Journal of Molecular Structure 1125 (2016) 781–787

Contents lists available at ScienceDirect

Journal of Molecular Structure

journal homepage: http://www.elsevier.com/locate/molstruc

A facile access to new diazepines derivatives: Spectral characterization and crystal structures of 7-(thiophene-2-yl)-5-(trifluoromethyl)-2,3-dihydro-1*H*-1,4-diazepine and 2-thiophene-4-trifluoromethyl-1,5-benzodiazepine

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ARTICLE INFO

Article history:
Received 6 June 2016
Received in revised form
11 July 2016
Accepted 13 July 2016
Available online 15 July 2016

Keywords:
2-Thenoyltrifluoroacetone
Trifluoroacethyl-derivatives
Diazepine
Benzodiazepine
Single-crystal X-ray diffraction
Imine-enamine tautomerism

ABSTRACT

The one-pot double condensation reaction of 2-thenoyltrifluoroacetone (2-TTA) with ethylendiamine or *o*-phenylenediamine, in a 2:1 stoichiometric molar ratio, leads to the formation of 7-(thiophene-2-yl)-5-(trifluoromethyl)-2,3-dihydro-1*H*-1,4-diazepine **2** and 2-thiophene-4-trifluoromethyl-1,5-benzodiazepine **3**, that were isolated in 56 and 53% yields, respectively. The *bis*(trifluoroacetamide) ethylene derivative **1** was also isolated in 32% yield as a side-product in the reaction of 2-TTA and ethylenediamine. Compounds **1**–**3** were fully characterized by elemental analysis, FT-IR and multinuclear (^{1}H, ^{13}C and ^{19}F) NMR spectroscopy. In addition, their molecular identities and geometries have been authenticated by single-crystal X-ray diffraction analysis. The spectroscopic and structural data confirm that the 1,4-diazepine **2** and the 1,5-benzodiazepine **3** exist in the imine-enamine and diimine tautomeric forms, respectively, both in solution and in the solid-state.

1. Introduction

Diazepines are found in various psychoactive pharmaceutical drugs, *v. g.* diazepam [1], and specifically as 1,4-diazepines [2]. Meanwhile, benzodiazepines have been thoroughly studied during a period of several decades, largely because of their relatively easy synthesis from common starting materials [3], and they have become of ever-increasing interest to investigators, inasmuch as their pharmacological activities (tranquilizers, substances that lower blood pressure, analgesics and sedative agents) [3]. On the other hand, the thienyl skeleton can be found in certain natural products and is also incorporated in several pharmacologically active compounds [4]. In medicinal chemistry, thiophene derivatives have been well known for their therapeutic applications [4]. Thus, it is attractive to obtain new heterocycles with potential biological properties from easy and minimum step reactions, involving inexpensive starting materials such as β-diketones which can be functionalized in three different sites of the molecule. In the last few years, our groups have been interested in the synthesis of β-diketones [5–7] as starting materials to be used in the preparation of heterocycles [8,9] and tridentate Schiff base ligands [10–12], via condensation with aliphatic or aromatic primary diamines [12,13], as well as for the design of asymmetric Schiff base ligands and their respective transition metal complexes [13]. Such reactions proceed via nucleophilic addition giving a hemiaminal intermediate containing the –C(OH)(NHR)– group which, depending on the R functional groups and the experimental conditions, evolves toward heterocycle or polydentate Schiff base compounds [14]. Now, our interest is focused on the use of the β-diketone 2-thenoyltrifluoroacetone (2-TTA) as starting materials for the synthesis of new thiophene-containing derivatives with potential

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http://dx.doi.org/10.1016/j.molstruc.2016.07.047
0022-2860/

electropolymerization properties. To the best of our knowledge, reactivity of the β-diketones containing thienyl moieties toward diamines has been scarcely reported in the literature [15]. The incorporation of thienyl units in the structure of a compound not only opens up opportunities to the formation of polymeric [16,17] and metallopolymeric materials [18,19], either through chemical or electrochemical oxidation of the thienyl units [20–22], but also to the development of new drugs [4].

With these ideas in mind, we report herein on the facile preparation of two new thienyl-containing diazepines, namely, the 7-(thiophene-2-yl)-5-(trifluoromethyl)-2,3-dihydro-1*H*-1,4-diazepine **2** and the 2-thiophene-4-trifluoromethyl-1,5-benzodiazepine **3**, formed upon condensation of 2-thenoyltrifluoroacetone with ethylenediamine and *o*-phenylenediamine, respectively (see formulas on Scheme 1). In addition, the known *N,N′*-ethylene-*bis*(trifluoroacetamide) **1** was also isolated as a by-product. These compounds were fully characterized by analytical and spectroscopic techniques, and authenticated by single crystal X-ray diffraction analysis.

2. Experimental

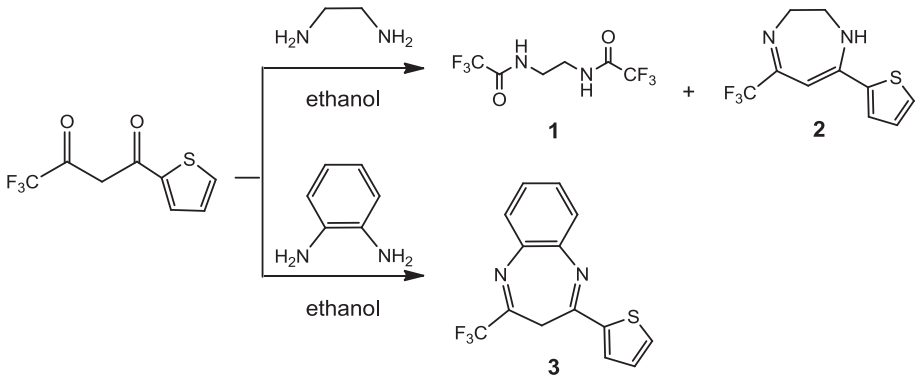
2.1. Materials and physical measurements

Reactions were performed under dry dinitrogen or argon atmosphere using standard Schlenk techniques. Solvents were dried and distilled according to standard procedures [23]. All starting materials were purchased from commercial sources and used as received. Chromatographic purification was performed with Silica gel 60 (0.063–0.200 μm). Solid-state FT-IR spectra were recorded on a Perkin-Elmer Model 1600 FT-IR spectrophotometer with KBr disks in the 4000 to 450 cm^{-1} range. NMR spectra were recorded at 298 K with a Bruker Avance III 400 spectrometer. All NMR spectra are reported in parts per million (ppm, δ) relative to tetramethylsilane (Me_4Si) for ^1H and ^{13}C NMR spectra, with the residual solvent proton and carbon resonances used as internal standards. Chemical shifts of ^{19}F NMR spectra are referenced against external $CFCl_3$. Coupling constants (J) are reported in Hertz (Hz), and integrations are reported as number of protons. The following abbreviations are used to describe peak patterns: s = singlet, d = doublet, t = triplet, m = multiplet, br = broad. ^1H and ^{13}C NMR chemical shift assignments are supported by data obtained from $^1H–^1H$ COSY, $^1H–^{13}C$ HMQC, and $^1H–^{13}C$ HMBC NMR experiments. Elemental analyses were conducted on a Thermo-FINNIGAN Flash EA 1112 CHNS/O analyzer by the Microanalytical Service of the Centre Regional de Mesures Physiques de l'Ouest (CRMPO) at the Université de Rennes 1, France. Melting points were determined in evacuated capillaries on a Kofler Bristoline melting point apparatus and were not corrected.

2.2. Reaction of 2-TTA with ethylenediamine: isolation of N,N′-etilene-bis(trifluoroacetamide) (1) and of 7-(thiophene-2-yl)-5-(trifluoromethyl)-2,3-dihydro-1H-1,4-diazepine (2)

In a Schlenk tube loaded with a magnetic stirrbar, 0.50 g (2.25 mmol) of 2-TTA were dissolved in 30 mL of dry ethanol. After 5 min of stirring, 0.08 mL (1.25 mmol) of 1,2-ethylendiamine was added dropwise by syringe. The solution turned light green. After refluxing for 12 h, the reaction mixture was cooled to room temperature (r.t.), the solvent was evaporated and the residue dried under vacuum. The oily residue was extracted with CH_2Cl_2. The extracts were combined and concentrated before being kept at −30 °C in the freezer overnight. The white precipitate that deposited was filtered off and washed with cold hexane and dried under vacuum for 2 h, to give 0.10 g (0.40 mmol, 32% yield) of *bis*-acetamide **1** (Rf 0.80, 1:1 hexane/dichloromethane (v/v) as eluent). Recristallyzation by slow evaporation of a methanol solution of **1** at r. t. produces suitable colorless single crystals for X-ray diffraction study. M.p. 190 °C. Anal. Calcd for $C_6H_6F_6N_2O_2$ (252.12 $gmol^{-1}$): C, 28.58; H, 2.40; N, 11.11. Found: C, 28.60; H, 2.50; N, 11.00. FT-IR (KBr, cm^{-1}): 3303(s) ν(N–H), 3109(w) ν(C–H arom), 2969(vw) ν(C–H aliph), 1705 (vs) ν(C=O), 1528(s) δ(N–H). ^1H NMR (400 MHz, $(CD_3)_2CO$): 3.58 (s, 4 H, CH_2CH_2), NH proton not observed. $^{13}C\{^1H\}$ NMR (100 MHz, $(CD_3)_2CO$): 38.53 (CH_2CH_2), 117.54 (q, $^1J_{C,F} = 285$ Hz, CF_3), 205.26 (C=O). ^{19}F NMR (366 MHz, $(CD_3)_2CO$): −76.96 (CF_3).

The above dichloromethane filtrate and hexane washings were combined, concentrated and the residual crude oil was absorbed on a column packed with silica gel (grade 60). Elution was carried out with hexane/dichloromethane mixture 1:1 (Rf. 0.95) and the collected colorless solution taken to dryness, affording 0.17 g (0.70 mmol, 56% yield) of the diazepine **2** as a white powder. Recristallyzation by slow evaporation of a methanol solution of **2** at r. t. afforded suitable single crystals for X-ray diffraction study. M.p. 103 °C. Anal. Calcd for $C_{10}H_9F_3N_2S$ (246.25 $gmol^{-1}$): C, 48.77; H, 3.68; N, 11.38; S, 13.02. Found: C, 48.18; H, 3.42; N, 10.85; S, 12.67. FT-IR (KBr, cm^{-1}): 3210(s) ν(N–H), 3108(m) ν(C–H arom), 2962(vw) ν(C–H aliph), 1618 (vs) ν(C=C), 1528(s) ν(C=N). ^1H NMR (400 MHz, $CDCl_3$): 3.56 (br s, 2 H, NCH_2CH_2NH), 3.99 (br s, 2 H, NCH_2CH_2NH), 5.53 (s, 1 H, CH=C), 7.07 (dd, $^3J_{H,H} = 5.1$ and 3.7 Hz, 1 H, H-4), 7.31 (dd, $^3J_{H,H} = 3.7$ Hz, $^4J_{H,H} = 1.1$ Hz, 1 H, H-3), 7.37 (dd, $^3J_{H,H} = 5.1$ Hz, $^4J_{H,H} = 1.1$ Hz, 1 H, H-5); NH proton not observed. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): 49.28 (NCH_2CH_2NH), 56.01(NCH_2CH_2NH), 87.59 (CH=C), 121.15 (q, $^1J_{C,F} = 279$ Hz, CF_3), 126.64 (C-3), 127.75 (C-5), 127.91 (C-4), 141.49 (C-2), 150.98 (C=N), 154.68 (CH=C). ^{19}F NMR (366 MHz, $CDCl_3$): −70.66 (CF_3).



Scheme 1. Syntheses of diazepines **2** and **3** and of diacetamide **1**.