$InCl_3$ Promoted Synthesis of Pyrano[3,2-*h*]quinolines via Microwave Irradiation

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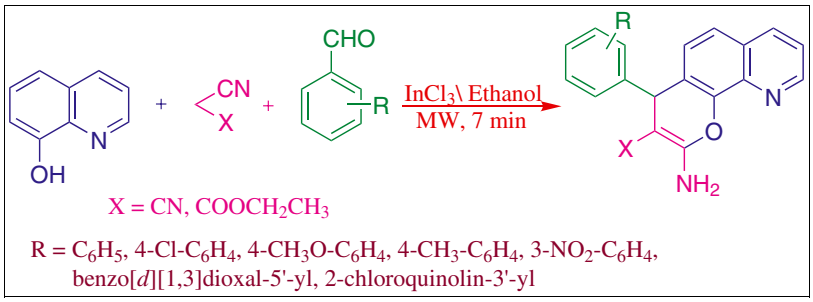

An efficient and economical method has been developed for the synthesis of pyrano[3,2-*h*]quinolines via an indium trichloride-catalyzed one-pot three-component reaction of 8-hydroxyquinoline with aromatic aldehydes and malononitrile/ethyl cyanoacetate under microwave irradiation.

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INTRODUCTION

Pyranoquinoline scaffolds are an important class of compounds widely distributed in nature. Notably, they are found in the plants of the Rutaceae family, commonly known as the rue or citrus family. The pyranoquinoline moiety naturally occurring in several plants, Simulenoline (**1**), peroxysimulenoline (**2**), and benzosimuline (**3**), for example, were isolated from the roots of *Zanthoxylum simulans* [1], (−)-ribalinine (**4**) was isolated from the stem bark of *Araliopsis tabouensis* [2], acetylribalinine (**5**) and ribaliprenylene (**6**) were found in the leaves of *Skimmia laureola* [3], and (+)-orixalone D (**7**) was isolated from the stem of *Orixa japonica* [4] (Fig. 1). Pyranoquinolines have attracted considerable attention because of a broad spectrum of pharmacological and biological properties that many of them exhibit [5]. Compounds with the pyranoquinoline motif possess a wide range of biological activities. They can be psychotropic [6], antiallergic [7], anti-inflammatory [8], estrogenic [9], antibacterial [10,11], antimalarial [12], antifungal [13], and anticancer [14] as well as inhibit calcium signaling [15]. Considering all of these potentially beneficial properties, they are currently tested as candidates for potential pharmaceuticals [16].

The advantages of a multi-component methodology are numerous. For example, procedures typically exhibit higher efficiency and operational simplicity, higher overall yield, use of fewer resources, and as a consequence, lower cost and a reduced environmental impact. Because of the increasing public concern toward environmental issues and the obvious advantages of shorter reaction time and higher yield, there is an increasing trend to wherever possible replace multi-step reaction sequences by multi-component reactions in both academic and industrial settings. This is especially factual for the synthesis of bioactive molecules, which are often quite complex and require substantial numbers of synthetic transformations even under the best of circumstances.

Numerous synthetic methodologies have been developed for the construction of pyranoquinolines [17,14,18]. Particularly, hydroxyquinolines are commonly used as reactants [19]. Recently, 2-amino-4*H*-pyrano[3,2-*h*]quinolines had been obtained by refluxing of reactive methylene compounds (i.e., malononitrile or ethyl cyanoacetate) with aldehydes and 8-hydroxyquinoline using an organic base as a catalyst. Catalysts that have been used in this reaction include piperidine [20], pyridine [21], and KF/Al_2O_3 [22]. El-Agrody *et al.* reported a similar kind of reaction leading to 2-styryl-8-hydroxyquinolines, the compounds with significant antitumor activity [23]. Each of these reported procedures has its own merit, but all suffer from limitation of the synthesis to only a narrow range of pyrano[3,2-*h*]quinolines, a difficulty to isolate products or long reaction time and harsh reaction conditions. Thus, there is a need to develop a more general procedure applicable for the preparation of a wide range of pyranoquinolines that at the same time is environmentally benign, rapid, and efficient. Recently, the efficacy of indium(III) as a Lewis acid catalyst [24] has received attention for a range of organic transformations because of the relatively low toxicity indium(III) compounds, their stability in air and water, and their recyclability. These features encouraged our interest in exploring the synthetic

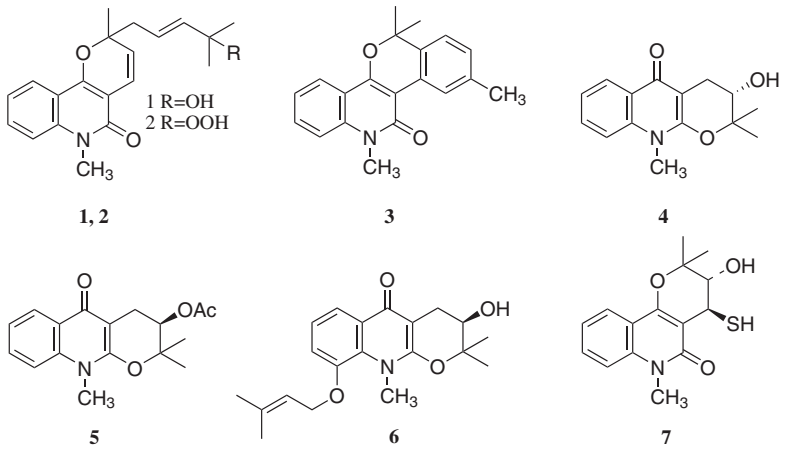


Figure 1. Naturally occurring pyranoquinoline alkaloids.

utility of indium(III) chloride as a catalyst for the synthesis of pyranoquinolines, and herein, we report a simple, high-yielding, convenient, and elegant procedure for the synthesis of 2-amino-4-aryl-4*H*-pyrano[3,2-*h*]quinolines.

RESULTS AND DISCUSSION

In an initial experiment, we investigated the reaction of 1 eq. of each benzaldehyde and malononitrile with 8-hydroxyquinoline in the presence of 20 mol% of various catalysts in refluxing ethanol. Using triethyl amine, dimethyl amino pyridine, L-proline, zinc(II) chloride, and indium triflate or chloride gave yield of only 20–55% of the expected product after recrystallization from ethanol. Several representative results are summarized in Table 1. After systematic screening of the results, indium(III) chloride in ethanol was selected as the most promising among the tested catalysts. In an attempt to improve the yield of the reaction and acknowledging the benefits of an ecologically friendly synthetic pathway, the same reaction was carried out using microwave irradiation. All reactants were sealed in a microwave vessel, mixed thoroughly, and kept in a Biotage microwave oven for 7 min. The completeness of the reaction was monitored by thin layer chromatography, which revealed one single spot of the desired product **5a**. After completion of the reaction, the reaction mixture was concentrated and dried in beaker. Subsequently, the reaction mixture was washed with ethanol to recover the catalyst. The recovered catalyst has been reused for the second time with the same reactivity of $InCl_3$. When the catalyst has been reused more than two times, the reactivity of $InCl_3$ was slightly decreased. To optimize the reaction condition, we evaluated the most appropriate catalyst loading. With the use of 5–25 mol %, increasing in 5 mol% increment of $InCl_3$ at 70°C, the yield steadily increased with a maximum of >85% at 25 mol% of catalyst (Table 2). No additional improvement in the yield was observed upon further increasing the quantity of $InCl_3$.

We then explored the scope and limitations of the reaction involving aromatic aldehydes and malononitrile with 8-hydroxyquinoline, which gave the corresponding 2-amino-4-aryl-4*H*-pyrano[3,2-*h*]quinolines **5** in good

Table 1

Screening of various catalysts on the one-pot reaction.

Entry	Catalyst (20 mol%)	Time (h)[a]	Yield (%)[b] **5a**	Yield (%)[b] **6a**
1	—	5	*d*	*d*
2	Et_3N	5	34	29
3	DMAP	5	20	17
4	L-proline	5	36	34
5	$ZnCl_2$	5	27	21
6	$In(OTf)_3$	5	52	43
7	$InCl_3$	5	54	48

Reaction conditions: 8-hydroxyquinoline (1 mmol), malononitrile/ethyl cyanoacetate (1 mmol), benzaldehyde (1 mmol) in 20 mL ethanol at reflux temperature. *d*, trace amounts.
[a]Time duration of reaction in hours.
[b]Isolated pure product.

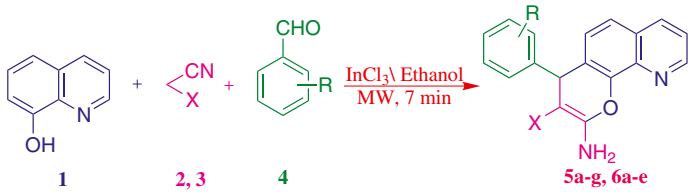
Table 2

Evaluation of most appropriate loading of indium(III) chloride.

Entry	Amount of $InCl_3$ (mol%)	Time (min)[a]	Yield (%)[b] **5a**	Yield (%)[b] **6a**
1	5	7	23	18
2	10	7	45	39
3	15	7	69	63
4	20	7	86	81
5	25	7	90	87

Reaction condition: 1 mmol eq. of each 8-hydroxyquinoline, malononitrile/ethyl cyanoacetate, and benzaldehyde in ethanol at 70°C in a Biotage microwave oven.
[a]No increase of yield after 7 min.
[b]Isolated pure product.

Scheme 1 [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]



1 **2, 3** **4** **5a-g, 6a-e**

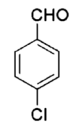
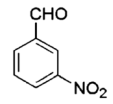
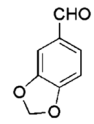
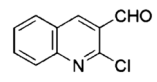
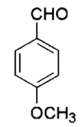
2) X = CN,
3) X = $COOCH_2CH_3$

5a-g) X = CN,
6a-e) X = $COOCH_2CH_3$

R = a) C_6H_5
b) 4-Cl-C_6H_4
c) 3-NO_2-C_6H_4
d) benzo[*d*][1,3]dioxal-5'-yl
e) 2-chloroquinolin-3'-yl
f) 4-CH_3O-C_6H_4
g) 4-CH_3-C_6H_4

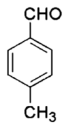
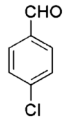
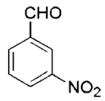
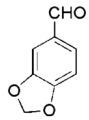
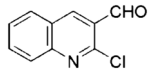
Table 3

Synthesis of 2-amino-4*H*-pyrano[3,2-*h*]quinoline derivatives.

Entry	R	X	Product	Time (min)	Yield (%)
1		CN	**5a**	7	90
2		CN	**5b**	7	88
3		CN	**5c**	7	89
4		CN	**5d**	7	85
5		CN	**5e**	7	86
6		CN	**5f**	7	87

(*Continued*)

Table 3
(Continued)

Entry	R	X	Product	Time (min)	Yield (%)
7		CN	**5g**	7	88
8		COOEt	**6a**	7	87
9		COOEt	**6b**	7	84
10		COOEt	**6c**	7	85
11		COOEt	**6d**	7	81
12		COOEt	**6e**	7	81

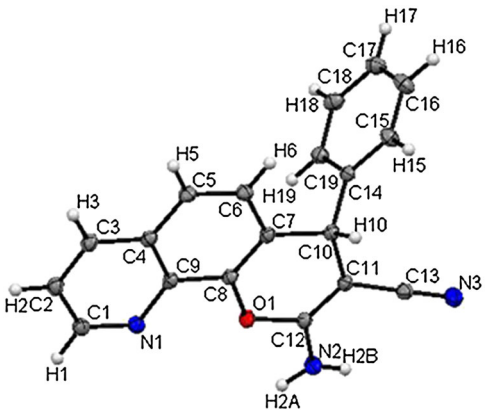


Figure 2. X-ray crystal structure of compound **5a**, thermal ellipsoid representation at the 50% probability level. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

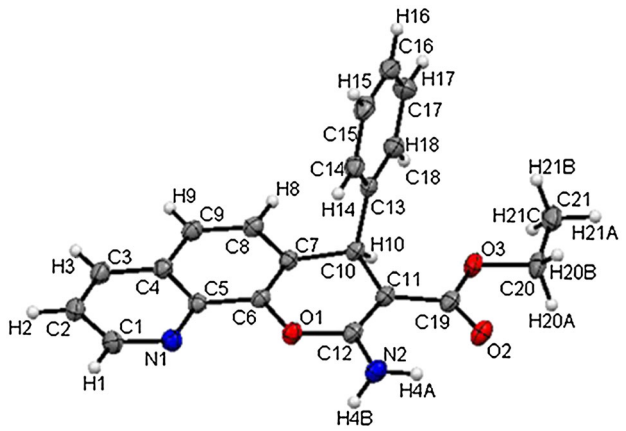


Figure 3. X-ray crystal structure of compound **6a**, thermal ellipsoid representation at the 50% probability level. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

yields as shown in Scheme 1. These results indicated that this one-pot reaction is quite general and has a very broad substrate scope (Table 3). All compounds were isolated by crystallization only, and no chromatographic work-up was required to obtain pure products. The structures of the 2-amino-4-aryl-4*H*-pyrano[3,2-*h*]quinolines **5** were confirmed by IR, mass spectrometry, ^{1}H and ^{13}C NMR spectroscopy, and elemental analysis. Additionally, the structure of one of the products was also determined by single crystal X-ray diffraction. The IR spectrum of compound **5a** shows absorption peaks at 3443, 3324, and 2192 cm^{-1}, which attest to the presence of amino and cyano groups, respectively. The ^{1}H NMR spectrum of **5a** exhibits a broad singlet at δ 7.18, which is the characteristic representation of the amino group protons. The proton at the 4-position of the pyrano[3,2-*h*]quinoline appears at δ 4.96. Finally, the structure of the compound **5a** was confirmed by single crystal X-ray analysis (Figure 2).

To further explore the potential of this protocol for heterocyclic synthesis, we investigated the one-pot reaction involving 8-hydroxyquinoline with aromatic aldehydes and using ethyl cyanoacetate as a third component, to give another series of pyrano[3,2-*h*]quinolines **6** in good yield as shown in Scheme 1. The IR spectrum of compound **6a** shows absorption peaks at 3389, 3285, and 1676 cm^{-1}, which attest to the presence of amino and ester groups, respectively. The two most distinctive ^{1}H NMR signals of **6a** are shifted slightly upfield from those of **5a** to δ 7.88 and 5.08, respectively. Finally, the structure of compound **6a** was also confirmed by single crystal X-ray analysis (Figure 3). These results showed that a one-pot reaction for the efficient synthesis of versatile functionalized pyrano[3,2-*h*]quinolines has been successfully established.

On the basis of the aforementioned experimental results together with related reports [25,26], a plausible mechanism for this multi-component one-pot reaction is suggested in Scheme 2. Initially, an $InCl_3$ mediated Knoevenagel type condensation of the aryl aldehyde **4** with the active methylene compounds **2** or **3** affords the arylidene adduct **A**. Then, Michael addition of 8-hydroxyquinoline **1** to the Knoevenagel adduct **A** yields intermediate **B**, which undergoes aromatization followed by intramolecular cyclization facilitated by $InCl_3$ to the C–N triple bond to give the cyclic intermediate **D** through intermediate **C**. Finally, the pyrano[3,2-*h*]quinolines **5/6** are formed *in situ* by tautomerization of the imino group to an amino group as shown in Scheme 2.

CONCLUSION

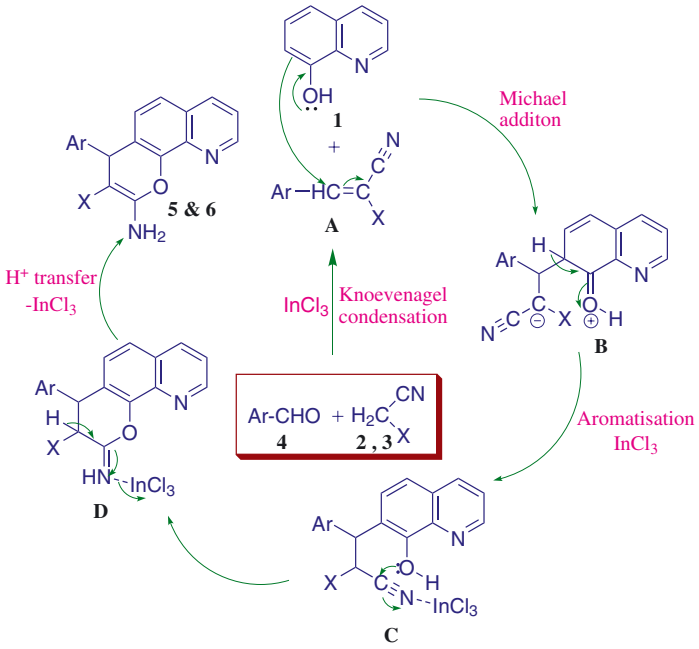
A systematic study on the synthesis and structural elucidation of pyrano[3,2-*h*]quinolines has been presented. We developed a mild and efficient method for the synthesis of pyrano[3,2-*h*]quinolines via a one-pot three-component reaction of 8-hydroxyquinoline with aromatic aldehydes and malononitrile/ethyl cyanoacetate using $InCl_3$ as a catalyst to afford 2-amino-4-aryl-4*H*-pyrano[3,2-*h*]quinoline-3-carbonitriles/carboxylates. The features of this procedure are mild reaction conditions, good to high yield, and operational simplicity.

Acknowledgment. Our sincere thanks go to the Director, ISO Quality Assurance Cell, IICT, Hyderabad, SAIF, IIT Madras, Chennai, for providing access to their mass and NMR spectral facilities. The diffractometer was funded by NSF grant 0087210, by the Ohio Board of Regents grant CAP-491, and by Youngstown State University.

SUPPLEMENTARY DATA

Complete cif files for compound **5a** and **6a** have been deposited with the Cambridge Crystallographic Data Centre

Scheme 2 [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]



as CCDC number 859185 and 871328. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK. [Fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk

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