



Highly efficient and regioselective synthesis of spirooxindolo pyrrolizidines by reaction of isatin, proline and acrylonitrile/methyl acrylate in water



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ABSTRACT

A simple, ecofriendly and regioselective three-component condensation of nonstabilized azomethine ylides generated in situ from isatins and L-proline with acrylonitrile/methyl acrylate to give spirooxindolo pyrrolizidines has been realized. The reaction highlights the use of water as a reaction medium with good to excellent yields of products from readily available precursors.

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Introduction

The synthesis of drug-like spirocyclic compounds has attracted considerable attention due to their wide spread applicability in biomedical sciences as they show great potential for binding to many biomolecules.¹ In particular, the spirooxindolo pyrrolidine kind of framework constitutes the core units of many naturally occurring alkaloids such as horsfiline,^{2,3} elacomine⁴ and mitraphylline.⁵ Recently, these kinds of molecules have been shown to possess promising antitubercular activity.⁶

Due to significant biological activities, the synthesis of spirocyclic oxindoles has been a matter of continuous research as a result various researchers around the world are actively involved in their designing and synthesis. For these kinds of molecules, generally isatin and their derivatives have been employed as a starting precursor.

The 1,3-dipolar cycloaddition of azomethine ylides generated in situ via decarboxylative condensation of isatins and α -amino acids with olefin have been widely utilized as a key approach for the regio- and stereoselective construction of a variety of spirooxindoles. In general, these reactions are highly favoured due to the milder reaction conditions as well as extension of the scope of substrates. A variety of spirooxindolo pyrrolidines having

a wide variation of α -amino acids,⁷ and 1,3-dipolarophiles such as α,β -unsaturated ketones,^{8–10} arylidenemalonodinitriles,¹¹ α,β -unsaturated lactones,¹² nitrostyrenes,¹³ acrylamides¹⁴ and various other electron deficient alkenes^{15–17} have been documented (Fig. 1).

Despite having significant advancement in these cycloaddition reactions, most of the literature protocols have utilized organic solvents like MeOH or EtOH as a reaction media. Recently, a great deal of attention has been paid on the use of water as a reaction media and it has been demonstrated as a better solvent despite having certain limitations.^{18–20} Water has emerged advantageous over many traditional organic solvents due to its properties like being non-toxic, easy availability and handling in workup processes.^{21–23}

As a part of our plan aimed at developing new methods for the synthesis of biologically important heterocycles,^{24–29} we were inspired to investigate the environment friendly conditions for

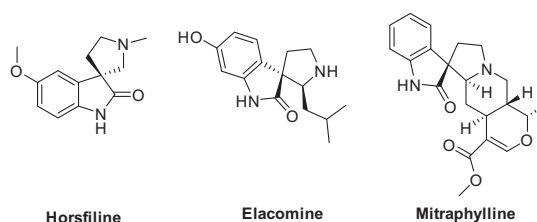
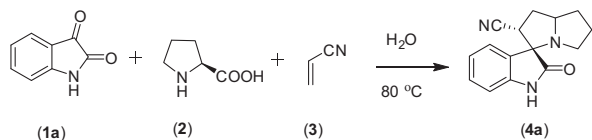


Figure 1. Some selected bioactive molecules having spirooxindole framework.

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Scheme 1. Three component synthesis of **4a**.

Table 1
Optimization of reaction with various solvents

| Entry | Solvent | Temp (°C) | Time (h) | Yield ^a (%) |
|-------|-----------------------------|-----------|----------|------------------------|
| 1 | CH ₃ CN | 80 | 2 | 70 |
| 2 | MeOH | 70 | 2.5 | 60 |
| 3 | EtOH | 80 | 2 | 75 |
| 4 | H ₂ O | 80 | 4 | 78 |
| 5 | Toluene | 100 | 3 | 55 |
| 6 | CHCl ₃ | 80 | 3 | 60 |
| 7 | MeOH/H ₂ O (1:1) | 70 | 2 | 65 |
| 8 | EtOH/H ₂ O (1:1) | 80 | 2 | 64 |
| 9 | THF | 60 | 3 | 58 |

^a Isolated yield, the reaction was performed on 200 mg scale.

the synthesis of spirooxindolo pyrrolizidine hybrid molecules. Herein, we wish to report an efficient and regioselective protocol for synthesis of spirooxindolo pyrrolizidines via three component reaction of isatin, L-proline and acrylonitrile and methyl acrylate in water.

Table 2
Various molecules with reaction time and yields

| Entry | Structure | Time (h) | Yield ^a (%) | Entry | Structure | Time (h) | Yield ^a (%) |
|-------|-----------|----------|------------------------|-------|-----------|----------|------------------------|
| 1 | | 4 | 78 | 9 | | 4 | 73 |
| 2 | | 4.5 | 74 | 10 | | 5 | 70 |
| 3 | | 5 | 75 | 11 | | 3.5 | 72 |
| 4 | | 4 | 72 | 12 | | 4.5 | 75 |
| 5 | | 4.5 | 70 | 13 | | 4 | 70 |
| 6 | | 3.5 | 70 | 14 | | 3.5 | 75 |
| 7 | | 4 | 72 | 15 | | 4 | 74 |
| 8 | | 4.5 | 75 | 16 | | 5 | 75 |

^a Yields are calculated after recovering the unreacted isatin.

Results and discussion

Initially, we began the reaction by taking isatin (**1a**), L-proline (**2**) and acrylonitrile (**3**) in equimolar ratio using water as a solvent and the reaction mixture was heated at 80 °C (Scheme 1). In the beginning, the reaction mixture appeared to be homogeneous and there was no solid visible but with the advancement of reaction some solid precipitated out.

The reaction mixture was heated for about 4 h after when TLC indicated the consumption of L-proline but small amount of isatin (**1a**) remained unreacted. Although, we added approximately 0.2 equiv of L-proline (**2**) and acrylonitrile (**3**) additional in order to consume the remaining isatin it did not affect the reaction. After the reaction, the reaction mixture was extracted with ethyl acetate and evaporated on rotary evaporator to provide yellow coloured solid. The solid was purified by column chromatography to give **4a** as a white solid which was characterized by 1D and 2D NMR studies as well as mass analysis. We carried out similar set of experiments with substituted isatin which gave similar kind of products (**4b–4g**). The reaction timing for various isatin varied from 3.5 to 5 h with the percentage yield from 70% to 78% (yield calculated based on recovered isatin) (Table 2).

In order to prove water as a better solvent for this 1,3-dipolar cycloaddition reaction, we performed similar set of reactions by changing the solvent like CH₃CN, THF, MeOH, EtOH, Toluene, MeOH/H₂O (1:1) and EtOH/H₂O (1:1) (Table 1). In case of CH₃CN and MeOH, the TLC indicated the formation of small amount of product less polar than desired compound which could be probably

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