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Sm(III)nitrate-catalyzed one-pot synthesis of furano[3,2c]-1,2,3,4-tetrahydroquinolines and DNA photocleavage studies

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ABSTRACT

The synthesis and DNA photocleavage studies of furano[3,2-c]-1,2,3,4-tetrahydroquinolines have been reported. Sm(III)nitrate was found to be an efficient for the Diels–Alder reaction of aryl amines with 2,3-dihydrofuran to offer the corresponding furano[3,2-c]-1,2,3,4-tetrahydroquinolines derivatives as a mixture of *cis/trans* stereoisomers in moderate yields. The aqueous solubility of acid catalyst can be recycled without significant loss of activity. The DNA photocleavage studies shows that, the *cis/trans* stereoisomers are good DNA cleavage mimic in terms of molecular structure.

1. Introduction

DNA is the primary intracellular target of anticancer drugs, due to the interaction between small molecules which cause DNA damage in cancer cells and resulting in cell death [1–3]. A more complete understanding of how to target DNA sites with specificity will lead not only to novel chemotherapeutics but also to a greatly expand ability for chemists to probe DNA and to develop highly sensitive diagnostic agents [2]. In order to develop new antitumor drugs which specifically target DNA, it is necessary to understand the different binding modes a molecule is capable of undertaking.

Chemists have made substantial contributions is in the design and development of nucleic acid cleavage agents for use as structural probes and therapeutic agents. In this photodynamic therapy (PDT) is an emerging method of non-invasive treatment of cancer in which drugs shows localized toxicity on photoactivation at the tumor cells leaving the healthy cells unaffected [4]. Importantly, the type and the efficiency of the photocleavage reaction will depend on the binding site that the photonuclease occupies.

Recently, the chemistry of 1,2,3,4-tetrahydroquinolines is of interest among many investigations during recent years. The growing interest in them can be explained by their biological activities. Substituted tetrahydroquinolines are the core structures in many important pharmacological agents [5–9], many relatively simple synthetic 1,2,3,4-tetrahydroquinolines are already in use or have been tested as potential drugs [10–12]. Substituted tetrahydroquinolines are the core structures in many important pharmacological agents and drug molecules, such as anti-arrhythmic and cardiovascular agents, anti-cancer drugs, immunosuppressants, ligands for 5-HT1A and NMDA receptors [13–20].

It was found that, furano[3,2-c]-1,2,3,4-tetrahydroquinolines stereoisomer mimic, martinelline and martinellic acid bearing a synthetically interesting heterocyclic ring, a pyrroloquinoline skeleton, were isolated from the roots of the tropical plant, *Martinella iquitosensis*, as the first natural occurring nonpeptide bradykinin receptor antagonists (Fig. 1) [21].

Tetrahydroquinoline moiety is an important structural feature of various natural products and pharmaceutical agents that continuous interest has been sustained to develop methods for the synthesis of tetrahydroquinolines. Among the many efforts for their synthesis is the Lewis-acid catalyzed Diels–Alder reaction of *N*-arylimines with cyclic enol ether 2,3-dihydrofuran was employed as the dienophile, tricyclic compound (furano-quinolines) were obtained [22]. Batey and co-workers are developed a $Dy(OTf)_3$-catalyst for the synthesis of hexahydrofuro[3,2-*c*]quinolines via 2:1 coupling of dihydrofuran with substituted anilines [23]. Along with them number of approaches have been developed for the synthesis of tetrahydroquinoline skeleton [24–26]. Recently, Lewis acids like $InCl_3$ and $FeCl_3$–NaI [27–29] have been found to catalyze this reaction. Heterogeneous catalyst likes montmorillonite KSF [30] and cation-exchange resin [31] has also been reported to be effective catalyst for the synthesis of these scaffolds. Although these methods are available, but new efficient, selective and facile protocols are still in strong demand.

In this article, we have reported a general and practical route for synthesis of 2,3,3a,4,5,9b-Hexahydro-4-(3-hydroxypropyl)-

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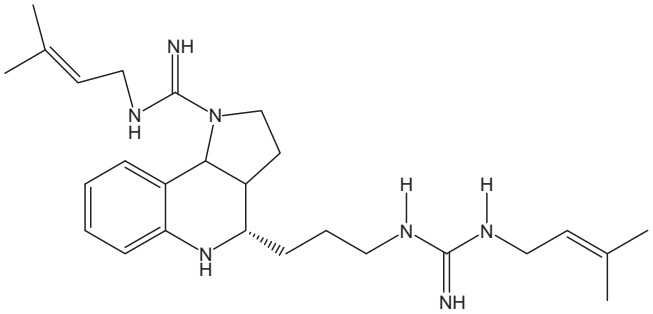


Fig. 1. Nonpeptide bradykinin receptor.

furano[3,2-c]quinolines catalyzed by Sm(III) promoted imino Diels–Alder reaction of substituted aromatic anilines and 2,3-dihydrofuran. The generality of the reaction was sufficiently investigated and demonstrated. The new reaction path way for this conversion was established by spectroscopic and analytical methods. Hence, in view of the biological importance of 1,2,3,4-tetrahydroquinolines, here-in we report the synthesis of 2,3,3a,4,5,9b-Hexahydro-4-(3-hydroxypropyl)-furano[3,2-c]quinolines and evaluated their nucleolytic activities.

2. Results and discussion

As a part of our ongoing research program on synthetic potential of quinolines, we recently found a facile synthesis of quinolines by Diels–Alder reaction [32]. The present work was aimed at developing convenient methodology for the synthesis of 2,3,3a,4,5,9b-Hexahydro-4-(3-hydroxypropyl)-furano[3,2-c]quinolines (**3a–g**) and (**4a–g**) (Scheme 1). For this purpose, we examined samarium nitrate as Lewis acid catalyst. We reviewed in the literature that the Sm(III) has been used as an efficient Lewis acid for various transformations in organic chemistry [33].

The mechanism involved in the synthesis of 2,3,3a,4,5,9b-Hexahydro-4-(3-hydroxypropyl)-furano[3,2-c]quinolines is as follows.

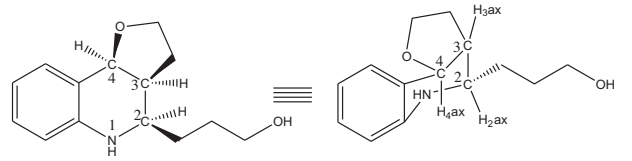
The synthesis described in this article is based on our earlier interest in the development of new and practical methods for the synthesis of biological active quinolines [34–36]. In view of this biological importance of quinolines, the following compounds (**3a–g**) and (**4a–g**) have been reported.

The model reaction was carried out with aniline and 2,3-dihydrofuran (DHF) in different organic solvents at room temperature. A mixture of *cis*-isomer **3a** and *trans*-isomer **4a** was isolated. It was found that a remarkable solvent effect will be exists and MeCN was the best solvent for good transformation in very short time (2–3 h), while other solvents such as, dichlomethane, THF, ethanol, afford either poor yields or trace products. On the other hand, the yields increase slightly as the amount of catalyst is increased from 10 to 20 mol%. Under the optimized reaction conditions, a variety of anilines (**1a–g**) were tested to react with **2** equiv. of 2,3-dihydrofuran (DHF) using 10 mol% of Sm(III) as a catalyst in CH_3CN at room temperature. We found that, interestingly the strong electron-withdrawing nitro substituted aniline gave 60% of product (Table 1, entry g). The reactions proceeded efficiently in high yields at ambient temperature. In all the cases, the products were obtained as a mixture of *cis*/*trans*-isomer (**3** and **4**), favoring the *cis*-isomer. The ratio of the isomers was determined by the ^{1}H NMR spectra of the crude products. The stereochemistry of the isomers was assigned on the basis of coupling constants and chemical shifts of protons, which was accordant with the results reported in the literatures [30]. All the products were characterized by ^{1}H, ^{13}C NMR, IR and mass spectroscopy. Hence the Sm(III) was found to be a suitable catalyst for the efficient synthesis of desired products (**3a–g**) and (**4a–g**) in high yields (Schemes 1 and 2).

Table 1
Synthesis of furano[3,2-c]-1,2,3,4-tetrahydroquinolines (**3a–g**) and (**4a–g**).

Entry[a]	R	Time (h)	*cis*/*trans*	Yield (%)[b]
3a+4a	C_6H_5	2–3	65:35	85
3b+4b	*p*-$CH_3C_6H_4$	2–3	64:36	90
3c+4c	*p*-FC_6H_4	2–3	64:36	80
3d+4d	*p*-ClC_6H_4	2–3	68:32	90
3e+4e	*p*-BrC_6H_4	2–3	69:31	85
3f+4f	*p*-$OCH_3C_6H_4$	2–3	65:35	82
3g+4g	*p*-$NO_2C_6H_4$	2–3	55:45	60

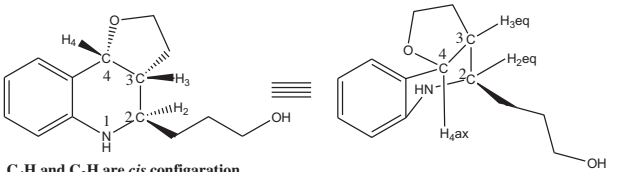
[a] All the products were characterized by elemental analysis, ^{1}H NMR, ^{13}C NMR and mass spectral data.
[b] Yields of isolated products.



C_4H and C_2H are *trans* configaration **C_4H and C_2H are axial to each other, hence large coupling constant.**

The enhanced *cis* diastereoselectivity (to form **3a**) was observed in each case of the investigation similar to as it was reported in literature [31].

Thus, the C_2H and C_4H carbons are *cis* and *trans* 1–3 diaxial to each other and hence they show large coupling constant between H_2 and H_4 at C_2 and C_4 carbon atoms. So C_2H exhibited coupling constant J = 7.2 Hz and C_4H exhibited coupling constant J = 8.0 Hz which are in consistent with *trans* diaxial relationships between C_2H and C_4H protons. Therefore they are *cis* to each other in structure-A (Figs. 2 and 3). Similarly structure-B is also established.



C_4H and C_2H are *cis* configaration **C_2H is in equatorial position where as C_4H is in axial position to each other, hence low coupling constant.**

Further all other derivatives were authenticated by comparing with the reported spectroscopic data and also compared with our earlier report [30]. Similarly several amines were examined and in all cases, the three-component one pot reaction proceeded smoothly to gave the corresponding 2,3,3a,4,5,9b-Hexahydro-4-(3-hydroxypropyl)-furano[3,2-c]quinolines **3a–g**. All these compounds could be separated by column chromatography in most cases. The structure of compounds was characterized by IR, ^{1}H NMR, ^{13}C NMR, mass and elemental analysis.

2.1. DNA photocleavage studies

Electrophoresis experiment was carried out with the circular form of the plasmid (pUC 19) DNA on 0.8% agarose.