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Research Article

SYNTHESIS, SPECTRAL CHARACTERIZATION AND ANTIOXIDANT ACTIVITIES OF 3'-METHYL-2',6'-DIPHENYL-1,3-DIHYDROSPIRO[BENZO[D]IMIDAZOLE-2,4'-PIPERIDINE]

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ABSTRACT

3'-methyl-2',6'-diphenyl-1,3-dihydrospiro[benzo[d]imidazole-2,4'-piperidine] was synthesized by condensing 3-methyl-2,6-diarylpiperidin-4-one with o-phenylenediamine. The synthesized compound was characterized by IR, Mass and NMR spectral studies. NMR spectral assignments are made clearly by their one-dimensional (^{1}H and ^{13}C NMR) and two-dimensional (HOMO COSY and NOESY) NMR spectra. The spectral data suggest that the compound adopt chair conformation with equatorial orientation of all the substituents. The target compound exhibited an excellent free radical scavenging activity on the stable DPPH free radical (88.8 %).

Keywords: Benzoimidazole. HOMOCOSY. NOESY. conformation. Antioxidant and DPPH.

1. INTRODUCTION

Poly functionalized heterocyclic compounds shows important roles in the drug discovery route and analysis of drugs in late development or on the market shows that 68% of them are heterocycles[1,2] Therefore, it is not amazing that research on the synthesis of poly functionalized heterocyclic compounds has received remarkable attention.

Spiro cyclic structures containing one carbon atom common to two rings are structurally interesting[3]. The asymmetric characteristic of the molecule due to the chiral spiro carbon is one of the significant criteria of the biological activities. The presence of the sterically constrained spiro structure in various natural products also adds to the interest in the investigations of spiro compounds[4]. Spiro compounds represent an important class of naturally occurring substances characteristic by their highly pronounced biological properties[5,6]. Consequently, many synthetic methodologies have been developed for constructing these spiro cycles, most of which were based on cyclo addition or condensation reactions[7-15].

Based on the views of the above reports, the development of new and simple synthetic methods for the efficient preparation of spiro hetero cycles containing piperidine ring is an interesting challenge. Very recently, we have reported the synthesis of 7,9-diphenyl-1,4,8-triaza spiro[4,5] decane derivatives by the reaction of piperidin-4-ones with 1,4-binucleophile[16]. This is the second report on the synthesis of 3'-methyl-2',6'-diphenyl-1,3-dihydro spiro [benzo[d] imidazole-2,4'-piperidine] by 3-methyl-2,6-diarylpiperidin-4-one to undergo condensation reaction with o-phenylene diamine.

Nuclear magnetic resonance spectroscopy has been used as a powerful tool determining the structure and stereochemistry of organic compounds. The conformations of six-membered ring compounds in solution, vicinal proton–proton coupling constants have been widely used in deriving information about the conformations of heterocyclic compounds[17–29]. Substituted piperidine adopts chair conformation with equatorial orientations of the bulky substituents because in these compounds nitrogen is in sp^3-hybridized[30] state and adopts tetrahedral geometry. However, such torsional angles determined from the vicinal coupling constants.

2. Experimental

2.1 MATERIAL AND METHODS

TLC was carried out to monitor the course of the reaction and purity of the product. The melting points were recorded in open capillaries and are uncorrected. IR spectra were recorded in KBr (pellet forms) on SHIMADZU FT-IR spectrophotometer and noteworthy absorption levels (reciprocal centimeters) alone are listed. ^1H and 2D NMR spectra were recorded BRUKER AMX 400 MHz spectrophotometer using $CDCl_3$ as solvent and TMS as internal standard.^{13}C NMR spectra were recorded at 100.6 MHz on BRUKER AMX 400 MHz spectrometer in $CDCl_3$.

2.2. General procedure

2.2.1. Preparation of compound 3

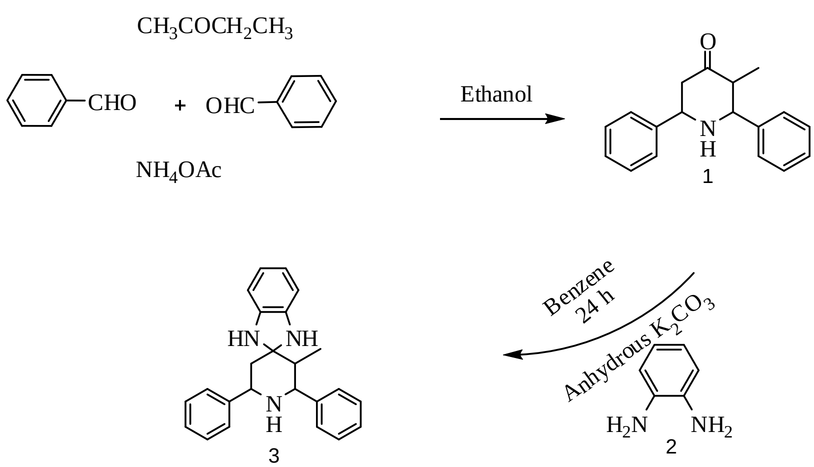
The compound t (3)-Methyl-r(2),c(6)-Diphenylpiperidin-4-one (1) was prepared Noller and Baliah[19], the target compound was prepared as described by Manivannan et al[16], in a stirred solid o-phenylene diamine (15 mmol,1.62g/45 ml of Benzene), t (3)-Methyl-r(2),c(6)-diphenylpiperidin-4-one (15 mmol, 3.975 g) was added to it. The reaction flask was fitted with a Dean-Stark water separator charged by anhydrous K_2CO_3 and the solution was gently refluxed for 24 h. The reaction completion was monitored by TLC. The solution was cooled to room temperature. Then the petroleum ether (60-80°C) was added to the yellow oily solution. The product separated as brown solid. It was repeatedly recrystallised from benzene-petroleum ether (60-80^{o}C) to get pure pale brown solid. The melting point is found to be at 78 ° C (yield 60%).

2.2.2Antioxidant activity (DPPH radical-scavenging activity)

The scavenging effects of target compound for DPPH radical were monitored according to the method of Yen and Chen (1995)[34-35]. Briefly, a 2.0 mL of aliquot of test sample was added to 2.0 mL of 0.16 mM DPPH methanolic solution. The mixture was vortexed for 1 min and then allowed to stand at room temperature for 30 min in the dark, and its absorbance was read at 517 nm. The ability to scavenge the DPPH radical was calculated using the formula given by Duan et al (2006)[33]. Synthetic antioxidants, Gallic acid and ascorbic acid were used as positive controls.

3. RESULTS AND DISCUSSION

After some preliminary experimentation, maximum yield of 60% of the target compound was achieved by refluxing for 24h in Benzene medium without any catalyst (Scheme 1).



Scheme-1

The compound is a stable solid, its structure is fully supported by Elemental analysis, IR, Mass, ^1H ,^{13}C and 2D NMR spectroscopy.

3.1 IR Spectral analysis

The carbonyl group stretching of compound (1) at 1710cm^{-1} disappeared in compound (3). The IR spectral data of compound 3'-methyl-2',6'-diphenyl-1,3-dihydrospiro[benzo[d]imidazole-2,4'-piperidine] are given in table-1

Table 1: IR stretching Frequencies

Absorption Band cm-1	Assignment
3398,3273,3311	NH
3062	Aromatic -CH
2970,1450	CH_3 in aliphatic
1604,1494	Benzene ring stretching
1269	CN stretching
1217	C-C-N bend
1024	Carbon ring in cyclic
470	C-N-C bend

3.2 Mass and Elemental analysis

Parent peak: $C_{24}H_{25}N_3$(355), Base peak$C_{24}H_{24}N_3$(354), $C_{23}H_{22}N_3$(340), $C_{20}H_{21}N_3$ (301), $C_{18}H_{21}N_3$(277), $C_{17}H_{17}N_3$(261), $C_{14}H_{13}N$(193), $C_{10}H_{12}N_2$(158), C_6H_5(77).
Elemental Analysis: C-81%; H-7%; N-11%

3.3 ^{1}H NMR spectral analysis

The signals were assigned based on their positions and multiplicities. Chemical shift and coupling constant values suggest that the compound have chair conformation. The ^{1}H NMR spectral data are given in table-2.

Table 2: Proton chemical shifts

Protons assignment	Chemical shifts (ppm)	Multiplicity	Coupling Constant (Hz)
CH_3	0.832-0.849	doublet	6.8
3Ha	2.86-2.97	multiplet	6.4, 12.4
5Ha,He	2.61-2.74	multiplet	11.6, 12.4, 14.8
6Ha	4.36-4.39	doublet(dd)	10
2Ha	4.65-4.68	doublet	11.2
Aromatic phenyl	7.20-7.53	multiplet	6.0,7.2, 7.6, 8.4
Bicyclic aromatic	7.03–7.07	multiplet	8.8, 9.6
NH	8.07	broad singlet	-

3.4 ^{13}C NMR spectral analysis

The ^{13}C NMR spectral data conform the Carbon skeleton of the compound. The ipso carbon or spiro carbon is confirmed by the signal at 108.90 ppm. ^{13}C NMR spectral are given in table-3

Table 3: ^{13}C- chemical shifts

Carbon assignment	Chemical shifts (ppm)
C-5	41.83
C-3	51.00
C-6	60.42
C-2	66.58
C-4(Spiro carbon)	108.90
Bicyclic aromatic carbon	125.58- 126.64
Aromatic phenyl carbons	126.89 – 130.16
Bicyclic ipso carbon	134.65 , 134.88
Phenyl ipso carbon	143.32 , 144.34

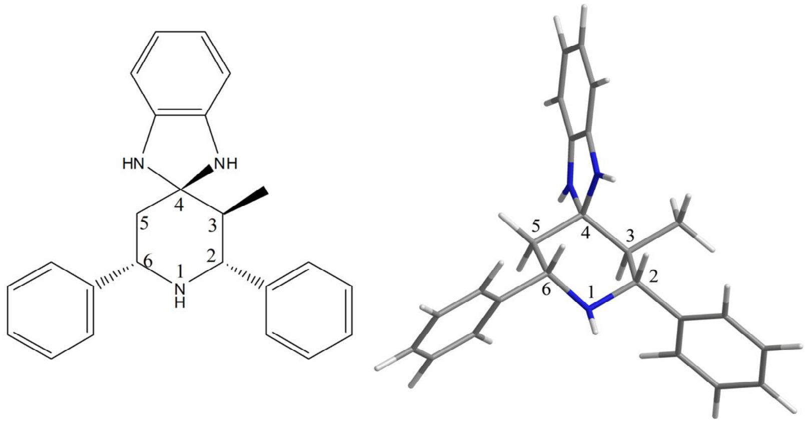


Fig. 1:

3.5 2D NMR spectral data's (HOMOCOSY)

The HOMOCOSY ,NOESY spectrum and their spectral data are given in Fig-2 and Fig-3, table-4 and 5 respectively.

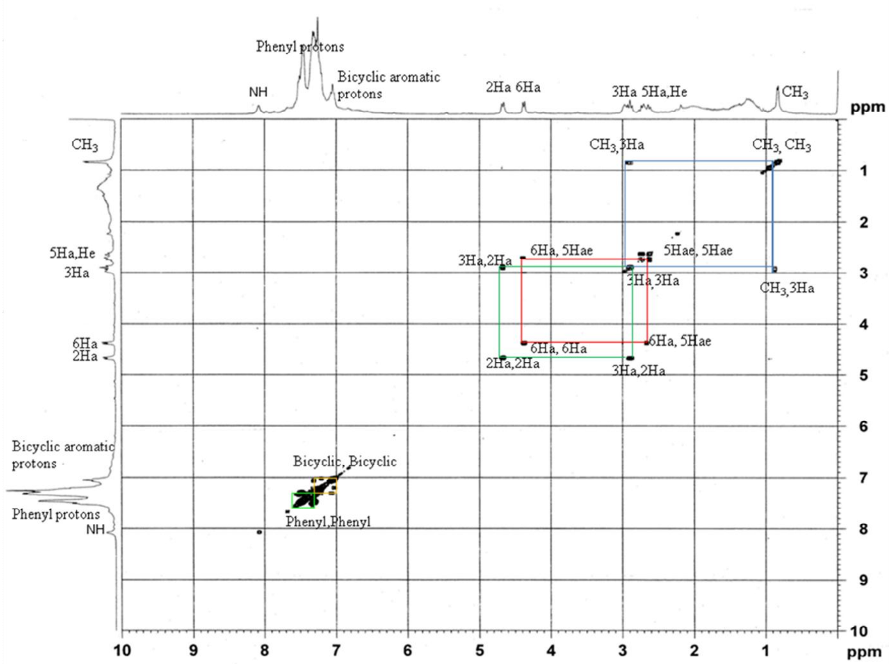


Fig. 2:

Table 4: ^{1}H-^{1}H NMR spectral analysis

Correlation ^{1}H – ^{1}H	Chemical shift (ppm)	0.83	2.61	2.86	4.36	4.65	7.03	7.20	8.07
Chemical shift (ppm)	Proton assignment	CH_3	5Ha,5He	3Ha	6Ha	2Ha	Bicyclic aromatic	Phenyl	NH
0.83	CH_3	✓	-	✓	-	-	-	-	-
2.61	5Ha,5He	-	✓	-	✓	-	-	-	-
2.86	3Ha	✓	-	✓	-	✓	-	-	-
4.36	6Ha	-	✓	-	✓	-	-	-	-
4.65	2Ha	-	-	✓	-	✓	-	-	-
7.03	Bicyclic aromatic	-	-	-	-	-	✓	-	-
7.20	Phenyl	-	-	-	-	-	-	✓	-
8.07	NH	-	-	-	-	-	-	-	✓

In the homonuclear correlation spectroscopy (HOMOCOSY) spectral data confirm the splitting pattern and nearest protons position. In this spectrum diagonal peaks represent similar types of protons and off diagonal peaks represents neighboring protons.

3.6 2D – NMR spectral data's (NOESY)

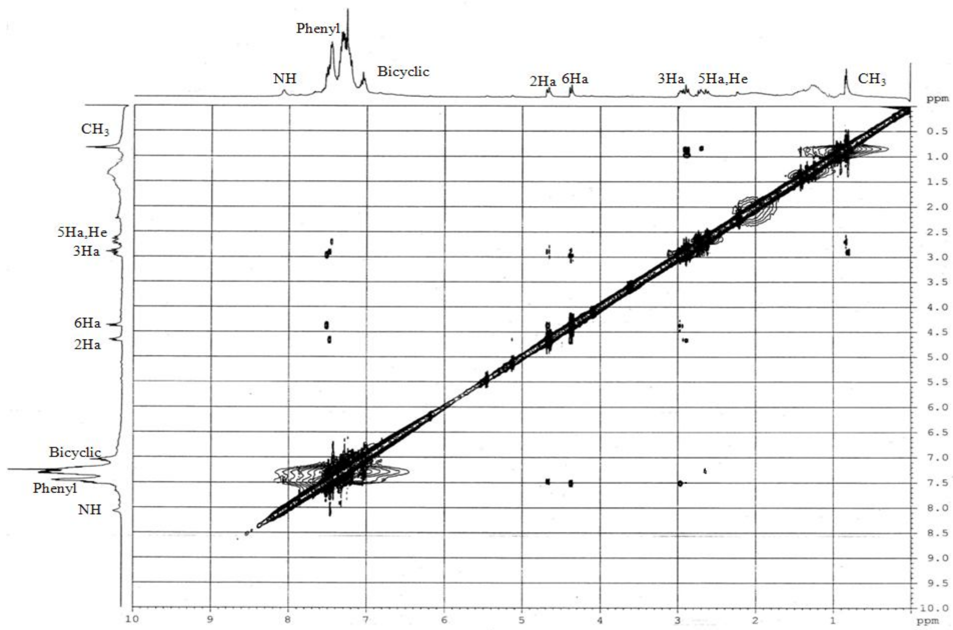


Fig. 3:

Table 5: NOESY Spectral analysis

Correlation ^1H – ^1H	**Chemical shift (ppm)**	**0.83**	**2.61**	**2.86**	**4.36**	**4.65**	**7.03**	**7.20**	**8.07**
Chemical shift (ppm)	Proton assignment	CH_3	5Ha,5He	3Ha	6Ha	2Ha	Bicyclic aromatic	Phenyl	NH
0.83	CH_3	✓	✓	✓	-	-	-	-	-
2.61	5Ha,5He	✓	✓	-	-	-	-	✓	-
2.86	3Ha	✓	-	✓	✓	✓	-	✓	-
4.36	6Ha	-	-	✓	✓	-	-	✓	-
4.65	2Ha	-	-	✓	-	✓	-	✓	-
7.03	Bicyclic aromatic	-	-	-	-	-	✓	-	-
7.20	Phenyl	-	✓	✓	✓	✓	-	✓	✓
8.07	NH	-	-	-	-	-	-	✓	✓

The NOE effect of the compound 3 is assigned by 2D NOESY. 2Ha is close proximity with 3Ha and equatorial substituted phenyl protons, 3Ha is close proximity with CH_3,6Ha 2Ha and phenyl.5Ha, 5He are close proximity with CH_3 and phenyl protons. 6Ha interact with 3Ha and phenyl protons. CH_3 interact with 5Ha,He and 3Ha. The NH proton interacts with phenyl protons. The phenyl protons interact with 2Ha,3Ha,6Ha,5Ha,He and NH. From off diagonal peaks of NOE effects show proximity proton interaction and it confirm the target compound 3 adopting chair conformation. The chair conformation structure is given in Fig-4

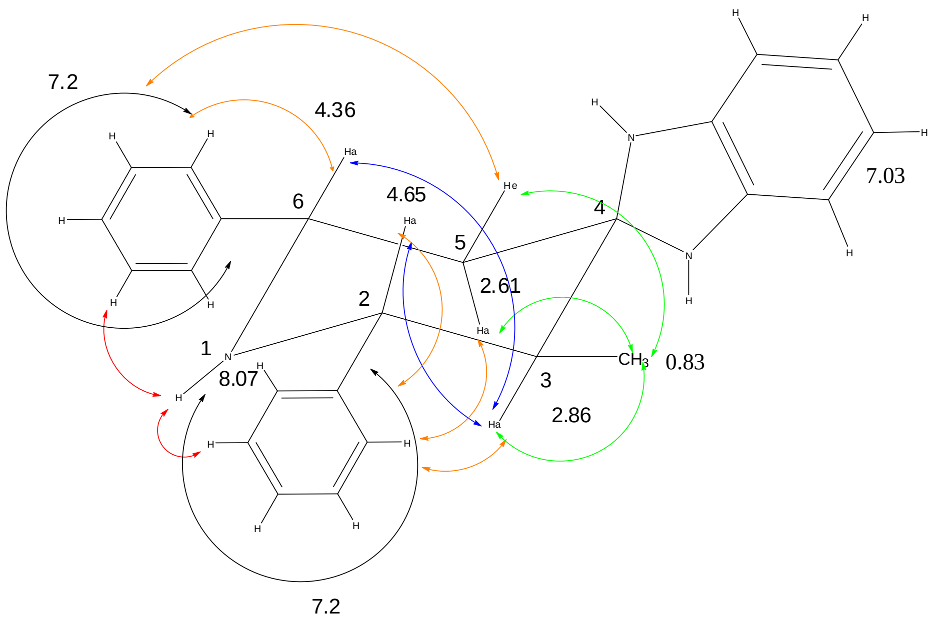


Fig. 4:

3.7 Antioxidant activities

The effect of antioxidants on DPPH radical scavenging is thought to be due to their hydrogen donating ability. DPPH is a stable free radical and it accepts an electron or hydrogen radical to become a stable diamagnetic molecule. When a DPPH solution is mixed with a substrate acting as a hydrogen atom donor, a stable non-radical form of DPPH is obtained with the simultaneous change of the violet color to pale yellow (Molyneux, 2004)[31]. Hence, DPPH has been used extensively as a free radical to evaluate reducing substances (Cotelle, 1996)[32] and is a useful reagent for investigating the free radical scavenging activities of compounds (Duan et al., 2006)[33]. The results of free radical scavenging activity (RSA) are presented in table-6. The target compound(3) exhibited an excellent free radical scavenging activity on the stable DPPH free radical (88.8 %). The scavenging effect of standards on the DPPH radical decreased in the order: ascorbic acid > gallic acid, which was 98 and 99 %, respectively.

Table 6: DPPH radical scavenging effect

Target com(3)	Gallic acid	Ascorbic acid
88.8%	98.8%	99.1%

4. CONCLUSION

The results show that the compound 3 exist in chair conformation with all the substituent's in equatorial orientations. The target compound exhibited an excellent free radical scavenging activity on the stable DPPH free radical (88.8 %). The scavenging effect of standards on the DPPH radical decreased in the order: ascorbic acid > gallic acid, which was 99 and 98 %, respectively.

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