

PEG-400 mediated and promoted eco-friendly one-pot synthesis of isoxazolyl pyridines, quinolines and 3-hydroxy-2-oxoindoles through sp^3 C-H bond functionalization of methyl aza-arenes

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Polyethylene glycol (PEG) promoted functionalization of sp^3 C-H bonds of methyl aza-arenes with 3-methyl-4-nitro-5-styrylisoxazoles for construction of isoxazolyl pyridines **3** and quinolines **5** is described. Nitrostyrylisoxazoles are proved to be good C=C electrophilic acceptors for the construction of various azaarene-containing Michael addition products. Functionalization of sp^3 C-H bonds of 3,5-dimethyl-4-nitroisoxazole is also described for synthesis of biologically active isoxazolyl 3-hydroxy-2-oxoindoles **8**.

Keywords: C-H activation, Michael addition, isoxazole, azaarene, isatin

The development of new strategies for the direct functionalization of sp^3 C-H bonds of methyl aza-arenes has become a major topic of research¹. The sp^3 C-H bond activation² adjacent to nitrogen followed by C-C bond forming reactions of aza-arenes provide³ straight forward access to useful building blocks for the design and synthesis of biologically active compounds.

To address the concerns raised by volatile organic solvents, liquid poly ethylene glycols (PEGs) have been subjected to an increasing number of scientific investigations⁴. The use of PEG as a greener alternative in the organic synthesis is advantageous over toxic organic solvents because of its low toxicity and solubility in both aqueous and non-aqueous media⁵. Meanwhile, using water as green solvent has been well documented, but the practical utilization is limited due to the hydrophobic nature of organic compounds and the sensitivity of catalysts to moisture⁶. The ILs, as another alternative reaction media instead of water and organic solvents, require tedious preparation, and their environment safety is still debatable⁷⁻¹⁰.

The functionalization of methyl pyridines and quinolines is a valuable chemical transformation in organic synthesis, since derivatives of these aromatic heterocycles can display extremely potent biological, chemical and pharmaceutical properties¹¹. Therefore, considering the value of azaarene-containing

compounds¹², it is inevitable that further studies in the search for new and simple solvent catalysed synthesis are highly desirable. Continuing our interest in the development of cheap and sustainable protocols for organic syntheses¹³, herein, we wish to report the utilization of simple solvent catalysed protocol, for the direct functionalization of sp^3 C-H bonds.

Results and Discussion

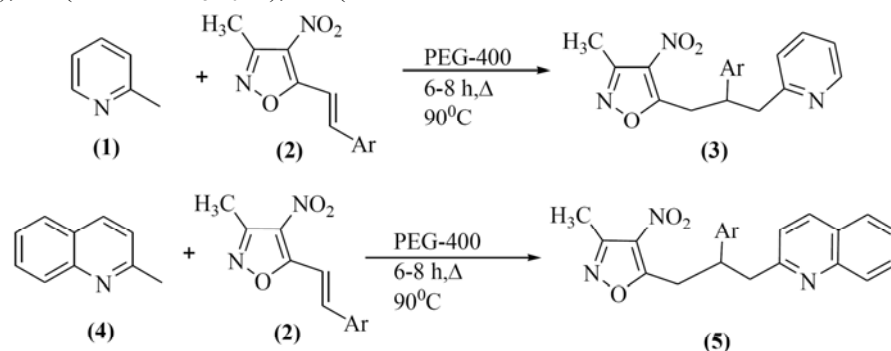
Initial studies were conducted on the reaction of 2-methyl pyridine **1**/ 2-methyl quinoline **4** and 3-methyl-4-nitro-5-styrylisoxazole **2a** in PEG-400 (10 mL) at 90°C. The reaction afforded the corresponding isoxazolyl 2-arylpropyl pridine **3a**/isoxazolyl 2-arylpropyl quinoline **5a** through sp^3 C-H bond activation followed by Michael addition. To establish the feasibility of the strategy and optimize reaction conditions, the initial reaction of methyl pyridine/ methyl quinoline **1** with nitrostyrylisoxazoles **2** was examined in different solvents such as THF, CH₃CN, DMSO, H₂O, diethylene glycol and PEG-400. Among the different solvents tested in the reaction, no product formation was observed with THF, CH₃CN solvents. Reaction in DMSO, diethylene glycol and H₂O solvents afforded low yields (20%). However, significant improvement in the reaction was observed in PEG-400, which afforded the products in excellent yields (80-90%). It may be noted that at ambient temperature the reaction produced low yield (10%).

By increasing the temperature to 90°C, the reaction afforded the good yields (80-90%). This large difference in the yields by changing the temperature clearly indicated that, the temperature plays an important role in increasing the reaction rate. Encouraged by these results, the reaction was performed in PEG-400 at 90°C for 6-8 h.

With optimized conditions in hand, we examined a variety of nitro styrylisoxazoles **2** in the reaction with azaarenes *viz.*, 2-methyl pyridine **1**/2-methyl quinoline **4**. Both electron-donating and electron-withdrawing substituents in the nitrostyrylisoxazole **2** phenyl ring are well tolerated affording the desired products in excellent yields ranging from 85% to 90%. **3b** (Ar=4-OCH₃C₆H₄), **3c** (Ar=2-OCH₃C₆H₄), **3d** (Ar=4-ClC₆H₄), **3e** (Ar=2-ClC₆H₄), **3f** (Ar=4-BrC₆H₄); **5b** (Ar=4-OCH₃C₆H₄), **5c** (Ar=2-OCH₃C₆H₄), **5d** (Ar=4-

ClC₆H₄), **5e** (Ar=2-ClC₆H₄) and **5f** (Ar=4-BrC₆H₄) (Scheme I). The structures of newly synthesized compounds **3a-f** and **5a-f** were confirmed by micro analytical and spectral data (Table I and Table II).

The recyclability of PEG-400 in the catalytic system was also evaluated for the reaction of azaarene **1** and 3-methyl-4-nitro-5-styrylisoxazole **2**. Hence, we attempted to reuse the PEG, which was one of the prime objectives in our quest. In this regard, we performed a set of experiments to explore whether PEG can be reused for further reactions. After completion of each reaction PEG was recovered and subjected to another run, affording the product in almost the same yields. This process was repeated four more times, affording the products in excellent yields (85-90%).



3 & 5 Ar

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|---|--------------------------------------|
| a) C ₆ H ₅ | d) 4-ClC ₆ H ₄ |
| b) 2-CH ₃ OC ₆ H ₄ | e) 2-ClC ₆ H ₄ |
| c) 4-CH ₃ OC ₆ H ₄ | f) 4-BrC ₆ H ₄ |

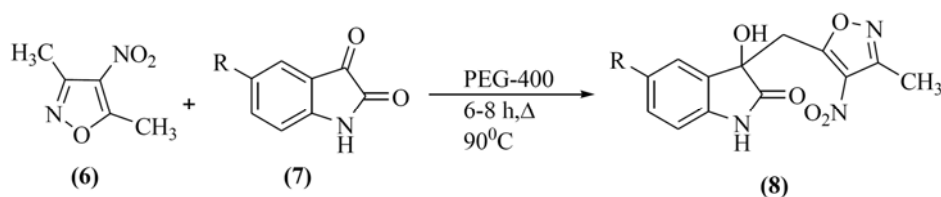
Scheme I

Table I — Characterization data of 2-[3-(3-methyl-4-nitro-5-isoxazolyl)-2-arylpropyl]pyridines **3**

Compd	Ar	m.p. (°C)	Yield (%)	Mol. Formula	Found (%) (Calcd)		
					C	H	N
3a	C ₆ H ₅	130-32	90	C ₁₈ H ₁₇ N ₃ O ₃	66.82	5.23	13.02
					(66.87)	5.26	(13.00)
3b	2-CH ₃ OC ₆ H ₄	115-17	85	C ₁₉ H ₁₉ N ₃ O ₄	64.61	5.34	11.85
					(64.58)	5.38	(11.89)
3c	4-CH ₃ OC ₆ H ₄	110-12	85	C ₁₉ H ₁₉ N ₃ O ₄	64.60	5.35	11.92
					(64.58)	5.38	(11.89)
3d	4-ClC ₆ H ₄	153-55	80	C ₁₈ H ₁₆ N ₃ O ₃ Cl	60.52	4.45	11.79
					(60.50)	4.48	(11.76)
3e	2-ClC ₆ H ₄	159-61	80	C ₁₈ H ₁₆ N ₃ O ₃ Cl	60.55	4.51	11.80
					(60.50)	4.48	(11.76)
3f	4-BrC ₆ H ₄	170-72	80	C ₁₈ H ₁₆ N ₃ O ₃ Br	53.82	3.96	10.50
					(53.86)	3.99	(10.47)

Table II — Characterization data of 2-[3-(3-methyl-4-nitro-5-isoxazolyl)-2-arylpropyl]quinolines **5**

Compd	Ar	m.p. (°C)	Yield (%)	Mol. Formula	Found (%) (Calcd)		
					C	H	N
5a	C ₆ H ₅	142-44	88	C ₂₂ H ₁₉ N ₃ O ₃	70.73 (70.77)	5.05 5.09	11.30 11.26
5b	2-CH ₃ OC ₆ H ₄	125-27	85	C ₂₃ H ₂₁ N ₃ O ₄	68.51 (68.48)	5.19 5.21	10.44 10.42
5c	4-CH ₃ OC ₆ H ₄	130-32	85	C ₂₃ H ₂₁ N ₃ O ₄	68.46 (68.48)	5.20 5.21	10.40 10.42
5d	4-ClC ₆ H ₄	164-66	82	C ₂₂ H ₁₈ N ₃ O ₃ Cl	64.85 (64.86)	4.41 4.40	10.33 10.31
5e	2-ClC ₆ H ₄	170-72	82	C ₂₂ H ₁₈ N ₃ O ₃ Cl	64.88 (64.86)	4.40 4.42	10.35 10.31
5f	4-BrC ₆ H ₄	188-90	80	C ₂₂ H ₁₈ N ₃ O ₃ Br	58.50 (58.53)	3.96 3.99	9.33 9.31

**8 R**

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| a) H | d) CH ₃ |
| b) Cl | e) OCH ₃ |
| c) Br | f) F |

Scheme II

Encouraged by the success in nitro styrylisoxazoles substrates we attempted to extend scope of functionalization of *sp*³ C-H bonds of 3,5-dimethyl-4-nitroisoxazole **7** for the synthesis of isoxazole substituted 3-hydroxy-2-oxindoles **8**. Direct addition of nucleophiles to isatins represents the most straight forward manner to construct 3-hydroxy-2-oxindoles. We initiated our endeavour by performing the reaction between 3,5-dimethyl-4-nitroisoxazole **6** and isatin **7** in the presence of PEG-400 (10 mL). After 9 h of refluxing at 90°C, 3-hydroxy-isoxazolyl-methyl-2-oxindole **8a** obtained in excellent yield (90%). Hence, delighted with the potential of PEG-400 in promoting the reaction, our attention was next focused on the reactivity of several substituted isatins. A similar range in yields was also obtained for all the employed substituted isatins (yields 83-90%). **8b** (R=Cl), **8c** (R=Br), **8d** (R=CH₃), **8e** (R=OCH₃) and **8f**

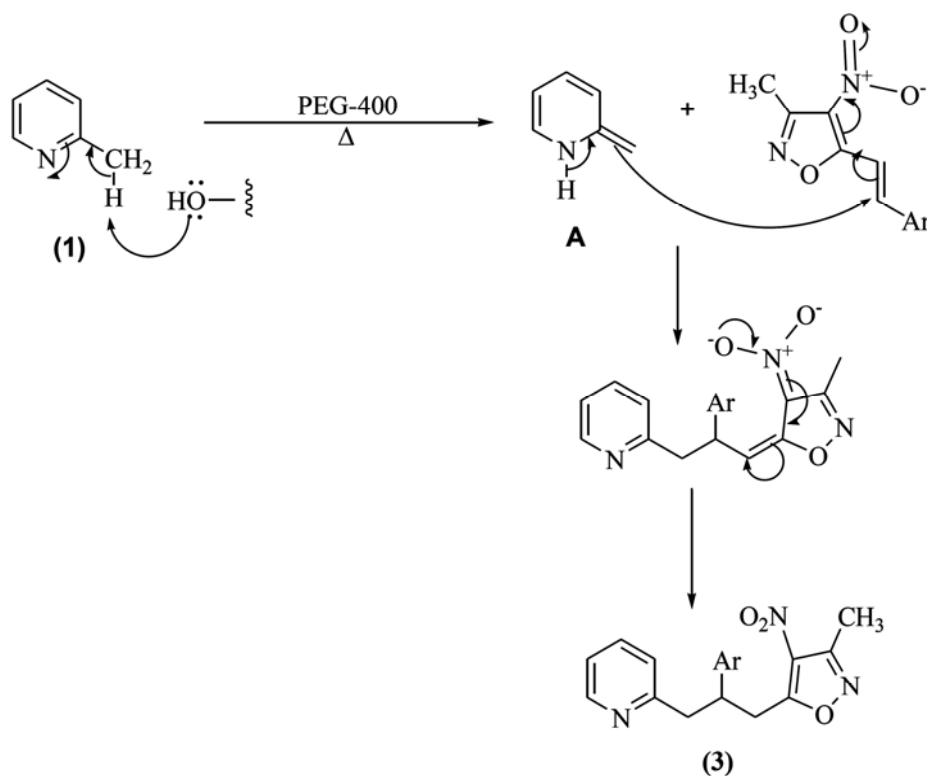
(R=F). (Scheme II). The structures of newly synthesized compounds **8a-f** have been established on the basis of micro analytical and spectral data (Table III).

The plausible mechanism for the formation of isoxazolyl pyridines/quinolines/and indoles is as follows: We believe that under heating with PEG-400, the *sp*³ C-H bond activated by hydroxyl group of PEG-400, generated enamine intermediate **A** by disruption of aromaticity of methyl pyridine **1**, methyl quinoline **4**. The Michael addition of enamine intermediate **A** to nitrostyrylisoxazole **14** would afford the addition product **3/5** (Scheme III).

Similarly, in the case of 3,5-dimethyl 4-nitroisoxazole an intermediate B is generated by disruption of aromaticity of isoxazole ring. Especially, in case of 3,5-dimethyl-4-nitroisoxazole **6**, only 5-methyl group is activated by the nitro group, which is in agreement with literature observation¹⁴. The Michael

Table III — Characterization data of 3-hydroxy-3-[(3-methyl-5-isoxazolyl)methyl]-1,3-dihydro-2H-indol-2-ones **8**

Compd	R	m.p. (°C)	Yield (%)	Mol. Formula	Found (%) (Calcd.)		
					C	H	N
8a	H	149-51	85	C ₁₃ H ₁₁ N ₃ O ₅	53.94 (53.97)	3.83 3.80	14.55 14.53
8b	Cl	168-70	80	C ₁₃ H ₁₀ N ₃ O ₅ Cl	48.31 (48.29)	3.06 3.09	13.03 13.00
8c	Br	177-79	80	C ₁₃ H ₁₀ N ₃ O ₅ Br	42.52 (42.50)	2.70 2.72	11.40 11.44
8d	CH ₃	139-41	82	C ₁₄ H ₁₃ N ₃ O ₅	55.41 (55.44)	4.32 4.29	13.85 13.86
8e	OCH ₃	156-58	82	C ₁₄ H ₁₃ N ₃ O ₆	52.62 (52.66)	4.02 4.07	13.19 13.16
8f	F	207-09	80	C ₁₃ H ₁₀ N ₃ O ₅ F	50.84 (50.81)	3.21 3.25	13.65 13.68



Scheme III

addition of intermediate **B** to isatin **7** would afford the addition product **8** (Scheme IV).

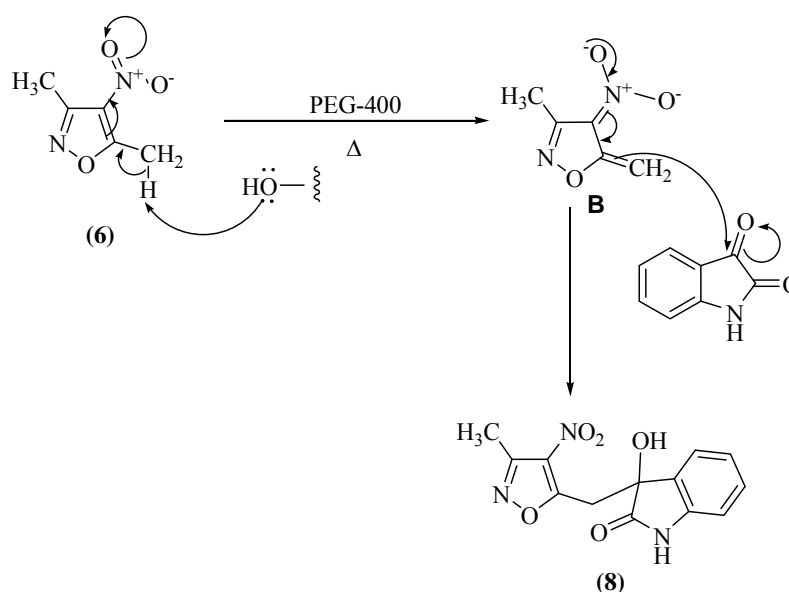
To the best of knowledge, no method has been reported till to-date for the synthesis of isoxazolyl pyridines, isoxazolyl quinolines and isoxazolyl 3-hydroxy-2-oxoindole derivatives.

This reaction is highly efficient, catalyst-free, and it is an environmentally benign synthetic methodology, and is often regarded as a goal in modern organic

synthesis for the rapid preparation of a library of isoxazolyl heterocycles, which may possess promising biological activity.

Experimental Section

All the melting points were determined on a Fisher-Johns melting point apparatus and are uncorrected. Analytical TLC was performed on Merck precoated 60 F₂₅₄ silica gel plates. Visualization was carried out by exposure to iodine vapour. IR spectra (KBr pellet)



Scheme IV

were recorded on a Perkin-Elmer BX series FT-IR spectrometer. ^1H NMR spectra were recorded on a Varian Gemini 300 MHz spectrometer. ^{13}C NMR spectra were recorded on a Bruker 75 MHz spectrometer. Chemical shift values are given in δ (ppm) with tetramethyl silane as an internal standard. ESI Mass spectra were recorded on a Agilent LC-MSD mass spectrometer. Elemental analyses were performed on a Carlo Erba 106 and Perkin-Elmer model 240 analyzers.

General procedure for PEG-400 mediated synthesis of new isoxazolyl-2-arylpropyl pyridines (3) /isoxazolyl-2-arylpropyl quinolines (5) by functionalization of sp^3 C-H bond

To methyl pyridine **1a** (1 mmol)/ methyl quinoline **1b** (1 mmol) in PEG-400 (10 mL), 3-methyl-4-nitro-5-styrylisoxazole **2** (1 mmol) was added and the contents are refluxed with stirring at 90°C for 8 h. After completion of the reaction, as was indicated by TLC, ether (10 mL) was added, and the reaction mixture was stirred for 2 min, and allowed to settle for 5 min. Cooling in an acetone dry ice-bath caused solidification of solvent medium. This allowed us to decant the ether layer. The sequence was repeated twice with 10 mL portion of ether, the combined ether layers were concentrated under reduced pressure, and the resulting crude product was purified by silica gel column chromatography. The product was eluted with ethyl acetate and hexane (2:1) to afford the pure product **3**.

Spectral data of compounds **3** and **5**

3a: IR (KBr): 1390, 1575 (NO_2) cm^{-1} ; ^1H NMR (300 MHz, CDCl_3): δ 2.20 (s, 3H, CH_3), 3.58 (dd, 2H, CH_2 , $J = 14.8$ Hz), 4.05 (m, 1H, Ar-H), 4.67 (dd, 2H, CH_2 , $J = 15.2$ Hz), 6.66-7.54 (m, 9H, Ar-H & pyridine-H); ^{13}C NMR (75 MHz, CDCl_3): δ 11.10, 33.37, 41.05, 64.55, 109.87, 125.10, 126.87, 127.35, 127.81, 130.35, 130.88, 136.42, 136.66, 137.70, 147.72, 155.20, 156.80, 157.82; ESI-MS: m/z 324 $[\text{M}+\text{H}]^+$.

3b: IR (KBr): 1380, 1595 (NO_2) cm^{-1} ; ^1H NMR (300 MHz, CDCl_3): δ 2.25 (s, 3H, CH_3), 3.62 (dd, 2H, CH_2 , $J = 14.8$ Hz), 3.80 (s, 3H, OCH_3), 4.15 (m, 1H, Ar-H), 4.68 (dd, 2H, CH_2 , $J = 15.2$ Hz), 6.75-8.00 (m, 8H, Ar-H & pyridine-H); ^{13}C NMR (75 MHz, CDCl_3): δ 11.82, 33.35, 42.05, 58.64, 65.05, 110.00, 124.25, 126.86, 127.30, 127.80, 130.65, 131.05, 136.62, 137.50, 138.80, 147.52, 156.10, 156.95, 158.60; ESI-MS: m/z 354 $[\text{M}+\text{H}]^+$.

5a: IR (KBr): 1362, 1556 (NO_2) cm^{-1} ; ^1H NMR (300 MHz, CDCl_3): δ 2.22 (s, 3H, CH_3), 3.66 (dd, 2H, CH_2 , $J = 14.8$ Hz), 4.11 (m, 1H, Ar-H), 4.65 (dd, 2H, CH_2 , $J = 15.4$ Hz), 6.75-7.50 (m, 11H, Ar-H & quinoline-H); ^{13}C NMR (75 MHz, CDCl_3): δ 12.00, 32.90, 42.50, 63.75, 109.88, 125.22, 126.86, 127.70, 127.92, 128.55, 130.35, 131.33, 136.42, 137.75, 138.85, 140.25, 147.92, 152.25, 156.25, 158.82, 159.00; ESI-MS: m/z 374 $[\text{M}+\text{H}]^+$.

5b: IR (KBr): 1345, 15940 (NO_2) cm^{-1} ; ^1H NMR (300 MHz, CDCl_3): δ 2.25 (s, 3H, CH_3), 3.65 (dd, 2H, CH_2 , $J = 14.8$ Hz), 3.75 (s, 3H, OCH_3), 4.10 (m, 1H,

Ar-H), 4.55 (dd, 2H, CH₂, $J = 15.4$ Hz), 6.66-8.15 (m, 10H, Ar-H & quinoline-H); ¹³C NMR (75 MHz, CDCl₃): δ 11.85, 33.15, 42.50, 62.50, 63.66, 109.75, 123.25, 125.96, 127.00, 127.85, 128.23, 130.12, 132.22, 135.85, 136.50, 137.82, 138.66, 140.25, 146.88, 151.23, 156.25, 157.95, 158.88; ESI-MS: m/z 404 [M+H]⁺.

General procedure for PEG-400 mediated synthesis of new 3-hydroxy-3-isoxazolylmethyl-2-oxoindoles (8) by functionalization of sp^3 C-H bond

To 3,5-dimethyl-4-nitroisoxazole **6** (1 mmol) in PEG-400 (10 mL), isatin **7** (1 mmol) was added and the contents are refluxed with stirring at 90°C for 9 h. After completion of the reaction, as was indicated by TLC, ether (10 mL) was added, and the reaction mixture was stirred for 2 min, and allowed to settle for 5 min. Cooling in an acetone dry ice-bath caused solidification of solvent medium. This allowed us to decant the ether layer. The sequence was repeated twice with 10 mL portion of ether, the combined ether layers were concentrated under reduced pressure, and the resulting crude product was purified by silica gel column chromatography. The product was eluted with ethyl acetate and hexane (2:1) to afford the pure product **6**.

8a: IR (KBr): 1362, 1556 (NO₂), 1680(C=O), 3280 (NH), 3315 (OH) cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 2.25 (s, 3H, CH₃), 2.98 (d, 1H, $J = 14.0$ Hz), 3.06 (d, 1H, $J = 14.0$ Hz), 5.14 (s, 1H, OH, D₂O exchangeable), 6.66-6.98 (m, 4H, Ar-H), 8.50 (s, 1H, NH, D₂O exchangeable); ¹³C NMR (75 MHz, CDCl₃): δ 12.05, 22.90, 42.42, 76.23, 109.72, 120.33, 123.65, 125.02, 127.44, 131.90, 155.66, 158.20, 176.80; ESI-MS: m/z 290 [M+H]⁺.

8b: IR (KBr): 1352, 1546 (NO₂), 1685(C=O), 3290 (NH), 3320 (OH) cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 2.20 (s, 3H, CH₃), 3.08 (d, 1H, $J = 14.0$ Hz), 3.36 (d, 1H, $J = 14.0$ Hz), 5.20 (s, 1H, OH, D₂O exchangeable), 6.75-7.22 (m, 3H, Ar-H), 8.05 (s, 1H, NH, D₂O exchangeable); ¹³C NMR (75 MHz, CDCl₃): δ 11.90, 22.85, 42.50, 65.60, 109.82, 121.35, 123.55, 125.08, 127.85, 132.05, 156.67, 158.66, 178.40; ESI-MS: m/z 324 [M+H]⁺.

Conclusion

In conclusion, we report the first PEG-400 catalysed sp^3 C-H bond functionalization of 2-methyl azaarenes to polar C=C bonds of nitro styrylisoxazoles under eco-friendly conditions. Various substituted nitro styrylisoxazoles were utilized to afford desired azaarene- containing Michael addition products in 90%

yields. In addition, with the eco-friendly PEG-400 as catalyst sp^3 C-H functionalization of 3,5-dimethyl-4-nitroisoxazole for the construction of substituted 3-hydroxy-2-oxoindoles was successfully demonstrated. The success of this reaction should broaden the synthetic utility of 3,5-dimethyl-4-nitroisoxazole and PEG-400 as catalyst in the functionalization of sp^3 C-H bonds in organic synthesis.

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