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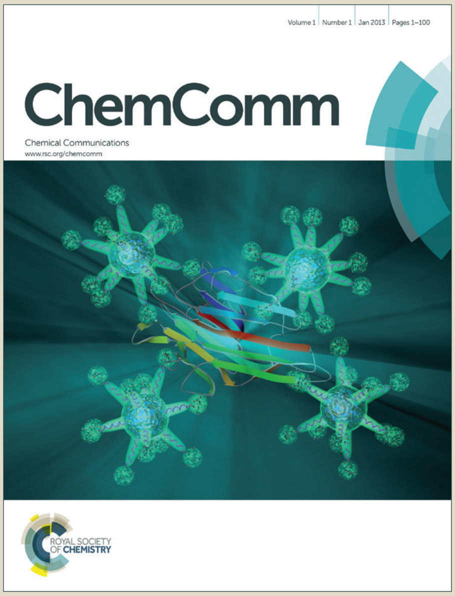
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TfOH-catalyzed synthesis of 3-aryl isoindolinones via tandem reaction

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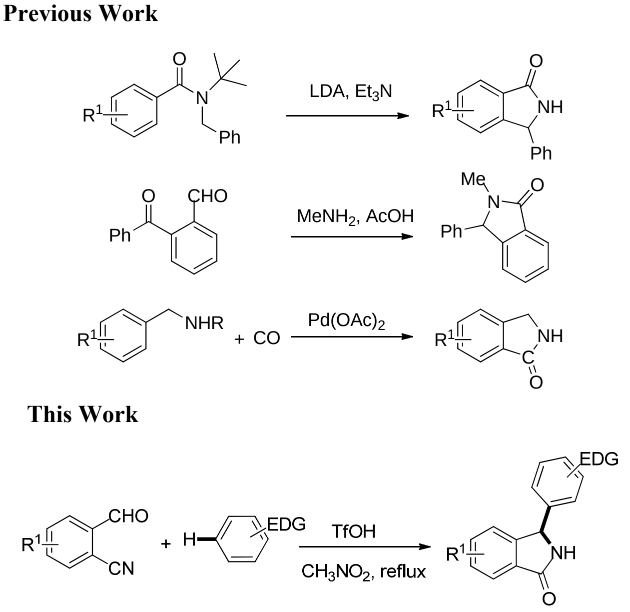
A convenient metal-free method for the synthesis of 3-aryl isoindolinones *via* TfOH catalyzed aromatic C−H functionalization of electron-rich arenes with 2-formylbenzonitriles is developed. This process provided a new efficient synthetic strategy to isoindolinone derivatives by forming two bonds in good to high yields and regioselectivities.

Isoindolinones can be found in natural products including stachybotrin C,[1] indoprofen,[2] Lennoxamineand,[3] and also in some pharmacologically important synthetic compounds, such as zopiclone[4] and pagoclone.[5] Numerous synthetic and natural molecules containing the isoidolinone skeleton have been reported to display significant biological activities including antimicrobials,[6] antiviras,[7] HIV-1 inhibitors,[8] TACE inhibitors,[9] antitumor activities,[2,10] hypnotic agents,[11] antidopaminergic agents and also protein kinase inhibiting activities.[12] Some isoindoline derivatives were also reported to exhibit local anesthetic activity superior to that of procaine.[13] Furthermore, these heterocyclic scaffolds have been found to have special fluorescent properties recently.[14]

Numerous methods for the construction of the isoindolinone ring system have been reported, among which. the more commonly used approaches are those from aromatic mono-carbonyl compounds, from 1,2-dicarbonyl compounds, and from the transformations of heterocycles, *via* the Diels–Alder reaction, and through the Wittig reaction.[7,15] Cyclizations of aryl lithium species of different N-acyl-benzylamine derivatives such as N-benzyl-N,N-dimethylureas were also reported in the literature with the using of strong basic organo-lithium regents, which are normally incompatible with functional groups sensitive to nucleophilic attack.[16] More recently, several metal-catalyzed approaches have been described for the synthesis of isoindolinones including carbonylation of benzylamines under CO atmosphere using the catalytic system $Pd(OAc)_2$-$Cu(OAc)_2$, a tandem limination-cyclization-Suzuki approach, Heck-Suzuki-Miyaura domino reaction involving ynamides, a Sonogashira reaction of 2-halobenzamides with terminal alkynes and alkynylation/lactamization cascade of available *o*-formyl methyl benzoates and *o*-formyl methyl arylacetates.[17] Other approaches to the isoindolinone system generally involved electrophilic cyclization, and an intramolecular cyclization of acyl radicals onto an azide group.[18]

Above all, most of the existing methods suffer from certain limitations with respect to yield, substrate scope, or apparative requirements, and are not suitable for the preparation of compound libraries. Therefore, there remains considerable scope for improvement, such as a more versatile catalyst and reaction conditions which prevent catalyst leakage, a voiding the use of highly toxic CO, and obtaining higher yields.



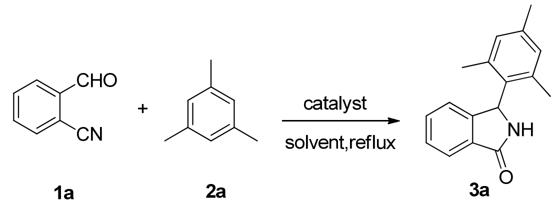
Scheme 1 Synthetic approaches for isoindolinones.

It was known that several classes of catalysts have been successfully applied to the FC reaction of aldehydes with nucleophiles, including brφnsted acids, conventional lewis acids, and transition metals.[19] Keeping the proposed intermediates of the FC reaction in view, we wished to construct the isoindolinone core from corresponding 2-formylbenzonitrile with arenes *via* the Friedel-Crafts reaction followed by assisted ring closing reaction route.

Our recent studies have been focusing on the development of new synthetic pathways for the preparation of heterocyclic compounds.[20] Herein, we report a novel and efficient route to isoindolinones through tandem reaction of 2-formylbenzonitriles with benzene derivatives catalysed by TfOH. To the best of our knowledge, this process was established for the first time as the tandem construction of isoindolinones.

For the synthesis of isoindolinones **3** via FC-ring closing reaction, 2-formylbenzonitriles **1a** and mesitylene **2a** was chosen as the model starting material. Accordingly different lewis acid[21] such as $FeCl_3$, CuCl, CuBr, CuI, BF_3•Et_2O and proton acid[22] such as H_2SO_4, CF_3COOH, TfOH, was selected as the catalyst. As anticipated in the previous section, the nature of the acid plays an important role in the efficiency of the process (Table 1). In fact, as reported in Table 1, it can be seen that the use of lewis acid (0.2 equiv) in 1, 2-dichloroethane (Table 1, entries 1-5) led to only less than 10% yields after 24 h. To our delight, a slight improvement in the yield of the desired product was observed when the reaction was carried out in protonic acid (Table 1, entries 6-8). The yields increased to 25% and 27% respectively when H_2SO_4, CF_3COOH were used as catalyst (entries 6-7). In addition, the reaction catalysed with TfOH provided 39% of the desired product (entry 8). In order to further improve the efficiency of this procedure, we screened the reaction in the presence of different solvents,[23] when the reaction was performed in the presence of protic solvent such as methanol, ethanol and water, the desired product was not detected and the reaction did not proceed (Table 1, entries 9-11), similar results were observed in the case of THF and acetone (Table 1, entries 12-13); To our delight, this reaction proceeded smoothly in CH_2Cl_2, CH_3CN, EtOAc and CH_3NO_2 (Table 1, entries 14-17), providing **3a** in moderate to good yields. On the basis of the above observations, CH_3NO_2 was chosen as the most promising solvent to optimize the reaction media, it gave the best isolated yield in 87%. The reaction was also performed in the presence of 0.3 eq. of TfOH, the yield of **3a** was only increased to 88% (entry 18), which indicated that additional amount of TfOH is not required for this transformation.

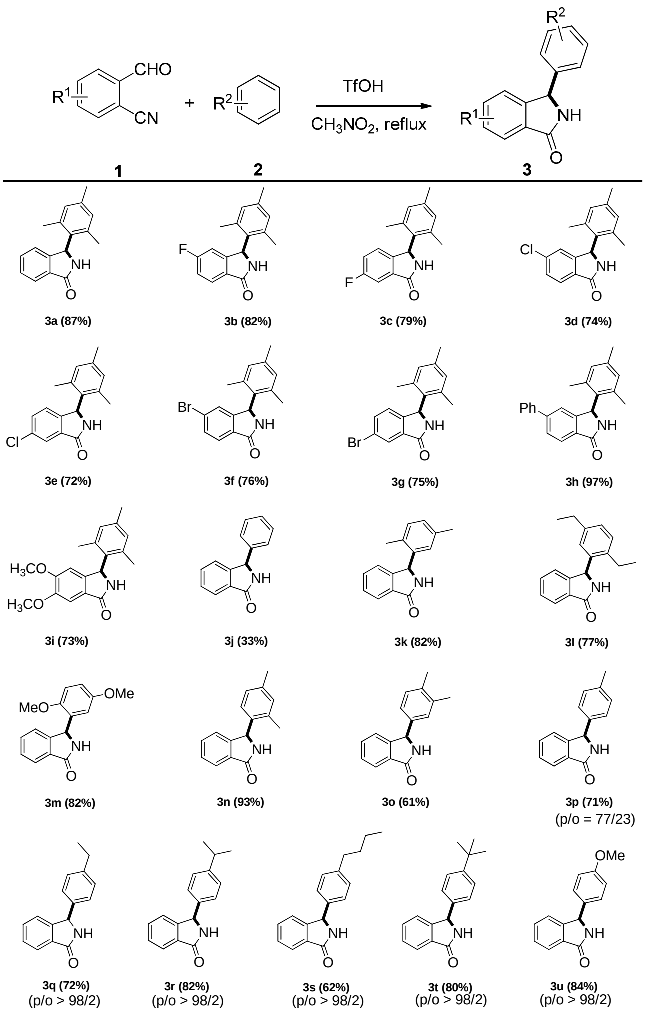
Table 1 Optimization of the reaction conditions screening for the synthesis of isoindolinone[a]



Entry	Catalyst (eq.)	Solvent	Yield[b] (%)
1	$FeCl_3$ (0.2 eq)	$ClCH_2CH_2Cl$	<10
2	CuCl (0.2 eq)	$ClCH_2CH_2Cl$	<10
3	CuBr (0.2 eq)	$ClCH_2CH_2Cl$	<10
4	CuI (0.2 eq)	$ClCH_2CH_2Cl$	<10
5	$BF_3 \cdot Et_2O$ (0.2 eq)	$ClCH_2CH_2Cl$	<10
6	H_2SO_4 (0.2 eq)	$ClCH_2CH_2Cl$	25
7	CF_3COOH (0.2 eq)	$ClCH_2CH_2Cl$	27
8	TfOH (0.2 eq)	$ClCH_2CH_2Cl$	39
9	TfOH (0.2 eq)	CH_3OH	nr
10	TfOH (0.2 eq)	C_2H_5OH	nr
11	TfOH (0.2 eq)	H_2O	nr
12	TfOH (0.2 eq)	acetone	<10
13	TfOH (0.2 eq)	THF	<10
14	TfOH (0.2 eq)	CH_2Cl_2	33
15	TfOH (0.2 eq)	CH_3CN	45
16	TfOH (0.2 eq)	EtOAc	55
17	TfOH (0.2 eq)	CH_3NO_2	87
18	TfOH (0.3 eq)	CH_3NO_2	88

[a] Reaction condition: Corresponding catalyst (0.2 mmol) was added to a stirred 5 mL solvent of 2-formylbenzonitrile (132 mg, 1 mmol) and mesitylene (601 mg, 5 mmol), The solution was stirred and heated to reflux, after reaction was completed (as indicated by TLC), the mixture was purified by flash chromatography on silica gel eluting with petroleum ether/ethyl acetate. [b] Yield of the isolated product after chromatography on silica gel.

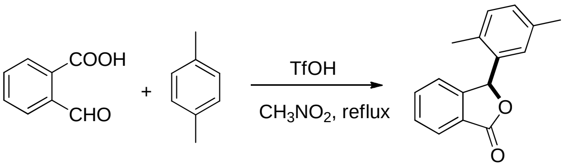
Table 2 Reaction of substituted isoindolinones under optimized conditions[a]



[a] Reaction condition: 20% equiv TfOH was added to a stirred 5 mL CH_3NO_2 of 2-formylbenzonitrile derivatives (1 mmol) and benzene derivatives (5 mmol), The solution was stirred and heated to reflux, after reaction was completed (as indicated by TLC), the mixture was purified by flash chromatography on silica gel eluting with petroleum ether/ethyl acetate. [b] Yield of the isolated product after chromatography on silica gel. [c] The para/ortho ratio was determined by ^1H NMR of the crude products.

With the optimum reaction conditions in hand, the scope and generality of this reaction were explored by treating different 2-formylbenzonitriles and benzene derivatives to generate various substituted isoindolinone products. The results showed that the reaction is quite general. First, the scope of 2-formylbenzonitriles[24] was investigated under the optimized reaction conditions. Substrates with F, Cl or Br groups on aromatic ring gave the desired products **3b-3g** in good yields (72%-82%). It is noteworthy that position of substituted groups and electron-withdrawing ability on the phenyl ring had less influence on the reaction. substrates with electron-donating group such as phenyl and 4,5-dimethoxy were also investigated under the optimum conditions, which proceeded smoothly to generate the products in good to excellent yields (**3h** and **3i**).

Next, different benzene derivatives in the reaction were examined. Benzene reacted with 2-formylbenzonitriles to give the corresponding products **3j** in 33% yield. Then, the treatment of **1a** with *p*-xylene and 1,4-diethylbenzene furnished the desired products **3k** and **3l** in good yield (82% and 77%) which might be due to strong electron-donating ability. To evaluate the reactivity of methoxy group on the benzene ring, 1,4-dimethoxybenzene was examined with **1a**, the desired product 3-(2,5-dimethoxyphenyl)isoindolin-1-one (**3m**) was finally produced in 82% yield under optimized conditions. We also tried the reaction of *m*-xylene and *o*-xylene with **1a**, it was pleased to find that high regioselectivity was observed in this reaction. The desired products **3n** and **3o** were afforded as single regioisomers exclusively and with the yield of 93% and 61% respectively. In order to further study the applicability and regioselectivity of this procedure, various mono-substituted benzene derivatives, including toluene, ethylbenzene, cumene, butylbenzene, tert-butylbenzene were investigated for the tandem reaction. From these results, it is concluded that the different electron-donating substituents on benzene has almost insignificant effect on the reaction yields. Major goal products (**3p**–**3t**) were gained as reaction occurred on the para position of benzene derivatives. When starting from toluene, the desired product was obtained as a mixture of regioisomers (para/ortho = 77/23), greater ratios (para/ortho > 98/2) were observed when benzene with an increase in alkyl group chain were tested, it could be due to the increasing steric hindrance effect. Finally, we tried the reaction of anisole with **1a** and produced the para-substituted desired product 3-(4-methoxyphenyl)isoindolin-1-one (**3u**) under optimized reaction conditions in 84% yield. Unfortunately, no products were obtained while electron-defcient benzenes such as chlorobenzene, nitrobenzene were investigated for this reaction, it proved that electron-withdrawing benzene derivatives couldn't proceed smoothly for this process.

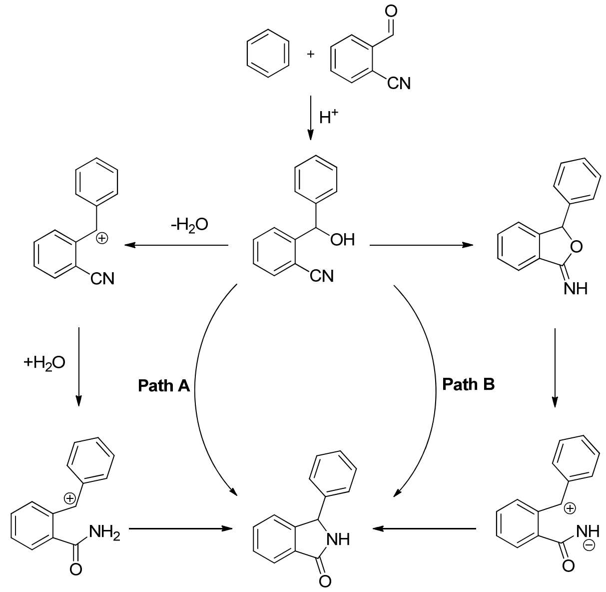


4a

Scheme 2 Synthesis of 3-(2,5-dimethylphenyl)isobenzofuran-1(3H)-one.

Furthermore, to explore the scope and application of the method, we examined the reaction of 2-formylbenzoic acid with p-xylene to generate isobenzofuranone derivative, it was found that the tandem reaction proceeded excellently to generate the product **4a** in 95% yield (Scheme 2).

The proposed reaction mechanism of the reaction between 2-formylbenzonitriles and arenes is shown in Scheme 3.[25] Arenes first couple with the aldehyde groups through Friedel-Crafts reaction to generate alcohol, which would then undergo a dehydration to afford intermediate carbocation, cyano group is subsequently converted to amide through hydrolysis reaction under strong acidic condition, finally an intramolecular aza-Michael addition process occurred to produce the isoindolinone framework (Path A); Moreover, intermediate alcohol also can be converted to imine through an intramolecular aza-Michael addition type of reaction, the imine is then converted to amide after rearrangement, the final product is finally generated through the conjugate addition of amide (Path B)..



Scheme 3 Proposed Mechanism for the Synthesis of isoindolinones.

In conclusion, we have developed an efficient and facile procedure for the synthesis of isoindolinones in good to excellent yields. The sequential reaction has been successfully applied with a wide scope of substituents on the 2-formylbenzonitrile and electron-rich arenes. The broad scope of this tandem reaction makes this procedure promising for practical usages. The investigation of the applications and the design of new synthetic crafts for these products are ongoing in our laboratory.

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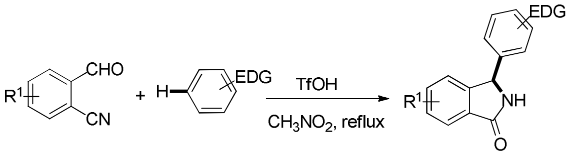

A convenient method for the synthesis of 3-arylisoindolinones *via* TfOH catalyzed C−H functionalization of arenes with 2-formylbenzonitriles is developed.