



Recyclable $[\text{Ru}_2\text{Cl}_3(p\text{-cymene})_2][\text{PF}_6]/\text{Cu}(\text{OAc})_2/\text{PEG-400}/\text{H}_2\text{O}$ system for oxidative annulation of alkynes by aniline derivatives: Green synthesis of indoles



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ARTICLE INFO

Article history:

Received 10 December 2016

Received in revised form

8 January 2017

Accepted 9 January 2017

Available online 11 January 2017

Keywords:

Ruthenium

Recycling

Oxidative annulation

Indole

Green chemistry

ABSTRACT

$[\text{Ru}_2\text{Cl}_3(p\text{-cymene})_2][\text{PF}_6]$ in a mixture of PEG-400 and water is shown to be a highly efficient catalyst for the oxidative annulation of alkynes by *N*-2-pyrimidyl-substituted anilines bearing a removable directing group. The reaction could be conducted at 100 °C using $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ (2.0 equiv) as oxidant, yielding a variety of indole derivatives in good to excellent yields. The isolation of the products was readily performed by extraction with petroleum ether and more importantly, both $[\text{Ru}_2\text{Cl}_3(p\text{-cymene})_2][\text{PF}_6]$ and $\text{Cu}(\text{OAc})_2$ in PEG-400/ H_2O system could be easily recycled and reused six times without any loss of catalytic activity.

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1. Introduction

The indole nucleus is one of the most ubiquitous moieties present in many biologically significant natural products as well as pharmaceuticals and agrochemicals.¹ Therefore, many efficient methods for their synthesis have been developed,² one of the most commonly used methods is the Fischer-type indole synthesis.³ In addition, transition-metal-catalyzed cross-coupling reactions and cyclizations have emerged as powerful tools for the selective assembly of indole derivatives.⁴ Numerous transition-metal-catalyzed syntheses of indoles such as cyclization of *o*-alkynylanilines,⁵ annulation of *ortho*-halo-substituted anilines with alkynes,⁶ reductive cyclization of *ortho*-substituted nitroarenes,⁷ and other coupling/condensation tandem reactions,⁸ have been reported in recent years. Very recently, Gu et al. reported the synthesis of indole derivatives via copper-catalyzed [4 + 2] annulation of 2-butoxy-2,3-dihydrofurans with pyrroles.⁹ Both Hegedus indole synthesis and Larock's annulation have proven particularly useful for the construction of indoles.¹⁰ However, most of these methods still suffer from limited availability or high cost of starting materials

due to the use of prefunctionalized starting materials, which reduces the overall atom and step economy.

Recently, transition-metal-catalyzed C–H bond activation (CHA) has provided an alternative tool for the synthesis of heterocycles,¹¹ and several indole syntheses using a C–H bond activation strategy have been reported. Stuart et al. reported an elegant Rh(III)-catalyzed oxidative annulation of internal alkynes by acetanilides leading to *N*-protected indoles.¹² Takemoto and co-workers described an efficient synthesis of indoles via Pd(OAc)₂-catalyzed benzylic C–H bond activation and insertion into isocyanides.¹³ Catalytic dehydrogenative cross-coupling reactions have also proven useful synthetic tools for indole derivatives.¹⁴ Afterward, Rh-, Pd-, and Ru-catalyzed C–H bond activation under oxidative or redox-neutral conditions were extensively explored for the synthesis of indoles.¹⁵ Despite these significant advances, industrial applications of these homogeneous palladium, rhodium, and ruthenium complexes remain a challenge because they are expensive, cannot be recycled, and difficult to be separated from the product mixture. These problems are of particular environmental and economic concerns in industry, especially the pharmaceutical industry. Therefore, from the standpoint of green and sustainable chemistry,¹⁶ the development of a recyclable and reusable catalyst system that allows for highly efficient and green

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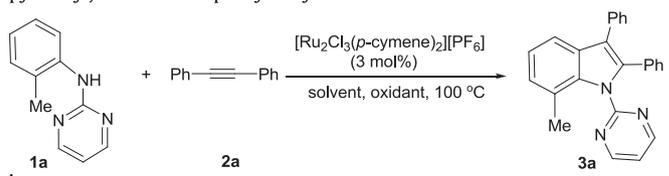
synthesis of indoles via C–H activation/cyclization strategy is worthwhile.

Development of recyclable catalytic systems for transition-metal-catalyzed organic transformations has become a task of great economic and environmental importance in chemical and pharmaceutical industries, especially when expensive and/or toxic heavy metal complexes are employed. In order to gratify both recyclability and environmental concerns, a simple and efficient method is to immobilize the catalyst in a liquid phase by dissolving it into a nonvolatile and nonmixing liquid, such as ionic liquids¹⁷ and PEGs.¹⁸ However, ionic liquids provide some disadvantages, such as a complicated method for the preparation of ionic liquids as well as their environmental safety is still debated since the toxicity and environmental burden data are unknown for the most of them. It is well documented that poly(ethylene glycols) (PEGs) are commercially easily available and inexpensive, thermally stable, recoverable, biodegradable and nontoxic compounds which serve as efficient media for environmentally friendly and safe chemical reactions.¹⁹ Recently, PEGs have been widely utilized as reaction media for the Pd-catalyzed carbon-carbon bond formation reactions such as Heck coupling,^{18a,b} Suzuki coupling,^{18c,d} the homocoupling and cross-coupling of aryl halides,^{18e} the direct arylation of 1,2,3-triazoles with aryl bromides,^{18f} and carbonylative Suzuki^{18g} or Sonogashira^{18h} cross-couplings with facile recyclability of solvents and palladium catalysts. Some organic transformations catalyzed by other transition metals in PEGs have also been described, including catalysis by Ru,²⁰ Pt,²¹ Ni²² and Cu²³ in recent years. However, to the best of our knowledge, the ruthenium-catalyzed oxidative C–H/N–H bond functionalizations of anilines with a removable directing group in PEGs have not been reported until now. We herein report the application of [Ru₂Cl₃(*p*-cymene)₂][PF₆]/Cu(OAc)₂·H₂O/PEG-400/H₂O system as a highly efficient and reusable catalytic medium for the oxidative annulation of alkynes by *N*-2-pyrimidyl-substituted anilines leading to a variety of indole derivatives in good to excellent yields (Scheme 1).

2. Results and discussion

Initially, we focused our optimization investigations on the use of *N*-2-pyrimidyl-substituted anilines since the 2-pyrimidyl group has proven to be easily removed from the indole nucleus.²⁴ The oxidative annulation of 2-methyl-*N*-(2-pyrimidyl)aniline **1a** with diphenylacetylene **2a** was chosen as a model reaction to determine the optimum conditions and the results are summarized in Table 1. At first, the solvent effect was examined by using [Ru₂Cl₃(*p*-cymene)₂][PF₆] complex as catalyst and Cu(OAc)₂·H₂O as oxidant, and a significant solvent effect was observed. When PEG-400 was used as solvent, the reaction proceeded slowly and the desired product **3a** was obtained in only 53% yield (Table 1, entry 1). To our delight, the use of a mixture of PEG-400 and H₂O as solvent could improve the yield of the product **3a** obviously (Table 1, entries 2–6). The reaction run in PEG-400/H₂O (3:2) gave **3a** in 93% yield (Table 1, entry 3). Our next studies focused on the effect of oxidant on the model

Table 1
Optimization of ruthenium-catalyzed oxidative annulation of 2-methyl-*N*-(2-pyrimidyl)aniline with diphenylacetylene^a.



Entry	Solvent (v/v)	Oxidant	Time (h)	Yield (%) ^b
1	PEG-400	Cu(OAc) ₂ ·H ₂ O	36	53
2	PEG-400/H ₂ O (3:1)	Cu(OAc) ₂ ·H ₂ O	24	72
3	PEG-400/H ₂ O (3:2)	Cu(OAc) ₂ ·H ₂ O	24	93
4	PEG-400/H ₂ O (1:1)	Cu(OAc) ₂ ·H ₂ O	24	90
5	PEG-400/H ₂ O (2:3)	Cu(OAc) ₂ ·H ₂ O	24	92
6	PEG-400/H ₂ O (1:3)	Cu(OAc) ₂ ·H ₂ O	24	89
7	PEG-400/H ₂ O (3:2)	benzoquinone	36	0
8	PEG-400/H ₂ O (3:2)	PhI(OAc) ₂	36	0
9	PEG-400/H ₂ O (3:2)	AgNO ₃	36	0
10	PEG-400/H ₂ O (3:2)	AgOAc	36	12
11	PEG-400/H ₂ O (3:2)	CuBr ₂	36	0
12	PEG-600	Cu(OAc) ₂ ·H ₂ O	36	48
13	PEG-1000	Cu(OAc) ₂ ·H ₂ O	36	39
14	PEG-600/H ₂ O (3:2)	Cu(OAc) ₂ ·H ₂ O	24	90
15	PEG-1000/H ₂ O (3:2)	Cu(OAc) ₂ ·H ₂ O	24	81
16 ^c	PEG-400/H ₂ O (3:2)	Cu(OAc) ₂ ·H ₂ O	36	61
17 ^d	PEG-400/H ₂ O (3:2)	Cu(OAc) ₂ ·H ₂ O	48	9

^a Reaction conditions: **1a** (0.5 mmol), **2a** (1.0 mmol), [Ru₂Cl₃(*p*-cymene)₂][PF₆] (3.0 mol%), oxidant (2.0 equiv), solvent (2.0 mL), 100 °C, under Ar.

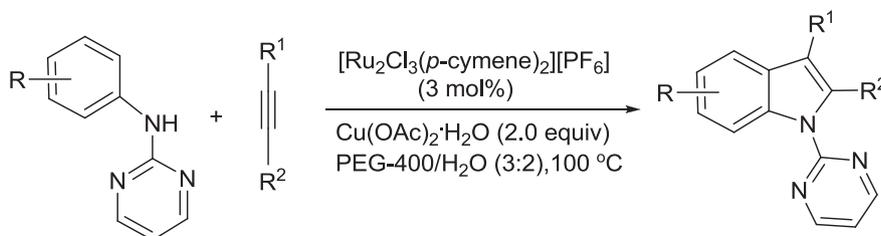
^b Isolated yield.

^c At 80 °C.

^d [RuCl₂(*p*-cymene)₂] (3.0 mol%) was used.

reaction. When benzoquinone, PhI(OAc)₂, AgNO₃ and CuBr₂ were used as the oxidant, no reaction was observed, whereas AgOAc afforded low yield (Table 1, entries 7–11). In addition, PEG-600 and PEG-1000 were also tested at the same reaction conditions to examine the efficiency of various chain length PEGs on the reaction, PEG-400 was superior to PEG-600 and PEG-1000 (Table 1, entries 12–15). It was found that the reaction was completed when it was performed in PEG-400/H₂O (3:2) at 100 °C for 24 h. Lowering reaction temperature to 80 °C resulted in a significant decrease in yield (Table 1, entry 16). When [RuCl₂(*p*-cymene)₂] (3.0 mol%) was used as catalyst, low catalytic efficacy was observed due to the absence of a weakly coordination anion²⁵ (Table 1, entry 17). Therefore, the optimal catalytic system involved the use of [Ru₂Cl₃(*p*-cymene)₂][PF₆] (3.0 mol%), Cu(OAc)₂·H₂O (2.0 equiv) in PEG-400/H₂O (v/v = 3:2) at 100 °C under Ar for 24 h (Table 1, entry 3).

With the optimized conditions established, we tried to investigate the scope of this Ru(II)-catalyzed oxidative annulation reactions in PEG-400/H₂O. Firstly, annulation reactions of 2-methyl-*N*-(2-pyrimidyl)aniline **1a** with various alkynes were examined and the results are summarized in Table 2. As shown in Table 2, it is evident that most of the Ru(II)-catalyzed oxidative annulation



Scheme 1. Synthesis of indole derivatives by Ru-catalyzed oxidative annulation of alkynes by *N*-2-pyrimidyl-substituted anilines in PEG-400/H₂O.

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