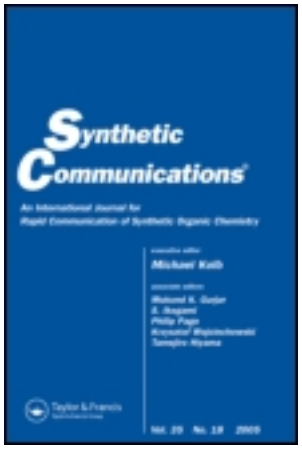

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Simple and Efficient Method for the Synthesis of 1-((Aryl)(2-oxoindolin-3-yl-)methyl)urea and 1-((Aryl)(2-oxoindolin-3-yl-)methyl)thiourea Derivatives

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SIMPLE AND EFFICIENT METHOD FOR THE SYNTHESIS OF 1-((ARYL)(2-OXOINDOLIN-3-YL-) METHYL)UREA AND 1-((ARYL)(2-OXOINDOLIN-3-YL-)METHYL)THIOUREA DERIVATIVES

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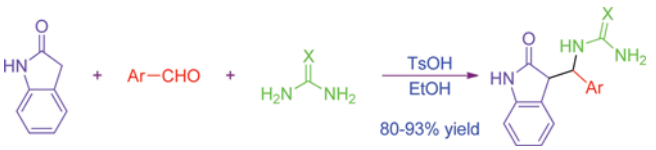
GRAPHICAL ABSTRACT



Abstract *A number of new1-((aryl)(2-oxoindolin-3-yl)methyl)urea and 1-((aryl)(2-oxoindolin-3-yl)methyl)thiourea derivatives have been prepared by simply combining 2-indolinone, aromatic aldehyde, and urea or thiourea in the presence of* p-*TsOH in EtOH. This new methodology affords the title compounds in good yields and without the use of chromatography.*

[Supplementary materials are available for this article. Go to the publisher's online edition of Synthetic Communications® *for the following free supplemental resource(s): Full experimental and spectral details.]*

Keywords Green chemistry; 2-indolinone; multicomponent reaction; *p*-TsOH

INTRODUCTION

The compounds containing urea functional groups are some of the predominant building blocks for a number of biologically active molecules and designed medicinal agents in medicinal chemistry.[1] For examples, Imidocarb, which has a urea functional group, is a drug for the treatment of piroplasmosis. In view of the importance of urea derivatives, many methods for their synthesis are reported using phosgene,[2] isocyanates,[3] carbonyldiimidazole,[4] and $Co_2(CO)_8$.[5] Nevertheless, none of these methods are environmentally benign because all of these procedures use toxic reagents as starting materials. Thus, developing a simple, benign, low cost protocol for the synthesis of urea derivatives is in constant demand.

As a part of our continual efforts towards the development of efficient synthetic procedures for multicomponent reactions,[6] we turned our attention to the

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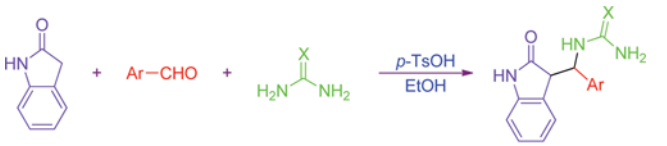


1 2 3 4

Scheme 1. Three-component condensation of 2-indolinone **1**, aromatic aldehyde **2**, and urea **3a** or thiourea **3b**. (Figure is provided in color online.)

synthesis of 1-((aryl)(2-oxoindolin-3-yl)methyl)urea and 1-((aryl)(2-oxoindolin-3-yl)methyl)thiourea derivatives because of their potential biological activities. However, to the best of our knowledge, there have been no reports of synthesis of these compounds. In 2008, Mizar and Myrboh reported a three-component condensation reaction of 2-indolinone, aromatic aldehyde, and urea to form fused pyrimidine derivatives in the presence of KF/alumina.[7] To our surprise, only uncyclized products were obtained when the same starting materials were heated in the presence of *p*-TsOH as the catalyst. We herein report for the first time a one-pot, three-component condensation of 2-indolinone **1**, aromatic aldehyde **2**, and urea **3a** or thiourea **3b** in EtOH that affords 1-((aryl)(2-oxoindolin-3-yl)methyl)urea and 1-((aryl)(2-oxoindolin-3-yl)methyl) thiourea derivatives in good isolated yields in the presence of *p*-TsOH as the catalyst (Scheme 1).

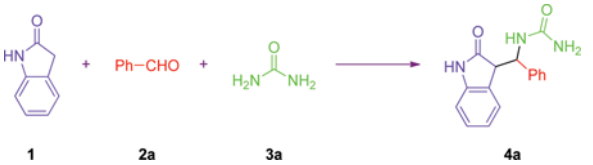
RESULTS AND DISCUSSION

Initially, we studied the one-pot, three-component condensation of 2-indolinone **1** (2 mmol), benzaldehyde **2a** (2 mmol), and urea **3a** (3 mmol) in the presence of 5 mol% of *p*-TsOH in EtOH as solvent at reflux temperature (Scheme 1). To our delight, we observed the formation of product **4a** in a 52% isolated yield after 5 h (Table 1, entry 2). Encouraged by the result, we studied different reaction parameters and the results are summarized in Table 1. As shown in Table 1, the reaction could not take place when the mixture of 2-indolinone **1**, benzaldehyde **2a**, and urea **3a** was stirred under similar conditions in the absence of *p*-TsOH even after heating for 12 h (Table 1, entry 1), thus highlighting the role of *p*-TsOH as a promoter.

We subsequently changed the amount of *p*-TsOH from 0 mol% to 30 mol% in EtOH as solvent under reflux temperature, finding that 15 mol% of *p*-TsOH was sufficient and an excessive amount of catalyst did not increase the yields significantly (Table 1, entries 1–6). Furthermore, we also carried out this three-component condensation in the presence of classical Lewis acid and Brønsted acid as the catalysts, such as $ZnCl_2$, $MgCl_2$, $Cu(ClO_4)_2 \cdot 6H_2O$, $Yb(OTf)_3$, trifluoroacetic acid (TFA), NH_2SO_3H, and MsOH (Table 1, entries 7–13). Unfortunately, the results clearly indicated that the reaction could not proceed smoothly to afford the corresponding products even after heating for 12 h (Table 1, entries 7–10). The reaction could proceed in the presence of Brønsted acid, such as TFA, NH_2SO_3H, MsOH, and *p*-TsOH, and *p*-TsOH showed the best result in terms of yields.

To optimize the reaction solvents, the model reaction was also examined in various solvents in the presence of 15 mol% *p*-TsOH (Table 1, entries 4 and 11–15). As shown in Table 1, THF and EtOAc afforded moderate yields (66–70%), whereas

Table 1. Optimization of the reaction conditions[a]



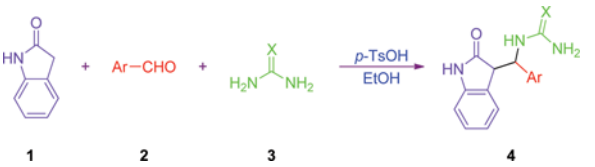
Entry	Catalyst (mol %)	Solvent	Temp. (°C)	Time (h)	Yield of **4a** (%)[b]
1	None	EtOH	Reflux	12	0
2	*p*-TsOH (5)	EtOH	Reflux	5	52
3	*p*-TsOH (10)	EtOH	Reflux	3	80
4	*p*-TsOH (15)	EtOH	Reflux	3	88
5	*p*-TsOH (20)	EtOH	Reflux	3	88
6	*p*-TsOH (30)	EtOH	Reflux	3	90
7	$ZnCl_2$ (30)	EtOH	Reflux	12	0
8	$MgCl_2$ (30)	EtOH	Reflux	12	0
9	$Cu(ClO_4)_2 \cdot 6H_2O$ (20)	EtOH	Reflux	12	0
10	$Yb(OTf)_3$ (20)	EtOH	Reflux	12	0
11	TAA (15)	EtOH	Reflux	10	40
12	NH_2SO_3H (15)	EtOH	Reflux	5	80
13	MsOH (15)	EtOH	Reflux	5	70
14	*p*-TsOH (15)	DCM	Reflux	12	Trace
15	*p*-TsOH (15)	THF	Reflux	5	66
16	*p*-TsOH (15)	EtOAc	Reflux	5	70
17	*p*-TsOH (15)	MeCN	Reflux	3	88
18	*p*-TsOH (15)	DMF	100	3	85

[a]Conditions: 2-indolinone **1** (2 mmol), benzaldehyde **2a** (2 mmol), urea **3a** (3 mmol), and solvent (2 mL).
[b]Isolated yields.

when dichloromethane (DCM) was used as solvent, only a trace amount of the target product **4a** was detected (Table 1, entry 11). The reactions using EtOH(88%), MeCN (88%), and dimethylformamide (DMF) (85%) as the solvents gave the corresponding product **4a** in good yields and short reaction time (Table 1, entries 4, 14, and 15). From the economical and environmental points of view, EtOH was chosen as the reaction medium for all further reactions.

Next, we examined the scope of the reaction by using various aromatic aldehydes **2** and urea **3a** or thiourea **3b** in the presence of 15 mol% *p*-TsOH in EtOH, and the results are summarized in Table 2. The results in Table 2 clearly demonstrated that this one-step, three-component condensation worked well for those aromatic aldehydes bearing a variety of functional groups, such as OCH_3, CH_3, OH, Cl, and Fin 80–93% yields (Table 2, entries 1–6, 11–15). However, we found that 80–85% yields of 3-arylidene-indolin-2-ones **5** (Scheme 2) were observed when using the aromatic aldehydes that carrying functional groups (-NO_2, -CN, -Cl_2) as the starting materials (Table 2, entries 7–10, 16, and 17). We attribute this to the stable nature of the intermediate **5** (Table 2, entries 7–10, 16, and 17) that could not take place with Michael addition with urea **3a** or thiourea **3b** (Scheme 2). Furthermore, both urea **3a** and thiourea **3b** could react smoothly to give the corresponding products **4** in good yields (80–93%) (Table 2). We also used alkyl

Table 2. Condensation of 2-indolinone **1**, aromatic aldehyde **2**, and urea **3a** or thiourea **3b**[a]



1 2 3 4

Entry	Ar	X	Time (h)	Product **4**	Yield (%)[b]
1	C_6H_5 **2a**	O	3	**4a**	88
2	4-MeC_6H_4 **2b**	O	3	**4b**	85
3	4-$MeOC_6H_4$ **2c**	O	2	**4c**	90
4	2-ClC_6H_4 **2d**	O	6	**4d**	84
5	4-ClC_6H_4 **2e**	O	3	**4e**	82
6	4-HOC_6H_4 **2f**	O	2	**4f**	93
7	4-$O_2NC_6H_4$ **2g**	O	12	**4g**	0[c]
8	3-$O_2NC_6H_4$ **2h**	O	12	**4h**	0[c]
9	4-CNC_6H_4 **2i**	O	12	**4i**	0[c]
10	2,4-$Cl_2C_6H_3$ **2j**	O	12	**4j**	0[c]
11	4-FC_6H_4 **2k**	O	3	**4k**	82
12	C_6H_5 **2a**	S	5	**4l**	80
13	4-MeC_6H_4 **2b**	S	5	**4m**	82
14	4-$MeOC_6H_4$ **2c**	S	2	**4n**	90
15	4-ClC_6H_4 **2e**	S	5	**4o**	80
16	4-$O_2NC_6H_4$ **2g**	S	12	**4p**	0[c]
17	4-CNC_6H_4 **2i**	S	12	**4q**	0[c]

[a]Conditions: 2-indolinone **1** (2 mmol), aromatic aldehyde **2** (2 mmol), urea **3a** (3 mmol) or thiourea **3b** (3 mmol), *p*-TsOH (0.3 mmol, 15 mol %), EtOH (2 mL), reflux temperature.
[b]Isolated yields.
[c]Only product **5** was observed.

aldehydes, such as propionaldehyde, butyraldehyde, and cyclopentanecarbaldehyde, as the starting materials, and several side reactions were observed.

To understand the products observed for the *p*-TsOH-catalyzed three-component condensation of 2-indolinone **1**, aldehyde **2**, and urea **3a** or thiourea **3b**, the proposed reaction mechanism is postulated onthe basis of experiment results (Scheme 3). Initially, intermediate **5** is formed by the condensation of 2-indolinone **1** and aldehyde **2** by the action of *p*-TsOH. Then, Michael addition of urea **3a** or thiourea **3b** on **5** leads to the product **4**.

In conclusion, we have developed a novel and efficient method for the synthesis of 1-((aryl)(2-oxoindolin-3-yl)methyl) urea and 1-((aryl)(2-oxoindolin-3-yl)methyl)

1 2 5

R = 3-NO_2, 4-NO_2, 4-CN, 2,4-Cl_2

Scheme 2. Synthesis of 3-arylidene-indolin-2-ones **5**. (Figure is provided in color online.)

Scheme 3. Plausible mechanism for the condensation of 2-indolinone **1**, aldehyde **2**, and urea **3a** or thiourea **3b**. (Figure is provided in color online.)

thiourea derivatives by a three-component condensation of 2-indolinone **1**, aldehyde **2**, and urea **3a** or thiourea **3b** in the presence of *p*-TsOH in EtOH. This process has several advantages from economical and environmental points of view such as short reaction time, good yields, and mild reaction conditions. Therefore, it is an attractive and promising method to synthesize1-((aryl)(2-oxoindolin-3-yl)methyl)urea and 1-((aryl)(2-oxoindolin-3-yl)methyl)thiourea derivatives.

EXPERIMENTAL

Melting points were measured on a WRS-1B micro-melting-point apparatus and are uncorrected. NMR spectra were recorded on a Bruker AMX 300 instrument or Bruker AMX 400 instrument using solvent peaks as dimethylsulfoxide (DMSO-d_6) solutions. HRESIMS were determined on a Micromass Q-T of Global mass spectrometer and ESIMS were run on a Bruker Esquire 3000 Plus spectrometer. Thin-layer chromatography (TLC) was performed on GF254 silica gel plates (Yantai Huiyou Inc., China).

A mixture of 2-indolinone **1** (2 mmol), aromatic aldehyde **2** (2 mmol), urea **3a** or thiourea **3b** (3 mmol), and *p*-TsOH (0.3 mmol, 15 mol%) in EtOH (2 mL) was heated to reflux under stirring for the given time (Table 2). After completion (determined by TLC), the reaction mixture was cooled to room temperature, and then water (10 mL) was added to the mixture and stirred for 5 min. The solid was filtered and recrystallized from EtOH–H_2O (3:1) to afford the pure products **4**.

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