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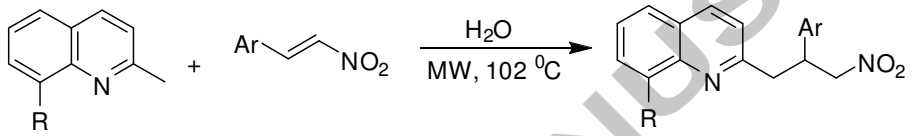

1 **2** **3**

R = H, NO_2

Ar = 3,4-Dimethoxyphenyl, 3 ,4-Methylenedioxyphenyl, 4-Methoxyphenyl, 4-Tolyl, Phenyl, 4-Chlorophenyl, 4-BromoPhenyl, 2-Furanyl, 2-Thienyl, 2-Napthyl, 2-Methoxyphenyl

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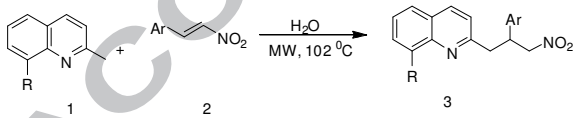
Abstract— A catalyst-free aqueous mediated C-H activation of methyl quinolines and addition to various beta-nitro styrenes was executed under Microwave irradiation. Catalyst-free, additive free, simple workup, clean reaction conditions, easy isolation and environmentally benign medium are the best features of the present protocol.

Keywords: Catalyst-free conditions, Microwave, Methyl quinoline, Nitro styrene and Water.

C-H functionalization by forming a carbon-carbon bond attracts considerable attention in modern organic synthesis. The advantage of the C-H functionalization lies in the simplicity of the total process. In respect of this, many excellent results have been reported on C- H activation, the majority of the catalytic processes reported were applicable to only sp^2 C-H bonds.[1] The functionalization of sp^3 C-H bonds is still a particularly difficult challenge owing to the strength of sp^3 C-H bonds. In context to this, in the last few years, some promising catalytic systems for the selective functionalization of sp^3 C-H bonds have been developed. Recently, sp^3 C-H bond activation of 2-alkyl substituted aza-arene catalyzed [2] by transition metals, Lewis acid or Bronsted acid have been reported. However, many of these methods are associated with various drawbacks such as use of metal catalysts, tedious experimental procedures, unsatisfactory yields, long reaction times, and usage of expensive and moisture sensitive catalysts. In continuation of our work, the development of catalyst-free and additive free carbon-carbon bond formation reactions, [3] we became interested in developing an efficient route to C-H bond activation of methyl quinolines. Herein, we wish to report the MW assisted catalyst-free sp^3 C-H functionalization of 2-methyl quinolines and Michael addition to nitro styrenes affording alkyl aza-arenes in good yields (Scheme 1). The aza-arenes products can exhibit potent biological, chemical and pharmaceutical properties. [4]



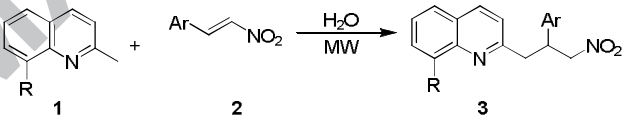
R = H, NO_2

Ar = 3,4 Dimethoxyphenyl, 3 ,4-Methylenedioxyphenyl, 4-Methoxyphenyl, 4-Tolyl, Phenyl, 4-Chlorophenyl, 4-BromoPhenyl, 2-Furanyl, 2-Thienyl, 2-Napthyl, 2-Methoxyphenyl

Scheme1: Activation of methyl quinoline sp^3 C-H bond and addition to nitro styrenes

MW energy has tremendous benefits in organic synthesis and represents now a reliable tool for organic chemists.[5] Water is the ideal solvent because of its abundance, and lack of toxic by-products, but often faces significant limitations with respect to dissolution and scope. Water above its boiling point acts as a pseudo organic solvent[5a] and also is a polar solvent, consequently microwaves interact well with water and have been successfully engaged as a catalyst for various organic reactions.[6] Thus, development of an efficient and convenient synthetic methodology employing water medium is the subject of interest in the recent days.

Table 1: Reaction condition screening[a]



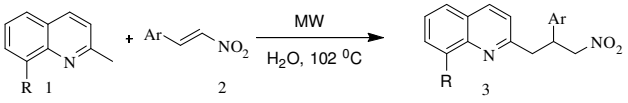
Entry	Solvent	Catalyst (mol %)	T (^{0}C)	Yield[b] (%)
1	THF	—	70	n.r
2	THF	Iodine	70	n.r
3	CH_3CN	—	90	n.r
4	CH_3CN	Iodine	90	n.r
5	1,2-DCE	Iodine	90	n.r
6	DMF	—	100	20
7	DMSO	—	100	30
8	H_2O	—	80	50
9	H_2O	—	100	70
10	H_2O	—	102	80

[a]Reaction conditions: methyl quinoline (1.5 mmol), nitro styrene (1 mmol) and H_2O (3 ml) under ambient conditions for 25 min. in MW. [b]Isolated yield

Initially, the reaction of methyl quinoline (1a) with β-nitro styrene (2e) was chosen as a model reaction and several solvents such as THF, acetonitrile, 1, 2-DCE, DMF, DMSO and H_2O were screened (Table 1). The optimization included selecting the most suitable solvents and proportions of

substrates as well ambient temperature and reaction time. No product formation was observed in THF, acetonitrile and DCE with or without iodine catalyst. When the reaction was carried out with DMF **3c** was obtained in low yield along with side products. Similarly, reaction in DMSO under MW irradiation afforded 30% yield. When the same reaction was carried out in H_2O afforded good yield of product. Encouraged by this result, the reaction was performed in water and repeated many times at different temperatures in a sealed vessel under microwave heating, which resulted in the respective products in good yields and the results are presented in Table 1. Interestingly, the yields of products increased from 40% to 70% as the temperature was raised from 80 to 102 ^{0}C. It may be stated that microwave irradiation of reaction mixture in aqueous medium at 102 ^{0}C is the best reaction condition.[7] Moreover, by increasing the amount of **1a** from 1 to 1.5 eq. increased, the yield of product **3a** to 70%.

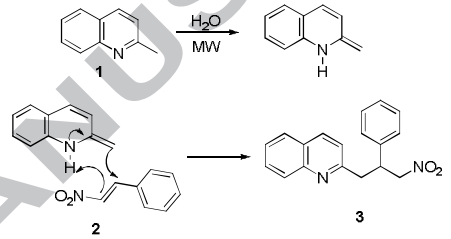
Table 2: Actvation of methyl quinoline and Michael addition to nitrostyrenes[a]



Entry	R (1)	Ar (2)	Product[a](3)	Time (min)	Yield[b](%)
1	H	2a	3a	20	85
2	H	2b	3b	25	60
3	H	2c	3c	25	80
4	H	2d	3d	25	75
5	H	2e	3e	25	70
6	H	2f	3f	30	60
7	H	2g	3g	30	60
8	H	2h	3h	20	80
9	H	2i	3i	18	85
10	NO_2	2j	3j	25	80
11	NO2	2k	3k	25	75
12	NO_2	2l	3l	20	85

[a] all products were characterised by IR, ^{1}HNMR, ^{13}CNMR and Mass[8]
[b] yield refers to pure produts after purification

With the optimized reaction conditions established, we investigated the scope of this protocol. We first explored the scope of reaction by using various methyl quinolines and β-nitro styrene derivatives. The results are summarized in Table 2. As expected, various aromatic nitro styrenes worked well under the reaction condition. Methyl quinolines with nitro styrenes bearing electron releasing groups such as methoxy and methyl, gave comparatively high yield (Table 2, entries 1, 2, 3, 4, 10 and 11), whereas electron withdrawing groups like chloro, bromo gave low yield of products (Table 2, entries 6 and 7). Moreover, the heterocyclic nitro styrenes (Table 2, entries 8 and 9) and 2-napthyl nitro styrene (Table 2, entry 12) still displayed high reactivity under the standard conditions. However, 2-methyl pyridine and 4-methyl pyridine did not participate under the standard reaction condition. The yield of **3c** was nearly same as **3k**, indicating that the nitro group on methyl quinoline had little influence on the reaction.



Scheme 2: A plausible mechanism of the reaction

We presume that under microwave irradiation, the enamine intermediate was generated via the requisite disruption of aromaticity of **1**. The Michael addition of the enamine intermediate to nitrostyrene would afford the coupled adduct (Scheme 2, Table 1).

In conclusion, we have developed an efficient microwave assisted catalyst-free addition of methyl quinolines to β-Nitro styrenes via sp^3 C-H bond functionalisation. This green protocol can be used in the drug discovery programme for the rapid preparation of library of quinoline derivatives.

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7. *General procedure:* A sealed 10 mL glass tube containing nitrostyrene (1 equiv.), methyl quinoline (1.5 equiv.) and water (3 mL) was placed in the cavity of a microwave reactor and irradiated for appropriate time, at 102^0C (temperature monitored by built in infrared sensor), and power 150 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 Na_2SO_4 and after removal of the solvent the mixture was purified by (silica gel) column chromatography (hexane/AcOEt, 80:20 as eluent) to give pure products.
8. *Spectral data of representative compounds*:
12-(2-(3, 4-dimethoxyphenyl)-3-nitropropyl)quinoline (**3a**) IR: ν_{max} 3006, 2927, 1597, 1550, 1514, 1461, 1427, 1378, 1262, 1144, 1026, 823 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.04 (dd, *J* = 8.1 Hz, *J* = 2.8 Hz, 2H), 7.76 (d, *J* = 8.1 Hz, 1H), 7.67-7.74 (m, 1H), 7.51 (t, *J* = 7.9 Hz, 1H), 7.14 (d, *J* = 8.4 Hz, 1H), 6.77-6.81 (m, 2H), 6.72 (d, *J* = 1.5 Hz, 1H), 4.69-4.85 (m, 2H), 4.10-4.22 (m, 1H), 3.81 (s, 3H), 3.77 (s, 3H), 3.36 (d, *J* = 7.7 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 158.3, 148.8, 148.2, 147.4, 136.6, 131.4, 129.6, 128.5, 127.4, 126.6, 126.2, 121.6, 119.2, 111.1, 110.7, 79.7, 55.6, 43.4, 42.2, 29.5; m/z (ESI); 353 $[M+H]^+$.
2-(2-(benzo[d][1,3]dioxol-5-yl)-3-nitropropyl)quinoline (**3b**) IR: ν_{max} 2956, 2924, 2855, 1600, 1551, 1503, 1487, 1444, 1377, 1247, 1039, 934, 819, 751 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.01-8.11 (m, 2H), 7.65-7.81 (m, 2H), 7.45-7.55 (m, 1H), 7.28 (d, *J* = 3.02 Hz, 1H), 7.15 (d, *J* = 8.3 Hz, 1H), 6.75 (s, 1H), 6.69 (s, 1H), 5.90 (s, 2H), 4.62-4.83 (m, 2H), 4.06-4.23 (m 1H), 3.31 (d, *J* = 7.5 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 158.3, 147.9, 147.7, 147.5, 136.6, 129.6, 129.4, 128.8, 127.5, 126.2, 125.6, 121.6, 120.8, 108.4, 107.6, 101.0, 79.8, 43.6, 42.3; m/z (ESI); 307 $[M+H]^+$.
2-(2-(4-methoxyphenyl)-3-nitropropyl)quinoline (**3c**) IR: ν_{max} 2926, 2841, 1606, 1550, 1510, 1377, 1250, 1179, 1032, 830, 769 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.04 (d, *J* = 8.4 Hz, 1H), 7.86-7.95 (m, 1H), 7.58-7.71 (m, 2H), 7.37-7.46 (m, 1H), 7.12 (d, *J* = 6.9 Hz, 2H), 6.99-7.07 (m, 1H), 6.70-6.79 (m, 2H), 4.60-4.81 (m, 2H), 4.09-4.21 (m, 1H), 3.63 (s, 3H), 3.27 (d, *J* = 6.6 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 158.5, 158.2, 147.3, 136.1, 130.8, 129.2, 128.4, 128.2, 127.2, 126.4, 125.8, 121.4, 113.8, 79.5, 54.6, 42.8, 41.9; m/z (ESI); 323 $[M+H]^+$.
*2-(3-nitro-2-p-tolylpropyl)quinoline (**3d**)* IR: ν_{max} 2924, 2854, 1599, 1551, 1507, 1428, 1377, 819, 749 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.03 (dd, *J* = 8.8 Hz, *J* = 1.7 Hz, 2H), 7.65-7.79 (m, 2H), 7.45-7.53 (m, 1H), 7.24-7.34 (m, 1H), 7.05-7.17 (m, 4H), 4.66-4.85 (m, 2H), 4.11-4.23 (m, 1H), 3.34 (d, *J* = 7.7 Hz,.2H), 2.28 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 158.5, 147.7, 137.2, 136.5, 136.2, 129.6, 129.5, 128.9, 127.4, 127.2, 126.8, 126.1, 125.7, 121.9, 121.6, 79.7, 43.4, 42.4, 29.6; m/z (ESI); 307 $[M+H]^+$.
*2-(3-nitro-2-phenylpropyl)quinoline (**3e**)* IR: ν_{max} 2956, 2924, 2854, 1599, 1551, 1501, 1457, 1376, 1261, 822, 752 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.03 (dd, *J* = 14.3 Hz, *J* = 8.1 Hz, 2H), 7.64-7.79 (m, 2H), 7.50 (t, *J* = 6.9 Hz, 1H), 7.20-7.32 (m, 5H), 7.11 (d, *J* = 8.3 Hz, 1H), 4.68-4.89 (m, 2H), 4.14-4.27 (m, 1H), 3.35 (d, *J* = 7.3 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 158.3, 147.6, 139.2, 136.5, 129.6, 128.7, 127.5, 127.4, 127.3, 126.7, 126.7, 126.1, 125.7, 121.9, 121.5, 79.5, 43.7, 42.2; m/z (ESI); 293 $[M+H]^+$.
2-(2-(4-chlorophenyl)-3-nitropropyl)quinoline (**3f**) IR: ν_{max} 2924, 2855, 1598, 1552, 1497, 1376, 1093, 826, 752 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.99-8.10 (m, 2H), 7.65-7.81 (m, 2H), 7.50 (t, *J* = 7.5 Hz, 1H), 7.08-7.35 (m, 5H), 4.66-4.88 (m, 2H), 4.16-4.28 (m, 1H), 3.24-3.38 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 157.8, 147.7, 137.7, 136.6, 136.4, 129.7, 128.9, 128.8, 127.5, 127.4, 126.3, 121.9, 121.5, 79.3, 42.0, 43.0; m/z (ESI); 327 $[M+H]^+$.
2-(2-(4-bromophenyl)-3-nitropropyl)quinoline (**3g**) IR: ν_{max} 2924, 2853, 1598, 1551, 1488, 1428, 1377, 1073, 1010, 826, 756 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.02 (t, *J* = 8.4 Hz, 2H), 7.66-7.77 (m, 2H), 7.45-7.53 (m, 1H), 7.38 (d, *J* = 8.3 Hz, 2H), 7.11 (dd, *J* = 8.3 Hz, *J* = 3.3 Hz, 3H), 4.66-4.87 (m, 2H), 4.16-4.27 (m, 1H), 3.23-3.38 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 157.8, 147.6, 138.2,

136.6, 131.2, 131.3, 129.6, 129.1, 128.7, 127.5, 126.7, 126.2, 121.5, 121.4, 79.2, 43.0, 41.8; m/z (ESI); 373 $[M+H]^+$.

2-(2-(furan-2-yl)-3-nitropropyl)quinoline (**3h**) IR: ν_{max} 2924, 2854, 1599, 1553, 1504, 1428, 1377, 1013, 824,743 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ ; 8.04 (d, *J* = 8.4 Hz, 2H), 7.67-7.81 (m, 2H), 7.51 (t, *J* = 7.5 Hz, 1H), 7.33-7.38 (m, 1H), 7.15 (d, *J* = 8.3 Hz, 1H), 6.22-6.26 (m, 1H), 6.09 (d, *J* = 3.2 Hz, 1H), 4.71-4.86 (m, 2H), 4.32-4.43 (m, 1H), 3.30-3.49 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 157.9, 152.1, 147.7, 142.1, 136.5, 129.6, 128.4, 127.4, 126.2, 121.5, 110.2, 107.3, 77.4, 39.6, 37.4; m/z (ESI); 283 $[M+H]^+$.

2-(3-nitro-2-(thiophen-2-yl)propyl)quinoline (**3i**) IR: ν_{max} 2924, 2854, 1558, 1550, 1502, 1428, 1376, 824, 701 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.04 (t, *J* = 8.1 Hz, 2H), 7.66-7.79 (m, 2H), 7.50 (t, *J* = 7.1 Hz, 1H), 7.13-7.20 (m, 2H), 6.87 (d, *J* = 3.3 Hz, 2H), 4.67-4.90 (m, 2H), 4.53-4.64 (m, 1H), 3.34-3.48 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 157.8, 147.7, 142.2, 136.5, 129.6, 128.8, 127.4, 126.8, 126.2, 125.3, 124.4, 121.6, 80.0, 42.9, 38.9; m/z (ESI); 299 $[M+H]^+$.

2-(2-(naphthalen-1-yl)-3-nitropropyl)-8-nitroquinoline (**3j**) IR: ν_{max} 2922, 2854, 1624, 1600, 1549, 1526, 1427, 1374, 750 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.05 (d, *J* = 8.4 Hz, 1H), 7.98 (d, *J* = 7.3 Hz, 1H), 7.92 (d, *J* = 8.1 Hz, 1H), 7.71 (m, 4H), 7.52 (t, *J* = 7.8 Hz, 1H), 7.37-7.46 (m, 3H), 7.28 (d, *J* = 8.4 Hz, 1H), 4.86-5.11 (m, 2H), 4.40-5.11 (m, 1H), 3.45-3.60 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 161.1, 147.9, 138.8, 136.4, 136.3, 133.3, 132.7, 131.5, 128.7, 127.8, 127.5, 126.9, 126.2, 126.0, 125.1, 124.8, 123.6, 123.5, 79.5, 42.7, 41.5; m/z (ESI); 388 $[M+H]^+$.

2-(2-(4-methoxyphenyl)-3-nitropropyl)-8-nitroquinoline (**3k**) IR: ν_{max} 2924, 2854, 1590, 1549, 1520, 1423, 1372, 770 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.09 (d, *J* = 8.3 Hz, 1H), 7.97 (t, *J* = 9.2 Hz, 2H), 7.55 (t, *J* = 7.9 Hz, 1H), 7.27 (d, *J* = 9.0 Hz, 1H), 7.16 (d, *J* = 8.4 Hz, 2H), 6.80 (d, *J* = 8.3 Hz, 2H), 4.71-4.99 (m, 2H), 4.11-4.28 (m, 1H), 3.74 (s, 3H), 3.30-3.48 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 158.8, 147.9, 138.8, 136.2, 131.5, 131.0, 128.7, 128.5, 127.5, 124.8, 123.5, 114.2, 79.7, 55.1, 42.1, 41.8; m/z (ESI); 368 $[M+H]^+$.

2-(2-(2-methoxyphenyl)-3-nitropropyl)-8-nitroquinoline (**3l**) IR: ν_{max} 2924, 2842, 1623, 1601, 1550, 1495, 1462, 1378, 1246, 1026, 757 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.01 (d, *J* = 7.5 Hz, 1H), 7.87 (t, *J* = 8.3 Hz, 2H), 7.44 (t, *J* = 8.3 Hz, 1H), 7.25 (d, *J* = 8.3 Hz, 1H), 7.09-7.19 (m, 2H), 6.75-6.86 (m, 2H), 4.91-5.04 (m, 2H), 4.39-4.51 (m, 1H), 3.82 (s, 3H), 3.45 (d, *J* = 7.5 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 161.7, 157.0, 147.5, 138.4, 135.9, 131.3, 129.0, 128.4, 127.2, 126.4, 124.4, 123.3, 123.1, 120.3, 110.6, 77.6, 55.1, 39.5, 38.8; m/z (ESI); 368 $[M+H]^+$.