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(±)-CSA catalyzed Friedel–Crafts alkylation of indoles with 3-ethoxycarbonyl-3-hydoxyisoindolin-1-one: an easy access of 3-ethoxycarbonyl-3-indolylisoindolin-1-ones bearing a quaternary α-amino acid moiety

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ABSTRACT

For the first time, a very simple, efficient, mild, catalytic, and one-step procedure for the synthesis of a series of new 3-ethoxycarbonyl-3-indolylsubstituted-isoindol-1-one derivatives has been achieved via a Friedel–Crafts alkylation of indoles with 3-hydroxy-3-ethoxycarbonylisoindolin-1-one at room temperature using easily available inexpensive camphor-10-sulfonic acid as an organocatalyst. The current protocol provides good to excellent yields of the title compounds with high substrate scope. In addition, the desired product possesses a chiral quaternary carbon center at the 3-position on isoindolin-1-one ring which is flanked by indole moiety, amino and ester groups for further elaborations.

The synthesis of 3-substituted isoindolin-1-one and its derivatives has been the subject of growing interest in recent years because of its application as a valuable pharmacophore exhibiting a wide range of therapeutic activities[1] and also found in various natural products (Fig. 1). For example, AKS-186 (**I**) inhibits vasoconstriction induced by thromboxane A2 analog,[2] (*R*)-Pazinaclone (**II**)[3] exhibits anxiolytic activity and is of interest as sedative, hypnotic, and muscle relaxant, (S)-PD172938 (**III**) shows a dopamine D4 receptor antagonist,[4] and compound **IV** inhibits microsomal triglyceride transfer protein (MTP) and/or apolipoprotein B secretion.[5] (+)-Lennoxamine (**V**) is a naturally occurring isoindolobenzazepine alkaloid.[6] In addition, 3-substituted isoindol-1-ones are valuable segments in the synthesis of important natural products.[7] Owing to their great biological activities, several methods have been documented for the syntheses of both racemic and enantio-enriched 3-substituted isoindolin-1-one derivatives.[8] Nonetheless, even with such progress, organocatalytic, direct syntheses of 3-indolyl substituted isoindol-1-one derivatives are rare. As far as we are aware, there are only two isolated examples available in the literature, all were reported recently. Namely, chiral BINOL-phosphoric acid catalyzed asymmetric Friedel–Crafts (F–C) alkylation of N-unprotected indoles with 3-alkyl-3-hydroxyisoindolin-1-ones reported by Zhou and co-workers.[9] There is no such report on the organocatalytic F–C alkylation of both N-protected and unprotected indoles with 3-ethoxycarbonyl-3-hydroxyisoindolin-1-one as a nucleophilic acceptor. Nevertheless, this combination constitutes an important indole-substituted non-natural cyclic α-amino acid moiety bearing a quaternary carbon center at the 3-position on isoindolin-1-one ring. As we know the synthesis of α-amino acid derivative with a chiral quaternary carbon center is a very challenging task for organic chemists and also has much biological significance.[10] Therefore, it would be highly desirable to synthesize the 3-ethoxycarbonyl-3-indolylsubstituted-isoindol-1-ones in a more practical and efficient manner.

Recently F–C alkylation of indoles[11] using a catalytic amount of Brønsted acid has paid much attention due to the potential environmental concerns of metal catalysis in general as well as the application of indole framework present in various range of natural products and medicinal chemistry.[12] In this regard, easily available, less toxic camphor-10-sulfonic acid (CSA) has emerged as a potent Brønsted acid catalyst for various organic transformations in recent years.[13] As part of our continued interest toward the development of organocatalyst mediated new synthetic transformations in an environment friendly manner[14] and synthesis of indole derivatives, in 14 h we wish to report a clean, organocatalytic, highly efficient

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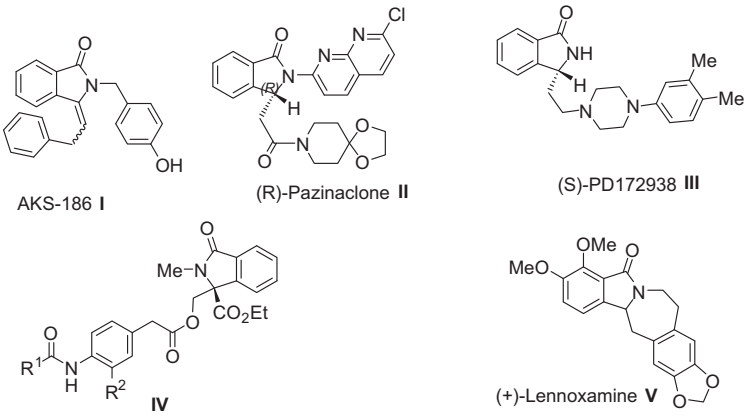
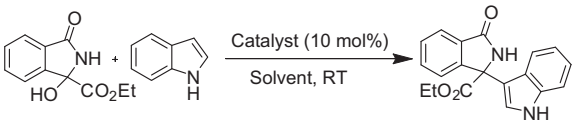


Figure 1. Some important biologically active 3-substituted-isoindolin-1-ones.

synthesis of 3-ethoxycarbonyl-3-(indol-3-yl)isoindol-1-one derivatives through a F–C alkylation of N-protected and unprotected indoles with 3-ethoxycarbonyl-3-hydroxyisoindolin-1-one in the presence of CSA as a Brønsted acid catalyst.

We chose the model reaction between 3-ethoxycarbonyl-3-hydroxyisoindolin-1-one (**1a**) and indole (**2a**) in the absence of catalyst at room temperature for 24 h in DCM medium. Unfortunately, the reaction did not proceed at all (Table 1, entry 1). From this result, we envisioned that a Brønsted acid activation is essential for initiation of this reaction to proceed. Therefore, we employed a well known pTSA (10 mol %) as catalyst for this reaction in CH_2Cl_2 medium at room temperature. Intriguingly, after 24 h, the desired product **3a** was obtained in 48% yield (Table 1, entry 2). The structure of the product was assigned by IR, ^{1}H NMR, ^{13}C NMR, and HRMS spectroscopy. Gratifyingly, these significant results motivated us to investigate the F–C alkylation reaction of indole in detail. In order to find out the best catalyst for this reaction, we screened readily available several Brønsted acids such as TfOH, CSA, TCA (trichloroacetic acid), TFA (trifluoroacetic acid), heterogeneous catalyst Amberlyst-15H, H_2SO_4, HCl etc in CH_2Cl_2 medium at room temperature. The results are summarized in Table 1. We were pleased to observe that in all these cases F–C alkylation product **3a** was isolated (Table 1, except entry 5). As shown in Table 1, with a 10 mol % loading catalysts of TfOH and TFA, both gave the desired product **3a** with moderate yields in 42% and 58% 'respectively' under similar reaction conditions (entries 3 and 7). It is noteworthy to mention that the reactions were smooth initially in case of TfOH and pTSA, but slowed down quickly afterward. Indole is not compatible with a strong Brønsted acid such as TfOH and pTSA. A little amount of indole self-trimerized product **4a** was observed in both the cases,[15] which might be detrimental to the rate of the reaction. Indeed, our control experiment verified this speculation. For the control experiment (Scheme 1), when a mixture of compound **1a,** indole **2a**, pTSA (10 mol %), and self-trimerized product **4** (10 mol %) in CH_2Cl_2 was stirred for 24 h at room temperature, very negligible amount of product **3a** was observed (2–3% conversion, Scheme 1). The inferior results were also observed when mild acid TCA (entry 6) and mineral acids such as H_2SO_4 and HCl (entries 8–9) were used. It was clear that organocatalyst like L-proline was unable to catalyze this transformation (entry 10) at our present conditions. Surprisingly, with a 10 mol % loading of CSA, the reaction was completed within 24 h and F–C product was obtained in 91% yield (entry 4).[16] For this catalyst, further screening of solvents revealed that normal organic ones, such as toluene (entry 12), hexane (entry 13), and THF (entry 14), all led to inferior results (27–32% yield) as compared to CH_2Cl_2 (entry 4). However,

Table 1
F–C alkylation of indole with 3-ethoxycarbonyl-3-hydroxyisoindolin-1-one (**3a**)[a]

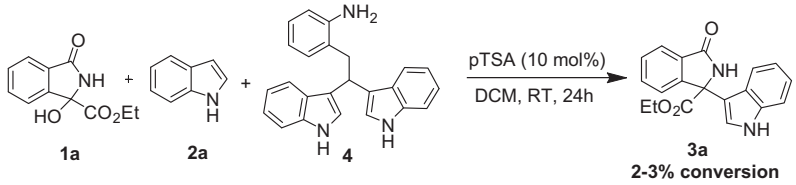


1a **2a** **3a**

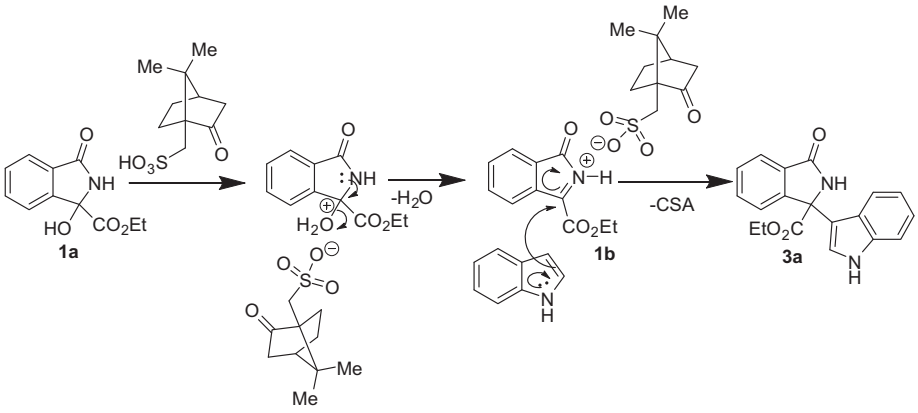
Entry	Catalyst	Solvent	T (h)	Yield[b] (%)
1[d]	None	CH_2Cl_2	24	NR
2	pTSA	CH_2Cl_2	24	48
3	TfOH	CH_2Cl_2	24	42
4	CSA	CH_2Cl_2	24	91
5[c]	Amberlyst-15H	CH_2Cl_2	24	10
6	TCA	CH_2Cl_2	24	28
7	TFA	CH_2Cl_2	24	58
8	H_2SO_4	CH_2Cl_2	36	30
9	HCl	CH_2Cl_2	36	10
10[d]	L-Proline	CH_2Cl_2	24	NR
11	(S,S)-BINOL-phosphate	CH_2Cl_2	48	>5
12	CSA	Toluene	48	28
13	CSA	Hexane	48	32
14	CSA	THF	48	27
15	CSA	$CHCl_3$	24	82
16	CSA	EtOH	24	>10
17	CSA	MeOH	24	>10
18	CSA	H_2O	24	>5
19[e]	(−)-CSA	CH_2Cl_2	20	85

[a] Unless otherwise mentioned, all reactions were carried out with compound **1a** (0.3 mmol), indole (0.45 mmol), and catalyst (0.03 mmol, 10 mol %) in specified solvent (2.0 mL) at room temperature.
[b] Yield of isolated product after column chromatography.
[c] 20.0 mg of Amberlyst-15H was used.
[d] NR = no reaction.
[e] 1*R*-Camphor-10-sulfonic acid was used for this reaction, enantiomers were separated by chiral OD-H column, enantiomeric excess (ee) was <5%.

$CHCl_3$ was also a good solvent for this reaction (entry 15). The reaction was witnessed to be much slower in case of protic solvents like EtOH, MeOH, and H_2O (Table 1, entries 16–18). The reactivity studies with various solvents exhibited that CH_2Cl_2 was the best solvent in terms of reactivity for this F–C alkylation reaction. Chiral BINOL-phosphoric acid was proven to be a superior Brønsted acid catalyst for the synthesis of 3-alkyl-3-indolylisoindolin-1-ones, where 3-alkylsubstituted-3-hydroxyisoindol-1-ones were employed as nucleophilic acceptors.[9] Strikingly, using similar BINOL-phosphoric acid catalyst, almost no conversion was observed when the substrate **1a** was used as a nucleophilic acceptor under the present reaction conditions (Table 1, entry 11). Hence improvised methodology was inevitable for these conversions.



Scheme 1. Control experiment for F–C alkylation of indole.



Scheme 2. Reaction mechanism of the F–C alkylation of indole catalyzed by (±)-CSA.

In this direction, we investigated the asymmetric version of this F–C alkylation reaction of indole **2a** with **1a** in CH_2Cl_2 medium using enantio-enriched (1*R*)-CSA (10 mol %) at room temperature (entry 19, Table 1). Unfortunately, almost no enantioselectivity was observed for compound **3a**.

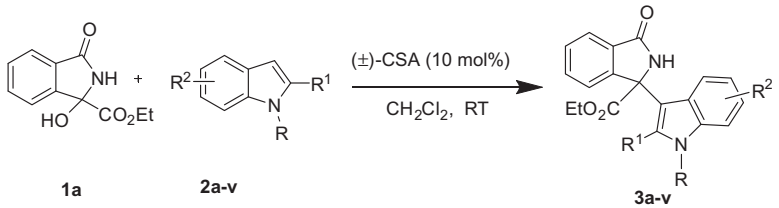
We propose the following probable mechanism for the formation of product **3a** (Scheme 2). The reaction is thought to proceed via an iminium ion mechanism. First, cyclic ketimine **1b** is generated through protonation of tertiary hydroxyl group of **1a** by CSA and followed by dehydration. In the second step, the nitrogen atom of cyclic ketimine (**1b)** is protonated by CSA to form cyclic iminium ion, which is subsequently attacked by indole (**2a**) resulting in product **3a**.

To study the scope and limitation of this F–C alkylation reaction, we studied a wide range of structurally varied diverse steric and stereoelectronic environments of indole derivatives with 3-hydroxy-3-ethoxycarbonylisoindolin-1-one (**1a**) using 10 mol % loading of CSA as catalyst at our standard conditions. The results are compiled in Table 2. As is evident from Table 2, various ranges of N-protecting groups of indole such as Me, OMe, allyl, propargyl, benzyl, *p*-methoxybenzyl, *p*-trifluoromethylbenzyl, and *tert*-butyl acetate were investigated (entries 2–9). In all these cases (except entry 7), F–C alkylation methods were very smooth at room temperature, leading to the formation of a series of new 3-indolylsubstituted-isoindol-1-ones with good to excellent yields (74–87%). However, *p*-trifluoromethylbenzyl group provided a very poor yield (>10%) at room temperature. Surprisingly, when the same reaction was performed at 40 °C, excellent yield (94%) was achieved (entry 7) within shorter time. Even sterically demanding 2-substituted indoles also reacted with compound **1a** at our present conditions. For example, 2-methylindole (entry 10), *N*-benzyl-2-methylindole (entry 11), and *N*-benzyl-2-thiomethylindole (entry 12) all led to good yields of the desired products (82–86% yields). Similarly, 7-methylindole (entry 18) was also a good substrate for this F–C reaction, providing the desired product with 87% yield after 24 h. Indoles with weak electron withdrawing substituents such as Br, Cl, and F at its 5-position afforded the targeted products with slightly lower yields and longer reaction times as compared to indole (entries 13–15) at room temperature. The reason might be that electron withdrawing nature of halides reduces the nucleophilicity of indoles which causes slower rate of the reaction. The N-unprotected indoles having substituents at 5-position like F, Me, OMe, and OBn did not react with **1a** at room temperature and starting materials were unchanged. Interestingly, as anticipated, all these cases, F–C reactions proceeded well within 10–12 h at 40 °C to furnish the desired products with excellent yields of the corresponding products (88–93%, entries 15–17). Next, we proceeded further with corresponding N-protected 5-substituted indoles for verifying their reactivities. To our pleasure, all these reactions ran efficiently at room temperature and produced the anticipated 3-(*N*-protected-5-substitutedindol-3-yl)-3-ethoxycarbonylisoindol-1-ones in good to high yields (59–84%, entries 19–22). Our present conditions are mild enough to tolerate several sensitive functional groups like allyl, propargyl, CO_2Bu^t, OMe, OBn, SMe, N-OMe, Cl, Br etc. Therefore, it is an amiable opportunity to achieve the suitable therapeutic targets by synthetic modifications of these functional groups depending on the requirement.

In order to envisage the application potential of the present methodology, we extended the synthesized compounds **3w** (48% yield) and **3x** (93%) into a novel access of spiro cyclic compound **5** (Scheme 3). For example, the excellent yield (94%) was obtained via a deprotection of Boc-group of compound **3x** using a TFA in DCM medium at room temperature and followed by cyclization.

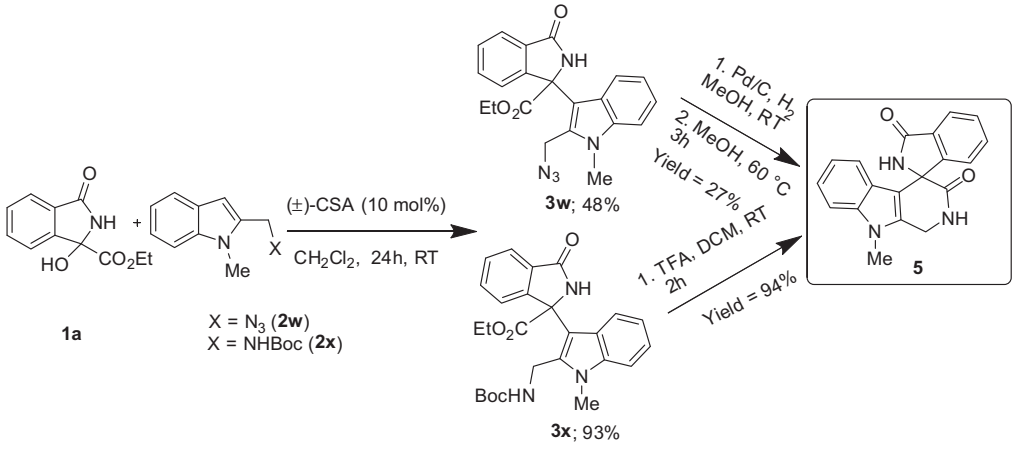
In this manuscript, we have developed a convenient and efficient organocatalytic one-step method for the syntheses of biologically significant 3-ethoxycarbonyl-3-(indol-3-yl)isoindol-1-one derivatives through a F–C alkylation of both N-protected and unprotected indoles with 3-ethoxycarbonyl-3-hydroxyisoindole-1-one at room temperature using commercial available less expensive CSA (10 mol %) as catalyst. The mild reaction conditions (room

Table 2
(±)-CSA catalyzed one-step synthesis of 3-ethoxycarbonyl-3-(indol-3-yl)isoindol-1-one derivatives (**3a–v**)[a]



Entry	R	R^1	R^2	*T* (h)	Yield[b] (%)
1	H	H	H	24	91
2	Me	H	H	22	87
3	CH_2=$CHCH_2$	H	H	25	81
4	CH≡CCH_2	H	H	24	85
5	$PhCH_2$	H	H	24	79
6	4-(MeO)–$C_6H_4CH_2$	H	H	26	86
7[c]	4-(CF_3)–$C_6H_4CH_2$	H	H	8	94
8	$CH_2CO_2Bu^t$	H	H	25	82
9	MeO	H	H	25	85
10	H	Me	H	24	83
11	$PhCH_2$	Me	H	26	81
12	$PhCH_2$	SMe	H	24	86
13	H	H	5-Br	36	78
14	H	H	5-Cl	36	75
15[c]	H	H	5-F	12	89
16[c]	H	H	5-Me	10	93
17[c]	H	H	5-OMe	11	88
18	H	H	7-Me	24	87
19	Me	H	5-F	36	59
20	$PhCH_2$	H	5-OMe	24	82
21	$PhCH_2$	H	5-OBn	24	79
22	$PhCH_2$	H	5-Me	24	84

[a] Unless otherwise specified, all reactions were carried out with compound **1a** (0.3 mmol), indole **2a–v** (0.45 mmol), and catalyst (0.03 mmol, 10 mol %) in CH_2Cl_2 (2.0 mL) at room temperature.
[b] Yield of isolated product after column chromatography.
[c] Reaction was carried out at 40 °C.



Scheme 3. Synthesis of spiro cyclic compound **5**.

temperature), simple operation, inexpensive organocatalyst, low catalyst loading, broad substrate scope, and high yields of adducts make this procedure attractive. Moreover, this procedure offers a non-natural cyclic α-amino acid derivative bearing a chiral quaternary carbon center at the 3-position on the isoindolin-1-one ring which is flanked by an indole moiety and an α-amino acid group for further elaborations. Furthermore, this method demonstrates the potential of camphor-10-sulfonic acid (CSA) as an organocatalyst. The enantioselective syntheses of these compounds and further applications to biological systems are in progress.

Acknowledgments

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Supplementary data

Supplementary data associated (copies of ^{1}H NMR and ^{13}C NMR spectra of all listed in Table 2 and Scheme 3) . with this article can

be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.01.010.

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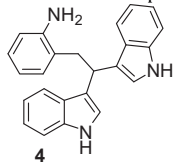
15. Indole self-trimerized product **4** was formed in the presence of a strong Brønsted acid in CH_2Cl_2 medium at room temperature.



4

16. *Synthesis of 3-ethoxycarbonyl-3-(1H-indol-3-yl)isoindolin-1-one*: To a stirred solution of 3-ethoxycarbonyl-3-hydroxyisoindolin-1-one (66.3 mg, 0.3 mmol) and indole (52.6 mg, 0.45 mmol) in CH_2Cl_2 (2.0 mL) was added CSA (7.0 mg, 0.03 mmol) at room temperature for 24 h. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was extracted with EtOAc (3×10 mL), washed with water and brine respectively and dried with Na_2SO_4. The organic phase was evaporated by rotary evaporator under reduced pressure to give the crude product. The crude product was purified by column chromatography over silica-gel to furnish the pure product (87.3 mg, 91% yield). The product was characterized by corresponding spectroscopic data (IR, NMR, HRMS).
*3-Ethoxycarbonyl-3-(1H-indol-3-yl)isoindolin-1-one (*Table 2 *entry 1,)*: Yield 91%, mp 190 °C; **IR** (KBr) ν 3061, 1736, 1697, 1615, 1468, 1352 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.26 (br s, 1H), 7.91 (d, J = 7.0 Hz, 1H), 7.78 (d, J = 7.0 Hz, 1H), 7.54–7.62 (m, 2H), 7.37 (d, J = 8.0 Hz, 1H), 7.15–7.24 (m, 3H), 7.02–7.05 (m, 1H), 6.91 (br s, 1H), 4.24–4.34 (m, 2H), 1.29 (t, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.9, 169.3, 145.1, 136.7, 132.5, 130.9, 129.4, 125.1, 124.7, 123.9, 122.9, 120.5, 119.2, 113.6, 111.6, 66.7, 62.7, 14.2; HRMS (ESI) m/z Calcd For $C_{19}H_{16}N_2O_3$ $[M+Na]^+$: 343.1053. Found 343.1099.