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Access to 3,3-disubstituted oxindoles via microwave-assisted Cannizzaro and aldol reactions of formaldehyde with isatins and their imines†

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3,3-Disubstituted oxindoles are important structure motifs in natural products and pharmaceutical agents. Here we disclose a simple and direct access to this class of molecules by using readily available formaldehyde and isatins (and their imines) as the substrates. The reaction proceeds with the assistance of microwave heating in the presence of a mild base. Formaldehyde behaves as both a reductant (*via* a Cannizzaro process with isatin) and an electrophile.

3,3-Disubstituted oxindoles are valuable structure motifs that have widely existed in biologically active natural products, alkaloids and pharmaceutical agents.^{1,2} For example, TMC-95A and its analogues are isolated from *Apoispora montagnei*. They can be used as specific proteasome inhibitors.³ Paratunamide D from paratide or *Cinnamodendron axillare* (Canellaceae) has shown moderate cytotoxicity against human epidermoid carcinoma KB cells ($IC_{50} = 6 \mu\text{g mL}^{-1}$).⁴ Convolutamydin A, which is isolated from the Floridian marine bryozoan *Amathia convoluta*, has exhibited significant antinociceptive effects.⁵ Maremycin B is another oxindole-containing natural product molecule that has been isolated from the *Streptomyces* species B 9173.⁶ The above natural products have shown proven biological activities such as antioxidant, antimicrobial or antitumor activities (Fig. 1a).⁷ Therefore, the synthesis of 3-hydroxyoxindole derivatives has long been interesting and attractive.⁸

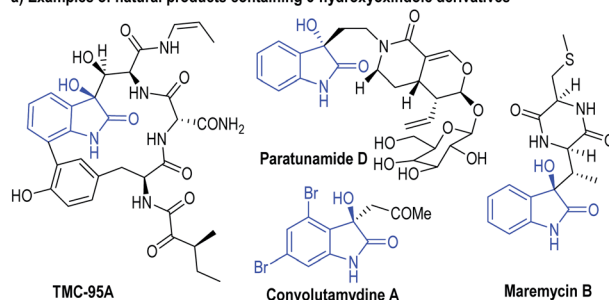
3-Hydroxyoxindole derivatives are one class of the most basic functional molecules containing oxindole scaffolds. Traditionally, 3-hydroxyoxindoles are obtained through aldol reactions, Friedel–Crafts reactions, Morita–Baylis–Hillman reactions and Hosomi–Sakurai allylation reactions.⁹ In 2014, Hu and co-workers¹⁰ developed a rhodium(II)-catalyzed three-component reaction for the synthesis of substituted 3-hydroxy(amino)-3-hydroxymethyloxindoles (Fig. 1b). Nobel metal catalysts and pre-functionalized diazo substrates are needed in this protocol.¹¹

Herein, we describe a microwave assisted Cannizzaro/aldol reaction of paraformaldehyde and isatins (or its imine derivatives). Paraformaldehyde behaves as both a reductant¹² (*via*

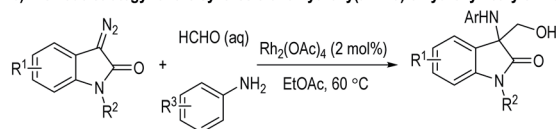
a Cannizzaro process with isatin) and an electrophile (Fig. 1c). Simple and inexpensive inorganic bases are applied as the only catalysts for this process, with the functionalized 3-hydroxymethyl-oxindole products afforded in good to excellent yields.

N-Methyl isatin **1a** and paraformaldehyde **2** were selected as the model substrates to evaluate the reaction condition for the synthesis of 3-hydroxy-3-hydroxymethyloxindole **3a** (Table 1).

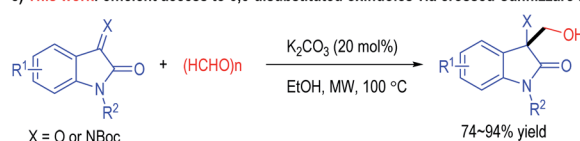
a) Examples of natural products containing 3-hydroxyoxindole derivatives



b) Previous strategy for the synthesis of 3-hydroxy(amino)-3-hydroxymethyloxindoles



c) This work: efficient access to 3,3-disubstituted oxindoles via crossed Cannizzaro reaction



- reaction of metal-free
- base and microwave promoted transformation
- reactive C₁ building block
- rapid, simple and highly efficient

Fig. 1 3-Hydroxyoxindole derivatives and their synthesis.

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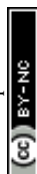
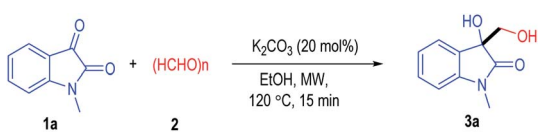


Table 1 Optimization of the reaction conditions^a


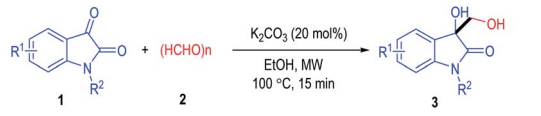
Entry	Base	Solvent	Yield ^b (%)
1	K ₂ CO ₃	EtOH (w/o MW)	29
2	—	EtOH	n.d.
3	K ₂ CO ₃	EtOH	94
4	Na ₂ CO ₃	EtOH	46
5	KOAc	EtOH	78
6	<i>t</i> -BuOK	EtOH	65
7	DBU	EtOH	70
8	Et ₃ N	EtOH	29
9	K ₂ CO ₃	CH ₃ CN	47
10	K ₂ CO ₃	Toluene	53
11	K ₂ CO ₃	DMF	49
12 ^c	K ₂ CO ₃	EtOH	92
13 ^d	K ₂ CO ₃	EtOH	34

^a Reaction condition: a mixture of 0.1 mmol of **1a**, 1.5 mmol of **2**, 20 mol% of base and 1.5 mL of solvent was irradiated in a microwave reactor at 120 °C for 15 min. ^b Yields are of isolated products based on **1a**. ^c Performed at 100 °C. ^d The reaction mixture of **2** is 0.1 mmol in 100 °C microwave reactor. n.d. = no detected. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene.

The target product **3a** could be obtained in 29% yield under the catalysis of K₂CO₃ at 120 °C in EtOH (Table 1 entry 1). Importantly, no desired product was detected under the absence of base (entry 2). To our delight, the yield of **3a** could be dramatically improved to 94% with the assistance of the microwave irradiation at 120 °C (entry 3). Switching the base catalyst to other organic or inorganic base cannot further increase the reaction yield (entries 4–8). The reaction can also be carried out in various organic solvent but can only be afforded in moderate yields (entries 9–11). Decreasing the reaction temperature to 100 °C led to little erosion on the product yield (entry 12). However, the product yield dropped significantly with a less amount of paraformaldehyde used as the starting material (entry 13).

Having established an optimal condition for the reaction, the scope of the isatin derivatives was examined (Table 2). The *N*-methyl group isatin **1a** could be switched to various alkyl groups, with the corresponding products afforded in good to excellent yields (**3b** to **3d**). Interestingly, the *N* protecting groups on the isatin substrates could even be removed and give the free oxindole derivatives **3e** in a 74% yield. Both electron-withdrawing and electron-donating groups were well tolerated on the benzene rings of the isatin substrates, with the substituted 3-hydroxy-3-hydroxymethyloxindole products formed in good to excellent yields (**3f** to **3m**).

It is worth to note that the isatin-derived ketimine substrates **4** could also be used as suitable reactants for this microwave assisted Cannizzaro/aldol reaction process (Table 3). Ketimine substrate **4** bearing an *N*-Me or an *N*-Bn group could give the

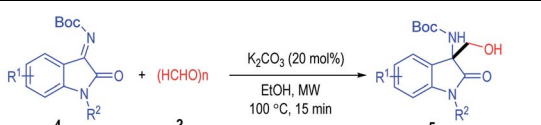
Table 2 Scope of isatin derivatives^a


Product	Yield (%)
3a , R = Me	92%
3b , R = Et	83%
3c	94%
3d	84%
3e	74%
3f , X = Cl	77%
3g , X = Br	76%
3h , R = Me	81%
3i , R = OMe	88%
3j , X = Cl	84%
3k , X = Br	81%
3l , R = Me	87%
3m , R = OMe	91%

^a Reaction condition: a mixture of 0.2 mmol of **1**, 3.0 mmol of **2**, 20 mol% of base and 1.5 mL of solvent was irradiated in a 100 °C microwave reactor with 15 min and yields are of isolated products based on **1**.

target product in a good yield (**5a** & **5b**). Substituents could also be installed on the 5-position of the ketimine substrate regardless of their electron properties, with the desired products afforded in good to excellent yields (**5c** to **5e**).

A postulated reaction mechanism is depicted in Fig. 2. The paraformaldehyde can react with the hydroxyl group under basic condition to give the intermediate **I**, which can be further deprotonated to give the dianion intermediate **II**. A hydride shift between the intermediate **II** and isatin substrate **1** leads to the formation of the reduced oxindole intermediate **III** with the elimination of the formic acid as the byproduct. An aldol reaction between the intermediate **III** and the formaldehyde gives the desired product **3**. To gain more insight into this mechanism, several control experiments were conducted. The 3-hydroxy-1-methylindolin-2-one instead of the isatin with K₂CO₃

Table 3 Scope of isatin-derived ketimines^a


Product	Yield (%)
5a	84%
5b	81%
5c , R = Me	85%
5d , R = OMe	90%
5e	78%

^a Reaction condition: a mixture of 0.2 mmol of **4**, 3.0 mmol of **2**, 20 mol% of base and 1.5 mL of solvent was irradiated in a 100 °C microwave reactor with 15 min and yields are of isolated products based on **4**.



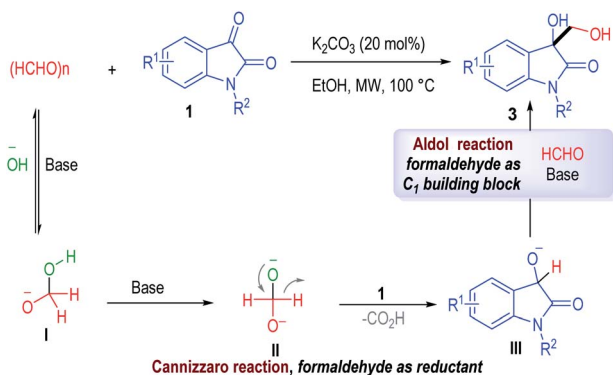


Fig. 2 Postulated pathway.

as the catalyst gave desired product in 90% yield. Based on this control experiment, we proposed the mechanism is reasonable.

In summary, we have developed an efficient Cannizzaro/aldol reaction with the assistance of microwave irradiation. Paraformaldehyde and isatin derivatives are successfully used as the reaction substrates. Functionalized 3-hydroxymethyloxindole derivatives bearing various substituents and substitution patterns are afforded as the reaction products in good to excellent yields. Inexpensive and the readily available K_2CO_3 is applied as the only catalyst in this protocol. Further application of the 3-hydroxymethyloxindole derivatives obtained through this method in synthetic chemistry and investigations into novel microwave assisted transformation are currently in progress in our laboratory.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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