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ARTICLE TYPE

CuSO₄ catalyzed three-component reaction of α-diazo ester, water and isatin : an efficient and green approach to oxindole derivatives

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A highly efficient three-component reaction of α -diazo ester, water and isatin was developed by using CuSO₄ as the catalyst. In this reaction, water was used as both a reactant and the solvent. With this highly environmentally benign and economical protocol, a series of 3-hydroxyindolin-2-one derivatives were efficiently produced in good yields with moderate to high diastereoselectivities.

Green chemistry has gained great attention in organic community in recent years due to its highly environmentally benign features from readily available starting materials to structurally complex molecules of biological activities.¹ In recent years, MCRs (Multi-Component Reactions) have been developed into highly powerful and atom-efficient strategies to form multiple chemical bonds from three or more starting materials in one single step.² However, it is still a big challenge in developing green and environmentally benign conditions for MCRs in modern organic chemistry. Within this context, the use of abundantly available and less toxic catalysts as well as the use of water as reaction media would be highly beneficial for us to develop green and environmentally benign MCRs.³ Herein, we reported a three-component reaction of α -diazo ester, water and isatin catalyzed by CuSO₄. In this transformation, water was used as both a reactant and the solvent and less toxic and abundantly available CuSO₄ was used as the catalyst. With this highly efficient three component reaction, a series of 3-hydroxyindolin-2-one products was produced.

The oxindole framework is a key motif in a large spectrum of bioactive natural products and medicinal agents.⁴ For instance, 3-hydroxyindolin-2-one moiety is found in an array of bioactive alkaloids (Figure 1).⁵⁻¹¹ In general, to generate the two vicinal stereocenters existing in a 3-hydroxyindolin-2-one moiety, stepwise synthesis including a nucleophilic addition to isatin and a following transformation was required.¹²⁻¹³ Our group has recently developed a highly efficient strategy for the rapid

synthesis of 3-*alkoxyl*indolin-2-one moieties via diastereoselective trapping of protic oxouim ylide with isatins.¹⁴ With this chemistry, we are particularly interested in developing a more straightforward strategy for the synthesis of 3-*hydroxy*indolin-2-one moieties by replacing alcohols with water. And on the other hand, to replace the toxic dirhodium catalyst with cheap and less toxic catalyst as well as using water itself as the solvent so we can make the desired transformation into a highly green and environmentally benign one.





Firstly, we chose water to react with α -diazo ester **1a** and isatin in CH2Cl2 in the presence of Rh(II) catalyst to test whether the hydroxyl ylide generated from **1a** and water¹⁵ could be trapped by isatin to afford 3-hydroxyindolin-2-one 3a. To our delight, 3a was produced in 84% yield with a 80:20 d.r. ratio (Table 1, entry 1). Then we replaced the solvent from CH_2Cl_2 to water,¹⁶ good result was also obtained (Table 1, entry 2)¹⁷. To further increase the green features of this transformation, we tested the catalytic abilities of a series of cheap and readily available copper salts.¹⁸ We found that CuSO₄ was most efficient to catalyze the desired three-component reaction in water to provide **3a** in 90% yield with similar d.r. ratio (Table 1, entry 7). Control experiment revealed that CuSO₄ is indispensable for this transformation (Table 1, entry 8). It was more striking that the product was readily separated by simple extraction of the reaction mixture with ethyl acetate, while impurities remained in aqueous phase. After removing the solvent, 3a was obtained in high purity, and no further isolation or purification steps were required. The structure as well as the stereochemistry of the major product was confirmed by single-crystal X-ray analysis as anti-3a (Figure 2).

Table 1 .Optimization of reaction conditions.^a

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^aReaction conditions: Unless otherwise noted, the reaction was carried out in a 0.5 mmol scale. A mixture of diazoester **1a** (2 mmol) and 5 mL water was syringed to the suspension of isatin **2a** (0.5 mmol) and metal catalyst in 2 ml water within one hour via syringe pump; ^bIsolated yield; ^cd.r. ratio were determined by ¹H NMR; ^dCH₂Cl₂ was used as the solvent.

Figure 2 .X-Ray crystal structure of anti-3a.



With the optimized reaction conditions in hand, we began to explore the substrate scope of diazo esters and isatins. With a variety of isatins bearing different substituents, the desired products could be achieved in moderate to high yields (40% – 90%) (Table 2, entries 2-8). When *tert*-butyl diazoacetate instead of ethyl diazoacetate was used, the desired product was obtained in good yield albeit with lower diastereoselectivity (Table 2, entry 9). With different α -alkyl-substituted diazoacetates, the reaction went smoothly to provide desired products in good yields (Table 2, entries 10-17). Different substituents on isatin had significant effects on the diastereoselectivities of this transformation, for example, when 5-methyl isatin was used, the products were produced in very good diastereoselectivities with either ethyl diazoacetate or *tert*-butyl diazoacetate (Table 2, entries 3 and 11).

Table 2. $CuSO_4$ -catalyzed three-component reaction ofdiazoacetate 1 and isatin 2 in water.^a



Entry	1	2	3	Yield (%) ^d	d.r. ratio (anti:syn) ^e
1	1 a	2a	3a	90	80:20
2 ^b	1 a	2b	3b	40	83:17
3	1a	2c	3c	85	89:11
4	1 a	2e	3d	65	91:9
5	1 a	2f	3e	64	69:31
6	1 a	2g	3f	54	72 :28
$7^{\rm c}$	1a	2h	3g	66	77:23
8	1a	2i	3h	78	80:20
9	1b	2a	3i	82	67:33
10	1c	2a	3j	92	63:37
11	1c	2c	3k	67	91: 9
12	1c	2d	31	73	58:42
13	1c	2f	3m	66	60:40
14	1c	2h	3n	60	64:36
15	1d	2a	30	82	56:44
16	1e	2a	3p	68	50:50

^aReaction conditions: Unless otherwise noted, the reaction was carried out in a 0.5 mmol sacle. A mixture of diazoester 1 (2 mmol) and 5 mL water was syringed into the suspension of isatin 2 (0.5 mmol) and 10 mol% CuSO₄ in 2 ml water within one hour via syringe pump; ^b4 mmol diazoester 1a was used; ^c3 mmol diazoester 1a was used. ^dIsolated yield; ^e d.r. ratio were determined by ¹H NMR.

Scheme 1. Plausible mechanism



A plausible mechanism for this transformation is proposed as shown in Scheme 1. $CuSO_4$ -catalyzed decomposition of diazoester 1 gave corresponding carbenoid 4, which reacted with water to generate hydroxyl ylide 5. In the presence of isatin, Published on 17 December 2012 on http://pubs.rsc.org | doi:10.1039/C2GC36708D

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The hydroxyl ylide 5 could be efficiently trapped to undergo the desired three-component reaction instead of 1,2-proton shift. The desired product was afforded with an intramolecular proton shift following the ylide trapping process.

One of the most unique features of this CuSO₄ catalyzed three-component reaction is that it is run in aqueous media under very mild reaction conditions. Moreover, this transformation is clean and easy to work up. In order to further demonstrate the scale-up potential of this efficient transformation, we conducted a gram-scale synthesis of 3a starting directly from cheap and easily available glycine ethyl ester through a "telescoped" process. In this protocol, ethyl diazoacetate was extracted directly from the aqueous diazotization reaction mixture of glycine ethyl ester (195g) with petroleum ether and used directly for the CuSO₄-catalyzed three-component reaction in the water/petroleum ether two-phase solvent media. In this scale-up synthesis, the minor diastereomer was directly crystalized from the reaction mixture during the reaction proceeded. And after the completion of the reaction, simple filtration provided 11.7 g pure syn-3a. The petroleum ether layer of the mother liquid which contained only impurities was separated and the solvent could be distilled for recycling use. The aqueous layer was extracted with ethyl acetate to finally provide 50.8 g 3a (anti:syn=92:8) after recrystallization from ethyl acetate/petroleum ether (1:1). After the whole procedures, the distilled organic solvent could also be recycled.

Scheme 2. Synthesis of 3a in large scale.



The three-component reaction catalyzed by CuSO₄ in aqueous media generates 3-hydroxyindolin-2-one derivatives, which are significant structural skeleton presented in a large number of natural products or medicinal agents. This reaction protocol embodies several principles of green chemistry. Green characters of this reaction lie in: 1) this three-component reaction is atom-economic and step-economic. Multiple chemical bonds are formed in one single step to provide complex target molecules and nitrogen gas is the only byproduct; 2) In this reaction abundantly available and less toxic CuSO₄ was used as the catalyst to replace the more expensive and toxic Rh(II) one; 3) water plays dual roles as both a reactant and the solvent. Water is more direct source of hydroxyl than alcohol and more friendly to environment than other conventional volatile organic solvent; 4) this transformation generates almost no organo wastes, in the scale-up synthesis, the procedures could be conducted in "telescoped" steps and all organic

solvents could be recycled after distillation.

Conclusions

We developed an efficient three-component reaction by trapping the protic oxonium ylide generated from α -diazo esters and water in the presence of Cu(II) catalyst with isatin in aqueous media. This environmentally benign transformation can be conducted in large scale with simple work up procedures therefore represents a novel "green" MCR protocol for the synthesis of diversely substituted 3-hydroxyloxiindole-2-one derivatives.

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Experimental

General procedure for the copper-catalyzed three-component reaction of diazoesters, water and isatins To a 10 mL flask with a stir bar was added isatin 2 (0.5 mmol) and 2 mL water, then the mixture was stirred vigorously to form suspension to which copper sulfate (0.05 mmol) was added in one portion. A mixture of diazoester 1 (2 mmol) in 5 mL water was syringed to the suspension within one hour. Eventually, colorful suspension turned into a clear solution. When the reaction was finished as monitored by TLC, the reaction mixture was washed with petroleum ether $(3 \times 3 \text{ mL})$ to remove impurities with low polarity, then extracted with 15 mL ethyl acetate for 3 times. The combined organic phase was washed with saturated brine, dried over anhydrous sodium sulfate, filtered and then concentrated to provide the product, which was then crystallized from petroleum ether and ethyl acetate.

Procedure for the scale-up synthesis of 3a from glycine ethyl ester

To a solution of glycine ethyl ester (195.4 g,1.4 mmol) and conc. HCl (40 mL) in water (100 mL) was added NaNO₂ (115.9 g, 1.68 mmol) in water (150 mL) slowly at -5 $^{\circ}$ C within 30 min. Then 80 mL petroleum ether was added and the reaction was stirred for 20 min. The two layers were separated and the aqueous phase was further extracted with petroleum ether (80 mL). The combined organic layer was washed with brine (40 mL) and directly used for the next step.

To a 1 L three-necked round-bottle flask equipped with a mechanical stirrer was added isatin 2 (51.5 g, 350 mmol) and 160 mL water, the mixture was then stirred vigorously to form a suspension to which copper sulfate (5.6 g, 0.05 mmol) was added in one portion. The solution of ethyl diazoester **1a** in petroleum ether was then added dropwise within 1 h. After the completion of the addition, the reaction mixture was further stirred for 30 min. During the reaction proceeded, crystal formation was observed in the two-phase reaction media. When the reaction is finished as monitored by TLC, the reaction was filtered and 11.7 g pure *cis*-**3a** was obtained as crystals. The

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two-phase mother liquid was separated to afford the petroleum ether layer that contained only impurities with low polarities and the aqueous layer, which was extracted with ethyl acetate (200 mL \times 4) and washed with brine (100 mL). 3/4 volume of the combined organic phase was removed by concentration and 200 mL petroleum ether was added to afford crystalized products. The solid was filtered, washed with petroleum ether and dried in high *vacuo* to afford 50.8 g products (d.r. = 92:8).

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