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Fridel-Crafts Alkylation of Arenes with Indolyl Alcohols for Construction of 3,3-Disubstituted Oxindoles

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An intriguing camphorsulfonic acid catalyzed Fridel-Crafts alkylation of arenes with indolyl alcohols has been developed featuring mild reaction condition, wide substrate scope and high yields. This reaction provides an efficient method to access biologically important heterocyclic oxindole derivatives.

The 3,3-disubstituted oxindole skeleton belongs to a privileged heterocyclic framework that constitutes the core structures of a large variety of biologically and pharmacologically significant natural alkaloids and medicines.[1] Among them, 3-functionalized 3-indolyloxindole skeletons are of particular interest which integrate two bioactive scaffolds of 3-indolylmethane and 3,3'-disubstituted oxindole together and this type of compounds have shown promising bioactivities.[2] Moreover, these building blocks have been extensively employed as key intermediates in the total synthesis of natural products such as hexahydropyrroloindoline alkaloids.[2a, 3] Due to the significance of this structural motif, the synthesis of 3,3'-indolyloxindole derivatives has attracted much attention from synthetic community and an array of methodologies have been developed in recent decades to prepare such skeletons.[1, 4] Among these methods, isatin derived 3-indolylmethanols have distinguished themselves as versatile reactants in nucleophilic substitutions for preparation of 3,3'-indolyloxindoles. However, most of the nucleophilic substitutions are limited to alkylation-related reactions, which incorporates alkyl,[5] alkenyl,[6] and allyl[7] groups to isatin derived 3-indolylmethanols. In sharp contrast, the arylation of 3-indolylmethanols has rarely been investigated and only sporadic examples were reported such as aniline,[8] phenol[9] and indole.[9b, 10]

The aromatic heterocyclic compounds such as furan, pyrrole and thiophene are biologically important moieties in medicinal chemistry and many derivatives of them exhibit remarkable pharmacological activities such as (-)-nupharamine[11], roseophilin[12] and olanzapine[13] (Figure 1). Based on the principle of superposition, new compounds with higher biological activity might be found by merging these pharmaceutically significant aromatic heterocycles into 3-functionalized 3-indolyloxindole skeletons. To the best of our knowledge, the direct arylation of 3-functionalized oxindolyl 3-indolylmethanols with furan, pyrrole and thiophene has never been reported. Therefore, it is highly desirable to develop the arylation reactions of 3-oxindolyl 3-indolylmethanols with these aromatic heterocycles. During our interest in developing efficient methods for functionlization of heterocycles,[14] herein we reported an intriguing arylation or Fridel-Crafts reaction[15] of 3-indolylmethanols with electron-rich furan, thiophene and pyrrole, leading to chemospecific functionalization of electron-rich aromatic rings and synthesis of indolyloxindoles containing quaternary carbon stereocenters in moderate to high yields.

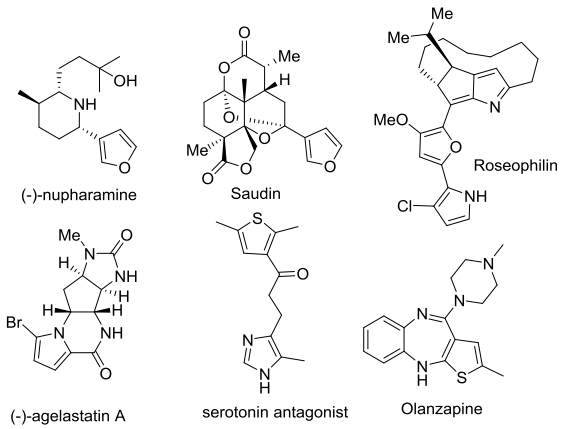
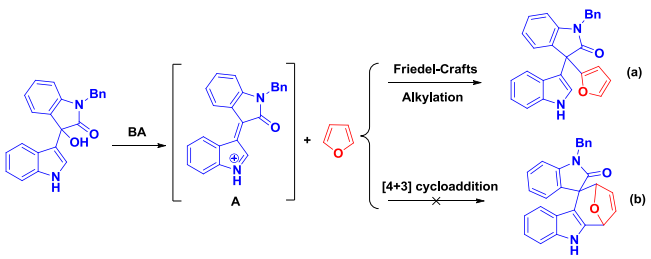


Figure 1. Natural products and pharmaceutical molecules containing indole, furan and thiophene moieties.



Scheme 1. Friedel-Crafts alkylation with furan instead of [4+3] cycloaddition

Furan can serve as a diene to perform [4+3][16] or [4+2][17] cycloaddition or a nucleophile to carry out Fridel-Crafts reaction. The electrophilic vinylogous iminium intermediate[18] derived from 3-functionalized oxindolyl 3-indolylmethanols can undergo [3+3][19] or [3+2][20] to construct 6- or 5-membered rings. Hence, we reasoned that two reaction pathway might operate for furan with vinylogous iminium intermediate **A**, i.e. Friedel-Crafts alkylation (Scheme **1a**) or [4+3] cycloaddition in the presence of Brønsted acid (Scheme **1b**).

Initially, isatin-derived 3-indolylmethanol **1a** and furan **2a** were examined as model substrates to investigate the feasibility of the reaction using DCM as solvent. Only Friedel-Crafts reaction product was found and no [4+3] cycloaddition product was observed. An array of Brønsted acids with different *p*Ka were evaluated and the results revealed that the acidities of the catalysts imposed drastic effect on the yields (Table 1, entries 1-6). The comparatively less acidic benzoic acid (*p*Ka 4.2) and 2,4-dinitrobenzoic acid (*p*Ka 1.42) failed to catalyze the arylation reaction (Table 1, entries 1-2). Gratifyingly, the desired product was furnished in high yield by using comparatively stronger acid, i.e. camphorsulfonic acid (CSA, *p*Ka 1.2) as the catalyst (Table 1, entry 3). Remarkably, further increasing the acidity of catalysts only resulted in inferior yields (Table 1, entries 4-5). When stronger acid like TfOH (*p*Ka -15) was employed, only trace of product was obtained (Table 1, entry 6). Subsequently, a variety of solvents were evaluated in the presence of CSA (10 mol%) and $CHCl_3$ was identified as the optimal catalyst (Table 1, entries 7-11). The structure of **3a** was unambiguously confirmed by single-crystal X-ray diffraction analysis (Figure 2).

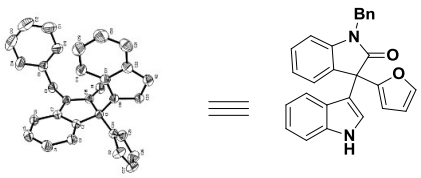
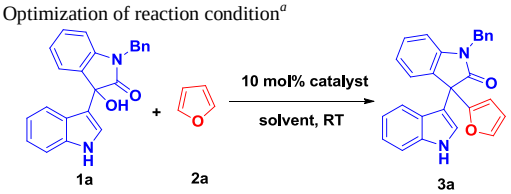


Figure 2 X-ray structure for compound **3a.** Ellipsoids depicted at the 50% probability level (some parts of the molecule have been removed for clarity).

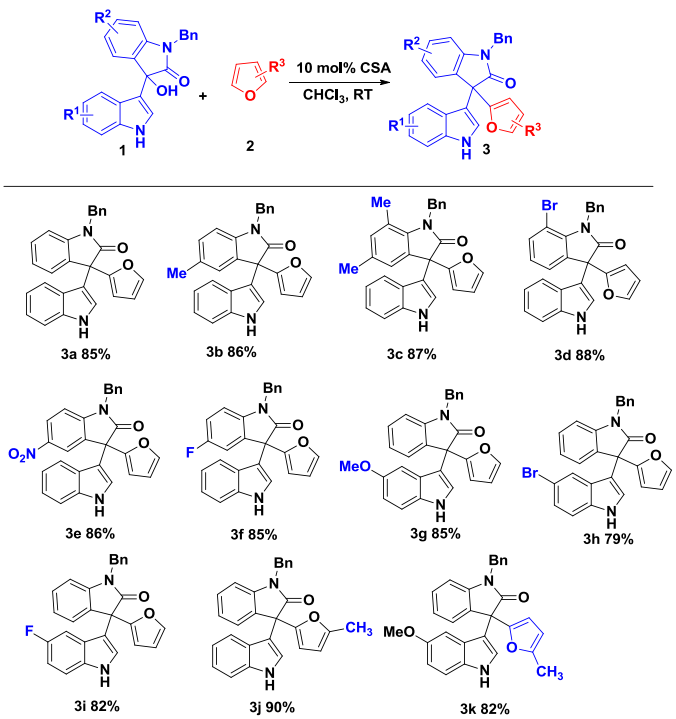
Table 1. Optimization of reaction condition[a]



Entry	Catalyst	*p*Ka	Solvent	Time (h)	Yield[b] (%)
1	benzoic acid	4.20	DCM	24	NR
2	2,4-dinitro-benzoic acid	1.42	DCM	24	NR
3	CSA	1.20	DCM	3	85
4	TFA	0.50	DCM	2	70
5	TsOH	-2.80	DCM	3	32
6	TfOH	-15.0	DCM	3	trace
7	CSA	1.20	DCE	3	50
8	CSA	1.20	Toluene	3	64
9	CSA	1.20	THF	3	60
10	CSA	1.20	$CHCl_3$	3	88
11	CSA	1.20	CH_3CN	3	75

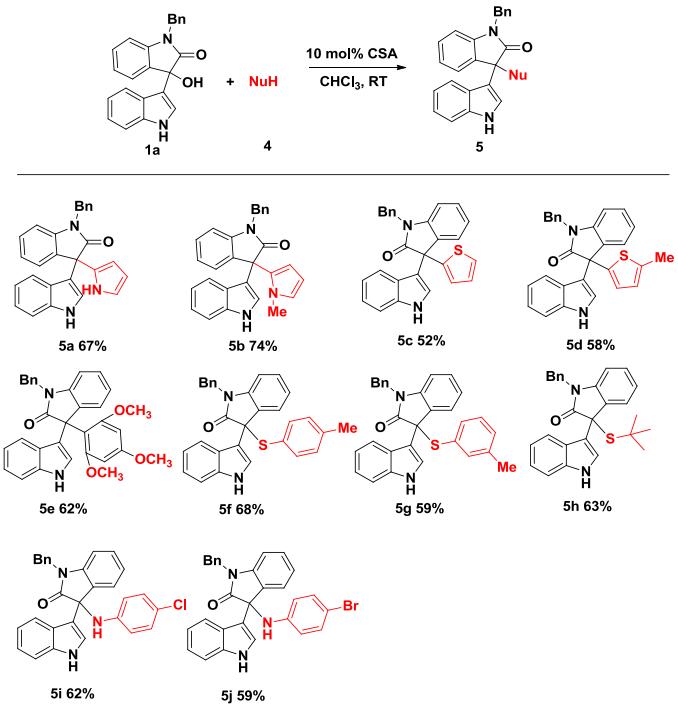
[a] The reaction was carried out with **1a** (0.1 mmol, 1eq), **2a** (0.3 mmol, 3eq) and catalyst (0.01 mmol) in 1.5 mL $CHCl_3$ at room temperature. [b] Isolated yield by column chromatography.

With optimized condition in hand, a variety of electronically and sterically diverse furans and isatin derived 3-indolylmethanols were subjected to this Friedel-Crafts arylation to investigate the substrate scope. All the substrates carrying electron-donating groups and electron-withdrawing groups were well tolerated to furnish the desired Friedel-Crafts products in high yields. Remarkably, the electronic nature of substituents on 3-indolylmethanols had trivial influence and high yields could be always achieved in the presence of either electron-donating or electron-withdrawing groups (Scheme 2, 3a-i). 2-Methylfuran was also investigated as nucleophile and higher yield was achieved (3j-k), which might be ascribed to stronger nucleophility of 2-methylfuran compared with unsubstituted furan.



Scheme 2. Substrate scope of reaction of **1** with other furans.

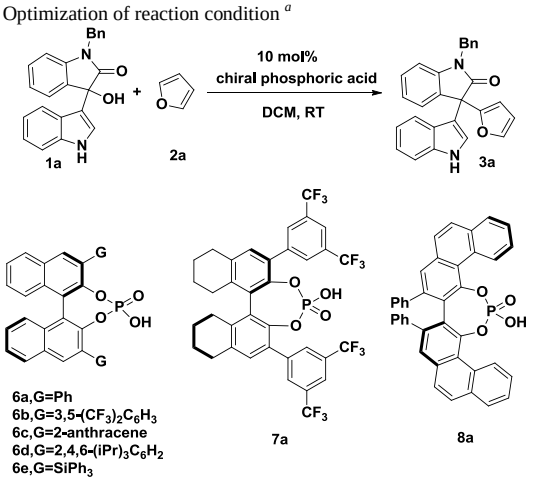
Afterwards, other electron-rich heterocyclic compounds **5**, such as pyrrole and thiophene were subjected to this Friedel-Crafts alkylation as nucleophiles under the optimal condition. The reaction proceeded smoothly to furnish the desired products in moderate yields (Scheme 3, **5a-d**). The yields of thiophenes was comparatively lower compared with that of pyrroles (**5c-d**), which might be attributed to weaker nucleophilicity of thiophenes. Furthermore, bulky trimethoxy-benzene was also examined as nucleophile, affording the desired product in 62% yield (Scheme 3, **5e**). Subsequently, nonaromatic nucleophiles were examined in this nucleophilic substitution. Sulfur is frequently found as constituent of pharmaceuticals and its selective incorporation into indole frameworks is highly significant in medicinal chemistry.[21] Thus thiophenols were tested as nucleophiles for this reaction, aiming to construct the sulphur-containing 3-indolyl derivatives. The coupling products **5f-h** were furnished in good yields. Additionally, substituted aniline were also subjected to this reaction and it was found that nitrogen atom attacked the electrophilic vinylogous iminium intermediate instead of nucleophilic *ortho* position of amino group, giving rise to the desired products in moderate yields (**5i-j**).



Scheme 3. Reaction of **1a** with other arenes and nucleophiles.

Finally, the asymmetric feasibility of the arylation of 3-indolylmethanol **1a** with furan **2a** was investigated. As shown in Table 2, various chiral phosphoric acids (**6a**-**e**, **7a** and **8a**) were employed as catalysts for this reaction, however, the arylation product was furnished in low enantioselectivities (<27% ee) and low yields. This result indicated that the chirality of the product was difficult to control under the current reaction conditions which might be attributed to that the oxygen atom of furan is a poor hydrogen acceptor.

Table 2. Optimization of reaction condition [a]



Entry	Catalyst	Time (d)	Yield[b] (%)	ee[c](%)
1	6a	7	32	0
2	6b	2	62	27
3	6c	3.5	41	-7
4	6d	7	39	21
5	6e	7	31	0
6	7a	3.5	39	23
7	8a	7.5	29	0

[a] The reaction was carried out with 1a (0.05 mmol, 1eq), 2a (0.15 mmol, 3eq) and catalyst (0.005 mmol, 10 mol%) in 1.0 mL DCM at room temperature. [b] Isolated yield by column chromatography. [c] Ee was determined by chiral HPLC.

Conclusions

In conclusion, a mild and efficient camphorsulfonic acid catalyzed Fridel-Crafts alkylation of arenes with indolyl alcohols has been developed to synthesize the heterocyclic substituted 3-indolyl-3,3'-disubstituted oxindole derivatives. This strategy features high yields, mild condition and wide substrate scope. Various aromatic heterocyclic compounds like furan, pyrrole, thiophene and trimethoxybenzene were conveniently incorporated to 3-indolyloxindole skeleton, as well as nonaromatic nucleophiles like sulphur-containing nucleophiles and anilines.

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Notes and references

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Fridel-Crafts Alkylation of Arenes with Indolyl Alcohols for Construction of 3,3-Disubstituted Oxindoles

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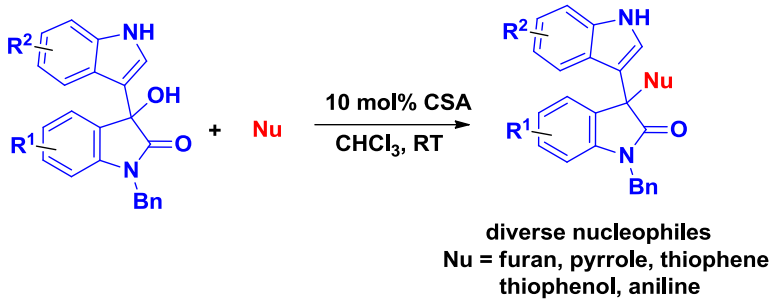

An intriguing camphorsulfonic acid catalyzed Fridel-Crafts alkylation or nucleophilic substitution of 3-indolylmethanols with diverse nucleophiles has been developed featuring mild reaction condition, wide substrate scope and high yields. This reaction provides an efficient method to access biologically important heterocyclic oxindole derivatives.