Synthesis of 2,9-dihydropyrano[2,3-b]-indoles via intramolecular Oxa-6π-electrocyclization reaction from synthesized 3-allylideneindolin-2-one intermediates

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Research Article

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Abstract

intramolecular Oxa-6π-electrocyclization reaction are described for 3-allylideneindolin-2-one derivatives in the presence of easily prepared $B(HSO4)_3$ catalyst and their conversion to 2,9-dihydropyrano[2,3-b]-indoles in up to 72% yield under mild condition. 3-allylideneindolin-2-one has been obtained from the reaction of isatin and 1,3-dichloropropene. comfortable synthetic conversions of the products readily lead to pharmacologically interesting numerous functional groups.

Introduction

Multi-cyclic scaffolds are considerable and useful for medicinal and synthetic chemistry in industry and research (Connor et al., 2012 ; Han et al., 2015 ; Garcia-Castro et al., 2016; Rodrigues et al., 2016 ; Xie et al., 2018 ; Bagheri et al., 2020 ; Yavari et al., 2023). Indole cycles are a prevalent part of natural products, pharmacology, and agrochemicals (Lounasmaa et al., 2000 ; Chen et al., 2011 ; Oeser et al, 2021). Fusional structure of pyran with indole is an exclusively noteworthy scaffold for drug expansion and often found in biologically active natural molecules (Fig. 1) (Demerson et al., 1975 ; Demerson et al., 1976 ; Jackson et al., 2011 ; Medeiros et al., 2011 ; Gharpure & Prasath .,2014 ; Praveen & Ananth ., 2016; Kam et al., 2008). Pyran-fused indole frameworks like **1** (Cebranopadol) actions as an opioid analgesic of the benzenoid series (Schunk et al., 2014), and **2** (Etodolac) derivatives have been widely applied as potent analgesic agents, anti-inflammatory drugs, and polymerase deterrents (Katz et al., 1988), and **3** (hyrtimomine A) is used as cytotoxic drug (Momose et al., 2013), and **4** (pleiomaltinine) can overrule multidrug resistance (Tan et al., 2010), and **5** prevents the RNA polymerase of the hepatitis C virus (Gopalsamy et al., 2004), and **6** demonstrates antiproliferative activity (Lacassagne et al., 1967 ; Peng et al.,2012) .

There are various methods for the synthesis of hydropyrano indoles using annulation of various catalysts as N-heterocyclic carbenes (Lv et al., 2010 ; Yang et al., 2012), tertiary amines (Mao et al., 2013), calcium phosphate catalysts (Wang et al., 2015), which are carried out through various mechanisms, for instance, the Enders research group, by passing through the Breslow intermediate, did researched [3 + 3] annulation of indolin-3-ones with bromo enals to form dihydropyrano[3,2-b]-indol-2-ones (Qijian et al., 2014), or by using the tandem cyclization reaction, Lu research group, synthesized the 1,3,4,9-tetrahydropyrano[3,4-b]-indoles product (Chen et al., 2017), and Oxa-Diels–Alder reaction is a way to synthesise of cyclic organic compound for instance Han's research group synthesized the hydropyrano[3,2-b]-indole product (Karimi-Jaberi et al. 2012; Jørgensen., 2004; Brieger et al., 1980).

In this context, as part of our interest in the use of effective catalysts for the synthesis of hydropyrano [2,3-b]-indoles based on the intramolecular Oxa-6π-electrocyclization reaction, we report here the use of 3-allylidene indoline-2 derivatives to catalyse constitution of 2,9-dihydropyrano [2,3-b]-indole derivatives by using $B(HSO_4)_3$, which is easy to use and safe and has been applied successfully different compound like biscoumarines (Karimi-Jaberi & Pooladian 2013) and arylidenebisamide (Flores et al., 2013) derivatives (Fig. 2). lately, a major focus has been placed on intramolecular Oxa-6π-electrocyclization

reactions due to their important role in synthesize of complex natural products. The Oxa-6π-electrocyclization reaction is one of the best way approaches for the construction of oxygen-containing heterocyclic frameworks and various cycloaddition reactions. (Uyanik et al., 2020 ; Roche et al, 2021).

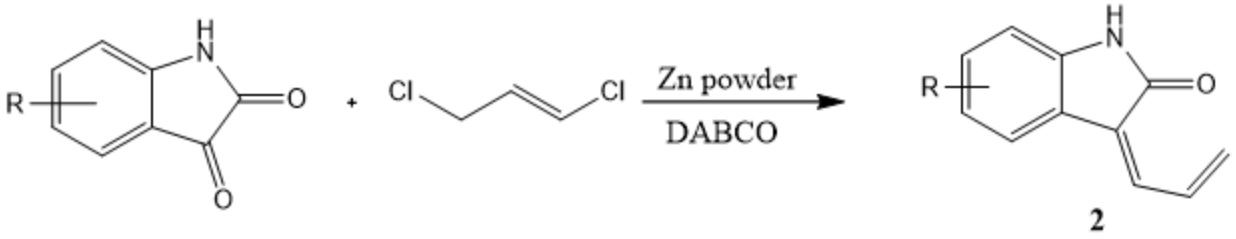
We report here a simple method to synthesis of 3-allylideneindolin-2-one derivatives for conversion to 2,9-dihydropyrano[2,3-b]-indoles from isatin and 1,3-dichloropropene. Isatin works as an important species for the synthesis of several heterocyclic materials, particularly indolic and quinolinic compounds (Havrylyuk et al., 2012). The biological applications of isatin derivatives have already been investigated and it has been shown that these medicinal compounds are used in great inhibition of HIV (Da Silva et al., 2001) and are well resistant to microorganisms (Noori et al., 2017 ; Bouhfid et al., 2011) and have antiviral, antibacterial, and antifungal activity (Abdelhamid & Gomha 2017).

Experimental section

General information

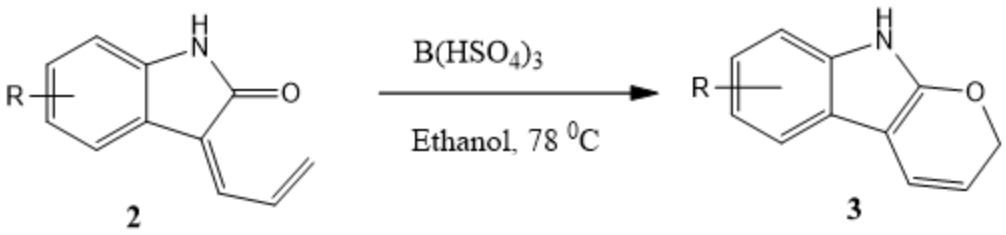
All chemicals were used and purchased from Sigma-Aldrich without purification unless otherwise commented. The products were characterized by NMR data that were acquired for ^{1}H at 500 MHz and for ^{13}C at 125 MHz with a BRUKER DRX-500 AVANCE instruments. Chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance in $CDCl_3$ solution as the internal standard. Melting points and IR spectra of all compounds were measured on an Electrothermal 9100 apparatus and a Shimadzu IR-460 spectrometer, respectively. The abbreviations used for NMR signals: s = singlet, d = doublet, t = triplet, and m = multiplet..

General procedure for 3-allylideneindolin-2-one (2a-2i)



0.02 gr DABCO was added to 5 mL ethanol solution containing 1 mmol isatin, 1 mmol 1,3-dichloropropene and 0.1 mmol Zn powder. The resulting mixture was heated at reflux temperature for 2 h. Then, 0.6 mL solution of NH4Cl were added drop by drop to the mixture within 1–2 min. After that, 0.1 mmol Zn powder was added and stirred for 3 h. The progress of reaction was monitored by Thin Layer Chromatography (TLC) using n-hexane/ethyl acetate (1:5) as eluent. Upon completion of the reaction, monitored by TLC, the reaction mixture was allowed to cool down to the room temperature. The solid was filtered off and washed with ether (10 mL) and purified by recrystallization. Recrystallization done by adding few amount of methanol to give pure needle crystal precipitate of 3-allylide indolin-2-one (2a-2i). The structures of all products were confirmed by FT-IR, ^{1}H-NMR and ^{13}C-NMR analysis.

General procedure for 2,9-dihydropyrano[2,3-b]-indole (3a-3i)



0.1 mmol Boron hydrogen sulfate was added to 5 mL ethanol solution containing 1 mmol 3-allylideneindolin-2-one **2**. The resulting mixture was heated at reflux temperature and stirred for 5 h. Upon reaction completion (TLC monitoring), the solvent was removed under reduced pressure, and the product was purified by flash column chromatography on silica gel (Merck 230–400 mesh) [EtOAc: n-hexane, 1:10] as eluent to afford the pure product **3**.

General procedure for Boron sulphonic acid $B(HSO_4)_3$

A constant pressure dropping funnel was attached to a 50 mL suction flask, which had its gas outlet connected to a vacuum system through an adsorbing solution (water) and an alkali trap. Boric acid (1.55 g, 25 mmol) was placed in the flask, and chlorosulfonic acid (8.74 g, ~ 5 mL, 75 mmol) was added drop by drop over a one hour period at room temperature. The addition of chlorosulfonic acid resulted in the immediate evolution of HCl. Once the addition was complete, the mixture was shaken for one hour, during which time the remaining HCl was removed by suction. The mixture was then washed with diethyl ether to eliminate any unreacted chlorosulfonic acid. The end result of this process was a gray solid material with a yield of 90% (7.0 g). (Kiasat et al., 2008).

RESULTS AND DISCUSSION

We expected that a sufficient catalyst could intramolecularly assemble 3-allylideneindolin-2-one **2a** as a model substrate by intramolecular Oxa-6π-electrocyclization reaction and afford 2,9-dihydropyrano[2,3-b] indole **3a** as oxa-cyclic scaffold after synthesized **2a** by reaction between Isatin **1a** and 1,3-dichloropropene by zinc powder catalyst and result shown (Table 3). The reaction did not fall out under no catalyst conditions in THF solvent at room temperature (entry 1). When [Bmim]BF_4 added at the rate of 5% mol, reaction become completed (entry 2). To obtain higher yields, various catalysts were used and $B(HSO_4)_3$ gave the adequate amount of product at this step (entry 3–6). Then the amount of catalyst addition was investigated and 10 mole percent of $B(HSO_4)_3$ gave the highest efficiency (Entry 7). Examining different solvents is one of the most important steps for catching optimum conditions and after THF using DMF as a solvent has not positive effect on the reaction's yield (Entry 8). Protic polar solvent showed positive results in efficiency by using methanol as solvent (Entry 9). Ethanol has the best result between solvents as protic polar solvent (Entry 10). Eventually, the effects of temperature change

on the reaction efficiency were measured in order to complete the optimal reaction conditions and reflux temperature was the best state (Entry 11–12).

we tested the generality and limitations of this intramolecular Oxa-6π-electrocyclization reaction, [4 + 2] annulation, with the optimal reaction conditions in hand. Screening of a series of 2,9-dihydropyrano[2,3-b]-indoles with different substituents affording products in 72–90% yield and results are shown (Table 4).

All demanded 2,9-dihydropyrano[2,3-b]-indole products were separated in good to excellent yields and both electron-donating substituted (**3b**-**3d**) and electron-withdrawing substituted (**3e**-**3i**) were well got. However, the slight decrease in yield after the addition of substituted shows that the steric effect has a small effect on the yield of the products and the presence of this substitution near the center of the reaction place has a more effect on reducing the yield. In general, products with electron-withdrawing substitution showed better in yield.

Based on the above outcomes a proposed plausible mechanism for this intramolecular Oxa-6π-electrocyclization reaction is shown (Fig. 3). First Zn powder in reaction condition was put between carbon-chlorine bonds and made product **A**, then DABCO absorb the Allylic hydrogen and after rearrangement and attack to ketone carbonyl and absorb hydrogen and made hydroxy group and made product **C**. After the elimination of water and the exit of Zn-Cl bonds by solvent, the equilibrium product of **D** is made. In the end, intramolecular Oxa-6π-electrocyclization made the final 2,9-dihydropyrano[2,3-b]-indole **3a-3i** by $B(HSO_4)_3$ catalyst coordination. Catalysts can boost bond formation between oxygen and carbon in neighbour site by providing sufficient coordination sites.

Conclusion

In summary, we have developed a synthesis way to product 3-allylideneindolin-2-one and then $B(HSO_4)_3$ catalyzed intramolecular Oxa-6π-electrocyclization and conversion it to 2,9-dihydropyrano[2,3-b]-indoles in good to excellent yield. This approach is functional group tolerant and practical, which allows for the assembly of substituent divergent products from isatins with high catalytic activity a simple workup, and has the potential to produce some bioactive materials. Our group is now screening the bioactivity of other compounds produced using this approach and carrying out further chemical biology studies which would greatly contribute to an environmentally benign process.

Declarations

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Conflict of interest

There is no confict of interest.

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Tables

Tables 1-4 is available in the Supplementary Files section.

Figures

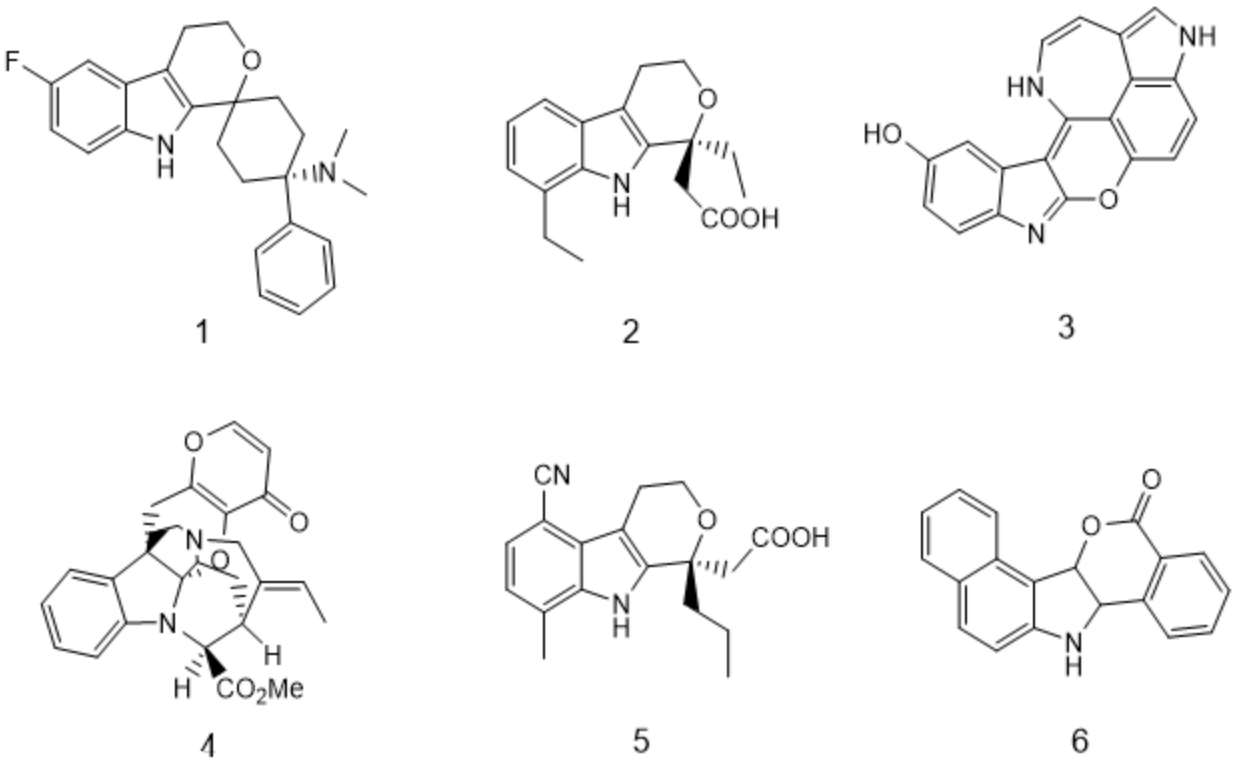

Figure 1

Some examples of Pyran-fused indole frameworks

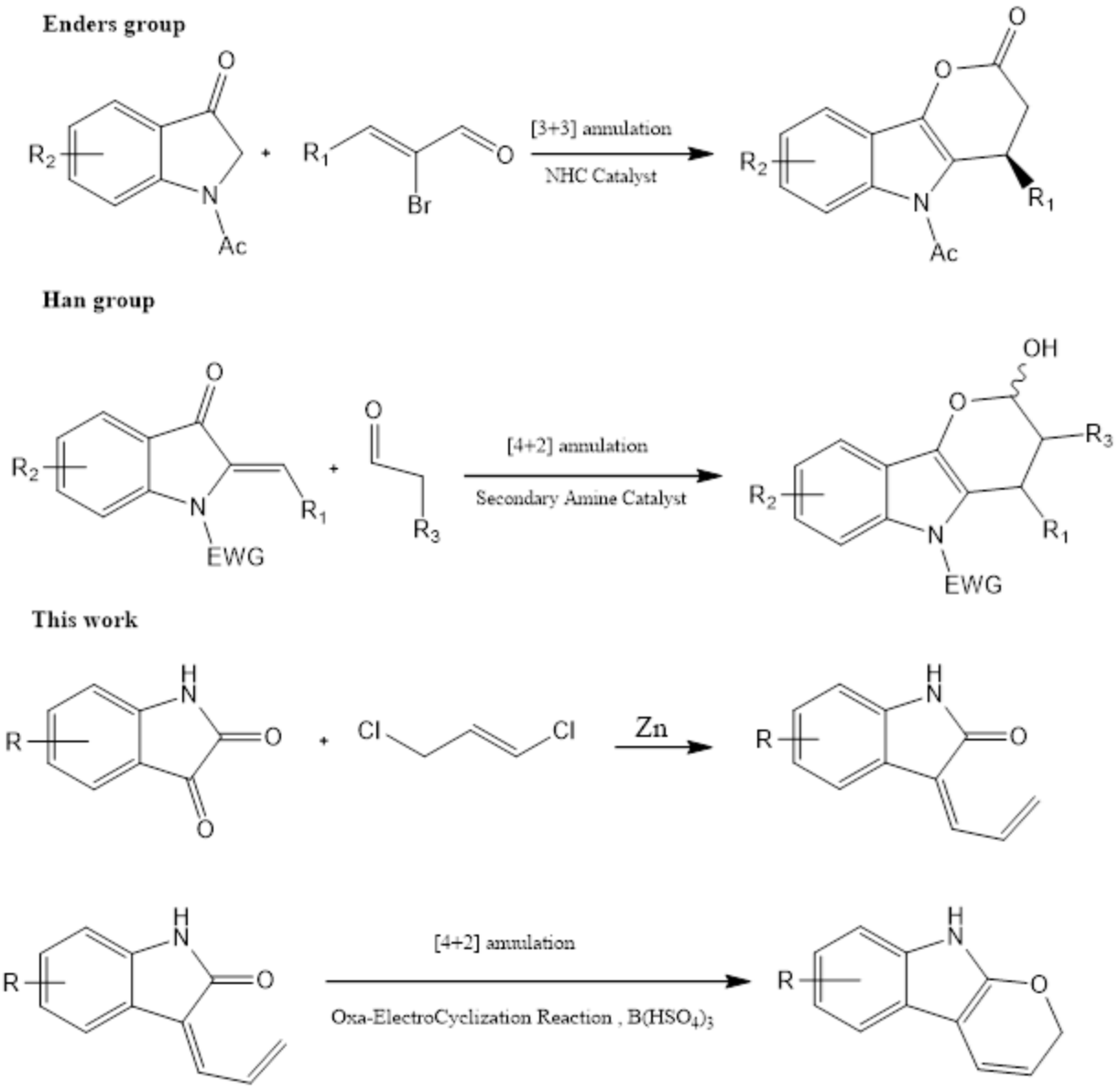

Figure 2

Methods for synthesis of hydropyran-fused indoles

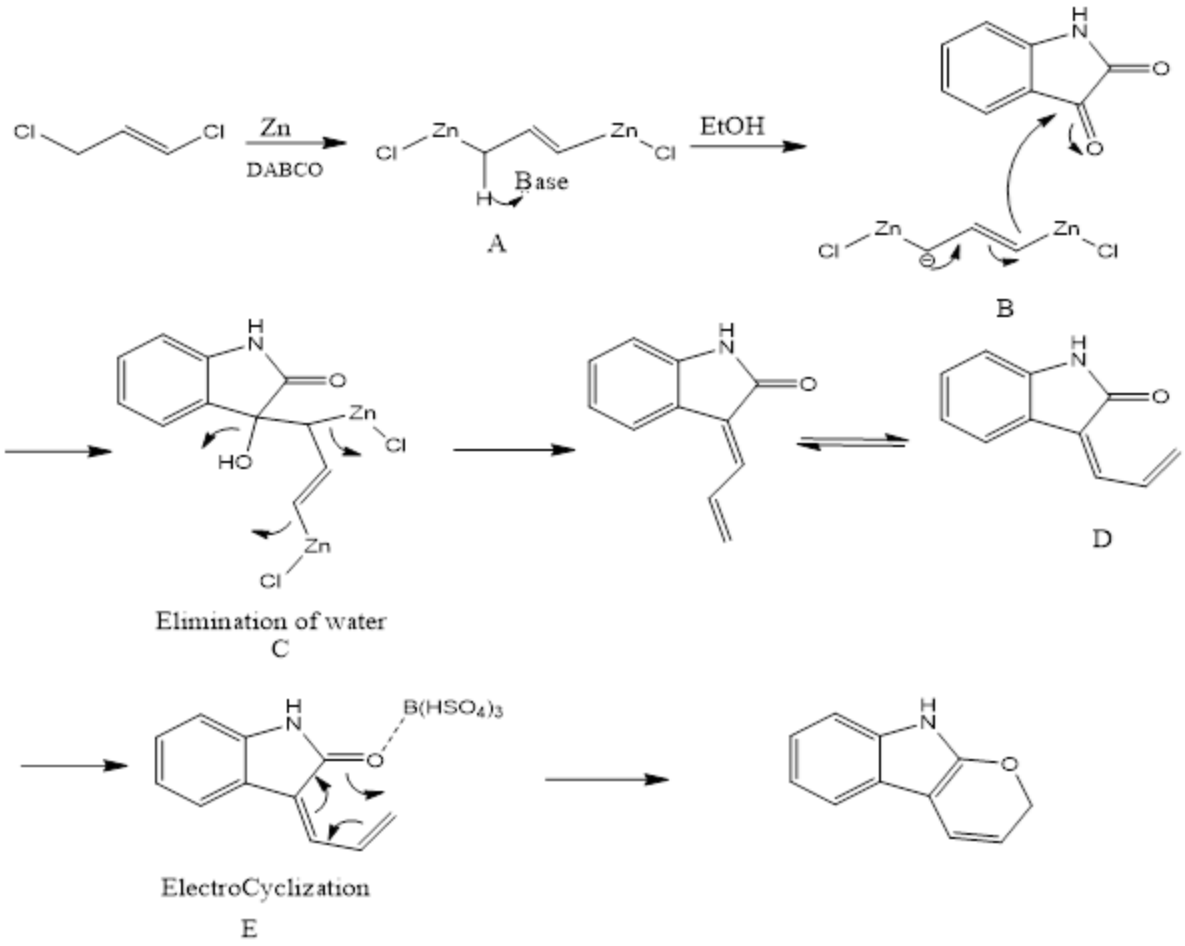

Figure 3

Proposed mechanism of process from start to 2a-2i intermediates and finally getting 3a-3i products

Supplementary Files

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