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Synthesis and anti-bacterial activity evaluation of cyclopentalene unit containing nitrogen and sulphur hetero atoms

SP Nanda[†], AK Padhy[††], RK Dey*

[†] Dept of Chemistry, Jagannath Institute for Technology & Management, Parlakhemundi, Orissa, INDIA
[††] Dept of Chemistry, National Institute of Science & Technology, Palur Hills, Berhampur-761 008, Orissa, INDIA
* Post Graduate Dept of Chemistry, Ravenshaw University, Cuttack-753 003, Orissa, INDIA

ABSTRACT

6a, 6b-diphenyl-tetrahydro-2a, 4a-diaza-cyclopenta[*cd*]pentalene-2, 5-dione and 2, 5-diamino-6a, 6b-diphenyl-3, 4, 6a, 6b-tetrahydro-2a, 4a–diaza–cylcopenta [*cd*] pentalene-1, 6-dicarbonitriles were prepared using simple laboratory procedure. The synthesized compounds were evaluated for their potential biological activity.
Keywords: Cyclopenta[*cd*]pentalene, Pyrazine, Anti-bacterial, Dicarbonitriles.

Corresponding author:

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INTRODUCTION

Aromatic systems which are distorted from planarity have long been objects of scientific interest. Classic examples include paracyclophanes, [1,2] peri-substituted acenes, [3] helicenes,[4,5] cyclacenes, [6,7] bridged annulenes,[8] and highly substituted porphyrins [9]. In this aspect, various molecules such as fullerenes, carbon nano-tubes, corannulene and related polycycles have also attracted much attention [10,11].

Pentalene is a molecule of significant interest for organic chemists since decades. This is because of the synthetic challenges, its aromaticity and structural properties. The unsubstituted molecule C_8H_6 is thermally unstable with respect to dimerisation, in a manner similar to cyclobutadiene. Le Goff [12] isolated the first simple pentalene in 1962-hexaphenylpentalene, stabilized both sterically and electronically; followed by the preparations of 1,3-bis(dimethylamino)pentalene [13] and aminopentalene carbonitrile, [14] containing electron-withdrawing substituents. Use of heterocyclic pentalenes in the analysis of sulphur containing substances of fossil fuels such as mineral oils, coal, carbonaceous oils, shale oils and tar sands has also attracted much attention scientifically. These compounds are also used as oxidation inhibitors and active substances in various research areas pertaining to biocides. [15-19]. Heterocyclic pentalenes also find applications in preparation of metallocene complexes and as catalysts for the polymerization of olefins. [20-21].

Quite recently bonding pattern in analogues compounds of pentalene is being studied by various researchers. [22] In this aspect crystal structures of 2,3-diethyl-6,7-dihydro-5*H*-2aλ^4-selena-2,3,4a,7a-tetraaza-cyclopent[*cd*] indene-1(2H),4(3H)-diselone and 1,4-bis(ethylimino)-5,6- dihydro- 2,2aλ^4,3-triselena-4a,6a-diazacyclopenta[*cd*]pentalene has been proposed [23]. In further development various research papers shows studies regarding electronic properties and the usage of dinaphthopentalenes for organic thin film transistors [24]. However, it is to be mentioned that reactions involving the diaza-cyclopenta[cd]pentalene is yet to be extensively studied. In present investigation we are reporting the synthesis of 6a,6b-diphenyl-tetrahydro-2a,4a-diaza-cyclopenta[cd]pentalene-2,5-dione & 2,5-diamino-6a,6b-diphenyl-3,4,6a,6b-tetrahydro-2a,4a–diaza–cylcopenta[cd] pentalene-1,6-dicarbonitriles starting from simple precursor such as pyrazines. The prepared compounds were studied for their potential biological activities for gram(+) and gram(-) bacterias.

MATERIALS AND METHODS

Experimental

All the chemicals were purchased from either E-Merck or Hi-Media. Solid compounds were used as such and all liquid compounds were distilled prior to their use. Melting points were determined using open capillary tubes and reported data are uncorrected values. NMR spectra of compounds were taken in Bruker DRX 300 spectrophotometer using DMSO-d_6/$CDCl_3$ as solvent and TMS as internal standard.

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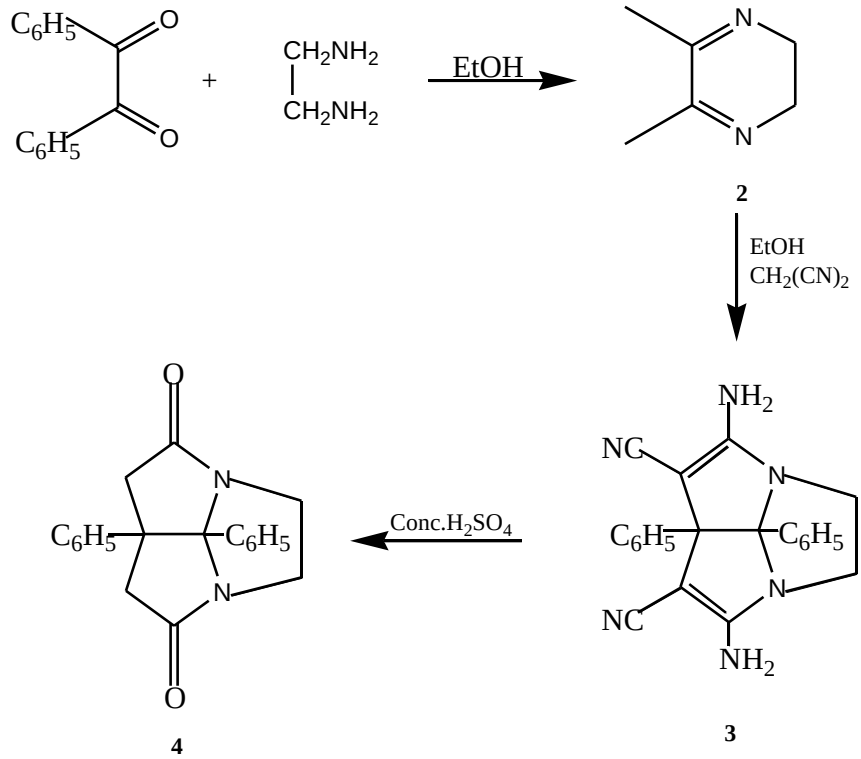
Synthesis

The organic compound was synthesized using following procedure. 1,2-Diketones on condensation with ethylenediamine in ethanolic medium produced 5,6-diphenyl-2,3-dihydropyrazine(2). In subsequent step, the obtained synthetic pyrazine subjected to condensation with malonodinitrile in ethanolic medium to produce corresponding 2,5-diamino-6a,6b-diphenyl-3,4,6a,6b-tetrahydro-2a,4a-diaza-cylcopenta[*cd*]pentalene-1,6-dicarbonitrile derivatives(3). The compound 3 subsequently underwent oxidative hydrolysis to produce 6a,6b-diphenyl-tetrahydro-2a,4a-diaza-cyclopenta[*cd*]pentalene-2,5-dione(4) in appreciably good yield. The reaction is outlined in (**Scheme-1)**. Further the synthetic 2,5-diamino-6a,6b-diphenyl-3,4,6a,6b-tetrahydro-2a,4a-diaza-cylcopenta[*cd*]pentalene-1,6-dicarbonitriles were condensed with aromatic aldehydes to give corresponding Schiff's bases (5). Compound 5 on condensation with thioglycolic acid following azeotropic method produced corresponding thiazolidinone derivative (6) in appreciably good yield **(Scheme-2).**



(**Scheme-1**)

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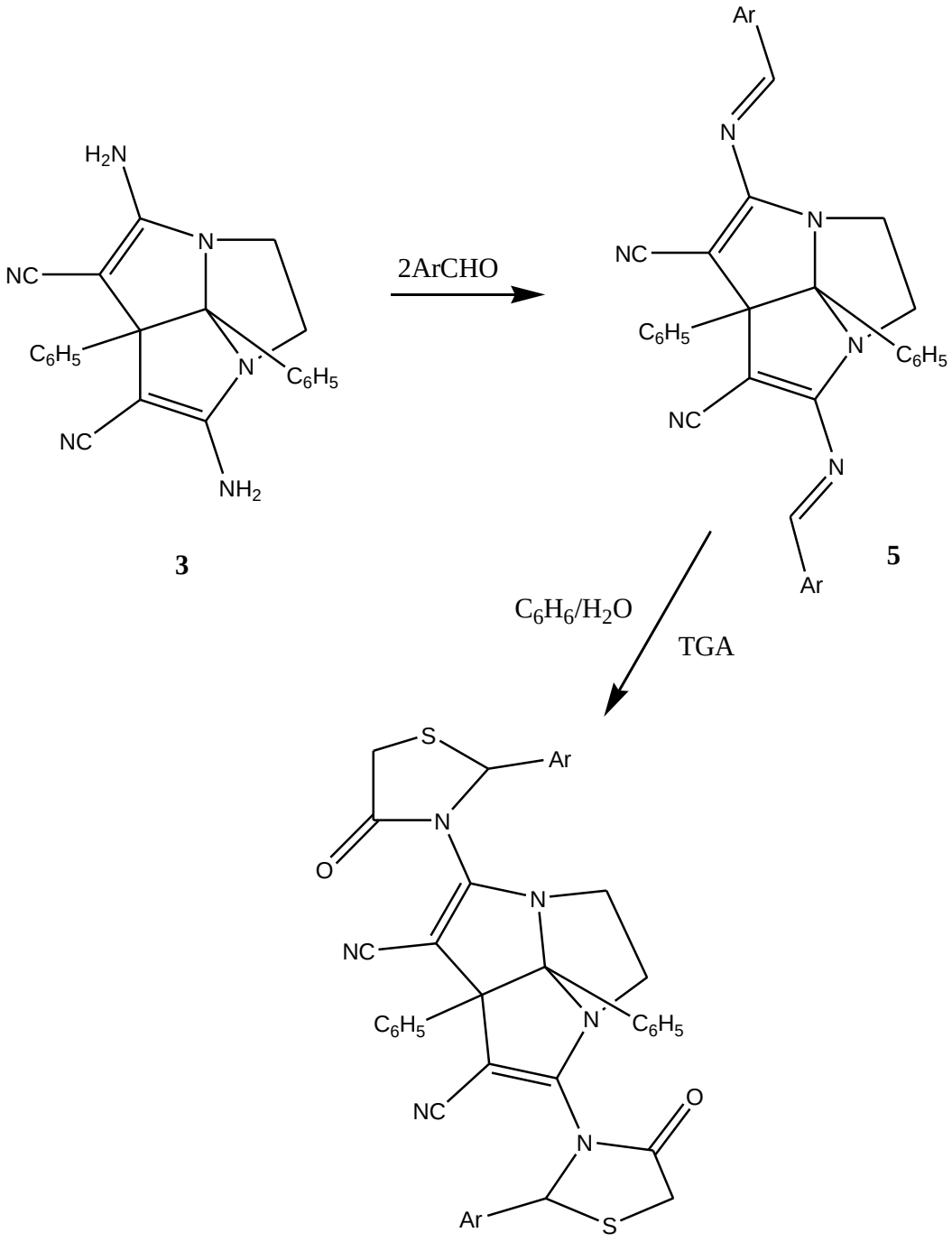

3 **5**

6

(Scheme-2)

RESULTS AND DISCUSSION

The structures of all the synthetic compounds were established on the basis of obtained analytical and spectral measurement data. The spectral results for compound **4** and **6** are furnished below:

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Compound: 4. ^{1}H NMR (300MHz in DMSO-d_6, TMS at 0ppm): δ 2.36(t, 2H, CH_2); δ 2.61(t, 2H, CH_2); 7.06 (m, 2H, ArH); 7.29(m, 2H, ArH); ^{13}C NMR (300MHz in DMSO-d_6, TMS at 0 ppm): 121-126, 135.2, 154.5, 172.

Compound 6. ^{1}H NMR (300MHz in $CDCl_3$, TMS at 0ppm): δ 2.6(2H, CH_2); 7.35(m, 1H, ArH); 7.46(m, 1H, ArH); ^{13}C NMR (300MHz in $CDCl_3$, TMS at 0ppm): 43.1, 59.1, 121-126.
Interestingly, all thiazolidinone derivatives exhibited significant methylene peak at 2.6δ with TMS as standard. Further, the analytical data of condensation of derivatives (5: Scheme-2) is furnished in Table-1 and analytical data of condensation of derivatives of (6: Scheme-2) is furnished in Table-2.

Table-1: Analytical data of compound (5) (Schiff's bases)

No.	Ar	color	m.p(^{0}C)	Yield (%)	Calculated(%)			Found(%)		
					C	H	N	C	H	N
A	Benzaldehyde	Brown	100	87	79.68	4.83	15.49	79.65	4.80	15.5
B	*p*-Cl-benzaldehyde	White	165	90	70.71	3.96	11.60	70.69	3.94	11.57
C	Anisaldehyde	White	90	84	75.73	5.02	13.94	75.7	4.99	13.91
D	*o*-NH_2-benzaldehyde	Brown	155	90	75.50	4.93	19.57	75.51	4.91	19.55
E	4-OH-benzaldehyde	Grey	80	90	75.25	4.56	14.63	75.21	4.55	14.61

Table-2: Analytical data of compound(6) (thiazolidinone derivative)

No.	Ar	Color	m.p(^{0}C)	Yield (%)	Calculated(%)			Found(%)		
					C	H	N	C	H	N
A	C_6H_5	White	205	77	69.54	4.38	12.17	69.51	4.37	12.15
B	*p*-ClC_6H_4	White	165	78	63.24	3.71	9.33	63.23	3.7	9.33
C	*p*-OHC_6H_4	Brown	178	85	66.46	4.18	11.63	66.44	4.15	11.6
D	*o*-$NH_2C_6H_4$	White	137	71	66.65	4.47	15.54	66.6	4.45	15.51
E	*p*-$OCH_3C_6H_4$	White	145	80	67.18	4.56	11.19	67.15	4.52	11.17

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Structures of all the synthetic compounds were established from the analytical and spectral data. The thiazolidinone derivative exhibited significant methylene peak at 2.6δ with TMS as standard. The synthesized thiazolidinone derivatives were screened for their potential biological activity against gram +ve and gram –ve bacteria such as Escherichia coli, Staphylococcus aureus, and Bacillus cereus. The antibacterial activity, presented in Table 3, was done by two-fold series dilution method. The minimum inhibitory concentration (MIC) was recorded as the lowest concentration at which no bacterial growth was observed [25]. Both the compounds demonstrated very good activity against Gram (+) and Gram (-) bacteria. As observed, compound 6 was found to be more active in comparison to compound 4. In the present case, the antimicrobial activities of both compounds could be explained on the basis of presence of attached carbonyl groups capable of forming hydrogen bonds with the active sites of the target enzymes [26]. The presence of sulphur and aromatic rings could also be factors contributing to the observed higher antimicrobial activity of compound 6 in comparison to compound 4. Previous studies in similar kind of compounds also noted anti-bacterial activities. [27]. Therefore, these compounds are projected as potential candidate for the development of fungicidals, inhibitors and possible drug against bacterias.

Table 3: Antibacterial activity of Compound 4 and 6

Bacteria	Minimum inhibitory concentration (µg / ml)		
	Compound 4	Compound 6	Gentamycin
Gram (+)			
Bacillus cereus	4.12	8.51	6.25
Staphylococus aureus	3.54	12.34	24.8
Gram (-)			
Escherichia coli	2.65	5.11	6.25

CONCLUSIONS

The present investigation reports synthesis of two pyrazines i.e., 6a,6b-diphenyl-tetrahydro-2a,4a-diaza-cyclopenta[*cd*]pentalene-2,5-dione and 2,5-diamino-6a,6b-diphenyl-3,4,6a,6b-tetrahydro-2a,4a–diaza–cylcopenta[*cd*] pentalene-1,6-dicarbonitriles which were prepared using condensation reaction procedure. The percentage of yield of both the compounds (6 and 4) were appreciable (>70%). The higher antibacterial activity of compound 6 could be attributed to the presence of aromatic group and sulphur atom in the moiety. Both the compounds could be projected as potential candidate for the development of anti-bacterial drugs and fungicides.

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