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ARTICLE

A simple and sustainable tetrabutylammonium fluoride–catalyzed synthesis of azaarene–substituted 3–hydroxy–2–oxindoles through sp^3 C–H functionalization

Cite this: DOI: 10.1039/x0xx00000x

Received 00th January 2012,
Accepted 00th January 2012

DOI: 10.1039/x0xx00000x

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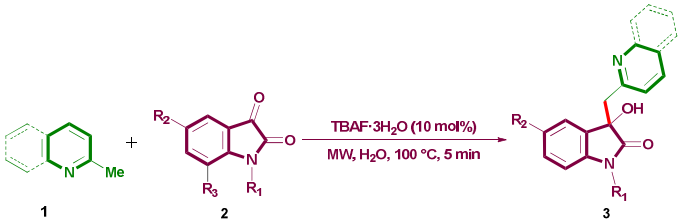
A green, practical, and metal–free protocol for direct addition of α–and γ–alkylazaarenes to isatins has been developed via sp^3 C–H functionalization in water under controlled microwave. This methodology provides a mild and fast access to biologically important azaarene–substituted 3–hydroxy–2–oxindoles in good to excellent yields.

Introduction

The concept of atom economy has driven chemists to develop more efficient and sustainable methodologies for new bond forming reactions. In this perspective, the direct functionalization of C–H bonds in organic compounds has emerged as a powerful and ideal method for the construction of carbon–carbon and carbon–heteroatom bonds.[1] The C–H functionalization logic provides step, atom, and redox economy to advance the organic synthesis.[2] The Lewis acid catalyzed activation of the sp^3 C–H bond of α–alkylazaarenes has become a focal point of the current research.[3] It is well-established that the benzylic C–H bonds of α–alkylpyridines react with electrophiles to form carbon–carbon bonds in nucleophilic fashion.[4] However, the substrate scope reported so far is limited to highly reactive polar electrophiles.[5] Despite its synthetic utility, only sporadic examples are reported and the functionalization of the sp^3 C–H bond in α–alkylquinolines remains less investigated.[6] Isatin as a core structure has inspired the development of useful catalytic strategies to give access to interesting molecular architectures with wide biological activities.[7] Interest in 3-substituted-3-hydroxy-2-oxindoles has increased rapidly as this core structure is present in a number of potential drug candidates for the treatment of proliferative diseases.[8] The direct addition of benzylic C–H bonds of α-alkylazaarenes to isatins for the synthesis of azaarene-substituted 3-hydroxy-2-oxindoles represents the most simple and straightforward method to construct such motifs.[9]

Water is the nature's most amazing gift.[10] The use of water as a solvent in organic synthesis is environmentally benign and safe.[11] Organocatalysis has emerged and applied rapidly because of its unique advantages.[12] The exploitation of organocatalysts that are compatible in aqueous media will provide attractive practical applications.[13] However, the use of water as a solvent is still challenging because of the highly insoluble nature of organic molecules in water and the possible reaction of their functional groups with water. Additionally water may weaken the catalytic activity and stereocontrol through interference of the hydrogen bonds and other polar interactions involving catalysts and substrates. Microwave (MW)-assisted synthesis has enriched the rapidly evolving landscape of C–H bond functionalization,[14] and results in dramatic rate accelerations, enhanced yields, and cleaner reactions. Therefore, from the point of sustainability and green chemistry, the development of new organocatalytic approaches for reactions in water using controlled MW is highly welcome.

Quaternary ammonium salts are readily available phase transfer catalysts.[15,16] Among them, tetraalkylammonium fluorides have been used as a source of naked fluoride ion.[17] The nucleophilic affinity of fluoride ion enables the generation of nucleophiles through a deprotonation process.[18] Tetrabutylammonium fluoride (TBAF) has been recently explored as a readily available, efficient and water compatible organocatalyst and additive for various organic transformations.[19]



Scheme 1. Functionalization of α–and γ–alkyl azaarenes

In light of the above specifics and as a part of our ongoing research interest,[20] we report herein the TBAF–catalyzed sp^3 C–H functionalization of α/γ–alkylpyridines and α–alkylquinolines in water under controlled MW (**Scheme 1**). To the best of our knowledge, the findings involve the first time sp^3 C–H bond functionalization of α–alkylquinolines for the construction of quinoline–substituted 3–hydroxy–2-oxindoles.

Results and discussion

The optimization of the reaction conditions was carried out by using α-methylquinoline (**1b**) and N-methylisatin (**2a**) as model substrates in the presence of TBAF·$3H_2O$ as a catalyst under various conditions (Table 1). The screening was initiated using 5 mol% of TBAF·$3H_2O$ as a catalyst in pure water at 80 °C, 80 W for 5 min. Gratifyingly, the reaction proceeded to afford selectively the target 3-hydroxy-1-methyl-3-(quinolin-2-ylmethyl)indolin-2-one (**3c**) in 55% isolated yield (entry 1). Increase of the catalyst concentration to 10 mol% delivered the product in 78% yield under the same conditions (entry 2).

Table 1 Evaluation of conditions for the model reaction[a]

Entry	Catalyst (mol %)	Solvent	T (°C)	Yield[b] (%)[b]
1.	TBAF·$3H_2O$ (5)	H_2O	80	55
2.	TBAF·$3H_2O$ (10)	H_2O	80	78
3.	TBAF·$3H_2O$ (10)	H_2O	100	90
4.	TBAF·$3H_2O$ (15)	H_2O	100	89
5.	TBAF·$3H_2O$ (10)	H_2O	120	85
6.	TBAF·$3H_2O$ (10)	–	100	80
7.	TBAF·$3H_2O$ (10)	EtOH	100	47
8.	TBAF·$3H_2O$ (10)	1,2-dichloroethane	100	39
9.	TBAF·$3H_2O$ (10)	1,4-dioxane	100	60
10.	TBAF·$3H_2O$ (10)	THF	100	80
11.	TBAF·$3H_2O$ (10)	DMSO	100	29
12.	TBAF·$3H_2O$ (10)	Toluene	100	20
13.	TBAB (10)	H_2O	100	69
14.	TBAI (10)	H_2O	100	70
15.	KF (20)	H_2O	100	85
16.	[Bmim]BF_4 (10)	H_2O	100	30
17.	–	H_2O	100	20[c]

[a]Reaction conditions: **1b** (2 mmol), **2a** (2 mmol), 80 W (MW), 5 min; [b]Isolated yield; [c]Reaction conducted for 20 min.

In order to further advance the yield, reaction temperature was raised to 100 °C, which provided the optimum yield (90%, entry 3). Further increase in the catalyst concentration, and temperature did not enhance the yield again (entries 4, 5). Various organic solvents like EtOH, 1,2-dichloroethane, 1,4-dioxane, THF, DMSO, and toluene were also probed for their effect on the reaction yield but did not help (entries 7–12). When the reaction was conducted under solvent-free conditions, a decrease in the product yield was noticed probably due to decomposition of the product (entry 6). To ascertain the role of fluoride ion, tetrabutylammonium salts with different counter ions such as bromide and iodide were also checked, but ended with much lower yields (entries 13–14). When potassium fluoride (20 mol%) was applied as a catalyst under the same set of reaction conditions, it gave rise to 85% product yield (entry 15). The use of neutral ionic liquid [Bmim]BF_4 proved rather less effective to deliver the product (entry 16). A control experiment without using TBAF·$3H_2O$, however, delivered the product in 20% yield after 20 min (entry 17).

The scope of the optimized procedure was subsequently studied for the reactions of various α/γ–alkylazaarenes with isatins. A number of α/γ–alkylazaarenes viz. α-methylpyridine (**1a**), α-methylquinoline (**1b**), γ-methylpyridine (**1c**), and α,α'–lutidine (**1d**) were successfully activated and made to react with different isatins such as *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**) to provide a diverse range of products **3a–3x** in good to excellent yields (**Table 2**). All the reactions underwent easily with specific product selectivity. Isatins with different substitution patterns participated well in the reaction to deliver the corresponding products. An increase in the yield was noticed for *N*-substituted isatins in comparison to unsubstituted one. Isatins containing halogen in the aromatic ring also participated well in the reaction. The present catalytic system was also found to be effective in activating the sp^3 C–H bond of α–methylquinoline, affording 3-hydroxy-3-(quinolin-2-ylmethyl)indolin-2-ones (**3c-3k**), although the formation of rather bis(quinolin-2-ylmethyl)indolin-2-one is described in the literature.[9a] No side products were observed under the present conditions. Interestingly in the case of α,α'-lutidine, only one α–methyl group participated in the functionalization and the corresponding products were isolated exclusively. To confirm the effectiveness of catalytic activity of TBAF·$3H_2O$ and to find out the origin of high reaction rates, a model reaction was carried out by using α-methylquinoline (**1b**) and N-methylisatin (**2a**) under conventional heating conditions instead of microwave irradiation using the same set of optimized reaction conditions (10 mol% TBAF·$3H_2O$, 100 °C, H_2O). To our delight, the reaction went smoothly to deliver the product **3c** in 83% yield within 3 h, which clearly demonstrates the efficient catalytic role of TBAF·$3H_2O$ in this methodology. However, we may not completely rule out the effect of MW irradiation to help further accelerate the reaction. The product structure of a representative product 1-allyl-3-hydroxy-3-(pyridin-4-ylmethyl)-indolin-2-one (**3n**) was conclusively confirmed by its single crystal X-ray determination (**Fig. 1**).

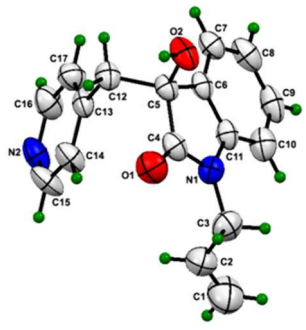
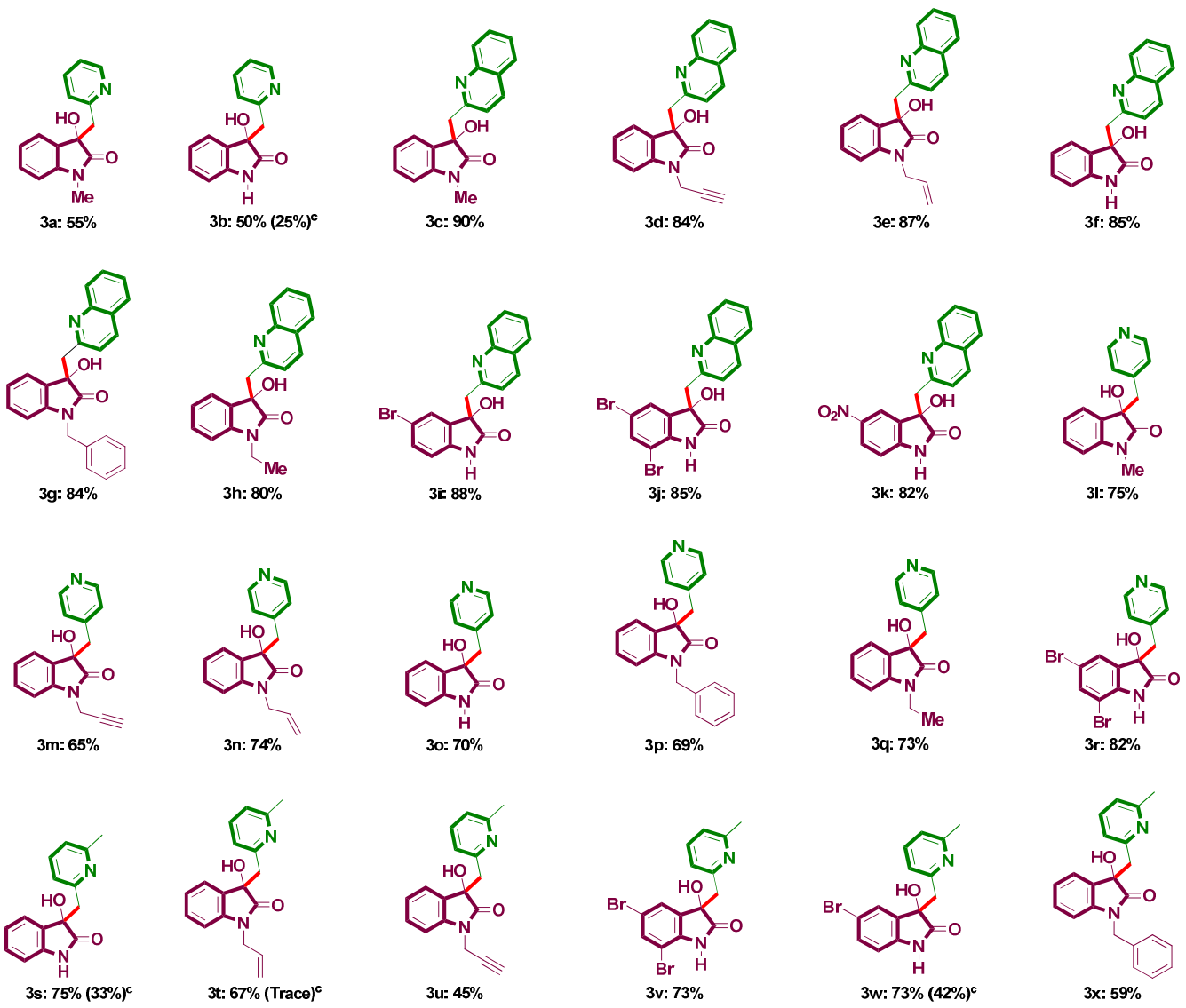


Fig. 1 ORTEP diagram of Product "**3n**" showing atomic numbering scheme with ellipsoid of 50% probability

Table 2 Substrate scope for the construction of azaarene-substituted 3-hydroxy-2-oxindoles[a]



[a]Reaction conditions: α/ γ–Alkylazaarene (2 mmol), isatin (2 mmol), TBAF·3H_2O (10 mol%), MW (80 W), 100 °C, 5 min; [b]Isolated yield; [c]Yields without catalyst.

Experimental

General experimental procedure:

In a sealed pressure regulation 10-mL pressurized vial were placed α/γ−alkyl azaarene (2 mmol), TBAF·3H_2O (10 mol%, 0.2 mmol, 62 mg), isatin (2 mmol), H_2O (2 mL), and a teflon coated magnetic stir bar. The vial was closed with a snap on cap, stirred at room temperature for 1 min and then placed into the MW cavity. Microwave irradiation of 80 W at a set temperature of 100 °C was used and the reaction was held under these conditions for 5 min. After completion of the reaction (monitored through TLC), the mixture was cooled to room temperature, poured to a vessel containing distilled water and then extracted with ethyl acetate (2 x 10 mL). The combined organic phase was dried over anhydrous Na_2SO_4, filtered and concentrated under rotary vacuum evaporator. The resulting crude product was purified using preparative TLC.

Conclusions

In conclusion, the work demonstrates a highly efficient, practical, and environmentally benign approach for the sp^3 C–H functionalization of α–and γ–alkyl azaarenes catalyzed by a simple water compatible organocatalyst in aqueous media under controlled MW. This study will open a new organocatalytic way for the functionalization of sp^3 C–H bonds. The application of this protocol for the functionalization of α–methyl benzothiazoles and α-methyl-1*H*-benzo[d]imidazoles is presently underway in our laboratory.

Acknowledgements

We acknowledge the financial support received from the Department of Biotechnology (DBT), New Delhi. K. K. and B. K. Allam thank Council of Scientific Industrial Research (CSIR), New Delhi for the award of Senior Research Fellowships.

Notes and references

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† Electronic Supplementary Information (ESI) available: [Detailed experimental procedure and full characterisation data for all the products along with the copies of ^{1}H and ^{13}C spectra are available and CCDC 980602 contains the supplementary crystallographic data of the product **3n.** This data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif]. See DOI: 10.1039/c000000x/

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RSC Author Templates - Graphical Abstract

A simple and sustainable tetrabutylammonium fluoride (TBAF)–catalyzed synthesis of azaarene-substituted 3–hydroxy–2–oxindoles through sp^3 C–H functionalization†

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A green, practical, and metal–free protocol for direct addition of α–and γ–alkylazaarenes to isatins has been developed via sp^3 C–H functionalization in water under controlled microwave. This methodology provides a mild and fast access to biologically important azaarene–substituted 3–hydroxy–2–oxindoles in good to excellent yields.