Novel synthesis of quinazolino[3,2-*a*][1,5]benzodiazepines: an experimental and computational study

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DOI: http://dx.doi.org/10.3998/ark.5550190.p009.141

Abstract

5-Substituted 7-methyl-6,7-dihydroquinazolino[3,2-*a*][[1,5]benzodiazepin-13(5*H*)-one derivatives were synthesized in a one-step sequential acylation-cyclization reaction with a simple procedure from an appropriate 5-substituted 3-methyl-1,3,4,5-tetrahydro-2*H*-1,5-benzodiazepin-2-one and 2-sulfinylaminobenzoyl chlorides. The mechanism of the heterocyclization reaction was studied by the DFT method using the B3LYP functional and 6-31+G(d, p) basis set.

Keywords: Fused quinazolines, 1,5-benzodiazepines, 2-sulfinylaminobenzoyl chloride, DFT calculations, quantum chemistry

Introduction

Benzodiazepines constitute an important class of psychopharmaceuticals due to their broad range of activities, in particular as tranquilizers, and they also have a traditional place in antiepileptic therapy.[1,2] Moreover, benzodiazepines are effective as nonnucleoside inhibitors of HIV-1 reverse transcriptase.[3] Therefore, the benzodiazepine nucleus is a well-studied pharmacophoric scaffold that has emerged as a core structure unit of various biological activities and the research in this area is very active.[4] It is well documented that the pharmacological activity could be increased when an additional heterocyclic ring is fused to the heptatomic diazepine nucleus.[5] Thus, considerable attention has been directed towards the synthesis of polycyclic 1,4-benzodiazepines, as well as the 1,5-isomers.[6] Recently, many novel compounds containing heterocyclic ring systems such as triazole, thiazole, imidazole, quinoline, oxadiazole, pyran, oxazole, furan and pyrimidine annelated to the bicyclic 1,5-benzodiazepine have been synthesized by our[7-12] and other research groups.[6,13,14] Fused quinazolinones are important heterocyclic compounds with

widespread occurrence in alkaloids possessing diverse biological activity.[15] Various methods for the synthesis of these alkaloids encompassing a quinazolino[1,4]benzodiazepine moiety in their skeleton have been developed and numerous research papers have recently appeared.[16,17]

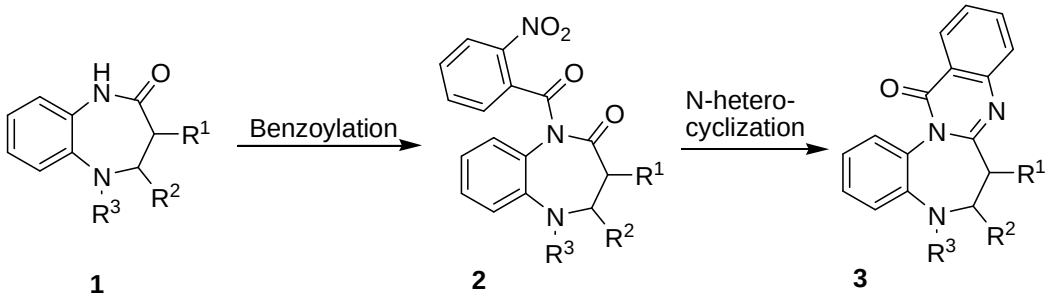
As part of our current studies on the development of efficient methods for the preparation of polycyclic 1,5-benzodiazepines we investigated the synthesis of quinazolino[1,5]benzodiazepines.[18,19] A wide range of novel 6,7-dihydroquinazolino[3,2-*a*][1,5]benzodiazepinone derivatives were synthesized in a two-step method involving (i) benzoylation of variously substituted 1,3,4,5-tetrahydro-1,5-benzodiazepin-2-ones with 2-nitrobenzoyl chloride, and (ii) a metal induced reductive N-heterocyclization of the obtained 2-nitrobenzoylamides. Although this method displayed notable advantages, such as mild reaction and simple operation, it is not suitable unfortunately for the transformation of appropriate 3-methyl substituted 1-(2-nitrobenzoyl)-1,5-benzodiazepinone derivatives. Herein we report a novel procedure for the synthesis of 7-methyl-6,7-dihydroquinazolino[3,2-*a*][1,5]benzodiazepinones from 5-substituted 3-methyl-1,5-benzodiazepin-2-one derivatives.

Also in this article, the quantum chemical analysis of acylation-cyclization reaction mechanism is presented by calculation of reaction stationary points: reactants (**R**), products (**P**), intermediates (**I**) and transition states (**T**) on the reaction potential energy profile.[20,21] Calculations of the intrinsic reaction coordinates (IRC) allow evaluate electron density changes along the reaction progress in the transformation from reactant to the final product. The most probable acylation-cyclization pathway is discussed in detail in the present study. Moreover, the variations of charge, bond order, and bonding character transformations on the reaction progress have been investigated.

Results and Discussion

Synthetic studies

In our previous works, the preparation of quinazolino[3,2-*a*][1,5]benzodiazepine derivatives **3** was achieved using the above-mentioned strategy which is shown in Scheme 1. Various 5-R^3(alkyl, acyl)-4-R^2(H, CH_3)-3-R^1(H, CH_3)-1,3,4,5-tetrahydro-2*H*-1,5-benzodiazepin-2-ones **1** were used as starting materials.

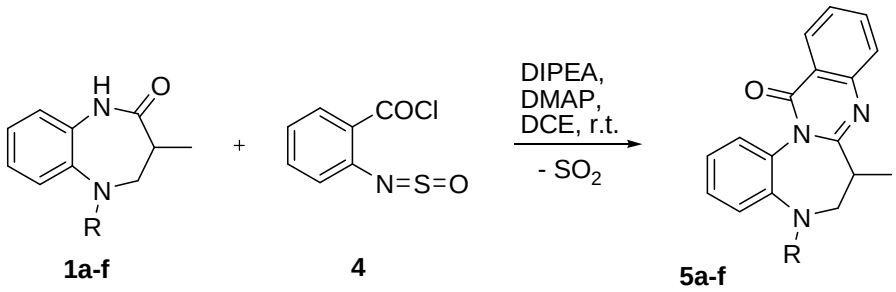


Scheme 1. Synthesis of quinazolino[3,2-*a*][1,5]benzodiazepines **3** by reductive cyclization.

In the course of these studies it was established that 3-methyl substituted 1-(2-nitrobenzoyl)-amides **2** (R^1=CH_3) did not cyclize under the reductive N-heterocyclization conditions and the appropriate tetracyclic 1,5-benzodiazepine derivatives were not formed. A theoretical computational investigation of the cyclization reaction mechanism revealed that the presence of substituents in a diazepine ring causes changes in the electron population of the frontier molecular orbitals. The presence of the electron donating 3-methyl substituent decreased the electrophilicity of the carbon C(2) atom of the heterocyclic C=O group, evoking thus the resistance for further intermolecular rearrangements.[18,19] This exclusive behavior of starting 3-methylsubstituted compounds prompted us to develop an effective synthetic method for the construction of polycyclic 1,5-benzodiazepine derivatives.

Our intention to benzoylate starting compounds **1** with N-protected anthranilic acid chloride to prepare appropriate 2-aminobenzoylamides instead of derivatives **2** was not implemented. For example, the interaction of *N*-trifluoroacetylanthranilic acid with thionyl chloride led to the cyclic 3,1-benzoxazin-4-one derivative.[22]

A new approach to the synthesis of the title compounds is shown in Scheme 2. It is based on the use of the activated form of anthranilic acid, 2-sulfinylaminobenzoyl chloride (**4**).[23]



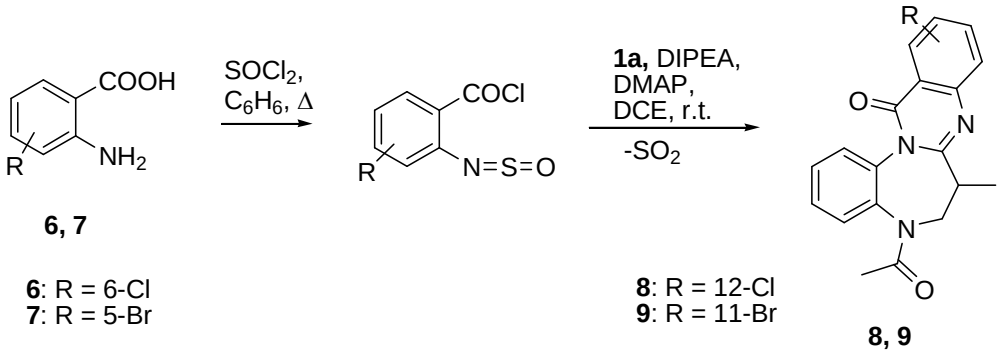
1a-f **4** **5a-f**

R = $COCH_3$ (**a**), CHO (**b**), COC_6H_5 (**c**), $COOC_2H_5$ (**d**), CH_3 (**e**), $CH_2C_6H_5$ (**f**)

Scheme 2. Synthesis of 7-methyl-6,7-dihydroquinazolino[3,2-*a*][1,5]benzodiazepin-13-ones **5a-f**.

The high reactivity of this reagent towards imines, amides and amines allows its use in the synthesis of various compounds.[24] Chloride **4** was prepared by refluxing anthranilic acid with 10-fold excess of thionyl chloride in dry benzene. After completion of the reaction (until reaction mixture turns clear, ~2h), benzene and unreacted thionyl chloride were removed in vacuum and the residual oil was used in the following experiments without additional purification. 5-Substituted 3-methyl-1,3,4,5-tetrahydro-2*H*-1,5-benzodiazepin-2-ones **1a-f** were treated with freshly prepared chloride **4** in the presence of *N*,*N*-diisopropylethylamine (DIPEA) and a catalytic amount of 4-dimethylaminopyridine (DMAP) in dry dichloroethane (DCE) at room temperature.

This 1-N-acylation process was accompanied by simultaneous N-heterocyclization leading to the 7-methyl-6,7-dihydroquinazolino[3,2-*a*][1,5]benzodiazepinones **5a-f** in 50–75% yield. Quinazolino[1,5]benzodiazepine derivatives described previously[18] were also synthesized using this method. For example, treatment of 5-acetyl- and 5-acetyl-4-methyl-1,3,4,5-tetrahydro-2*H*-1,5-benzodiazepin-2-ones with 2-sulfinylaminobenzoyl chloride led to 5-acetyl- and 5-acetyl-6-methyl-6,7-dihydroquinazolino[3,2-*a*][1,5]benzodiazepin-13(5*H*)-ones in 65% and 77% yields, respectively. Whereas the use of reductive cyclization reaction, provided these compounds in lower yields (45-57%).[18] It should be noted that during this cyclofunctionalization reaction the formation of the intermediate acylation products, 1-*N*-benzoylamides, was not observed (TLC). We also found that the corresponding 2-sulfinylaminobenzoyl chlorides could be prepared from ring-substituted anthranilic acids such as 6-chloro- and 5-bromoanthranilic acids. 5-Acetyl-3-methyl-1,3,4,5-tetrahydro-2*H*-1,5-benzodiazepine **1a** was treated with these reactants under analogous conditions and the corresponding quinazolino[3,2-*a*][1,5]benzodiazepinones **8** and **9** were synthesized (Scheme 3).



Scheme 3. Synthesis of 5-acetyl-11-bromo(or 12-chloro)-7-methyl-6,7-dihydroquinazolino-[3,2-*a*][1,5]benzodiazepine-13-ones **8** and **9**.

The structures of all synthesized compounds were characterized by elemental analysis, IR, ^{1}H and ^{13}C NMR spectra.

The IR spectra of quinazolinobenzodiazepines **5a-f**, **8** and **9** show two (**5a-d**, **8** and **9**) or one (**5e**,**f**) typical bands in the region of the carbonyl group at 1654–1706 cm^{-1} and C=N bond absorption peak at 1608–1619 cm^{-1}.

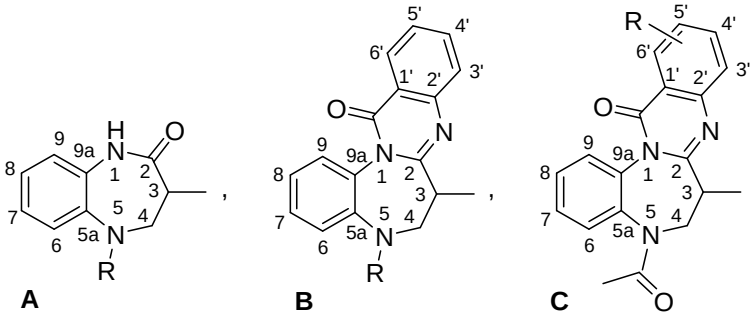


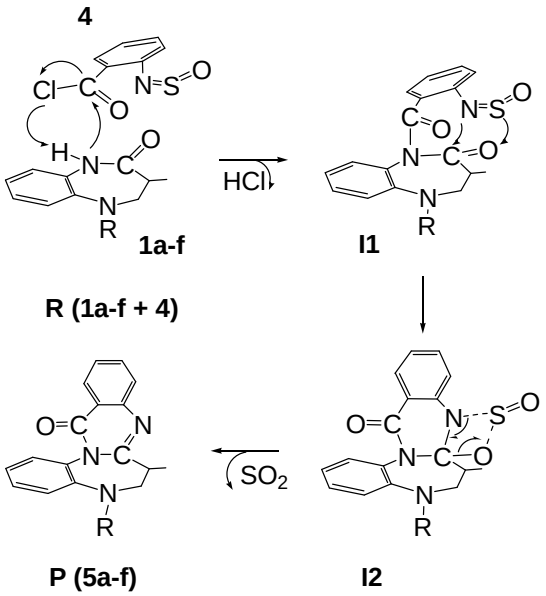
Figure 1. The arbitrary numbering of atoms common for all study compounds **1d**, **5a-f**, **8**, **9**.

The assignment of the NMR spectral lines was carried out using the substituents additivity rules, signal intensities, multiplicities, and NMR data of structurally related compounds.[18,19] Carbon atoms are marked arbitrarily in the Figure 1 (**A**- for compound **1d**, **B**- for compounds **5a-f**, and **C**- for compounds **8**,**9**) for easier comparison and systematization of obtained data which are presented in the Experimental section.

Starting compounds **1a-f** showed characteristic resonances of the NH group proton in region of 8.1–8.8 ppm and of the CO group carbon at 173.5–176.0 ppm in ^{1}H and ^{13}C NMR spectra, respectively. The disappearance of these resonances in the NMR spectra suggested the formation of compounds **5a-f**. The resonances of 3-CH_3 protons in the case of **5a-f** compounds were shifted about 0.3 ppm downfield in comparison with starting compounds **1a-f**. The integration of ^{1}H NMR spectra of the newly synthesized 7-methyl-6,7-dihydroquinazolino[3,2-*a*][1,5]benzodiazepin-13-ones showed the required number of aromatic protons: eight for **5a**,**b**,**d**,**e**, thirteen for **5c**,**f** and seven for compounds **8**,**9**. The new characteristic resonances in ^{13}C NMR spectra in the region of 155.7–158.3 ppm and at about 160 ppm assigned to C=N and to 1-CO groups carbon respectively also confirmed the predicted structures of compounds **5a-f**.

Theoretical studies

The most possible reaction mechanism for acylation-cyclization reaction of 5-substituted 3-methyl-1,3,4,5-tetrahydro-2*H*-1,5-benzodiazepin-2-ones **1a-f** with 2-sulfinylaminobenzoyl chloride **4** exhibited in Scheme 4.



Scheme 4. Possible mechanism for the acylation-cyclization reaction of 5-substituted 3-methyl-1,3,4,5-tetrahydro-2*H*-1,5-benzodiazepin-2-ones **1a-f** with 2-sulfinylaminobenzoyl chloride **4**.

In order to confirm this mechanism, Density Functional Theory (DFT) analysis of possible acylation-cyclization reaction pathways was performed by calculation of reaction stationary points along minimal energy path given as IRC.[20,21,25-27] Theoretical studies on heterocyclization reactions indicated that the activation energies as well as properties of stationary points were in a good agreement with the experimental results if the B3LYP hybrid functional at the DFT was used for the calculation.[28-33] An attempt to choose basis sets 6-311++G(d, p), 6-31+G(d), 6-31G(d, p) and 6-31G(d) for evaluation reactions of heterocyclic systems with heavy atoms revealed that all basis sets provided almost identical results.[9,34-37] Thus, we chose 6-31+G(d, p) basis set as the best compromise between speed and accuracy for the investigation of the acylation-cyclization reaction.

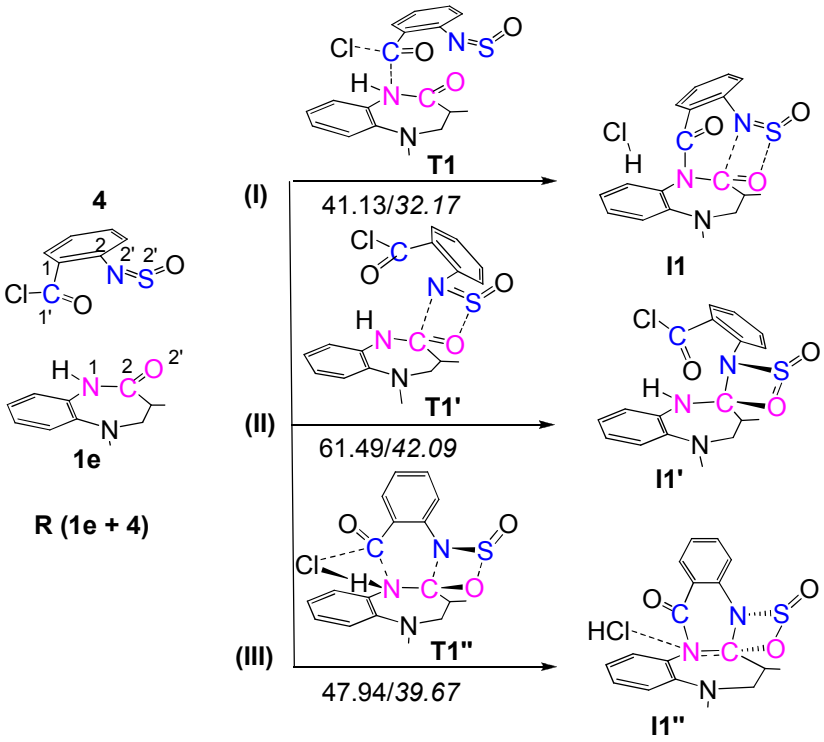
The precursors **1e** and **4** were selected as a model and the detailed reaction mechanism study was carried out using a transition state theory approach.[20,21,25,26] Additionally the electron density transformation along the reaction minimal energy path was evaluated by calculation of Natural Bond Orbital (NBO) charges and Wiberg bond indexes (BI).[38]

The polarity of reaction conditions should play a very important role in stabilization of different intermediates and transition states.[26] The acylation-cyclization reaction was modeled in the consideration of DCE solvent to simulate experimental conditions.

Three presumed most probable reaction pathways (I-III) analyzed on the basis of the known experimental investigations dealing with sulfinylamine and carbonyl group interaction and acylation reaction mechanism[39] for the theoretical study of acylation-cyclization reaction are presented in Scheme 5.

Thus, in reaction pathway (I) the attack of the carbon atom C(1') of **4** on the N(1) atom of **1e** proceeds through transition structure **T1** and transforms to intermediate **I1** together with the migration of chloride and hydrogen atoms until HCl forms. The calculated Gibbs free energies of activation ($\Delta G^{\ddagger}$) for pathway (I) were 41.13 and 32.17 kcal/mol in the gas phase and in the solvent, respectively. In pathway (II), the initial attack of N(2') and S(2') atoms of the 2-sulfinylamino group of **4** on the C(2)=O(2') bond atoms proceeds via transition state **T1'** leading to intermediate **I1'**. The $\Delta G^{\ddagger}$ for pathway (II) were 61.49 and 42.09 kcal/mol in the gas phase and in the solvent, respectively. In pathway (III), the simultaneous interaction of both reacting centers, C(1') and the N(2') and S(2') atoms of **4** with N(1) and the C(2)=O(2') bond atoms of **1e** accordingly, goes *via* transition state **T1''** leading to the formation of the new N(1)-C(1'), C(2)-N(2'), S(2')-O(2) bonds in one step. The calculated $\Delta G^{\ddagger}$ for pathway (III) were 47.94 and 39.67 kcal/mol in the gas phase and in the solvent, respectively. The obtained results indicate that the reaction pathway (I) is the most energy-favorable pathway for initial interaction of chloride **4** with benzodiazepinone **1e**. Considering this, we further focused our attention on the detailed description of this reaction pathway. The B3LYP/6-31+G(d,p) calculated geometric parameters of the reaction stationary points: **R**, **T**, **I** and **P** for pathway (I) located along the reaction coordinate are presented in Scheme 6.

The $\Delta G^{\ddagger}$ of **T** activation or **I** stabilization were calculated as the difference of free energies between **T** and the prereactive complexes (**R** or **I**) discussed throughout the text and shown in the reaction free-energy profile in Figure 2.



Scheme 5. B3LYP/6-31+G(d,p) calculated possible reaction pathways (I-III) for acylation-cyclization reaction of **1e** and **4**. Activation Gibbs free energies ($\Delta G^{\ddagger}$, kcal/mol) for gas phase (regular font) and for solvent phase (*italic font*) were taken as the difference between **T** and **R** of free energies.

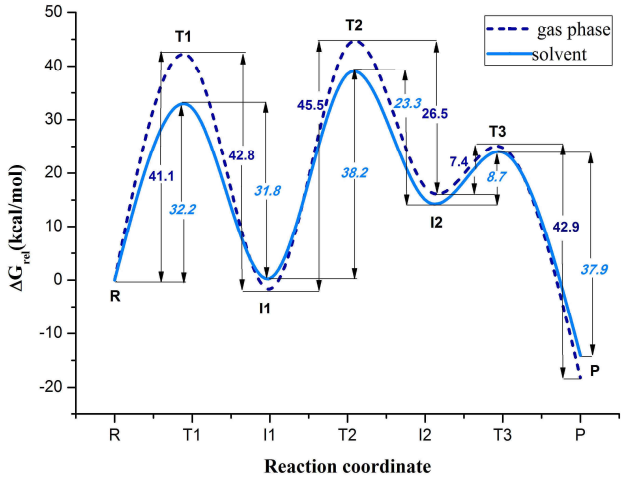
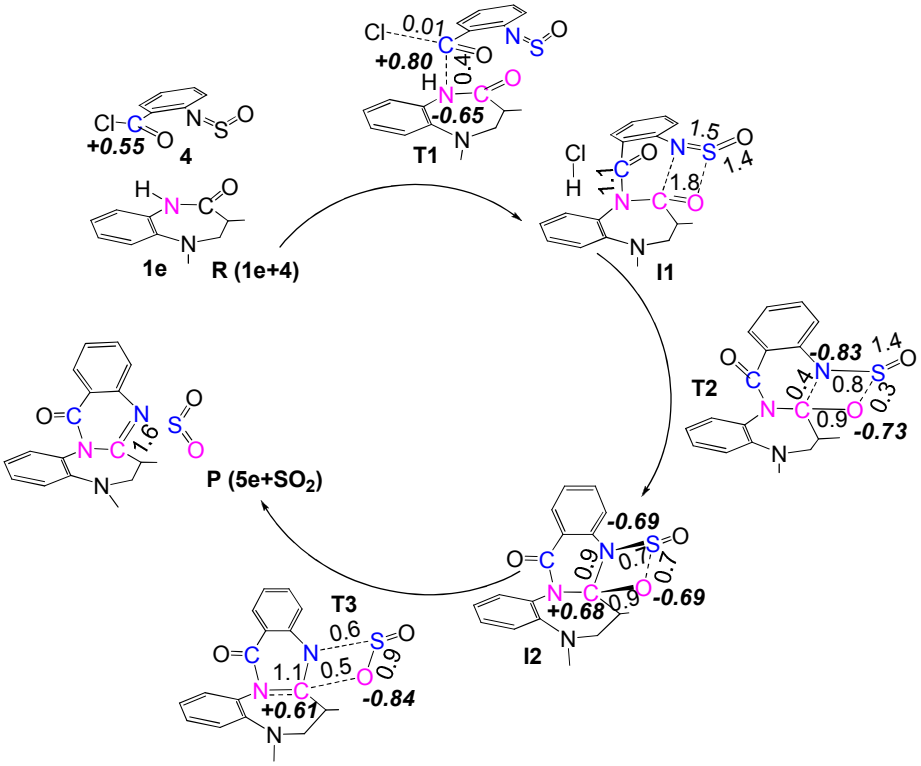


Figure 2. Schematic relative Gibbs free-energy profile for the formation of **5e** from **1e** and **4** in the gas phase (dashed line) and solvent phase (solid line). ΔG_{rel} of activation and stabilization for gas phase (regular values) and solvent phase (*italic values*).

The relative B3LYP/6-31+G(d,p) Gibbs free energy ($\Delta G^{\ddagger}$ (kcal/mol), relative to **R**) for all stationary points are given in Table S1. (Tables S1-S5 are listed in supplementary information file). The B3LYP/6-31+G(d,p) calculated total energies (E) and Gibbs free energies (G) with the imaginary frequency (*vi*) modes of transition states are listed in Table S2. The important for acylation-cyclization reaction progress bond distances (BD), Wiberg bond indexes (BI) and the charges on the selected atoms calculated using natural population analysis (NPA) for all stationary points are summarized in Tables S3, S4 and S5.

As shown in Scheme 6, the reaction starts with the interaction of the electrophilic C(1') carbon atom of the C(1')=O(1') group of **4** with the N(1) atom of **1e** under the formation of intermediate **I1**. As the system moves to transition state **T1**, significant structural changes occur. Firstly, the chloride atom migrates toward the hydrogen atom of the N(1)-H group until the C(1')-Cl bond disruption due to the stabilizing Van der Waals interaction between the Cl and H(1') atoms within a distance of 2.7 Å. Secondly, **4** approaches **1e** until the distance between the C(1') and N(1) atoms (BD C(1')-N(1)) shortens to 1.95 Å and the Wiberg bond index (BI C(1')-N(1)) increases to 0.41. Simultaneously, the positive charge on the C(1') atom in **4** increases progressively from +0.55 in **R** to +0.80 in **T1**, whereas N(1) of **1e** becomes more negative (-0.65) in **T1** along the same path. This exhibits a weak and highly polarized C(1')-N(1) bond formation at **T1**.



Scheme 6. B3LYP/6-31+G(d,p) calculated geometries of optimized **R**, **T**, **I**, and **P** for reaction pathway (I) of **1e** and **4** to **5e**. Wiberg bond index (regular values) and NPA charges (***bold italic values***).

As the system goes further to intermediate **I1**, H(1') migrates toward chloride until HCl molecule creation. BD C(1')-N(1) further shortens to 1.39 Å and BI C(1')-N(1) increases to 1.05. The stabilization energy of **I1** is 31.84 kcal/mol for the solvent phase. The complete migration of Cl to H(1') and C(1')-N(1) σ-bond formation is the most significant change from **T1** to **I1**. The transition of **I1** via **T2** to **I2** requires activation energy 38.18 kcal/mol for a solvent. At this step, **4** together with N(2')-S(2')=O(2') moiety migrates towards the C(2)=O(2') bond plane of **1e** with the nitrogen N(2') atom heading towards C(2) and the S(2') atom heading towards the O(2') atom until the system reaches **T2**. With this migration, the π-electrons from C(2)=O(2') of **1e** and N(2')=S(2') of **4** are used to form new N(2')-C(2) and S(2')-O(2') σ bonds. As a result, the negative charge on the N(2') atom of the N(2')=S(2') bond decreases gradually from -0.83 in **T2** to -0.69 in **I2** and O(2') charge of the C(2)=O(2') bond changes from -0.73 in **T2** to -0.69 in **I2**. It causes the N(2')-S(2') bond weakening from BI N(2')-S(2') 1.50 in **I1** to 0.81 in **T2** and the C(2)=O(2') bond weakening from BI C(2)=O(2') 1.75 to 0.90, respectively. Simultaneously, the new bonding interactions N(2')---C(2) and S(2')----O(2') form until the bond index increases to BI N(2')-C(2) 0.36 and BI S(2')-O(2') 0.33 at **T2**. As the system moves to **I2**, the N(2')-C(2) and S(2')-O(2') bonds further strengthen to BI N(2')-C(2) 0.96 and BI S(2')-O(2') 0.72 respectively, whereas, the N(2')-S(2') bond further weakens from BI N(2')-S(2') 0.81 in **T2** to 0.74 for **I2** at this step. The structure of **I2** is analogous to that of **T2** with the stabilization energy 23.29 kcal/mol for a solvent. The main structural change of this step is N(2')=S(2') and C(2)=O(2') bond transformations from π- to a σ-bonding character until the formation of cyclic tetragonal σ-bonded intermediate complex **I2**. Starting from **I2**, the reacting system easily reaches the transition state **T3** leading to final products.

The energy barrier of the third step is 8.68 kcal/mol for a solvent. The N(2')=S(2') and C(2)=O(2') bonds disruption with simultaneous S(2')=O(2') and C(2)=N(2') π bonds creation is the main structural change of this step. Starting from **I2** to **T3**, the electron density flows to the O(2') atom of **1e** increasing the negative charge from -0.69 at **I2** to -0.84 at **T3**, whereas, the positive charge on the C(2) atom decreases from +0.68 to +0.61 along the same path. With this charge transfer, the polarization, weakening and lengthening of C(2)-O(2') and N(2')-S(2') bonds occur. For example, the C(2)-O(2') bond weakens from BI C(2)-O(2') 0.90 at **I2** to BI C(2)-O(2') 0.47 at **T3** upon bond disruption at **P**, whereas, C(2)=N(2') bond strengthening occurs from BI C(2)-N(2') 1.08 at **T3** to BI C(2)-N(2') 1.59 at the product **5e** along the same path.

The detailed theoretical analysis of the interaction of 3,5-dimethyl-1,3,4,5-tetrahydro-2*H*-1,5-benzodiazepin-2-one (**1e**) with 2-sulfinylaminobenzoyl chloride (**4**) showed that the acylation-cyclization reaction can be described as sequential three-step process. Firstly, the pre-reactive reactant complex is activated to intermediate with stabilized Van der Waals interaction between Cl and H atoms. Secondly, the Van der Waals stabilized intermediate complex transforms to the cyclic tetragonal σ-bonded intermediate complex with the activation barrier of 38.18 kcal/mol suggesting that this step along the reaction path is rate limiting. Thirdly, the tetragonal σ-bonded intermediate transforms into the final product 5,7-dimethyl-6,7-dihydroquinazolino[3,2-*a*][1,5]benzodiazepin-13(5*H*)-one (**5e**) and SO_2 with the activation barrier of 8.68 kcal/mol.

During the acylation-cyclization reaction pathway, the transfer of the charge and π bond electron density is significant. This suggests the complicated nature of σ- and π-bonding transformations on the reaction path. The solvent influence on reaction rate points out that the solvents effectively lower the energy of reaction barrier and favor the reaction path.

Conclusions

A simple and efficient method for the preparation of 5-substituted 7-methyl-6,7-dihydro-quinazolino[3,2-*a*][1,5]benzodiazepine-13-ones via a single acylation-cyclization process using readily available 2-sulfinylaminobenzoyl chlorides is described. Operational simplicity and good yields are the salient features of this method. This method may be applicable for the synthesis of libraries of fused polycyclic 1,5-benzodiazepin-2-ones. Furthermore, a detailed theoretical analysis of the acylation-cyclization reaction is described for the first time.

Experimental Section

Computational details

The relevant stationary points were fully optimized in the gas phase using DFT method with hybrid density functional B3LYP using 6-31+G(d,p) basis set. Stationary points were further characterized as minima with all real frequencies or as transition states with only one imaginary frequency by computations of harmonic vibrational frequencies at the same theory level as geometry optimization. The connection between the different transition states and reaction intermediates was ensured by intrinsic reaction coordinate calculations.[27] "$\Delta G^{\ddagger}$ were calculated as the difference of free energies between transition states and intermediate complexes. Zero-point energies and thermodynamic parameters at 298 K and 100 kPa were obtained from harmonic vibrational frequency calculations. In order to account for the solvent effects, the solvation energies were calculated on the gas-phase optimized structures with the self-consistent reaction field method on the basis of the polarized continuum model (PCM).[40] In this work, single-point energy calculations at the PCM/6-31+G(d,p) level were carried out in DCE solution on the basis of the gas-phase optimized geometries as implemented in Gaussian03.[41]

Experimental details

Melting points were determined in open capillaries on a MEL-TEMP 1202D apparatus. The IR spectra (potassium bromide) were taken on a Perkin Elmer Spectrum GX FT-IR spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on Bruker Ascend™ 400 at 302 K. Chemical shifts (δ) are reported relative to tetramethylsilane (TMS) with the solvent reference: $CDCl_3$ (δ 7.26 ppm), for ^{1}H NMR and $CDCl_3$ (δ 77.0 ppm), for ^{13}C NMR. The reaction progress and the purity of the compounds were controlled by TLC on a Merck precoated silica gel aluminum roll (60F254)

with chloroform-ethyl acetate-methanol (v/v, 14:7:1) as the eluent. Dry column vacuum chromatography[42] was performed with silica gel 60 (0.015–0.040 mm, Merck). Microanalyses were performed with Thermo Scientific™ Flash 2000 CHNS/O analyser. The synthesis and NMR spectral data of the starting 5-acetyl- (**1a**),[43] 5-formyl- (**1b**),[44] 5-benzoyl- (**1c**),[19] 5-methyl- (**1e**)[45] and 5-benzyl- (**1f**)[46] benzodiazepinones were published previously; the newly synthesized 5-ethoxycarbonyl compound **1d** is described here.

General procedure for the synthesis of 5-R-7-methyl-6,7-dihydroquinazolino[3,2-*a*]-[1,5]benzodiazepin-13(5*H*)-ones (5a-f, 8 and 9). A suspension of anthranilic acid (0.82 g, 6.0 mmol) or substituted anthranilic acid **6**,**7** and thionyl chloride (4.3 mL, 60 mmol) in dry benzene (60 mL) was refluxed until the reaction mixture became clear (2–3 h). The solvent was evaporated under vacuum. Then, dry benzene (30 mL) was added and distilled out. After repeating this procedure twice, the resulting dark oil was dissolved in dry DCE (10 mL) and added to a dry DCE solution (60–80 mL) of the appropriate 5-substituted benzodiazepin-2-one **1a-f** (4 mmol) with stirring, which contains DIPEA (1.7 mL, 10 mmol) and catalytic amount of DMAP. The reaction mixture was stirred at room temperature for 18–24 h and then diluted with 150 mL of DCE. The solution washed with 5% $NaHCO_3$ and water, dried and evaporated to dryness in vacuum. The obtained oily residues were then subjected to a dry column vacuum chromatography (silicagel) using a mixture of DCE and ethyl acetate (3:1) as eluting solvent. After chromatographic purification, the resulting compounds **5a-f**, **8** and **9** were recrystallized from dichloromethane-diethyl ether mixture.

5-Acetyl-7-methyl-6,7-dihydroquinazolino[3,2-*a*][1,5]benzodiazepin-13(5*H*)-one (5a). Sandy crystals, yield 74%, 0.68 g, mp 248–250 °C. IR (KBr, ν_{max}, cm^{-1}): 1687 and 1660 (C=O), 1609 (C=N). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 1.41 (3H, d, $^3J_{HH}$ 6.5 Hz, 3-CH_3), 1.84 (3H, s, $COCH_3$), 2.86 (1H, ddq, $^3J_{HH}$ 12.6 Hz, $^3J_{HH}$ 12.6 Hz, $^3J_{HH}$ 6.4 Hz, 3-CH), 3.42 (1H, dd, $^3J_{HH}$ 5.9 Hz, $^2J_{HH}$ 12.5 Hz, 4-CH_2), 4.54 (1H, dd, $^3J_{HH}$ 12.5 Hz, $^2J_{HH}$ 12.5 Hz, 4-CH_2), 7.32–8.29 (8H, m, CH_{arom}). ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 13.8 (3-CH_3), 22.7 (CO*C*H_3), 36.5 (C-3), 54.6 (C-4), 121.0 (C-1′), 127.1 (2CH), 127.8 (CH), 128.7 (CH), 129.0 (CH), 129.3 (CH), 129.9 (CH), 133.8 (C-9a or C-5a), 134.7 (CH), 136.2 (C-5a or C9a), 146.9 (C-2′), 155.8 (C-2), 161.0 (1-CO), 170.2 (5- CO); Anal. Calcd. for $C_{19}H_{17}N_3O_2$ (319.36): C, 71.46; H, 5.37; N, 13.16. Found: C, 71.67; H, 5.50; N, 13.00 %.

7-Methyl-13-oxo-7,13-dihydroquinazolino[3,2-*a*][1,5]benzodiazepine-5(6*H*)-carbaldehyde (**5b**). Yellowish crystals, yield 53%, 0.65 g, mp 254–250 °C. IR (KBr, ν_{max}, cm^{-1}): 1687 and 1667 (C=O), 1609 (C=N). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 1.32 (3H, d, $^3J_{HH}$ 6.5 Hz, 3-CH_3), 2.89–3.09 (1H, m, 3-CH), 3.52 ((0.86)1H, dd, $^3J_{HH}$ 5.5 Hz, $^2J_{HH}$ 12.5 Hz, 4-CH_2), 3.82 ((0.14)1H, dd, $^3J_{HH}$ 5.5 Hz, $^2J_{HH}$ 11.7 Hz, 4-CH_2), 3.97 ((0.14)1H, dd, $^3J_{HH}$ 11.7 Hz, $^2J_{HH}$ 11.7 Hz, 4-CH_2), 4.03 ((0.86)1H, dd, $^3J_{HH}$ 12.5 Hz, $^2J_{HH}$ 12.5 Hz, 4-CH_2), 7.44–8.17 (8H, m, CH_{arom}), 8.23 ((0.14)1H), s, COH), 8.26 ((0.86)1H, s, COH). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 13.9 (3-CH_3), 35.3 (C-3), 52.7 (C-4), 120.7 (C-1′), 126.7 (CH), 127.2 (CH), 127.3 (CH), 128.0 (2CH), 128.2 (CH), 129.6 (CH), 132.5 (C-5a or C-9a), 134.1 (C-9a or C-5a), 135.0 (CH), 146.4 (C-2′),

156.5 (C-2), 160.1 (1-CO), 162.0, 162.5 (5-CO); Anal. Calcd. for $C_{18}H_{15}N_3O_2$ (305.33): C, 70.81; H, 4.95; N, 13.76. Found: C, 71.02; H, 5.08; N, 13.94 %.

5-Benzoyl-7-methyl-6,7-dihydroquinazolino[3,2-*a*][1,5]benzodiazepin-13(5*H*)-one (**5c**). Sandy crystals, yield 69%, 1.05 g, mp 164–166 °C. IR (KBr, ν_{max}, cm^{-1}): 1687 and 1654 (C=O), 1609 (C=N). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 1.51 (3H, d, $^3J_{HH}$ 6.5 Hz, 3-CH_3), 3.02 (1H, ddq, $^3J_{HH}$ 12.6 Hz, $^3J_{HH}$ 12.6 Hz, $^3J_{HH}$ 6.4 Hz, 3-CH), 3.74 (1H, dd, $^3J_{HH}$ 5.7 Hz, $^2J_{HH}$ 12.6 Hz, 4-CH_2), 4.38 (1H, dd, $^3J_{HH}$ 12.6 Hz, $^2J_{HH}$ 12.6 Hz, 4-CH_2), 6.81–8.37 (13H, m, CH_{arom}); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 14.0 (3-CH_3), 36.1 (C-3), 56.5 (C-4), 121.1 (C-1′), 127.1 (CH), 127.3 (CH), 127.6 (CH), 127.9 (CH), 128.0 (*o*-CHPh), 128.9 (CH), 129.1 (*m*-CHPh), 129.3 (CH), 129.5 (CH), 130.6 (*p*-CHPh), 132.8 (*i*-CPh), 134.2 (C-5a or C-9a), 134.8 (CH), 137.4 (C-9a or C-5a), 146.8 (C-2′), 156.3 (C-2), 161.0 (1-CO), 170.7 (5-CO); Anal. Calcd. for $C_{24}H_{19}N_3O_2$ (381.43): C, 75.57; H, 5.02; N, 11.02. Found: C, 75.72; H, 4.83; N, 10.88 %.

Ethyl 7-methyl-13-oxo-7,13-dihydroquinazolino[3,2-*a*][1,5]benzodiazepine-5(6*H*)-carboxylate (**5d**). Yellowish solid, yield 50%, 0.70 g, mp 196–198 °C. IR (KBr, ν_{max}, cm^{-1}): 1706 and 1686 (C=O), 1609 (C=N). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 1.09 (3H, br s, OCH_2CH_3), 1.49 (3H, d, $^3J_{HH}$ 6.5 Hz, 3-CH_3), 2.84–2.93 (1H, m, 3-CH), 3.59 (1H, dd, $^3J_{HH}$ 5.2 Hz, $^2J_{HH}$ 11.2 Hz, 4-CH_2), 3.97 (1H, br s, OCH_2CH_3), 4.07–4.15 (1H, m, 4-CH_2), 4.20 (1H, br s, OCH_2CH_3), 7.35–8.31 (8H, m, CH_{arom}). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 13.8 (3-CH_3), 14.3 (OCH_2CH_3), 36.5 (C-3), 56.6 (C-4), 62.0 (OCH_2CH_3), 121.2 (C-1′), 126.9 (CH), 127.1 (CH), 127.6 (CH), 127.7 (CH), 128.6 (CH), 129.0 (CH), 129.3 (CH), 133.0 (C-5a or C-9a), 134.5 (CH), 135.1 (C-9a or C-5a), 146.9 (C-2′), 155.0 (C-2), 156.2 (5-COO), 160.8 (1-CO); Anal. Calcd. for $C_{20}H_{19}N_3O_3$ (349.38): C, 68.75; H, 5.48; N, 12.03. Found: C, 68.50; H, 5.35; N, 11.82 %.

5,7-Dimethyl-6,7-dihydroquinazolino[3,2-*a*][1,5]benzodiazepin-13(5*H*)-one (**5e**). Sandy crystals, yield 62%, 0.72 g, mp 109–111 °C. IR (KBr, ν_{max}, cm^{-1}): 1676 (C=O) and 1609 (C=N). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 1.38 (3H, d, $^3J_{HH}$ 6.4 Hz, 3-CH_3), 2.72 (3H, s, 5-CH_3), 2.91–3.04 (2H, m, 3-CH + 4-CH_2), 3.26 (1H, dd, $^3J_{HH}$ 9.5 Hz, $^2J_{HH}$ 11.7 Hz, 4-CH_2), 7.16–8.32 (8H, m, CH_{arom}). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 14.0 (3-CH_3), 37.1 (C-3), 40.2 (5-CH_3), 66.8 (C-4), 119.0 (CH), 121.4 (C-1′), 122.6 (CH), 126.5 (CH), 127.1 (CH), 127.27 (CH), 128.36 (CH), 129.61 (CH), 129.69 (C-5a or C-9a), 134.27 (CH), 144.84 (C-9a or C-5a), 146.85 (C-2′), 158.1 (C-2), 160.9 (1-CO); Anal. Calcd. for $C_{18}H_{17}N_3O$ (291.35): C, 72.20; H, 5.88; N, 14.42. Found: C, 72.39; H, 6.06; N, 14.60 %.

5-Benzyl-7-methyl-6,7-dihydroquinazolino[3,2-*a*][1,5]benzodiazepin-13(5*H*)-one (**5f**). Sandy solid, yield 53%, 0.78 g mp 68–70 °C. IR (KBr, ν_{max}, cm^{-1}): 1686 (C=O), 1608 (C=N). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 1.32 (3H, d, $^3J_{HH}$ 6.1 Hz, 3-CH_3), 2.95–3.03 (2H, m, 3-CH + 4-CH_2), 3.20 (1H, dd, $^3J_{HH}$ 11.5 Hz, $^3J_{HH}$ 13.5 Hz, 4-CH_2), 4.00 and 4.39 (2H, AB_q, $^2J_{HH}$ 10.2 Hz, 5-CH_2), 7.10–8.38 (13H, m, CH_{arom}). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 14.0 (3-CH_3), 37.0 (C-3), 56.9 (5-CH_2), 64.1 (C-4), 120.4 (CH), 121.2 (C-1′), 123.2 (CH), 126.6 (*p*-CHPh), 127.1 (2CH), 127.4 (CH), 128.0 (*o*-CHPh), 128.3 (CH), 128.4 (*m*-CHPh), 129.6 (CH), 130.7 (C-5a or C-9a), 134.4 (CH), 137.3 (*i*-CPh), 144.4 (C-9a or C-5a), 146.8 (C-2′), 158.3 (C-2), 161.0 (1-CO) ppm. Anal.

Calcd. for $C_{24}H_{21}N_3O$ (367.44): C, 78.45; H, 5.76; N, 11.44. Found: C, 78.23; H, 5.65; N, 11.26 %.

5-Acetyl-12-chloro-7-methyl-6,7-dihydroquinazolino[3,2-*a*][1,5]benzodiazepin-13(5*H*)-one (**8**). Yellowish crystals, yield 68%, 0.89 g, mp 264–266 °C. IR (KBr, ν_{max}, cm^{-1}): 1699 and 1661 (C=O), 1619 (C=N). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 1.38 (3H, d, $^3J_{HH}$ 6.5 Hz, 3-CH_3), 1.86 (3H, s, $COCH_3$), 2.83 (1H, ddq, $^3J_{HH}$ 12.5 Hz, $^3J_{HH}$ 12.5 Hz, $^3J_{HH}$ 6.3 Hz, 3-CH), 3.41 (1H, dd, $^3J_{HH}$ 5.9 Hz, $^2J_{HH}$ 12.5 Hz, 4-CH_2), 4.53 (1H, dd, $^3J_{HH}$ 12.5 Hz, $^2J_{HH}$ 12.5 Hz, 4-CH_2), 7.31–7.68 (7H, m, CH_{arom}). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 13.6 (3-CH_3), 22.8 (CO*C*H_3), 36.5 (C-3), 54.4 (C-4), 118.2 (C-1′), 127.1 (CH), 128.7 (CH), 129.9 (CH), 129.5 (CH), 129.0 (CH), 130.0 (CH), 134.0 (CH), 133.6 (C-9a or C-5a), 134.5 (C-6′), 136.1 (C-5a or C-9a), 149.3 (C-2′), 156.6 (C-2), 159.1 (1-CO), 170.3 (5-CO); Anal. Calcd. for $C_{19}H_{16}ClN_3O_2$ (353.80): C, 64.50; H, 4.56; N, 11.88. Found: C, 64.29; H, 4.64; N, 11.80 %.

5-Acetyl-11-bromo-7-methyl-6,7-dihydroquinazolino[3,2-*a*][1,5]benzodiazepin-13(5*H*)-one (**9**). Yellowish crystals, yield 51%, 0.93 g, mp 286–289 °C. IR (KBr, ν_{max}, cm^{-1}): 1686 and 1656 (C=O), 1611 (C=N). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 1.39 (3H, d, $^3J_{HH}$ 6.5 Hz, 3-CH_3), 1.84 (3H, s, $COCH_3$), 2.79-2.90 (1H, m, 3-CH), 3.41 (1H, dd, $^3J_{HH}$ 5.5 Hz, $^2J_{HH}$ 12.4 Hz, 4-CH_2), 4.54 (1H, dd, $^3J_{HH}$ 12.4 Hz, $^2J_{HH}$ 12.4 Hz, 4-CH_2), 7.33–8.40 (7H, m, CH_{arom}). ^{13}C NMR (100 MHz, $CDCl_3$): δ_H 13.8 (3-CH_3), 22.7 (CO*C*H_3), 36.6 (C-3), 54.5 (C-4), 120.6 (C-5′), 122.4 (C-1′), 128.8 (CH), 129.1 (CH), 129.2 (CH), 129.6 (CH), 129.6 (CH), 130.2 (CH), 133.5 (C-9a or 5a), 136.1 (C-5a or C-9a), 137.9 CH), 145.8 (C-2′), 156.3 (C-2), 159.9 (1-CO), 170.2 (5-CO); Anal. Calcd. for $C_{19}H_{16}BrN_3O_2$ (456.38): C, 57.30; H, 4.05; N, 10.55. Found: C, 57.49; H, 4.20; N, 10.37 %.

Ethyl 3-methyl-4-oxo-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine-1-carboxylate (**1d**). Compound **1d** was obtained according to the procedure described[18] from 3-methyl-1,3,4,5-tetrahydro-2*H*-1,5-benzodiazepin-2-one[43] (3.6 g, 20 mmol), triethylamine (2.8 mL, 20 mmol) and ethyl chloroformate (2.1 mL, 22 mmol) in dry THF. Crystallization from ethyl acetate-diethyl ether gave **1d** (4.1 g, 86%), mp 101–103 °C. IR (KBr, ν_{max}, cm^{-1}): 3187 and 3124 (NH), 1703 and 1668 (C=O). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 1.13 (3H, d, $^3J_{HH}$ 6.6 Hz, 3-CH_3), 1.11–1.42 (3H, br m, OCH_2CH_3), 2.78 (1H, pd, $^3J_{HH}$ 6.6 Hz, $^3J_{HH}$ 13.0 Hz, 3-CH), 3.73 (1H, dd, $^3J_{HH}$ 6.6 Hz, $^2J_{HH}$ 12.3 Hz, 4-CH_2), 3.95–4.35 (3H, br m, 4-CH_2 + OCH_2CH_3), 7.06–7.41 (4H, m, CH_{arom}), 8.16 ((0.26)1H, s, NH), 8.35 ((0.74)1H, s, NH). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 12.7 (3-CH_3), 14.4 (OCH_2CH_3), 35.5 (C-3), 55.9 (C-4), 62.1 (OCH_2CH_3), 122.7 (C-9), 125.7 (C-7), 128.0 (C-6), 129.7 (C-8), 133.3 (C-5a), 134.7 (C-9a), 155.0 (COO), 175.21 (C-2); Anal. Calcd. for $C_{13}H_{16}N_2O_3$ (220.27): C, 62.89; H, 6.50; N, 11.28. Found: C, 63.01; H, 6.41; N, 11.49 %.

Acknowledgements

The authors are grateful to the Digital Science and Computing Center at Vilnius University for computational facilities.

Supplementary Material

Copies of IR, ^{1}H, ^{13}C and NMR spectra and some computational data associated with this work are available as supplementary information in separate file.

References

1. Archer, G. A.; Sternbach, L. H. *Chem. Rev.* **1968**, *68*, 747. http://dx.doi.org/10.1021/cr60256a004
2. Rogowaski, M. A.; Porter, R. *J. Pharm. Rev.* **1990**, *42*, 223.
3. Smith, R. H.; Jorgensen, W. L.; Tirado-Rives, J.; Lamb, M. L.; Janssen, P. A. J.; Michejda, C. J.; Kroeger Smith, M. B. *J. Med. Chem.* **1998**, *41*, 5272.
4. Sternbach, H. *J. Med. Chem.* **1979**, *22*, 1. http://dx.doi.org/10.1021/jm00187a001
5. Ambrogi, V.; Grandolini, G.; Perioli, L.; Giusti, L.; Lucacchini, A.; Martini, C. *Eur. J. Med. Chem.* **1995**, *30*, 429. http://dx.doi.org/10.1016/0223-5234(96)88253-5
6. Chimirri, A.; Gitto, R.; Grasso, S.; Monforte, A. M.; Romeo, G.; Zappala, M. *Heterocycles* **1993**, *36*, 865. http://dx.doi.org/10.3987/REV-92-442
7. Kosychova, L.; Stumbreviciute, Z.; Pleckaitiene, L.; Janciene, R.; Puodziunaite, B. D. *Chem. Heterocycl. Compd*, **2004**, *40*, 811. http://dx.doi.org/10.1023/B:COHC.0000040781.41929.9c
8. Janciene, R.; Stumbreviciute, Z.; Podeniene, D.; Puodziunaite, B. D. *J. Heterocycl. Chem.* **2006**, *43*, 979. http://dx.doi.org/10.1002/jhet.5570430424
9. Janciene, R.; Vektariene, A.; Stumbreviciute, Z.; Puodziunaite, B. *Monatsh. Chem.* **2011**, *142*, 609. http://dx.doi.org/10.1007/s00706-011-0496-4
10. Kosychova, L.; Pleckaitiene, L.; Staniulyte, Z.; Janciene, R.; Palaima, A.; Puodziunaite, B. D. *Arkivoc* **2006**, (*xiii*), 158. http://dx.doi.org/10.3998/ark.5550190.0007.d16
11. Janciene, R.; Stumbreviciute, Z.; Vektariene, A.; Kosychova, L.; Klimavicius, A.; Palaima, A.; Puodziunaite, B. *J. Heterocycl. Chem.* **2009**, *46*, 1339. http://dx.doi.org/10.1002/jhet.226
12. Kosychova, L.; Stumbreviciute, Z.; Janciene, R.; Staniulyte, Z.; Puodziunaite, B. D. *Arkivoc* **2011**, (*xi*), 82. http://dx.doi.org/10.3998/ark.5550190.0012.b08

13. El-Sayed, A. M.; Abdel-Ghany, H.; El-Saghier, A. M. M. *Synth. Commun.* **1999**, *29*, 3561. http://dx.doi.org/10.1080/00397919908085990
14. Yuskovets, V. N.; Ivin, B. A. *Russ. J. Gen. Chem.* **2007**, *77*, 2162. http://dx.doi.org/10.1134/S1070363207120146
15. Mhaske, S. B.; Argade, N. P. *Tetrahedron* **2006**, *62*, 9787. http://dx.doi.org/10.1016/j.tet.2006.07.098
16. Al-Said, N. H.; Shawakfeh, K. Q.; Ibrahim, M. I.; Tayyem, S. H. *Arkivoc* **2010**, (*ix*), 282. http://dx.doi.org/10.3998/ark.5550190.0011.926
17. Taher, D.; Ishtaiwi, Z. N.; Al-Said, N. H. *Arkivoc* **2008**, (*xvi*), 154. http://dx.doi.org/10.3998/ark.5550190.0009.g15
18. Janciene, R.; Mikulskiene, G.; Javorskis, T.; Vektariene, A.; Vektaris, G.; Kosychova, L. *J. Heterocycl. Chem.* **2015**, *52*, 243. http://dx.doi.org/10.1002/jhet.2038
19. Janciene, R.; Vektariene, A.; Mikulskiene, G.; Javorskis, T.; Vektaris, G.; Klimavicius, A. *Arkivoc* **2013**, (*iv*), 57. http://dx.doi.org/10.3998/ark.5550190.p008.073
20. Truhlar, D. G.; Garrett, B. C.; Klippenstein, S. J. *J. Phys. Chem.* **1996**, *100*, 12771. http://dx.doi.org/10.1021/jp953748q
21. Vektariene, A.; Vektaris, G. Z. *Naturforsch. B*, **2011**, *66*, 850. http://dx.doi.org/10.5560/ZNB.2011.66b0850
22. Davies, S. G.; Ling, K. B.; Roberts, P. M.; Russell, A. J.; Thomson, J. E.; Woods, P. A. *Tetrahedron* **2010**, *66*, 6806.
23. Garin, J.; Merino, P.; Orduna, J.; Tejero, T.; Uried, S. *Tetrahedron Lett.* **1991**, *32*, 3263. http://dx.doi.org/10.1016/S0040-4039(00)79739-5
24. Wang, H.; Ganesan, A. *Tetrahedron Lett.* **1998**, *39*, 9097. http://dx.doi.org/10.1016/S0040-4039(98)02004-8
25. Sousa, F.; Fernandes, P. E.; Ramos, M. J. *J. Phys. Chem. A.* **2007**, *111*, 10439. http://dx.doi.org/10.1021/jp0734474
26. Vektariene, A. *J. Phys. Chem A.* **2013**, *117*, 8449. http://dx.doi.org/10.1021/jp402257u
27. Fukui, K. *Acc. Chem. Res.* **1981**, *14*, 363. http://dx.doi.org/10.1021/ar00072a001
28. Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648. http://dx.doi.org/10.1063/1.464913
29. Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B.* **1988**, *37*, 785. http://dx.doi.org/10.1103/PhysRevB.37.785
30. Morgado, C. C.; McNamara, J. P.; Hillier, I. H.; Burton, N. A.; Vincent, M. A. *J. Chem. Theory. Comput.* **2007**, *3*, 1656. http://dx.doi.org/10.1021/ct700072a

31. Vektariene, A.; Vektaris, G.; Svoboda, J. *Arkivoc* **2009**, (*vii*), 311. http://dx.doi.org/10.3998/ark.5550190.0010.730
32. Vektariene, A.; Vektaris, G.; Rankin, D. W. H. *Heteroat. Chem.* **2007**, *18*, 695. http://dx.doi.org/10.1002/hc.20378
33. Vektariene, A.; Vektaris, G. *Heteroat. Chem.* **2004**, *15*, 263. http://dx.doi.org/10.1002/hc.20015
34. Choe, S. J. *Bull. Korean Chem. Soc.* **2012**, *33*, 2861. http://dx.doi.org/10.5012/bkcs.2012.33.9.2861
35. Carlson, H. A.; Nguyen, T. B.; Orozco, M.; Jorgensen, W. L. *J. Comput. Chem.* **2004**, *14*, 1240. http://dx.doi.org/10.1002/jcc.540141013
36. Vektariene, A.; Vektaris, G. *Arkivoc* **2006**, (*xvi*), 23. http://dx.doi.org/10.3998/ark.5550190.0007.g03
37. Ledesma, A. E.; Contreras, C.; Svoboda, J.; Vektariene, A.; Brandán, S. A. *J. Mol. Struct.* **2010**, *967*, 159; **2014**, *1063*, 356. http://dx.doi.org/10.1016/j.molstruc.2014.01.087
38. Reed, A. E.; Curtiss, L. A.; Weinhold, F. *Chem. Rev.* **1988**, *88*, 899. http://dx.doi.org/10.1021/cr00088a005
39. Carey, F. A.; Sundberg, R. J. *Advanced Organic Chemistry, Part A: Structure and Mechanisms.* Springer, 2008, 485.
40. Barone, V.; Cossi, M.; Tomasi, J. *J. Comput. Chem.* **1998**, *19*, 404. http://doi: 10.1002/(SICI)1096-987X(199803)19:4<404:AID-JCC3>3.0.CO;2-W
41. Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery Jr, J. A.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C. ; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J., Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; Pople, J. A. *Gaussian03, revision C 02*, Gaussian, Inc., Wallingford, CT, 2004.
42. Pedersen, D. S.; Rosenbohm, C. *Synthesis* **2001**, *16*, 2431 http://dx.doi.org/10.1055/s-2001-18722
43. Puodzhunaite, B. A.; Yanchiene, R. A.; Talaikite, Z. A.; Zaks, A. C.; Rabotnikov, Yu, M.; Uzachev, E. A. *Khim-Farm. Zh.* **1985**, *19*, 1195. *Chem. Abstr*. **1986**, *105*, 133861g.

44. Puodzhyunaite, B. A.; Yanchene, R. A.; Stumbryavichyute, Z. A. *Chem. Heterocycl. Compd.* **1988**, *24*, 786. http://dx.doi.org/10.1007/BF00633177
45. Aversa, M. C.; Giannetto, P.; Romeo, G.; Ficarra, P.; Vigorita, M. G. *Org. Magn. Reson.* **1981**, *15*, 394. http://dx.doi.org/10.1002/mrc.1270150414
46. Puodžiūnaitė, B.; Kosychova, L.; Jančienė, R.; Stumbrevičiūtė, Z. *Monatsh. Chem*. **1997**, *128*, 1275. http://dx.doi.org/10.1007/BF00807260

