# Combining Indolizines and Isatins *via* Brønsted-Acid catalyzed Friedel-Crafts Alkylation in Water

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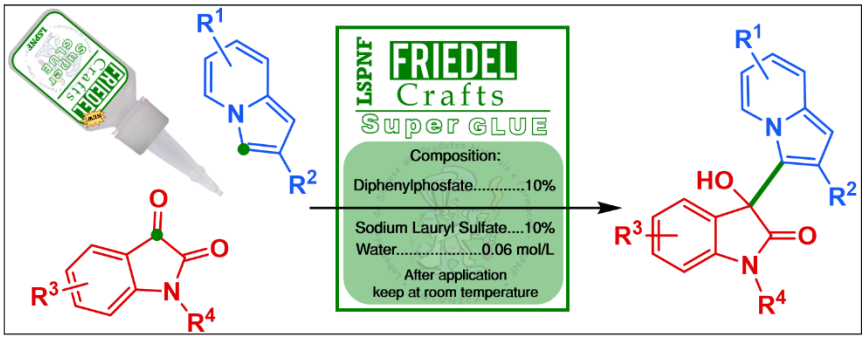



**ABSTRACT:** The controlled mono-addition of indolizines to isatins under very mild conditions is described. The reaction occurs in water using diphenylphosphate (DPP) as catalyst and is dramatically accelerated by adding a surfactant (sodium dodecyl sulfate – SDS). Using this methodology, 19 new 3-hydroxy-3-indolizinyl-2-oxindoles scaffolds were synthesized (up to >99% yield). Notably, in organic solvents only bis-addition products were observed, in poor yields and in prolonged times. The very low solubility of the mono-addition product in water was determinant for the observed selectivity .

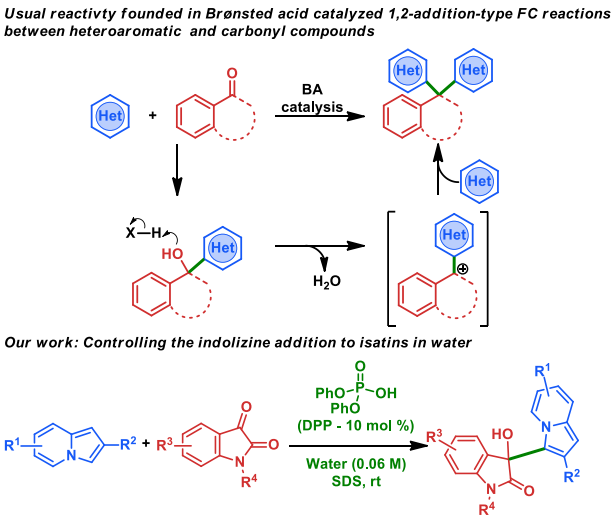
We are surrounded by a myriad of natural and synthetical heterocyclic molecules, widely found in food, materials, cosmetics, agrochemicals, drugs and in living beings.[(1)] One important class of heterocycles is the indolizine which has drawn attention in recent years due its presence in the core of compounds with a wide range of biological activities like antineoplastic,[(2)] antibacterial and antifungal,[(3)] anti-HIV,[(4)] antihistaminic,[(5)] analgesic and anti-inflammatory,[(6)] anticonvulsant[(7)] and central nervous system depressant activities[(7),(8)], and in photophysical applications as biosensors for reactive oxygen species (ROS) and lipid droplets (LD).[(9)]

Many syntheses were accomplished over the years owing the relevance of the indolizine core,[(10)] however its post-functionalization is still an underexplored field. Most of the reports on post-functionalization of indolizines relies on the use of transition-metal catalysis in coupling reactions,[(11)] metalation reactions [(12)] or in Lewis acid catalyzed Friedel-Crafts(FC)-type additions.[(13)] Examples of metal-free methodologies for indolizine functionalization are much more scarce,[(14)] nevertheless, in recent years our group have been successful in the development of these methodologies, reporting the use of indolizines as nucleophilic partners in 1,4-addition-type FC alkylations with α,β-unsaturated olefins.[(15)]

Seeking for other substrates that could act as electrophile on FC reactions with indolizines, we envisioned that isatins could be a proper choice (Scheme 1). Isatins can undergo nucleophilic attacks on C-3 to yield 3-hydroxy-2-oxindoles derivatives, which are known as nucleus of natural products and bioactive molecules.[(16)] Furthermore, there are plenty of methodologies for the 1,2-addition-type FC alkylation between isatins and heteroarenes – such as pyrroles,[(17)] and indoles[(18)] – or electron-rich arenes,[(19)] but to the best of our knowledge, the use of indolizines for this transformation remains unknown.

Inspired by our previous success in FC alkylation between indolizines and enones under Brønsted acid (BA) catalysis,[15] we speculated if diphenyl phosphate (DPP) would be a suitable catalyst for isatin activation. Furthermore, the use of acid catalysis in nucleophilic 1,2 additions to carbonyl compounds to obtain mono alkylated FC adducts is usually avoided due to the tendency of obtained alcohols to form stabilized carbocations that reacts with another nucleophile molecule to afford bis-substituted FC adducts.[20] We describe herein our efforts to developed a FC reaction between indolizines and isatins that exclusively affords mono-addition products even under acid catalysis (Scheme 1).

**Scheme 1. FC alkylation of carbonyl compounds under BA catalysis.**

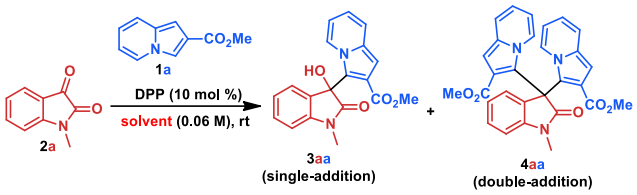



We began our investigations by studding the reaction between methyl 2-indolizinecarboxylate **1a** and the N-methyl-isatin **2a** in set of organic solvents (see Table S1 in the SI). At first, **2a** (1 equiv) was exposed to excess of **1a** (2.3 equiv) in the presence of DPP (10 mol %) and benzene (0.06 M) at room temperature. The reaction took place in 96 hours and only the bis-addition adduct **4aa** was obtained in 40% yield (Table 1, entry 1). Further solvent screening proved to be ineffective for reaction improvement (Table S1), and only **4aa** was obtained in all cases in poor to moderate yields. The best result was achieved using 1,2-DCE as solvent, 61% yield in 96 hours (Table 1, entry 2).

Considering the possibilities of organic solvents being exhausted (Table S1), the last solvent tested was water (Table 1, entries 3 – 11). To our surprise and delight, the completely heterogeneous reaction furnished the mono-addition adduct **3aa** in 95% yield as a single product and in a shorter reaction time - 65 h (entry 3). The reaction stoichiometry and catalytic loading were further investigated. Reducing the catalyst load to 5 mol %, led to a significant decrease in the reaction conversion (entry 4). Likewise, an attempt to set **1a** as the limiting reagent led to 41% conversion (entry 5). Prolonging the reaction time for 7 days, leads to a slightly decrease of **3aa** yield to 88% and **4aa** also could be isolated in 5% yield (entry 6).

Aiming to enhance the solubility of components in water, in order to accelerate the transformation without compromise the selectivity, sodium dodecyl sulfate (SDS) was used as additive (Table 1, entries 7-12).[21] Fortunately, this additive was capable of dramatically reduce the reaction time to 16 h , maintaining a high conversion rate (93%) to **3aa** (Table 1, entry 7). Optimal conditions were then obtained when we reduced the amount of **1a** to 1.2 equivalents in the presence of SDS (10 mol %, 6 mM), affording **3aa** with conversion of 91% in 16 h (entry 8). Noteworthy, in the best conditions (entries 6 and 7) the surfactant concentration is a small value below of the SDS critical micellar concentration (CMC) of ~8.2 mM,[22] a serendipitous finding. Decreasing the amount of **1a** to 1.0 equiv led to a significant lowering of conversion rate (entry 9). Increasing the reaction molarity (Entries 10 and 11), led to observation of a complex mixture of products what could be correlated with the SDS concentration values in these cases, 12 mM and 24 mM, were above the CMC value.[23] Increasing the reaction temperature to 50 °C was detrimental to the process and the product was obtained in a lower conversion accompanied by side products (entry 12).

**Table 1. FC Reaction Optimization**[a]




| Entry | Solvent | **2a/1a** (equiv) | *t* (h) | **3aa** (%) | **4aa** (%) |
|---|---|---|---|---|---|
| 1 | Benzene | 1.0/2.3 | 96 | n.o. | 40[b] |
| 2 | 1,2-DCE | 1.0/2.3 | 96 | n.o. | 61[b] |
| 3 | $H_2O$ | 1.0/2.3 | 65 | 95[b] | n.o. |
| 4[d] | $H_2O$ | 1.0/2.3 | 65 | 73[b] | n.o. |
| 5 | $H_2O$ | 2.0/1.0 | 65 | 41[b] | n.o. |
| 6 | $H_2O$ | 1.0/2.3 | 168 | 88[b] | 5[b] |
| 7[e] | $H_2O$ | 1.0/2.0 | 16 | 93[c] | n.o |
| **8[e]** | **$H_2O$** | **1.0/1.2** | **16** | **91[c](90%)[b]** | **n.o** |
| 9[e] | $H_2O$ | 1.0/1.0 | 13 | 45[c] | n.o |
| 10[e,f] | $H_2O$ | 1.0/1.0 | 13 | Complex mixture | |
| 11[e,g] | $H_2O$ | 1.0/1.0 | 13 | | |
| 12[e,h] | $H_2O$ | 1.0/1.2 | 24 | 57[c] | n.d. |

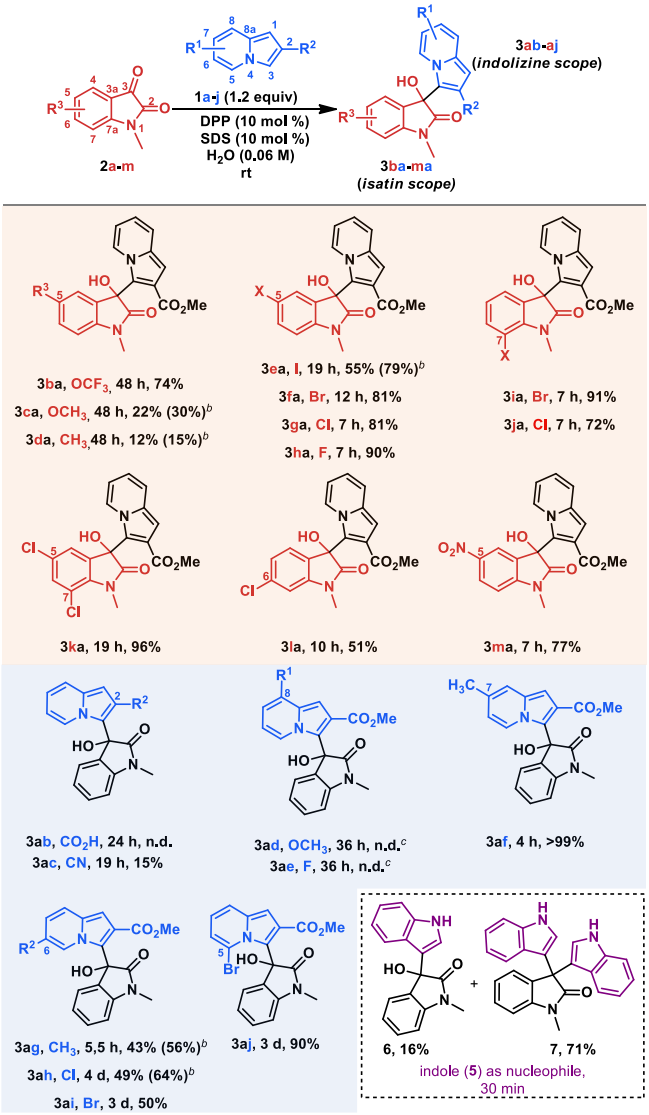
[a]Reactions were carried out at 0.05 mmol scale. n.d.=not determined. n.o.=not observed. [b] Isolated yield (in entry 8 the yield in parenthesis refers to a reaction carried out at 0.25 mmol scale). [c] Conversions direct measured by $^1$H NMR (relaxation time of 20 s). [d]DPP (5 mol%). [e]SDS (10 mol%). [f]$H_2O$ (0.12 M). [g]$H_2O$ (0.24 M). [h]Temperature at 50 °C.

With the optimized conditions in hands, the scope and limitations of the methodology were evaluated. First, structurally diverse isatins **2b–2m** were tested in the presence of **1a** (Scheme 2). Isatins with electron-donor groups in the C-5 position yielded the mono-addition adducts **3ba** (74%), **3ca** (22%) and **3da** (12%) in a much less efficient way comparing to the model **3aa**, suggesting that electron-donor groups strongly disfavor the reaction. C-5 halogenated isatins **2e-2h** showed that the efficiency of the reaction increases with the electronegativity, delivering **3ea** (5-I) in 19 h and 55% yield, whereas **3ha** (5-F) was obtained in 7 h and 90% yield. However, this effect was not observed for C-7 halogenated isatins **2i** (7-Br) and **2j** (7-Cl), which afforded **3ia** in 91% yield and **3ja** in 72% yield (7-Cl) both in 7 hours. The 5-7-dichloro-*N*-methyl-isatin **2k** furnished the FC adducts **3ka** in 96% yield, better yield comparing with the mono-chloride derivatives (**3ga**, **3ja** and **3la**). Nitro-substituted isatin **2m**, whose we expected to give an excellent yield due the activation of the C-3 position by the presence of a strong electro-withdrawing group, afforded **3ma** in moderate 77% yield, what was attributed to byproducts formation, specially the bis-addition adduct (not isolated).

Next, we investigated the reactivity between indolizines **1a-j** and isatin **2a** (Scheme 2). Substitution at the indolizine C-2 position for a nitrile group (**1c**) furnished the adduct **3ac** in poor yield (15%), and the hydrolyzed indolizine ester **1b** did not react under reaction conditions. C-8 substituted indolizines **1d** and **1e** also did not reacted and after 36 h, almost all isatin **2a** was recovered in both cases. Indolizines substituted at C-6 delivered FC adducts in moderated yields, 43% to 50%, with methyl group (**3ag**) and halogens atoms (**3ah** and **3ai**). Despite that, reaction with 7-methyl substituted indolizine **1f** and, unexpectedly, with 5-Br substituted indolizine **1j** presented excellent yields. **3af** was delivered in >99% yield in only 4 h suggesting that this group can favor the nucleophilic attack by enhancement of electron density at C-3 indolizine carbon. **3aj** was formed in 91% yield but required 3 days of reaction, and, although we did not expect that the presence of an electron-withdrawing group in the nucleophile **1j** could be beneficial

for reaction yield, the increase of product steric hindrance due the position of bromine atom in **1aj** could reduce parallel reactions like a second addition or even a retro-FC reaction.

**Scheme 2. Scope of FC reaction between Isatins (2b-n) and indolizines (1b-1k)[a]**



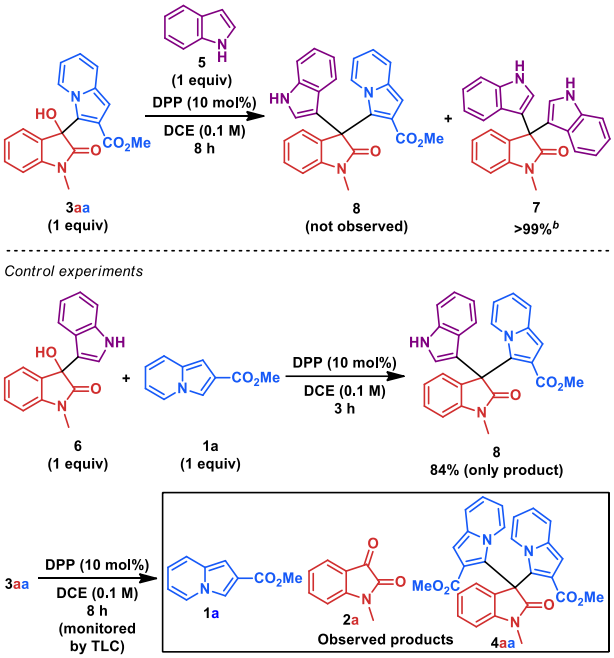

[a]Reactions were carried at 0.25 mmol scale and the yields refers to isolated and purified products. n.d.=not determined. [b]Yields in parenthesis take into account the recovery of **2**. [c]Recovery of >98% of **2a**.

In contrast with the controlled indolizine 1,2-additions, indole (**5**) addition to isatin **2a** under optimized conditions favored majoritary the dialkylation product **7**, obtained in 71% yield together with the mono-FC adduct **6** (16% yield). The reaction was considerably faster (30 min) than those with indolizine analogues (Scheme 1, dashed box). The observed differences in product distribution, served as a hint that reaction selectivity was not only associated with the solvent choice.

Aiming explore the reactivity of the FC adducts in the presence of other nucleophiles, we reacted **3aa** with indole under Brønsted acid catalysis in an organic solvent (DCE) expecting to obtain unsymmetrical 3,3' disubstituted oxindole **8** (Scheme 4).[24] Unexpectedly, after 8 hours, disubstituted indole **7** was obtained in quantitative yield, what suggested two possible scenarios: 1) the indole in **7** induced an indolizine retro-FC reaction, generating an alkylidene intermediate that was attacked by a second indole

molecule ; 2) a Brønsted acid induced a retro-FC reaction of adduct **3aa**, followed by indole bis-addition to isatin. Control experiment using 3-hydroxy-3-indole-2-oxaindole **6** and indolizine **1a** as nucleophile, gave the desired compound **5** in 84% yield in 3 hours, which excluded the first scenario. Next, a stability test in which **3aa** was mixed with DPP (10 mol%) in 1,2-DCE in the absence of a nucleophile revealed its progressive degradation, with concomitant formation of free isatin **2a** and indolizine **1a** alongside with the bis-addition product **4aa** (see Figure S3 in the SI)**.**

**Scheme 3. Attempted of unsymmetrical disubstituted 2-oxindoles synthesis from 3aa and control experiments**[a]

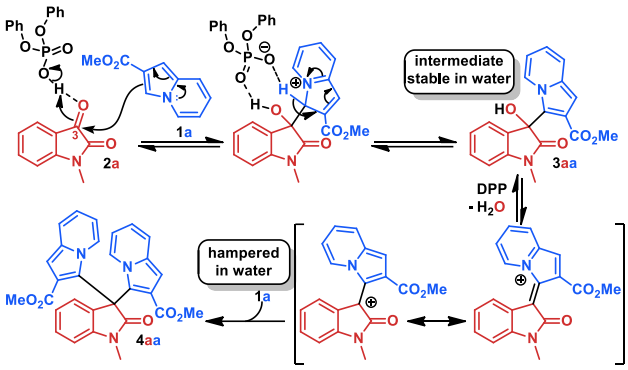



[a]Reactions were carried at 0.1 mmol scale and yields refer to isolated and purified products. [b]Yield considering indole (**4**) as the limiting reagent.

The previous observations suggests that there is a dynamic equilibrium between the first indolizine addition and a retro-FC reaction, and, in organic medium, the indolizine mono-addition adducts tend to suffer a retro-FC more rapidly than the addition of a second nucleophile (Scheme 4). This would explain the low yields and long reaction times observed in reactions between indolizine **1a** and isatin **2a** in organic solvents (Table S1). We postulated that this equilibrium is hampered under aqueous condition due the insolubility of reactants and the mono alkylated products **3** , explaining their stability in water.

The fact that a simple solvent shifting made a complete change in the selectivity of the reaction is very intriguing. It is plausible that the very low solubility of the components in water could lowered the reaction rate disfavoring a second addition of **1a** (Scheme 4), what is in accordance with the previous result (entry 6 of table 1), in which the bis-addition adduct **4aa** was observed in low yield (5%) after extending the reaction time to 168 h (7 days), causing a little erosion in the yield of **3aa**. This hypothesis also explains the fail attempts in increase reaction molarity maintaining the same amount of surfactant (Table 1, entries 10 and 11),[(23)] exhibiting the thin line between a positive surfactant effect on the reaction acceleration and a detrimental one. Although we cannot completely rule out the reversibility of water dissociation, dislocating the equilibrium in favor of the mono-addition product, as a factor for the observed reactivity, carbocation substitutions reactions in water are reported in literature,[(20)] and also observed under our conditions (Scheme 1, **2m** and **6**).

**Scheme 4. Proposed mechanism for the formation of 3aa and 4aa**




In summary, we disclosed a FC alkylation between indolizines and isatins under Brønsted acid catalysis. Noteworthy, this is the first report of an organocatalyzed 1,2 FC addition using the indolizine nucleus. This methodology is very mild, and its selectivity strongly depends on the solvent used. While organic solvents gave exclusively dialkylated adducts in poor yields and long reaction times, employment of water as the solvent allowed the obtention of acid labile mono-substituted FC adducts in improved yields and in shorter reaction times when a surfactant was present. Theoretical studies to have new insights about the reactivity of the FC adducts are currently underway along with efforts for the development of an asymmetric variation.

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### Author Contributions

The manuscript was written through contributions of all authors./ All authors have given approval to the final version of the manuscript.

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### Notes

The authors declare no competing financial interest.

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