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A Sustainable Dual Catalytic Approach to The Synthesis of Azaarene-Substituted 3-Hydroxy-2-Oxindoles by Sp 3 C -H And Metal-Free Sulfono Functionalization

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Abstract

A dual catalytic reaction is a way of organic synthesis in which two catalysts are used to react to a chemical reaction to give rise to new or more efficient reactions. This scheme may be a combination of two independent catalysts, e.g., a photocatalyst and a metal catalyst, or a sequence of catalysts, e.g., a relay or cooperative catalysis system. The current study presents a sustainable synthetic methodology of synthesizing azaarene-substituted 3-hydroxy-2-oxindoles through sp^3 C-H functionalization, as well as a complementary metal-free sulfono functionalization methodology of benzyl and alkyl halides, and methylarenes. It employs the TBAF- $3H_2O$ as an effective organocatalyst in a water system under microwave irradiation to catalyze sp^3 C-H activation of alpha/gamma-alkylazaarenes and alpha-alkylquinolines with high yield. The reaction parameters were optimized to show that at 100 C, 10 mol% TBAF- $3H_2O$ catalyst gave up to 90% of the target 3-hydroxy 2-oxindoles. It was also extended to a range of isatin analogues, which afforded a range of azaarene-substituted oxindoles in good to excellent yields. It is concluded that the study successfully demonstrates two sustainable methodologies for synthesizing functionalized heterocyclic compounds.

Keywords: Catalyst, Dual Catalytic, Azaarene-Substituted, Metal-Free Sulfono etc.

Introduction

Chemists have been motivated to create more sustainable and efficient methods for novel bond-forming processes by the idea of an atom economy. The optimal and most effective way to generate carbon-carbon and carbon-heteroatom bonds, according to this view, is by directly functionalizing C-H bonds in organic molecules. Organic synthesis is advanced by the C-H functionalization logic, which offers a redox economy, atoms, and steps. New study is mostly focused on the activation of the sp^3 C-H bond of α-alkylazaarenes by Lewis acids. The fact that α-alkylpyridines' benzylic C-H bonds may create nucleophilic carbon-carbon bonds when they react with electrophiles is well recognized.

Having said that, all the reports about substrates have focused on polar electrophiles that are very reactive. There have been few reports of its synthetic value, and even fewer investigations into functionalizing the sp3 C-H bond in α-alkylquinolines. Using isatin as a starting point, scientists have created practical catalytic methods that open the door to intriguing molecular structures with diverse biological functions. The fundamental structure of 3-substituted-3-hydroxy-2-oxindoles is found in many possible pharmacological candidates for the treatment of proliferative disorders, which has led to a significant surge in interest in these compounds. To create azaarene-substituted 3-hydroxy-2-oxindoles, the simplest and most direct way is to directly add benzylic C-H bonds of α-alkylazaarenes to isatins.

The use of oxindoles has garnered tremendous interest because the synthesis of heterocyclic scaffolds is of key biological and pharmaceutical interest, and in many cases,

3-hydroxy-2-oxindoles have broad-based pharmacological activity. However, their conventional ways of being synthesized have severe reaction conditions, transition-metal catalysts, and reagents that are not environmentally friendly, which restrict their sustainability and scalability. The current paper aims at creating a green and atom-economical methodology of azaarene-substituted 3-hydroxy-2-oxindoles synthesis by means of sp^3 C-H functionalization in aqueous media, with tetrabutylammonium fluoride trihydrate (TBAF-$3H_2O$) serving as the catalyst.

It is an effective and environmentally friendly alternative to the traditional metal-catalyzed transformations. The conditions under which the microwave aids are characterized by a considerably short reaction time, enhanced selectivity, and yield. The approach is useful in activating 2-oxindoles with azaarene substitution at higher yields, and it activates 2-oxindoles without azaarene substitution in high yields by using 2-alpha/ 2- gamma-alkylpyridines and 2- alpha/ 2- gamma-alkylquinolines in water. Alternative, complementary metal-free combination of sulfono functionalization is introduced in the study as involving iodine, TBHP and DBU in CH 3CN at 29oC in benzyl halides, alkyl halides and methylarenes. Both of the reaction systems rely on low-cost, low-cost and environmental-friendly solvents, low-cost reagents and mild conditions. The two catalytic systems TBAF-C H functionalization and iodine-based sulfono coupling is also a sustainable development in organic synthesis, and therefore demonstrates the possibility of building up complex heterocyclic structures under the concept of green chemistry.

Literature Review

Quinolines and their derivatives have long been seen as interesting candidates for novel catalyst design, material applications, and medication development. Over the last ten years, one of the most straightforward synthetic pathways for creating novel chemical libraries of quinolines has been the C(sp^3)-H functionalization of 2-methyl azaarenes, especially 2-methyl quinolines. We highlight the synthetic efforts on C(sp^3)-H functionalization of 2-methyl quinolines in this minireview, Sneha Latha (2020) [30].

For the purpose of synthesizing diaryl-pyridinium-azaarene-butenolate zwitterionic derivatives, it has been reported that a metal-free, iodine-mediated C(sp^3)-H bond activation of alkyl-azaarenes when they are added to α,β-unsaturated carbonyls is an effective and efficient approach. Atul Kumar, *et al*. (2013) [2].

A variety of physiologically active natural items and medications include 3-substituted-3-hydroxy-2-oxindoles, hence it is crucial to find effective techniques for building this essential motif. 2- or 4-methyl azaarenes were added to isatins by C-H functionalization, which was catalyzed by Yb(OTf)3. For different isatins and azaarenes, moderate to excellent yields were found. A quick methodology for the one-step synthesis of physiologically significant azaarene-substituted 3-hydroxy-2-oxindoles is provided by this technique. Lewis acid's synthetic value in the catalytic functionalization of sp3 C-H bonds in organic synthesis is increased by the success of this reaction. Rui Niu, *et al*. (2012) [1].

Experimental Set Up

General experimental procedure

The following ingredients were added to a sealed, pressurized 10-milliliter vial: α/}-A magnetic stir bar coated with teflon, isatin (2, 2 mmol), water (2 mL), TBAF·3H2O (10 mol%, 0.2 mmol, 62 mg), and alkyl azaarene (1, 2 mmol) are all required. At room temperature, the vial was stirred for one minute before being sealed with a snap-on lid and placed into the MW cavity. The reaction was maintained under these circumstances for 5 minutes using 80 W of microwave irradiation keeping the temperature at 100 °C throughout. Once the reaction was complete, the mixture was cooled to room temperature using a thermogravimetric technique. It was then transferred to a container containing distilled water and extracted using ethyl acetate (2 × 10 mL). We used a rotary vacuum evaporator to concentrate the organic phase after filtering it and drying it over anhydrous Na_2SO_4. Preparative TLC was used to purify the resultant crude product.

Synthesis of Sulfonyl hydrazides

Sulfonyl chloride (1.05 mol) and THF (340 mL) were put features a dropping funnel, magnetic stirrer, thermometer, and a round-bottomed flask with three necks. Using an acetone ice bath to cool the agitated mixture to 10 °C, a solution of hydrazine in water (135 mL of 85% $N_2H4{\cdot}H_2O$, 2.22 mol) is gradually added while maintaining a temperature between 10-15 °C. The reaction mixture was transferred to a separatory funnel after 30 minutes of continuous stirring after the completion of the addition. To wash the top THF solution, 2-60 mL sections of saturated aq. NaCl were added after drawing off the bottom layer. Prior to suction filtration, the THF layer was allowed to dry on 20 g of anhydrous magnesium sulfate. Dry THF (40 mL) was used to wash the filtered cake and remove any adsorbed hydrazide. Approximately 500 mL of the transparent mixed filtrate was transferred to a flask and, while being rapidly agitated, diluted with the same amount of petroleum ether. As white platelets, sulfonyl hydrazide was isolated. After letting the hydrazide chill in the fridge for the night, it went via a Buchner filter. The sulfonyl hydrazide was made by repeatedly washing the filtered cake with petroleum ether, sucked dry, and then allowed to air dry.

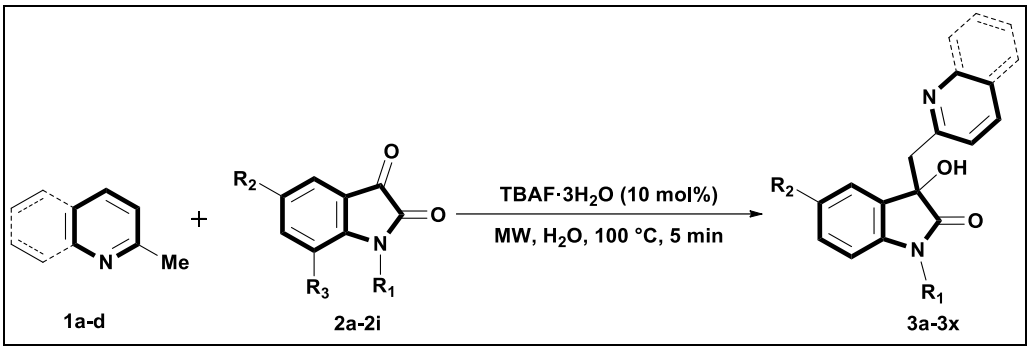
Sulfono functionalization: General procedure

Within a 10-milliliter borosilicate vial, a combination of benzyl halide (1, 2 mmol)/methyl arene (2, 4 mmol), sulfonyl hydrazide (3, 2.4 mmol), I2 (40 mol%), DBU (2.5 mmol), TBHP (4 mmol), and CH3CN was mixed and agitated for a predetermined amount of time under an open environment at room temperature. After the reaction was finished after the reaction mixture has been separated using thin-layer chromatography worked up in stages using aqueous solutions of sodium thiosulfate pentahydrate and sodium bicarbonate, in that order. Using anhydrous Na2SO4, filtering, reduced-pressure drying, and silica gel column chromatography with n-hexane and ethyl acetate as eluents, the organic phase was then purified.

Representative products were characterized as detailed in the chapter (e.g., 1-(benzylsulfonyl)-4-methylbenzene (4a), 1-(benzylsulfonyl)-4-methoxybenzene (4b), etc.), with yields and $^1H/^{13}C$ NMR and IR data exactly as reported.

Results and Discussion

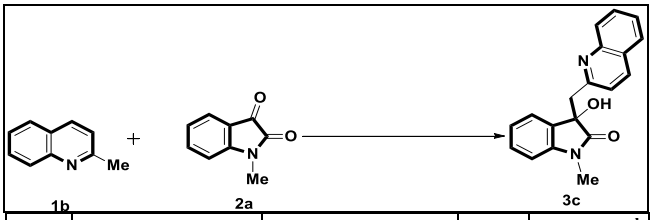
We present here the results of the TBAF-catalyzed sp3 C-H functionalization of α/γ-alkylpyridines and α-alkylquinolines in water under regulated MW (Scheme 1), taking into consideration the details mentioned above and continuing our research interest. As far as we are aware, the results pertain to the first use of α-alkylquinolines functionalized via sp3 C-H bonds in order to build 3-hydroxy-2-oxindoles that are substituted with quinoline.



Scheme 1: Making α-and γ-alkyl azaarenes functional.

Table 1 shows that under various circumstances, the reaction conditions were optimized using α-methylquinoline (1b) and N-methylisatin (2a) as model substrates with TBAF·3H$_2$O as a catalyst.

Table 1: Analysis of the model reaction's reaction conditions[a].



Entry	Catalyst mol (%)	Solvent	T (°C)	Yield (%)[b]
1.	TBAF·3H$_2$O (5)	H$_2$O	80	55
2.	TBAF·3H$_2$O (10)	H$_2$O	80	78
3.	TBAF·3H$_2$O (10)	H$_2$O	100	90
4.	TBAF·3H$_2$O (15)	H$_2$O	100	89
5.	TBAF·3H$_2$O (10)	H$_2$O	120	85
6.	TBAF·3H$_2$O (10)	–	100	80
7.	TBAF·3H$_2$O (10)	EtOH	100	47
8.	TBAF·3H$_2$O (10)	1,2-dichloroethane	100	39
9.	TBAF·3H$_2$O (10)	1,4-dioxane	100	60
10.	TBAF·3H$_2$O (10)	THF	100	80
11.	TBAF·3H$_2$O (10)	DMSO	100	29
12.	TBAF·3H$_2$O (10)	Toluene	100	20
13.	TBAB (10)	H$_2$O	100	69
14.	TBAI (10)	H$_2$O	100	70
15.	KF (20)	H$_2$O	100	85
16.	[Bmim]BF$_4$ (10)	H$_2$O	100	30
17.	–	H$_2$O	100	20[c]

Two molecules of 1b and two molecules of 2a were subjected to a 5-minute, 80 W (MW) reaction.

[b] Total yield in isolation.

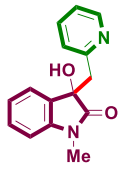
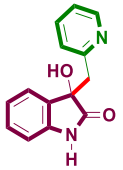
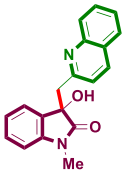
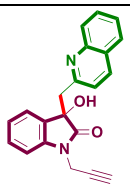
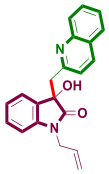
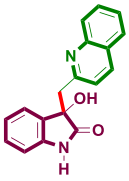
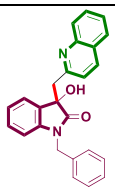
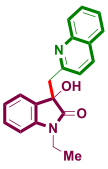
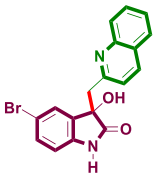
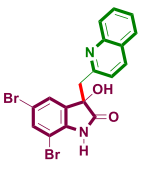
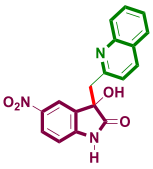
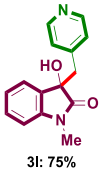
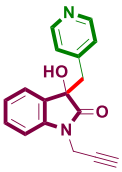
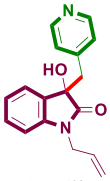
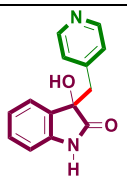
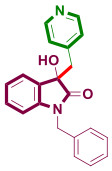
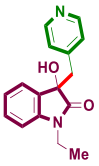
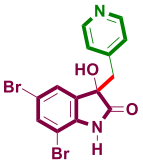
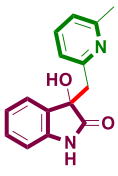
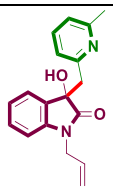
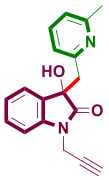
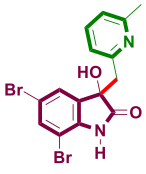
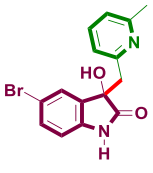
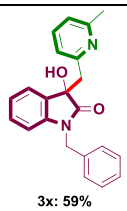
[c] A twenty-minute reaction was performed.

The process of screening began with 5 mol% of TBAF·3H2O in clean water for 5 minutes under 80 W MW electricity and 80 °C. The procedure successfully produced Indoline-2-one (3c)-3-hydroxy-1-methyl-3-(quinolin-2-ylmethyl) in a yield of 55% (entry 1). Under identical circumstances (entry 2), a 78% yield was achieved by increasing the catalyst concentration to 10 mol%. The ideal yield of 90% was achieved by increasing the reaction temperature to 100 °C, which significantly advanced the yield (entry 3). Entries 4 and 5 show that increasing the catalyst concentration and temperature further did not accelerate the yield. There was no improvement in the reaction yield when other solvents such as toluene, 1,2-dichloroethane, 1,4-dioxane, THF, DMSO, and others were tested (entries 7–12). Decomposition of the product likely caused a drop in reaction yield when the reaction was carried out without solvents (entry 6).

Checking the activity of tetrabutylammonium salts with other counter ions, such as bromide and iodide, was done to determine the involvement of the fluoride ion, which resulted in decreased product yields (entry 13 and 14). Under the same reaction conditions, 85% product yield was achieved when potassium fluoride (20 mol%) was used as a catalyst (entry 15). In comparison, the neutral ionic liquid [Bmim]BF4 had a much lower success rate in product delivery (entry 16). However, after 20 minutes (entry 17), the product was supplied in a 20% yield in a control experiment that did not include TBAF·3H2O.

The optimization procedure's scope was then examined for the reactions of several α/γ-alkylazaarenes with isatins. The following α/γ-alkylazaarenes were activated and made to react smoothly with various isatins: N-methylisatin (2a), isatin (2b), N-propargylisatin (2c), N-allylisatin (2d), N-benzylisatin (2e), N-ethylisatin (2f), 5-bromoisatin (2g), 5,7-dibromoisatin (2h), and 5-nitroisatin (2i). The result was a diverse range of products 3a-3x with good to excellent yields, as shown in Table 2. With high product selectivity, all reactions proceeded without a hitch. The intended products were successfully delivered by isatins with various replacement patterns. Compared to unsubstituted isatins, those with N substituents had a higher yield. Isatins that had their aromatic rings halogenated also played an important role in the process. using effectively activating the sp3 C-H bond of α-methylquinoline, the expected product Using the existing catalytic system, 3-hydroxy-3-(quinolin-2-ylmethyl) indolin-2-ones are generated. The 3-hydroxy-3-(quinolin-2-ylmethyl) indolin-2-one that we sell is distinct from the bis(quinolin-2-ylmethyl) indolin-2-one that is described in the literature (31). In these reactions, we did not find any byproducts.

Table 2: Platform potential for the synthesis of 3-hydroxy-2-oxindoles replaced with azaarene 3.[a]

 3a: 55%	 3b: 50%	 3c: 90%	 3d: 84%	 3e: 87%	 3f: 85%
 3g: 84%	 3h: 80%	 3i: 88%	 3j: 85%	 3k: 82%	 3l: 75%
 3m: 65%	 3n: 74%	 3o: 70%	 3p: 69%	 3q: 73%	 3r: 82%
 3s: 75%	 3t: 67%	 3u: 45%	 3v: 73%	 3w: 73%	 3x: 59%

[a]The given reaction conditions are as follows: α/γ-alkylazaarene (1, 2 mmol), isatin (2, 2 mmol), TBAF·3H2O (10 mol%), MW, 80 W, 100 °C, 5 minutes.; [b]Separate output.

Curiously, when dealing with α, α'-lutidine, the functionalization was carried out by a single α-methyl group, and the same product was isolated alone. A model reaction was conducted using α-methylquinoline (1b) and N-methylisatin (2a) under conventional heating conditions instead of microwave irradiation, using the same set of optimized reaction parameters, to confirm the high catalytic activity of TBAF·3H2O and to determine the source of high reaction rates. We were elated when the reaction proceeded without a hitch, yielding 3c with an 83% yield in only 3 hours. The effectiveness of TBAF·3H2O as a catalyst in this approach is evident from this. While we were unable to totally exclude MW irradiation, its effects and activation might serve as a boost to the reaction rate.

Single crystal X-ray analysis of Indol-2-one, which is 1-allyl-3-hydroxy-3-(pyridin-4-ylmethyl) (3n)provided irrefutable structural confirmation (Figure. 1).

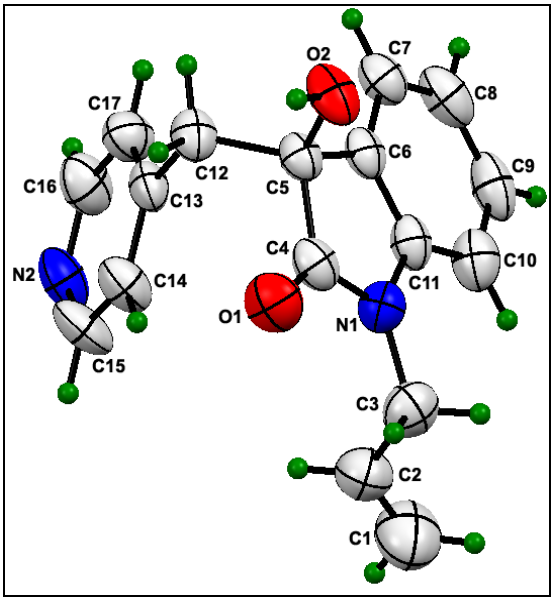


Fig 1: Product "3n" ORTEP diagram displaying atomic numbering method with ellipsoid of 50% probability

Figure 2 shows a possible mechanism that has been proposed based on the products isolated and the current literature. The naked fluoride ion has a strong ability to form hydrogen bonds, and the +N(n-Bu)4 ion acts like a proton to activate the >C=O functionality of isatin, which allows for subsequent nucleophilic attack. The fluoride catalyzed reactions provide a good description of the hydrogen-bonded type intermediates that are suggested in the reaction mechanism. The selective deprotonation of the C-H proton of 2-methyl pyridine in the presence of more acidic protons of isatin and water may be driven by the stability of the transition states afforded by the stronger hydrogen bound network.

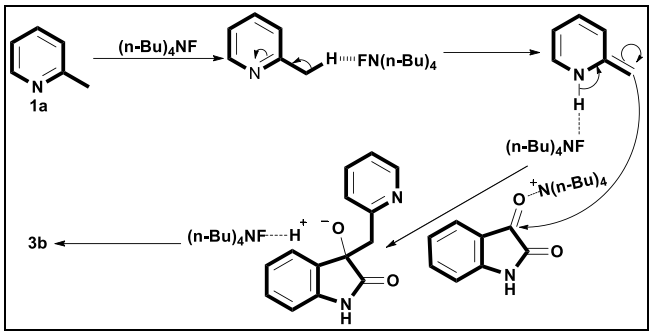


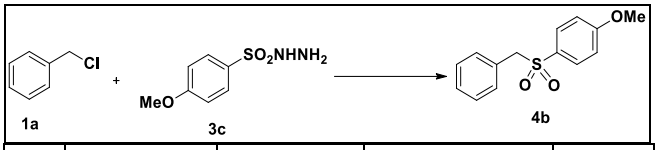
Fig 2: Possible process

Table 3 shows the first steps of our inquiry into a room temperature sulfono functionalization method, which included a reaction between benzyl chloride (1a) and p-methoxyphenyl sulfonyl hydrazide (3c) in an air environment with 20 mol% I2 as the catalyst and CH_3CN as the solvent. The formation of the target product 4b in a 10% yield (entry 1) was a pleasing development.

A considerable improvement in yield was found when the mol% of I2 was increased to 40 (entry 2), but additional increases in the concentration of I2 did not improve the yield again (entry 3), although there was a noteworthy production of disulfide and unreacted benzyl chloride. And therefore, we reasoned, a radical initiator in conjunction with a base may be useful for increasing yield. As predicted, a remarkable improvement in yield was seen with the addition of 1.5 equiv of TBHP (70% solution), and a fairly enhanced yield of the product could be achieved with 4.0 equiv of TBHP (entries 4-6).

After that, we looked at how various bases affected the reaction profile and settled on 2.5 equiv of DBU (entry 8) as the optimal option. Then, in order to speed up the process, other solvents were tested; ultimately, CH_3CN proved to be the most effective solvent for this change. It was only after optimizing the reaction conditions [40 mol% I_2, 2.5 equiv DBU, and 4.0 equiv TBHP in CH_3CN] (entry 10) that the method's generalizability was investigated, as the employment of I_2, TBHP, and DBU are essential to this reaction.

Table 3: Analyzing the parameters of the model's response from 1a to 3c.[a]

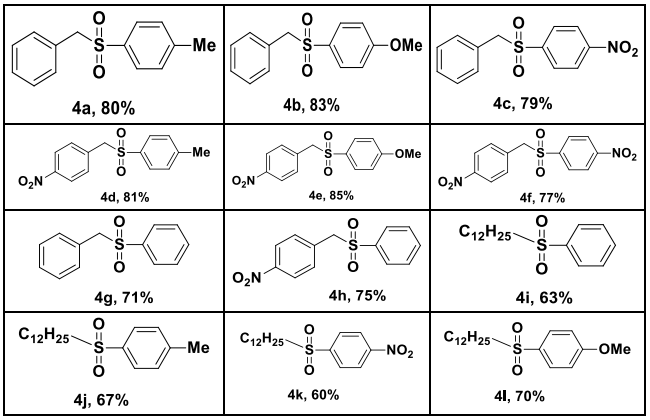


Entry	Catalyst (mol%)	Base (mol%)	Radical initiator (mol%)	Yield (%) [b]
1.	I_2 (20)	–	–	10
2.	I_2 (40)	–	–	25
3.	I_2 (60)	–	–	25
4.	I_2 (40)	–	TBHP (200)	50
5.	I_2 (40)	–	TBHP (400)	65
6.	I_2 (40)	–	TBHP (600)	65
7.	I_2 (40)	DBU (150)	TBHP (400)	74
8.	I_2 (40)	DBU (200)	TBHP (400)	78
9.	I_2 (40)	DBU (250)	TBHP (400)	83
10.	I_2 (40)	DBU (300)	TBHP (400)	83
11.	I_2 (40)	DBU (250)	–	40
12.	–	DBU (250)	TBHP (400)	35
13.	I_2 (40)	DBU (250)	AIBN (400)	0
14.	I_2 (40)	^{t}BuOK (300)	TBHP (400)	0

[a] For 30 minutes in an open environment at room temperature in CH3CN, using 1a (2 mmol) and 3c (2.4 mmol).
[b] Product yield after column chromatography was isolated.

The required products were produced in high to outstanding yields by subjecting several sets of benzyl halides and sulfonyl hydrazides with different substitution patterns to a smooth sulfono functionalization (Table 4). In order to get high product yields, the reaction was effectively carried out by the benzyl halides and sulfonyl hydrazides that included electron-donating groups. Dodecyl bromide, like other common long-chain aliphatic alkyl halides, likewise proceeded through the process without a hitch.

Table 4: Potential substrates for the sulfonyl hydrazide-benzyl/alkyl halide reaction. [a, b]



[a]After 30 minutes at room temperature (RT), 1 (2 mmol), 3 (2.4 mmol), I_2 (40 mol%), DBU (2.5 equiv), and TBHP (4.0 equiv) were added to CH3CN.
[b]Result from column chromatography in isolation.

Conclusion

In Conclusion, the paper manages to showcase two viable green approaches to the preparation of functionalized heterocyclic products. The former is the catalytic sp 3 C H functionalization of 3H 2 O aqueous medium isostatins with 3H 2 O of alkylazaarenes and 3H 2 O of alkylquinolines under microwave irradiation in the presence of the TBAF. The second approach outlines a metal-free sulfono functionalization of benzyl and alkyl halides and methylarenes catalyzed by iodine in the presence of sulfonyl hydrazides in the mild conditions with environmentally benign conditions. The two reactions are highly efficient with high atom economy, short reaction time and high substrate tolerability.

All these methodologies can help to develop green organic synthesis, where the toxic metals and harsh reagents are substituted with the less toxic ones, and the reactivity and the yield of products remain high. The findings support the use of fluoride and iodine catalysis as feasible and environmentally-friendly methods in synthetic organic chemistry and pave the way to the creation of sustainable methods of heterocyclic compounds synthesis.

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