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# Polyethylene glycol (PEG-400) as an efficient and recyclable reaction media catalyst-free benzyl C–H fictionalisation of methyl quinoline and Michael addition to beta-nitro styrene

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**ABSTRACT**

*Polyethylene glycol (PEG-400) was found to be an effective reaction medium C–H activation of methyl quinolines and addition to various beta-nitro styrenes were executed under PEG-400 under mild reaction conditions. The use of PEG-400 is low, recyclable, and eco-friendly solvent.*

**Key words:** Methyl quinoline, Nitro styrene**,** Catalyst-free conditions, Polyethylene glycol.

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## INTRODUCTION

Quinoline derivatives have been widespread and have growing applications in drug discovery and material sciences due to their special physical, chemical, and biological properties [1]. Among them, 2-alkenyl pyridine and quinoline derivatives not only are ubiquitous structural motifs in biologically relevant molecules but also serve as valuable precursors for a wide range of 2-alkyl heterocycles [2], moreover the aza-arene products can exhibit potent biological, chemical and pharmaceutical properties [3]. 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 sp2 C–H bonds [4] . The functionalization of sp3 C–H bonds is still a particularly difficult challenge owing to the strength of sp3 C–H bonds. In context to this, in the last few years, some promising catalytic systems for the selective functionalization of sp3 C–H bonds have been developed. Recently, sp3 C–H bond activation of 2-alkyl substituted aza-arene catalysed [5] by transition metals, Lewis acid or Bronsted acid has been reported. Recently, microwave irradiation has also been used to enhance the reaction rates [6]. 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 recent years, the use of alternative solvents such as ionic liquids, polyethylene glycol and super critical fluids has gained importance as green reaction media in view of environmental perception [7, 8]. Though water is a safe alternative, it is not always possible to use water as a solvent due to hydrophobic nature of the reactants and the sensivity of many catalysts to aqueous conditions [9]. In this context, PEG has become an alternative reaction media to perform organic synthesis due to its inherent advantages over toxic solvents. Furthermore, PEG is inexpensive, easy to handle, thermally stable, non-toxic and recyclable.

In continuation of our interest on PEG mediated organic transformations [10] ,we herein report a simple and efficient approach for the sp3 C-H functionalization of 2-methyl quinolines and Michael addition nitro styrenes affording alkyl aza-arenes in good yields under catalyst-free conditions using PEG-400 as an eco-friendly and recyclable media. To the best of our knowledge, there are no reports for the synthesis of alkyl aza-arenes using PEG-400 as a reaction medium under catalyst-free conditions **(Scheme 1).**

## MATERIALS AND METHODS

In general, all the reactions were clean affording the alkyl aza-arenes derivatives in high yields under the above conditions. Both electron rich and electron-deficient nitro styrene derivatives gave the desired products in good yields (Table 1). Furthermore, Methyl quinolines with nitro styrenes bearing electron releasing groups such as methoxy and methyl, gave comparatively high yield (Table 1, entries 1, 2, 6, 7, 8 and 11), whereas electron withdrawing groups like chloro and bromo gave low yield of products (Table 2, entries 4 and 9). Moreover, heterocyclic nitro styrenes (Table 1, entries 8 and 9) and 2-napthyl nitro styrene (Table 1, entry 10) 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 3g was nearly same as 3k, indicating that the nitro group on methyl quinoline had little influence on the reaction. (Table 1). The structures of all the products were determined from their spectral (IR, $^{1}$H NMR, $^{13}$C NMR and ESI-MS) data and also by direct comparison with authentic samples [6].

The generality of this reaction was investigated with substituted nitro styrene and methyl quinoline and the results are presented in Table 1. As seen in Table 1, a variety of nitro styrene underwent smooth condensation with methyl quinoline in PEG-400 at 85 $^{O}$C to provide a diversified aza-arenes derivatives (Table 1).

***General procedure***: A sealed 10 mL glass tube containing nitro styrene (1 equiv) methyl quinoline (1.5 equiv) and was taken in 5 mL polyethylene glycol-400. The resulting mixture was allowed to stir at 85 $^{o}$C for the appropriate time. After completion of the reaction, as monitored by TLC, the reaction mass was poured into water and extracted with ethyl acetate. The organic layer was removed under reduced pressure, and the crude product was purified by column chromatography to yield the desired product.

***The characteristic data of compounds are given below.***

***Compound (1).*** **2-(2-(Naphthalen-1-yl)-3-nitropropyl)-8-nitroquinoline** $^{1}$H NMR (300 MHz, $CDCl_3$): d 8.08 (d, *J* = 8.6 Hz, 1H), 7.99 (d, *J* = 7.8 Hz, 1H), 7.99 (d, *J* = 8.5 Hz, 1H), 7.77 (m,4H), 7.56 (t, J = 7.9 Hz, 1H), 7.37–7.48 (m, 3H), 7.26 (d, J = 8.5 Hz, 1H), 4.86–5.15(m, 2H), 4.43–5.12 (m, 1H), 3.44–3.66 (m, 2H); $^{13}$C NMR (75 MHz, $CDCl_3$): d161.3, 145.9, 138.9, 135.4, 136.3, 134.3, 132.9, 131.6, 128.9, 127.8, 127.7, 126.9,126.4, 126.1, 125.2, 124.8, 123.8, 123.4, 79.6, 42.9, 41.4; m/z (ESI); 388 [M+H]+.

***Compound (2).*** **2-(3-Nitro-2-p-tolylpropyl)quinoline** $^{1}$H NMR (300 MHz, $CDCl_3$): d 8.05 (dd, *J* = 8.9 Hz,*J* = 1.8 Hz, 2H), 7.67–7.79 (m, 2H), 7.48–7.55 (m, 1H), 7.26–7.35 (m, 1H), 7.06–7.19 (m, 4H), 4.69–4.88 (m, 2H), 4.15–4.26 (m, 1H), 3.35 (d, *J* = 7.9 Hz,.2H), 2.29(s, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$): d 158.5, 147.9, 137.3, 136.6, 136.5, 129.8,129.8, 128.9, 127.5, 127.5, 126.9, 126.5, 125.9, 121.9, 121.8, 79.9, 43.6, 42.5,29.5; m/z (ESI); 307 [M+H]+.

***Compound (3).*** **2-(3-Nitro-2-(thiophen-2-yl) propyl) quinoline** $^{1}$H NMR (300 MHz, $CDCl_3$): d 8.04 (t, *J* = 8.5 Hz,2H), 7.69–7.79 (m, 2H), 7.55 (t, J = 7.1 Hz, 1H), 7.14–7.22 (m, 2H), 6.87 (d, *J* = 3.4 Hz, 2H), 4.69–4.93 (m, 2H), 4.55–4.66 (m, 1H), 3.36–3.49 (m, 2H); $^{13}$CNMR (75 MHz, $CDCl_3$): d 157.9, 147.9, 142.5, 136.6, 129.8, 128.9, 127.6, 126.9,126.5, 125.6, 124.6, 121.9, 80.1, 43.9, 39.9; m/z (ESI); 299 [M+H]+.

***Compound (4).*** **2-(2-(Furan-2-yl)-3-nitropropyl)quinoline** $^{1}$H NMR (300 MHz, $CDCl_3$): d; 8.05 (d,*J* = 8.6 Hz, 2H), 7.69–7.84 (m, 2H), 7.54 (t, *J* = 7.6 Hz, 1H), 7.34–7.39 (m, 1H), 7.16(d, J = 8.3 Hz, 1H), 6.25–6.26 (m, 1H), 6.09 (d, J = 3.5 Hz, 1H), 4.75–4.86 (m, 2H),4.35–4.45 (m, 1H), 3.33–3.49 (m, 2H); $^{13}$C NMR (75 MHz, $CDCl_3$): d 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]+.

***Compound (5).*** **2-(3-Nitro-2-phenylpropyl)quinoline** $^{1}$H NMR (300 MHz, $CDCl_3$): d 8.05 (dd, *J* = 14.5 Hz, *J* = 8.5 Hz, 2H), 7.66–7.79 (m, 2H), 7.55 (t, *J* = 6.9 Hz, 1H), 7.25–7.36(m, 5H), 7.15 (d, *J* = 8.5 Hz, 1H), 4.69–4.89 (m, 2H), 4.16–4.29 (m, 1H), 3.35 (d,*J* = 7.5 Hz, 2H); $^{13}$C NMR (75 MHz, $CDCl_3$): d 158.6, 147.9, 139.5, 136.6, 129.5,128.9, 127.5, 127.5, 127.6, 126.9, 126.9, 126.5, 125.5, 121.9, 121.8, 79.6, 43.9,42.3; m/z (ESI); 293 [M+H]+.

***Compound (6).*** **12-(2-(3,4-Dimethoxyphenyl)-3-nitropropyl)quinoline**. $^{1}$H NMR(300 MHz, $CDCl_3$): d 8.03 (dd, J = 8.4 Hz, J = 2.7 Hz, 2H), 7.79 (d, J = 8.2 Hz, 1H), 7.69–7.76 (m, 1H), 7.55 (t, J = 7.9 Hz, 1H), 7.16 (d, J = 8.4 Hz, 1H), 6.79–6.84 (m,2H), 6.75 (d, J = 1.7 Hz, 1H), 4.72–4.88 (m, 2H), 4.13–4.25 (m, 1H), 3.85 (s, 3H),3.79 (s, 3H), 3.39 (d, J = 7.7 Hz, 2H); $^{13}$C NMR (75 MHz, $CDCl_3$): d 158.6, 148.9,148.3, 147.6, 136.8, 131.8, 129.5, 128.6, 127.6, 126.8, 126.5, 121.5, 119.5, 111.5,110.5, 79.8, 55.3, 43.6, 42.5, 29.6; m/z (ESI); 353 [M+H]+.

***Compound (7).*** 2-(2-(4-Methoxyphenyl)-3-nitropropyl)quinoline $^{1}$HNMR (300 MHz, $CDCl_3$):d 8.05 (d, *J* = 8.6 Hz, 1H), 7.88–7.98 (m, 1H), 7.59–7.73 (m, 2H), 7.39–7.48 (m,1H), 7.15 (d, *J* = 6.9 Hz, 2H), 6.99–7.06 (m, 1H), 6.71–

6.79 (m, 2H), 4.62–4.82 (m,2H), 4.09–4.23 (m, 1H), 3.65 (s, 3H), 3.29 (d, *J* = 6.8 Hz, 2H); $^{13}$C NMR (75 MHz,$CDCl_3$): d 158.3, 158.0, 147.5, 136.4, 130.8, 129.5, 128.6, 128.6, 127.6, 126.5,125.8, 121.5, 113.8, 79.9, 54.5, 42.8, 41.9; m/z (ESI); 323 [M+H]+.

***Compound (8).*** **2-(2-(Benzo[d][1,3]dioxol-5-yl)-3-nitropropyl)quinoline** $^1$HNMR (300 MHz, $CDCl_3$): d 8.03–8.14 (m, 2H), 7.64–7.80 (m, 2H), 7.458–7.57 (m,1H), 7.29 (d, *J* = 3.03 Hz, 1H), 7.17 (d, *J* = 8.5 Hz, 1H), 6.77 (s, 1H), 6.72 (s, 1H),5.93 (s, 2H), 4.64–4.85 (m, 2H), 4.08–4.25 (m 1H), 3.33 (d, *J* = 7.5 Hz, 2H); $^{13}$CNMR (75 MHz, $CDCl_3$): d 158.5, 147.9, 147.9, 147.6, 136.8, 129.7, 129.5, 128.6,127.5, 126.5, 125.8, 121.9, 120.9, 108.6, 107.8, 101.1, 79.9, 43.6, 42.5; m/z (ESI);307 [M+H]+.

***Compound (9).*** **2-(2-(4-Chlorophenyl)-3-nitropropyl)quinoline** $^1$H NMR (300 MHz, $CDCl_3$): d 7.99–8.12(m, 2H), 7.67–7.83 (m, 2H), 7.50 (t, *J* = 7.7 Hz, 1H), 7.09–7.36 (m, 5H), 4.66–6.89(m, 2H), 4.15–4.29 (m, 1H), 3.24–3.39 (m, 2H); $^{13}$C NMR (75 MHz, $CDCl_3$): d157.8, 147.7, 137.7, 136.8, 136.4, 129.7, 128.9, 128.8, 127.8, 127.5, 126.8, 121.9,121.7, 79.5, 42.1, 43.2; m/z (ESI); 327 [M+H]+.

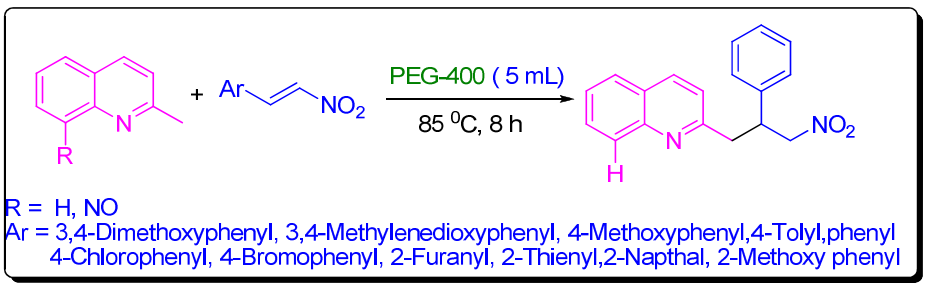
***Compound (10).*** 2-(2-(2-Methoxyphenyl)-3-nitropropyl)-8-nitroquinoline $^1$H NMR (300 MHz,$CDCl_3$): d 8.05 (d, *J* = 7.6 Hz, 1H), 7.88 (t, *J* = 8.7 Hz, 2H), 7.46 (t, *J* = 8.8 Hz, 1H),7.26 (d, J = 8.4 Hz, 1H), 7.19–7.29 (m, 2H), 6.79–6.88 (m, 2H), 4.95–5.05 (m, 2H),4.39–4.55 (m, 1H), 3.88 (s, 3H), 3.48 (d, J = 7.8 Hz, 2H); $^{13}$C NMR (75 MHz,CDCl3): d 161.9, 157.1, 147.8, 138.5, 135.9, 131.7, 129.3, 128.8, 127.7, 126.8,124.7, 123.4, 123.9, 120.4, 110.8, 77.8, 55.3, 39.7, 38.9; m/z (ESI); 368 [M+H]+.

***Compound (11).*** **2-(2-(4-Methoxyphenyl)-3-nitropropyl)-8-nitroquinoline** $^1$H NMR (300 MHz, CDCl3): d 8.09 (d,*J* = 8.5 Hz, 1H), 7.99 (t, J = 9.5 Hz, 2H), 7.59 (t, *J* = 7.9 Hz, 1H), 7.29 (d, *J* = 9.1 Hz,1H), 7.19 (d, J = 8.5 Hz, 2H), 6.86 (d, *J* = 8.6 Hz, 2H), 4.71–4.99 (m, 2H), 4.11–4.33(m, 1H), 3.78 (s, 3H), 3.30–3.49 (m, 2H); $^{13}$C NMR (75 MHz, CDCl3): d 158.8,147.9, 138.9, 136.5, 131.7, 131.3, 128.9, 128.7, 127.8, 124.9, 123.7, 114.3, 79.9,55.8, 42.5, 41.8; m/z (ESI); 368 [M+H]+.

***Compound (12).*****2-(2-(4-Bromophenyl)-3-nitropropyl)quinoline** $^1$HNMR (300 MHz, $CDCl_3$):d 8.02 (t, *J* = 8.5 Hz, 2H), 7.68–7.79 (m, 2H), 7.48–7.56 (m, 1H), 7.41 (d, J = 8.4 Hz,2H), 7.15 (dd, J = 8.5 Hz, J = 3.5 Hz, 3H), 4.68–4.89 (m, 2H), 4.19–4.29 (m, 1H),3.25–3.39 (m, 2H); $^{13}$C NMR (75 MHz, $CDCl_3$): d 157.9, 147.8, 138.5, 136.9, 135.2,135.3, 129.5, 129.2, 128.9, 127.5, 126.9, 126.5, 121.7, 121.5, 79.2, 44.0, 41.9; m/z(ESI); 373 [M+H]+.

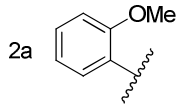
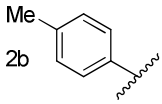
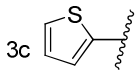
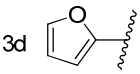
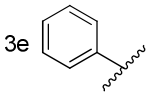
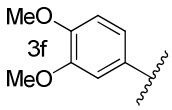
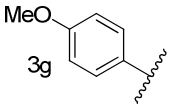
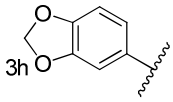
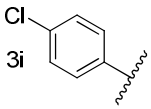
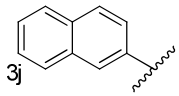
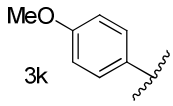
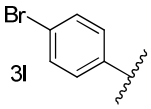
## RESULTS AND DISCUSSION

In this study, a model reaction was conducted by reacting nitro styrene (1 equiv) methyl quinoline (1.5 equiv) in water medium at room temperature to obtain the corresponding the alkyl aza-arenes derivatives in low yields (52%). The poor solubility of nitro styrene in water at elevated temperatures resulted in the formation of undesired products. When the same reaction was conducted using PEG-400 at room temperature the product was obtained in moderate yield (69%). However by a controlled experiment using PEG-400, as a recyclable media, at 85 $^0$C the product was obtained in excellent yield (89%) (Scheme 1) (Table 1)




**Scheme 1. Activation of methyl quinoline sp$^3$ C-H bond and addition to nitro styrenes**

**Table 1**

| Entry | R(1) | Ar (2) | Product | Yield (%) |
|---|---|---|---|---|
| 1 | $NO_2$ |  | 3 a | 80 |
| 2 | H |  | 3 b | 75 |
| 3 | H |  | 3 c | 85 |
| 4 | H |  | 3 d | 80 |
| 5 | H |  | 3 e | 70 |
| 6 | H |  | 3 f | 85 |
| 7 | H |  | 3 g | 80 |
| 8 | H |  | 3 h | 60 |
| 9 | H |  | 3 i | 60 |
| 10 | H |  | 3 j | 85 |
| 11 | $NO_2$ |  | 3 k | 75 |
| 12 | H |  | 3 l | 60 |

[a] *Reaction conditions: Methyl quinoline (1.5 mmol), Nitro styrene (1.0 mmol), PEG (5 mL), 85 $^0$C*
[b] *Isolated yields.*

## CONCLUSION

In conclusion, we have developed an efficient and metal-free approach for the synthesis of various alkyl aza-arenes derivatives using PEG-400 as a recyclable reaction medium without the need of any additive or acid catalyst. The mild reaction conditions, inexpensive reaction medium, operational simplicity and high yields are the advantages of this protocol.

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