Tetrahedron 74 (2018) 3596–3601

Contents lists available at ScienceDirect

Tetrahedron

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

An expeditious access of 2,5′-dioxo-5′,6′,7′,8′-tetrahydro-1′H-spiro [indoline-3,4′-quinoline]-3′-carboxylate by reaction of isatin, ethyl cyanoacetate and enaminone in water

Keshri Nath Tiwari*, S.M. Prabhakaran, Vaneet Kumar, Thakar Snehal Rajendra, Shintu Mathew

Department of Medicinal Chemistry, National Institute of Pharmaceutical Education and Research (NIPER), ITI Compound, Raebareli, 229010, India

ARTICLE INFO

Article history:
Received 21 February 2018
Received in revised form
4 May 2018
Accepted 7 May 2018
Available online 16 May 2018

Keywords:
Isatin
Enaminone
Ethyl cyanoacetate
Spirooxindole
Multicomponent reaction

ABSTRACT

We have demonstrated three component reaction of isatin, enaminone and ethyl cyanoacetate leading to sprirooxindole scaffold without catalyst in water. The synthetic protocol has several advantages like wide substrate scope, atom-economy and operationally simple experimental procedures which provides rapid access to library of compounds. The mechanistic details of the reaction has been investigated during the course of study.

1. Introduction

Multicomponent reactions are widely explored as a synthetic tool due to their atom economy, operationally simple procedures and flexible substrate scope.[1] Such reactions create several covalent bonds in one pot and provide a quick access to library of molecules for combinatorial chemistry. These reactions also provide opportunity to create complex molecular structure with several contiguous stereocentres which otherwise require several steps in linear synthesis. There has been major concerns in development of multicomponent reactions with respect to reaction media particularly solvents.

Now a days, much attention is also being paid on the development of synthetic methods using water as a reaction media in view of the fact that many toxic solvents contribute to the environmental pollution.[2] Water is a non-hazardous, non-toxic and inexpensive solvent and despite having certain limitations like poor solubility of organic substrates, many organic reactions have now been widely demonstrated using water as a reaction media.[3] Several metal catalyzed reactions which were initially considered difficult are now also carried out in aqueous media for the synthesis of pharmaceutically active ingredients.[4] It is also considered as near to ideal green solvent due to its recyclability and environmental benign reasons. Therefore, it is highly desirable to develop synthetic processes that can be performed in aqueous media.

The nitrogen containing spirocyclic oxindoles are featured in a number of natural products as well as medicinally active compounds and exhibit a broad spectrum of bioactivities like antimicrobial, antibacterial and anti-inflammatory.[5] Particularly, the six member nitrogen containing spirooxindoles have garnered considerable interest due to their pharmaceutical applications as well as structural complexity.[6]

For example Surugatoxin, having similar spirooxindole have been found as ganglionic blocker of nicotinic acetylcholine receptors and cipargamin (NITD609) is an antimalarial drug belonging to spiroindolone class (Fig. 1).[7]

The reaction of isatin with 1,3-cyclohexadione leading to spirooxindoles[8] has been recently reported. However, the reaction of isatin with enaminones have been shown to yield pyrroloquinolones under cascade conditions.[9] The three component reaction of isatin, enaminone and ethyl cyanoacetate have not been explored so far to the best of our knowledge.

* Corresponding author.
E-mail address: keshri.tiwari@niperraebareli.edu.in (K.N. Tiwari).

https://doi.org/10.1016/j.tet.2018.05.020
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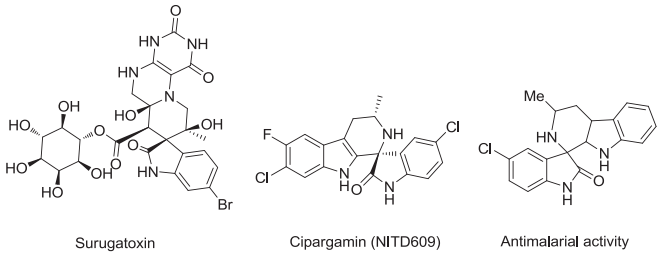


Fig. 1. Some biologically active spirooxindoles.

As a part of our research plan aimed at developing new synthetic methodologies for the creation of biologically important molecules,[10] we inspired to investigate greener protocols for generation of dihydropyridine fused spirooxindoles. Along this line, we wish to report the synthesis of 2,5′-dioxo-5′,6′, 7′, 8′-tetrahydro-1′H-spiro [indoline-3,4′-quinoline]-3′-carboxylate by reaction of isatin, ethyl cyanoacetate and enaminone using water as a solvent.

2. Results and discussion

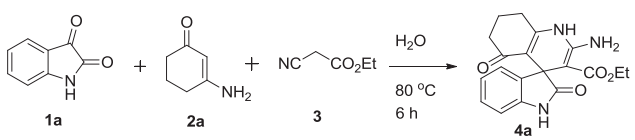
The reaction of isatin (**1a**), enaminone (**2a**) and ethyl cyanoacetate (**3**) was chosen as a model substrate using water as a reaction media. The three substrates in equimolar ratio were heated at 80 °C without catalyst. In the beginning, the colour of reaction mixture was orange but after the few hours of reaction, the light yellow solid precipitated out.

The solid precipitated in small amount was identified as product (**4a**) by TLC. The aqueous layer was extracted with ethyl acetate several times. The precipitated solid was further dissolved in combined organic layer which was evaporated and purified by silica gel column chromatography to afford product (**4a**) in 61% of yield (Scheme 1). On structural characterization by NMR spectral analysis, the product was identified as ethyl 2′-amino-2,5′,6′, 7′, 8′-tetrahydro-1′H-spiro [indoline-3,4′-quinoline]-3′-carboxylate (**4a**).

The reaction provided the expected product in good yield with relatively shorter duration. To obtain the optimized conditions, the reaction was screened in different solvents using model substrate. It is quite evident from Table 1 that water acts as better solvent in comparison to organic solvents like MeOH, EtOH, THF, CH_3CN etc. for this reaction. The yield of the reaction was found maximum in water as compared to other solvents after six hours of reaction. The reactions in other solvents were continued for even longer hours (up to 24 h) but either reaction was not completed or degradation happened. The yield is based on isolation of expected product after 6 h of reaction. The temperature of reaction was fixed based on reflux temperature of particular solvent in order to keep optimal conditions as at higher temperature decomposition was observed.

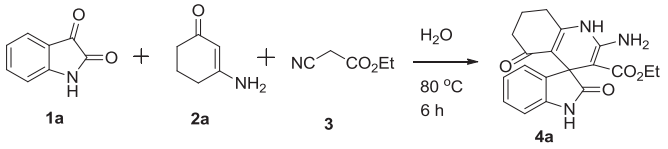
To investigate further, the scope of reaction was explored with different substituted isatin and enaminone. Firstly, the scope of isatin substitution was examined on the course of reaction and to our happiness all the isatins were found reactive towards the optimized reaction conditions to provide good to excellent yield of products (Scheme 2).

To extend the synthetic strategy, the scope of enaminone was



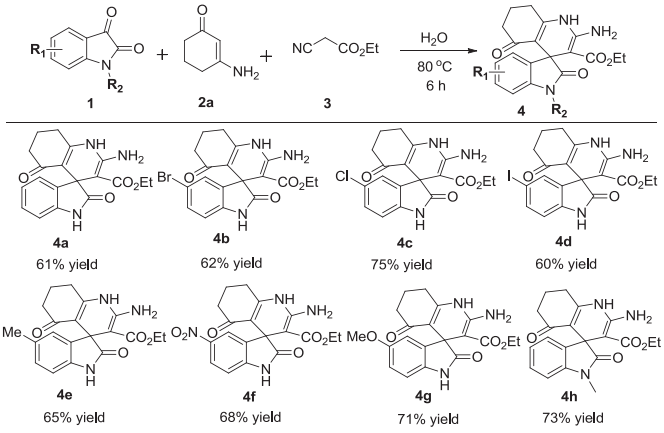
Scheme 1. Three component reaction of isatin, enaminone and ethyl cyanoacetate.

Table 1
Optimization of condition[a].



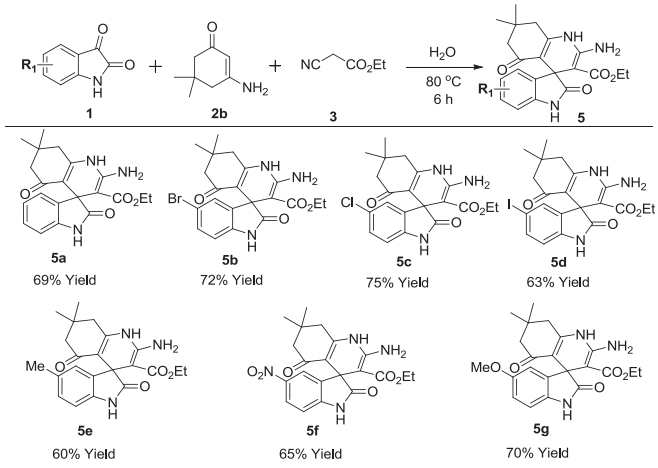
Entry	Solvent	Temp. (°C)	Time (h)	Yield (%)[b]
1	MeOH	65	6	30
2	EtOH	75	6	35
3	DCE	80	6	20
4	CH_3CN	80	6	45
5	DMF	120	6	50
6	H_2O	80	6	61
7	Toluene	100	6	35
8	THF	60	6	50

[a] Reaction conditions Isatin (1.36 mmol), Enaminone (1.36 mmol), ECA (1.36 mmol).
[b] Isolated yield after silica gel chromatography.



Scheme 2. Examples of three component reaction with **2a**.

next studied. The enaminone with dimedone was prepared by our recently developed protocol in water.[10c] Consequently, the two enaminones **2a** (Scheme 2) and **2b** (Scheme 3) were found compatible with several isatins and provided expected product



Scheme 3. Examples of three component reaction with **2b**.