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Microwave assisted water mediated benzylic C–H functionalization of methyl aza-arenes and nucleophilic addition to aromatic aldehydes

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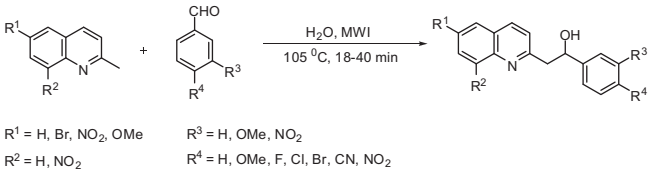
ABSTRACT

A highly efficient method is described for the sp^3 C–H bond functionalization of methyl aza-arenes in the presence of water under microwave irradiation and subsequent addition to aromatic aldehydes. This transformation represents an efficient way to synthesize 2-alkyl aza-arene derivatives from simple starting materials.

Formation of carbon–carbon bond by sp^3 C–H functionalization is an important transformation in organic chemistry.[1] In particular, the benzylic sp^3 C–H functionalization of 2-alkyl aza-arenes is a challenging task due to less reactivity of alkyl groups. This type of reaction is particularly important because, alkyl aza-arene derivatives are known to possess a wide range of pharmaceutical activities, such as anti-inflammatory agents, anti cancer, anti-HIV agents, and usage as molecular probes.[2] Consequently, many approaches have been developed for the activation of sp^3 C–H bond of alkyl aza-arenes catalyzed by transition metals,[3] Lewis acids[4] and Bronsted acids.[5] In addition, different protocols have been reported for the sp^3 C–H activation of methyl aza-arenes involving highly reactive carbonyl compounds.[6] It was reported that Lewis acid catalyzed reaction of methyl aza-arenes with aldehydes at elevated temperatures produced dehydrated products.[7] To the best of our knowledge only one method is known for the benzylic C–H bond functionalization of aza-arenes promoted by Bronsted acid.[5b] Indeed, this protocol is limited only to aromatic aldehydes bearing electron withdrawing groups. Though the reported methods are satisfactory, they suffer from certain drawbacks like the use of expensive catalysts, toxic metals, extended reaction times, and environmentally hazardous organic solvents. In view of this, the development of a mild and highly efficient method for the direct sp^3 C–H functionalization of alkyl aza-arenes is desirable.



R^1 = H, Br, NO_2, OMe
R^2 = H, NO_2
R^3 = H, OMe, NO_2
R^4 = H, OMe, F, Cl, Br, CN, NO_2

Scheme 1. sp^3 C–H activation of methyl aza-arene and nucleophilic addition to aromatic aldehydes.

Table 1
Screening of solvents and temperature[a]

Entry	Solvent	Temperature (°C)	Yield[b] (%)
1	THF	90	NR[c]
2	CH_3CN	90	NR[c]
3	DCE	110	NR[c]
4	DMF	110	30
5	DMSO	110	40
6	Ionic liquid	110	60
7	PEG-400	110	60
8	D_2O	105	70
9	H_2O	80	50
10	**H_2O**	**105**	**85**
11	H_2O	120	60

[a] Reaction conditions: methylquinoline (1.8 mmol) and 4-nitrobenzaldehyde (1 mmol) in 2 mL of the solvent for 20 min under MW irradiation.
[b] Isolated yield.
[c] No reaction.

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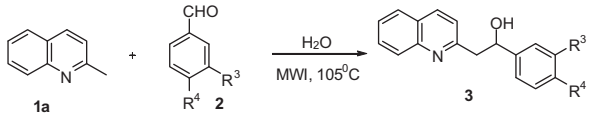
Microwave irradiation has become a complementary tool in the development of green chemistry.[8] Microwave irradiation with water as reaction medium is a highly reliable and sustainable chemical approach. Water is a clean and safe solvent which is cheap, non-toxic, non-combustible, non-explosive, and the most benign environmentally.[9] However, water has been rarely used as a solvent for organic reactions due to the poor solubility of most of the organic compounds in water. But at elevated temperatures under microwave irradiation, the physical and chemical properties of water are altered in such a way that it behaves both as a pseudo-organic solvent and a phase transfer catalyst too.[10]

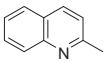
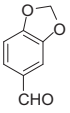
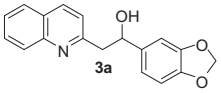
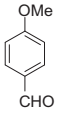
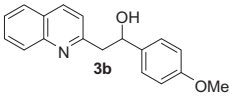
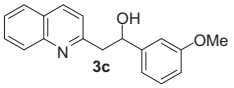
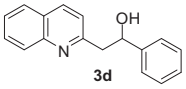
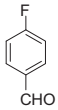
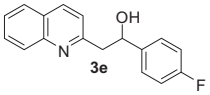
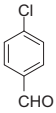
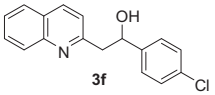
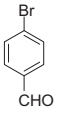
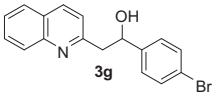
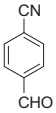
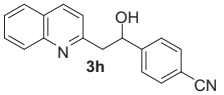
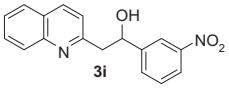
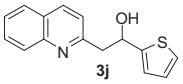
In continuation of our research on sp^3 C–H functionalization,[11] herein we wish to report a novel, efficient, and catalyst-free method for the sp^3 C–H bond activation of methyl aza-arene and nucleophilic addition to aromatic aldehydes (Scheme 1).

Reaction of 2-methyl quinoline (**1a**) with *p*-nitro benzaldehyde (**2k**) in the presence of water under microwave irradiation proceeded smoothly to give the expected product in excellent yield (**3k**). To check the efficiency of water as a solvent under similar conditions, a study has been made by varying the solvent system of the reaction. As seen in Table 1, a variety of reaction conditions were employed to find out the optimal reaction conditions.

The result of which revealed that solvents such as tetrahydrofuran, acetonitrile, and 1,2-dichloroethane are not suitable for this reaction as there is no formation of the desired product even in a trace quantity (Table 1, entries 1–3). When *N*,*N*-dimethylformamide and dimethylsulfoxide were employed as reaction media, the desired product was obtained in lower yields (Table 1, entries 4 and 5). However, moving on to check some alternative greener

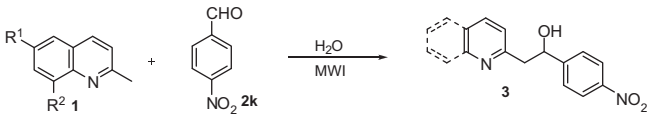
Table 2
sp^3 C–H activation of methyl quinoline and nucleophilic addition to various aromatic aldehydes

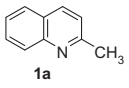
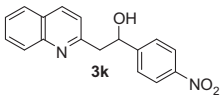
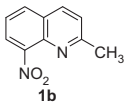
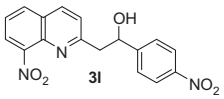
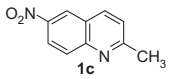
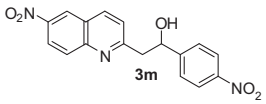
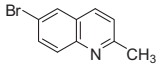
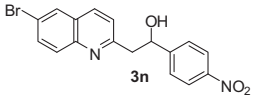
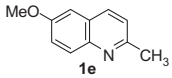
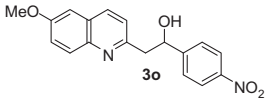
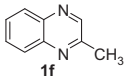
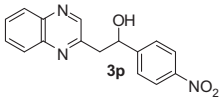
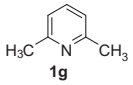
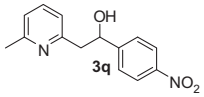
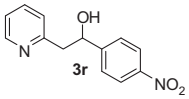


Entry	Methyl quinoline	Aldehyde (**2**)	Product[a] (**3**)	Time (min)	Yield[b,c] (%)
1	 **1a**	 **2a**	 **3a**	45	40
2	**1a**	 **2b**	 **3b**	40	55
3	**1a**	 **2c**	 **3c**	30	65
4	**1a**	 **2d**	 **3d**	30	65
5	**1a**	 **2e**	 **3e**	25	70
6	**1a**	 **2f**	 **3f**	25	70
7	**1a**	 **2g**	 **3g**	25	70
8	**1a**	 **2h**	 **3h**	25	75
9	**1a**	 **2i**	 **3i**	18	85
10	**1a**	 **2j**	 **3j**	20	70

[a] All the products were characterized by ^{1}H NMR, IR, ^{13}C NMR, mass, HRMS.
[b] Yield refers to isolated products after purification.
[c] Starting materials were recovered.

Table 3
sp^3 C–H activation of methyl aza-arenes and nucleophilic addition 4-nitrobenzaldehydel



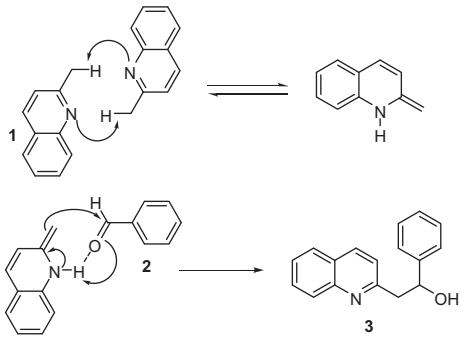
Entry	Methyl quinoline	Product[a] (**3**)	Temperature	Time (min)	Yield[b,c] (%)
1	 **1a**	 **3k**	102	15	85
2	 **1b**	 **3l**	102	28	75
3	 **1c**	 **3m**	102	35	65
4	 **1d**	 **3n**	102	28	65
5	 **1e**	 **3o**	102	30	70
6	 **1f**	 **3p**	102	25	60
7	 **1g**	 **3q**	110	40	55
8	 **1h**	 **3r**	110	45	50

[a] All the products were characterized by IR, mass, HRMS, ^{1}H and ^{13}C NMRS.
[b] Yield refers to pure products after purification.
[c] Starting materials were recovered.

media such as ionic liquid and PEG-400 produced the product in moderate yields (Table 1, entries 6 and 7). Also, a reaction carried out under neat condition led to an inseparable mixture of various products. In addition, among the wide range of solvent systems tested, the water mediated reactions were the most effective in terms of yields. Furthermore, varying the temperature below or above the optimal 105 °C temperature led to a decrease in yields (Table 1, entries 9 and 11). The time duration of the reaction was particularly important as longer reaction time, will result in the formation of the by-products.

Having the optimized reaction conditions in hand,[12] the scope of the reaction with regard to the electronic structure of aldehydes was screened (Table 2). It was found that all aromatic aldehydes bearing an electron withdrawing group as well as electron-releasing groups underwent smooth coupling though the latter was less efficient compared to the former. The present protocol is found to be advantageous over the previous report which only worked with aromatic aldehyde bearing electron withdrawing groups.[5b] Reaction of methyl quinoline 1a with aromatic aldehydes bearing electron neutral and electron-donating substituents led to a modest yield of the product (Table 2, entries 1–4). Aromatic aldehydes attached to electron-withdrawing substituents proceeded effectively and provided the desired products in excellent yields (Table 2, entries 8 and 9). Aromatic aldehydes bearing halogen substituents were well tolerated and gave a good yield of the products (Table 2, entries 5–7). Furthermore, we extended the scope of aldehydes to hetero aromatic aldehydes. Hetero aromatic aldehydes gave the corresponding product in good yield (Table 2, entry 10). Next, an attempt was made to examine the reactivity of aliphatic aldehydes and benzophenones, they however failed to give the desired product.

Next we moved onto check the scope of 2-alkyl aza-arenes and the results are summarized in Table 3. Various substituents on the aromatic ring of the 2-alkyl aza-arenes were well tolerated and the reaction was found comparable to the unsubstituted aza-arenes. Both electron-poor (Table 3, entries 2 and 3) and electron-rich (Table 2, entry 5) substituted 2-alkyl aza-arenes were effective to furnish the desired products. It was remarkable that halide substituent was tolerated in the quinoline ring (Table 3, entry 4). When 2-methyl-quinoxaline was used as the substrate, the yield of the corresponding adduct was only modest (Table 3, entry 6). Therefore, this process was not only applicable to quinolines and quinoxalines but also to 2, 6-lutidine and 2-picoline though with modest yields (Table 3, entries 7 and 8). Pyrimidine and pyrazines



Scheme 2. A plausible mechanism of the reaction.

failed to react with aromatic aldehydes under the optimized conditions.

We presume that under microwave irradiation, the acidity of aza-allylic protons and the ligating ability of the nitrogen atom of 2-methyl aza-arene (**1**) were increased and facilitated the enamine formation. The nucleophilic addition of enamine intermediate to aromatic aldehyde (**2**) would afford the desired adduct. An experiment was conducted to check the deuterium exchange during the reaction. The reaction was performed in deuteriated water which did not result in any deuteriated product and thereby eliminating any assumption of a proton exchange from the medium during the course of the reaction (see Scheme 2).

In summary, we have developed a mild, highly efficient, and water mediated protocol for the sp^3 C–H functionalization of methyl quinolines with aromatic aldehydes. The method is extensively applicable for the rapid preparation of a library of biologically active pyridine and quinoline derivatives.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.07.053.

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12. *General procedure*: A sealed 10 mL glass tube containing aldhyde (1 equiv), methyl quinoline (1.8 equiv) and water (2 mL) was placed in the cavity of a microwave reactor and irradiated for the appropriate time, at 105 °C (temperature monitored by a built-in infrared sensor), and power 160 W. After cooling to room temperature by an air-flow, the tube was removed from the rotor. The reaction mixture was diluted with water and extracted with ethyl acetate. The combined ethyl acetate extracts were then dried over anhydrous Na_2SO_4 and after removal of the solvent, the mixture was purified by (silica gel) column chromatography (hexane/AcOEt, 70:30 as eluent) to give pure products.