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Graphical Abstract

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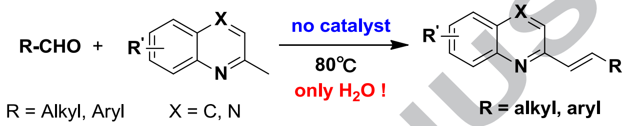

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ABSTRACT

A catalyst-free dehydrative coupling of 2-methylazaarenes with aldehydes "on water" has been developed for efficient synthesis of (*E*)-2-alkenylazaarenes. The challenging addition/dehydration of aliphatic aldehyde was successfully implemented by using water as a solvent. A variety of 2-methylazaarenes, aromatic and aliphatic aldehydes were well tolerated.

The use of water as a reaction medium in organic synthesis has emerged as an attractive research area since the pioneering works of Breslow[1] and Sharpless.[2] Owing to the fascinating advantages of water over traditional organic solvents,[3] various type of "in water" or "on water" reactions are completely in conformity with the standpoint of green chemistry and the development of green protocols for the synthesis of highly functionalized bio-active motifs in aqueous medium is highly desirable.[4] In addition to the environmental issue, the unique physical and chemical properties such as high dielectric constant, strong ability to form hydrogen bonds and amphoteric nature can not only dramatically accelerate the rate of the reaction but also positively influence the reactivity and selectivity of chemical reactions. Therefore, the current challenges in organic synthesis might be tackled by using water as solvent. The tandem nucleophilic addition/dehydration of aldehydes or ketones represented an important methodology towards the green synthesis of a variety of valuable vinylogous compounds as water is the only by-product. In contrast to traditional dehydrative coupling of aldehydes in organic solvents, this type of reaction "on water" was undisputably fascinating.

2-Alkenylazaarenes motif can be frequently found in an ocean of biologically active molecules as antagonist, antiproliferative, antiviral and antimicrobial agents such as Chimanine B **I**, VUF5017 **III**, CGS23113 **II**, Montelukast **IV**, L-660,711 **V** and **VI** (Figure 1).[5] More interestingly, 2-alkenylazaarenes contain embedded imines and alkenes, which can be employed as versatile synthetic precursors to access a variety of functionalized azaarenes.[6] Considering the importance of 2-alkenylazaarenes, it is highly desirable to develop simple and efficient methods to synthesize 2-alkenylazaarenes. Although direct olefination of azaarenes has been developed to construct such motifs,[7] expensive and toxic noble metals and high temperatures are always necessary.

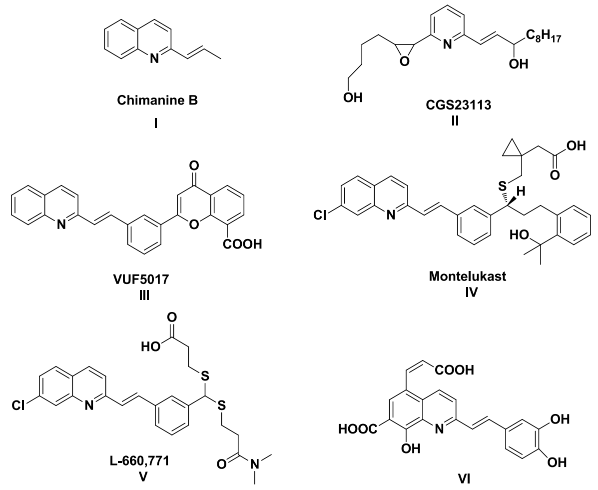
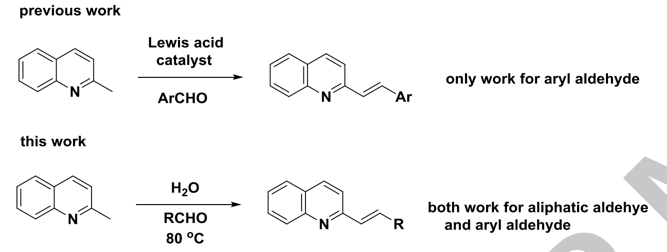


Figure 1 Biologically active 2-alkenlyazaarene derivatives.

Recently, a number of efficient methods through direct C(sp^3)–H functionalization of 2-alkylazaarenes has been developed.[8-11] For example, an iron or lanthanide catalyst has been used for olefination of 2-alkylazaarenes with aldehydes.[9] The similar transformation could also be accomplished with aldimines as electrophiles under catalyst-free condition only using toluene as solvent.[10] The oxidative olefination of 2-

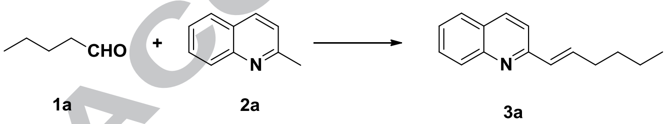
alkylazaarenes with *N*-alkylanilines in the presence of DDQ or with dimethylformamide (DMF) mediated by TBHP have also been explored.[11] However, all these methods suffered from the use of organometallic compounds, organic solvents, prepared imines and harsh conditions. Furthermore, in most cases, aromatic aldehydes were employed as electrophiles, and in contrast, comparatively less investigation was conducted on aliphatic aldehydes despite that 2-alkenylazaarenes with alkyl group are important such as Chimanine B.[9b,10] Although the work of Zhou[9b] and Wang[10] showed the sporadic examples of aliphatic aldehydes, the yields were low and not satisfied.

During our research interest in C(sp^3)-H functionalization of azaarenes,[11] our group reported the first organocatalytic C(sp^3)–H functionalization of 2-alkylazaarenes and followed by that, the catalyst-free C(sp^3)-H functionalization of 2-alkylazaarenes were also achieved by the rational substrate design.[12a-c] As a continuation of that, we developed a facile catalyst-free protocol to synthesize 2-alkenylquinolines in good yields via C(sp^3)-H functionalization of 2-alkylazaarenes with aromatic aldehydes in dioxane, whereas the employment of aliphatic aldehydes still remained elusive.[11c] Keeping the challenges in mind and inspired by our "on water" reactions,[13] we envisaged that this issue might be addressed by the hydrophobic effect and emulsions of aqueous solutions. Herein, we would like to report our new catalyst-free synthesis of (*E*)-2-alkenylazaarenes via C(sp^3)-H functionalization of 2-alkylazaarenes with aldehydes "on water". Considering that water is the most inexpensive and environmentally benign reaction medium, together with the catalyst-free condition and only water as side product, this process is highly desirable and environmentally valuable for direct synthesis of (*E*)-2-alkenylazaarenes.



Scheme 1 Synthesis of 2-alkenylquinolines

Table 1. Optimization Studies[a]

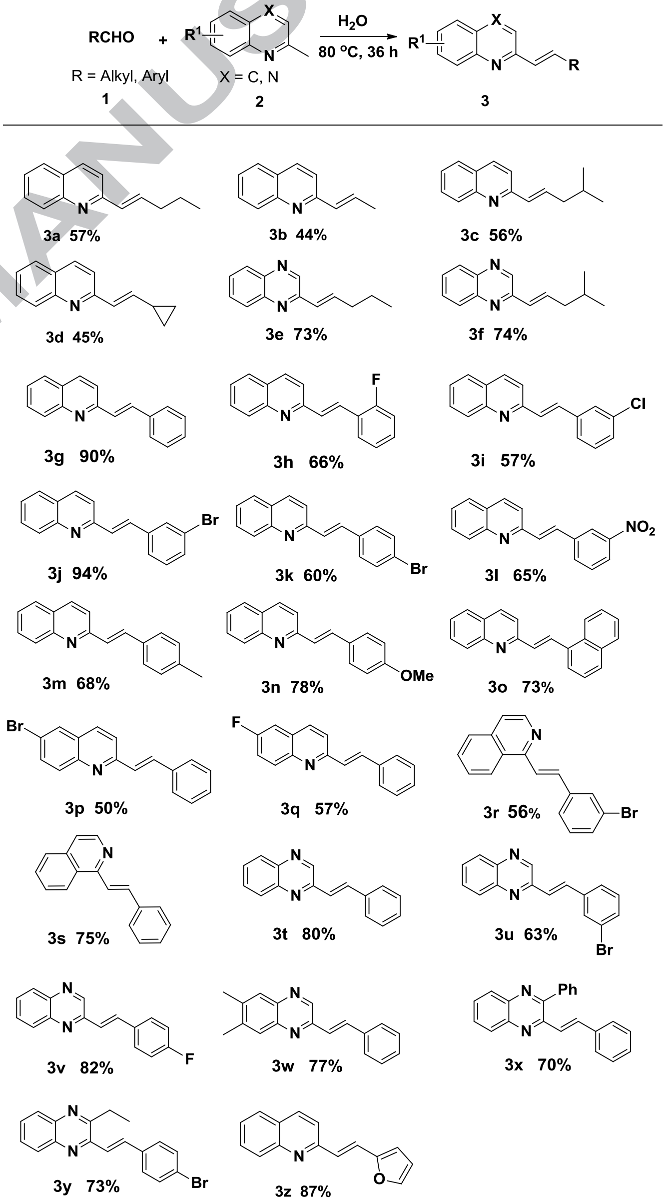


Entry	Solvent	T [℃]	Yield (%)
1	toluene	80	52
2	MeOH	80	46
3	i-PrOH	80	21
4	DMF	80	NR
5	1,4-dioxane	80	NR
6	DMSO	80	NR
7	H_2O	80	74
8	H_2O	90	72
9	H_2O	100	68
10	H_2O	120	65

[a] Reactions were conducted with 1a (5 mmol), 2a (0.5 mmol) in 5 mL H_2O, 36 h.

Initially, the reaction of valeraldehyde **1a** and 2-methylquinoline **2a** was carried out in toluene at 80℃ and moderate yield could be obtained (Table 1, entry 1). The desired product was also observed in alcoholic solvents, albeit with lower yields (Table 1, entries 2-3). However, no reaction occurred in other solvents such as DMF and DMSO (Table 1, entries 4-6). Consistent with our proposal, this reaction proceeded smoothly in water and afforded the product **3a** in 74% yields (Table 1, entry 7). The higher temperature did not benefit the yields and the employment of excessive aldehydes was critical to the good yield of this transformation (Table 1, entries 8-10). Hence, water was identified as the optimal solvent in terms of reaction efficiency and benignity as well as the cost.

Afterwards, a variety of sterically and electronically diverse substrates were examined to investigate the generality of this transformation under the optimal condition (Scheme 1). The reaction of 2-methylquinoline and with aliphatic aldehydes such as butyraldehyde and isovaleraldehyde could give the corresponding products in moderate to good yields (**3a-3f**).



Scheme 2 Substrate scope of 2-alkylazaarenes and aldehydes. Reactions were conducted with **1a** (10 mmol for aliphatic aldehyede and 5 mmol for aryl aldehyde), **2a** (1 mmol) in 5 mL H_2O, 36 h.

Compared with aromatic aldehydes and 2-methylquinoxaline, aliphatic aldehydes and 2-methylquinoline were less-than-ideal substrates, with which only moderate yields could be achieved (**3a**-**3d**). In addition to the desired products, much of the substrates remained intact. Meanwhile, trace side products were indeed observed. Subsequently, a multitude of diverse 2-methylquinolines and aromatic aldehydes were tested. Electron-deficient or electron-rich aromatic aldehydes were well tolerated to furnish the analogous products in good yield (**3g-3z**). When aromatic aldehydes were substituted with electron-rich groups such as methoxyl group (**3n**), the yields were superior to those of electron-poor aldehydes such as fluorine (**3h**) and nitro-group substituted ones (**3l**). 1-Methylisoquinoline and the quinoxaline ring were also good substrates for this reaction, furnishing the desired product in good yields (**3r-3y**). In addition to phenyl aldehydes, furanyl aldehyde also worked very well (**3z**). At last, formaldehyde, acetophenone, and cyclohexanone were subjected to the reaction under the standard condition, aiming to access 2-vinylquinoline, trisubstituted alkenes or tertiary alcohols, whereas no transformation could be observed and all the reactants remained intact.

Conclusions

In summary, we have developed a facile catalyst-free protocol to synthesize (*E*)-2-alkenylquinolines "on water". The challenging addition/dehydration of aliphatic aldehyde was successfully implemented by using water as a solvent. Compared with the traditional methods, the advantages of using water as solvent and only water as side product render this methodology atom-economic and environmentally friendly to access (*E*)-2-alkenylquinoline derivatives, which can be further employed as synthetic precursors to build an army of functionalized heterocycles. Further development of green methods for C(sp^3)-H functionalization of azaarenes "on water" are ongoing in our laboratory.

Acknowledgments

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Highlights

- Synthesis of 2-alkenylazaarenes via reaction of 2-methylazaarenes with aldehydes.
- The aliphatic aldehyde problem was harnessed by using water as a solvent.
- Water as solvent and no catalyst render this method atom-economic and green.