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ARTICLE

Catalyst-free dehydrative S_N1-type reaction of indolyl alcohols with diverse nucleophiles “on water”

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A green and efficient dehydrative S_N1-type reaction of indolyl alcohols with diverse nucleophiles was developed using water as solvent, affording versatile 3-indolyl derivatives in high yields. The advantage of catalyst-free, environmental benignity, wide substrate scope and easy workup render it promising methods for preparation of indolyl compounds.

Introduction

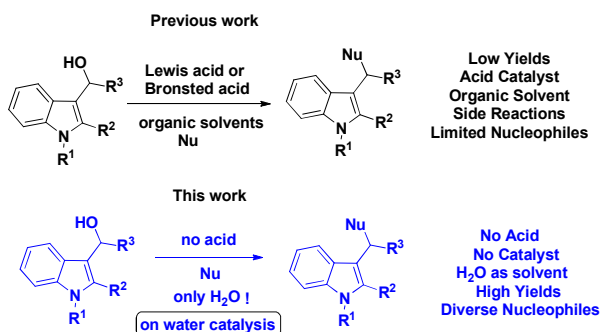
Water is a nontoxic, non-flammable and green solvent, featuring unique physical and chemical properties such as high dielectric constant, amphoteric nature and strong ability to form hydrogen bonds.¹ Nature does not only carry out the syntheses in water but also use water as an electron transport, which has been exemplified by many biological and synthetic reactions.² The unique properties of water render it highly appealing for biomimetic chemistry and organic chemistry such as new reactivity and selectivity and protecting-group free synthesis. Water as a solvent to implement organic transformations has been largely explored in the last twenty years due to its fascinating advantages over traditional organic solvents, such as the relative abundance, low cost, inherent safety and environmental benignity.³ The pioneering works of Breslow⁴ and Sharpless,⁵ demonstrated the rate enhancements “on water” by hydrophobic effects, inspiring intense research “on water” catalysis and green protocols for synthesis of highly functionalized and biologically important compounds. Despite the great achievements, most of the organic transformations in organic solvents are incompatible with water since most of organic compounds do not dissolve in water while solubility is generally considered a prerequisite for reactivity.

The direct dehydrative coupling of plentifully available alcohols with nucleophiles represents an important methodology towards green synthesis of valuable compounds as water is the only by-product.⁶ In sharp contrast to the large amount of literatures on Lewis acid or Bronsted acid catalyzed nucleophilic substitution of alcohols in organic solvents,⁶ this type of reaction “in water” or “on water” was sporadic. In 2007, Kobayashi disclosed the first example of dehydrative coupling of benzylic alcohols with carbon nucleophiles in water,⁷ in which the surfactant-type dodecylbenzenesulfonic acid (DBSA) was necessary for success of the reaction. Similarly, another recyclable surfactant-type Brønsted

acid catalyst calix[n]arene-SO₃H was also reported for reaction of benzylic or allylic alcohols with arenes.⁸ Later on, the direct substitution of ferrocenyl alcohols “on water” was presented and the substrate scope was further expanded to other alcohols and nucleophiles.⁹ Recently, hydrothermal water conditions (220 °C) was also developed for Friedel–Crafts reaction with benzyl and allylic alcohols.¹⁰ However, in all these reactions, alcohols and nucleophiles are always limited, which is far from the demand of diversity-oriented target synthesis. Therefore, it highly desirable to explore new application of “on water” catalysis for construction of highly functionalized and biologically important compounds.

The indole skeleton is ubiquitous in a plethora of naturally occurring compounds, drugs, agrochemicals and materials.¹¹ Consequently, intensive research has been involved in synthesis and functionalization of this fascinating heterocyclic system for further applications. Recently, indolyl alcohols stand up as an easily accessible electrophiles for functionalization of indoles.¹² However, the reported indolyl alcohols involved transformations always employ Bronsted acids or Lewis acids as necessary catalysts. In these reactions, alkylideneindoleninium ion intermediates were *in situ* generated from 3-indolylmethanols in the presence of acids, which can be trapped by various nucleophiles. However, undesired reactions always occur and nucleophiles were limited to acid-insensitive substrates. Moreover, acids catalysts, especially for Lewis acids catalysts, are environmentally harmful and troublesome during working up. To circumvent these drawbacks, catalyst free, green and mild conditions is highly desirable for diversity-oriented synthesis. During our effort to develop water-based reactions and S_N1-type reaction of alcohols,¹³ it was found that water can serve as a weak acid to facilitate a number of organic reactions with alcohols. As a consequence of that, we envisage that water might form the alkylideneindoleninium ion through the hydrogen bonding interaction with 3-indolylmethanols. Herein,

we reported the first dehydrative S_N1 -type reaction of 3-indolylmethanols with diverse nucleophiles “on water”, addressing the current challenges for functionalization of indoles (Scheme 1). This protocol offers a green and efficient manner for synthesis of a variety of 3-indolyl derivatives.



Scheme 1. Reaction of 3-indolylmethanol with nucleophiles.

Results and discussion

At the outset, 3-indolylmethanol **1a** and indole **2a** were selected as model substrates to investigate the feasibility of this reaction. Different solvents were tested at room temperature, surprisingly, the desired product **3a** could be obtained in both protonic solvent and aprotic solvent (Table 1, entries 1-3). However, this reaction did not proceed in dioxane and acetonitrile (Table 1, entries 4-5). This reaction can be

Table 1. The examination of solvents^a

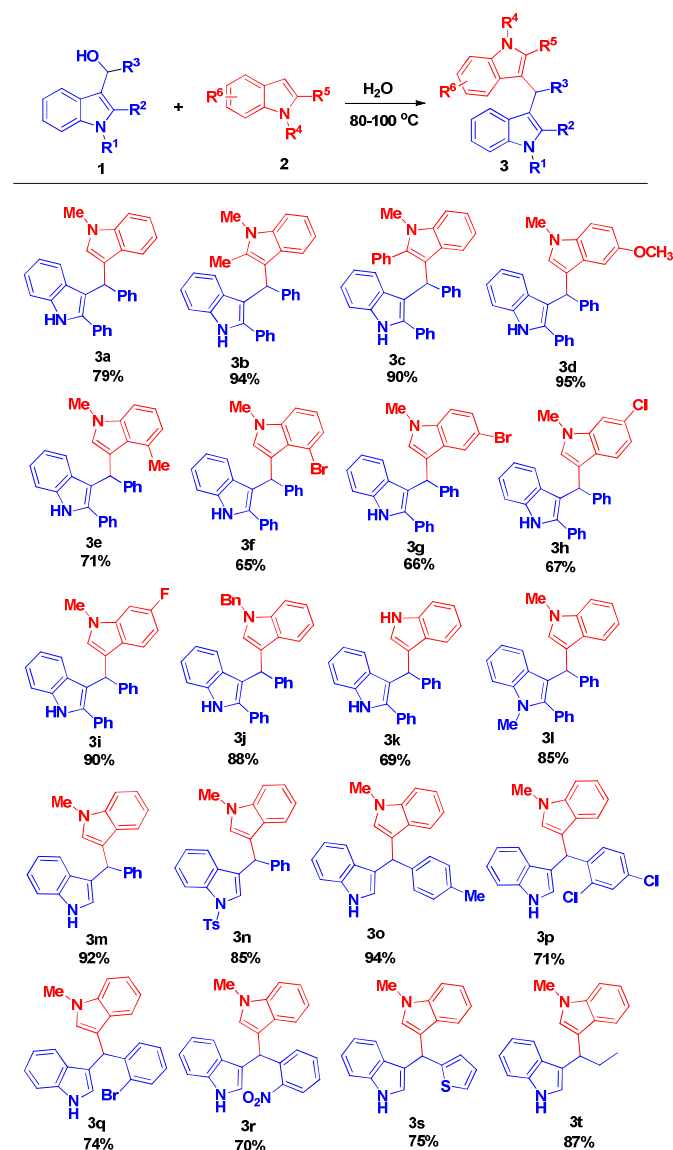
Entry	Solvent	Time (h)	Temp. (°C)	Yield ^b [%]
1	MeOH	24	25	62
2	DCM	24	25	56
3	THF	24	25	60
4	Dioxane	48	25	Trace
5	CH ₃ CN	48	25	Trace
6	Ionic Liquid	24	25	68
7	H ₂ O	72	25	Trace
8	H ₂ O	48	40	14
9	H ₂ O	48	60	42
10	H ₂ O	48	80	79
11	H ₂ O	48	100	83

^a Reactions were performed with **1a** (0.2 mmol) and **2a** (0.4 mmol) in 2 mL solvent. ^b Isolated yield after column chromatography.

performed in acidic ionic liquid at room temperature, producing the desired product in 68% yield (Table 1, entry 6).

When the mixture was stirred in water at room temperature, only trace of product was observed (Table 1, entry 7). When the temperature was elevated to 80 °C, satisfactory yield could be obtained and higher yield was detected at 100 °C (Table 1, entries 9-11). Among these solvents, water was found to be the optimal medium in terms of the yield, cost, reaction efficiency and environmental benignity. It is an obvious “on water” reaction since the reactants are glued to the magnetic stirring bar in the reaction vial. As the product was insoluble in water, it could be isolated from the reaction mixture via simple filtration.

With the optimized condition in hand, the substrate scope with respect to indoles was investigated and a variety of electronically and sterically diverse indoles could be tolerated in

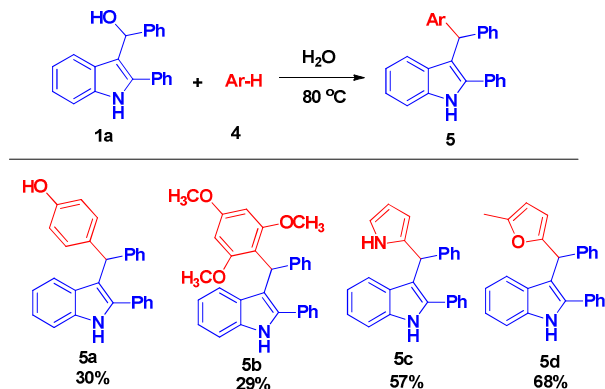


Scheme 2. Substrate scope of reaction of indoles with 3-indolylmethanols. Reactions were performed with **1** (0.2 mmol) and **2** (0.4 mmol) in 2 mL H₂O at 80-100 °C.

this reaction, affording the desired products in moderated to good yields (Scheme 2, 3a-3i). The yields were not affected by steric hindrance remarkably, but significantly influenced by electronic characteristics of indoles. The bulky and C2-substituted indoles had positive effect on the yield which might be helpful to stabilize the cationic intermediate (Scheme 2, 3b-3c). Electron-donating groups on indole phenyl ring generally gave high yield while electron-withdrawing groups decreased the yields a little bit (Scheme 2, 3d-3h). This outcome could be interpreted that electron-rich indoles did not only increase their nucleophilicities, but also stabilize the cationic intermediates. Surprisingly, fluorine substituent afforded 90% yield, which might be ascribed to the stabilization of the transition state through strong hydrogen bonding interaction (Scheme 2, 3i). N-H free or N-H protected indoles also afforded the products in good yields, albeit with lower yield for N-H free case (Scheme 2, 3j-3l).

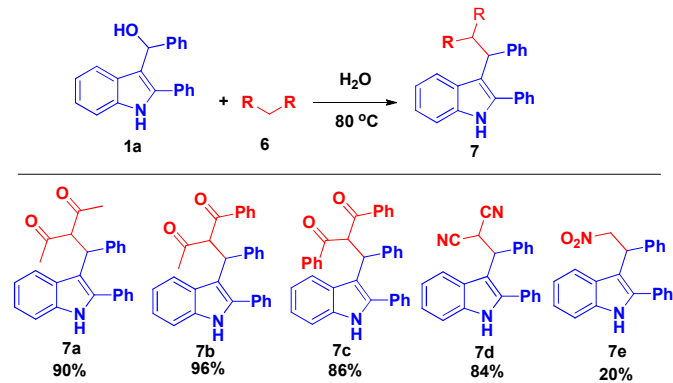
Next, we moved to check the applicability of 3-indolylmethanols. 3-indolylmethanols without 2-substitution are always problematic substrates for 3-indolylmethanol chemistry as side reactions are consistently involved, resulting in low yields and low selectivities under Lewis acids or Bronsted acids catalysis.¹³⁻¹⁴ Intriguingly, in this reaction, (1H-indol-3-yl)(phenyl)methanols could react with N-methyl indole successfully to afford the N-H free or N-H protected products in excellent yields (Scheme 2, 3m-3n). Further experiments indicated that either electron-rich or electron-poor substituents on the aryl ring could be well tolerated (Scheme 2, 3o-3r). Similar tendency was also observed with higher yields for electron-donating groups and lower yields for electron-withdrawing groups. In addition to phenyl substituted 3-indolylmethanols, other heteroaryl group such as thienyl group and aliphatic group such as ethyl group could also be well tolerated in this reaction to afford 3s and 3t in 75% yield and 87% yield correspondingly. Thus, this methodology could functionalize 2-substituted or non-2-substituted 3-indolylmethanols with diverse indoles, affording unsymmetrical bisindolylmethanes and triarylmethanes in good to excellent yields. Despite unsymmetrical bisindolylmethanes and triarylmethanes are privileged structures possessing important bioactive profiles and therapeutical applications, only few approaches were reported for synthesis of them.¹⁵ The current method has significant advantages over aforementioned reports with ready availability and environmental benignity since water as solvent and water is the only by-product.

In addition to indoles, other aromatic compounds such as phenol, 1,3,5-trimethoxybenzene, pyrrole and 2-methylfuran were also examined as nucleophiles. Gratifyingly, all these aromatic compounds reacted with 1a smoothly to furnish aromatics installed triarylmethanes 5 (Scheme 3). Phenol and 1,3,5-trimethoxybenzene afforded the desired product 5a and 5b in comparably lower yield.



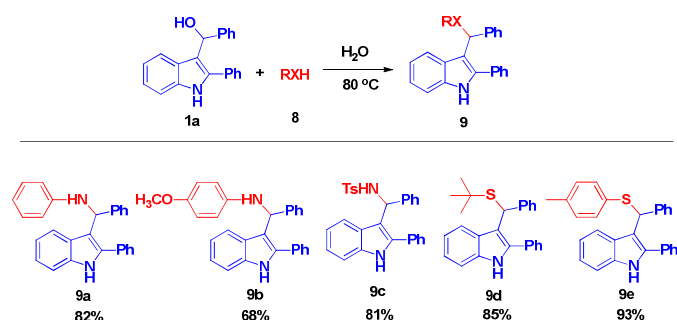
Scheme 3. Reaction of 1a (0.2 mmol) with aromatic compounds 4 (0.6 mmol) in 2 mL water at 80-100 °C.

Although the active methylene compounds have been widely used as nucleophiles in miscellaneous organic transformations, they have rarely been employed as nucleophiles in dehydrative coupling with 3-indolylmethanols for preparation of arylmethanes. To further demonstrate the generality of this strategy, a variety of 1,3-dicarbonyl compounds were examined and it was found that they could be conveniently incorporated into indole skeleton, furnishing the desired coupling products 7a-c in high yields (Scheme 4). Another methylene compound, malononitrile could also work very well to give the coupling product 7d in 84% yield. Even nitromethane could successfully participate in this reaction, albeit with lower yield for 7e.



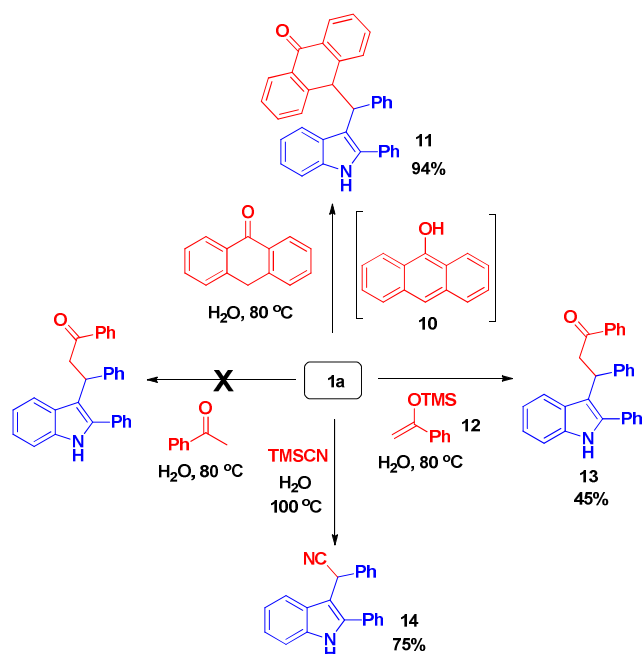
Scheme 4. Reaction of 1a (0.2 mmol) with methylene compounds 6 (0.4 mmol) in 2 mL water at 80 °C and 5 equiv nitromethane was used for 7e.

Sulfur and nitrogen are frequently found in an ocean of pharmaceuticals and biologically active compounds. It is of high significance in pharmacology by incorporation of sulfur and nitrogen into other biologically important frameworks such as indoles. Nevertheless, there is so such chemistry reported till now. Thus amines, thiol and thiophenol were examined as nucleophiles in this reaction, aiming to construct sulphur- and nitrogen-containing 3-indolyl derivatives. Gratifyingly, the coupling products 9 were furnished in high yields which might be ascribed to their good nucleophilicity (Scheme 5).



Scheme 5. Reaction of **1a** (0.2 mmol) with **8** (0.4 mmol) in 2 mL water at 80-100 °C.

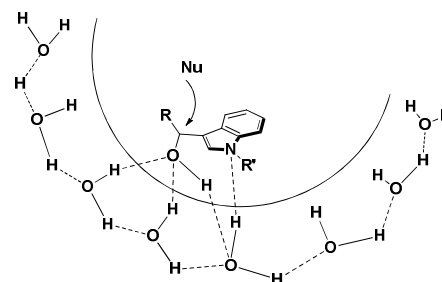
Anthrones are key ingredients in a lot of natural products and compounds with biological and pharmaceutical significance.¹⁶ However, to the best of our knowledge, no protocol is available to merge this fascinating fragments into the indole skeleton, although it holds great potential for finding novel pharmaceutically significant agents. Keeping this in mind, the comparatively less reactive anthrone was tested and the desired product **11** was obtained in 94% yield (Scheme 6). The high yield should be attributed to high nucleophilicity and solubility of the enol form **10**, which was tautomerized from anthrone with the assistance of water through hydrogen bonding. In this reaction, water plays the double role, activating **1a** and anthrone synchronously. Although acetophenone did not work in this reaction, however, the silyl enol ether **12** derived from acetophenone was successful in this reaction, affording the coupling product **13** in 45% yield. Remarkably, when TMSCN was exploited in this reaction, the desired product **14** was afforded in good yields, however, TMSCN did not work on water reactions in previous report.⁹



Scheme 6. Reaction of **1a** (0.2 mmol) with anthrone (0.4 mmol), **12** (0.4 mmol) and TMSCN (0.4 mmol) in 2 mL water at 80-100 °C.

Mechanistically, higher temperature results in stronger ionization of water, thus increasing concentration of H^+ . The pK_a of H_2O at 80 °C is 6.52, indicating that water might play the role of a weak acid, which can hydrolyze the hydroxyl group to form cationic intermediate. It is also reasonable that hydrogen bonds

formation drive the reaction to completion. The well-organized transition state was stabilized by cooperative hydrogen bonds network at the oil–water interface as proposed by Marcus.¹⁷ In this process, the dangling OH groups overhang into the organic phase, which is different from the tangentially oriented water molecules in homogeneous solution (Scheme 7).



Scheme 7. Proposed mechanism of the reaction on water.

In summary, we have described an environmentally benign and efficient dehydrative S_N1 -type reactions of indolyl alcohols with diverse nucleophiles “on water”, affording diverse 3-indolyl derivatives as well as biarylmethanes or triarylmethanes in high yields. For the first time, reaction of 3-indolylmethanols with nucleophiles were carried out without any acid catalysts only using water as solvent. Furthermore, this work overcomes the difficulties in acid-catalysed 3-indolylmethanol-involved reactions and contributes greatly to the chemistry of 3-indolylmethanols for construction of 3-indolyl derivatives. Lastly, this reaction significantly advances the use of water as a medium for organic reactions, demonstrating that water can promote reactions with alcohols which are sensitive to acid.

Acknowledgements

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Experimental Sections

Reagents were purchased from chemical companies. All the reactions were performed in sealed tube and monitored by

TLC (0.2 mm silica gel-coated HSGF 254 plates). The products were purified by flash column chromatography (200-300 mesh silica gel) eluted with the gradient of petroleum ether and ethyl acetate. Proton nuclear magnetic resonance spectra (^1H NMR) were recorded on a Bruker 500 MHz NMR spectrometer (CDCl_3 or DMSO-d_6 solvent). The chemical shifts were reported in parts per million (ppm), downfield from SiMe_4 (δ 0.0) and relative to the signal of chloroform-d (δ 7.26, singlet) or dimethyl sulfoxide- d_6 (δ 2.54, singlet). Multiplicities were given as: s (singlet); d (doublet); t (triplet); q (quartet); dd (doublets of doublet) or m (multiplets). The number of protons for a given resonance is indicated by nH. Coupling constants are reported as a J value in Hz. Carbon nuclear magnetic resonance spectra (^{13}C NMR) were reported in ppm using solvent CDCl_3 (δ (ppm) = 77.16 ppm) as an internal standard. HRMS analyses were performed on a Waters XEVO QTOF mass spectrometer.

General experimental procedure for synthesis of 3

A 15 mL sealed tube was charged with 1 (0.2 mmol) and 2 (0.3 mmol). Then H_2O (2 mL) was added and the resulting mixture was stirred at 80-100 $^\circ\text{C}$. The reaction was monitored by TLC until starting material disappeared. The mixture was extracted with ethyl acetate (3 \times 5 mL) and the extract dried with MgSO_4 . Then the solvent was removed *in vacuo* and the residue was purified by flash chromatography to give the desired product 3.

Notes and references

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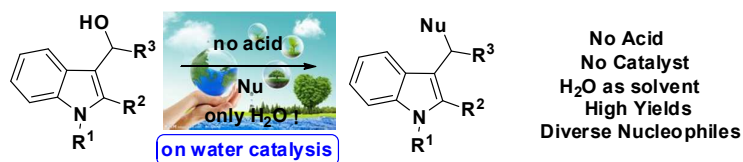
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Catalyst-free dehydrative S_N1-type reaction of indolyl alcohols with diverse nucleophiles “on water”

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Chang-Yun Wang^b



An efficient dehydrative S_N1-type reaction of indolyl alcohols with diverse nucleophiles was developed using water as solvent, affording versatile 3-indolyl derivatives in high yields. The advantage of catalyst-free, environmental benignity, wide substrate scope and easy workup render it promising methods for preparation of indolyl compounds.