

Synthesis and Reactions of 1-Hydroxy-9,9a-dihydro-1*H*-imidazo[1,2-*a*]-indol-2(3*H*)-ones

Vytas Martynaitis,^a Rasa Steponavičiūtė,^a Sonata Krikštolaitytė,^a Joana Solovjova,^b Sven Mangelinckx,^{c,†} Norbert De Kimpe,^c Wolfgang Holzer,^d and Algirdas Šačkus^{a,b,*}

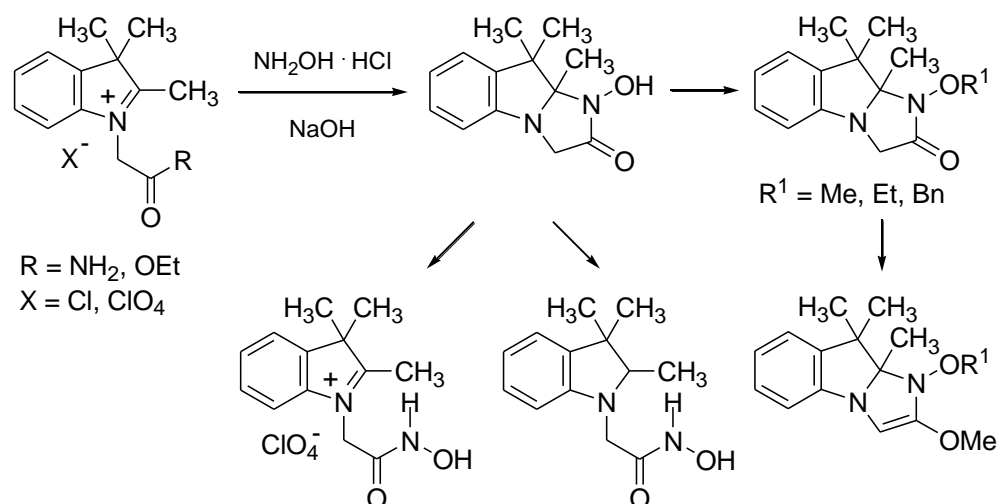
^a*Department of Organic Chemistry, Kaunas University of Technology, LT-50270 Kaunas, Lithuania*

^b*Institute of Synthetic Chemistry, Kaunas University of Technology, LT-50270 Kaunas, Lithuania*

^c*Department of Sustainable Organic Chemistry and Technology, Faculty of Bioscience Engineering, Ghent University, Coupure links 653, B-9000 Gent, Belgium*

^d*Department of Drug Synthesis, Faculty of Life Sciences, University of Vienna, Pharmaziezentrum, A-1090 Vienna, Austria*

Graphical abstract



Keywords: hydroxamic acids, indolium salts, imidazolidinones, ring opening

[†] Postdoctoral Fellow of the Research Foundation – Flanders (FWO), Belgium

* Corresponding author. Fax: +370(37)451432; e-mail: algirdas.sackus@ktu.lt

Abstract

1-Hydroxy-9,9a-dihydro-1*H*-imidazo[1,2-*a*]indol-2(3*H*)-ones, as a new type of azaheterocyclic hydroxamic acids, have been synthesized regioselectively from 1-carbamoylmethyl- or 1-(methoxycarbonyl)methyl-2,3,3-trimethyl-3*H*-indolium salts by reaction with hydroxylamine in the presence of a strong base. The alkylation and reduction with sodium borohydride of these novel heterocycles have been investigated. When treated with protic acids 1-hydroxy- or 1-alkoxy-9,9a-dihydro-1*H*-imidazo[1,2-*a*]indol-2(3*H*)-ones underwent ring opening of the imidazolidine to afford 1-[2-(hydroxyamino)-2-oxoethyl]-2,3,3-trimethyl-3*H*-indolium salts. The structural assignments are based on extensive ¹H, ¹³C and ¹⁵N NMR spectroscopic studies and single crystal X-ray analyses.

1. Introduction

1-Substituted 3*H*-indolium salts are important synthetic precursors in the preparation of functionalized organic dyes with wide technical and biomedical applications.¹ Quaternisation of 2,3,3-trimethyl-3*H*-indole with 2-haloacetamides affords reactive 1-carbamoylmethyl-2,3,3-trimethyl-3*H*-indolium salts,² possessing several reactive centres, which allow them to participate in various chemical transformations. The reaction of the latter with squaric acid afforded squaraine dyes, which have been investigated as non-covalent protein probes with high fluorescence quantum yield and good photostability.³ When condensed with salicylic aldehydes, they underwent spirocyclization due to intramolecular addition of the phenolic oxygen atom across the carbon atom at the 2-position of the indole to give photochromic and thermochromic 1-carbamoylmethylindoline[2,2']spirobenzopyrans.⁴ It is known also that 1-carbamoylmethyl-2,3,3-trimethyl-3*H*-indolium chloride upon treatment with base undergoes cyclization to 9,9a-dihydro-1*H*-imidazo[1,2-*a*]indol-2(3*H*)-ones by nucleophilic addition of the amide nitrogen atom across the carbon atom at the 2-position of the indole.² Furthermore, 9a-styryl-9,9a-dihydro-1*H*-imidazo[1,2-*a*]indol-2(3*H*)-one derivatives were designed as color formers for pressure- and heat-sensitive recording materials.⁵ Finally, reaction of 1-carbamoylmethyl-3*H*-indolium chloride with hydrazine bishydrate selectively afforded 1-amino-9,9a-dihydro-1*H*-imidazo[1,2-*a*]indol-2(3*H*)-ones, possessing a cyclic hydrazide moiety, which was easily transformed to various heterocyclic structures.⁶

In an effort to expand the chemical space of ring fused indoline derivatives bearing an annelated heterocycle at the N-1 – C-2 bond of the indole nucleus, the objective of this work

was to investigate the reaction of 1-carbamoylmethyl-2,3,3-trimethyl-3*H*-indolium salts with hydroxylamine, and the structure of the indolyl hydroxamic acid derivatives obtained. The targeted heterocyclic compounds contain a 1-hydroxy-9,9a-dihydro-1*H*-imidazo[1,2-*a*]indol-2(3*H*)-one core (Figure 1), which is, to the best of our knowledge, unreported in the literature. This new azaheterocyclic scaffold is however interesting in view of its similarity with the isomeric 1-hydroxy-9,9a-dihydro-1*H*-imidazo[1,2-*a*]indol-3(2*H*)-one core which is present in the natural hydroxylamine alkaloids tryptoquivaline, possessing tremorgenic activity, and asperlicin B, which is a competitive cholecystinin (CCK) antagonist (Figure 1).⁷ Hydroxamic acids are versatile analytical reagents for the analysis and separation of metals⁸ and possess also wide biomedical applications.⁹ More specifically, 5-bromo-1*H*-indole-3-acetohydroxamic acid was recently identified as a potent inhibitor of bacterial deformylases (Figure 1),¹⁰ while 1*H*-indole-1-acetohydroxamic acid derivatives were used for the preparation of electroconductive polymer films.¹¹ *O*-Alkylated hydroxamic acids are active inhibitors of lypogenase-mediated processes,¹² while cyclic hydroxamic acids exhibit metal chelating abilities and various biological activities.¹³

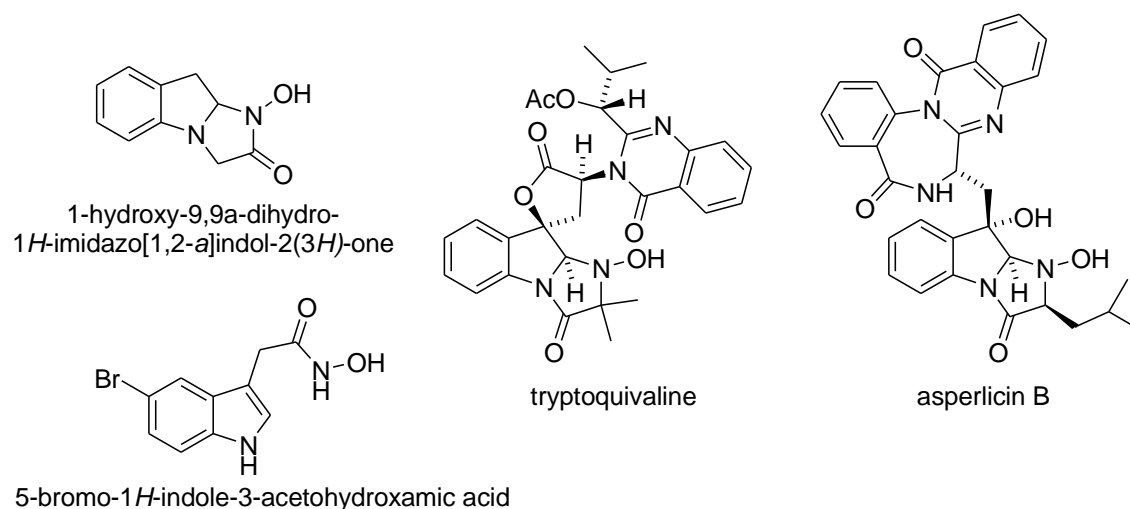
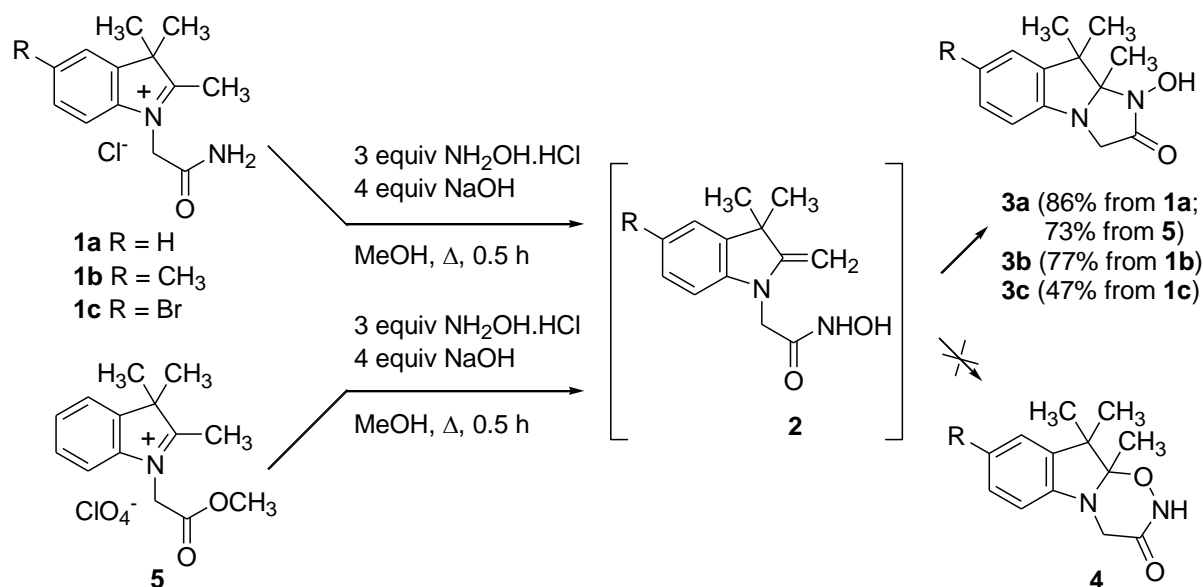


Figure 1

2. Results and discussion

It is known that a hydroxamic acid moiety can be easily introduced by treatment of amides with hydroxylamine at neutral or at alkaline pH,¹⁴ while the corresponding reaction with esters requires alkaline conditions (pH > 10).¹⁵ When 1-carbamoylmethyl-2,3,3-trimethyl-3*H*-indolium chlorides **1** were heated with hydroxylamine hydrochloride in the presence of

sodium hydroxide, selective formation of the 1-hydroxy-9,9,9a-trimethyl-9,9a-dihydro-1*H*-imidazo[1,2-*a*]indol-2(3*H*)-ones **3** took place without any observation of the corresponding six-membered compounds **4**. Similarly, 1-(methoxycarbonyl)methyl-3*H*-indolium perchlorate **5**, prepared by treatment of 2,3,3-trimethyl-3*H*-indole with methyl 2-bromoacetate,¹⁶ efficiently reacted with hydroxylamine under basic conditions to afford the five-membered compound **3a** (Scheme 1).



Scheme 1

The formation of derivatives **3** likely proceeds through a mechanism that includes formation of the enamine intermediate **2** that undergoes cyclization to the tricyclic compound by intramolecular addition of the hydroxamic nitrogen across the electrophilic indole C-2 atom. Formation of cyclic hydroxamic acid derivatives by addition of the hydroxamic nitrogen across a triple bond has been reported earlier by Elguero et al.¹⁷

The structure of azaheterocyclic hydroxamic acids **3a-c** was determined by microanalyses and spectral data. The IR spectrum of **3a** showed absorption bands at 3110 and 1702 cm^{-1} attributable to O-H and C=O groups, respectively. The ^{15}N NMR spectrum of **3a** showed two different N-atoms with chemical shifts at -193.0 (N-1) and -298.6 (N-4) ppm. In ^{15}N DEPT experiments without ^1H -decoupling, the resonance signal (-193.0 ppm) of the N-1 atom of **3a** appeared as a singlet, thus indicating the absence of an NH moiety. This definitely ruled out the corresponding six-membered structure **4**, for which signals of a NH substructure and tertiary nitrogen atom would be expected. The assignments presented in Figure 2 were based on the combined application of standard NMR techniques such as NOE-difference (Figure 2b),

NOESY, APT, DEPT, HSQC, HMBC and long-range INEPT spectra with selective excitation.¹⁸

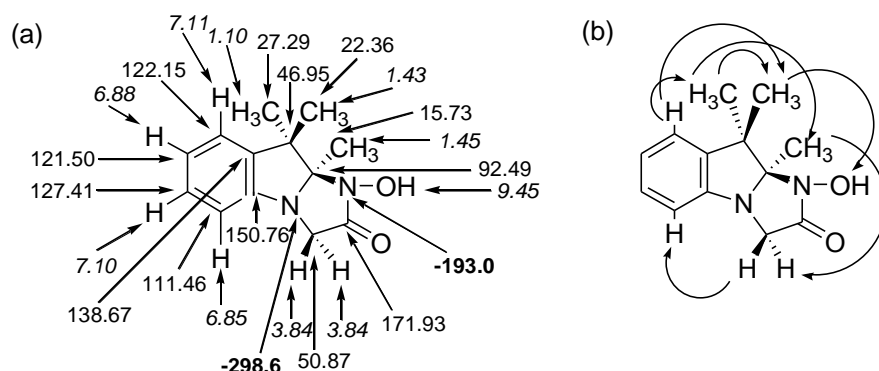


Figure 2. (a) ¹H NMR (italics), ¹³C NMR (plain) and ¹⁵N NMR (bold) chemical shifts [ppm; ref. TMS (¹H and ¹³C) and CH₃NO₂ (¹⁵N)] for **3a** in DMSO-*d*₆. (b) Relevant NOE correlations.

The single crystal X-ray structure of **3a** (Figure 3)¹⁹ shows that the skeleton of the asymmetric unit contains the imidazo[1,2-*a*]indole ring system, with the external hydroxy group attached to the atom N(1). The bond lengths, bond angles and dihedral angles are typical for the azaheterocyclic hydroxamic acid core and related to 1-hydroxy-1,3-imidazolidin-4-one.²⁰⁻²²

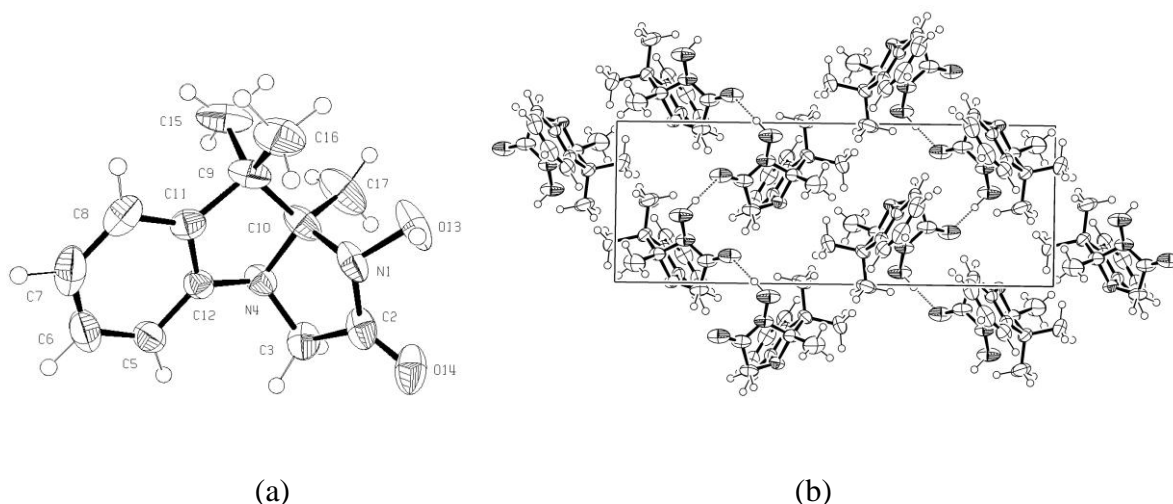


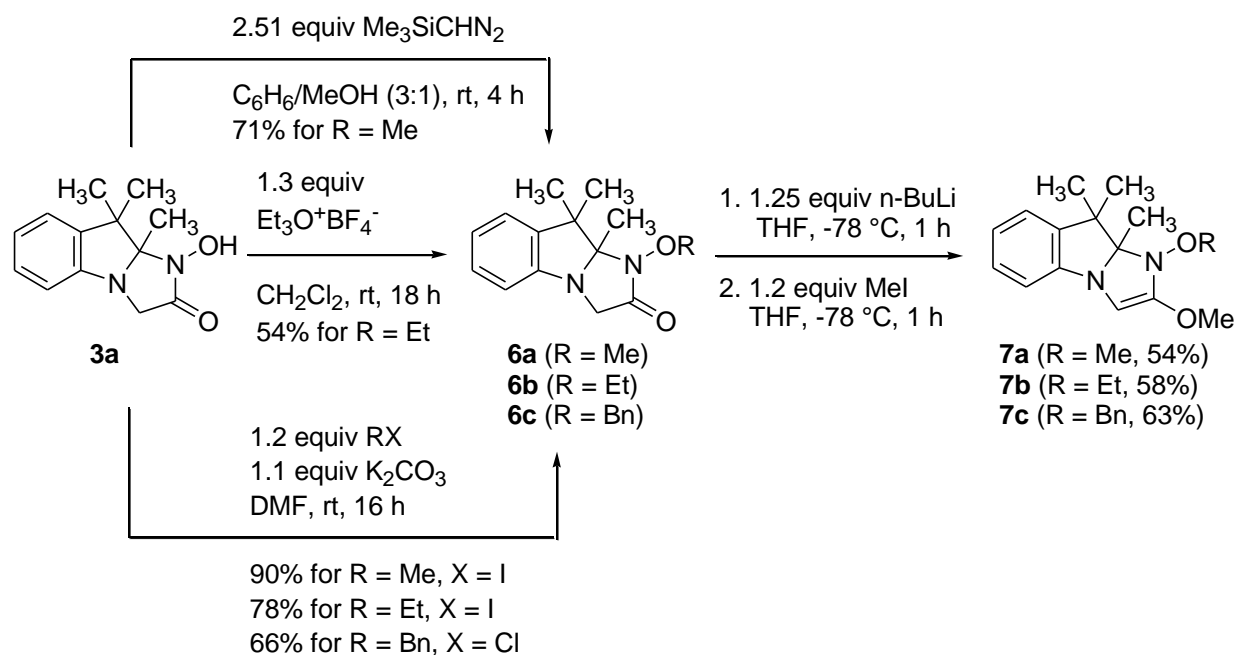
Figure 3. (a) ORTEP drawing of 1-hydroxyimidazo[1,2-*a*]indol-2(3*H*)-one **3a**. (b) Fragment of the heterochiral layer of the racemic crystals of **3a**.

The packaging of the chiral molecules **3a** into a racemic crystal occurs in such a way that mirror *R*- and *S*-enantiomers are self-assembled into alternate chiral chains of opposite chirality, which are connected by strong intermolecular O-H...O=C type hydrogen bonds (Figure 3b).

Hydroxamic acids are ambident nucleophiles. However, deprotonation of the OH group usually results in *O*-alkylation products. Leggio *et al.* used diazomethane as selective *O*-alkylation agent of aliphatic hydroxamic acids.²³ In that case diazomethane reacted as a base to deprotonate the hydroxamic acid, resulting in a methyldiazonium ion which selectively methylated the generated hydroxamate anions.²⁴ The alkylation of hydroxamic acid **3a** with trimethylsilyldiazomethane – a mild and efficient reagent used for the *O*-methylation of carboxylic acids and alcohols as a safer alternative for highly toxic and explosive diazomethane – was investigated.²⁵

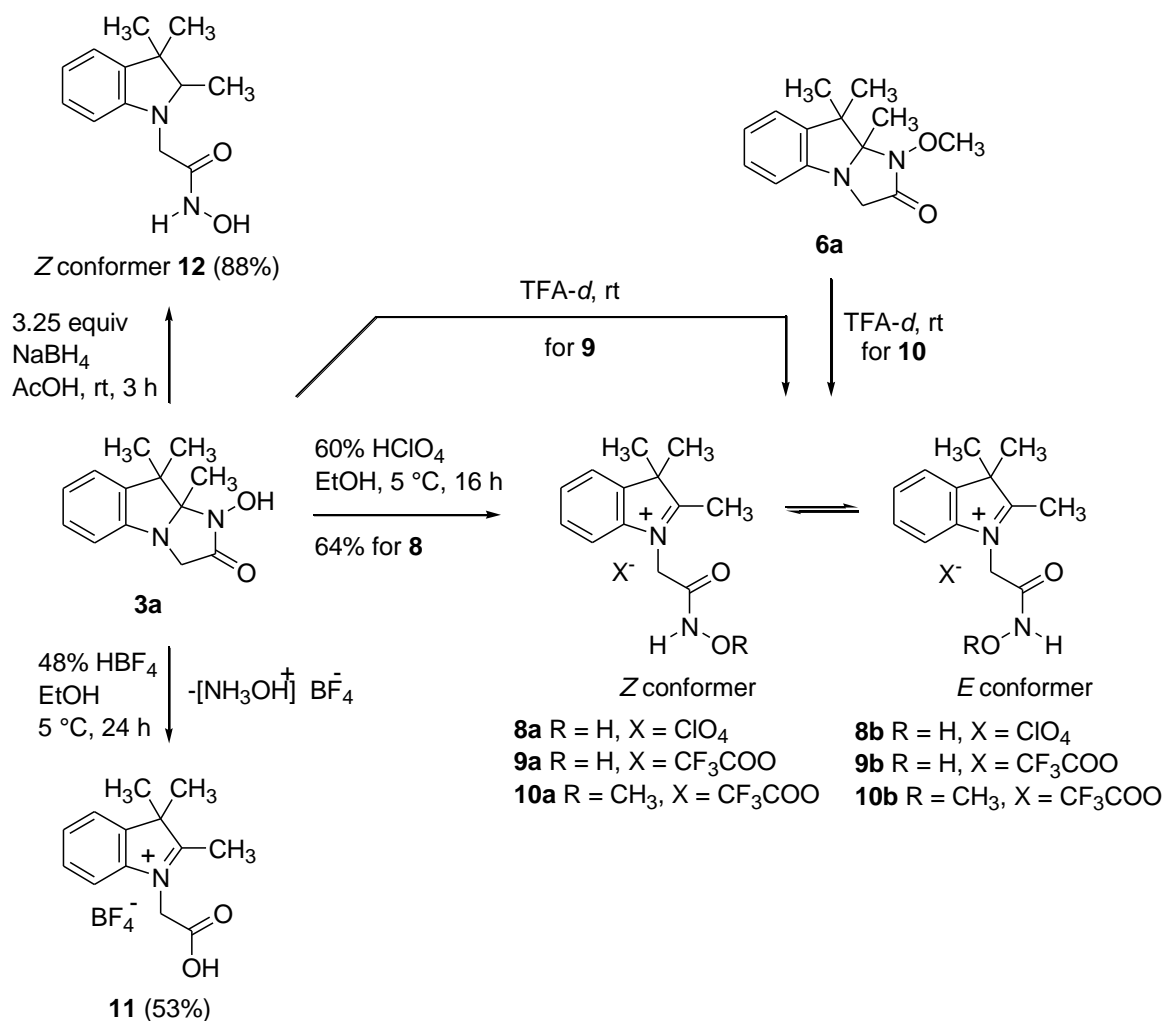
Treatment of hydroxamic acid **3a** with trimethylsilyldiazomethane in a mixture of benzene and methanol (3:1) at room temperature afforded 1-methoxy-1*H*-imidazo[1,2-*a*]indol-2(3*H*)-one **6a** in 71% yield after column chromatography (Scheme 2). *O*-Ethylation of compound **3a** was easily achieved by reaction of hydroxamic acid **3a** with triethyloxonium tetrafluoroborate, a reagent used for the selective alkylation of *O*-alkylarylhydroxamic acids,²⁶ and gave compound **6b** in 54% yield. Further experiments showed that the hydroxy functionality of **3a** can be smoothly *O*-alkylated with methyl and ethyl iodide in the presence of potassium carbonate, providing the desired products **6a,b** in 90% and 78% yield, respectively. The reaction with benzyl chloride resulted similarly in benzyl ether **6c** in 66% yield (Scheme 2).

The deprotonation of *N*-substituted lactams with a strong lithium base in THF, followed by reaction of the formed enolates with haloalkanes is known to lead to α -*C*-alkylated lactams.²⁷ However, treatment of compounds **6** possessing the *N*-(alkyloxy)lactam moiety, with *n*-BuLi in THF followed by addition of iodomethane afforded exclusively the *O*-methylated products **7**. The structure of the latter was confirmed by the presence of a singlet of H-3 in the range of 4.98-5.16 ppm in the ¹H NMR spectra and a signal of C-3 at ~89.0 ppm in the ¹³C NMR spectra (CDCl₃).



Scheme 2

Under the influence of strong protic acids 9,9a-dihydro-1*H*-imidazo[1,2-*a*]indol-2(3*H*)-ones undergo imidazolidine ring opening and are converted to 1-carbamoylmethyl-3*H*-indolium salts.² When the ethanolic solution of 1-hydroxy-9,9a-dihydro-1*H*-imidazo[1,2-*a*]indol-2(3*H*)-one **3a** was treated with perchloric acid in ethanol at 5 °C for 16 h, formation of 1-[2-(hydroxyamino)-2-oxoethyl]-2,3,3-trimethyl-3*H*-indolium perchlorate (**8a**) took place (Scheme 3). X-ray diffraction analysis of the crystal structure of **8a** revealed the presence of the tautomeric keto form and *Z*-configuration of the hydroxamic acid moiety (Figure 4).²⁸ Nevertheless, the ¹H and ¹³C NMR spectra of perchlorate **8a** at room temperature (20 °C) in TFA-*d* exhibited two sets of resonance signals. The appearance of signals at 203.39 and 203.43 ppm in the ¹³C NMR spectrum, was indicative of a $\text{N}^+=\text{C}$ carbon. The ¹H NMR spectrum of **8a** contained signals at 1.69 (non-resolved signals of 3,3- CH_3), 2.86 and 2.90 (minor and major peaks of 2- CH_3 , respectively), 5.49 and 5.78 ppm (major and minor peaks of CH_2 , respectively), with a 7:3 ratio of the major and minor isomers. The analogous ¹H and ¹³C NMR spectra obtained from the solution of 1-hydroxy-9,9a-dihydro-1*H*-imidazo[1,2-*a*]indol-2(3*H*)-one **3a** in TFA-*d* demonstrated the cleavage of the imidazolidine ring with formation of the corresponding 3*H*-indolium cations.



Scheme 3

Theoretically, hydroxamic acids can exist in solution as an equilibrium mixture of the two tautomers: RC(=O)NHOH (I) \rightleftharpoons RC(OH)=NOH (II), where (I) is the hydroxamide (or hydroxamic acid) form, and (II) the hydroxyimine form.²⁹ As such, structural complications of hydroxamic acids can occur due to different conformations of the C-N bond of the hydroxamic tautomer and, as well, different configurations of the C=N bond of the hydroxyimic form. Nevertheless, recent NMR structural investigations of hydroxamic acids (for example of ¹⁵N-enriched dihydroxamic acids in solutions of DMSO) showed that hydroxyimic forms of the acids are not present in a detectable amount.³⁰ It was established by Brown *et al.* that acetoxhydroxamic acids are present in DMSO solutions as an equilibrium mixture of *Z* and *E* conformers with the *Z*-conformer prevailing.³¹ In the solid state, acetohydroxamic acid hemihydrate exists as the *Z*-isomer only.³² Most secondary hydroxamic acids, except *N*-aryl derivatives, in turn, exist as *E* conformers.³³ Therefore, the presence of

two sets of signals in the NMR spectra of perchlorate **8** in TFA-*d* can be rationalized by the formation of an equilibrium mixture of isomeric salts **8a** and **8b** possessing a different geometry (*Z* or *E*) of the hydroxamic acid moiety (Scheme 3). Neutralization of the perchlorate **8** with a solution of sodium carbonate gave the starting tricyclic compound **3a** only.

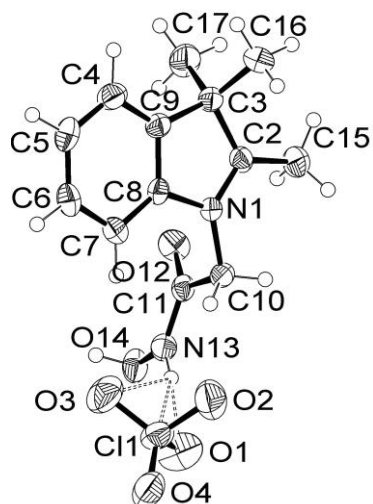


Figure 4. Crystal structure of perchlorate **8a** showing the most significant intermolecular interactions

Analogously, the ^1H and ^{13}C NMR spectra of 1-methoxy-9,9a-dihydro-1*H*-imidazo[1,2-*a*]indol-2(3*H*)-one **6a** in TFA-*d* at room temperature (20 °C) exhibited two sets of peaks, which can be attributed to the *Z*- and *E*-cations **10a** and **10b**. The ^1H NMR spectrum contained the singlets of the 2- CH_3 group at 3.89 ppm (major isomer) and 4.06 ppm (minor isomer), and the singlets of the CH_2CO group at 5.40 ppm (major isomer) and 5.65 ppm (minor isomer), with a 5:2 ratio of the major/minor isomer. The corresponding ^{13}C NMR spectrum showed the characteristic carbon signal of the $^+\text{N}=\text{C}$ moiety at 201.4 ppm.

It is known that hydroxamic acids are more stable in basic medium than in acidic medium. The products resulting from their acidic hydrolysis usually are hydroxylamine and the parent carboxylic acid.³⁴ Prolonged storage of the solution of 1-hydroxy-9,9a-dihydro-1*H*-imidazo[1,2-*a*]indol-2(3*H*)-one **3** in ethanol, containing water and HBF_4 , at 5 °C, afforded crystalline 1-carboxymethyl-3*H*-indolium tetrafluoroborate monohydrate **11** (Scheme 3). In contrast to the 1-[2-(hydroxyamino)-2-oxoethyl]-2,3,3-trimethyl-3*H*-indolium perchlorate (**8a**), the NMR spectra of tetrafluoroborate **11** in TFA-*d* contains only one set of signals. In

the ^{13}C NMR spectrum, the characteristic carbon signal of the $^+\text{N}=\text{C}$ moiety is present at 203.3 ppm.

The single crystal X-ray analysis of tetrafluoroborate **11** discloses that a molecule of crystallization water is present in the crystal lattice which bridges the oxygen of the carboxyl group and the BF_4^- anion via hydrogen bonding (Figure 5a). The crystal structure is assembled from hydrogen-bonded dimers (Figure 5b).³⁵

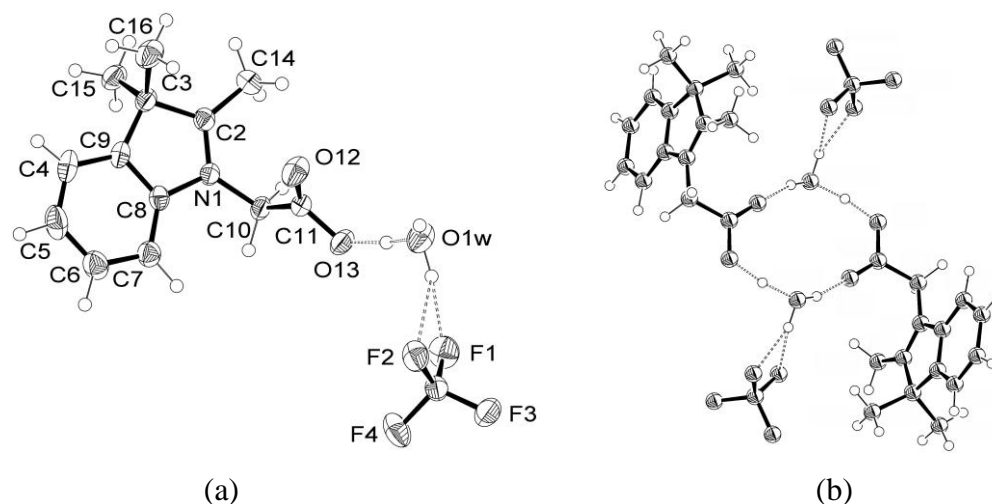
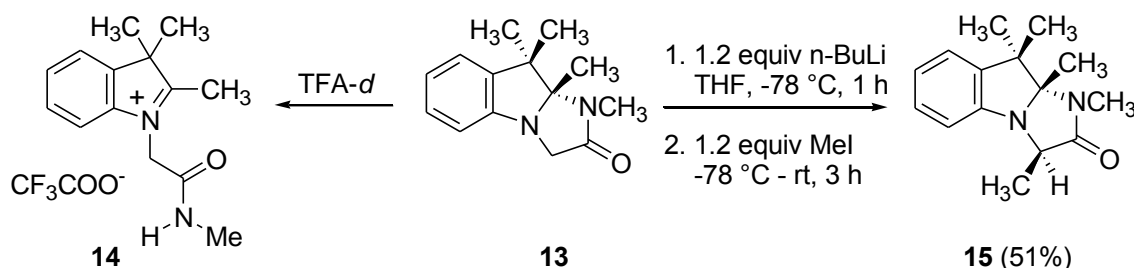


Figure 5. (a) Crystal structure of tetrafluoroborate monohydrate **11** showing the most significant intermolecular interactions. (b) Hydrogen-bonded dimer of **11**

It has been reported recently that 1-amino-9,9a-dihydro-1*H*-imidazo[1,2-*a*]indol-2(3*H*)-ones smoothly underwent reductive ring opening upon treatment with NaBH_4 in ethanol to give 1-substituted 2,3-dihydro-1*H*-indole derivatives.⁶ When 1-hydroxy-9,9a-dihydro-1*H*-imidazo[1,2-*a*]indol-2(3*H*)-one **3a** was reacted under similar reducing conditions, the expected reaction did not occur and most of the starting material was recovered unchanged. However, transformation of cyclic hydroxamic acid **3a** to the reduced compound **12** was easily achieved by treatment with NaBH_4 in glacial acetic acid as solvent instead of ethanol (Scheme 3). It can be assumed that in the first step of this reductive ring opening, acetic acid promotes cleavage of the annelated lactam moiety leading to the formation of the corresponding 1-[2-(hydroxyamino)-2-oxoethyl]-3*H*-indolium acetate. Subsequently, *in situ* generated acetoxyborohydride^{36,37} smoothly reduces the iminium group to afford indoline **12**. The structure of 1-[2-(hydroxyamino)-2-oxoethyl]-2,3,3-trimethylindoline **12** was confirmed by the presence of characteristic signals of the CHCH_3 moiety, consisting of a doublet at 1.26 ppm and a quadruplet at 3.15 ppm, in the ^1H NMR spectrum (CDCl_3). The ^1H NMR spectrum

exhibited only one set of signals attributed to the more stable *Z*-isomer form in accordance with literature data.³²⁻³⁴

After having explored the reactivity of 1-hydroxy-9,9a-dihydro-1*H*-imidazo[1,2-*a*]indol-2(3*H*)-ones, it was decided also to explore the chemistry of the corresponding known *N*-methylated compound **13** in more detail.^{4d} It is interesting to note that the ¹H NMR spectrum of the cyclic lactam **13** in TFA-*d*, possessing the methyl group at the nitrogen atom N-1 exhibited, as it was expected, only one set of signals, including the characteristic singlets at 1.44 [3,3-(CH₃)₂], 2.61 (N²HCH₃), 2.76 (2-CH₃) and 5.14 ppm (CH₂) corresponding with the formation of the ring opened cation **Z-14** (Scheme 4). It is known that *N*-substituted amides exist in solution generally as the *Z*-conformers, and only in the case of *N*-methylacetamide the *E*-conformer was found experimentally to occur in a low population of 1.5% besides the prevailing *Z*-conformer.³⁸



Scheme 4

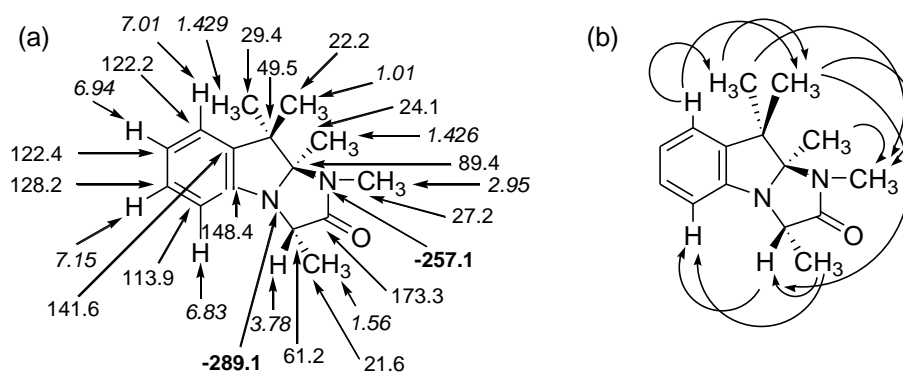


Figure 6. (a) ¹H NMR (italics), ¹³C NMR (plain) and ¹⁵N NMR (bold) chemical shifts [ppm; ref. TMS (¹H and ¹³C) and CH₃NO₂ (¹⁵N)] for **15** in CDCl₃. (b) Relevant NOE correlations

The methylation of lactam **13** *via* formation of the corresponding lithium enolate was next evaluated. It was found that the deprotonation of **13** with *n*-BuLi at -78 °C in THF, and subsequent alkylation by treatment with iodomethane proceeded diastereoselectively to afford C-3-methylated lactam **15**. The structure and stereochemistry of lactam **15** was confirmed by methods of NMR spectroscopy (Figure 6a, b). The assignments presented in Figures 6a,b were based on the combined application of standard NMR techniques such as NOE-difference, NOESY, APT, DEPT, HSQC, HMBC and long-range INEPT spectra with selective excitation.¹⁸ The ¹H NMR spectrum of substituted lactam **15** contained a doublet at 1.56 ppm ($J = 6.9$ Hz) and a quadruplet at 3.78 ppm characteristic for the CH₃CH moiety. The NOE experiments (NOESY, NOE-difference) of compound **15** revealed a through-space interaction between H-3 (3.78 ppm) and the 9-CH₃ group resonating at 1.01 ppm, but no interaction between H-3 and 9a-CH₃ (1.426 ppm). On the other hand, both geminal CH₃ groups at C-9 were easily identified on the basis of NOE's with aromatic ring proton H-8 and via HMBC (correlation to C-8a). These observations indicate that compound **15** corresponds to the structure possessing the (3*R**,9a*S**)-relative configuration. Molecular modelling³⁹ confirmed that in the latter case H-3 and the 9-CH₃ group occupy a spatial orientation for which the observed NOE effects are expected, while (3*R**,9a*R**)-relative configuration would lead to interaction of H-3 with the 9a-CH₃.

3. Conclusion

1-Carbamoylmethyl- and 1-(methoxycarbonyl)methyl-3*H*-indolium salts **1** and **5**, respectively, are regioselectively cyclized into five-membered ring compounds, as new azaheterocyclic hydroxamic acids, that is, 1-hydroxy-9,9a-dihydro-1*H*-imidazo[1,2-*a*]indol-2(3*H*)-ones **3**. Alkylation of 1-hydroxy-9,9a-dihydro-1*H*-imidazo[1,2-*a*]indol-2(3*H*)-ones with trimethylsilyldiazomethane, triethyloxonium tetrafluoroborate or haloalkanes in the presence of base gave exclusively *O*-substituted products **6a-c**. The action of strong protic acids on 1-hydroxy-9,9a-dihydro-1*H*-imidazo[1,2-*a*]indol-2(3*H*)-ones causes opening of the imidazolidine ring, annelated to indole system, to afford 1-[2-(hydroxyamino)-2-oxoethyl]-3*H*-indolium salts **10**, **11**, while treatment with sodium borohydride in acetic acid led to reductive ring opening with formation of *N*-hydroxy-2-(2,3,3-trimethyl-2,3-dihydro-1*H*-indol-1-yl)acetamide **12**.

4. Experimental

4.1. General

The melting points were determined in open capillary tubes on a Büchi B-540 melting point apparatus and are uncorrected. Infrared spectra were recorded with a Perkin Elmer Spectrum One spectrometer using potassium bromide pellets. ¹H NMR spectra were recorded at 300 MHz on a Varian Unity Inova spectrometer and at 500 MHz on a Bruker Avance 500 spectrometer; ¹³C NMR spectra were registered at 75 and 125 MHz, respectively. Chemical shifts, expressed in ppm, were relative to tetramethylsilane (TMS). ¹⁵N NMR spectra (50.69 MHz) were obtained on a Bruker Avance 500 spectrometer using a ‘directly’ detecting broadband observe probe and were referenced against neat, external nitromethane (coaxial capillary). Mass spectra were measured using a Waters ZQ instrument (ion spray). Diffraction data were collected on a Bruker-Nonius KappaCCD diffractometer at room temperature and also at –100 °C. The crystal structures were solved using known programs.⁴⁰ Elemental analyses were conducted using a Elemental Analyzer CE-440 (Exeter Analytical, Inc.) by the Microanalytical Laboratory, Department of Organic Chemistry, Kaunas University of Technology. For thin layer chromatographic (TLC) analyses, Merck precoated TLC plates (silica gel 60 F254) were used. Dry THF was distilled from sodium and benzophenone.

4.2. Procedures for preparation of 1-hydroxy-9,9,9a-trimethyl-9,9a-dihydro-1H-imidazo[1,2-a]indol-2(3H)-ones (3)

4.2.1. 1-Hydroxy-9,9,9a-trimethyl-9,9a-dihydro-1H-imidazo[1,2-a]indol-2(3H)-one (3a)

Method A: To a solution of chloride **1a** (3.79 g, 15 mmol) in dry methanol (20 mL) hydroxylamine hydrochloride (3.13 g, 45 mmol) and powdered sodium hydroxide (2.40 g, 60 mmol) were added and the mixture was refluxed for 0.5 h. The insolubles formed were removed by filtration and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel with hexane/EtOAc (2:1 v/v) as eluent to give **3a** (2.98 g, 86%) as colourless crystals. Mp 168-169 °C (from EtOH). ¹H NMR (500 MHz, DMSO-*d*₆): δ 1.10 (s, 3H, 9-CH₃), 1.43 (s, 3H, 9-CH₃), 1.45 (s, 3H, 9a-CH₃), 3.84 (s, 2H, CH₂), 6.83-6.94 (m, 2H, 5-H, 7-H), 7.07-7.13 (m, 2H, 6-H, 8-H), 9.45 (s, 1H, OH). ¹³C NMR (125 MHz, DMSO-*d*₆): δ 15.7 (9a-CH₃), 22.4 (9-CH₃), 27.3 (9-CH₃), 47.0 (C-9), 50.9

(C-3), 92.5 (C-9a), 111.5 (C-5), 121.5 (C-7), 122.1 (C-8), 127.4 (C-6), 138.7 (C-8a), 150.8 (C-4a), 171.9 (C=O). ¹⁵N NMR (50.69 MHz, DMSO-*d*₆): δ -193.0 (N-1), -298.6 (N-4). IR (KBr, cm⁻¹): ν_{OH} = 3110, ν_{C=O} = 1702. MS (ES+) *m/z* (%): 233 (M + H⁺, 100). Anal. Calcd. for C₁₃H₁₆N₂O₂: C, 67.22; H, 6.94; N, 12.06. Found: C, 66.95; H, 6.68; N, 12.33.

Method B: A mixture of 2,3,3-trimethyl-3*H*-indole (2.39 g, 15 mmol), methyl 2-bromoacetate (2.29 g, 15 mmol) and *o*-xylene (5 mL) was heated at 70 °C for 5 h and then left to reach ambient temperature. The solvent was decanted, the residue was dissolved in ethanol (8 mL), perchloric acid (70%) was added to pH 1 and the mixture was kept at 5 °C for 16 h. Crystals formed were filtered and recrystallized from ethanol to yield perchlorate **5** (2.24 g, 45%), mp 172-174 °C (with decomposition). The obtained perchlorate **5** (1.66 g, 5 mmol) was dissolved in dry methanol (8 mL), hydroxylamine hydrochloride (1.04 g, 15 mmol) and powdered sodium hydroxide (0.8 g, 20 mmol) were added and the mixture was refluxed for 0.5 h. The insolubles formed were removed by filtration and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel with hexane/EtOAc (2:1 v/v) as eluent to give **3a** (0.85 g, 73%). Mp and NMR spectroscopy data of the title product **3a** were identical with those obtained by *Method A*.

4.2.2. 1-Hydroxy-7,9,9,9a-tetramethyl-9,9a-dihydro-1*H*-imidazo[1,2-*a*]indol-2(3*H*)-one (**3b**)

Similar treatment (*Method A*) of chloride **1b** (1.33 g, 5 mmol) with hydroxylamine hydrochloride (1.04 g, 15 mmol) in the presence sodium hydroxide (0.8 g, 20 mmol) gave the title compound **3b** (0.95 g, 77%) as colourless crystals, mp 161-162 °C (from EtOH). ¹H NMR (300 MHz, DMSO-*d*₆): δ 1.08 (s, 3H, 9-CH₃), 1.40 (s, 3H, 9-CH₃), 1.42 (s, 3H, 9a-CH₃), 2.22 (s, 3H, 7-CH₃), 3.79 (s, 2H, CH₂), 6.73 (d, *J*=7.8 Hz, 1H, 5-H), 6.89-6.92 (m, 2H, 6-H, 8-H), 9.44 (s, 1H, OH). ¹³C NMR (75 MHz, DMSO-*d*₆): δ 15.9 (9a-CH₃), 20.6 (9-CH₃), 22.2 (7-CH₃), 27.3 (9-CH₃), 46.9 (C-9), 50.9 (C-3), 92.7 (C-9a), 111.2, 122.7, 127.7, 130.3, 138.7, 148.5, 172.0 (C=O). IR (KBr, cm⁻¹): ν_{OH} = 3111, ν_{C=O} = 1702. MS (ES+) *m/z* (%): 247 (M + H⁺, 20), 269 (M + Na⁺, 100). Anal. Calcd. for C₁₄H₁₈N₂O₂: C, 68.27; H, 7.37; N, 11.37. Found: C, 68.47; H, 7.53; N, 11.35.

4.2.3. 7-Bromo-1-hydroxy-9,9,9a-trimethyl-9,9a-dihydro-1*H*-imidazo[1,2-*a*]indol-2(3*H*)-one (**3c**)

Similar treatment (*Method A*) of chloride **1c** (1.66 g, 5 mmol) with hydroxylamine hydrochloride (1.04 g, 15 mmol) in the presence sodium hydroxide (0.8 g, 20 mmol) gave the

title compound **3c** (0.73 g, 47%) as colourless crystals, mp 186-187 °C (from EtOH). ¹H NMR (300 MHz, DMSO-*d*₆): δ 1.11 (s, 3H, 9-CH₃), 1.41 (s, 3H, 9-CH₃), 1.42 (s, 3H, 9a-CH₃), 3.85 (s, 2H, CH₂), 6.85 (d, *J*=8.1 Hz, 1H, 5-H), 7.26 (dd, *J*=8.1 Hz, *J*=2.1 Hz, 1H, 6-H), 7.32 (d, *J*=2.1 Hz, 8-H), 9.44 (s, 1H, OH). ¹³C NMR (75 MHz, DMSO-*d*₆): δ 15.8 (9a-CH₃), 22.0 (9-CH₃), 27.0 (9-CH₃), 47.2 (C-9), 50.8 (C-3), 92.7 (C-9a), 111.8, 113.5, 125.2, 130.0, 141.5, 150.1, 171.9 (C=O). IR (KBr, cm⁻¹): ν_{OH} = 3138, ν_{C=O} = 1704. MS (ES⁺) *m/z* (%): 313/315 (M + H⁺, 100). Anal. Calcd. for C₁₃H₁₅BrN₂O₂: C, 50.18; H, 4.86; N, 9.00. Found: C, 50.46; H, 4.97; N, 9.02.

4.3. Procedures for preparation of 1-alkoxy-9,9,9a-trimethyl-9,9a-dihydro-1*H*-imidazo[1,2-*a*]indol-2(3*H*)-ones (6)

4.3.1. 1-Methoxy-9,9,9a-trimethyl-9,9a-dihydro-1*H*-imidazo[1,2-*a*]indol-2(3*H*)-one (**6a**)

Method A: To a solution of compound **3a** (100 mg, 0.43 mmol) in 4 mL of benzene/methanol (3:1 v/v) 2.0 M solution of trimethylsilyldiazomethane in Et₂O (0.54 mL, 1.08 mmol) was added dropwise and the reaction mixture was stirred for 4 h at room temperature. Then the solvent was evaporated under reduced pressure, the residue dissolved in Et₂O (4 mL) and the solution was washed with water (5 mL). The organic layer was separated and the aqueous layer was extracted with another 5 mL of Et₂O. The combined organic layers were dried over MgSO₄ and filtered. The solvent was evaporated under reduced pressure and the product was isolated by flash chromatography on a silica gel column using hexane/EtOAc (3:1 v/v) as eluent to give the title compound **6a** (75 mg, 71%) as colorless crystals, mp 89-90 °C (from EtOH). ¹H NMR (300 MHz, CDCl₃): δ 1.21 (s, 3H, CH₃), 1.50 (s, 3H, CH₃), 1.53 (s, 3H, CH₃), 3.81 (AB-d, *J*=17.0 Hz, 1H, 3-H_A), 3.83 (AB-d, *J*=17.0 Hz, 1H, 3-H_B), 3.84 (s, 3H, CH₃O), 6.71-7.20 (m, 4H, Ar-H). ¹³C NMR (75 MHz, CDCl₃): δ 17.0 (CH₃), 22.6 (CH₃), 27.4 (CH₃), 47.0 (C-9), 51.3 (C-3), 62.4 (OCH₃), 93.8 (C-9a), 111.3, 122.1, 122.3, 127.8, 138.6, 150.2 (Ar-C), 175.2 (C=O). IR (KBr, cm⁻¹): ν_{C=O} = 1748. MS (ES⁺) *m/z* (%): 247 (M+H⁺, 100), 269 (M+Na⁺, 60). Anal. Calcd. for C₁₄H₁₈N₂O₂: C, 68.27; H, 7.37; N, 11.37. Found: C, 67.89; H, 7.26; N, 11.13.

Method B: To a solution of compound **3a** (465 mg, 2 mmol) in DMF (5 mL), K₂CO₃ (304 mg, 2.2 mmol) was added and the mixture was stirred for 15 min. Then methyl iodide (0.15 mL, 0.34 g, 2.4 mmol) was added to the mixture and stirring was continued for 16 h. The reaction mixture was poured into water (15 mL), extracted with EtOAc (3×15 mL), the combined organic layers were dried over Na₂SO₄ and filtered. The solvent was evaporated under

reduced pressure and the product was isolated by chromatography on a silica gel column using hexane/EtOAc as eluent (3:1 v/v) to give the compound **6a** (0.44 g, 90%). Mp and NMR spectroscopy data of the title product **6a** were identical with those obtained by *Method A*.

4.3.2. 1-Ethoxy-9,9,9a-trimethyl-9,9a-dihydro-1H-imidazo[1,2-a]indol-2(3H)-one (**6b**)

Method A: To a solution of compound **3a** (100 mg, 0.43 mmol) in dichloromethane (3 mL), triethyloxonium tetrafluoroborate (106 mg, 0.56 mmol) was added and the reaction mixture was stirred for 18 h at room temperature. Then the mixture was washed with water (5 mL), dried over MgSO₄ and filtered. The solvent was evaporated under reduced pressure and the product was isolated by chromatography on a silica gel column using hexane/EtOAc (4:1 v/v) as eluent to give the title compound **6b** as colorless oil (60 mg, 54%). ¹H NMR (300 MHz, CDCl₃): δ 1.21 (s, 3H, CH₃), 1.24 (t, *J*=7.2 Hz, 3H, CH₂CH₃), 1.49 (s, 3H, CH₃), 1.55 (s, 3H, CH₃), 3.80 (AB-d, *J*=16.8 Hz, 1H, 3-H_A), 3.83 (AB-d, *J*=16.8 Hz, 1H, 3-H_B), 3.83-3.91 (m, 1H, OCH₂), 4.33 (dq, *J*=8.4, *J*=7.2 Hz, 1H, OCH₂), 6.71-7.20 (m, 4H, Ar-H). ¹³C NMR (75 MHz, CDCl₃): δ 13.6 (CH₃), 17.2 (CH₃), 22.5 (CH₃), 27.4 (CH₃), 47.1 (C-9), 51.5 (C-3), 70.5 (OCH₂), 93.7 (C-9a), 111.4, 122.1, 122.2, 127.8, 138.8, 150.3 (Ar-C), 174.7 (C=O). IR (KBr, cm⁻¹): ν_{C=O} = 1739. MS (ES⁺) *m/z* (%): 261 (M+H⁺, 100), 283 (M+Na⁺, 60). Anal. Calcd. for C₁₅H₂₀N₂O₂: C, 69.20; H, 7.74; N, 10.76. Found: C, 68.89; H, 7.26; N, 10.36.

Method B: The procedure for the synthesis of **6a** (*Method B*) was followed using compound **3a** (465 mg, 2 mmol), K₂CO₃ (304 mg, 2.2 mmol) and ethyl iodide (0.192 mL, 374 mg, 2.4 mmol) at room temperature for 16 h to give **6b** (405 mg, 78%). NMR spectroscopy data of the title product **6b** were identical with those obtained by *Method A*.

4.3.3. 1-Benzoyloxy-9,9,9a-trimethyl-9,9a-dihydro-1H-imidazo[1,2-a]indol-2(3H)-one (**6c**)

The procedure for the synthesis of **6a** (*Method B*) was followed using compound **3a** (465 mg, 2 mmol), K₂CO₃ (304 mg, 2.2 mmol) and benzyl chloride (0.335 mL, 304 mg, 2.4 mmol) at room temperature for 16 h to give **6c** as colorless crystals (425 mg, 66%), mp 86-87 °C (from EtOH). ¹H NMR (300 MHz, CDCl₃): δ 1.23 (s, 3H, CH₃), 1.56 (s, 3H, CH₃), 1.60 (s, 3H, CH₃), 3.89 (s, 2H, NCH₂), 4.83 (d, *J*=9.0 Hz, 1H, OCH₂), 5.33 (d, *J*=9.0 Hz, d, 1H, OCH₂), 6.75-7.46 (m, 9H, Ar-H). ¹³C NMR (75 MHz, CDCl₃): δ 17.2 (CH₃), 23.1 (CH₃), 27.4 (CH₃), 47.2 (C-9), 51.4 (C-3), 76.2 (OCH₂), 94.0 (C-9a), 111.3, 122.1, 122.3, 127.8, 128.5 (2×C), 128.6, 129.1 (2×C), 134.9, 138.7, 150.3 (Ar-C), 175.2 (C=O). IR (KBr, cm⁻¹): ν_{C=O} = 1739.

MS (ES⁺) *m/z* (%): 323 (M+H⁺, 50), 345 (M+Na⁺, 100). Anal. Calcd for C₂₀H₂₂N₂O₂: C, 74.51; H, 6.88; N, 8.69. Found: C, 74.03; H, 7.13; N, 8.75.

4.4. General procedure for the preparation of 1-alkoxy-2-methoxy-9,9,9a-trimethyl-9,9a-dihydro-1*H*-imidazo[1,2-*a*]indoles (7)

n-BuLi (1.25 mL, 1.25 mmol, 2.5 M in cyclohexane) was added dropwise to a solution of appropriate 1-alkoxyimidazo[1,2-*a*]indole **6** (1 mmol) in dry THF (5 mL) under argon at -78 °C. After 1 h a solution of methyl iodide (170 mg, 1.2 mmol) in dry THF (2 mL) was added dropwise over 0.5 h. The mixture was stirred at -78 °C for 1 h and then left to reach ambient temperature. The reaction mixture was quenched with 15 mL of ammonium chloride solution (10%) and extracted with EtOAc (3×10 mL). The combined organic layers were washed with water (15 mL), dried over Na₂SO₄ and the solvent was evaporated under reduced pressure. The residue was chromatographed on a silica gel column with hexane/EtOAc (2:1 v/v) as eluent to yield compounds **7a-c**.

4.4.1. 1,2-Dimethoxy-9,9,9a-trimethyl-9,9a-dihydro-1*H*-imidazo[1,2-*a*]indole (**7a**)

Yield 54%. Oil. ¹H NMR (300 MHz, CDCl₃): δ 0.93 (s, 3H, CH₃), 1.47 (s, 3H, CH₃), 1.50 (s, 3H, CH₃), 2.98 (s, 3H, OCH₃), 3.47 (s, 3H, OCH₃), 4.98 (s, 1H, NCH), 6.92-7.20 (m, 4H, Ar-H). ¹³C NMR (75 MHz, CDCl₃): δ 21.7 (CH₃), 22.6 (CH₃), 27.2 (CH₃), 28.7 (CH₃), 49.1 (C-9), 52.5 (CH₃), 88.9 (C-3), 91.2 (C-9a), 113.9, 122.0, 123.0, 128.4, 141.5, 145.5, 167.9 (Ar-C, C-2). IR (KBr, cm⁻¹): ν_{C=C(OMe)} = 1715. MS (ES⁺) *m/z* (%): 283 (M+Na⁺, 100). Anal. Calcd for C₁₅H₂₀N₂O₂: C, 69.20; H, 7.74; N, 10.76. Found: C, 68.97; H, 7.82; N, 11.04.

4.4.2. 1-Ethoxy-2-methoxy-9,9,9a-trimethyl-9,9a-dihydro-1*H*-imidazo[1,2-*a*]indole (**7b**)

Yield 58%. Oil. ¹H NMR (300 MHz, CDCl₃): δ 0.94 (s, 3H, CH₃), 1.32 (t, *J*=7.0 Hz, 3H, CH₂CH₃), 1.46 (s, 3H, CH₃), 1.49 (s, 3H, CH₃), 2.97 (s, 3H, OCH₃), 3.65 (dq, *J*=8.7 Hz, *J*=7.0 Hz, 1H, OCH₂), 3.84 (dq, *J*=8.7, *J*=7.0 Hz, 1H, OCH₂), 5.0 (s, 1H, NCH), 6.91-7.20 (m, 4H, Ar-H). ¹³C NMR (75 MHz, CDCl₃): δ 15.2 (CH₃), 21.8 (CH₃), 22.6 (CH₃), 27.2 (CH₃), 28.6 (CH₃), 49.1 (C-9), 61.1 (OCH₂), 88.9 (C-3), 90.5 (C-9a), 113.7, 122.0, 122.9, 128.3, 141.4, 145.6 168.3 (Ar-C, C-2). IR (KBr, cm⁻¹): ν_{C=C(OMe)} = 1715. MS (ES⁺) *m/z* (%): 297 (M+Na⁺, 95). Anal. Calcd for C₁₆H₂₂N₂O₂: C, 70.04; H, 8.08; N, 10.21. Found: C, 69.89; H, 7.76; N, 10.13.

4.4.3. 1-Benzyloxy-2-methoxy-9,9,9a-trimethyl-9,9a-dihydro-1H-imidazo[1,2-a]indole (7c)

Yield 63%. Oil. ^1H NMR (300 MHz, CDCl_3): δ 0.97 (s, 3H, CH_3), 1.49 (s, 3H, CH_3), 1.55 (s, 3H, CH_3), 3.02 (s, 3H, OCH_3), 4.65 (d, $J=11.1$ Hz, 1H, OCH_2), 4.86 (d, $J=11.1$ Hz, 1H, OCH_2), 5.16 (s, 1H, NCH), 6.88-7.49 (m, 9H, Ar-H). ^{13}C NMR (75 MHz, CDCl_3): δ 21.9 (CH_3), 22.7 (CH_3), 27.3 (CH_3), 28.6 (CH_3), 49.1 (C-9), 67.2 (OCH_2), 89.1 (C-3), 90.2 (C-9a), 113.9, 122.1, 123.0, 126.9, 127.6, 128.2 (2 \times C), 128.3, 128.4, 137.7, 141.4, 145.5, 168.1 (Ar-C, C-2). IR (KBr, cm^{-1}): $\nu_{\text{C}=\text{C}(\text{OMe})} = 1713$. MS (ES $^+$) m/z (%): 359 (M+Na $^+$, 100). Anal. Calcd for $\text{C}_{21}\text{H}_{24}\text{N}_2\text{O}_2$: C, 74.97; H, 7.19; N, 8.33. Found: C, 74.40; H, 7.33; N, 8.35.

4.5. Procedure for the preparation of 1-[2-(hydroxyamino)-2-oxoethyl]-2,3,3-trimethyl-3H-indolium perchlorate (8a)

To a solution of compound **3a** (232 mg, 1 mmol) in ethanol (3 mL), 60% perchloric acid was added dropwise to pH 2 and the solution was kept at 5 $^\circ\text{C}$ for 16 h. The precipitated crystalline material was filtered, washed with cold ethanol (1 mL) and recrystallized from ethanol, to give perchlorate **8a** (213 mg, 64%), mp 192-195 $^\circ\text{C}$ (from EtOH, with decomposition). ^1H NMR (300 MHz, TFA- d): δ 1.69 (s, 6H, 3,3- CH_3 , major and minor isomers), 2.86 (s, 3H, 2- CH_3 , minor isomer), 2.90 (s, 3H, 2- CH_3 , major isomer), 5.49 (s, 2H, CH_2 , major isomer), 5.78 (s, 2H, CH_2 , minor isomer), 7.59-7.70 (m, 4H, major and minor isomers). ^{13}C NMR (75 MHz, TFA- d), mixture of isomers: δ 15.50, 15.60, 23.84, 49.23, 49.44, 57.66, 57.69, 116.33, 116.42, 116.5, 125.30, 131.90, 131.94, 133.01, 133.08, 142.97, 143.22, 143.30, 164.82, 203.39, 203.43. IR (KBr, cm^{-1}): $\nu_{\text{OH, NH}} = 3310, 3271, 3212$, $\nu_{\text{C}=\text{O}} = 1690$, $\nu_{\text{ClO}_4} = 1111, 1098$. Anal. Calcd. for $\text{C}_{13}\text{H}_{17}\text{ClN}_2\text{O}_6$: C, 46.93; H, 5.15; N, 8.42. Found: C, 46.84; H, 5.06; N, 8.28.

4.6. Procedure for the preparation of 1-carboxymethyl-2,3,3-trimethyl-3H-indolium tetrafluoroborate monohydrate (11)

To a solution of compound **3a** (232 mg, 1 mmol) in ethanol (3 mL), tetrafluoroboric acid (48%) was added dropwise to pH 2 and the solution was kept at 5 $^\circ\text{C}$ for 24 h. The precipitated crystalline material was filtered, washed with cold ethanol (1 mL) and recrystallized from ethanol, to give tetrafluoroborate **11** (172 mg, 53%), mp 195-197 $^\circ\text{C}$ (from EtOH). ^1H NMR (300 MHz, TFA- d): δ 1.85 (s, 6H, 2 \times 3- CH_3), 3.04 (s, 3H, 2- CH_3), 5.67 (s,

2H, CH₂), 7.80-7.87 (m, 4H, Ar-H). ¹³C NMR (75 MHz, TFA-*d*): δ 15.5 (2-CH₃), 23.9 (2×3-CH₃), 50.2 (C-3), 57.9 (CH₂), 116.3, 125.6, 132.1, 133.4, 143.0, 143.5 (Ar-C), 170.9 (CO₂H), 203.3 (N⁺=C). IR (KBr, cm⁻¹): ν_{OH} = 3436, ν_{C=O} = 1634, ν_{BF₄} = 1053, 768. Anal. Calcd. for C₁₃H₁₆BF₄NO₂·H₂O: C, 48.33; H, 5.62; N, 4.34. Found: C, 47.93; H, 5.46; N, 4.67.

4.7. Procedure for the preparation of *N*-hydroxy-2-(2,3,3-trimethyl-2,3-dihydro-1*H*-indol-1-yl)acetamide (**12**)

To a solution of compound **3a** (200 mg, 0.8 mmol) in glacial acetic acid (2 mL), sodium borohydride (98.8 mg, 2.6 mmol) was added in portions and the mixture was stirred at ambient temperature for 3 h. The reaction mixture was poured into water (5 mL), the solution was neutralized with sodium carbonate to pH 9 and extracted with Et₂O (3×5 mL). The combined organic extracts were washed with brine (3 mL), dried over Na₂SO₄ and filtered. The solvent was evaporated under reduced pressure and the residue was chromatographed on a silica gel column with hexane/EtOAc (1:1 v/v) as eluent to yield compound **12** (165 mg, 88 %) as white crystals, mp 119-120 °C. ¹H NMR (300 MHz, CDCl₃): δ 1.11 (s, 3H, 3-CH₃), 1.26 (d, *J*=6.6 Hz, 3H, CHCH₃), 1.35 (s, 3H, 3-CH₃), 3.15 (q, *J*=6.6 Hz, CHCH₃), 3.74 (s, CH₂), 6.50-7.17 (4H, m, Ar-H), 9.21 (br. s, 1H, NH or OH), 9.46 (br. s, NH or OH). ¹³C NMR (75 MHz, CDCl₃): δ 12.9 (CH₃), 23.5 (CH₃), 25.8 (CH₃), 43.1 (C-3), 51.9 (CH₂), 72.2 (C-2), 108.4, 120.8, 122.4, 127.9, 139.5, 150.2, 168.6 (C=O). IR (KBr, cm⁻¹): ν_{OH, NH} = 3203, ν_{C=O} = 1656. MS (ES⁺) *m/z* (%): 257 (M+Na⁺, 60). Anal. Calcd. for C₁₃H₁₈N₂O₂: C, 66.64; H, 7.74; N, 11.96. Found: C, 66.86; H, 7.77; N, 11.53.

4.8. Procedure for the preparation of 1,3,9,9,9a-pentamethyl-9,9a-dihydro-1*H*-imidazo[1,2-*a*]indol-2(3*H*)-one (**15**)

n-BuLi (3 mL, 4.8 mmol, 1.6 M in hexane) was added to a solution of compound **13** (920 mg, 4 mmol) in THF (13 mL) under argon at -78 °C. After stirring for 1 h, a solution of methyl iodide (681 mg, 4.8 mmol) in dry THF (8 mL) was added dropwise over 20 min, and the mixture allowed to reach ambient temperature. After 3 h, the reaction mixture was quenched with an ammonium chloride solution (10%, 25 mL) and extracted with EtOAc (2×15 mL). The combined organic extracts were washed with water (15 mL), dried over Na₂SO₄, filtered and the solvent was evaporated under reduced pressure. The residue was chromatographed on a

silica gel column with hexane/EtOAc (9:1 v/v) as eluent to give compound **15** (495 mg, 51%) as colourless oil. ¹H NMR (300 MHz, CDCl₃): δ 1.01 (s, 3H, CH₃), 1.426 (s, 3H, CH₃), 1.429 (s, 3H, CH₃), 1.56 (d, *J*=6.9 Hz, 3H, CH₃), 2.95 (s, 3H, CH₃), 3.78 (q, *J*=6.9 Hz, 1H, CHCH₃), 6.82-7.18 (m, 4H, Ar-H). ¹³C NMR (75 MHz, CDCl₃): δ 21.6, 22.2, 24.1, 27.2, 29.4, 49.5, 61.2, 89.4 (9a-C), 113.9, 122.2, 122.4, 128.2, 141.6, 148.4 (Ar-C), 173.3. ¹⁵N NMR (50.69 MHz, CDCl₃): δ -257.1 (N-1), -289.1 (N-4). IR (KBr, cm⁻¹): ν_{C=O} = 1699. Anal. Calcd. for C₁₅H₂₀N₂O: C, 73.74; H, 8.25; N, 11.47. Found: C 73.51; H 8.15; N 11.68.

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