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NOVEL SYNTHESIS OF FUSED SPIRO β-LACTAMS FROM *N*-METHYL-ISATIN

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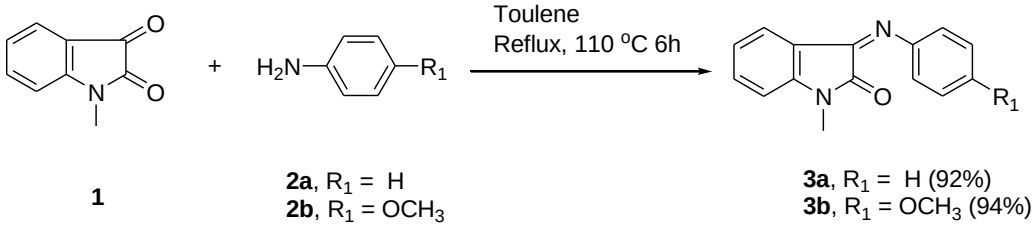
ABSTRACT: Among the different classes of useful heterocyclic molecules, the spiro-lactams synthesised from indole derivatives were extensively explored due to their bioactivity and utility in an array of scientific domain like drug design and organic synthesis. In the present study, several spiro β-lactams have been synthesised by Staudinger (2+2) cycloaddition reaction of *N*-methyl isatin derived Schiff bases with various acid chlorides in the presence of triethylamine and anhydrous dichloromethane. Two new distinctive diastereomeric spiro β-lactams were prepared by the above reaction.

KEYWORDS: Isatin, Spiro β-Lactam, Schiff base, Acid chloride, Heterocycles

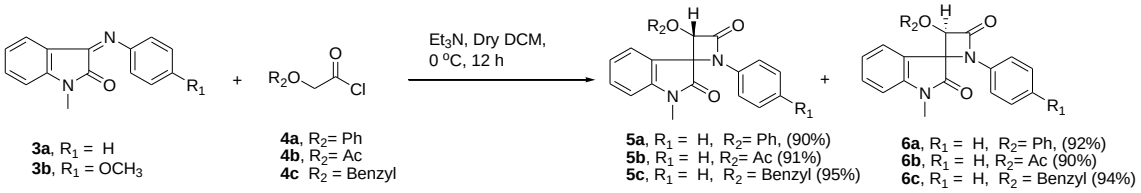
INTRODUCTION:

The β-lactam skeleton has gained significant interest among synthetic as well as medicinal chemists over the last decade, as it represents the core structure of synthetic and natural β-lactam antibiotics. The importance of the β-lactam unit as a synthon has been recognised in the synthesis of a variety of natural β-lactam antibiotics and other spirocyclic lactam derivatives[i-iv]. The constant need for new drugs displaying broader antibacterial activity and the necessity for new β-lactam antibiotics to combat microorganisms that have built up resistance against traditional drugs have sustained the interest of organic chemists for decades[v]. Spiro azetidin-2-ones have created continuous interest to the synthetic and medicinal chemists[vi]. β-Lactams function as antibacterial agents by inhibiting the synthesis of bacterial cell walls[vii]. Recent studies have shown that spiro β-lactams have antiviral and antibacterial properties[viii]. The goal of the present study is to synthesise spiro β-lactams *via* the Staudinger (2+2) cycloaddition method using isatin derivatives and acid chlorides in the presence of triethylamine and anhydrous dichloromethane.

We have demonstrated significant research on β-lactams for the past more than 30 years[ix,x,xi,xii,xiii-xxviii]. New synthetic routes and medicinal properties of β-lactams have been available through our independent research[xxix]. Although a number of methods are available for the preparation of β-lactams, cycloaddition of imines with acid chloride (equivalent) in the presence of tertiary amines remains the best choice[xxx]. This reaction produces β-lactams stereoselectivity. The stereochemistry of the products depends on numerous factors. Out of these factors, structures of the reactants (acid chloride and imine), condition of the experiments, order of addition of the reagents and temperature of the reaction affects the stereochemistry of the products[xxxi]. However, stereochemistry remains the same regardless of the conditions of the experiments in some examples[xxxii]. In the present investigation, first Schiff bases were synthesised (**3a-b**) (Scheme-I) and then, Staudinger (2+2) cycloaddition reaction was carried out using these Schiff bases in dry dichloromethane with acid chlorides **4a-c** in the presence of triethylamine to afford two types of diastereomeric β-lactams **5a-c** and **6a-c** (Scheme-II).



Scheme-I. Synthesis of Schiff bases from N-methyl isatin and aromatic amines



Scheme-II. Synthesis of fused spiro β-lactams

EXPERIMENTAL:

The progress of the reaction was monitored by thin layer chromatography on silica gel coated aluminum plates (Merck) as adsorbent and UV light as visualizing agent. The purity of the compounds was monitored by TLC and UV light as visualizing agents. ^{1}H NMR spectra were recorded on Varian 500 MHz NMR spectrophotometer using $CDCl_3$/DMSO-d6 as solvent and TMS as an internal standard (chemical shifts in δ ppm).

GENERAL PROCEDURE:

For the Synthesis of Diastereomeric β-Lactams

A solution consisting of acid chloride (1.5 mmol) in dichloromethane (2 mL) was added to imine (1 mmol) and triethylamine (3 mmol). The reactants were stirred for 10-12h at cold conditions. The reaction mixture, washed with saturated sodium bicarbonate solution (10 mL), dilute hydrochloric acid (10%, 10 mL), brine (10 mL), dried with anhydrous sodium sulfate and evaporated to obtain the crude product. The proton NMR was performed to calculate the ratio of the isomeric β-lactams. The pure products were then obtained *via* column chromatography over silica gel using ethyl acetate-hexanes (1:4) as the solvent.

RESULTS AND DISCUSSION:

Among the heterocyclic molecules, isatin has an activated carbonyl group with indole skeleton. The reactivity of this carbonyl group was used by our group during the preparation of pyrrole-substituted isatins. In the step one of the current methodology, *N*-methyl isatin **1** condensed with different aromatic amines **2** in anhydrous toluene in the ratio of 1:1 to prepare various Schiff bases **3** (Scheme-I). The reactants were refluxed to produce the imines in excellent yield. Subsequently, Staudinger (2+2) cycloaddition reaction was performed using Schiff bases **3a-b** in dry dichloromethane with acid chlorides **4a-c** in the presence of triethylamine to afford two types of diastereomeric β-lactams **5a-c** and **6a-c** in more than 90% yields (Scheme-II).

The ^{1}H NMR data of the crude products was used to determine the ratio of the products. In general, isomeric ratio was 1:1 regardless of the substituents. The compounds **5a-c** and **6a-c** were separated using column chromatography (15% EtOAc/Hexane solvent). They are unique in structures as a 4-membered cyclic amide is fused with a five-membered cyclic amide in a spiro derivative.

CONCLUSION:

The present study focused mainly on the synthesis of beneficial scaffolds like fused spiro β-lactams from isatin derivatives in excellent yields. Structurally these spiro β-lactams are novel and sterically congested.

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