Available online at www.scholarsresearchlibrary.com

Scholars Research Library

Der Pharmacia Lettre, 2015, 7 (8):152-155
(http://scholarsresearchlibrary.com/archive.html)

Scholars Research Library
ISSN 0975-5071
USA CODEN: DPLEB4

An efficient Synthesis of dispiro heterocycles from Claisen –Schmidt adduct through 1, 3-dipolar cycloaddition protocol and study on its biological properties

Augustine Arul Prasad T.[a*], Scholastica Mary Vithiya B.[b] and Suganya Kumaresh K.[b]

[a]*Postgraduate and Research Department of Chemistry, D. G. Vaishnav College, Chennai, India*
[b]*Post graduate and Research Department of Chemistry, Auxilium College Vellore, India*

ABSTRACT

Intermolecular 1, 3-dipolarcycloaddition reaction of azomethine ylides, generated through decarboxylative route, with Claisen –Schmidt adducts dipolarophiles has been investigated. A new class of functionalized spiroheterocyclic framework has been generated with high regioselectivity. The structures were established by spectroscopic techniques as well as single crystal X-ray analysis. As a part of our ongoing research program in the area of cycloaddition reaction of azomethine ylides with Claisen –Schmidt adducts, we herein report the highly region and stereo selective synthesis of spiro- bis - arylidene cycloalkanone pyrrolidines through 1, 3 –dipolar cycloaddition protocol. The Spiro compounds obtained were characterized by ^{1}H NMR, ^{13}C NMR, Mass and the stereo chemical outcome of the regioselective product was ascertained by XRD studies. The synthesis was also tried under microwave conditions and the results are presented here. The compounds were subjected biological study and the results are promising.

Key words: Spiropyrrolidines,1, 3-Dipolar addition, Azomethine ylides, cycloalkanones, Oxindole,Claisen –Schimdt adducts.

INTRODUCTION

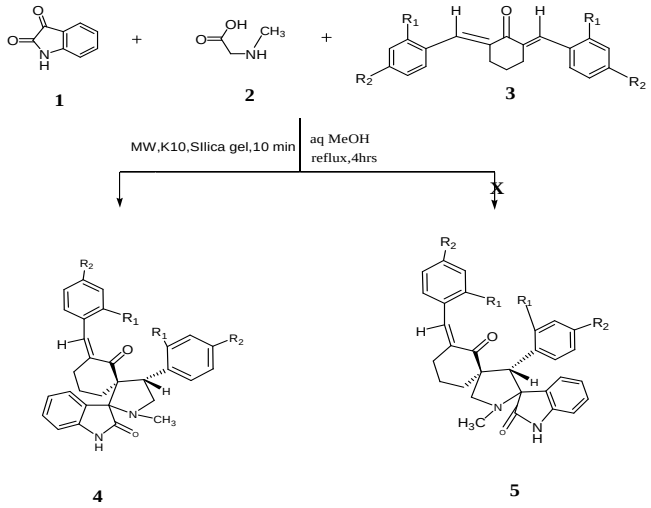
Spiroheterocycles and nitrogen heterocycles such as pyridines, pyrroles, and pyrrolizines display good biological properties. The synthesis of spiroheterocycles has drawn considerable attention of chemists, in view of their very good biological activity [1-4]. In particular, 1,3-Dipolar cycloaddition of nonstabilised azomethine ylides generated in situ from isatin or acenaphthenequinone and α-amino acids through decarboxylative route, to the olefinic dipolarophiles having an exocyclic bond provides a facile route for the construction of many spiro-heterocycles, which are prevalent in nature and in a variety of biologically active compounds, and find utility in the treatment of diseases such as cancer and viral infections [5,6].1, 3-Dipolar cycloaddition of azomethine ylides to alkenes affords pyrrolidines with good selectivities [7,8]. Recently, we had reported an highly atom economic synthesis of spiro pyrrolidines and spiro oxindole derivatives [9]. We are also in the process of optimizing the entire synthetic route through greener approach by conducting all the reactions under solvent free microwave conditions. The biological importance of spiro-pyrrolidines, and our ongoing effort[10-13] to discover novel anticancer lead candidates, led us to synthesize novel spiro heterocycles via 1,3-dipoar cycloaddition of azomethine ylides to a series of novel spiropyrrolidines from bis arylidene cyclohexanone and cyclopentanone. We present the preliminary results on the synthesis and the structure of the first representative series of this family.

MATERIALS AND METHODS

Refluxing a solution of (E)- 2, 6-bis-(Benzylidene) Cyclohexanone (**3**) in boiling aqueous methanol with isatin (**1**) and sarcosine (**2**) afforded 1-N-Methyl-Spiro [2.3'] Oxindole-Spiro[3.2'']6''-BenzylideneCyclohexanone-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-f**) through regioselective cycloaddition of azomethine ylides with the exocyclic double bond of 2, 6-bis-(Benzylidene) Cyclohexanone (**3**) in all cases. No trace of the other regioisomer (**5a-f**) 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 1-N-methyl-spiro [2.3'] oxindole-spiro[3.2'']6''-benzylidenecyclohexanone-4-Pheny-l pyrrolidine **(4a)** showed two carbonyl peaks at 1699 cm^{-1} and 1780 cm^{-1} which corresponded to benzoyl and Isatin ring carbonyl groups. The ^{1}H NMR of the cyclo adduct exhibited a singlet δ 2.39 which corresponded to N – Methyl protons. A singlet at δ 7.80 for one -CONH proton. A multiplet at δ 3.44 corresponds to benzylic proton. A doublet at δ 5.42 corresponds to N – CH_2 proton. Multiplet from δ 6.85 –δ 7.9 corresponds to 14 aromatic protons. The ^{13}C NMR showed a signal at δ 79.05 due to the spiro carbon atom, and peaks at δ 189.71 and δ 197.54 correspond to benzoyl and Isatin carbonyl groups. The mass spectrum of the compound showed a peak at m/z 448.22 (M^{+}), which corresponded to the molecular weight of the compound.

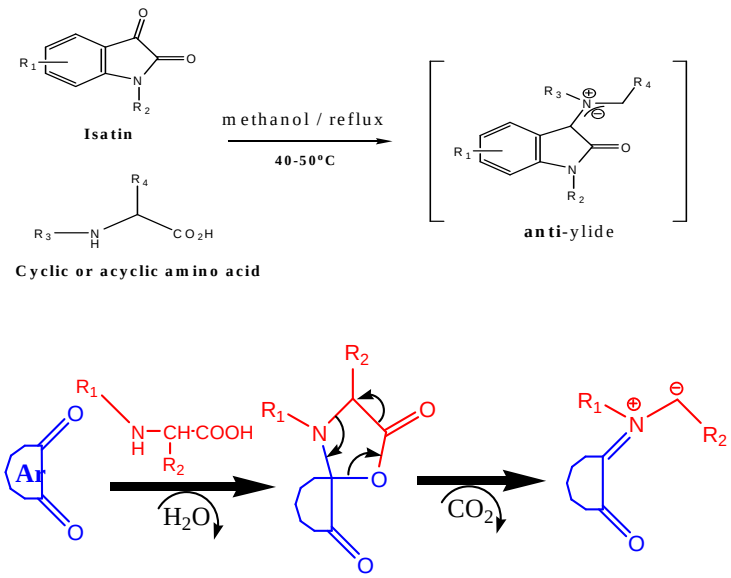


1 **2** **3** **4** **5**

SCHEME 1

Table 1. Synthesis of 1-N-Methyl-Spiro [2.3'] Oxindole-Spiro [3.2''] 6''-Benzylidene Cyclohexanone-4-Phenyl Pyrrolidine (4a-f) *via* Scheme 1

Compound	R_1	R_2
4a	H	H
4b	OH	H
4c	H	OH
4d	H	Cl
4e	H	NO_2
4f	H	OCH_3



Scheme 2 .Mechanism of azomethine ylide formation

Spiro-Compound 4a: IR (KBr): 1699, 1780 cm^{-1}; ^1H NMR (CDCl$_3$/400 MHz): δ 2.39 (s, 3H,-CH$_3$), 3.44 (d, 2H, J=5.2 Hz), 5.42 (d, 2H, J=12.4 Hz), 7.80 (s, 1H), 6.85-7.90 (m,14H); ^{13}C NMR (CDCl$_3$/400 MHz): δ 34.64, 44.01, 55.78, 56.93, 65.70, 79.05, 108.80, 117.75, 124.38, 126.93, 127.33, 128.50, 129.06, 129.44, 141.11, 155.91, 189.71, 197.54 ppm; EIMS m/z : 448.22 (M^+)

Spiro-compound 4b: IR (KBr): 1697, 1780 cm^{-1}; ^1H NMR (CDCl$_3$/400 MHz): δ 2.39 (s, 3H,-CH$_3$), 3.44 (d, 2H, J=5.2 Hz), 5.21 (s,1H), 5.42 (d, 2H, J=12.4 Hz), 7.80 (s, 1H), 6.87-7.85 (m,12H); ^{13}C NMR (CDCl$_3$/400 MHz): δ 34.64, 44.01, 55.78, 56.93, 65.70, 79.05, 108.80, 117.75, 124.38, 126.93, 127.33, 128.50, 129.06, 129.44, 141.11, 155.31,158.35 189.71, 197.54 ppm; EIMS m/z : 480.55 (M^+)

Spiro-compound 4c: IR (KBr): 1697, 1780 cm^{-1}; ^1H NMR (CDCl$_3$/400 MHz): δ 2.39 (s, 3H,-CH$_3$), 3.44 (d, 2H, J=5.2 Hz), 5.21 (s,1H), 5.42 (d, 2H, J=12.4 Hz), 7.80 (s, 1H), 6.87-7.85 (m,12H); ^{13}C NMR (CDCl$_3$/400 MHz): δ 34.64, 44.01, 55.78, 56.93, 65.70, 79.05, 108.80, 117.75, 124.38, 126.93, 127.33, 128.50, 129.06, 129.44, 141.11, 155.91,158.35, 189.71, 197.54 ppm; EIMS m/z : 480.55 (M^+)

Spiro-compound 4d: IR (KBr): 1689, 1729 cm^{-1}; ^1H NMR (CDCl$_3$/400 MHz): δ 2.34 (s, 3H,-CH$_3$), 3.47 (d, 2H, J=5.2 Hz), 5.40 (d, 2H, J=12.4 Hz), 7.78 (s, 1H), 6.92-7.89 (m,12H); ^{13}C NMR (CDCl$_3$/400 MHz): δ 34.64, 44.01, 55.78, 56.93, 65.70, 79.25, 108.80, 117.75, 124.38, 126.93, 127.33, 128.50, 129.06, 129.44, 131.11,133.35,141.11, 155.91,158.35, 189.71, 197.54 ppm; EIMS m/z : 516.14 (M^+)

Spiro-compound 4e: IR (KBr): 1690, 1735 cm^{-1}; ^1H NMR (CDCl$_3$/400 MHz): δ 2.37 (s, 3H,-CH$_3$), 3.65 (d, 2H, J=5.2 Hz), 5.38 (d, 2H, J=12.4 Hz), 7.54 (s, 1H), 6.90-7.78 (m,12H); ^{13}C NMR (CDCl$_3$/400 MHz): δ 34.64, 44.01, 55.78, 56.93, 65.70, 79.25, 108.80, 117.75, 124.38, 126.93, 127.33, 128.50, 129.06, 129.44, 131.11,133.35,141.11, 145.21,147.32,158.35, 190.25, 198.36 ppm; EIMS m/z : 538.19 (M^+)

Spiro-compound 4f: IR (KBr): 1697, 1780 cm^{-1}; ^1H NMR (CDCl$_3$/400 MHz): δ 2.39 (s, 3H,-CH$_3$), 3.44 (d, 2H, J=5.2 Hz), 3.73 (s,3H),5.21 (s,1H), 5.42 (d, 2H, J=12.4 Hz), 7.80 (s, 1H), 6.87-7.85 (m,12H); ^{13}C NMR (CDCl$_3$/400 MHz): δ 34.64, 44.01, 55.90, 56.93, 65.70, 79.05, 108.80, 117.75, 124.38, 126.93, 127.33, 128.50, 129.06, 129.44, 141.11, 155.31,158.35 189.71, 197.54 ppm; EIMS m/z : 508.24 (M^+)

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
b	OH	H	70	85	74
4c	H	OH	72	84	76
4d	H	Cl	75	89	88
4e	H	NO_2	78	92	94
4f	H	OCH_3	88	94	92

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 Spiroheterocycles

S.NO	MICRO ORGANISMS	4a	4b	4c	4d	4e	4f	CIPROFLOXACIN
1.	*Enterococcus faecalis*	13	11	6	10	6	11	23
2.	*Staphylococcus aureus*	5	4	5	15	5	09	25
3.	*Escherichia coli*	5	4	4	17	9	08	22

(-zone inhibition in mm)

In conclusion, we here in report the regioselective synthesis of dispiroheterocycles through 1,3–dipolar cycloaddition of azomethine ylides generated through decarboxylative route using Isatin and secondary amino acids with Claisen –Schmidt adducts from cyclohexanone, and aldehydes. The reactions in all cases gave a single product in a highly regioselective manner. The synthesized compounds were characterized using UV, ^{1}H NMR, ^{13}C NMR, IR and mass and the results are present here. The compounds were also synthesized under solvent free condition since it paves the way for the synthesis of a variety of biologically significant Spiro-oxindole derivatives using easily available starting materials. The compounds were also subjected to biological activity and the results are promising.

Acknowledgement
The author thanks UGC for financial support by granting the funds to carry out the project during the 12th five year plan 2012 – 17.

REFERENCES

[1] Pluta K,Morak-Mlodawska B,Jelen M. *Eur J Med Chem* , **2011**,46(8):3179-3189**.**
[2] Rani M,Ramachandran R,Kabilan S. *Bioorg Med Chem Lett*, **2011 ,** 20(22):6637-6643.
[3]Zhang FY,Wu CL,Zhang C,Liu HM. *Chinese Chemical Letters*, **2010,** 21(7):798-801.
[4] Xi HT,Yi TT,Sun XQ. *Chinese Chemical Letters*, **2010,** 21(6):633-636**.**
[5] Kumar RR,Perumal S,Senthilkumar P,Yogeeswari P,Sriram D. *J Med Chem*, **2008,** 51(18):5731-5735.
[6] Girgis A S. *Eur J Med Chem*, **2009,**44(1):91-100**.**
[7] Kumar RR,Loganayaki B,Perumal S. *Synthetic Communications*, **2009**,39(18):3197-3216**.**
[8] Huang KSL,Lee EH,Olmstead MM,Kurth MJ. *The Journal of Organic Chemistry*, **2000,**65(2):499-503.
[9] Ramu.P., Augustine Arul Prasad T, Scholastica Mary Vithiya and S. Arul Antony, *Der Pharma Chemica*, **2014,**6(4):30-36.
[10] Augustine,A.P.T.; Charles C.Kanakam.;Scholastica Mary Vithiya.;Ramkumar,V. , *Tetrahedron Lett.* , **2009,** 50**,** *5906-09***.**
[11] Augustine,T.;Scholastica Mary Vithiya., V. *Acta cryst* , **2010,** E66, o3002**.**
[12]T.Augustine Arul Prasad., B.Scholastica Mary Vithiya., *Der Pharma Chemica*, **2011,**3(3):293-299,.
[13] Scholastica Mary Vithiya. B, Indumathi. U., Augustine Arul Prasad. T, *Der Pharma Chemica*, **2012,**4(5):1906-1912.