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Catalyst-free aqueous-mediated conjugative addition of indoles to β-nitrostyrenes

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ABSTRACT

A catalyst free aqueous-mediated alkylation of indoles with various β-nitrostyrenes was performed at elevated temperature. No catalyst, clean reaction conditions, simple workup procedure, easy isolation, viability for large scale preparation, and environmentally acceptable medium are the best features in this process.

The use of water as a green media for organic synthesis has become an important research area. Other than the economical and environmental benefits, water also exhibits unique physical and chemical properties which lead to unique reactivity and selectivity in comparison with organic solvents. Thus, the development of organic reaction in water medium is necessitating in the present days.[1] Indole and many of its derivatives are widely distributed in the nature, which possesses biological and pharmacological activity.[2] For instance, the hapalindole alkaloids, which exhibit significant antibacterial and antimycotic activity, and several indole alkaloids such as uleine, aspidospermidine, ibophyllidine alkaloids, and numerous tryptamine derivatives are also associated with important biological activity.[3] Therefore, the development of new strategies to synthesize indole derivatives has been the subject of interest in the present days. Michael addition is one of the most important tools for the synthesis of 3-substituted indole derivatives.[4] Nitroalkenes are strong Michael acceptors, and Michael adducts of nitroalkenes can be readily transformed into different functionalities.[4]

Owing to the importance of this transformation, several procedures have been reported in literature using acid catalysts.[5] A wide variety of Lewis acids such as $Yb(OTf)_3$,[6a] $InCl_3$,[6b] $InBr_3$,[6c] $Yb(OTf)_3$ in $ScCO_2$,[6d] SmI_3,[6e] $CeCl_3{\cdot}7H_2O$–NaI–SiO_2,[6f] and iodine[6g] were used for this purpose. Other catalysts such as $[Al(DS)_3]{\cdot}3H_2O$,[6h] heteropolyacids,[6i] and basic alumina[6j] were also used for this reaction. Very recently, sulfamic acid[6k] and carbohydrate-based tolylsulfonyl hydrazines[6l] were reported as catalysts for this transformation. Chiral version of this reaction was also reported using various chiral catalysts.[7]

Although metal salts, triflates, and other acidic catalysts are effective for the Friedel–Crafts alkylation reaction, their use is limited. The strong acidic character of triflates results in side reactions and toxicity of metal salts makes methods less attractive. The drawbacks associated with some of the procedures reported in literature are the use of hazardous catalysts, tedious workup procedures, and difficulties in product isolation. The most important drawback is the tendency of electron-rich hetero aromatics to undergo polymerization in the presence of acid catalyst. In this context, the search for achieving a general and environmental accessible method for conjugative addition of indoles to β-nitrostyrene remains in great demand. Hence, we reveal a new, mild, and easy procedure for conjugative addition of indole to β-nitrostyrenes in aqueous medium without any catalyst.

Conjugative addition of indoles to β-nitroalkenes in presence of acid catalyst in aqueous medium has been reported in literature.[6c,6h,6i,6k] It was observed that the reaction of β-nitrostyrene with indole under catalyst-free conditions, in aqueous medium, resulted in 28% of product formation. However, upon addition of the surfactant (SDS) did not show any improvement in the reaction.[6h] Recently, Kusurkar group have described catalyst-free Michael addition of β-nitrostyrene with indole at 120–140 °C in benzene in 48 h.[8] It has been proven that water acts as an acid at elevated temperature in different reactions.[9] Recently, many of the acid-catalyzed reactions were carried out successfully without any catalyst in aqueous medium.[10] Based on the above reports, we assume that the reaction of β-nitrostyrene with indole could work in water without any catalyst under thermal conditions.

In our initial efforts, we observed that the reaction of β-nitrostyrene **1** (2 mmol) with indole (2.4 mmol) in water (5 ml) without any catalyst, ca. 30% of the product was formed after 24 h at room temperature. When the reaction was conducted at 50–60 °C, the reaction proceeded to near completion in 20 h. However, upon further increasing the temperature to 100 °C, the reaction was completed in 6 h. With this preliminary success, further we focused our attention to extend the scope of the reaction by choosing wide varieties of indoles and β-nitrostyrenes. This synthetic approach allows the facile introduction of 2-nitroethyl-functionalized

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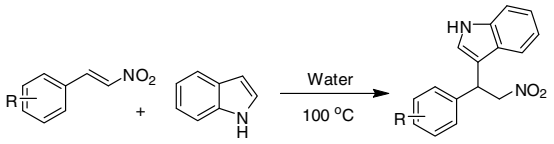
substituents into the 3-position of indole nucleus, possibly serving as a source for the corresponding amino-based building blocks for the construction of biomolecules.[11]

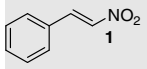
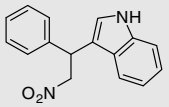
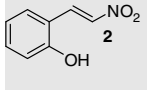
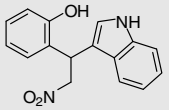
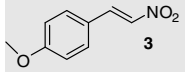
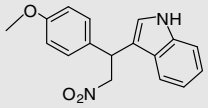
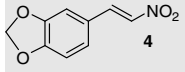
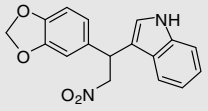
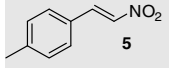
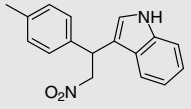
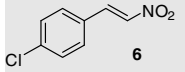
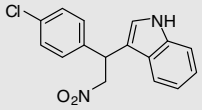
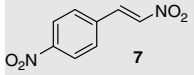
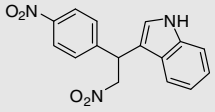
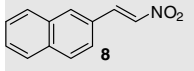
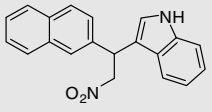
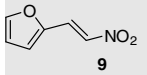
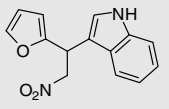
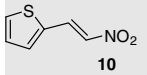
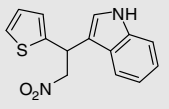
The reaction time varied according to the nature of the substituent on the β-nitrostyrene. For example, β-nitrostyrene possessing strong electron-releasing group (OMe) such as 4-methoxy-(β-nitrostyrene) (**3**) and 3,4-methyleneoxy-(β-nitrostyrene) (**4**) underwent slow reaction (12 h and 10 h) to obtain their corresponding adducts (**3a** and **4a**), respectively. Similar trend was observed in case of 4-methyl-(β-nitrostyrene) (**5**). Whereas β-nitrostyrenes bearing electron-withdrawing groups (Cl, NO_2), such as 4-chloro (β-nitrostyrene) (**6**) and 4-nitro-(β-nitrostyrene) (**7**), proceed smoothly in short reaction times (6 h and 4 h) to their corresponding indole adducts. Moreover, sterically hindered naphthyl nitroalkene (**8**) reacted with indole to afford the product (**8a**) in good yield. It's important to note that the acid-sensitive moieties such as furan (**9**) and thiophene (**10**) survived under the present reaction conditions (Table 1).

The electronic density of the indole ring would also play an important role in this reaction. The electron-rich indole such as 5-methoxy indole alkylated with β-nitrostyrene in shorter time to obtained (**1e**) in high yield. The reaction of *N*-methylindole with β-nitrostyrene underwent smoothly to furnish the product (**1c**) in high yield. This may be due to the presence of electron-releasing methyl group which activates the indole ring towards the nucleophilic attack. It was observed that increasing the size of the substituent close to the reaction center, as in case of 2-methyl indole and 2-phenyl indole, also added to β-nitrostyrene without any difficulty, which cannot be attained in basic conditions.[6j] However, electron-withdrawing group (Br) bearing indole such as 5-bromo indole took longer reaction period to obtain good yield of product (**1f**). The results are summarized in Table 2.

The most important feature of this method is dialkylation of 1,4-bis-(2-nitrovinyl)benzene with substituted indoles. Under the

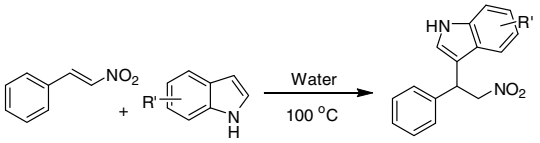
Table 1
Reaction of various β-nitrostyrenes with indoles in water[12]

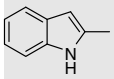
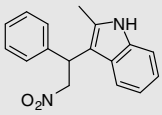
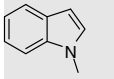
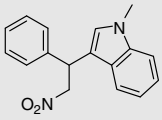
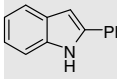
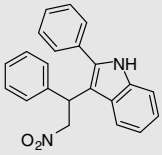
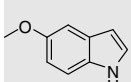
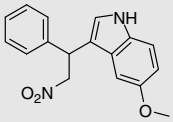
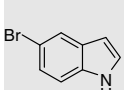
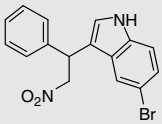


Substrate[a]	Product[b]		Time (h)	Yield[c] (%)
		**1a**	5	85
		**2a**	6	69
		**3a**	12	76
		**4a**	10	64
		**5a**	8	81
		**6a**	6	80
		**7a**	4	78
		**8a**	10	70
		**9a**	5	68
		**10a**	9	65

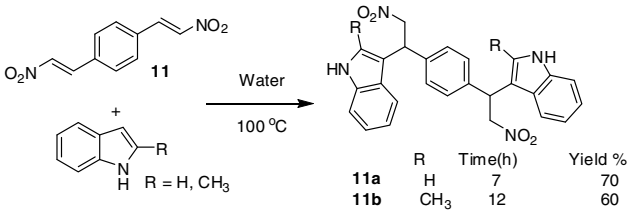
[a] All reactions were performed at 2 mmol scale.
[b] All products were well characterized by ^{1}H NMR, ^{13}C NMR, and mass spectroscopy.[13]
[c] Isolated yields.

Table 2
Reaction of β-nitrostyrene with various indoles in water[12]

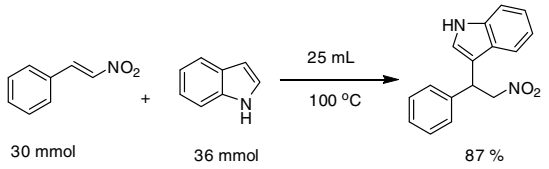


Substrate[a]	Product[b]		Time (h)	Yield[c] (%)
		**1b**	6	80
		**1c**	6	82
		**1d**	8	78
		**1e**	5	83
		**1f**	15	73

[a] All reactions were performed at 2 mmol scale.
[b] All products were well characterized by ^{1}H NMR, ^{13}C NMR, and mass spectroscopy.[13]
[c] Isolated yields.



Scheme 1. Reaction of 1,4-bis-(2-nitrovinyl)benzene with various indoles.



Scheme 2. Large-scale reaction of β-nitrostyrenes with indole.

present reaction conditions, various indoles reacted with 1,4-bis-(2-nitrovinyl)benzene to give moderate yields of bis-indolyl adducts (Scheme 1).

In order to extend the scope of the methodology, we carried out the reaction in large scale by taking 30 mmol of nitrostyrene and 36 mmol of indole in 25 ml water at 100 °C. The reaction proceeded without any difficulty to obtain high yield of product (Scheme 2).

In conclusion, we have achieved an un-catalyzed Friedel–Craft's alkylation of indole with β-nitrostyrenes in water. The procedure is entirely green, and applied for structurally diverse indoles as well as for β-nitrostyrenes to obtained good yields. Simple reaction conditions, easy isolation of the products, use of green solvent and viability for the large-scale preparation are the advantages of the present method over the reported procedures. Hence, this method is not only representing green alternatives to the literature procedures but also would find practical use in the construction of 3-substituted indole derivatives.

Acknowledgments

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12. *Typical experimental procedure*: A mixture of indole (1.2 mmol) and β-nitrostyrene (1 mmol) was suspended in 2 mL of water, and the reaction mixture was heated at 100 °C. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was extracted with ethyl acetate (2 × 10 mL). The organic layer was separated, dried over anhydrous sodium sulfate, and concentrated to obtain crude product. Further purification was achieved by column chromatography using EA/hexane as eluent.
13. Spectral data: **1a**,[6f,6g,6i,6k] **3a**,[6e,6g,6i] **4a**,[6g], **6a**,[6g,8] **9a**,[6g,6k,8] **10a**,[6g,8] **1b**,[6g,6i] **1c**,[6g,6i,6k] **1e**,[6f,6i] **1f**,[6k] and **11a**[6k] are known compounds. *2-(1-(1H-Indol-3-yl)-2-nitroethyl) phenol* (**2a**): colorless solid, mp 72–74 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.10 (br s, 1H), 7.48 (d, J = 7.8 Hz, 1H), 7.33 (d, J = 8.0 Hz, 1H), 7.18–7.06 (m, 5H), 6.84 (t, J = 8.0 Hz, 1H), 6.76 (d, J = 8.0 Hz, 1H), 5.48 (t, J = 7.8 Hz, 1H), 5.34 (br s, 1H), 5.12–5.00 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 154.3, 136.6, 129.3, 128.7, 126.6, 125.7, 122.6, 122.3, 120.6, 119.8, 119.2, 116.2, 113.8, 111.5, 78.2, 36.3. Ms (m/z) (relative intensity) 282(M^+, 30), 235(12), 234(18), 220(100), 204(12), 165(12), 143(12), 130(12), 117(24), 91(12), 77.1(10). HRMS: calcd for $C_{16}H_{14}N_2O_3$: calcd 282.0999 found 282.1000. *3-(2-Nitro-1-p-tolylethyl)-1H-indole* (**5a**): viscous liquid ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.06 (br s, 1H), 7.43 (d, J = 8.0 Hz, 1H), 7.32 (d, J = 8.0 Hz, 1H), 7.16–7.25 (m, 3H), 7.11 (d, J = 8.0 Hz, 2H), 7.06 (t, J = 7.6 Hz, 1H), 7.00 (d, J = 1.8 Hz,1H), 5.14 (t, J = 8.0 Hz, 1H), 5.01–5.07 (m, 1H), 4.88–4.93 (m, 1H), 2.3 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 137.4, 136.7, 136.4, 129.8, 127.8, 126.3, 122.8, 121.7, 120.1, 119.2, 114.8, 111.5, 79.8, 41.4, 21.2. MS m/z (relative intensity) 280(M^+, 63), 233(100), 235(12), 220(80), 218(48), 204(15), 132(18), 115(20), 108(24), 89(9). HRMS: calcd for $C_{17}H_{16}N_2O_2$: calcd 280.1206 found 280.1210. *3-(1-(4-Nitrophenyl)-2-nitroethyl)-1H-indole* (**7a**): colorless solid; mp 145–147 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.22 (br s, 1H), 8.18 (d, J = 8.8 Hz, 2H), 7.52 (d, J = 8.4 Hz, 2H), 7.37 (t, J = 7.8 Hz, 2H), 7.22 (t, J = 8.0 Hz, 1H), 7.09 (t, J = 7.6 Hz, 1H), 7.05 (s, 1H), 5.30 (t, J = 8.0 Hz, 1H), 5.08–5.13 (m, 1H), 4.95–5.02 (m, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 147.6, 146.9, 136.7, 128.9, 125.8, 124.4, 123.3, 121.8, 120.5, 118.7, 113.2, 111.8, 78.9, 41.4. MS m/z (relative intensity): 311(M^+, 44), 264(100), 218(28), 204(16), 143(4), 108(12). HRMS: calcd for $C_{16}H_{13}N_3O_4$: calcd 311.0901 found 311.0896. *3-(1-(Naphthalen-2-yl)-2-nitroethyl)-1H-indole* (**8a**): colorless solid; mp 140–142 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.27 (d, J = 8.4 Hz, 1H), 8.04 (br s, 1H), 7.88 (d, J = 8.0 Hz, 1H), 7.78 (t, J = 4.8 Hz, 1H), 7.57–7.50 (m, 2H), 7.43 (d, J = 8.0 Hz, 1H), 7.38–7.33 (m, 3H), 7.19 (t, J = 8.0 Hz, 1H), 7.05 (t, J = 8.0 Hz, 1H), 6.99 (d, J = 2.0 Hz, 1H), 6.07 (t, J = 7.8 Hz, 1H), 5.06–5.11 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 136.6, 134.6, 134.2, 131.1, 129.2, 128.3, 126.8, 126.1, 125.9, 125.3, 124.6, 122.7, 122.6, 122.5, 120.0, 118.8, 114.3, 111.4, 78.5, 36.9. MS m/z (relative intensity): 316(M^+,40), 269(76), 268(100), 254(57), 241(18), 226(9), 153.1(78), 115(28), 89.(9). HRMS: calcd for $C_{20}H_{16}N_2O_2$: calcd 316.1206 found 316.1213. *3-(2-Nitro-1-phenylethyl)-2-phenyl-1H-indole* (**1d**): colorless solid; mp 143–145 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.14 (br s, 1H), 7.52 (d, J = 7.6 Hz, 1H), 7.43 (br s, 5H), 7.38–7.26 (m, 5H), 7.28–7.17 (m, 2H), 7.1 (t, J = 7.4 Hz, 1H), 5.31 (t, J = 8.0 Hz, 1H), 5.09–5.20 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 140.1, 137.1, 136.3, 132.4, 129.1, 129.0, 128.9, 128.8, 127.7, 127.4, 122.7, 120.5, 120.1, 111.6, 109.8, 79.3, 40.9. MS m/z (relative intensity): 342(M^+, 96), 296(18), 294(90), 282(50), 280(18), 218(60), 207(100), 165 (16), 139(14), 103(12), 77(18). HRMS: calcd for $C_{22}H_{18}N_2O_2$: calcd 342.1363 found 342.1366. *1,4-Bis(1-(2-methyl-1H-indol-3-yl)-2-nitroethyl) benzene* (**11b**): colorless solid mp 238–240 °C. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 10.9 (br s, 2H), 7.44 (d, J = 8.0 Hz, 2H), 7.30 (s, 4H), 7.22 (d, J = 8. Hz, 2H), 6.95 (t, J = 7.6 Hz, 2H), 6.84 (t, J = 7.6 Hz 2H), 5.47–5.42 (m, 2H) 5.25–5.31 (m, 2H), 4.97–5.10 (m, 2H), 2.39 (s, 6H). ^{13}C NMR (DMSO-d_6, 100 MHz): δ 138.9, 135.5, 133.2, 127.6, 126.5, 120.3, 118.7, 118.5, 110.9, 108.2, 78.2, 11.7. MS m/z (relative intensity): 482(M^+, 12), 422(9), 374(16), 216(6), 187(6), 143(100), 129(30). HRMS: calcd for $C_{28}H_{26}N_4O_4$: calcd 482.1954. found 482.1949.