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(±)-CSA catalyzed one-pot synthesis of 6,7-dihydrospiro[indole-3,1′-isoindoline]-2,3′,4(1*H*,5*H*)-trione derivatives: easy access of spirooxindoles and ibophyllidine-like alkaloids

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ABSTRACT

The domino dehydration/condensation/cyclization sequence reaction of cyclic enaminones with 3-hydroxy-3-ethoxycarbonylisoindolin-1-one derivatives has been successfully realized for the first time in toluene at 90 °C by using a catalytic amount of commercially available inexpensive (±)-CSA (30 mol %). Gratifyingly, this novel domino protocol provides good to excellent yields of previously unknown class of 1-aryl/alkyl-substituted 6,7-dihydrospiro[indole-3,1′-isoindoline]-2,3,4(1*H*,5*H*)-trione derivatives. Moreover, biologically attractive spirooxindoles and ibophyllidine-like alkaloids have been prepared.

The spirocyclic compounds are one of the most important classes of building blocks found in a variety of natural products and pharmacophores.[1] Due to their unique structural features, they are commonly employed for chiral ligands, and organometallic complexes in addition to their traditional roles as synthetic intermediates.[2] Apart from that, their several synthetic analogues show a broad range of biological activities.[3] Owing to their immense applications in various fields, a large number of protocols have been developed to construct this motif.[1–3] Even with such progress, the development of metal-free based new synthetic strategies for easier access of spiroisoindolinone compounds remains a great challenge for organic and medicinal chemists.

3-Substituted isoindolin-1-ones and their spiro cyclic derivatives are important privileged structures in a variety of pharmacophore exhibiting a broad range of therapeutic activities (Fig. 1).[4] On the other hand, dihydroindol-2-one derivatives also exhibit potential biological activities toward human ELOVL6 inhibitors (Fig. 1).[5] Therefore, it will be a great idea to assemble these two important privileged scaffolds into one molecule in a spiro manner which may lead to a series of possible pharmacologically exciting spiroisoindolinone fused heterocycles.

Literature survey shows that little progress has been made toward the synthesis[6] of spiroisoindolinone, which includes silver carbonate catalyzed spirolactonization of 3-propargyl-substituted isoindolin-1-one,[6a] Rh-(III) catalyzed C–H activation reaction of cyclic diazo compound with O-pivaloyl benzhydroxamic acids[6b] and heterocyclization of 2-iodobenzoyl chloride with ketimines using palladium.[6c]

As far as we are aware, there is no such method available for the synthesis of 6,7-dihydrospiro[indole-3,1′-isoindoline]-2,3,4(1*H*,5*H*)-trione derivatives including the use of transition metal catalyst. To address this synthetic challenge, we sought to devise a metal-free one-pot reaction that would involve simple starting materials. Easily accessible cyclic enaminones have been used as versatile reactive intermediates in multicomponent reactions and domino processes for expedient synthesis of various heterocycles and total synthesis of natural products.[7] In this regard, domino process[8] is one of the most suitable and practical approaches for assembling a diverse range of structural and stereochemical architectures in an efficient manner. Recently, we have reported on camphor-10-sulfonic catalyzed domino Friedel–Crafts reaction for the preparation of 3-ethoxycarbonyl-3-indolylisoindolin-1-ones and spiroisindolin-1-one fused heterocycle.[9] Against these backgrounds, we envisioned that cyclic enaminone **2** may efficiently be involved in the condensation–cyclization reaction with cyclic

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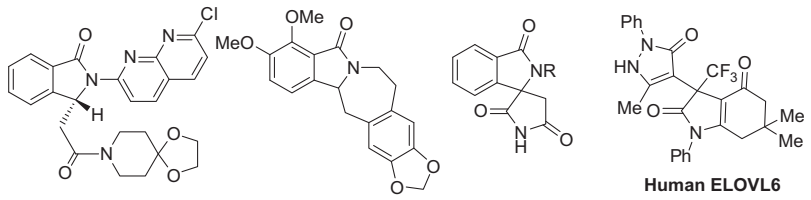


Figure 1. Natural product and biologically active compounds that have isoindolin-1-one and dihydroindol-2-one moieties.

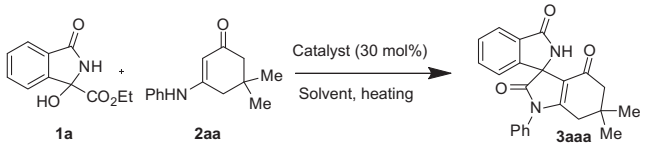
ketimine **4** in the presence of Brønsted acid to access this spirocyclic compound **3** (Scheme 1). During our continuing efforts toward the development of metal-free based domino protocols as well as synthesis of *N*-heterocycles,[10] we report a simple, mild, and robust procedure for the synthesis of 1-aryl/alkyl-substituted-6,7-dihydrospiro[indole-3,1′-isoindole]-2,3′,4(1*H*,5*H*)-trione derivatives via a domino dehydration/condensation/cyclization sequence reaction of cyclic enaminones with 3-ethoxycarbonyl-3-hydroxyisoindolin-1-one derivative using (±)-CSA as a Brønsted acid catalyst.

In order to establish the optimal conditions, we tested the model reaction between 3-ethoxycarbonyl-3-hydroxyisoindolin-1-one (**1a)** and 5,5-dimethyl-3-(phenylamino)cyclohex-2-enone (**2aa**) under a variety of reaction conditions (solvent, catalyst and temperature). The results are summarized in Table 1. It was observed that (±)-camphor-10-sulfonic acid was unable to trigger this reaction at room temperature in CH_2Cl_2 medium (Table 1, entry 2). However, at 40 °C, after 24 h, a very low yield (19%) of 6,6-dimethyl-1-phenyl-6,7-dihydrospiro[indole-3,1′-isoindole]-2,3′,4(1*H*,5*H*)-trione (**3aaa)** was obtained (entry 3). The product was fully characterized by its spectroscopic data (^{1}H, ^{13}C NMR and HRMS). Gratifyingly, these significant results motivated us to examine this domino reaction in detail. For this catalyst, further screening of other organic solvents such as toluene, $CHCl_3$, xylene, dioxane, and EtOH was carried out under heating conditions (entries 4–9). The results clearly demonstrated that at 90 °C, toluene and xylene provided the highest yields (82% and 79% respectively, entries 6 and 7) of targeted spiro product **3aaa** than those using other organic solvents (entries 8 and 9). On further increasing the reaction temperature from 90 °C to 120 °C in xylene, no improvement in yield (77%) and reaction time was observed (entry 11). Considering the lower boiling point of toluene, it was chosen as the best solvent for all the further reactions. Next, we examined several well known Brønsted acid catalysts namely pTSA, trichloroacetic acid (TCA), TFA, TfOH, H_2SO_4, and HCl for this domino process. As shown in Table 1, all these catalysts were able to promote this reaction effectively (except TCA, 33% yield, entry 12), resulting in moderate to good yields of desired compound **3aaa** (57–74%, entries 13–17).

A reasonable mechanism for the formation of compound **3aaa** has been proposed as shown in Scheme 2. This domino reaction is thought to proceed via an iminium ion mode of activation mechanism. At first, cyclic ketimine **4a** is generated from **1a** through a dehydration process. In the second step, the nitrogen atom of cyclic ketimine **4a** is protonated by CSA to form cyclic iminium ion **5**, which is subsequently attacked by cyclic enaminone **2aa**, leading to intermediate **6**. The latter undergoes an imine-enamine tautomerism to form condensation product **7**, which, finally, is converted into **3aaa** via intramolecular cyclization.

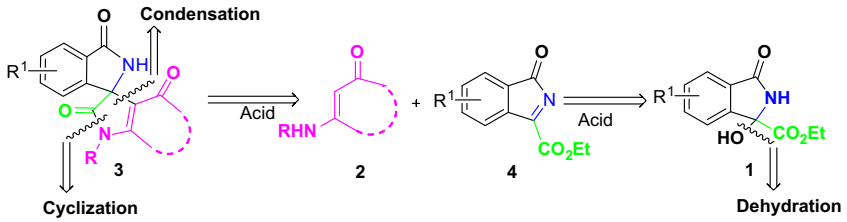
With these acceptable results in hand, we examined the scope of this domino process by using several *N*-aryl/alky-substituted cyclic enaminones **2** with 3-ethoxycarbonyl-3-hydroxyisoindolin-1-one derivatives **1** under our standard conditions. The results are summarized in Table 2. As is evident in Table 2, a series of six-membered cyclic enaminones derived from several aromatic amines with various substituents on phenyl rings (entries 1–9) condensed efficiently (74–85%) with substrate **1a**, providing a straightforward way to construct the previously unknown class of spiro products possessing both isoindolin-1-one and dihydroindol-2-one frameworks. Importantly, *N*-benzyl substituted cyclic enaminone (entry 10) also resulted in good yield when substrate **1a** was employed. Not only **1a** but also 5-halide-substituted 3-ethoxycarbonyl-3-hydroxyisoindolin-1-ones (**1b**–**e**) too were witnessed to be good enamine acceptors. For example, after 24 h, high yield (80–85%) of the corresponding products (**3baa**–**3eaa**, entries 11–14) were obtained when 5,5-dimethyl-3-(phenylamino)cyclohex-2-enone (**2aa**) was used. Similarly, substrate **1a** underwent clean reactions of several 3-(arylamino)-cyclohex-2-enones by this protocol providing the corresponding anticipated products in good yields (75–78%, entries 15–17). By this synthetic operation, several functional groups including Me, OMe, Bn, Cl, Br,

Table 1
Domino reaction of 5,5-dimethyl-3-(phenylamino)cyclohex-2-enone (**2aa**) with 3-ethoxycarbonyl-3-hydroxyisoindolin-1-one (**1a**)[a]

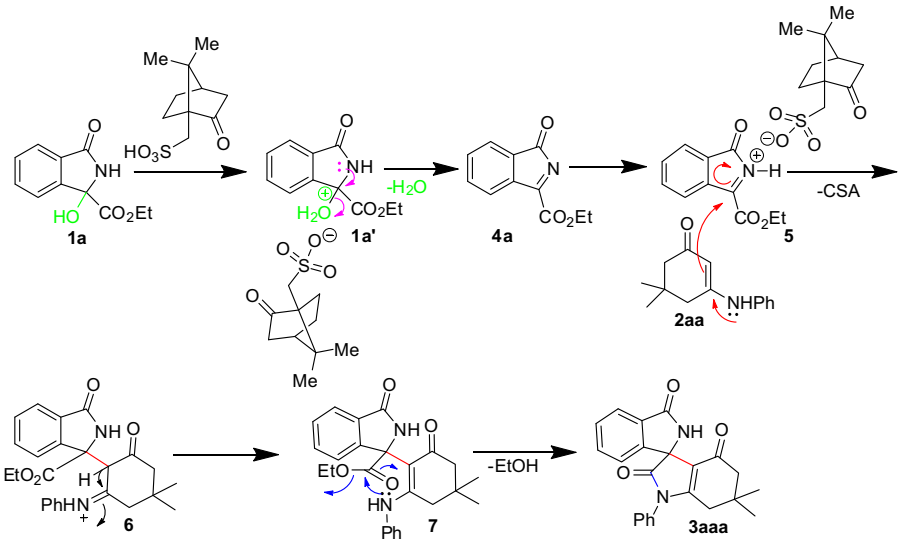


Entry	Catalyst	Solvent	*T* (°C)	*T* (h)	Yield[b] (%)
1[c]	Nil	CH_2Cl_2	rt	24	NR
2[c]	CSA	CH_2Cl_2	rt	24	NR
3	CSA	CH_2Cl_2	40	24	19
4	CSA	$CHCl_3$	60	24	37
5	CSA	Toluene	60	24	45
6	CSA	Toluene	90	24	82
7	CSA	Xylene	90	24	79
8[d]	CSA	EtOH	90	24	25
9	CSA	Dioxane	90	24	51
10	CSA	Toluene	110	24	79
11	CSA	Xylene	120	24	77
12	TCA	Toluene	90	40	33
13	pTSA	Toluene	90	24	72
14	TFA	Toluene	90	24	73
15	TfOH	Toluene	90	24	74
16	H_2SO_4	Toluene	90	30	69
17	HCl	Toluene	90	30	57

[a] Unless otherwise mentioned, all the reactions were carried out with compound **1a** (0.2 mmol), **2aa** (0.25 mmol) and catalyst (0.06 mmol, 30 mol %) in specified dry solvent (0.5 mL) and temperature.
[b] Yield of isolated product after column chromatography.
[c] NR = no reaction.
[d] Reaction was performed in the sealed tube.



Scheme 1. Domino strategy for the synthesis of spiroisoindolin-1-one fused heterocycle **3**.



Scheme 2. Proposed mechanism of this domino reaction.

I, F etc were well tolerated. Moreover, the desired product possesses a chiral quaternary carbon center at the 3-position on the isoindolin-1-one ring which is flanked by dihydroindol-2-one moiety for further elaborations.

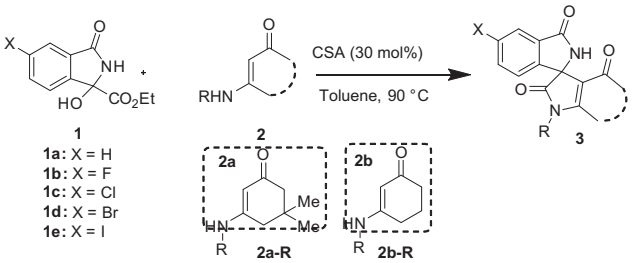
However, to our surprise, 5-membered cyclic enamines (**2ca**–**2cb**) containing a γ-lactone moiety reacted with substrate **1a** under the present conditions, affording only uncyclized ethyl 3-oxo-1-(2-oxo-4-(arylamino)-2,5-dihydrofuran-3-yl)isoindoline-1-carboxylates (**3aca**–**3acb**) in excellent yields (87–90%, Scheme 3).

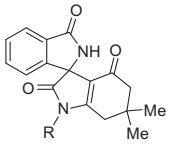
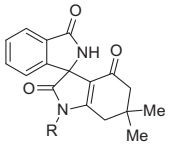
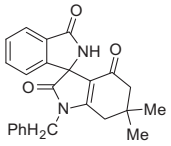
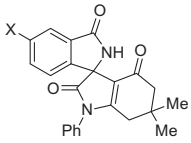
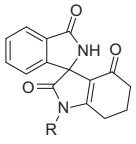
Functionalized spirooxindole framework has been the subject of growing interest in recent years because this motif is present in a variety of drug candidates and natural products.[11] Many of their synthetic analogs exhibit a broad range of biological activities such as anti-microbial, anti-tumor, anti-diabetic, anti-inflammatory, anti-tubercular etc.[12] In view of great applications, enormous efforts have been put into developing highly efficient synthetic routes to prepare these important motifs.[11,12] To the best of our knowledge, there is no fruitful report on the metal-free mediated preparation of spiro[indoline-3,1′-isoindoline]-2,3-dione. Toward this goal, we have realized that cyclohexene moieties of spiro compounds **3aba** and **3abe** could be aromatized in $CHCl_3$ at 70 °C using NBS,[13] leading to the corresponding spirooxindole fused heterocycles **8** and **9** in high yields 83% and 89%, respectively (Scheme 4).

Next, we turned our attention toward the stereoselective reduction of the double bond of compound **3aba** under hydrogen atmosphere using 10% Pd/C in EtOH at room temperature for 2 h, resulting in hydrogenated product **10** with excellent diastereoselectivity (**10a**:**10b** = 19:1 dr, Scheme 5) and 87% yield of **10a.** The relative configuration of major isomer **10a** (*cis*–*cis*) was unambiguously confirmed by its single crystal X-ray diffraction data (Fig. 2, details in ESI). These results clearly revealed that stereoselective hydrogenation occurs at sterically less congested side of C=C bond. Furthermore, we extended the major isomer **10a** into novel access of ibophyllidine-like alkaloid **11**,[14] which was obtained in good yield (61%) via a Fischer indole reaction using phenylhydrazine in AcOH medium at 120 °C under microwave irradiation.

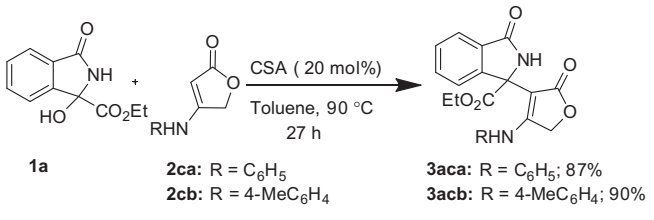
In conclusion, we have developed a simple, efficient, and straightforward method for the one-pot novel domino dehydration/condensation/cyclization reactions of 3-ethoxycarbonyl-3-hydroxyisoindolin-1-one derivatives with several cyclic enaminones to produce a series of biologically attractive 6,7-dihydrospiro[indole-3,1-isoindole]-2,3,4(1*H*,5*H*)-trione derivatives using (±)-CSA as an inexpensive Brønsted acid catalyst. In addition, a simple operation, mild, metal-free based catalytic system, and high yields may open up a new synthetic avenue for assembling of isoindolin-1-one and dihydroindol-2-one moieties in a spiro fashion. Moreover, the spirooxindoles and ibophyllidine-like alkaloids have been successfully prepared for the first time through this methodology. Further endeavors toward the development of enantioselective methods as well as the applications of these spirocyclic compounds are under investigation and will be communicated in due course.

Table 2
(±)-CSA catalyzed one-pot synthesis of 6,7-dihydrospiro[indole-3,1′-isoindole]-2,3′,4(1*H*,5*H*)-trione derivative (**3aaa**–**3abe**)[a]

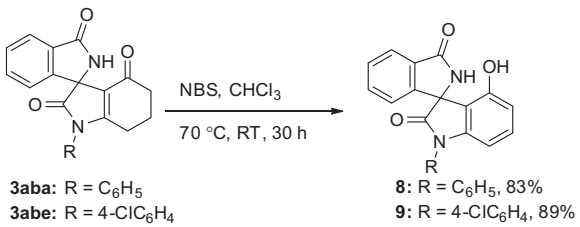


Entry	Product		Time (h)	Yield[b] (%)
1		**3aaa**: R = C_6H_5	24	82
2		**3aab**: R = 4-MeC_6H_4	24	84
3		**3aac**: R = 4-MeOC_6H_4	24	81
4		**3aad**: R = 4-FMeC_6H_4	28	79
5		**3aae**: R = 4-ClC_6H_4	27	85
6		**3aaf**: R = 4-BrC_6H_4	27	84
7		**3aag**: R = 4-IC_6H_4	24	80
8		**3aah**: R = 2-MeC_6H_4	28	77
9		**3aai**: R = 2-MeOC_6H_4	30	74
10		**3aaj**	24	87
11		**3baa**: X = F	24	82
12		**3caa**: X = Cl	24	80
13		**3daa**: X = Br	24	85
14		**3eaa**: X = I	24	83
15		**3aba**: R = C_6H_5	24	76
16		**3aba**: R = 4-MeC_6H_4	24	78
17		**3abe**: R = 2-Cl-C_6H_4	24	75

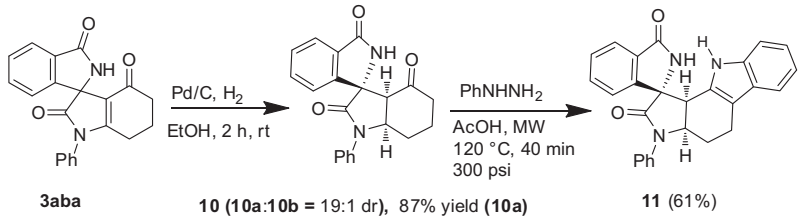
[a] Unless otherwise mentioned, all reactions were carried out with compounds (**1a**–**e**, 0.2 mmol), cyclic enaminones (0.25 mmol) and (±)-CSA (0.06 mmol, 30 mol%) in toluene (0.5 mL) at 90 °C.
[b] Yield of isolated product after column chromatography.



Scheme 3. Condensation reaction between **1a** and 5-membered cyclic enaminino esters (**2ca**–**cb**).



Scheme 4. Synthesis of spirooxindole moiety.



Scheme 5. Highly diasteroselective reduction of C=C bond and synthesis of ibophyllidine-like compound.

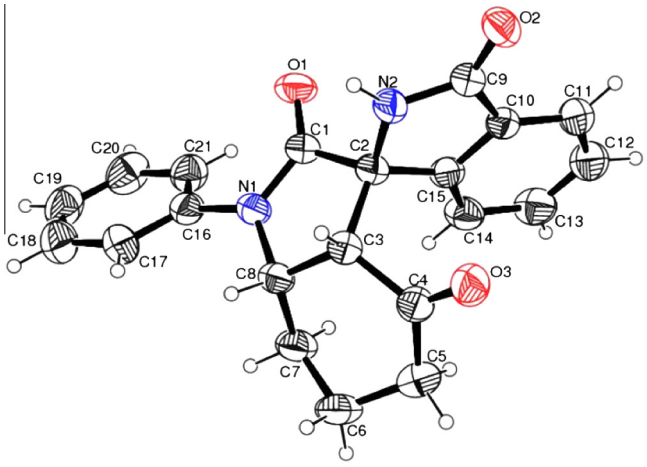


Figure 2. ORTEP-diagram of major isomer **10a**, thermal ellipsoids drawn at the 50% probability level.

Acknowledgments

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Supplementary data

Supplementary data (copies of ^{1}H NMR and ^{13}C NMR spectra of all listed in Table 2 and Schemes 3–5, **CCDC 965178**) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.01.154.

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