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An Efficient and Green Synthesis of isatin Derivatives under Ultrasound Irradiation

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ABSTRACT: A simple, fast and green synthetic protocol is described for one-pot aldolization of isatins and ketones under ultrasound irradiation and conventional thermal method. The 3 mol % of ruthenium catalyst is sufficient to catalyze the aldol reaction of ketones and isatins provided aldol adducts in moderate to good yield and complete diastereoselectivity. Compared with classical methods, ultrasound irradiation procedure provided shorter reaction times and higher yields. The methodology highlights the importance of low catalyst loading in achieving high chemoselectivity under silent and sonochemistry. As this approach involves time conservation and minimal waste generation, it is embraced as a green chemistry method.

Keywords: Isatin, Ruthenium catalyst, Aldol reaction, Sonochemistry

INTRODUCTION

Isatin (1H-indole-2,3-dione) was discovered by Laurent and Erdmann in 1840 as a major product of the oxidation of indigo with nitric and chromic acids (Silva *et al.,* 2001)., it is a synthetically versatile substrate used for the production of a variety of heterocyclic compounds, such as indoles and quinolines, and as a raw material for Pharmaceutical Industry (Cândido-Bacania *et al.,* 2011). Isatin, an inborn compound recognized in many organisms, displays a wide range of biological activities (Prakash and Raja, 2013). In human, it nominates in the central nervous system and has a distinguished distribution in brain. It is also widely applied in analytical chemistry as reagent and chelating agent towards metal ions. Various isatin derivatives and their metal complexes are reported for their considerable biological activities. Significant antitumor, anticonvulsant, herbicidal, antimicrobial and antiviral properties were reported.

The aldol reaction is one of the most prospected marking transformations using various catalysts. Specifically, it ranks at the top for testing and comparing the effect of new catalyst designs. The products of this reaction, β-hydroxy carbonyl compounds are main structural motifs, which are found in many bioactive natural compounds and drug products. Among the various aldol substrates, isatins entice great attention as they conduce to the formation of oxindole derivatives, which serve as valorous templates for producting bioactives. From a literature survey, isatins were found to be rare substrate partners for aldol reactions. Although a large number of organocatalysts such as proline derivatives, bifunctional thioureas, and others have been reported for several asymmetric reactions, only some of them have been considered for aldol reactions with isatin derivatives (Kumar *et al.,* 2015). The first enantioselectivealdol reaction of isatin with acetone was reported by Tomasini *et al.* using a dipeptide-based organocatalyst. Later on, Zhao *et al.* successfully developed a quinidine thiourea, which was used as the organocatalyst in the asymmetric aldol reaction of inactivated ketones and activated carbonyl compounds. Chen *et al.* reported an example of carbohydrate-derived alcohols as organocatalysts in aldol reactions of isatins with ketones. Recently, an enzyme from *Penicillium citrinum*, was successfully used to directly catalyze asymmetric aldol reactions between isatin derivatives and cyclic ketones under mild conditions (Liu *et al.,* 2014).

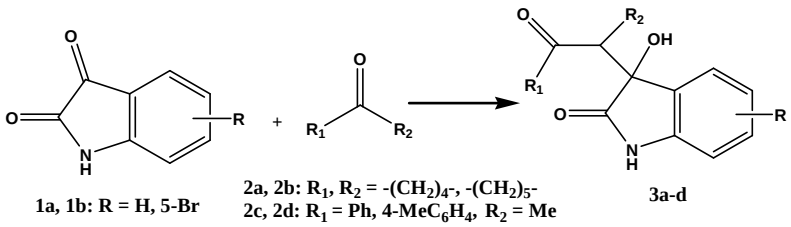
Despite the last success, applying new catalyst with operation simplicity and catalyst efficiency for the synthesis of this structural moiety still attracts considerable interest. Recently, we have reported a method that RuIII used as an efficient catalyst for cross aldol reactions with cycloalkanones and aldehydes under solvent free reaction conditions (keshavarz *et al.,* 2015). In continuation of our research interests on aldol reactions (Tabatabaeian *et al.,* 2011, Tabatabaeian *et al.,* 2010, Keshavarz *et al.,* 2012), we evaluated the catalytic performance of $RuCl_2(PPh_3)_3$ for aldol reactions of isatins and various ketones. We herein report the first example of a catalytic aldol reaction between isatins and ketones using RuII catalyst in conventional conditions and under ultrasonic iradiation.

RESULTS AND DISCUSSION

In the following decades, the aldehyde-aldehyde and aldehyde-ketone aldol reaction had been extensively researched (Dalko and Moisan, 2001, 2004, Kochetkov *et al.,* 2012, Sreenithya and Sunoj, 2012, Ramachandran, and Chanda, 2013, Qiao *et al.*, 2013, Zayas *et al.*, 2013, Almasi *et al.*, 2008, Wang, 2010), however, the intermolecular ketone-ketone asymmetric aldol addition is rare and remains a significant challenge (List *et al.*, 1999, Guo *et al.*, 2010, Guo and Zhao, 2012). A few reports about the aldol reactions between isatins and ketones had been published, but the catalysts were inevitably a base, an organic molecule and a metal complex (Zhang *et al.*, 2013, Raj *et al.*, 2010, Liu *et al.*, 2012, Deng *et al.*, 2013). In view of green chemistry, herein we wish to report a succinct and upstanding approach to synthesize isatin aldol derivatives under mild conditions.

In order to explore the ability of $RuCl_2(PPh_3)_3$ as catalyst for aldol reactions of isatins and ketones, a series of screening studies were directed to instate the optimal parameters by using isatin1a (1 mmol) and ketone 2a(2 mmol) as the model substrates.

Initially, the reaction was performed in the presence of RuII (4mol %) and 2mol% of KOH as an additive in dioxane to give the desired compound 3a at room temperature, but the yield was low. In contrast, at 40°C the reaction improved yield. By using 3mol% of catalyst instead of 4mol%, the yield of product did not change, but the time of reaction was short. The yield was improved to 68% when the reaction was carried out at 60°C and prolonging the reaction time to 50 Min. As expected, Ru catalyst (2mol %) exhibited excellent reactivity but some loss in yield at 60°C occurred. Also, a further decrease in the catalyst loading to 1mol % rendered the reaction unacceptably slow. When the reaction was carried out at CH_2Cl_2 as solvent, the yield decreased to 20%. Also, it is noteworthy that when the reactions were carried out with 1 ml of dioxane as a solvent at 60°C, products in good yields were obtained. Thus, the optimized catalyst loading was chosen as 3mol % of RuII and 2mol% of KOH in dioxane (1 ml) at 60°C.



Scheme 1.

Table 1: The scope of the ruthenium-catalyzed aldol reaction of isatins with ketones under silent conditions.

Entry[1]	Isatin derivatives	Ketone	Time (min)	Yield (%)[2]
1	Isatin**1a**	Cyclohexanone **2a**	50	65
2	Isatin**1a**	Cyclopentanone **2b**	55	60
3	Isatin**1a**	Acetophenone **2c**	60	41
4	Isatin**1a**	4-methyl-acetophenone **2d**	70	55
5	5-Br-Isatin**1b**	Cyclopentanone **2b**	350	64
6	5-Br-Isatin**1b**	Cyclohexanone **2a**	270	67

[1]Identified by comparison with authentic samples (Kumar *et al.*, 2015, Liu *et al.*, 2014). [2]The absolute configuration was determined by comparison of the specific rotation with that of a literature value.

The results of these studies are summarized in Table 1. The absolute configuration of the product 3a was determined to be (S) by comparing the specific rotation with the literature values. As shown in Table 1, with isatin as the substrate, various ketones may be applied in the aldol reaction. When acetophenone 2c was used as a substrate under the optimized conditions, the yield value was generally low. When cycloalkanones 2a-b was used instead of 2c, the reaction with isatin gave the corresponding products in moderate to good yields.

Next, our intention was to develop an eco-friendly methodology for the synthesis of aldol adducts under sonochemical conditions.

Preliminary studies were carried out using isatin (1.0 mmol), ketones (2.0 mmol) and catalyst (3 mol%) under ultrasound irradiation, with using dioxane as a solvent. Experiments were conducted under ultrasound irradiation at 25 (RT), 40 and 50°C. Impressively, at 50°C, the ultrasonic method gave the preferred product (3a) selectively with 80% yield. Based on the results, taking 50 °C as optimum condition, all the reactions were conducted at that temperature, and obtained results are summarized in Table 2.

This study validates that sonochemical approach is ideal for one-pot aldol reaction to achieve good yields.

Table 2: Ruthenium-catalyzed aldol reaction of isatins with ketones under sonochemical conditions.

Entry[1]	Isatin derivatives	Ketone	Time (min)	Yield (%)
1	Isatin	cyclohexanone	10	75
2	Isatin	cyclopentanone	16	63
3	Isatin	acetophenone	18	45
4	Isatin	p-methyl-acetophenone	23	56
5	5-Br-Isatin	cyclopentanone	30	70
6	5-Br-Isatin	cyclohexanone	28	80

[1]Identified by comparison with authentic samples [4, 8].

The results of Table 2 confirm the advantage of ultrasound method over conventional thermal method, in terms of (i) time required for the formation of new C-C bonds under ultrasonic irradiation is shorter, (ii) aldolization takes place at low temperature compared to conventional heating, (iii) the isolated products are in higher yields.

In summary, we report a remarkable, eco-friendly and convenient one-pot technique for rapid aldolization of isatin derivatives from easily accessible starting ketones. This method will be of choice for the preparation of a variety of aldol adducts some of which are difficult to make via silent approaches.

CONCLUSION

An investigation into new catalytic approaches for aldol reaction of isatin using RuII serves as valuable addition to the existing methods and expands the horizons of Ru catalyst. Compared to conventional heating which provides thermal energy in the system, sonification reduces reaction times, and minimizes side product formation in good yield and complete diastereoselectivity.

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