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Synthesis and characterization of new 1,2-diazepine derivative

Majal Sapnakumari[1], Badiadka Narayana[1]*, Seranthimata Samshuddin[1] and Balladka Kunhanna Sarojini[2]

[1]Department of Studies in Chemistry, Mangalore University, Mangalagangotri-574 199, Karnataka, India
[2]Research Department of Chemistry, P. A. College of Engineering, Nadupadavu, Mangalore 574153, Karnataka, India

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ABSTRACT

*The reaction of (1Z)-1-[(2E)-3-(4-bromophenyl)-1-(4-fluorophenyl)prop-2-en-1-ylidene]-2-(2,4-dinitrophenyl) hydrazine (**2**) with ethyl chloroacetate in the presence of base affords a new 1,2-diazepine derivative, 5-(4-bromophenyl)-1-(2,4-dinitrophenyl)-3-(4-fluorophenyl)-1H-1,2-diazepin-6-ol (**3**). The intermediate **2** in turn prepared from 4-bromo-4'-fluorochalcone (**1**). The structure of the newly synthesized compound is characterized by IR, NMR and mass spectral data.*

Keywords: Ethyl chloroacetate, 1,2-Diazepine, 4-Bromo-4'-fluorochalcone

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INTRODUCTION

Diazepine derivatives are seven membered heterocyclic ring compounds with two nitrogen atoms possessing a wide range of medicinal properties [1]. Introduction of substituted group in the diazepine segment is expected to improve its pharmacological activities [2]. Some of the 1,2-diazepine derivatives are used in the treatment of epilepsy, malignant gliomas and amyotrophic lateral sclerosis (ALS) [3-5]. In view of the biological importance of diazepine derivatives [6-8] and in continuation of our work on the synthesis of various derivatives of 4-bromo-4'-fluorochalcone [9-12], the compound **3** is synthesized.

MATERIALS AND METHODS

Melting point was taken in open capillary tube and was uncorrected. The purity of the compound was confirmed by thin layer chromatography using Merck silica gel 60 F_{254} coated aluminium plates. IR spectrum was recorded on Shimadzu-FTIR Infrared spectrometer in KBr (ν_{max} in cm^{-1}). ^{1}H-NMR (400 MHz) spectrum was recorded on a Varian 400 spectrometer, with 5 mm PABBO BB-1H TUBES and ^{13}C-NMR (100 MHz) spectrum was recorded for approximately 0.03 M solutions in DMSO-d_6 at 100 MHz with TMS as internal standard. LCMS was obtained using Agilent 1200 series LC and Micromass zQ spectrometer. Elemental analysis was carried out by using VARIO EL-III (Elementar Analysensysteme GmBH).

Synthesis of (1Z)-1-[(2E)-3-(4-bromophenyl)-1-(4-fluorophenyl)prop-2-en-1-ylidene]-2-(2,4-dinitrophenyl) hydrazine (**2**)**:**
A mixture of (2*E*)-3-(4-bromophenyl)-1-(4-fluorophenyl)prop-2-en-1-one (3.05 g, 0.01 mol) and 2,4-dinitrophenylhydrazine (1.98 g, 0.01 mol) in 50 ml of glacial acetic acid was refluxed for 6 hrs. The reaction mixture was cooled to produce red crystals. Yield: 82 %; Melting point: 141-143°C. The structure of compound **2** was

confirmed by single crystal XRD and is given in **Fig.1** [Monoclinic, $P2_1/c$, a = 15.0738 (12) Å, b = 10.6511 (5) Å, c = 14.3353 (8) Å, V = 2068.5 (2) $Å^3$, Z=4] [9].

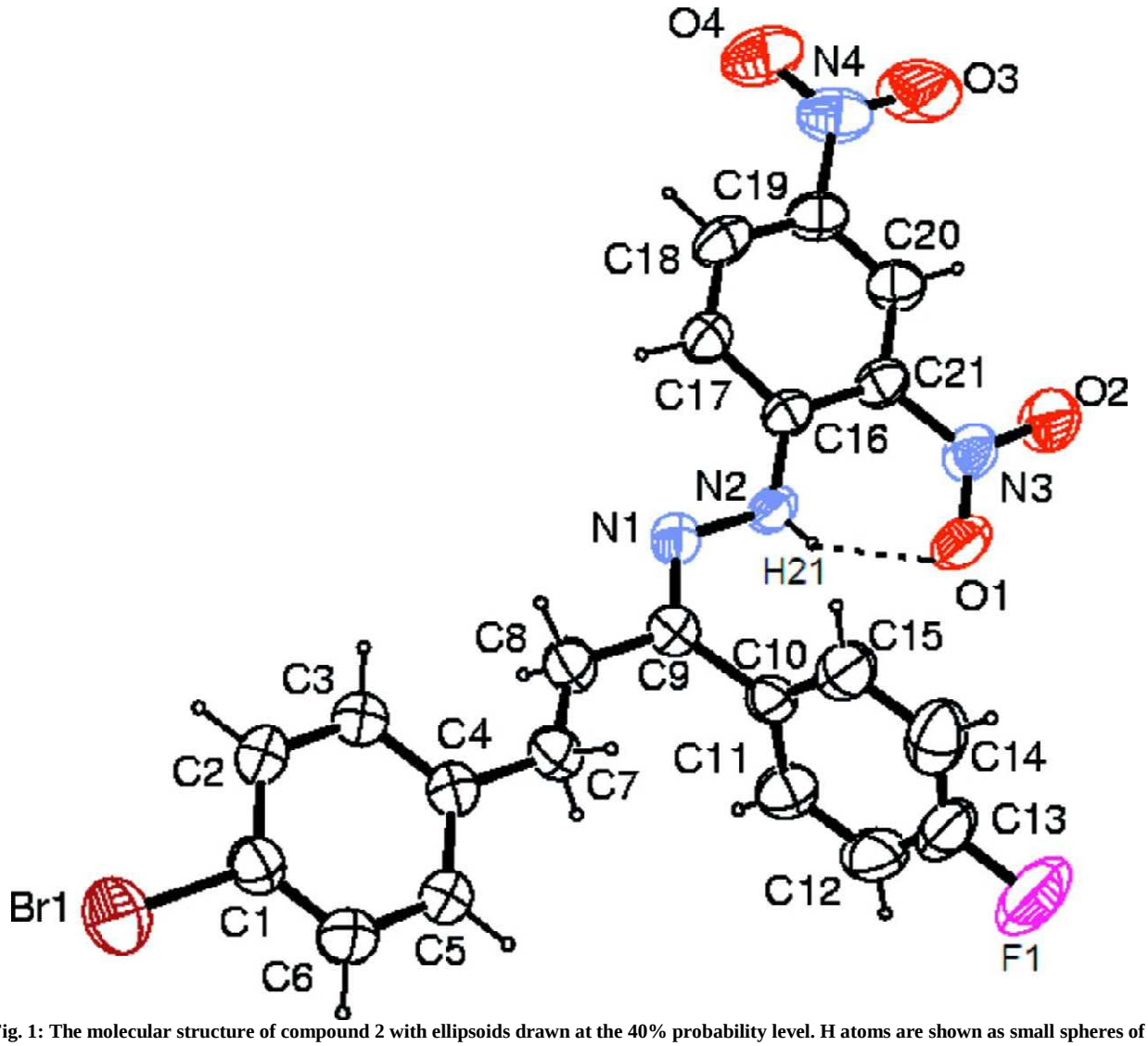


Fig. 1: The molecular structure of compound 2 with ellipsoids drawn at the 40% probability level. H atoms are shown as small spheres of arbitrary radii. The dashed line indicates a hydrogen bond.

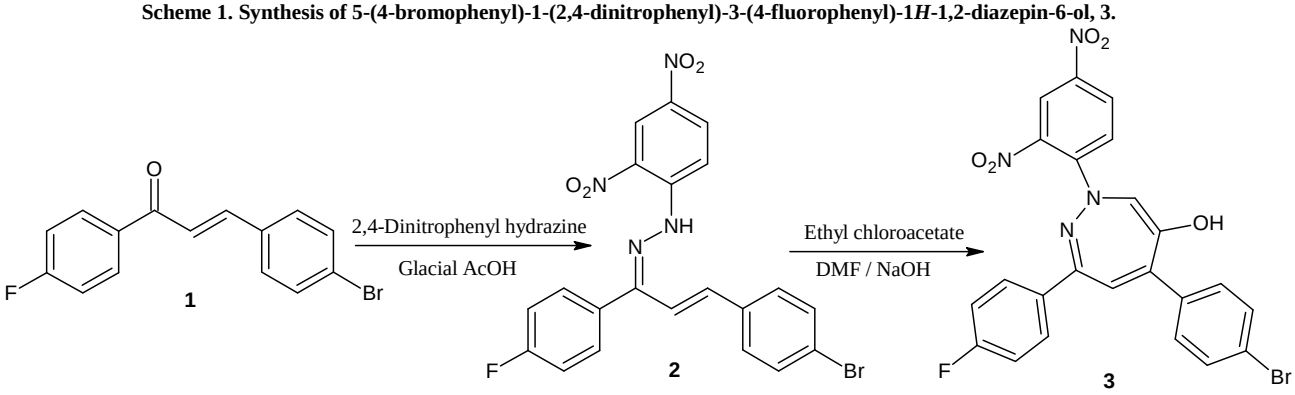
Synthesis of 5-(4-bromophenyl)-1-(2,4-dinitrophenyl)-3-(4-fluorophenyl)-1H-1,2-diazepin-6-ol (**3**):
A mixture of (1*Z*)-1-[(2*E*)-3-(4-bromophenyl)-1-(4-fluorophenyl)prop-2-en-1-ylidene]-2-(2,4-dinitrophenyl) hydrazine **2** (0.001 mol, 0.485 g) and ethyl chloroacetate (0.001 mol, 0.122 g) in DMF was refluxed for 24 h. After the completion of reaction as indicated by TLC, the reaction mixture was cooled to room temperature and quenched with ice cold water and acidified with concentrated HCl. The resulting precipitate was filtered and recrystallized from ethanol. Yield: 76 %; Melting point: 95-97 °C.

LCMS: *m/z* 525.1 (M^+).
IR (KBr): ν_{max} (cm^{-1}), 3421 (OH), 3065 (Ar-H), 1602 (C=N, Ar C=C), 1500, 1224 (N-O),1155 (C-F).
^{1}H-NMR (400 MHz, DMSO-d_6): δ ppm, 5.90 (broad s, 1H, OH), 7.10 (d, 1H, *J* = 8 Hz, proton attached to C-6 of 2,4-dinitrophenyl ring), 7.23–7.30 (m, 7H, 5 ArH + 2H attached to C-4 and C-7 of diazepine ring), 7.58 (d, 2H, *J* = 8 Hz, protons attached to C-3 and C-5 of 4-bromophenyl ring), 7.71 (s, 1H, proton attached to C-3 of 2,4-dinitrophenyl ring), 7.94 (t, 2H, *J* = 7.2 Hz, protons attached to C-3 and C-5 of 4-fluorophenyl ring).
^{13}C-NMR (100 MHz, DMSO-d_6): δ ppm, 163.30 (C-OH), 160.86 (C-F), 151.11 (C-NO_2), 148.08 (C-NO_2), 145.67 (C-N), 144.21, 131.64, 129.79, 129.45, 129.04, 128.76, 128.49, 127.56, 115.48 (d, J = 22 Hz) (aromatic C's), 127.48, 122.05, 110.03, 109.79, 104.75 (diazepine C's).
Elemental analysis: Calculated for $C_{23}H_{14}BrFN_4O_5$, C, 52.59%; H, 2.69%; N, 10.67%; Found: C, 52.54%; H, 2.72%; N, 10.63%.

RESULTS AND DISCUSSION

The 1,2-diazepine derivative, 5-(4-bromophenyl)-1-(2,4-dinitrophenyl)-3-(4-fluorophenyl)-1*H*-1,2-diazepin-6-ol (**3**), was prepared by the condensation of (1*Z*)-1-[(2*E*)-3-(4-bromophenyl)-1-(4-fluorophenyl)prop-2-en-1-ylidene]-2-(2,4-dinitrophenyl)hydrazine (**2**) with ethyl chloroacetate in the presence of sodium hydroxide (**Scheme 1**). The intermediate **2**, in turn prepared by the reaction of 4-bromo-4'-fluorochalcone **1** with 2,4-dinitrophenylhydrazine in glacial acetic acid and structure is confirmed by single crystal XRD data. The product **3** was obtained *via* the initial *N*-alkylation of compound **2** by ethyl chloroacetate followed by intramolecular cyclization. The title compound **3** was characterized by NMR, IR and mass spectral data.

Scheme 1. Synthesis of 5-(4-bromophenyl)-1-(2,4-dinitrophenyl)-3-(4-fluorophenyl)-1*H*-1,2-diazepin-6-ol, 3.



The IR spectrum of 5-(4-bromophenyl)-1-(2,4-dinitrophenyl)-3-(4-fluorophenyl)-1*H*-1,2-diazepin-6-ol (**3**) showed an absorption band at 3421 cm^{-1} indicated the presence of OH group. Absorption bands at 1500 and 1224 cm^{-1} indicated the presence of nitro group in the compound **3**. The ^{1}H NMR spectrum showed a broad singlet at δ 5.90 ppm due to the presence of OH group in the molecule. A triplet appeared at δ 7.94 ppm (J = 7.2 Hz) integrating for two protons attached to C-3 and C-5 of 4-fluorophenyl ring. A singlet observed at δ 7.71 ppm was due to the presence of proton at C-3 of 2,4-dinitrophenyl ring. A doublet appeared at δ 7.58 ppm (J = 8 Hz) was due to two protons attached to C-3 and C-5 of 4-bromophenyl ring. Another doublet observed at δ 7.10 ppm (J = 8 Hz) was due to the proton attached to C-6 of 2,4-dinitrophenyl ring. However, the signals due to remaining protons of compound **3** merged in the region δ 7.23-7.30 ppm as a multiplet integrating for seven protons. Mass spectrum showed a molecular ion peak at *m/z* 525.1 (M^{+}) corresponding to the molecular formula of $C_{23}H_{14}BrFN_4O_5$. The ^{13}C NMR spectrum displayed a peak at δ 163.30 ppm for C-6 carbon of diazepine ring for which hydroxy group is attached. The signals due to C-4 and C3/C5 carbons of 4-fluorophenyl ring was observed at δ 160.86 and 115.48 ppm as doublets due to 1 and 2 bond coupling of C-4 and C3/C5 with ^{19}F. The other signals observed at 151.11 (C-NO_2), 148.08 (C-NO_2), 145.67 (C-N), 144.21, 131.64, 129.79, 129.45, 129.04, 128.76, 128.49, 127.56 (aromatic C's), 127.48, 122.05, 110.03, 109.79, 104.75 (diazepine C's). Elemental analysis also gave satisfactory results for the title compound.

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