluent, to obtain pure compound.

Microwave irradiation: The reaction mixture as specified above was taken in a dry 250 mL beaker. It was mixed properly with the help of glass rod. An inverted funnel was placed over the rim of the beaker and irradiated in a microwave oven at 800 W for 14-15 min while monitoring the reaction with the help of TLC. After the completion of the reaction, immediate temperature of the reaction mixture was taken out by the thermometer, which is recorded as 75 ºC.The reaction was worked-up and purified as described above under conventional method.

Adopting the above described two alternative methods, four different substituted 1-phenylnaphthoic acids (**7a-7d**) were identified and characterized (Table-2).

Path-B

Conversion of α-arylidine β-benzoyl propionic acid (4) to α-arylidine-β-methylene-β-benzoyl propionic acid (5)

To a solution of α-arylidine-β-benzoyl propionic acid in 10 % aq. NaOH solution was added 40 % formalin solution and was left overnight. It was then cooled and dried with anhydrous sodium sulphate. Ethanol is added to separate the product. Evaporation of solvent gave a gummy solid which was crystallized from ethanol/water to give α-arylidine-β-methylene-β-benzoyl propionic acid. The IR spectra of (**5**) showed broad peak at 1660 cm^{-1} for carboxyl and keto group.

Cyclization of α-arylidine-β-methylene-β-benzoyl propionic acid (5) to 1-phenyl naphthalene lactone/pericarbonyl lactone (8)

Conventional method: A mixture of 1 mmol of α-arylidine-β-benzoyl propionic acid, 0.2 mmol (20 mmol %) sulphamic acid and ethanol 10 mL was taken as a reaction solvent and stir the mixture vigorously (using magnetic stirrer) by keeping in reflux at 118-120 ºC for an appropriate time (Table-1). The reaction was worked-up and purified as described above (Path-A).

Microwave irradiation: The reaction mixture as specified above was taken in a dry 250 mL beaker. It was mixed properly with the help of glass rod. An inverted funnel was placed over the rim of the beaker and irradiated in a microwave oven at 800 W for 14-15 min while monitoring the reaction with the help of TLC. After the completion of the reaction, immediate temperature of the reaction mixture was taken out by the thermometer, which is recorded as 75 ºC.The reaction was worked-up and purified to give 1-phenyl-naphthalene lactone/pericarbonyl lactone. Adopting the above described two alternative methods, four different substituted 1-phenyl naphthalene lactones (**8a-8d**) were identified and characterized (Table-2).

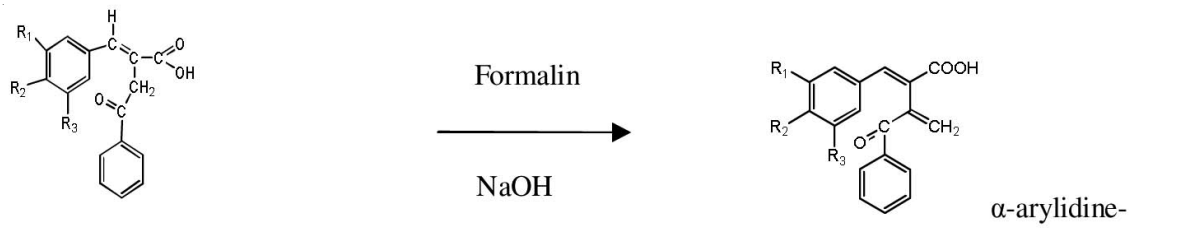
Path-C

Conversation of α-arylidine-β-benzoyl propionic acid (4) to methyl-α-arylidine-β-benzoyl propionic acid (6): α-Arylidine-β-benzoyl propionic acid was converted to its ester by CH_2N_2 to give methyl-α-arylidine-β-benzoyl propionic acid having melting point of 96 ºC. Its IR spectra showed absorption at 1680 cm^{-1}.

Cyclization of methyl α-arylidine-β-benzoyl propionic acid (6) to 1-phenyl naphthoate (9)

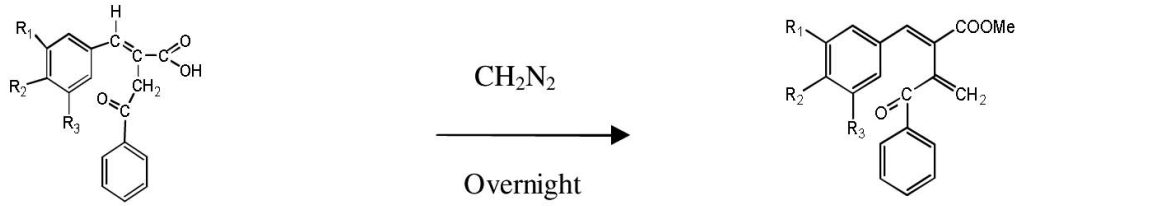
Conventional method: A mixture of 1 mmol of α-arylidine-β-methylene-β-benzoyl propionic acid, 0.2 mmol (20 mmol %) sulphamic acid and ethanol 10 mL was taken as a reaction solvent and stir the mixture vigorously (using magnetic stirrer) by keeping in reflux at 118-120 ºC for an appropriate time (Table-1). The reaction was worked-up and purified (likewise Path-A) to give 1-phenylnaphthoate.

Microwave irradiation: The reaction mixture as specified above was taken in a dry 250 mL beaker. It was mixed properly with the help of glass rod. An inverted funnel was placed over the rim of the beaker and irradiated in a microwave oven at 800 W for 14-15 min while monitoring the reaction with the



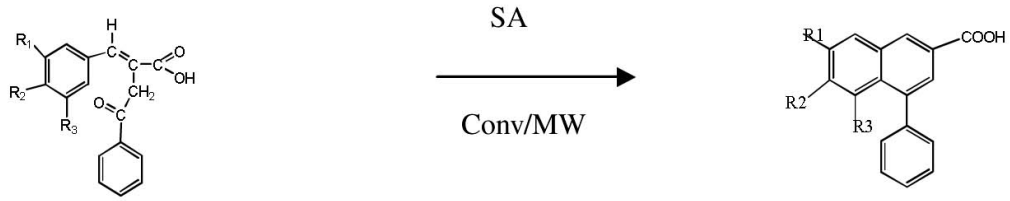
α -arylidine-β-benzoyl propionic acid **(4)**

α-arylidine-β-methylene -β-benzoyl propionic acid **(5)**



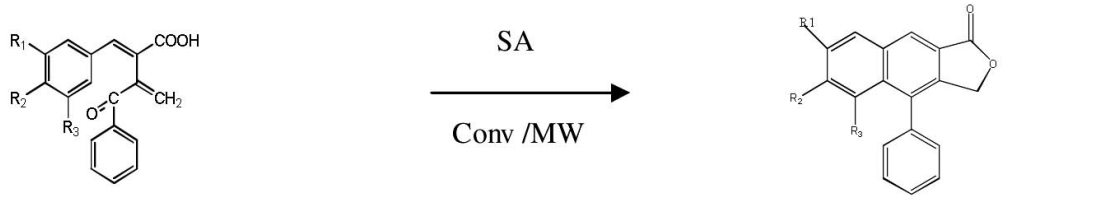
α-arylidine-β-benzoyl propionic acid **(4)**

methyl-α-arylidine-β-benzoyl propionic acid **(6)**



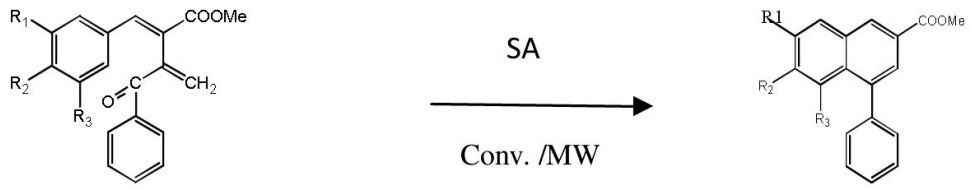
α-arylidine-β-benzoyl propionic acid **(4)**

1-Phenylnaphthoic acid **(7)**



α-arylidine-β-methylene
β-benzoyl propionic acid **(5)**

1-Phenylnaphthalene lactone **(8)**



Methyl -α-arylidine -β-benzoyl propionic acid **(6)**

1-Phenylnaphthoate **(9)**

Substitutions

a: $R_1 = R_2 = OCH_3$, $R_3 = H$

b: $R_1 = R_2 =$ O-CH_2-O , R_3=H

c: $R_1 = OCH_3$, $R_2 = OH$,$R_3 = H$

d: $R_1 = R_2 = R_3 = OCH_3$

Scheme-II

TABLE-1
COMPARATIVE DATA ON CONVENTIONAL ACID AND GREEN ACID CATALYZED SYNTHESIS OF 1-PHENYLNAPHTHALENE SYSTEMS

Entry	Products[a]	Time (min)				Yield (%)				m.p. (ºC)	
		PPA	H_2SO_4	Green-sulphamic acid		PPA	H_2SO_4	Green-sulphamic acid			
		OB	CC	MS	MW	OB	CC	MS	MW	Found	Lit.
1	**7a**	60	1440	90	15	85	85	93	96	215-217	217-218 [12]
2	**7b**	60	1440	88	14.5	84	85	93	95	238-240	238-239 [12]
3	**7c**	60	1440	90	15	78	78	85	85	177-179	179-180 [12]
4	**7d**	60	1440	88	14.5	82	81	89	96	220-223	221-223 [12]
5	**8a**	60	1440	90	15	82	80	95	94	203-205	203-205 [12]
6	**8b**	60	1440	88	14.5	83	83	88	92	209-211	208-209 [12]
7	**8c**	60	1440	90	15	78	78	86	89	209-210	209-210 [14]
8	**8d**	60	1440	89	14	84	82	92	95	233-235	231-233 [14]
9	**9a**	60	1440	90	15	80	79	92	94	122-124	123-124 [14]
10	**9b**	60	1440	89	14.5	83	83	90	92	170-171	169-171 [14]
11	**9c**	60	1440	88	14.5	82	82	91	95	150-152	152-153 [14]
12	**9d**	60	1440	89	15	83	83	91	94	130-132	130-132 [14]

[a]Yields refer to pure isolated products; OB = Oil bath; CC = Cold condition; MS = Magnetic stirrer; MW = Microwave.

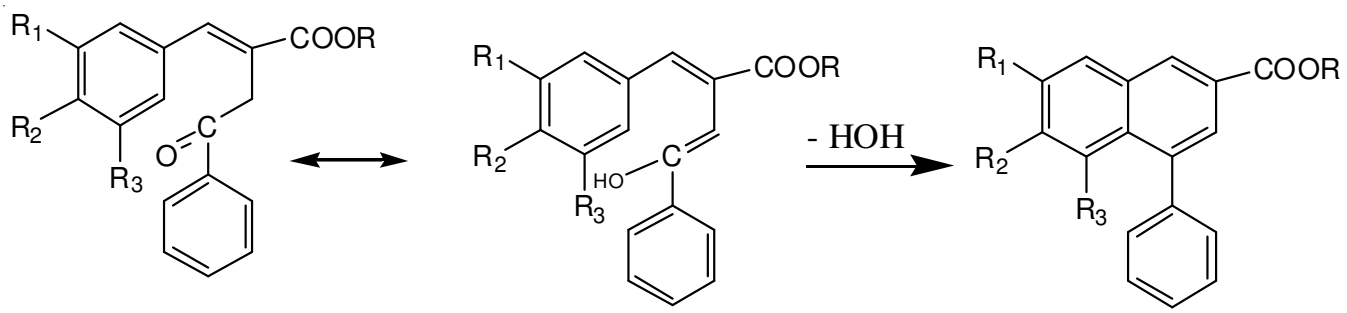
TABLE-2
CHARACTERIZATION AND SPECTRAL ANALYSIS OF 1-PHENYLNAPHTHALENE SYSTEMS

Sr. No.	1-Phenylnaphthalene system	m.f.	Elemental analysis (%): Obs. (calcd.)		IR (cm^{-1})	NMR (δ)
			C	H		
1	**7a** (1-Phenyl -6,7-dimethoxy naphthalene 3-carboxylic acid)	$C_{19}H_{16}O_4$	74.75 (74.02)	5.24 (5.19)	1680	3.84 (s, 6H, 20 CH_3), 7.2 (s, 1H, C_8-H), 7.35(s, 1H, C_5-H), 7.43-7.85 (5H, Phenyl) & 8.45(s, 1H, C_4-H)
2	**7b** (1-Phenyl-6,7-methylenedioxy naphthalene-3-carboxylic acid)	$C_{19}H_{12}O_4$	75.24 (75.00)	3.96 (3.94)	1680	–
3	**7c** (1-Phenyl-6-methoxy,7-hydroxy-naphthalene-3-carboxylic acid)	$C_{18}H_{14}0_4$	74.22 (73.46)	4.81 (4.46)	1681	4.1(s, 10 CH_3), 4.5(s, 1H, OH aromatic protons), 7.0 (s, 1H, C_8-H), 7.0-8.8 (s, aromatic protons), 7.5(m, 5H, Phenyl)
4	**7d** (1-Phenyl-6,7,8-trimethoxy naphthalene-3-carboxylic acid)	$C_{20}H_{16}0_5$	72.07 (71.42)	4.80 (4.80)	1683	3.8-3.9-3.95 (s, 9H, 3 OCH_3), 6.5-8.5 (m, aromatic protons, 7.5(m, 5H, phenyl)
5	**8a** (1-Phenyl-6,7-dimethoxy naphthalene lactone)	$C_{20}H_{16}O_4$	75.04 (75.47)	5.39 (5.03)	1760	3.86 & 4.06 (s, 6H, 2-OCH_3)5.22 (s, 2H, Lactone CH_2), 7.16 (s, 1H, C_8- H), 7.37(s, 1H, C_5 - H) 7.6 (br, s, 5H.phenyl) & 8.36 (s, 1H, C_4 -H)
6	**8b** (1-Phenyl-6,7-methylenedioxy naphthalene lactone)	$C_{19}H_{12}O_4$	75.01 (75.12)	3.87 (3.94)	1762	5.23, (s, 2H lactone CH_2), 6.10(s, 2H, O-CH_2O-) 7.13-7.4, (d, 6H, aromatic), 8.28(s, 1H, C_4-H)
7	**8c** (1-Phenyl-6-methoxy-7-hydroxy-naphthalene lactone)	$C_{20}H_{16}0_4$	75.02 (75.00)	5.01 (5.08)	1761	3.83, (s, 3H, 10CH_3), 5.20 (s, 2H, lactone CH_2), 7.04-7.30(m, 7H, 1H, OH aromatic), 8.25 (s, 1H, C_4-H)
8	**8d** (1-Phenyl-6,7,8-trimethoxy naphthalene lactone)	$C_{21}H_{19}0_5$	71.48 (71.79)	5.70 (5.41)	1762	3.90, 4.01, 4.25(s, 9H, 3-OCH_3), 5.30 (s, 2H, lactoneCH_2), 7.1- 7.7 (m, 6H, aromatic), 8.4(s, 1H, C_4 - H)
9	**9a** (1-Phenyl-3-carbomethoxy-6,7-dimethoxy naphthoate)	$C_{20}H_{18}O_4$	74.14 (74.52)	5.52 (5.88)	1720	3.85, 3.96, 4.03 (s, 9H, CO_2, CH_3, OCH_3), 7.24 &7.30 (s, sh) C_3-H & C_8-H), 7.85 (s, sh, phenyl), 7.9 (d, *J* = $2H_2$, 1H, C_4-H), 8.47(d, *J* = $2H_2$, C_2 - H)
10	**9b** (1-Phenyl-3-carbomethoxy-6,7-methylenedioxy naphthoate)	$C_{21}H_{14}O_4$	76.19 (76.36)	4.12 (4.24)	1720	4.02 (s, 3H, OCH_3), 5.94 (s, 2H, OCH_2O-), 7.32&7.38 (5(sh)2H, C_5-H & C_8-H), 7.60 (s, sh, phenyl), 8.04 (d, *J* = $2H_2$, 1H, 2H) and 8.86 (d, *J* = $2H_2$, 1H, C_4 - H)
11	**9c** (1-Phenyl-6-methoxy-7-hydroxy-naphthoate)	$C_{19}H_{18}O_4$	73.38 (73.54)	5.68 (5.80)	1720	–
12	**9d** (1-Phenyl-3-carbomethoxy-6,7,8-trimethoxy naphthoate)	$C_{21}H_{22}O_5$	71.02 (71.18)	6.05 (6.21)	1720	–

help of TLC. After the completion of the reaction, immediate temperature of the reaction mixture was taken out by the thermometer, which is recorded as 75 ºC.The reaction was worked -up and purified to give 1-phenyl-naphthoate. Adopting the above described two alternative methods, four different substituted 1-phenylnaphthoates (**9a-9d**) were identified and characterized (Table-2).

RESULTS AND DISCUSSION

To prepare 1-phenylnaphthalene system and pericarbonyl lactone lignans, β-benzoyl propionic acid[16] was used which has two reactive methylene groups and a carboxylic functional group which could lead to the basic skeleton of lignans. The carboxyl group would yield part of furan ring and the oxo



Scheme-III

group could be reduced. β-Benzoyl propionic acid with aryl aldehydes underwent Perkin condensation at α-methylene to give α-arylidine-β-benzoyl propionic acid (**Scheme-I**). This condensation reaction is restricted to aldehydes having hydroxyl, methoxy or methylenedioxy groups at *para* positions only[17]. Further cyclization of Perkin condensation product-α-arylidine-β-benzoyl propionic acid using sulphamic acid gives 1-phenyl-naphthalene system and pericarbonyl lactone lignans under two experimental conditions-conventional and microwave (**Scheme-II**).

To extend the scope of reaction and to generalize the procedure, we carried out the reaction of β-benzoyl propionic acid with a series of aryl aldehydes (veratraldehyde, pipernol, vanillin, 3,4,5-trimethoxy-benzaldehyde) to obtain the corresponding 1-phenylnaphthalene systems **7a-d**, **8a-d** and **9a-d** by adopting the above described two alternative methods. All the cyclized products have been characterized by their IR, ^{1}H NMR spectral values and elemental analysis (Table-2).

The synthesis of (**4**) to (**7**) and (**6**) to (**9**) takes place involving keto-enol tautomerism followed by removal of H and OH. While in system (**5**) (α-arylidine-β-methylene-β-benzoyl propionic acid) there is hyper-conjugation at CH_2 and cyclization take place by keto-enol tautomerism. The aromatic atmosphere spread is more on S-*cis* butadiene than S-*trans* orientation. Though the S-*trans* is more stable, here S-*cis* has more chance to exit. Hence the facile cyclization *via* keto-enol tautomerization which in turn existed due to hyper conjugation which is possible due to methylene group. All these intermediate structures drive the reaction towards aryl lactonization *via* cyclization by removal of H and OH and simultaneous tautomerism at the COOH and positive CH_2 positive centre which leads to the formation of pericarbonyl lactone.

The literature survey disclose plethora of cyclizing reagents such as H_2SO_4, polyphosphoric acid[18], CH_3COOH/HCl[19,20], lead tetra acetate[21] for the synthesis of 1-phenylnaphthalene system. However, processes involving conventional acids are inherently associated with problems such as high toxicity, corrosion, catalyst waste, difficulty in separation and recovery. Replacement of these conventional acids by solid catalyst is desirable to achieve effective catalyst handling, product purification and to decrease waste production.

Also the above conventional cyclization reactions have been done using traditional heat transfer equipments such as oil-bath, sand bath and heating jackets. These heating techniques are however, rather slow and a temperature gradient can develop. Therefore it is seen that above cyclization reactions have been plagued by a number of serious disadvantages. Now we have found an analogous cyclization reaction which can be conveniently performed under neutral and mild conditions in the presence of catalytic amount of sulphamic acid under the cooperative effect of microwave radiation and a novel conventional refluxing/stirring method.

When compared to other acid catalysts, the use of sulphamic acid facilitated the smooth conduct of the cyclization reactions. The work out of the product was very simple and better yields were recorded. As expected, the alternative microwave-assisted method was found to be more convenient over that of conventional, in terms of considerable reduction in reaction time, improved yields and facile nature of reaction.

In this method the use of 20 mol % of the catalyst was quite sufficient to promote the reaction; higher amount of the catalyst did not improve the yield. The use of sub-stoichiometric quantity of sulphamic acid indicated its true catalytic nature and also gave an advantage over other classical Bronsted acids. Recovery of catalyst was very easy so that the sulphamic acid could be recycled upto three cycles without significant loss in its activity (Table-3).

TABLE-3
RECYCLABILITY OF SULPHAMIC ACID IN THE CYCLIZATION REACTIONS

Cycle No.	Yield (%) **7a**		Yield (%) **8a**		Yield (%) **9a**	
	Conv.	MW	Conv.	MW	Conv.	MW
Fresh	93	96	95	94	92	94
1	92	95	94	93	91	92
2	90	94	92	91	90	91
3	88	92	91	90	88	88

[a]Isolated yield.

Conclusion

In summary, we have developed a simple and general method for the synthesis of 1-phenylnaphthalene system and pericarbonyl lactone lignans by using sulphamic acid as a recyclable heterogeneous catalyst under the cooperative effect of microwave radiation and a novel conventional method. The procedure is convenient and highly efficient since the titled compounds are produced in good to excellent yields after shot reaction times. Moreover, sulphamic acid showed high thermal stability and can be recovered and reused for at least three consecutive cycles without significant loss of its activity. Consequently, our method can be as a viable alternative to the presently existing procedures.

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