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Synthesis, spectral characterization, crystal structure and molecular docking study of 2,7-diaryl-1,4-diazepan-5-ones

S. Sethuvasan [a], P. Sugumar [b], V. Maheshwaran [b], M.N. Ponnuswamy [b], S. Ponnuswamy [a, *]

[a] P.G. & Research Department of Chemistry, Government Arts College (Autonomous), Coimbatore, 641 018, India
[b] Centre of Advanced Study in Crystallography and Biophysics, University of Madras, Guindy Campus, Chennai, 600 025, India

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ABSTRACT

In this study, a series of variously substituted *r*-2,*c*-7-diaryl-1,4-diazepan-5-ones **9**–**16** have been synthesized using Schmidt rearrangement and are characterized by IR, mass and 1D & 2D NMR spectral data. The proton NMR coupling constant and estimated dihedral angles reveal that the compounds **9**–**16** prefer a chair conformation with equatorial orientation of alkyl and aryl groups. Single crystal X-ray structure has been solved for compounds **9** and **11** which also indicates the preference for distorted chair conformation with equatorial orientation of substituents. The compounds **9**–**16** have been docked with the structure of Methicillin-resistant *Staphylococcus aureus* (MRSA) and the results demonstrate that compound **10** is having better docking score and glide energy than others and it is comparable to co-crystal ligand. Furthermore, all the compounds have been evaluated for their antibacterial and antioxidant activities. All the compounds show moderate antibacterial activity and only **11** exhibits better activity against *S. aures* and *Escherichia coli*. The compounds **11**, **13** and **14** exhibit half of the antioxidant power when compared to the BHT and the remaining compounds show moderate activity.

1. Introduction

ε-Caprolactam plays an important role for the preparation of modified nylons [1] and nanogels [2]. The 1,4-diazepanone ring nucleus acts as anticonvulsant agent and is present in the liposidomycin nucleoside antibiotics that inhibits bacterial peptidoglycan synthesis [3]. Furthermore, recent studies on 1,4-diazepan-5-ones reveal their antimicrobial [4], antitrypanosomal and antiplasmodial activities [5]. However, a little information is only available on the synthesis, stereochemistry and biological evaluation of 2,7-diaryl-1,4-diazepan-5-ones. Hence, it is of interest to report the synthesis and characterisation of 2,7-diaryl-1,4-diazepan-5-ones by the ring expansion of 2,6-diarylpiperidin-4-ones using Schmidt rearrangement. Only a few 2,7-diaryl-1,4-diazepan-5-ones have been already reported using Beckmann rearrangement of piperidin-4-ones oximes [4,6,7] as well as Schmidt rearrangement of piperidin-4-ones [8–16].

The present work involves the synthesis of a new series of 2,7-diaryldiazepan-5-ones **9**–**16** from their corresponding piperidin-4-ones **1**–**8** using Schmidt rearrangement with a modified procedure (Scheme 1). Earlier the Schmidt rearrangement of piperidin-4-ones have been carried out in two steps *i.e.* converting piperidin-4-ones into hydrochlorides and subjecting them to Schmidt rearrangement after isolation [8,11–14]. The conversion in one step with simple reaction conditions is reported now.

The structural characterization and analysis of solution state conformation are made using IR, mass, 1D and 2D NMR spectral studies. Furthermore, the X-ray crystal structures of **9** and **11** have been solved in order to confirm their preferred conformation in solid state. Baliah et al. [6]. reported only the synthesis of diazepan-5-one **12** from its oxime derivative of piperidin-4-one by Beckmann rearrangement. However, the spectral data and stereochemistry of **12** have not been reported. Depending on the migratory aptitude of the C-3 and C-5 carbons in piperidin-4-ones **1**–**8**, two kinds of isomers are possible for the products in the Schmidt rearrangements. The spectral data of earlier studies [8,11] confirmed the migration of C-3 to form diazepan-5-ones **9**–**16** as expected product. All the synthesised compounds have been tested for their antibacterial and antioxidant activities. In addition, molecular docking studies have been carried out for compounds **9**–**16**. The docking studies show that the compounds inhibit at the active site of the target protein and can be utilized as potential drug

* Corresponding author. Post Graduate and Research Department of Chemistry, Government Arts College (Autonomous), Coimbatore, 641 018, Tamil Nadu, India.
E-mail address: kspons2001@gmail.com (S. Ponnuswamy).

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molecules.

2. Experimental

2.1. Materials and methods

All the reported melting points which are uncorrected have been taken in open capillaries using melting point apparatus with a calibrated thermometer. FT-IR spectra have been recorded on a Bruker alpha spectrophotometer using KBr pellets. ^{1}H and ^{13}C NMR spectra have been recorded in $CDCl_3$ and DMSO-d_6 on a Bruker NMR spectrometer (400 & 500 MHz for ^{1}H and 100 & 125 MHz for ^{13}C), using TMS as internal standard. Chemical shifts (δ) are expressed in ppm where abbreviations s, bs, d, dd, and m stand for the resonance multiplicities singlet, broad singlet, doublet, doublet of doublet and multiplet, respectively, and coupling constants are given in Hz. Electron impact mass spectra have been recorded using JEOL GCMS spectrometer. Elemental analyses have been carried out in Carlo Erba 1108 CHN analyser and are within 0.4% of the calculated values.

All the parent *r*-2,*c*-6-diarylpiperidin-4-ones **1**–**8** have been prepared according to the reported procedures [17].

2.2. General procedure for the synthesis of r-2,c-7-diaryl [1,4] diazepan-5-ones 9–16

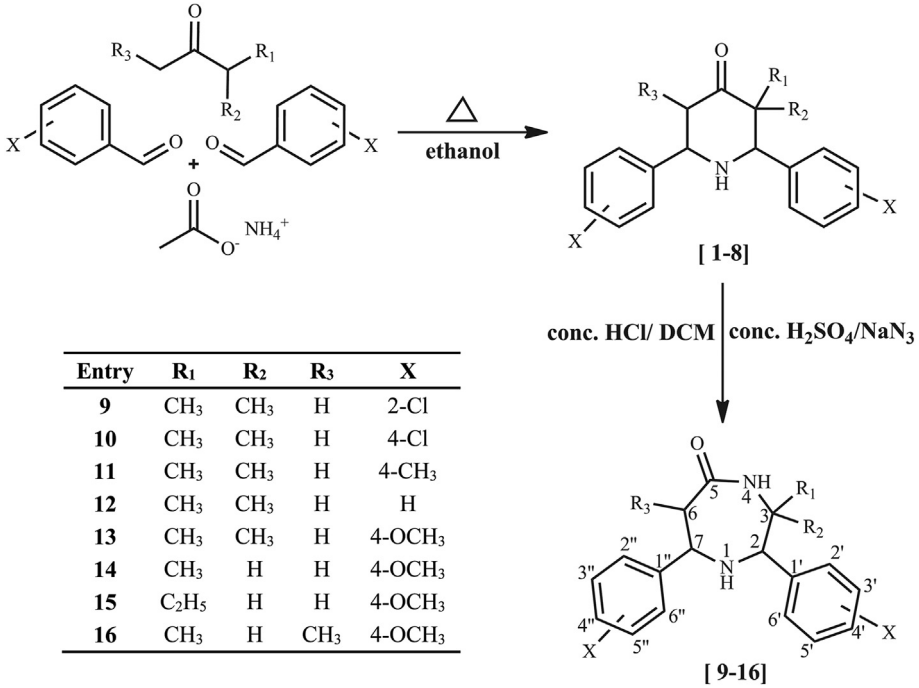
r-2,*c*-6-Diarylpiperidin-4-ones **1**–**8** (0.03 mol) in conc. HCl (2 ml) and dichloromethane (60 ml) are stirred well in a beaker for a few minutes. To this stirred solution, conc. H_2SO_4 (20 ml) is added in dropwise at 0–5 °C for 1 h. Temperature of the solution is allowed to rise at 25 °C. While stirring, NaN_3 (0.09 mol) is added over a period of 1 h and stirring is continued for another 2–3 h. The solution is poured into crushed ice and stirred well. Ammonium hydroxide is added slowly with stirring to reach pH = 11. The resulting mass is washed with water and about 20 ml of dichloromethane is added. The organic layer is separated, dried over anhydrous Na_2SO_4 and concentrated for crystallization. The crystals thus obtained are recrystallized from dichloromethane-pet ether (60–80 °C) in the ratio of 5:1.

2.3. Single crystal X-Ray studies

X-ray diffraction intensity data have been collected for the 2,7-diaryl-1,4-diazepan-5-ones **9** and **11** on Bruker axs Kappa ApexII [18] single crystal X-ray diffractometer equipped with graphite mono-chromated MoKα (λ = 0.7103 Å) radiation and CCD detector. Crystals have been cut to suitable size and mounted on a glass fibre using cyanoacrylate adhesive. The unit cell parameters have been determined from 36 frames measured (0.5° phi-scan) from three different crystallographic zones and using the method of difference vectors. An average four-fold redundancy per reflection has been used to collect the data at an optimum resolution of 0.75 Å. The intensity data collection, frames integrations (Lorentz and polarization) and decay correction have been done using SAINT-NT (version 7.06) [18] software. Empirical absorption correction (multi-scan) has been performed using SADABS [18] program. Crystal structures have been solved by direct methods using SHELXS-97 [19]. The phase sets with the best combined figure of merits reveal the positions of all non-hydrogen atoms in both the structures. The structures have been then refined by full-matrix least-squares procedures using SHELXL-97 [19].

2.4. Molecular docking studies

Molecular docking studies have been performed to examine the binding mode and pattern of ligands with MRSA, for which the structural coordinates have been retrieved from Protein Data Bank (PDB ID: 4D7I) [20]. The target protein is optimized after removal of the water molecules from the crystal structure and partial atomic charges assigned according to the force field. Minimization of target is performed until the average root mean square (rms) deviation of the non-hydrogen atoms reached 0.3 Å (OPLS-2005 force field) to



Entry	R_1	R_2	R_3	X
9	CH_3	CH_3	H	2-Cl
10	CH_3	CH_3	H	4-Cl
11	CH_3	CH_3	H	4-CH_3
12	CH_3	CH_3	H	H
13	CH_3	CH_3	H	4-OCH_3
14	CH_3	H	H	4-OCH_3
15	C_2H_5	H	H	4-OCH_3
16	CH_3	H	CH_3	4-OCH_3

Scheme 1. Synthesis of *r*-2,*c*-7-diaryl [1,4]diazepan-5-ones **9**–**16**.