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Communication

Facile Synthesis of Enol Ethers *via* Zn(OTf)$_2$-mediated Formal Alkyne Hydration-Smiles Rearrangement

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**An efficient protocol involving commercially available zinc trifluoromethanesulfonate was able to transform a terminal alkyne to an enol ether *via* a formal tandem Markovnikov hydration-Smiles type rearrangement. The chemoselective**
10 **reaction was able to work with a range of heteroaromatics tethers such as diazine, pyridine, benzimidazole and benzothiazole.**

Alkyne hydration or the addition of water to alkyne is an atom-economical[1] method to generate the useful carbonyl compounds
15 and therefore is a subject of much interest. Since the discovery of mercury(II) salts that hydrate alkynes with Markovnikov selectivity to give ketones,[2] most of the research focuses on the development of less toxic, more selective and efficient metal and acid catalysts or biocatalysts for this process.[3] Non-metal based
20 catalysts such as formic acid,[4] triflic acid[5] or trifluoroacetic acid[6] can be used to hydrolyze terminal alkynes to the Markovnikov ketone product at elevated temperatures in water. Numerous metal salts and complexes have also been identified to convert terminal alkynes to ketones (Markovnikov product) or aldehydes
25 (anti-Markovnikov product), (Scheme 1) with the most prominent being palladium(II),[7] gold(I),[7e,8] gold(III)[9], platinum(II)[10] and ruthenium[11] catalysts. Catalytic anti-Markovnikov alkyne hydration is a relatively new and exciting area where ruthenium[12] has emerged to be a highly efficient catalyst.
30 Being in the same group as mercury, studies using zinc for alkyne hydrations was reported as early as 1909 by Kutscheroff[2c] but was found to require very harsh conditions.[13] There were few reported research using zinc thereafter. In 1994, an anti-Markovnikov hydration using silica gel-supported zinc
35 borohydride to afford terminal alcohols rather than the aldehyde was disclosed.[14]

During the course of our investigations on diazines, we discovered an extremely facile protocol to convert the terminal alkynes to enol ethers using cheap and commercially available
40 reagent, zinc triflate (Scheme 2). We believed that the terminal alkyne **1a** was first hydrated in a Markovnikov manner to give an intermediate **A** that underwent an intramolecular Smiles-type rearrangement[15] to yield the diazine-protected enol ether **2a**. No ketone was ever observed or isolated.
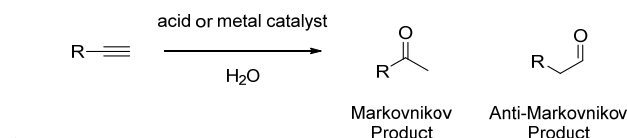
45 **Scheme 1.** General Scheme of Terminal Alkyne Hydration
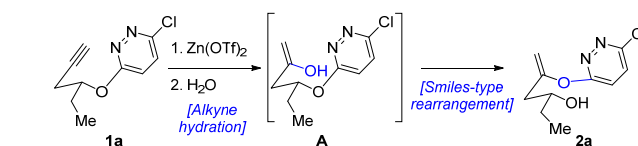
Scheme 2. Zinc-mediated Formal Alkyne Hydration-Smiles
50 Rearrangement of Diazine **1a**.

Table 1. Initial Screening for the Alkyne Hydration-Smiles Rearrangement.[a]
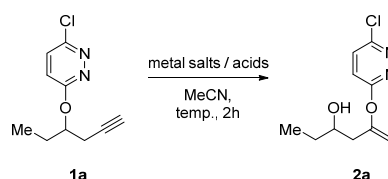
| Entry	Metal salt/Acid	Temp. (°C)	Conv. (%)[b]	Yield (%)[b]
1	Zn(OTf)$_2$	25	60	50
2	AgOTf	25	15	10
3	CuOTf	25	45	25
4	FeCl$_3$	25	0	0
5	PdCl$_2$	25	100	0
6	CuF$_2$	25	10	0
7	RuCl$_3$	25	100	0
8[c]	TfOH	80	16	7
9	AgNTf$_2$	80	80	40
10	AgOTf	80	50	45
11	CuOTf	80	100	40
12	**Zn(OTf)$_2$**	**80**	**100**	**95**
13[d]	Zn(OTf)$_2$	80	48	45

55

[a] Conditions: **1a** (1 equiv), metal salt/acid (1 equiv), MeCN (0.1 M), 2 h; then H$_2$O, 80 °C, 1 h. [b] Determined by ^{1}H NMR with 2,4,6-collidine as an internal standard. . [c] 5mol% of TfOH was used instead. [d] 50mol% of Zn(OTf)$_2$ was used instead.

An initial experiment was performed using **1a** with Zn(OTf)$_2$ in MeCN at ambient temperature. To our pleasant surprise, the reaction proceeded cleanly to give new product in nearly quantitative yield (95%) after 16 h. After extensive NMR, mass and IR spectroscopic analyses, the product was characterized to be **2a**.[16] As Zn(OTf)$_2$ is not known to mediate alkyne hydration nor Smiles rearrangement to the best of our knowledge, we decided to further investigate this serendipitous observation.

A range of metal salts and acids commonly known to effect alkyne hydrations were first screened to determine if the observed reactivity behavior was exclusive (Table 1).[17] It was found that a variety of other metal salts such as AgNTf$_2$, AgOTf[18] and CuOTf could yield the same product **2a** (Table 1, entries 2-3 and 9-11). A control experiment with triflic acid was carried out to determine whether the reaction was mediated by Brønsted acid and only a small amount (7%) of the desired product could be obtained with catalytic amount of TfOH (Table 1, entry 8). Zn(OTf)$_2$ was by far superior in terms of efficiency and yield (Table 1, entries 1 and 12). At elevated temperature (80 °C), the reaction could be completed within 2 h to give **2a** in 95% NMR yield (Table 1, entry 12). Stoichiometric amount of Zn(OTf)$_2$ was necessary to effect the reaction as the conversion and yield dropped drastically with sub-stoichiometric amount of Zn(OTf)$_2$ (Table 1, entry 13).

Different polar solvents were screened to determine the effect of solvents on the reaction (Table 2). Whilst solvents like MeOH, acetone, 1,4-dioxane and EtOAc were found to give some

Table 2. Solvent Optimization for the Alkyne Hydration-Smiles Rearrangement.[a]
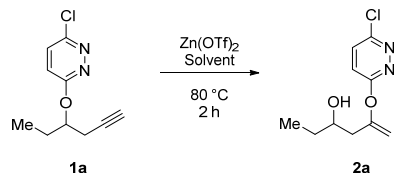
Entry	Solvent	Conv. (%)[b]	Yield (%)[b]
1	MeCN	100	95
2	MeOH	15	10
3	DMSO	0	0
4	acetone	100	25
5	1,4-dioxane	100	20
6	EtOAc	100	40
7	H$_2$O	10	5
8	MeCN/H$_2$O (9:1)	100	75
9	MeCN/H$_2$O (4:1)	90	70
10	MeCN/H$_2$O (1:1)	75	55
11	MeCN/H$_2$O (1:4)	0	0
12	MeCN/H$_2$O (1:9)	0	0

[a] Conditions: **1a** (1 equiv), Zn(OTf)$_2$ (1 equiv), solvent (0.1 M), 80 °C, 2 h; then H$_2$O, 80 °C, 1 h. [b] Determined by ^{1}H NMR with 2,4,6-collidine as an internal standard.

Table 3. Hydration-rearrangement of diazines **1**.[a]
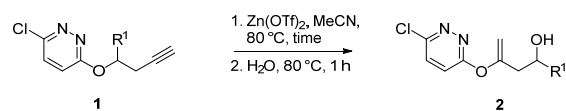
Entry	Substrate	Product	T (h)[b]	Yield (%)[c]
1	**1a**	**2a**	2	97
2	**1b**	**2b**	2	95
3	**1c**	**2c**	2	95
4	**1d**	**2d**	3	88
5	**1e**	**2e**	3	86
6	**1f**	**2f**	3.5	85
7	**1g**	**2g**[d]	3	87

[a] Conditions: substrate **1** (1 equiv), Zn(OTf)$_2$ (1 equiv), MeCN (0.1 M), 80 °C, for specified time; then H$_2$O (1 mL/mmol), 80 °C for 1 h. [b] Reaction was monitored by tlc until all starting material was consumed. [c] Isolated yields. [d] The dehydrated product **2g** was isolated instead of the expected tertiary alcohol.
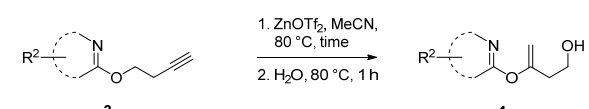
conversion (Table 2, entries 2, 4, 5 and 6), MeCN was found to be the best solvent. It is interesting to note that the reaction proceeded even in pure water, albeit with very low conversion (Table 2, entry 7). We then studied the water tolerance level of this reaction (Table 2, entries 8-12). For reactions in a mixture of MeCN and water, the efficiency of the reaction decreases as the water content increases. At 1:1 MeCN/H$_2$O mixture, the conversion dropped to 75% whilst the yield was only 55% (Table 2, entry 10).
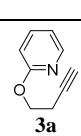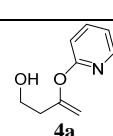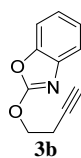
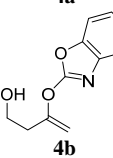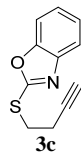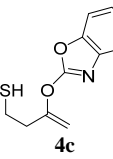In order to confirm that an external molecule of water was added during the hydration-rearrangement, **1c** was treated with Zn(OTf)$_2$ in MeCN at 80 °C for 2 h followed by a few drops of enriched ^{18}O[H$_2$O]. Indeed, mass spectroscopic analysis of the product ^{18}O-**2c** found incorporation of heavy water, affording a

product of m/z 225.0278 for $[M+Na]^+$.[19] Based on the above optimized conditions of using stoichiometric amount of $Zn(OTf)_2$ in MeCN at 80 °C, the scope of the reaction was then examined.[20]

A range of diazines **1** were explored (Table 3). In general, the reactions proceeded smoothly with excellent yields (85-97%) to afford the co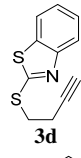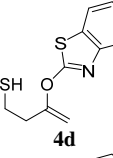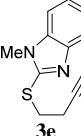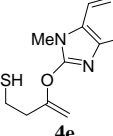rresponding enol ethers. The reaction was found to be tolerant of ether (Table 3, entry 4) as well as alkene functional groups (Table 3, entry 7). As expected, the stereochemistry of **1d** was retained in the hydration-rearrangement process (Table 3, entry 4).[21] Excellent chemoselectivity was observed as demonstrated by substrate **1f** where the integrity of the second alkyne remained intact under the reaction conditions (Table 3, entry 6). The expected tertiary alcohol product for substrate **1g** was not obtained; instead the dehydrated triene **2g** was isolated (Table 3, entry 7).

**Table 4.** Other successful hydration-rearrangements.[a]

Entry	Substrate	Product	T (h)[b]	Yield (%)[c]
1	**3a**	**4a**	24	89
2	**3b**	**4b**	24	0
3	**3c**	**4c**	3	45[d]
4	**3d**	**4d**	6	92
5	**3e**	**4e**	6	81

[a] Conditions: substrate **3** (1 equiv), $Zn(OTf)_2$ (1 equiv), MeCN (0.1 M), 80 °C, for specified time; then H_2O (1 mL/mmol), 80 °C for 1 h. [b] Reaction was monitored by tlc until all starting material was consumed. [c] Isolated yields. [d] 25% of side product **4c'** was obtained.

The presence of the diazine was vital for the success of the hydration-rearrangement reaction. Apart from diazine as the tether for the hydration-rearrangement, we decided to explore if other similar aromatic groups could be used. Numerous functionalities were attempted, Table 4 detailed some of the results.

The pyridinyl **3a** proceeded smoothly to afford the corresponding enol ether **4a** in excellent yields (89%) (Table 4, entry 1). Benzoxazole ether **3b** did not react while the corresponding benzoxazole thioether **3c** gave the expected product **4c** in 45% yield together with another by-product **4c'** in 25% (Table 4, entries 2-3). **4c'** was presumed to be formed through a transfer of the benzoxazole group from another starting molecule **3c**. A similar reaction involving benzothiazole thioether **3d** afforded the expected enol ether **4d** in 92% yield in 6 h (Table 4, entry 4). Similarly, the benzimidazole thioether **3e** proceeded smooothly to give **4e** in 81% yield (Table 4, entry 5). No side products were observed in both cases. This difference in reactivity remains unclear at this point and is subject to further investigation.

4c'
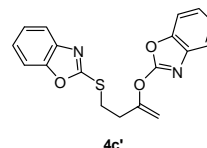
Conclusions

In summary, a mild and efficient protocol to transform terminal alkynes to enol ethers *via* a formal tandem Markonikov hydration-Smiles rearrangment using cheap and commercially available zinc triflate has been developed. The reaction is highly chemoselective and works in a range of heteroaromatic such as diazine, pyridine, benzimidazole, benzoxazole and benzothiazole. The present study also highlights $Zn(OTf)_2$ as an eco-friendly reagent where the transformation is 100% atom-economical. Further investigations into the mechanism as well as other applications in synthesis are currently in progress.

Acknowledgements

Notes and references

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[b] *Singapore Bioimaging Consortium (SBIC), Agency for Science, Technology and Research (A*STAR), 11 Biopolis Way, #01-02 Helios Block, Singapore 138667*

† Electronic Supplementary Information (ESI) available. See DOI: 10.1039/b000000x/

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16 For more details on the structural assignment of **2a**, please see supporting information.

17 For detailed screening results, please see supporting information.

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19 **2c**: $C_8H_9N_2O_2ClNa$ has $[M+Na]^+$ calcd: 223.0245, found: 223.0249. ^{18}O-**2c**: $C_8H_9N_2O^{18}OClNa$ has $[M+Na]^+$ calcd: 225.0293, found: 225.0278.

20 Representative procedure: To a solution of **1a** (182 mg, 1 mmol) in MeCN (10 ml) was added $Zn(OTf)_2$ (365 mg, 1 mmol) and the reaction mixture was stirred at 80 °C until consumption of **1a**. Water (1 mL) was then added and the reaction was stirred for another 1 h. Solvent was removed and the crude was diluted with EtOAc and washed with saturated $NaHCO_3$. The crude was purified by column chromatography to afford the desired product **2a** as a colorless oil (95%).

21 See supporting information for more details on determination of absolute configuration.

Graphical Abstract
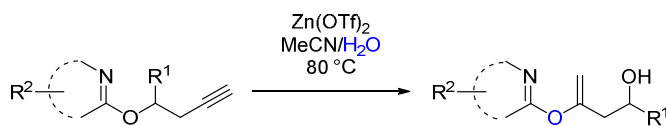
Terminal alkyne can be chemoselectively transformed into an enol ether *via* a formal tandem Markovnikov hydration-Smiles type rearrangement using Zn(OTf)$_2$.