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Hydrative Amide Synthesis

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Rate-Accelerated Nonconventional Amide Synthesis in Water: A Practical Catalytic Aldol-Surrogate Reaction**

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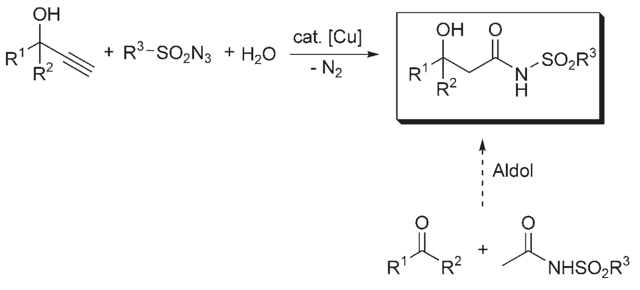
Dedicated to Professor Hong-Ku Shim on the occasion of his 60th birthday

The aldol reaction is a powerful method for installing β-hydroxycarbonyl units, which are extremely versatile building blocks in organic synthesis.[1] Although tremendous progress has been made during the last few decades in the development of highly stereoselective aldol reactions, they usually rely on a similar basic strategy: the addition of enolizable carbonyl compounds to an aldehyde or ketone in the presence of promoters.[2] Accordingly, substrates containing labile functional groups are not amenable under conditions for enol formation.[3]

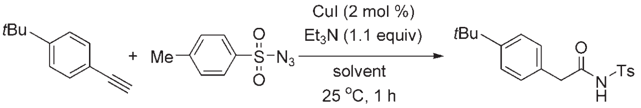
Recently, we reported the highly efficient Cu-catalyzed three-component reactions of terminal alkynes, sulfonyl azides, and amines or alcohols to afford amidines or imidates.[4] It is believed at present that the reaction proceeds via a common ketenimine intermediate, which is generated from the copper-mediated intermolecular cycloaddition of azides and alkynes followed by the release of N_2.[5] On the basis of this postulate, a novel nonconventional amide synthesis could be realized by allowing the plausible ketenimine intermediate to react with water.[6] We subsequently envisioned that application of this protocol to propargyl alcohol substrates might lead to β-hydroxy *N*-sulfonamides under mild and practical conditions. Since these components are not easily accessed through traditional aldol processes,[7] we anticipated that our approach would be an excellent aldol surrogate for the preparation of these synthetically versatile compounds. Our results are described herein (Scheme 1).[8]



Scheme 1.

In initial studies we planned to examine the feasibility of performing the Cu-catalyzed hydrative amide synthesis in aqueous solvent systems, as the development of organic reactions in aqueous solvents is in strong demand these days. Additionally, reactions are frequently observed to be faster in aqueous solvent systems than in organic solvents.[9] Various reaction media were first scrutinized in a test reaction of 4-*tert*-butylphenylacetylene with *p*-toluenesulfonyl azide in the presence of CuI catalyst and triethylamine (Table 1). We found that while the reaction in organic solvents proceeded with moderate rates in the presence of water as a stoichiometric reagent (e.g. entry 1, Table 1), the use of a range of aqueous cosolvent systems improved the conversion and product yields to some extent (entries 2–6, Table 1). A more dramatic rate enhancement was observed when water was employed as the sole solvent, and the desired *N*-sulfonyl amide was obtained in satisfactory yield (entry 7, Table 1). Triethylamine was the most efficient additive, whereas the use of other organic or inorganic bases led to decreased yields under the otherwise identical conditions.[10]

Table 1: Hydrative amide synthesis in various solvent systems.[a]



Entry	Solvent	Conv. [%][b]	Yield [%][b]
1[c]	$CHCl_3$	38	35
2	$CHCl_3/H_2O$ (2:1)	64	55
3	CH_3CN/H_2O (2:1)	54	48
4	DMF/H_2O (2:1)	55	47
5	*t*BuOH/H_2O (2:1)	58	44
6	*t*BuOH/H_2O (1:5)	74	55
7	H_2O	>99	87

[a] Alkyne (0.5 mmol), sulfonyl azide (0.55 mmol), Et_3N (0.55 mmol), and CuI (2 mol%) were stirred in the indicated solvent (1.0 mL). Ts = 4-$MeC_6H_4SO_2$, DMF = *N*,*N*-dimethylformamide. [b] Conversion and yield were determined by ^1H NMR spectroscopy with 1,1,2,2-tetrachloroethane as an internal standard. [c] 2.5 equiv H_2O was added.

The optimized environmentally friendly protocol for the hydrative amide synthesis in water proved to be quite general, and a wide range of alkynes and sulfonyl azides were readily incorporated leading to the sulfonamide product in high yields even after simple recrystallization in most cases

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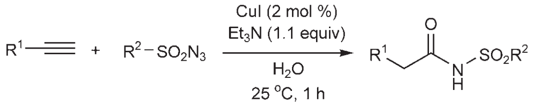
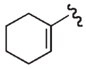
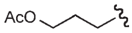
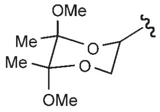
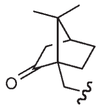
(Table 2). The reaction was complete usually within 1 h when 2 mol% CuI catalyst was used, and this efficiency was not significantly affected by electronic and/or steric variation of the reacting substrates.

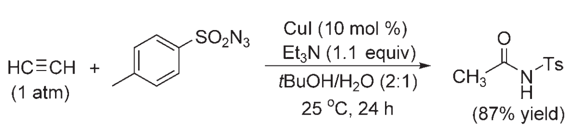
Table 2: Catalytic nonconventional amide synthesis in water.[a]



Entry	R^1	R^2	Yield [%][b]
1	C_6H_5	$4\text{-}MeC_6H_4$	84
2	$4\text{-}MeC_6H_4$	$4\text{-}MeC_6H_4$	72
3	$4\text{-}CF_3C_6H_4$	$4\text{-}MeC_6H_4$	87
4		$4\text{-}MeC_6H_4$	91
5		$4\text{-}MeC_6H_4$	81
6		$4\text{-}MeC_6H_4$	99
7	C_6H_5		93[c]
8	C_6H_5		79[c]

[a] Alkyne (0.5 mmol), azide (0.55 mmol), Et_3N (0.55 mmol), and CuI (2 mol%) were stirred in in H_2O (1.0 mL). [b] Yield after recrystallization. [c] Yield after chromatography.

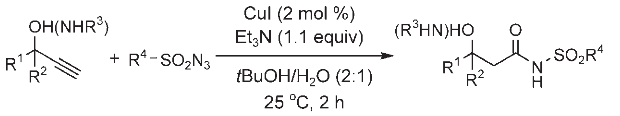
An additional notable utility of this methodology was demonstrated when acetylene gas at atmospheric pressure was allowed to react with *p*-toluenesulfonyl azide and water [Eq. (1)]. The reaction took place more smoothly in an aqueous cosolvent system in this case, presumably owing to the poor solubility of acetylene gas in pure water.[11] Although the reaction with acetylene was slower that with terminal alkynes, the desired product, *N*-sulfonyl acetamide, was obtained in satisfactory yield.

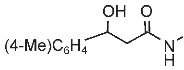
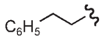
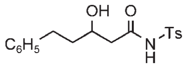
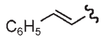
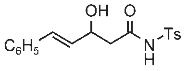
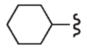
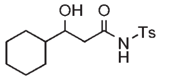
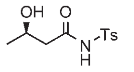
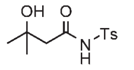
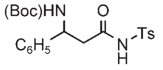


(1)

We then turned our attention to utilizing propargyl alcohol substrates in a practical aldol-surrogate procedure.[12] We were pleased to observe that the catalytic reaction of propargyl alcohols with *p*-toluenesulfonyl azide and water efficiently produced the corresponding β-hydroxy *N*-sulfonamides in good to excellent yields (Table 3).[13] In this case, the product yields obtained in *t*BuOH/H_2O (2:1) were higher than those in pure water.[10] Apparently the reaction is so exothermic in pure water that side reactions such as hydrolysis of azides and dehydration of initially generated β-hydroxy amides occur more readily under the reaction conditions.

Table 3: Cu-catalyzed aldol-surrogate reactions.[a]



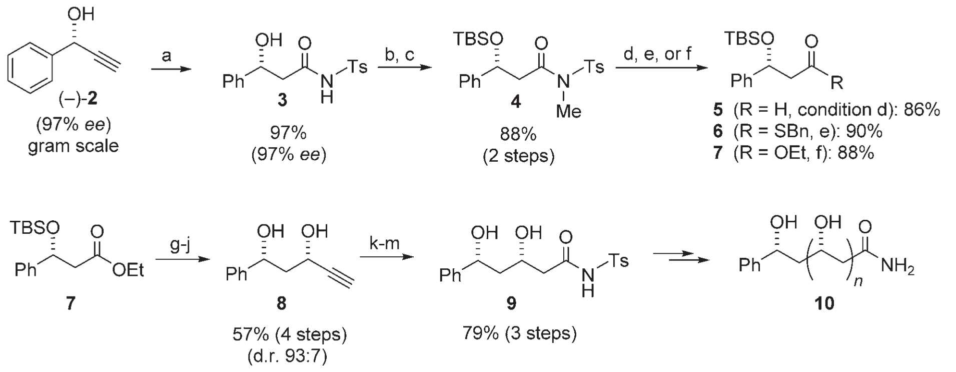
Entry	R^1	R^2	Product	Yield [%][b]
1	$4\text{-}MeC_6H_4$	H		85
2		H		95
3		H		88
4		H		90
5	(*R*)-Me	H		90[c]
6	Me	Me		87
7[d]	C_6H_5	H		83

[a] Alkyne (0.5 mmol), sulfonyl azide (0.55 mmol), Et_3N (0.55 mmol), and CuI (2 mol%) were stirred in *t*BuOH/H_2O (2:1, 1.0 mL). $R^4 = 4\text{-}MeC_6H_4$ in all cases. [b] Yield of isolated product. [c] Both the propargyl alcohol substrate and product were determined to be > 96% *ee*. [d] H_2O alone was used as solvent; R^3 = *tert*-butyloxycarbonyl (Boc).

We applied the optimized conditions to a wide range of propargyl alcohols bearing aryl, alkyl, and conjugated vinyl groups with high efficiency (entries 1–4, Table 3). It is especially noteworthy that the reaction with an enantiomerically enriched propargyl alcohol proceeds without racemization to afford the product in an optically active form with high yield (entry 5, Table 3). Additionally, tertiary propargyl alcohols could be also included as a viable substrate type, giving tertiary β-hydroxy amides in good yield (entry 6, Table 3). It was interesting to observe that the same protocol could be applied successfully to protected propargyl amines in pure water as solvent to produce β-amino carboxylic acid derivatives (entry 7, Table 3), which are also versatile synthetic intermediates.[14]

With the developed protocol in our hands, we demonstrated its utility further with the synthesis of a range of synthetically valuable building blocks (Scheme 2).[15] When the optically active propargyl alcohol (*R*)-1-phenyl-2-propyn-1-ol (**2**) was subjected to the synthetic procedure in aqueous cosolvent system, β-hydroxy amide **3** was isolated in excellent yield (97%) without racemization even on a gram scale.

Subsequent protection of the free hydroxy moiety of **3** as a silyl ether group was followed by N-methylation to provide the key synthetic precursor **4**, from which various valuable β-hydroxycarbonyl compounds can be derived. For example, the hydride reduction of **4** afforded aldehyde **5**,[16] the $AlMe_3$-mediated treatment of **4** with a thiol gave thioester **6**,[17] and



Scheme 2. Reagents and conditions: a) TsN_3 (1.1 equiv), Et_3N (1.1 equiv), CuI (2 mol%), tBuOH/H_2O (2:1), 25 °C, 2 h; b) TBDMSCl (1.1 equiv), imidazole (2.0 equiv), CH_2Cl_2, 25 °C, 5 h; c) MeI (4.0 equiv), K_2CO_3 (2.0 equiv), DMF, 25 °C, 4 h; d) DIBAL (1.1 equiv), CH_2Cl_2, −78 °C, 1.5 h; e) nBuLi (1.5 equiv), BnSH (1.5 equiv), $AlMe_3$ (1.5 equiv), Et_2O, 0 °C, 1 h; f) NaOEt (1.1 equiv), EtOH, 25 °C, 2 h; g) TMS-acetylene (4.0 equiv), nBuLi (4.1 equiv), $BF_3\cdot Et_2O$ (4.0 equiv), THF, −78 °C, 2 h; h) HF-Pyridine, CH_3CN, 25 °C, 3 h; i) DIBAL (1.1 equiv), THF, −78 °C, 2 h; j) K_2CO_3 (2.0 equiv), MeOH, 25 °C, 2 h; k) $CuSO_4$ (2.0 equiv), PPTS (0.1 equiv), acetone, 25 °C, 12 h; l) TsN_3 (1.1 equiv), Et_3N (1.1 equiv), CuI (2 mol%), H_2O, 25 °C, 1 h; m) 1 N HCl/THF (1:1), 25 °C, 3 h. Bn = benzyl, DIBAL = diisobutylaluminum hydride, PPTS = pyridinium *p*-toluenesulfonate, TBDMS = *tert*-butyldimethylsilyl, TMS = trimethylsilyl.

transesterification under basic conditions resulted in ester **7** with good yields in all cases.[18] The β-*O*-silyl ester derivative (**7**) was readily converted into the propargyl 1,3-diol **8** with high diastereoselectivity (d.r. 93:7) in 57% yield in four convenient steps.[19] The relative stereochemistry of the newly generated hydroxy group in **8** was unambiguously established by an NOE experiment after conversion to its ketal derivative.[10]

The second operation of the catalytic hydrative amide protocol was also successfully carried out with a ketal derivative of **8** in water, and the subsequent deketalization afforded the β,δ-dihydroxy sulfonamide **9** in 79% yield (three steps) without racemization. It should be mentioned that this approach can be potentially utilized as an iterative aldol surrogate to synthesize polyhydroxy amides (e.g. **10**) when the same procedures are repeated.

In summary, we have shown that Cu-catalyzed hydrative amide synthesis is significantly accelerated in aqueous solvent systems. Under environmentally friendly conditions and with N_2 released as the single side product, this reaction can be applied to a wide range of propargyl alcohols and sulfonyl azides as highly viable substrates, and β-hydroxy *N*-sulfonamides are obtained in good to excellent yields. It was also demonstrated that the method can be applied readily in an iterative manner to produce polyhydroxy amides; in this way it serves as a new practical aldol-surrogate strategy.

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Keywords: β-hydroxy amides · alkynes · azides · copper · water

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