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Green synthesis of dispiroheterocycles through a microwave induced solvent free approach and a study on its biological activity

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ABSTRACT

1, 3 dipolar cycloaddition reactions offer a versatile route for the synthesis of multi component heterocyclic molecules. Solvent-free Claisen-Schmidt reactions of cycloalkanones with various substituted benzaldehydes (aryl aldehydes) using solid NaOH (20 mol%) and applying a grinding technique is used to synthesize Quantitative yields of α,ά-bis-(substitutedbenzylidene) cycloalkanones. Using the same technique we could synthesize the corresponding bis-benzylidene- and monobenzylideneacetone derivatives. The derivatives are then subjected to 1,3 dipolar cycloaddition reaction with azomethine ylides to yield the corresponding dispiroheterocycles through a microwave induced solvent free approach.

Key words: 1, 3 dipolar cycloaddition, Claisen-Schmidt reaction, cycloalkanones, azomethine ylides, dispiroheterocycles, microwave, solvent free approach

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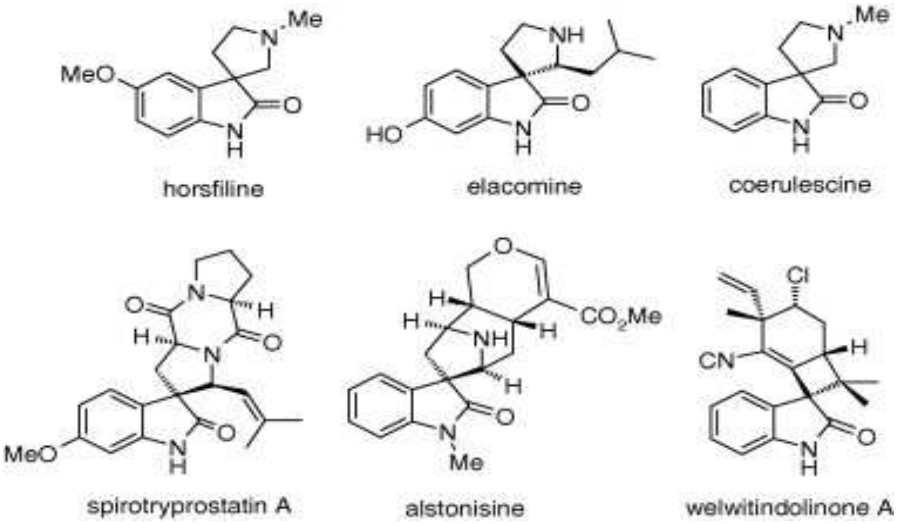
INTRODUCTION

Multicomponent reactions, especially those run under solvent-free conditions, have been attracted increasing research interest from chemists in recent years.[1a–c]Most of the organic reactions are conventionally carried out in solvent media. However, to minimize the environmental pollution caused by solvents, the chemists have been showing more concern for developing environment-friendly synthetic procedures. This initiative, aided with the recent development of new strategies in solid–solid reactions has prompted them to develop sufficiently valuable methodologies to achieve organic synthesis under solvent-free condition.[1d–f] Especially, multicomponent reactions that provide poly-functionalized heterocyclic scaffolds in single operation and in stereo-specific manner are of great importance in synthetic organic and medicinal chemistry.[2a-b]

The Claisen-Schmidt reaction (crossed-aldol reaction) is a condensation reaction of aldehydes and carbonyl compounds leading to β-hydroxycarbonyl compounds and it has played an important role in synthetic organic chemistry.[3–7] Subsequent dehydration of the β-hydroxycarbonyl compounds afford α-alkylidene or α-arylidene compounds. Although studies on the Claisen-Schmidt reaction have been focused on α -alkylidene- and α -arylidene-carbonyl compounds, interest in α,ά –bisalkylidene and α,ά -bisarylidene-carbonyl compounds is increasing. Particularly, α,ά *bis*-(substitutedbenzylidene)-cycloalkanones have been attracting much more attention, not only due to their intriguing biological activities such as antiangiogenic [8,9] quinine reductase inducer [10], arginine methyltransferase inhibitor [11], cytotoxicity [12,13], cholesterol-lowering activity [14], uses in agrochemicals, pharmaceuticals and perfumes [15], in *bis*-spiropyrrolidines [16,17], and as liquid crystalline polymer units [18], but also as

important precursors for the synthesis of pyrimidine derivatives [19], 2,7-disubstituted tropones [20], and they are the synthetic intermediates of choice to functionalize the α, β-position during the total synthesis of natural products such as the cystodytins [21]. They have also been reported to possess drug resistance reversal properties [22,23].

Intermolecular cycloaddition reactions of azomethine ylides with α,β-unsaturated ketones and acetylenic dipolarophiles lead to a number of novel compounds. These compounds are very useful for the construction of diverse chemical libraries of drug-like molecules.[24] Spiro-oxindoles (Figure 1) exist in nature and most of them exhibit significant biological activity.[25] A number of natural products having the skeleton of functionalized pyrrolidines and oxindoles[26] possesses well-defined biological properties such as glycosidase inhibitory activity an potent antiviral, antibacterial, antidiabetic, and anticancer activity, and they also act as a potent non-peptide inhibitor of the p53-MDM2 interaction.[27] Elacomine is a naturally occurring hemiterpene spiro-oxindole alkaloid isolated from the roots of *Elaeagnus commutate*.[28] The unsubstituted spiro-oxindole core of (–)-horsfiline is an interesting target and has been reported by many synthetic groups.[29] Coerulescine was isolated in 1998 and its total synthesis is often reported together with that of horsfiline. Some spirooxindole-pyrrolidine derivatives are potential antileukemic and anticonvulsant agents and possess antiviral and local anesthetic activities.[30] The spirotryprostatins A and B were isolated from the fermentation broth of *Aspergillus fumigatus* and have been shown to inhibit completely the G2/M progression of mammalian tsFT210 cells at concentrations in excess of 12.5 mg/mL.[30a,b]



SCHEME 1

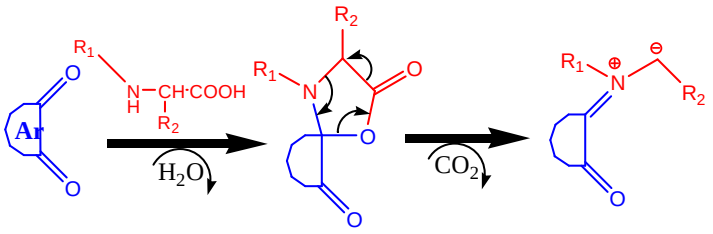
MATERIALS AND METHODS

Refluxing a solution of (E)- 2, 5-bis-(Benzylidene) Cyclopentanone (**3**) in boiling aqueous methanol with acenapthenequinone (**1**) and sarcosine (**2**) afforded 1-N-Methyl-Spiro [2.2'] acenapthene-one-Spiro[3.2'']5''-BenzylideneCyclopentanone-4-Phenyl Pyrrolidine (**4**) (Scheme1, Table 1). The reaction gave a single product in all cases as evidenced by thin layer chromatography (TLC). The reaction afforded a series of novel Spiro derivatives (**4a-e**) through regioselective cycloaddition of azomethine ylides with the exocyclic double bond of 2, 5-bis-(Benzylidene) Cyclopentanone (**3**) in all cases. No trace of the other regioisomer (**5a-e**) was detected. The cycloaddition proceeded smoothly to afford the *syn-endo* cycloadduct. The regio and stereo chemical outcome of the cycloaddition was determined by spectrochemical and single crystal X-ray analysis.

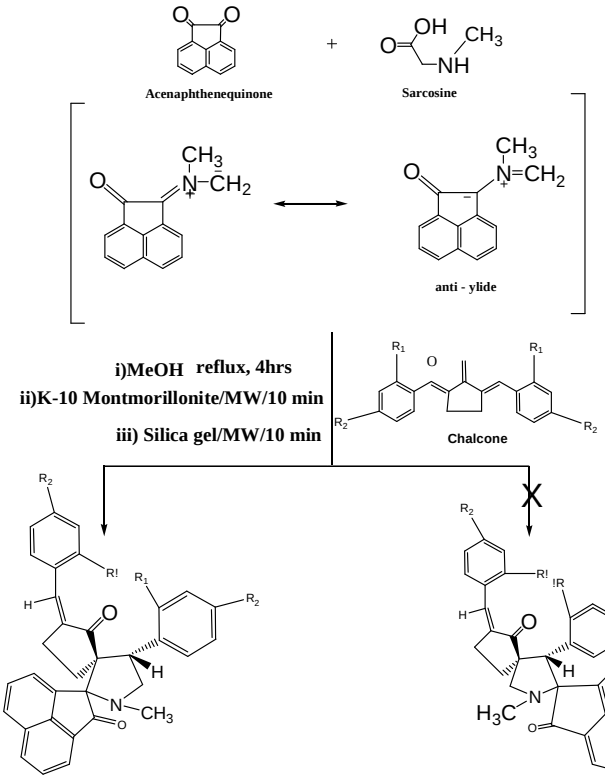
RESULTS AND DISCUSSION

The IR spectral analysis of 1-N-Methyl–spiro [2.2'] acenapthen-1'-one-spiro [3.2''] -5"-Benzylidene Cyclopentanone-4-Phenyl Pyrrolidine **(4a)** showed two carbonyl peaks at 1636 cm^{-1} and 1744 cm^{-1} which correspond to the benzyl and acenaphthenequinone carbonyl groups respectively. The H^1 NMR spectrum of the cycloadduct in DMSO-d6 exhibited a singlet at δ 2.25 which corresponds to N-CH_3 protons. A doublet at δ 1.91 corresponds to N-CH_2 proton. A multiplet at δ 4.52 corresponds to benzylic proton. A doublet at δ7.09 corresponds

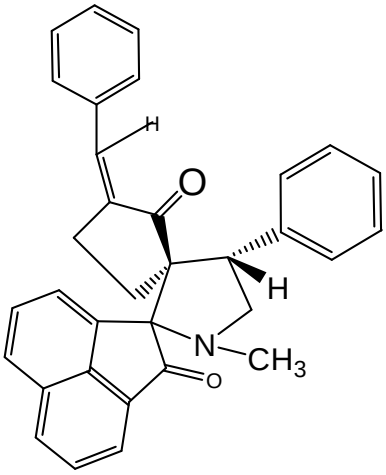
to benzylic proton. A multiplet from δ 7.19-7.99 corresponds to 16 aromatic protons. Also the ^{13}C NMR showed a signal at δ 66.52 and 80.11 due to the two spiro carbon atoms, and peaks at δ 205.67 and δ 207.94 correspond to the cyclopentanone and acenaphthenequinone carbonyl groups respectively. The mass spectrum of the compound shows a peak at m/z 469.11 (M^+) which corresponds to the molecular weight of the compound.

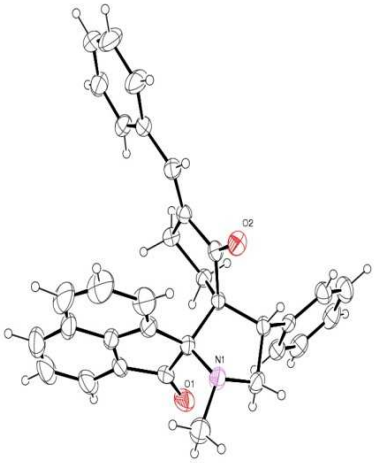


Scheme 2 .Mechanism of azomethine ylide formation



Compound	R_1	R_2
4a	H	H
4b	OH	H
4c	H	OH
4d	H	Cl
4e	H	NO_2





ORTEP diagram of 1-N-methyl-spiro[2.2'] acenapthen-1'-one-spiro [3.2'']-5''-Benzelizene Cyclopentanone-4-Phenyl Pyrrolidine.

Spiro-compound 4a :92% yield, mp 150-155°C. IR (KBr): 1686, 1744 cm^{-1}; 1H-NMR ($CDCl_3$ /500 MHz) δ: 1.390 (2H, m, $-CH_2$); δ 1.912, δ 2.076(2H, m,-N-CH_2); δ 2.253(3H, s, N-CH_3); δ 3.544, δ 4.039 (2H, m, $-CH_2$); δ 3.585 (1H, m,-CH); δ 7.093(1H, s, Ar-CH=); δ 7.198 – 7.996 (16H, m, Ar-H). ^{13}C NMR ($CDCl_3$/400 MHz): δ 34.64, 44.01, 55.78, 56.93, 66.52, 80.11, 108.80, 117.75, 124.38, 126.93, 127.33, 128.50, 129.06, 129.44, 141.11, 155.91, 205.67, 207.94 ESI-MS m/z: 469.11 calcd. for $C_{33}H_{29}NO_2$:469.55.

Spiro-compound 4b: 94% yield, mp120-124°C. IR (KBr): 1678, 1732, 3050 cm^{-1}; 1H-NMR ($CDCl_3$) δ: 1.390 (2H, m, $-CH_2$); δ 1.912, δ 2.076(2H, m,-N-CH_2); δ 2.253(3H, s, N-CH_3); δ 3.544, δ 4.039 (2H, m, $-CH_2$); δ 3.585 (1H, m,-CH); δ 5.05 (1H,m,-Ar -OH) , δ 7.093(1H, s, Ar-CH=); δ 7.198 – 7.996 (15H, m, Ar-H). ^{13}C NMR ($CDCl_3$/500 MHz): δ 34.64, 44.01, 55.78, 56.93, 66.70, 80.05, 108.80, 117.75, 124.38, 126.93, 127.33, 128.50, 129.06, 129.44, 141.11, 155.91, 158.35, 205.67,207.94 ESI-MS m/z: 501.19 calcd. for $C_{33}H_{27}NO_4$: 501.19

Spiro-compound 4c: 94% yield, mp 120-124°C. IR (KBr): 1678, 1732, 3010 cm^{-1}; 1H-NMR ($CDCl_3$) δ: 1.390 (2H, m, $-CH_2$); δ 1.912, δ 2.076(2H, m,-N-CH_2); δ 2.253(3H, s, N-CH_3); δ 3.544, δ 4.039 (2H, m, $-CH_2$); δ 3.585 (1H, m,-CH); δ 5.05 (1H,m,-Ar -OH) , δ 7.093(1H, s, Ar-CH=); δ 7.277 – 7.954 (15H, m, Ar-H). ^{13}C NMR ($CDCl_3$/500 MHz): δ 34.64, 44.01, 55.78, 56.93, 66.70, 80.05, 108.80, 117.75, 124.38, 126.93, 127.33, 128.50, 129.06, 129.44, 141.11, 155.91, 158.35, 205.67,207.94 ESI-MS m/z: 501.19 calcd. for $C_{33}H_{27}NO_4$: 501.22

Spiro-compound 4d: 96% yield, mp 118-122°C. IR (KBr): 1676, 1730 cm^{-1}; 1H-NMR ($CDCl_3$) δ: 1.389 (2H, m, $-CH_2$); δ 1.967, δ 2.076(2H, m,-N-CH_2); δ 2.253(3H, s, N-CH_3); δ 3.556, δ 4.054 (2H, m, $-CH_2$); δ 3.585 (1H, m,-CH); δ 7.093(1H, s, Ar-CH=); δ 7.155 – 7.967 (15H, m, Ar-H). ^{13}C NMR ($CDCl_3$/500 MHz): δ 34.64, 44.01, 55.78, 56.93, 66.70, 80.05, 108.80, 117.75, 124.38, 126.93, 127.33, 128.50, 129.06, 129.44, 131.55, 133.65, 141.11, 155.91, 205.67, 207.94 ESI-MS m/z: 537.13 calcd. for $C_{33}H_{25}Cl_2NO_2$: 538.46

Spiro-compound 4e: 90% yield, mp 130-132°C. IR (KBr): 1670, 1730 cm^{-1}; 1H-NMR ($CDCl_3$) δ: 1.390 (2H, m, $-CH_2$); δ 1.912, δ 2.076 (2H, m,-N-CH_2); δ 2.221(3H, s, N-CH_3); δ 3.544, δ 4.039 (2H, m, $-CH_2$); δ 3.585 (1H, m,-CH); δ 7.093(1H, s, Ar-CH=); δ 7.277 – 7.954 (15H, m, Ar-H). ^{13}C NMR ($CDCl_3$/500 MHz): δ 34.64, 44.01, 55.78, 56.93, 66.70, 80.05, 108.80, 117.75, 124.38, 126.93, 127.33, 128.50, 129.06, 129.44, 141.11, 145.65, 147 .64 , 155.91, 205.67,207.94 ESI-MS m/z: 559.17 calcd. for $C_{33}H_{25}N_3O_6$: 559.57

As a part of our ongoing research program, we had synthesized the above mentioned compounds under solvent free conditions using microwave. For the above synthesis we had used the conventional household microwave oven at 60w power and the solid support was silica gel and K10 montmorinollite. The reaction was monitored using TLC at regular interval and in all case it was ascertained that only one product was forms in a regioselective manner. The microwave synthesis gave better yield in all the cases and the reaction proceeded without any solvent in a greener manner.

Table 2 : Synthesis of spirohetrocycles using conventional and solvent free condition

Compound	R_1	R_2	Conventional MeOH/reflux 4hrs Yield (%)	Microwave (10 min) /K10 montmorillonite Yield (%)	Microwave (10 min) Silca gel Yield (%)
4a	H	H	62	83	71
4b	OH	H	70	85	74
4c	H	OH	72	84	76
4d	H	Cl	75	89	88
4e	H	NO_2	78	92	94

The synthesized compounds were subjected to antibacterial activity and the results are promising. Antimicrobial analysis was followed using standard agar well diffusion method to study the antimicrobial activity of prepared compounds (Perez *et al*., 1990; Erdemoglu *et al*., 2003; Bagamboula *et al*., 2004). Antimicrobial activity was evaluated by measuring the diameter of the zone of inhibition in mm against the test microorganisms and the solvent. DMSO was used as solvent control. Ciprofloxacin was used as reference antibacterial agent. The tests were carried out in triplicates.

Table 3: Antibacterial activity of Spiroheterocycle (4a) : (-zone inhibition in mm)

S.NO	MICRO ORGANISMS	Concentration in ppm/zone inhibition in mm				Streptomycin (Control)
		100	200	300	400	-
1.	*Micrococcus luteus*	8	9	10	11	6
2.	*Enterobacter agerogens*	6	8	9	10	6
3.	*Salmonella enterica typhimorium*	8	9	10	11	6
4.	*Eubacterium lentum*	6	7	8	9	6

CONCLUSION

We here in report a highly regioselective and atom economic green synthesis of dispiroheterocycles through 1,3–dipolar cycloaddition of azomethine ylides generated through decarboxylative route using Acenaphthenequinone and sarcosine with Claisen –Schmidt adducts from cyclopentanone and aldehydes. The reactions in all cases gave a single product in a highly regioselective manner. The synthesized compound were characterized using ^{1}H NMR, ^{13}C NMR , IR and mass and the results are present here. Single crystal XRD was used to ascertain the stereochemical outcome of the regioselective product. The compounds were also subjected to biological activity and the results are promising. The present synthesis had envisaged a new route for the synthesis of chalcones which are potential anti cancer agents as reported in the literature.

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