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Synthesis of polysubstituted 5-hydroxyhydantoins via ring-opening of isatins

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ABSTRACT

A simple and efficient tandem reaction approach was developed for the synthesis of 5-hydroxyhydantoins from one-pot reaction of isatins, phthalic anhydride or succinic anhydride, and 1,3-dimethylurea (1,3-diethylurea). The products were gained through the ring-opening of isatins process. The advantages of this report are simple operation, mild reaction conditions, good yields and easily available raw materials. It was very important for us to obtain the intermediate product and that provided a solid basis for the correct interpretation of the reaction mechanism.

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The hydantoin skeleton is an important structural component that appears in many natural products[1–5] and drug structures,[6–12] with various activities, such as anticonvulsive,[13] antidepressant,[14] antiviral,[15] or anticoagulant[16] and so on. For example, Phenytoin[17] was used in treatment of epilepsy disease; Nilutamide[18] was a very efficient nonsteroidal, orally active antiandrogen in the therapy of metastatic prostate cancer, which was approved by the FDA in 1996; (+)-hydantocidin[19] has herbicidal and plant growth regulatory activities; (R)-5-(4-bromobenzyl)-3-(3,5-dimethylphenyl)-1,5-dimethylimidazolidine-2,4-dione[6] is a potent antagonists of LFA-1-mediated cell adhesion, which was regarded as potential therapeutic agents in autoimmune diseases; Compound (Z)-5-(3-hydroxy-4-methoxybenzylidene)imidazolidine-2,4-dione[20] has the efficient inhibitory effect on tyrosinase and melanin; Moreover, the natural product, Exiguamine A[21], isolated from the marine sponge Neopetrosia exigua, was found to be the most potent inhibitor of IDO to date. 5-Hydroxyhydantoins were also the crucial derivatives of hydantoin, which was found involving in some inflammatory processes.[22] 5-Hydroxyhydantoin and 5-methyl-5-hydroxyhydantoin were obtained from oxidative degradation of cytosine and thymine, and have been detected in cancer cells, and that could damage DNA resulting in some mutagenesis and carcinogenesis processes.[23] (Fig. 1).

Considering the importance of hydantoin derivatives, many synthetic strategies have been reported for the synthesis of these compounds,[24] especially the 5-substituted hydantoin (Figure 1). For example, Murray reported to synthesize 5-substituted and 5,5-disubstituted hydantoins from the corresponding aldehydes or ketones using gallium(III) triflate as catalyst.[25] 5-Methylenehydantoins could be gained from different synthetic routes via a variety of reactions, such as Dielse-Alder, epoxidation, methanol addition and conjugate addition reactions.[26] Meza-León reported to give 5-hydroxy hydantoins from the reaction of *a*-ketoacids and carbodiimides under visible light conditions.[27] Investigating these reported methods, the disadvantages are obvious, such as multi-steps procedures, strong acidic or basic conditions, relatively low yields.

Therefore, to develop the new synthetic approaches for the preparation of 5-substituted hydantoins is still an important research subject. Herein, we report a facile route for the syntheses of 5-hydroxyhydantoins form the tandem reactions of isatins, phthalic anhydride or succinic anhydride, and 1,3-dimethylurea (or 1,3-diethylurea) under mild conditions.

As the versatile synthetic material, isatins could be used to synthesize many important compounds.[28] In our recent reported reactions, isatins reacted with substitutional acetophenone to give 3-(2-aryl-2-oxoethylidene)indolin-2-one, then it reacted with 1,3-dimethylurea and the corresponding polysubstituted imidazole derivatives could be gained with good yields.[29] In order to continue the application of isatins in organic synthesis, we use isatin, phthalic anhydride and 1,3-dimethylurea, catalyzed by *p*-toluenesulfonic acid monohydrate (PTSA·H_2O) in acetonitrile medium, to our delight, the adventitious product was obtained with high yield.

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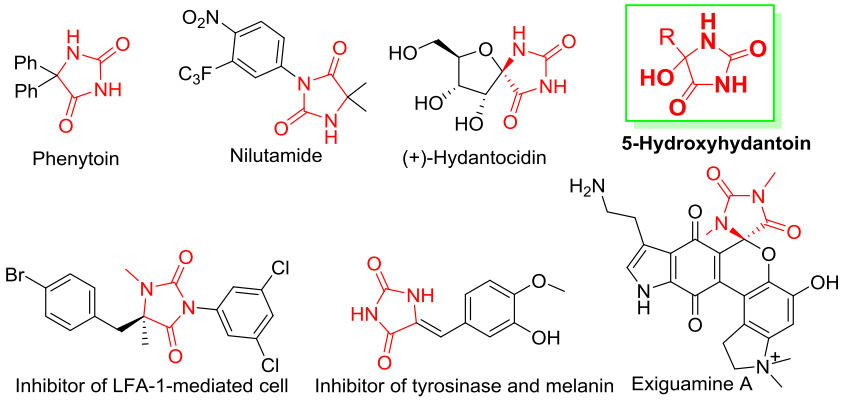
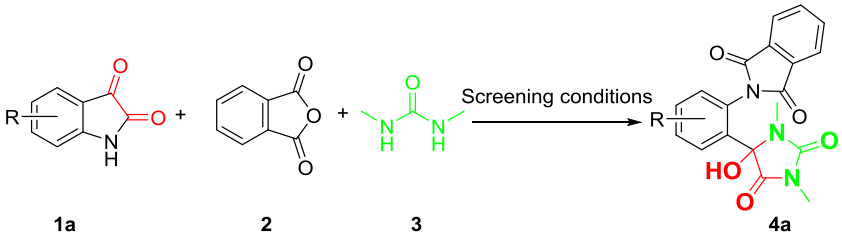


Fig. 1. Some important 5-substituted hydantoins.



Scheme 1. The model reaction of isatin, phthalic anhydride and 1,3-dimethylurea.

Table 1
Screening the reaction conditions.[a]

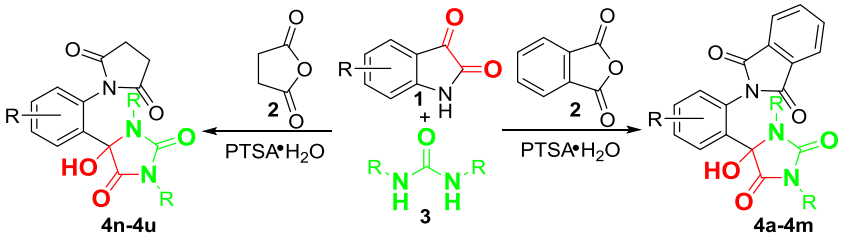
Entry	Catalyst mol%	Solvent	Time/h	Yield[a]/%
1	Et_3N (20)	CH_3CN	3	0
2	$C_5H_{11}N$ (20)	CH_3CN	3	0
3	DBU (20)	CH_3CN	3	0
4	DMAP (20)	CH_3CN	3	0
5	K_2CO_3	CH_3CN	3	0
6	NaOH	CH_3CN	3	0
7	$ZnCl_2$ (20)	CH_3CN	3	0
8	$SnCl_2 2H_2O$ (20)	CH_3CN	3	0
9	I_2 (20)	CH_3CN	3	0
10	HOAc (20)	CH_3CN	3	trace
11	NH_2SO_3H (20)	CH_3CN	3	12
12	*p*-TSA·H_2O (20)	CH_3CN	3	51
13	*p*-TSA·H_2O (20)	THF	3	32
14	*p*-TSA·H_2O (20)	Toluene	3	17
15	*p*-TSA·H_2O (20)	CH_3CH_2OH	3	41
16	*p*-TSA·H_2O (20)	DMF	3	29
17	*p*-TSA·H_2O (20)	CH_3CN	4	62
18	*p*-TSA·H_2O (20)	CH_3CN	5	83
19	*p*-TSA·H_2O (20)	CH_3CN	6	82
20	*p*-TSA·H_2O (30)	CH_3CN	5	83
21	*p*-TSA·H_2O (40)	CH_3CN	5	84
22	*p*-TSA·H_2O (50)	CH_3CN	5	83

Conditions: isatin **1a** (1 mmol), phthalic anhydride 2 (1 mmol), 1,3-dimethylurea **3** (1.5 mmol), Temperature (80 °C), Solvent (3 mL).
[a] Isolated yields.

Based on the spectral data (IR, ^1H NMR, ^{13}C NMR, and HRMS), we can determine it is polysubstituted 5-hydroxyhydantoins. Under investigation, this is novel process for preparation of 5-hydroxyhydantoins from isatin. Encouraged by this result, we want to synthesize more 5-hydroxyhydantoins compounds.

Firstly, we screened the reaction conditions. Isatin **1a**, phthalic anhydride **2** and 1,3-dimethylurea **3** were reacted in different solvents used various catalysts to obtain the optimal conditions (Scheme 1). The results were summarized in Table 1. As shown in Table 1, the alkaline catalysts have no catalytic effect on the model reaction (Table 1, entries 1–6), so do the Lewis catalysts (Table 1, entries 7–9). However, Brönsted acids showed the very good catalytic effect on the model reaction, and *p*-toluenesulfonic acid monohydrate (PTSA·H_2O) performed particularly outstanding (Table 1, entries 10–12). Subsequently, we mainly study the model reaction under different loading of PTSA·H_2O, solvents and reaction time conditions (Table 1, entries 13–16). The results showed that the best results could be obtained when the catalyst loading was 20%, acetonitrile as solvent and 5 h reaction time (Table 1, entry 18).

From the preferred condition in hand, also for testing the effectiveness of the present method, different isatins were chosen to react with phthalic anhydride and 1,3-dimethylurea under screened condition (Scheme 2), and expected products were



Scheme 2. The reaction of isatin, anhydride, and 1,3-dimethylurea.

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