Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron
ELSEVIER
Tetrahedron 62 (2006) 3309–3319

Synthesis and ring transformations of 1-amino-1,2,3,9a-tetrahydroimidazo[1,2-*a*]indol-2(9*H*)-ones

Joana Dumčiūtė,[a] Vytas Martynaitis,[a] Wolfgang Holzer,[b] Sven Mangelinckx,[c] Norbert De Kimpe[c] and Algirdas Šačkus[a,*]

[a]*Department of Organic Chemistry, Kaunas University of Technology, LT-50270 Kaunas, Lithuania*
[b]*Department of Drug Synthesis, Faculty of Life Sciences, University of Vienna, Pharmaziezentrum, A-1090 Vienna, Austria*
[c]*Department of Organic Chemistry, Faculty of Bioscience Engineering, Ghent University, Coupure links 653, B-9000 Gent, Belgium*

Received 14 December 2005; revised 11 January 2006; accepted 17 January 2006

Available online 20 February 2006

Abstract—Heating 1-carbamoylmethyl-2,3,3-trimethyl-3*H*-indolinium chloride in the presence of hydrazine bishydrate produces regioselectively the five-membered heterocycle 1-amino-1,2,3,9a-tetrahydro-9,9,9a-trimethylimidazo[1,2-*a*]indol-2(9*H*)-one. The assignment of the structure is based on extensive ^{1}H, ^{13}C and ^{15}N NMR spectroscopic studies. No ring-chain tautomerism of the 1-amino-1,2,3,9a-tetrahydroimidazo[1,2-*a*]indol-2(9*H*)-one was observed to open-chain hydrazides or the corresponding six-membered 1,2,10,10a-tetrahydro[1,2,4]triazino[4,3-*a*]indol-3(4*H*)-one. Further transformations of 1-amino-1,2,3,9a-tetrahydroimidazo[1,2-*a*]indol-2(9*H*)-one were performed by treatment with aromatic aldehydes, acid chlorides and isocyanates giving access to 40 novel hydrazones, *N*,*N*′-diacylhydrazines, *N*-acyl-*N*′-carbamoylhydrazines and 1,3,4-oxadiazoles.

1. Introduction

1-Carbamoylmethyl-3*H*-indolinium salts **1** are known to cyclize to 1,2,3,9a-tetrahydroimidazo[1,2-*a*]indol-2(9*H*)-ones upon treatment with base.[1] If, however, the 1-carbamoylmethyl-3*H*-indolinium salts **1** are transformed to the corresponding hydrazides **2**, further cyclization could either lead to 1-amino-1,2,3,9a-tetrahydroimidazo[1,2-*a*]indol-2(9*H*)-ones **3**, similar as to ring closure of the amides, or to the corresponding six-membered ring systems, that is, 1,2,10,10a-tetrahydro[1,2,4]triazino[4,3-*a*]indol-3(4*H*)-one **4**, if the terminal NH_2 group enters into reaction (Scheme 1). The objective of this work is to investigate the reaction of such hydrazides and, apart from the structural investigations, to study the reactivity of the novel cyclic products and route to novel heterocyclic compounds. The potential biological activity of the unknown 1-amino-1,2,3,9a-tetrahydroimidazo[1,2-*a*]indol-2(9*H*)-ones is also of interest, as these tricyclic derivatives contain both the 2,3-dihydro-1*H*-indole and imidazolidin-4-one nuclei. Via the reaction of an α-amino amide with a carbonyl compound followed by intramolecular cyclization, the conformationally rigid imidazolidin-4-one scaffold has already been introduced in some compounds to modify their physiological activities such as cognition enhancing activity,[2] nootropic activity,[3] antimalarial activity,[4] and analgesic activity.[5] Metabolic stable N-terminal imidazolidin-4-one prodrugs of Leu-enkephalin have also been prepared.[6] Compounds containing the indole-1-acetamide moiety also exhibit interesting physiological activities such as central muscle relaxation,[7] anticonvulsive activity,[8] and CNS depressant activity.[9]

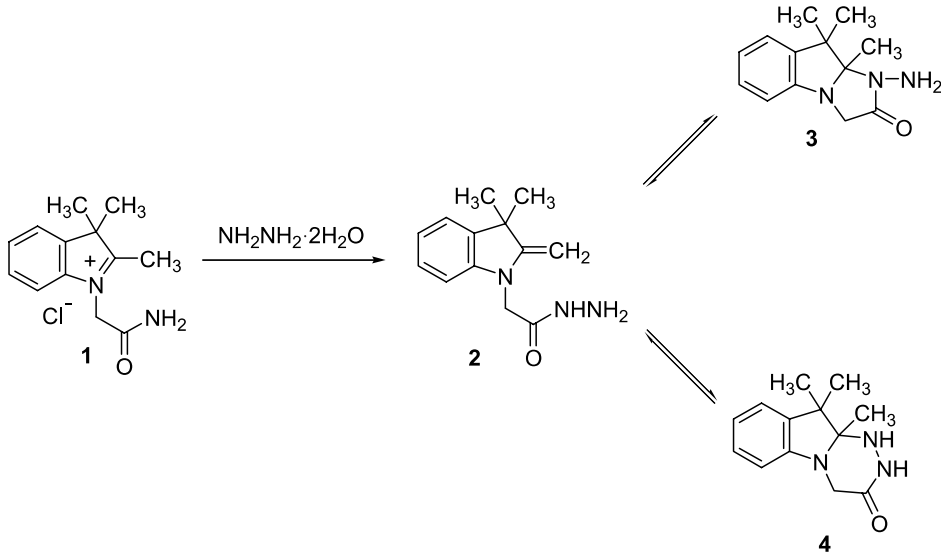
2. Results and discussion

Heating 1-carbamoylmethyl-2,3,3-trimethyl-3*H*-indolinium chloride **1** in the presence of hydrazine bishydrate, resulted in the isolation of a cyclized compound identified as the racemic five-membered heterocycle 1-amino-1,2,3,9a-tetrahydro-9,9,9a-trimethylimidazo[1,2-*a*]indol-2(9*H*)-one (**3**) (Scheme 2).

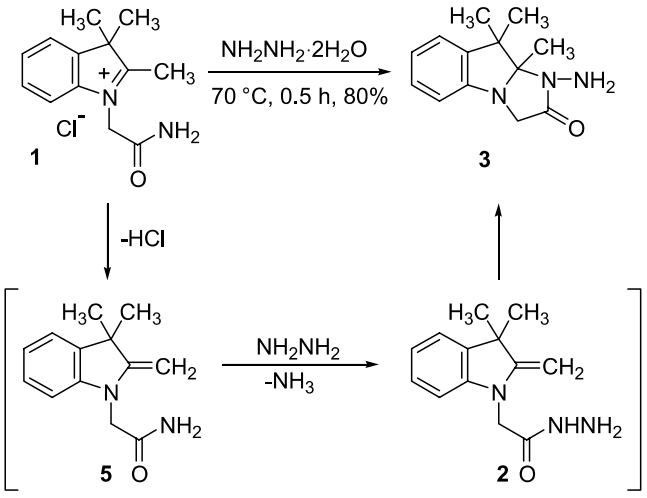
The main evidence for the assignment of structure **3**, containing the 3-aminoimidazolidin-4-one ring, follows from the ^{15}N NMR data. The ^{15}N,^{1}H HMBC spectrum shows three different N-atoms (δ −317.6, −299.1 and −224.6 ppm). In a ^{15}N DEPT experiment (optimized for $^{1}J_{NH}$=70 Hz) only the N-atom with the smallest chemical shift (δ −317.6) emerges, namely as a triplet (^{1}J=68.9 Hz)

Keywords: Hydrazides; Structural identification; 1,2,3,9a-Tetrahydroimidazo[1,2-*a*]indol-2(9*H*)-ones; Hydrazines; Oxadiazoles.
* Corresponding author. Tel./fax: +370 37 451432; e-mail: algirdas.sackus@ktu.lt

0040–4020/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2006.01.054



Scheme 1.



Scheme 2.

and thus proving to origin from an NH_2 moiety what definitely rules out structure **4**. Moreover, the ^{15}N, ^{1}H HMBC spectrum exhibits a correlation between the nitrogen atom with the largest chemical shift (N-1, δ −224.6) and the protons of 9a-CH_3 (δ 1.40 ppm), what seems improbable with structure **4** where the involved nuclei would be separated by four bonds and thus no correlation is expected. In addition, in the ^{1}H NMR spectrum there is only one sharp signal of relative intensity two for the NH-protons. For structure **4**, two different type of NH-signals have to be expected (CONH, N–NH). The assignments presented in Figure 1a are based on the combined application of standard NMR techniques such as NOE-difference (Fig. 1b), NOESY, APT, DEPT, HSQC, HMBC and long-range INEPT spectra with selective excitation.[10]

Although the amino nitrogen atom of the hydrazide moiety of **2** is more reactive[11] than the amide one, the condensation reaction involves the latter exclusively to give a five-membered ring. This observed reactivity is similar to addition reactions of phenylhydrazine in which it was proven that the N-1 of phenylhydrazine reacts as the nucleophilic site and not the NH_2-group.[12] The exclusive formation of the five-membered ring can be tentatively rationalized on the basis of the *E*/*Z* rotamerism of hydrazide **2** with respect to the nitrogen–carbon hydrazide bond with partial double bond character (Scheme 3). Studies concerning this hindered rotation of hydrazine derivatives have shown that steric effects of the substituents are driving the equilibrium towards the (*Z*) forms, augmented by intramolecular hydrogen bonding in the (*Z*) form.[13] It can be assumed that the large steric effect of the indolylmethyl carbonyl substituent of hydrazide **2** and the two possible intramolecular hydrogen bonds between the hydrogen atoms attached to the nitrogen and the oxygen atom, make the (*Z*) form much more favored. This (*Z*)-hydrazide is

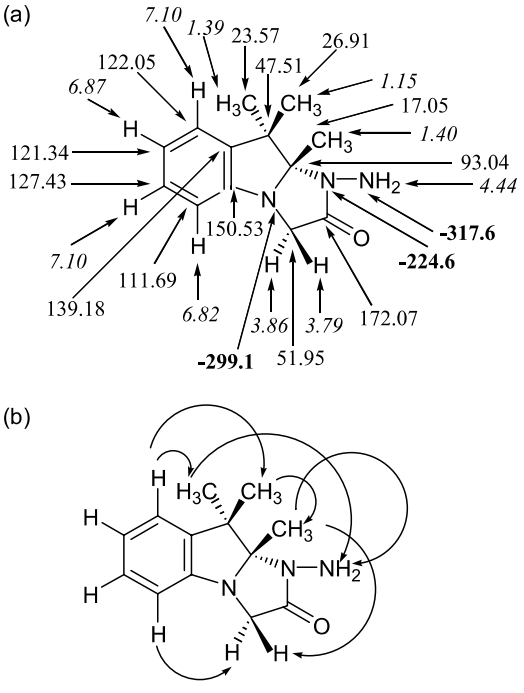


Figure 1. (a) ^{1}H (italics), ^{13}C and ^{15}N NMR (bold) chemical shifts [ppm; ref. TMS (^{1}H and ^{13}C) and CH_3NO_2 (^{15}N)] for **3** in DMSO-d_6. (b) Relevant NOE correlations.