A mild and efficient THP protection of indazoles and benzyl alcohols in water

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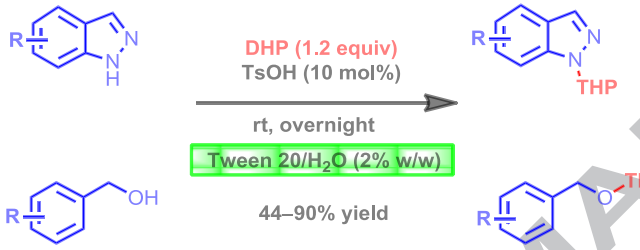

- Water as the solvent
- Mild reaction condition
- Wide substrate scope
- Convenient purification

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A mild and efficient THP protection of indazoles and benzyl alcohols in water

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ABSTRACT

Abstract: A mild and efficient method for THP protection of indazoles and benzyl alcohols has been developed in water, the most environmentally friendly solvent, in which Tween 20 (2% w/w) was added to form aqueous micelles to increase the solubility of starting materials. This aqueous protocol allowed the reaction to proceed smoothly at room temperature and with only 1.2 equiv of DHP, providing moderate to good yields of THP protected products for a wide scope of substrates. In addition, the methodology was highly practical in the large-scale synthesis (1 g synthesis of **2c** as an example), wherein the convenient work-up and purification procedure (simple filtration) made the protocol even more attractive.

Introduction

In the syntheses of complex natural products and bioactive compounds, a multiplicity of functional groups requires protecting group manipulation to avoid side product formation and/or to improve reaction efficiency.[1] A variety of protecting groups such as trimethylsilyl (TMS), methoxymethyl (MOM), tetrahydropyranyl (THP), *tert*-butyloxycarbonyl (Boc), and benzyl (Bn) has been developed to block the corresponding functional groups including hydroxyl (-OH), amine (-NH-) or carbolic acid (-COOH).[2] Among them, THP represents one of the most common protective groups, which has been extensively applied in the synthesis of peptides,[3] carbohydrates,[4] and other biologically active molecules.[5] The prevalence of using THP as a protecting group could be attributed to the ease of introduction, the low cost of the starting material dihydropyran (DHP), and its excellent stability under various conditions such as strong basic media, oxidizing and reducing agents.[2] Besides, THP group could be easily removed under mild acidic conditions[6] or transferred to other functional groups[7].

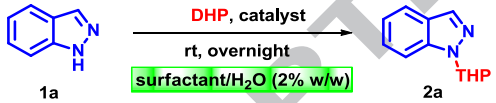
Several methods have been reported in the past decades for the THP protection of different functional groups using acidic catalysts such as *p*-toluenesulfonate (TsOH),[8] pyridinium *p*-toluenesulfonate (PPTS),[9] and bismuth triflate[10] in aprotic solvents such as CH_2Cl_2, THF, and diethyl ether. However, most of the reported protocols were limited to the protection of the hydroxyl group, and were not generalized to a broader scope of other functional groups. Ashok's group reported a magnesium halide catalyzed THP protection of alcohols, thiols, phenols and primary amines in CH_2Cl_2 at room temperature, but limited functional group tolerability was evaluated in the examples.[11] Mezei and co-workers[12] developed a solvent- and catalyst-free protocol for the THP protection of hydroxyl and various heterocyclic amino groups, however high temperature (125 °C) was required for good conversions. Besides, some functional groups such as indole and pyrrole were not tolerated.[12] Up to date, the reported protocols for THP protection often suffer from obvious disadvantages such as high reaction temperature, large excess of the starting material DHP, and narrow substrate scope. In addition, the THP protection of indazoles was widely used in pharmaceutical industry including anti-cancer drug Axitinib, PI3K inhibitors, LRRK2 inhibitors and others.[13] However, the protocol for the THP protection of indazoles was rarely explored. Herein, we report a mild and efficient method for the THP protection of indazoles and benzyl alcohols in water, the most environmentally friendly solvent. This aqueous protocol allowed the THP protection reactions to proceed smoothly at room temperature and with only 1.2 equiv of DHP, providing moderate to high yields of THP protected products with a wide substrate scope. The methodology was further evaluated in the large-scale synthesis (1 g scale for 5-methoxy-1*H*-indazole **1c** as an example), and the desired THP protected product (**2c**) was obtained in high yield (90%) with high purity (99%) after a convenient work-up procedure (simple filtration) without further purification. The practicability especially for large scale makes the protocol even more attractive.

Results and discussion

To address the ever-increasing health and environmental concerns, significant progresses have been achieved to replace organic solvent with the most environmentally friendly solvent, water, in organic synthesis.[14] One focus in this area was adding readily available surfactants to water to form aqueous micellar system.[15] The "nonreactor" formed by the hydrophobic tail of the surfactant favored the compartmentalization of organics, therefore improving the solubility and the local concentration of organic reagents in the micelles, which resulted in the enhancement of reactivity and selectivity of organic reactions in the aqueous micellar system.[16] We have developed several novel protocols in the aqueous micellar system with mild reaction conditions and high yields, including Ullmann reaction of indazoles,[17] N-alkylation of pyridines,[18] and C-H arylation reactions.[19] As our continued efforts to develop environmentally friendly organic reactions, we started to explore THP protection of indazoles, the prevalent intermediates in pharmaceutical industry,[13] in water.

We initiated our exploration using indazole (**1a**) as the model substrate. TPGS-750-M was selected as the surfactant since it has been successfully utilized in a variety of reactions.[20] It was encouraging that 79% conversion to *N*-1 THP-protected product (**2a**) was observed when using 1.2 equiv of DHP and catalytic amount (0.1 equiv) of *p*-toluenesulfonate (TsOH) in TPGS-750-M/water micellar solvent (2% w/w) after overnight reaction at room temperature (entry 1, Table 1). Besides, based on HPLC analysis, only trace amount of *N*-2 THP-protected product was detected, indicating high selectivity of this reaction. With this preliminary result, we then investigated the effect of different surfactants on the reaction including PTS (entry 2), TritonX-100 (entry 3) and SPGS-550-M (entry 4) and they all resulted in similar conversions compared to that of TPGS-750-M. Adding

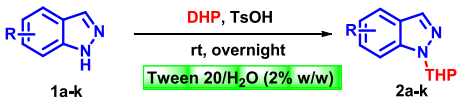
Table 1. Optimization of reaction conditions for THP protection of indazole[a]

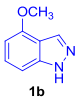
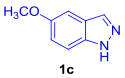
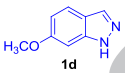
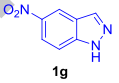
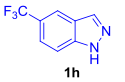


entry	catalyst	surfactant	conversion (%)[b]
1	TsOH	TPGS-750-M	79
2	TsOH	PTS	76
3	TsOH	Triton X-100	77
4	TsOH	SPGS-550-M	75
5	TsOH	Tween 20	96
6	TsOH	Tween 40	85
7	TsOH	Tween 80	93
8	H_2SO_4	Tween 20	78
9	TFA	Tween 20	79
10	PPTS	Tween 20	10
11	$Bi(OTf)_3$	Tween 20	90
12	$Sc(OTf)_3$	Tween 20	40
13	$Yb(OTf)_3$	Tween 20	0
14	$FeCl_3$	Tween 20	59

[a]Reaction Conditions: Indazole **1a** (1.0 eq), DHP (1.2 eq), catalyst (10 mol%), surfactant/H_2O (2% w/w, 2.5 mL), room temperature, overnight. [b]Conversion was determined by HPLC peak areas at 214 nm for indazole **1a** and **2a** after extraction with EtOAc.

Table 2. Substrate scope of indazoles for THP protection in water[a]

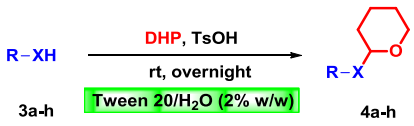


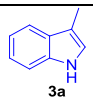
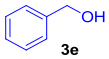
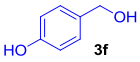
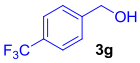
entry	1	conversion (%)[b]	isolated yield of **2** (%)
1		96	**2a**, 89
2		87	**2b**, 72
3		96	**2c**, 84
4		81	**2d**, 75
5		75	**2e**, 62
6[c]		88	**2f**, 82
7[c]		78	**2g**, 58
8[c]		52	**2h**, 44
9		64	**2i,** 44
10		96	**2j**, 89
11[c]		52	**2k**, 51

[a]Reaction Conditions: Indazoles **1a** (1.0 equiv), DHP (1.2 equiv), TsOH (10 mol%), Tween 20/H_2O (2% w/w, 2.5 mL), room temperature, overnight. [b]Conversion was determined by HPLC peak areas at 214 nm for indazole **1** and **2** after extraction with EtOAc. [c]The reaction was run at 70 °C. [d]Not Determined.

excess starting material DHP (up to 5 equiv), prolonged reaction time, and elevated reaction temperature (up to 70 °C) didn't result in significant improvement in conversion. To our delight, the conversion was much improved when using Tweens as the surfactant, especially Tween 20 (entry 5) and Tween 80 (entry 7) which provided 96% and 93% conversion, respectively. Tween 20 proved to be the most optimal among the surfactants evaluated with almost full conversion observed. In addition to the surfactants, the catalysts also demonstrated significant impact on the reactivity of THP protection reaction. H_2SO_4 (entry 8), trifluoroacetic acid (TFA, entry 9), and pyridinium *p*-toluenesulfonate (PPTS, entry 10) resulted in much decreased reactivity compared to TsOH. Especially for PPTS, only 10% conversion was observed from HPL analysis, likely due to its weak activation on DHP in water. On the other hand, Lewis acid gave moderate to high conversions for the THP protection reaction, with the highest conversion of 90% using $Bi(OTf)_3$ as the catalyst and no conversion using $Yb(OTf)_3$. Thus, the most optimal condition was concluded using Tween 20/water (2% w/w) as the solvent, TsOH (10 mol%) as the catalyst, and at room temperature.

Table 3. Substrate scope beyond indazoles for THP protection in water[a]



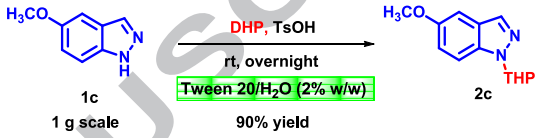
entry	3	conversion (%)[b]	isolated yield of 4 (%)
1	 3a	51	**4a**, 44
2[c]	 3b	33	**4b**, 30
3[c]	 3c	35	**4c**, 33
4[c]	 3d	66	**4d**, 61
5	 3e	50	**4e**, 44
6	 3f	65	**4f**, 56
7	 3g	78	**4g**, 73
8[c]	 3h	trace	**4h**, ND[d]

[a]Reaction Conditions: Indazole **1a** (1.0 equiv), DHP (1.2 equiv), TsOH (10 mol%), Tween/H_2O (2% w/w) 2.5 mL, room temperature, overnight. [b]Conversion was determined by HPLC peak areas at 214 nm for indazoles **3** and products **4** after extraction with EtOAc. [c]The reaction was run at 70 °C. [d]Not Determined.

We then started to explore the substrate scope of indazoles for the THP protection reaction (Table 2). A variety of different substitutions were well tolerated for the reaction condition. Indazoles bearing the electron-donating substitution (methoxy) at different positions (4-, 5-, 6-, and 7-position) underwent the reaction efficiently, providing the corresponding THP protected products in high conversions and good yields (entries 2–5). Compared with the un-substituted indazole, the yields were slightly decreased which may be due to the lower solubility of the substrates in the Tween 20/water micellar system. Among them, the 7-methoxy-1*H*-indazole (**1e**) gave the lowest yield, which was likely attributed to the steric hindrance of the methoxy group. Introducing electron-withdrawing substituents at the 5-position of the indazole such as -F, -NO_2, and -CF_3 (entries 6–8) resulted in slower reactions compared with the electron-donating substituent (**1c**), and a higher reaction temperature was necessary (70 °C) for reasonable conversions, which might be due to the reduced nucleophilicity of the indazole nitrogen. Substituents on the C-3 position of indazole were also tolerated, and moderate yields were obtained for methyl and nitrile substitutions (entries 9 and 11) and high yield (entry 10) was observed for methoxy substitution.

We then further expanded the substrate scope to other heterocyclic amino groups and hydroxyl functionality. As illustrated in Table 3**,** indole (entry 1)**,** benzoimidazole (entry 2), benzotriozle (entry 3) and pyrazole (entry 4) all showed much lower conversions thus lower isolated yields compared indazoles, even at an elevated temperature (70 °C). Benzyl alcohols were also investigated and to our delight, both electron-withdrawing and electron-donating substitutions on the benzyl ring were well tolerated for the reaction condition and moderate to high yields of desired THP protected products were obtained at room temperature (entries 5–7). It was noteworthy that the phenol group of substrate **3f** was not affected and the THP protecting group was selectively on the benzyl alcohol. To further confirm the result, we subjected the unsubstitutied phenol to the reaction condition and no THP protected phenol (**4h**) was detected even after prolonged reaction time and elevated temperature. This might be due to the lower nucleophilicity of the phenol alcohol.

Scheme 1. Large scale synthesis of 5-methoxy-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazole **2c** in water[a, b]



Precipitate formed when additional water was added after the reaction

[a]Reaction Conditions: 5-methoxy-1*H*-indazole **1c** (1.0 g), DHP (852 mg, 1.2 equiv), TsOH (128 mg, 10 mol%), Tween/H_2O (2% w/w, 35 mL), room temperature, overnight. [b]Water was added after the reaction and the solid precipitated was filtrated to give the compound **2c** with high purity (>99%) and high yield (90%).

To further evaluate the practicability of this protocol for industrial applications, a scale-up synthesis was conducted using 1 g of 5-methoxy-1*H*-indazole (**1c**) as the substrate (Scheme 1). The reaction was performed at room temperature with 1.5 equivalents of DHP and catalytic amount of TsOH (10 mol%). After stirring overnight, more water was added to the reaction mixture to break the aqueous micellar system, and the product was directly precipitated out as a solid (please see the picture). The solid was simply filtered and the desired product (**2c**) was obtained with high yield (90%) and high purity (>99%) without further purification.

Conclusion

In conclusion, we have developed a mild and efficient method for THP protection of indazoles, benzyl alcohols and other heterocyclic amino groups in water. Tween 20 (2% w/w) was added as the surfactant to form aqueous micelles to improve solubility of substrates and increase local reaction concentration. This aqueous protocol allowed the reactions to proceed smoothly at room temperature with only 1.2 equiv of DHP, and showed a broad substrate scope with moderate to good isolated yields for the examples examined. In addition, the protocol demonstrated practicability in the gram-scale synthesis of compound **2c** as an example. The convenient work-up and purification procedure (simple filtration) made the protocol even more attractive. Further exploration of aqueous protocols on other protecting groups is ongoing.

Acknowledgements

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Supporting Information

Experimental data, ^{1}H and ^{13}C NMR spectra for the compounds. The Supporting Information is available free of charge which can be found:

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Highlights:

- THP protected indazoles are widely used in pharmaceutical industry
- Efficient and mild methodology of THP protection of indazoles is an unmet need
- A mild THP protection of indazoles and benzyl alcohols in water is reported
- Tween 20 (2% w/w) was added to form aqueous micelles to improve solubility
- Product could be obtained in high yield and purity after easy work-up (filtration)