PEG-400 mediated sp^3 C-H functionalization of aza-arenes: an enroute to the synthesis of 2-(2-(6-methylpyridin/quinolin-2-yl)-1-phenylethyl)malononitriles

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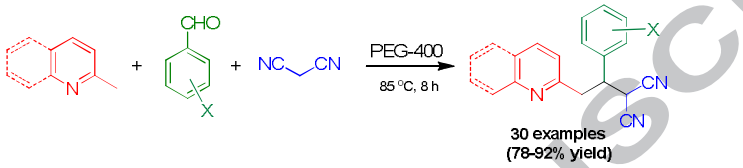
Raghu Mallepalli,[a][b] Dinesh Kumar Reddy Vennam[a][b] and Ramu Sridhar Perali *[a]



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ABSTRACT

Polyethyleneglycol (PEG-400) has been discovered to be an effective eco-friendly solvent cum activator for the one-pot coupling of 2,6-dimethyl-pyridine or 2-methylquinoline, malononitrile and aldehydes to produce aza-arene derivatives through a sp^3 bond functionalization. The reaction was performed under mild conditions and the generality of the one-pot reaction was investigated.

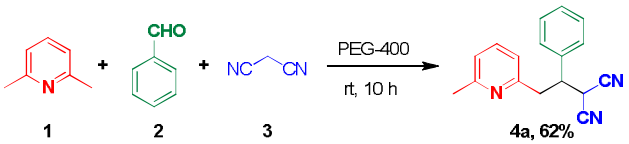
1. Introduction

Green chemistry relates to the design of a process that minimizes the use and generation of hazardous substances. Green catalysis is one of the key areas of green chemistry. In the past decade, 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.[1] In this context, PEG has become an alternative reaction media to perform organic synthesis due to its inherent advantages over toxic solvents. Furthermore, PEG has emerged as a powerful phase transfer catalyst and performs many useful organic transformations under mild reaction conditions. In addition, PEG is inexpensive, easy to handle, thermally stable, non-toxic and recyclable. In this perspective, PEG as a solvent has been played a key role in the practice of green chemistry.[2]

On the other hand, substituted pyridines or quinoline derivatives represent a significant class of nitrogen-fused heterocycles, which are ubiquitous in many natural products and biologically active compounds.[3] These compounds play an important role in drug discovery and development. Many synthetic and naturally occurring 2-substituted pyridines and quinolines have found wide applications in treating protozoal/retroviral co-infections,[4] antileishmanial agents[5] *etc*. One of the intellectual protocol for the synthesis of 2-substituted aza-arenes is through the sp^3 C-H functionalization of 2-alkyl pyridines and quinolones. This reaction is feasible particularly due to the formation of enamine by increasing the acidity of the benzylic proton using suitable metal catalyst or a Lewis acid. [6] Activated sp^3 C-H of 2-methyl pyridine and quinolones have been reacted successfully with C=O,[7] C=N[8] and N=N[9] using Lewis acid catalysis. Recently, the addition of 2-alkylaza-arenes to activated C=C has been achieved by Lewis acid catalysis.[10] However, to the best of our knowledge, a one-pot Knoevenagel condensation of active methylene compound and an aldehyde followed by the addition of sp^3 C-H bond in 2-alkylaza-arenes to give 2-substituted pyridine and quinolone derivatives is not yet reported. In continuation of our work on PEG-400 mediated transformations,[11] herein we report an efficient synthesis of 2-(2-(6-methylpyridin-2-yl)-1-phenylethyl)malononitrile derivatives, *via* a one-pot Knoevenagel condensation followed by sp^3 C-H bond addition, using polyethylene glycol as a green solvent through the condensation of 2,6-dimethylpyridine or 2-methylquinoline, malononitrile and aldehydes under catalyst-free conditions.

2. Results and discussion

PEG was shown to be a green solvent system for the condensation of aldehydes with active methylene compounds. Keeping the mild acidic characteristics of PEG and previous reports on the sp^3 C-H functionalization of 2-methyl aza-arenes by Lewis acid catalysis, we envisaged that generation of an α,β-unsaturated system *insitu* in presence of 2-methyl aza-arenes might lead to the formation of 2-substituted aza-arene derivatives. Thus, 2,6-dimethylpyridine **1** was treated with benzaldehyde **2** and malononitrile **3** in PEG-400 as a solvent system at room temperature. After stirring the reaction for 10 h followed by general workup, the product 2-substituted aza-arene derivatve, 2-(2-(6-methylpyridin-2-yl)-1-phenylethyl) malononitrile **4** was isolated in 62% yield (**Scheme 1**). Interestingly, when the reaction was conducted at 85 °C over 8 h the isolated yield was improved to 85%.

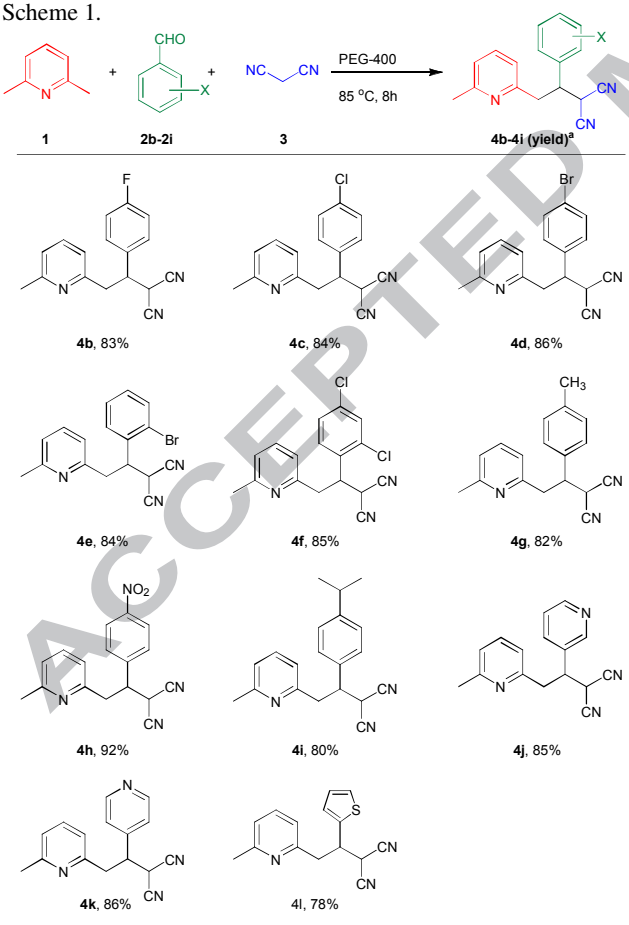


Scheme 1. One-pot synthesis of 2-substituted aza-arenes by PEG mediated Knoeveanagel condensation through sp^3 C-H functionalization reaction.

After finding the optimized reaction conditions, the generality of the reaction was evaluated by synthesizing a series of aza-arene derivatives. Thus, reactions with substituted aldehydes possessing halogens or alkyl groups proceeded smoothly to give the corresponding aza-arene derivatives in good yield (**4b**-**4g**). Interestingly, aldehydes having an electron withdrawing nitro group reacted smoothly and provided the corresponding aza-arene derivative **4h** in high yield (92%) compared to the aldehyde having an electron donating methyl (**4g**) or isopropyl (**4i**) group, which provided the aza-arene derivative in comparatively lower yield (82% and 80% respectively). Unfortunately, no reaction was observed with electron rich aldehydes like anisaldehyde *etc*. The generality of the reaction was further extended to aldehydes derived from hetero aromatic compounds. Thus, pyridine-3-carbaldehyde, pyridine-4-carbaldehyde and thiophene-2-carbaldehyde in presence of 2,6-dimethyl pyridine and malanonitrile, under the one-pot reaction conditions, provided the corresponding aza-arene derivatives **4j**, **4k** and **4l**, respectively, in good yield (table 1).

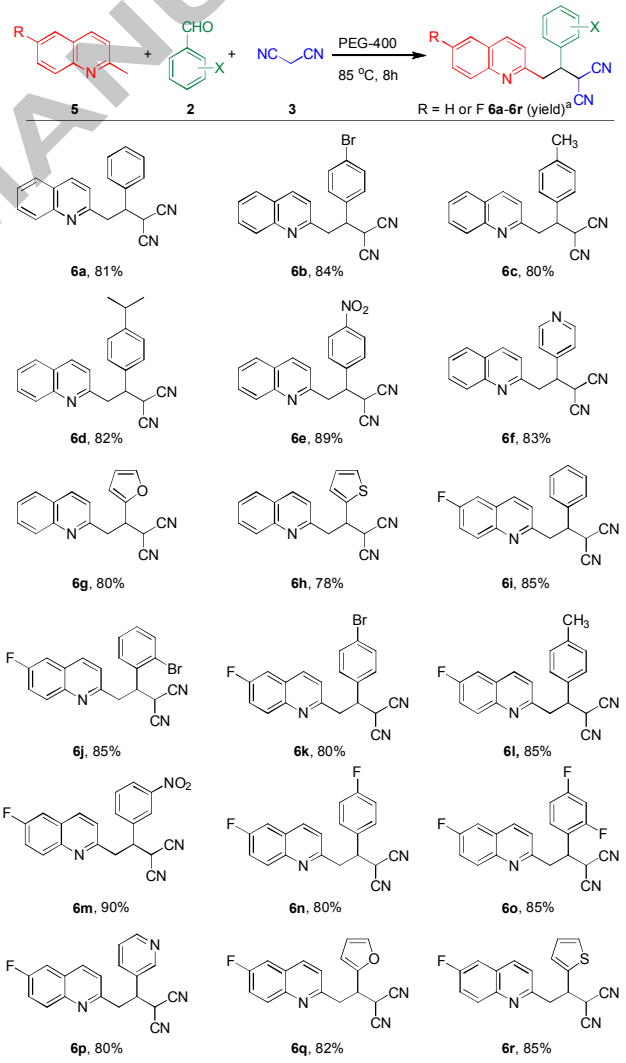
We further focused on the synthesis of quinoline derived aza-arene moieties. Towards this, 2-methylquinoline was reacted with a series of aldehydes and melanonitrile to provide the corresponding aza-arene derivatives **6a**-**6h** in 78-89% yield (Table 2). A similar kind of reactivity pattern was observed in the case of **1** with various aldehydes. In addition, another derivative of quinoline, 2-methyl-6-fluoroquinoline, was also reacted with a variety of aldehydes, possessing electron-donating and electron-withdrawing groups, providing the corresponding aza-arene derivatives **6i**-**6o**. Interestingly, the reaction also works well with heterocyclic aldehydes, pyridine 3-carbaldehyde, furfuraldehyde and thiophene 2-carbaldehyde, in presence of melanonitrile providing the aza-arene derivatives **6p**, **6q** and **6r** respectively. These results indicate that, the one-pot aza-arene synthesis is highly feasible in PEG-400 using 2-alkyl pyridine derivatives, with aryl or heteroaryl aldehydes, and melanonitrile. It is also worth to mention that, the halo substituted aza-arenes could be further functionalized by using cross coupling reactions to obtain a variety of highly substituted aza-arene moieties.

Table 1. Synthesis 2-(2-(6-methylpyridin-2-yl)-1-phenylethyl)malononitrile derivatives **4b**–**4l** produced via Scheme 1.



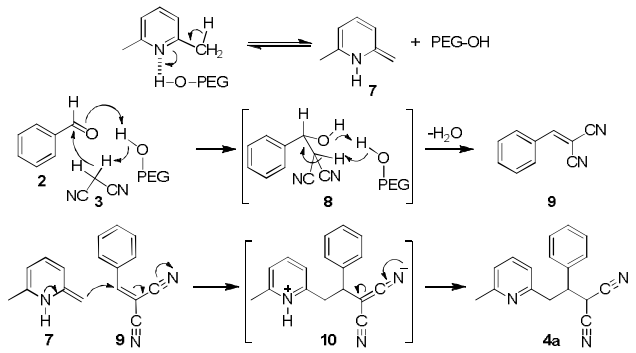
[a] Yield refers pure and isolated products.

Table 2. Synthesis of quinoline based aza-arene derivatives **6a**-**6r** produced via Scheme 1.



[a] Yield refers pure and isolated products.

A proposed mechanistic pathway for the formation of aza-arene derivatives is shown in scheme 2. One can visualize that 2,6-dimethyl pyridine will exist in an equilibrium with the corresponding enamine **7** in PEG-400 solvent probably due to the protonation of ring nitrogen. In the similar reaction conditions, PEG-400 initiated knoevenagel condensation of benzaldehyde **2** and malononitrile **3** to provide the 2-benzylidenemalononitrile **9** via the intermediate **8**. Michael addition of enamine **7** on to α,β-unsaturated compound **9** facilitates the formation of aza-arene intermediate **10** which further converts to the desired product 2-(1-phenyl-2-(pyridin-2-yl)ethyl)malononitrile **4a** (Scheme 2).



Scheme 2. Proposed mechanism for the synthesis of aza-arene derivatives.

In conclusion, an expeditious protocol for the synthesis of 2-(2-(6-methylpyridin-2-yl)-1-phenylethyl)malononitrile derivatives using PEG-400 as an eco-friendly, recyclable reaction medium is developed. Notifyingly, the reaction doesn't require any additive or acid catalyst. The mild reaction conditions, inexpensive reaction medium, operational simplicity and high yields are the main advantages of this protocol. To the best of our knowledge, the present protocol is the first report on the one-pot Knoevenagel condensation followed by sp^3 C-H functionalization for the synthesis of aza-arene derivatives.

Acknowledgments

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Supplementary Material

Supplementary data (experimental procedures, characterization of compounds, and copies of NMR spectra) associated with this article are available.

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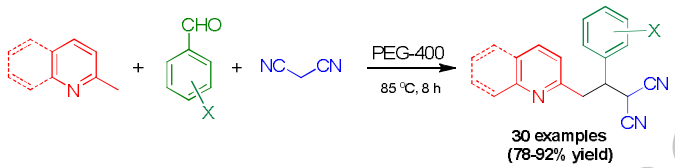

Highlights:

- A one-pot protocol for the synthesis of substituted aza-arenes is revealed.
- Functionalization of the Sp^3 C-H of 2-alkyl pyridines/quinolines is achieved
- The generality of the reaction was proved by synthesizing 30 various aza-arene motifs
- PEG-400 as an eco-friendly and recyclable reaction medium was developed
- The reaction doesn't require any additive or acid catalyst