Tetrahedron Letters 56 (2015) 6988–6993

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

# A facile, one pot method for the synthesis of 4-acyl-1,2-dihydro-3-benzazepines, based on the ring expansion of natural and synthetic 3,4-dihydroisoquinoline pseudo bases

Viktor G. Kartsev [a], Alexander A. Zubenko [b], Anatolii S. Morkovnik [c,*], Ludmila N. Divaeva [c]

[a] InterBioScreen Ltd, Moscow, 119019, Russia
[b] North-Caucasian Zonal Research Veterinary Institute, Novocherkassk 346406, Russia
[c] Research Institute of Physical and Organic Chemistry, Southern Federal University, Rostov-on-Don 344090, Russia

ARTICLE INFO

*Article history:*
Received 27 April 2015
Revised 7 October 2015
Accepted 29 October 2015
Available online 30 October 2015

*Keywords:*
Pseudo bases
Cotarnine
3,4-Dihydroisoquinolines
α-Haloketones
Alkaloids recyclization
3-Benzazepines

ABSTRACT

A new, one-pot approach to 4-acyl-1,2-dihydro-3-benzazepines has been proposed proceeding via a six- to seven-membered heterocyclic ring expansion under the action of α-haloketones.



Benzazepines are of significant interest as they represent carbon isosteres of the 1,4-benzodiazepine motif which is a privileged[1] bicyclic nucleus present in a number of potent and widely used[2] GABAergic pharmaceuticals.

3-Benzazepines and their more studied hydrogenated derivatives (as cyclic structural analogs of the neurotransmitter dopamine) mainly possess dopaminergic (antagonistic or agonistic) activity against central and peripheral dopamine receptors.[3] Other receptor types and biomacromolecules may also be affected by these compounds, such as, the vascular 5-$HT_2$ receptor,[4] NMDA receptor,[5] melanin-concentrating hormone receptor 1 (MCHR1),[6] $\sigma_1$ receptor,[5a,7] and monoaminergic transporters.[8] 3-Benzazepines also exhibit antihypertensive,[9] antidepressant,[10] antipsychotic,[11] anticancer[12] (in relation to MDR tumor cells), antidiabetic, and erectile dysfunction normalizing action.[13] The 3-benzazepine motif is also present in various alkaloids: cephalotaxine and its semi-synthetic derivatives which are of interest as anticancer agents,[14] chilenine,[15] lennoxamine[16] and rheadan[17] as well as in some experimental and approved drugs: anilopam, fenoldopam, trepipam, ivabradine, lorcaserin, semagacestat, omacetaxine, mepesuccinate, SKF-38,393 and SKF-82,958.

Methods for the preparation of 3-benzazepines have been reviewed in a number of articles and monographs.[18] Several synthetic routes to these compounds[19] based on the heterocyclic ring expansion of isoquinolines or their hydrogenated derivatives proceed under the action of various reagents: $MeSO_2Cl$,[20] strong bases,[21–23] $Ph_3P$-$H_2$/Pd-C,[24] *t*-BuOK,[25] $Pb(OAc)_4$,[26] $SO_2Cl_2$/$Et_3N$,[27] and $CH_2N_2$.[28]

Herein, we describe a new method for the synthesis of 3-benzazepine derivatives starting from natural or synthetic 3,4-dihydroisoquinoline pseudo bases or their 3,4-dihydroisoquinolinium salt precursors which can easily be prepared from 3,4-dihydroisoquinolines.

The above-mentioned pseudo bases are highly prone to prototropic ring chain tautomerism proceeding with heterocyclic ring opening.[29] In solution their main cyclic form **A** is in equilibrium with the open-chain form **B** (Scheme 1). Additionally, the ionic form **C**, which is stabilized by polar solvents, can participate in this equilibrium.[30] Although each of these forms is able to react with both nucleophilic and electrophilic reagents, the most reactive tautomer is probably form **B** which contains two functional groups with nucleophilic and electrophilic centers.

A typical and well known isoquinoline pseudo base is the alkaloid cotarnine.[31] According to quantum chemical data (B3LYP/6-311G**; $T = 298.15$ K, $P = 1.013 \cdot 10^5$ Pa), both tautomeric

* Corresponding author. Tel.: +7 863 297 5196; fax: +7 863 243 4667.
*E-mail address:* asmork2@ipoc.rsu.ru (A.S. Morkovnik).

http://dx.doi.org/10.1016/j.tetlet.2015.10.103
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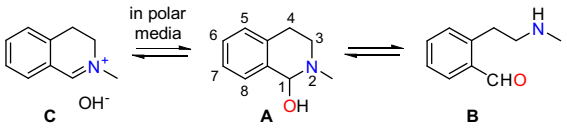


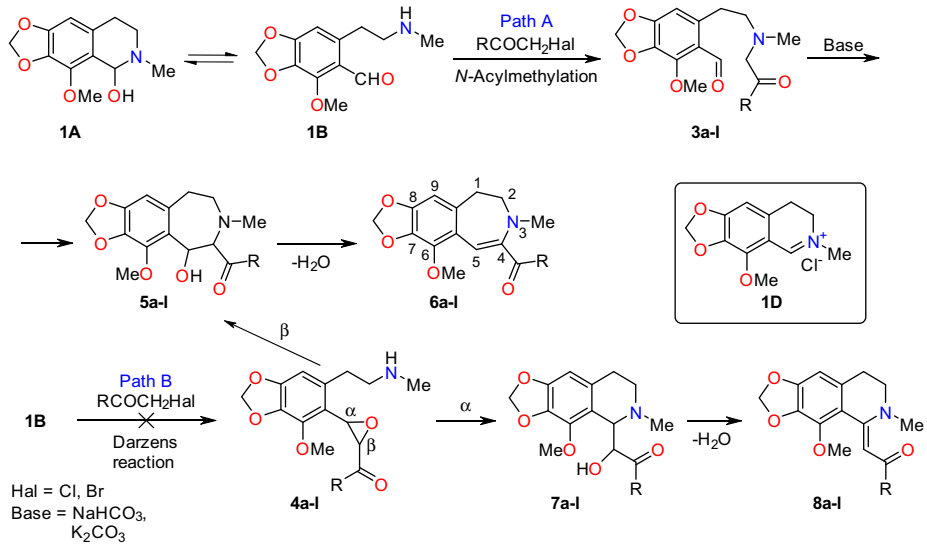

**Scheme 1.**

forms of the compound are close in energy (Scheme 2). The cyclic form **1A** in gas phase, has only 0.2 kcal/mol lower energy than acyclic form **1B** (cf.[32]) (Fig. 1) which strongly supports the earlier conclusions regarding the role of **1B** in the reaction of cotarnine with nucleophilic reagents.[33]

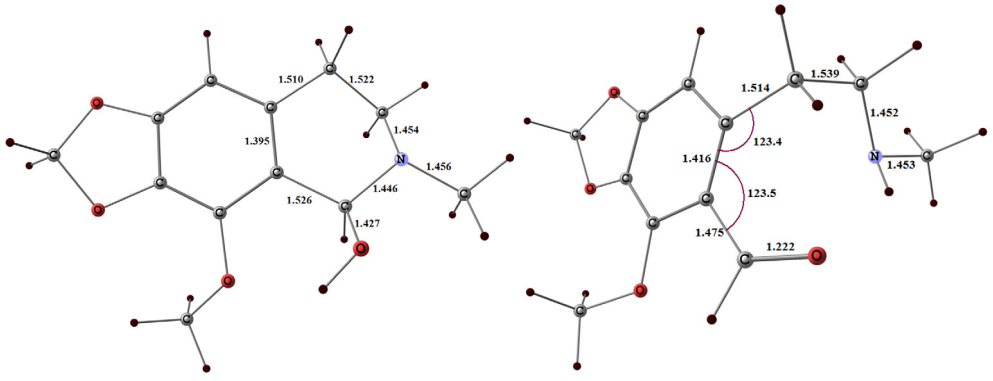
Taking into account the relative stability and reactivity of the open-chain tautomer **1B**, we proposed the possibility of recyclization reactions occurring for cotarnine **1** and other 3,4-dihydroisoquinoline pseudo bases. Herein, we report the use of α-haloketones (**2**) in the presence of base as suitable reagents for this reaction. These reagents interact with the **B** form of the pseudo bases, giving the products of $S_N2$ substitution and/or the Darzens reaction which proceeds easily, even with rather weak bases, such as potassium carbonate.[34] In the case of alkaloid **1**, *N*-acylmethyl derivative **3** and the acyl oxirane **4** are both possible intermediates (Scheme 2).

If initial $S_N2$ substitution occurs, then conversion of compound **1** into 4-acyl-5-hydroxy-1,2,3,4-tetrahydro-3-benzazepines **5** or the products of their dehydration, 4-acyl-1,2-dihydro-3-benzazepines **6**, would be expected as a result of the subsequent cyclization of *N*-acylmethyl derivatives **3** (Scheme 2). This corresponds to a recyclization with six- to seven-membered ring expansion proceeding through the insertion of one carbon atom (Path A). In the opposite case, formation of isoquinoline derivatives **7** and **8** and/or the same benzazepines as in Path A would be expected as a consequence of tandem ring-opening/ring-closing (RORC) rearrangement of oxiranes **4** by attack of the secondary amino groups onto the oxirane ring (Path B) (Scheme 2).

Experiments showed that cotarnine **1**, as well as cotarnine chloride **1D**, reacted with α-haloketones in the presence of $NaHCO_3$ or $K_2CO_3$ under mild conditions (reflux, $H_2O$:EtOH, 1:2 (v/v), $NaHCO_3$, 10–30 min, or methanol, $K_2CO_3$, 2–3 h)[35] to give the poorly studied 4-acyl-1,2-dihydro-3-benzazepines as crystalline solids[25,28,36] (Scheme 2, compounds **6a–l**). The recyclization reaction proceeded smoothly giving **6a–l** in moderate to good yields (38–94%) (Table 1).




**Scheme 2.**




**1A**, $E_{tot}$ = -821.8575 a.u. **1B**, $E_{tot}$ = -821.8572 a.u.

**Figure 1.** Optimized structures and energies (with ZPE corrections) of the tautomers of cotarnine, **1A** and **1B**, according to quantum chemical calculations (B3LYP/6-311**).