Tetrahedron 69 (2013) 10933–10939

Contents lists available at ScienceDirect

Tetrahedron

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

A one-pot synthesis of isoindolin-1-imine derivatives

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ARTICLE INFO

Article history:
Received 10 September 2013
Received in revised form 16 October 2013
Accepted 21 October 2013
Available online 30 October 2013

Keywords:
2-Cyanobenzaldehyde
4-Hydroxycoumarin
Isoindolin-1-imine
4-Hydroxyquinolin-2(1*H*)-one
One-pot reaction

ABSTRACT

A one-pot procedure was developed for the synthesis of isoindolin-1-imine derivatives by a simple three-component condensation of 2-cyanobenzaldhyde, ammonium acetate, and 4-hyroxycoumarin derivatives or 1,3-dicarbonyl compounds or 4-hydroxyquinolin-2(1*H*)-one in ethanol under reflux for 20–60 min with excellent yields. The advantages of this procedure are operational simplicity, excellent yields, and short reactive time, without catalyst, easy workup, and green environmental impact.

1. Introduction

Isoindole and its derivatives are one of the most important classes of *N*-heterocyclic biological active compounds.[1] They have been received considerable attention from synthetic pharmacists and chemists due to their potent therapeutic and pharmacological activities.[1,2] Isoindolin-1-imine series are an important class of isoindoles, and have exhibited typical pharmacological activities, including as NR2B-selective NMDA receptor antagonists,[2c] the thrombin receptor (PAR-1) inhibitors,[2c,d] and antiproliferative effect.[2]

Since the first multi-component reaction (MCR) was accomplished in 1850 by Strecker,[4a] MCRs have been especially important to the organic synthesis due to operational simplicity, high productivity, short reaction time, and high yield without isolating the intermediates from simple and popular starting materials.[4] Up to date, many well-known MCRs, such as alkyne trimerization,[4b] Kabachnik–Fields reaction,[4c] Biginelli reaction,[4d] Asinger reaction,[4e] Mannich reaction,[4f] Passerini reaction,[4g] and Ugi reaction[4h] have been described. Interestingly, in the past few years, many previous studies have provided useful pharmacological and biological testing results in in vitro, in vivo, and animal models,[1–3] therefore the important aspects of MCRs have been widely recognized and applied as a powerful tool for the general synthesis of important biologically active compounds, in particular the synthesis of *N*-heterocyclic compounds.[1–4]

The literature procedures for the synthesis of isoindolin-1-imine derivatives involved in multi-step strategies not only in low yields, but also required tough reaction conditions and prolonged reaction time.[2a,3,4i,k] Therefore, to develop useful and efficient methods for the synthesis of isoindolin-1-imine derivatives is necessary.

Very recently, our research group reported a novel procedure for 2-substituent-3-alkoxy-isoindolin-1-imine via a three-component reaction of 2-cyanobenzaldehyde, primary amine, and alcohol in the presence of acetic acid[4i] or 3-methyl-1*H*-pyrazol-5(4*H*)-one[4k] with good yields and wide scope. As the continuing work for further development of new procedures for the synthesis of isoindolin-1-imine derivatives, we sought to take our interest to highly biologically active substrates, such as coumarin derivatives.

4-Hydroxycoumarin and its derivatives are a well-known class of coumarins, which was isolated from various plants.[5] Some of them have exhibited useful pharmacological properties, such as anticancer,[6] antibacterial,[6] anti-HIV, and antioxidant activities.[5,6] In addition, 4-hydroxycoumarin and its derivatives are also known as vitamin K antagonist anticoagulant drugs, which have widely used in USA and Canada under the name of racemic sodium warfarin (Fig 1), for anti-HIV-1 PR activity,[6] acetyl cholinesterase (AChE) inhibitor,[6] epilepsy, stroke, schizophrenia, and Alzheimer disease.[6] Due to their potential biological activities, we initially chose 4-hydroxycoumarin derivatives as the nucleophilic reagent to

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http://dx.doi.org/10.1016/j.tet.2013.10.076

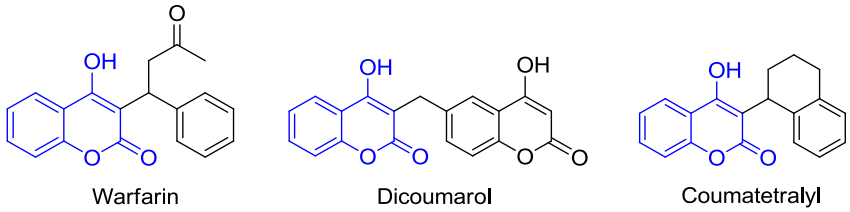
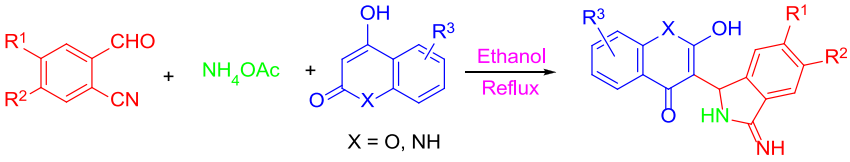


Fig. 1. Some biologically active 4-hydroxycoumarin derivatives.[5]

investigate the one-pot procedure for the synthesis of isoindolin-1-imine derivatives.

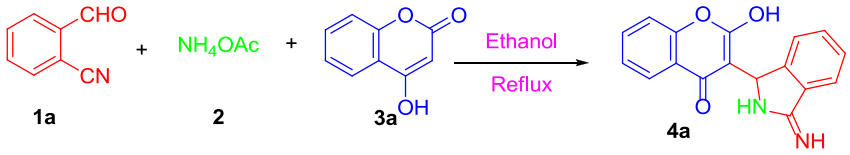
In continuing effort of our laboratory toward the further synthesis of isoindolin-1-imine derivatives, herein we report a simple one-pot method for the synthesis of isoindolin-1-imine derivatives via a three-component condensation of 2-cyanobenzaldehyde, ammonium acetate, and 4-hydrocoumarin derivatives or 1,3-dicarbonyl compounds, or 4-hydroxyquinolin-2(1*H*)-one derivatives in dry ethanol with excellent yields (Scheme 1).



Scheme 1. Synthesis of isoindolin-1-imine derivatives.

2. Results and discussion

Based on our previous results,[4i,k] we continued to explore the three-component condensation reaction of 2-cyanobenzaldehyde **1** (3 mmol), ammonium acetate **2** (3 mmol), 4-hydroxycoumarin (4-hydroxy-2*H*-chromen-2-one) **3a** (3 mmol) in dry ethanol under reflux for 20 min (Scheme 2). The condensation reaction proceeded smoothly, quickly, and a white solid was formed in reaction solution. When the reaction completed, the white solid was filtered and washed with acetone to give 2-hydroxy-3-(3-iminoisoindolin-1-yl)-4*H*-chromen-4-one **4a** in excellent yield (95%). Its structure was confirmed by NMR data and LC–MS.



Scheme 2. Synthesis of 2-hydroxy-3-(3-iminoisoindolin-1-yl)-4*H*-chromen-4-one (**4a**).

Initially, the influence of different solvents on this condensation was investigated. The results were summarized in Table 1. It was showed that the target product **4a** was afforded in low to moderate yields in DCM (entries 1, 2), benzene (entry 3), DCE (entry 4), CH_3CN (entry 5), THF (entry 6), H_2O (entries 11–13), and in good yield in MeOH (entry 10). The multi-component reaction was also carried out in EtOH at room temperature for 20 min, to give the product in about 30% yield (entry 7), and then the reaction was also carried out under reflux for 20 and 120 min, and gratifyingly, under reflux condition afforded product **4a** in excellent yields (entries 8, 9). Thus, dry ethanol was selected as the condensation media for further reactions. Finally, the best reaction conditions were obtained in ethanol under reflux for 20 min without any catalyst, and this condition was chosen for further synthesis of isoindolin-1-imine derivatives.

To further demonstrate the scope of this condensation reaction, we continued to screen the significant effects of reagent **2** to this three-component reaction on the yields (Table 2). When reagent **2** was ammonium salts of strong acids, such as HCl and H_2SO_4 (Table 2, entries 5, 6), only a trace amount of compound **4a** was observed in reaction solution. When NH_3, NH_3/AcOH (1/1, equiv/equiv) or NH_4OAc was used as reagent **2** under similar conditions (Table 2, entries 1–4, 7–11), compound **4a** was obtained in moderate to excellent isolated yields (40–95%). When ammonia solution or ammonia/AcOH solution was used, the yield of this condensation reached 78% (Table 2, entries 10, 11), whereas ammonium acetate (**2**) was the most effective reagent in term of yields of product **4a** (Table 2, entries 1–4). When the amount of ammonium acetate increased from 1.0 (equiv) to 2.0 (equiv), no significant impact had

Table 1
Solvent screening for the synthesis of **4a**

Entry	Solvent	Time (min)	Yield **4a**[a] (%)
1	DCM	20	33
2	DCM	120	46
3	Toluene	20	30
4	DCE	20	35
5	CH_3CN	20	47
6	THF	20	32
7	EtOH	20	30
8	EtOH	20	95
9	EtOH	120	96
10	MeOH	20	88
11	H_2O	20	15
12	H_2O	20	60
13	H_2O	120	65

Conditions: 2-cyanobenzaldehyde **1** (2 mmol), ammonium acetate (2 mmol), 4-hydroxycoumarin **3a** (2 mmol), solvent (3 mL), reflux.
[a] Isolated yields.