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Dimethyl Sulfoxide and *N*-Iodosuccinimide Promoted 5-*exo*-*dig* Oxidative Cyclization of Yne-Tethered Ynamide: Access to Pyrrolidones and Spiro-pyrrolidones

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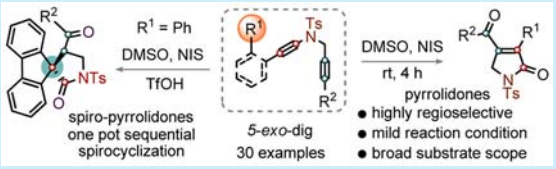
Supporting Information

ABSTRACT: An unprecedented metal-free dimethyl sulfoxide (DMSO) and *N*-iodosuccinimide mediated regioselective 5-*exo*-*dig* oxidative cyclization of an in situ generated enol equivalent of amides from ynamides bearing internal alkynes is demonstrated. The reaction allows easy access to functionalized pyrrolidone skeletons. Pyrrolidones having 3-*o*-biaryl motifs successfully undergo intramolecular electrophilic cyclization with the α,β-unsaturated olefin, furnishing spiro-pyrrolidone motifs. A one-pot sequential 5-*exo*-*dig* cyclization of the yne-tethered ynamides, followed by electrophilic cyclization of the pyrrolidone, is presented. The role of DMSO in the transformation is clarified, and a tentative reaction pathway is proposed.



Pyrrolidone derivatives are useful building blocks in organic synthesis, as these motifs are widely distributed in the molecules that show promising antimicrobial, antifungal, antitumor, and antituberculosis activity (Figure 1).[1] Furthermore,

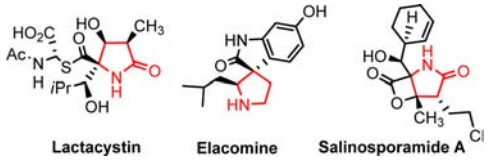
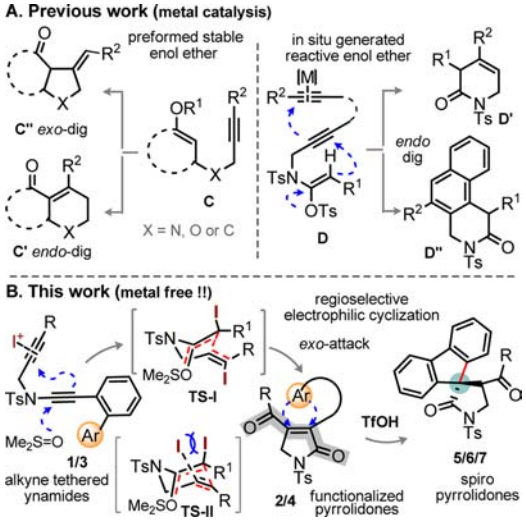


Figure 1. Pyrrolidone derivatives containing natural products.

analogous to spiro-*N*-heterocycles, spiro-pyrrolidone scaffolds would show superior biological activity.[2] Ynamides, the nitrogen-substituted alkynes, are versatile scaffolds extensively used in the design and development of novel synthetic transformations.[3] They are also used in the preparation of complex *N*-heterocycles as well as highly reactive intermediates that are inaccessible by conventional syntheses.[4] In particular, cyclization and cycloisomerization of yne-tethered ynamides would allow for the construction of a novel molecular framework.[5] However, the 6-*endo*-*dig* cyclization of yne−ynamide motifs readily afford 6-membered *N*-heterocycles, while the 5-*exo*-*dig* mode cyclization to yield pyrrolidine scaffolds remains elusive. Given the aforementioned significance of pyrrolidones and ynamides, the development of efficient and reliable synthetic routes to highly functionalized pyrrolidone derivatives from readily accessible ynamides is desirable.

The preformed enol ethers successfully undergo *exo*- and *endo*-cyclization with tethered alkyne motifs under the influence of metal catalysis (Scheme 1A, **C**).[6] Interestingly, the *p*-toluenesulfonic acid (*p*-TsOH) promoted Au(I)-catalyzed 6-*endo*-*dig* cyclization of the in situ generated enol equivalent of amides from ynamides with an internal yne moiety affords novel dihydropyridinone and

Scheme 1. Enol Equivalent for Regioselective Cyclization



benzo[*f*]dihydroisoquinolone frameworks (Scheme 1A, **D**).[5b,c] At this conjecture, we envision to explore the 5-*exo*-*dig* oxidative cyclization of inherently polarized ynamide motifs with a tethered alkyne to build the pyrrolidone skeleton under metal-free conditions (Scheme 1B). To the best of our knowledge, no such transformations of yne−ynamides are so far known. A recent report on the synthesis of pyrrolidone discusses the oxidative cycloisomerization of Rh(I) carbene, generated from a ynamide in the presence of pyridine *N*-oxide and a Rh catalyst, with the internal alkyne.[7] We could therefore visualize 5-*exo*-*dig* cyclization of the ketene *N*,*O*-acetal of TS-**I**, attained through the preferential attack of polarizable DMSO/*N*,*N*-dimethylformamide (DMF)

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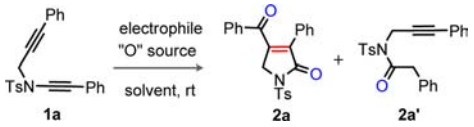
on the NIS-activated ynamide,[8] with the alkyne motif followed by oxidation to give pyrrolidone in a single step.[9] The steric features of TS-**II** would probably rule out the possibility of participation of the 6-*endo-dig* cyclization.[10] We herein demonstrate a unified metal-free method for the construction of pyrrolidones and spiro-pyrrolidones from easily accessible and stable yne-tethered ynamides at room temperature.

To search for the possibility of the projected transformation in Scheme 1B, investigations were attempted to establish 5-*exo-dig* cyclization of 1,5-yne−ynamide **1a** to yield **2a** (Table 1).

Table 1. Optimization of the Reaction Conditions[a]



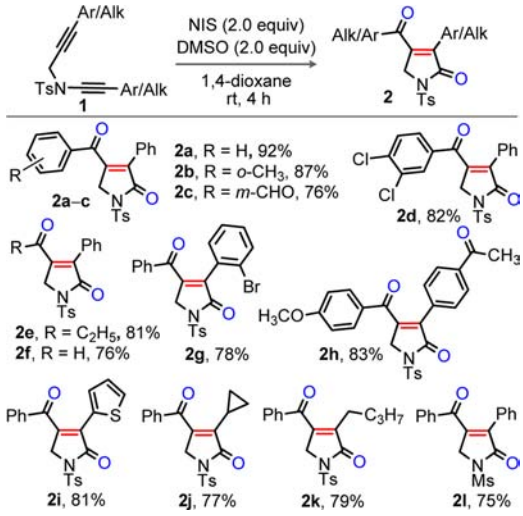
entry	"O" source (2.0 equiv)	electrophile (2.0 equiv)	solvent	yield[b] (%) 2a	2a′
1	DMSO	NIS	$ClCH_2CH_2Cl$	35	60
2	DMSO	NCS	dioxane		40
3	DMSO	NBS	dioxane	15	50
4	DMSO	NIS	dioxane	92	
5	DMF	NIS	dioxane	72	
6	DMF	NIS	acetone	30	65
7	DMF	NIS	THF	25	60
8	DMSO	I_2	dioxane	75	20
9	DMSO	ICl	toluene	35	65
10[c]	DMSO	Au(I)[d]	dioxane		
11[e]	DMSO	CF_3COOAg	dioxane		
12	acetone	NIS	dioxane		75
13	H_2O	NIS	dioxane	20	70

[a]Reactions were carried out using **1a** (0.5 mmol), electrophiles (1.0 mmol), and O-source (1.0 mmol) in solvent (3.0 mL) at rt for 4 h. [b]Isolated yields. [c]Complex mixture. [d]XPhosAu(MeCN)SbF_6. [e]Unreacted starting material.

To begin, compound **1a** was exposed to NIS (2.0 equiv) in the presence of DMSO (2.0 equiv) in 1,2-dichloroethane (DCE) at rt. Gratifyingly, the desired 2-pyrrolidone **2a** (35%) was obtained along with 60% monohydration product **2a′** (entry 1). The other promoters *N*-chlorosuccinimide (NCS)/*N*-bromosuccinimide (NBS) were ineffective (entries 2 and 3). To our delight, **2a** (92%) was exclusively obtained when the reaction was performed in dioxane at rt (entry 4). DMF also served as a good nucleophile; however, it provided inferior results (entries 5−7). Iodine and ICl were also suitable promoters to produce **2a** and **2a′** (entries 8 and 9). In contrast, the effective Au(I) and CF_3CO_2Ag agents arbitrarily failed (entries 10 and 11). The combinations of acetone and NIS or water and NIS were not suitable, producing major amounts of **2a′** (entries 12 and 13). It appears that DMSO serves as an effective nucleophile in this reaction.

We next surveyed the scope of the 5-*exo-dig* cyclization of yne-tethered ynamides **1** for the synthesis of pyrrolidone derivatives under the optimal reaction conditions in entry 4, Table 1; the results were detailed in Scheme 2. The compound **1a** (0.5 mmol) readily provided 92% of **2a**. The cyclization of **1** having *o*-Me-, *m*-formyl-, or *m,p*-di-Cl-substituted aryl moieties in the propargyl terminus reacted efficiently to deliver the desired **2b−d** in excellent yields. Compound **1e** with the ethyl group on the propargyl alkyne terminus was also suitable, constructing 81% of **2e**. Notably, the unsubstituted propargylalkyne terminus

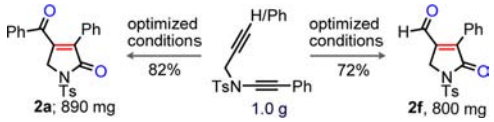
Scheme 2. Synthesis of Pyrrolidones: Substrate Scope I[a,b]



[a]Reactions were carried out using **1** (0.5 mmol), NIS (1.0 mmol), and DMSO (1.0 mmol) in dioxane (3.0 mL) at rt for 4 h. [b]Isolated yields.

ynamide **1f** reacted smoothly to yield **2f** with a modifiable formyl moiety on the periphery of the pyrrolidone skeleton. The *o*-Br-substituted aryl moiety in the ynamide terminus of **1g** did not affect the reaction efficiency, manufacturing **2g** (78%). Cyclization of **1h** (electron-donating and electron-withdrawing groups bearing aryl moieties on the propargyl and ynamide terminus, respectively) yielded **2h** (83%). Pleasingly, a thiophene-bearing ynamide **1i** effectively underwent cyclization to provide **2i** in high yield. Cyclization of **1** having aliphatic substitution at the ynamide terminus was next probed. The 3-cyclopropyl **2j** (77%) and 3-butyl-substituted pyrrolidone **2k** (79%) were constructed; the labile cyclopropyl group survived. The pyrrolidone **2l** (75%), having an easily removable NMs moiety, was also prepared. Thus, stereoelectronic factors at the propargyl and ynamide terminus of **1** did not show a pronounced impact on the current 5-*exo-dig* cyclization of **1**, constructing wide arrays of pyrrolidone motifs in appreciable yields. The robustness of this reaction is validated through gram-scale reaction of **1a** and **1f** for the synthesis of **2a** (890 mg, 82%) and **2f** (800 mg, 72%), respectively (Scheme 3).

Scheme 3. Gram-Scale Synthesis of 2a and 2f



The olefin in the 3-aryl-substituted pyrrolidone skeleton in Scheme 2 serves as a Michael acceptor. We speculate that a 3-biaryl-bearing pyrrolidone would undergo electrophilic cyclization with the α,β-unsaturated ketone to afford spiro-pyrrolidones.[11] We thus consider introducing an *o*-biaryl moiety in the pyrrolidone periphery and examine the electrophilic cyclization reaction. Accordingly, we tested the NIS-mediated cyclization of yne-tethered ynamide derivatives **3** having a biaryl group at the ynamide terminus (Scheme 4). The reaction of **3a** under the optimized conditions (entry 4, Table 1) led to **4a** in excellent yield. X-ray crystallographic analysis data established the structure of **4a**.[12] Similarly, the 2-naphthyl-bearing pyrrolidone derivative **4b** was accessed in 82% yield. Electron-donating and electron-withdrawing groups on the biphenyl ring did not affect

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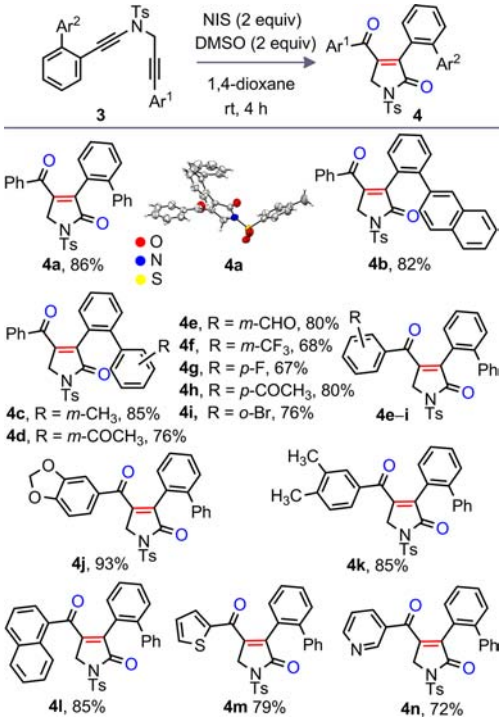
Scheme 4. Synthesis of Pyrrolidones: Substrate Scope II[a,b]

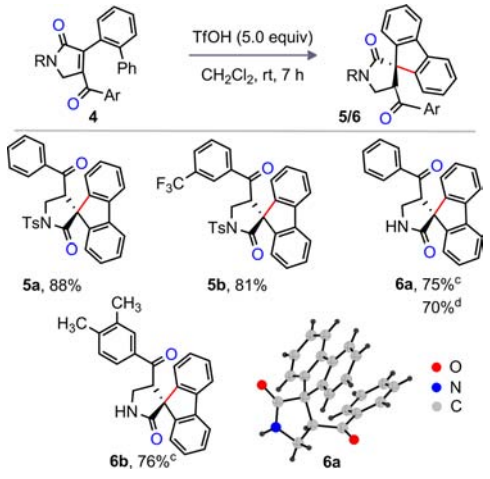


[a]Reactions were carried out using **3a** (0.5 mmol), NIS (1.0 mmol), and DMSO (1.0 mmol) in dioxane (3.0 mL) at rt for 4 h. [b]Isolated yields.

the reaction, providing **4c** (85%) and **4d** (76%). Likewise, precursors **3e**−**k** (with different aryl and *o*-biphenyl at the propargyl and ynamide terminus, respectively) fruitfully underwent cyclization to deliver the corresponding products **4e**−**k**; formyl, CF_3, F, keto, and Br were compactible. The naphthyl moiety on the propargyl terminus did not show adverse effects, furnishing **4l** (85%). Gratifyingly, heteroaryl-substituted 3-biphenyl-bearing pyrrolidones **4m** (79%) and **4n** (72%) were effectively constructed.

With the 3-*o*-biaryl-molded pyrrolidone skeletons **4** in hand, we then performed the acid-mediated electrophilic cyclization of the aryl motif with the unsaturated ketone in **4** (Scheme 5).[11c]

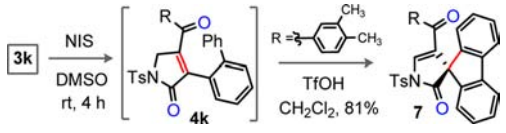
Scheme 5. Synthesis of Spiro-pyrrolidone Derivatives[a,b]



[a]Reactions were carried out using **4** (0.3 mmol) and TfOH (1.5 mmol) in CH_2Cl_2 (2.0 mL) at rt for 7 h. [b]Isolated yields. [c]TfOH (3.0 mmol) at rt for 15 h. [d]TfOH (1.5 mmol) at 70 °C for 7 h.

Screening of various Lewis and Brønsted acids for the electrophilic cyclization of **4a** led to the optimized conditions [TfOH in CH_2Cl_2 at rt], affording the unusual spiro-pyrrolidone derivative **5a** in 88% yield. Likewise, **4f** was readily transformed to **5b** (81%). Interestingly, the reaction of **4a** with TfOH (10 equiv) at rt for 15 h or TfOH (5.0 equiv) at 70 °C for 7 h gave *N*-Ts-deprotected spirocylic product **6a** in good yield. The structure of **6a** was elucidated by X-ray analysis (Scheme 5).[12] Similarly, compound **6b** (76%) was obtained from **4k**. Thus, the current method allows easy access to build fluorene (spiro-pyrrolidone) scaffolds. We next performed a one-pot DMSO- and NIS-promoted 5-*exo-dig* cyclization of **3k** followed by the TfOH-assisted electrophilic cyclization of **4k**; surprisingly, a dehydrogenative spirocyclic product **7** was obtained in 81% yield (Scheme 6). We believe the

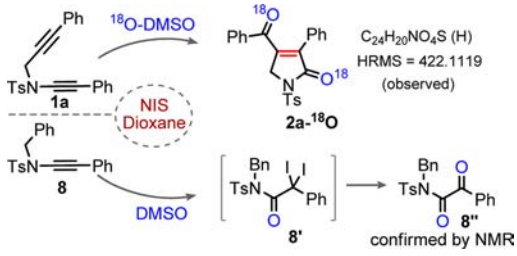
Scheme 6. One-Pot 5-*Exo-Dig* and Spiro-cyclization of 3k



TfOH-mediated cyclization of **4k** in the presence of unreacted NIS would produce 4-iodospiro-pyrrolidone, which subsequently undergoes dehydrohalogenation to form **7**,[13] whereas the reaction of **5a**/**6a** with NIS and TfOH failed to deliver the corresponding dehydrgenative spirocyclic product.

To acquire preliminary insight into the mechanism, **1a** was exposed to the optimized conditions in the presence of ^{18}O-DMSO;[13a] gratifyingly, we observed the formation of ^{18}O-labeled pyrrolidone **2a**-^{18}**O** (confirmed by HRMS) (Scheme 7).[12] By contrast, under the standard conditions,

Scheme 7. Mechanistic Investigations



ynamide **8** without a pendant alkyne exclusively furnished the corresponding α-keto amide **8"** (Scheme 7).[8] The α-keto amide is possibly formed by β-iodination of the ynamide, followed by the attack of DMSO at the α-position of the transient keteniminium species, and finally through enolization, iodination, and oxidation (Scheme 7).[13b−d,14] We therefore believe that the reaction involves a ketene *N*,*O*-acetal obtained in situ by the nucleophilic attack of DMSO to the β-iodoketeniminium species.

Although the mechanism of this cyclization is not yet fully known, a tentative mechanism is proposed on the basis of the above-mentioned results (Scheme 8). The reaction begins with the attack of DMSO onto the transient ketiniminium species I, obtained from the ynamide and NIS, to deliver ketene *N*,*O*-acetal II,[8] which undergoes S_N2-type 5-*exo-dig* cyclization with the NIS-activated tethered alkyne to give III.[15] TS-I preferably participates in the cyclization favoring the 5-*exo* mode attack over the conformationally unfavorable 6-*endo*-attack in TS II.[16] Expulsion of the allylic iodo group via attack of DMSO to the exocylic double bond then generates IV. Finally, iodide-mediated

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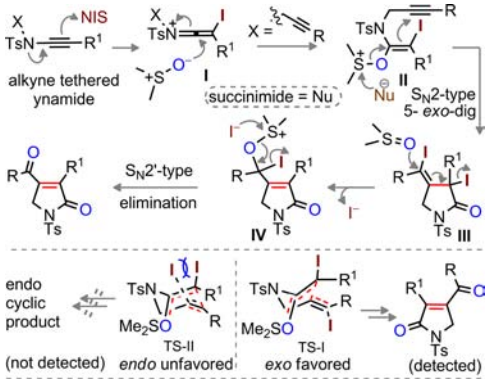
Scheme 8. Plausible Mechanism



nucleophilic displacement of the S and O bond of **IV** provides the desired product.[17,18]

In conclusion, a metal-free 5-*exo-dig* cyclization of yne-tethered ynamides is showcased for the first time; the reaction has a broad scope, furnishing peripherally decorated pyrrolidone and spiro-pyrrolidone derivatives. The 5-*exo-dig* cyclization of yne-tethered ynamides in the presence of the [DMSO + NIS] system is notable, as this species preferably undergoes 6-*endo-dig* cyclization under Au catalysis. A one-pot synthesis of spiro-pyrrolidone from the yne-tethered ynamide is also demonstrated. The cleavage of the *N*-Ts bond makes this process synthetically viable and useful.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01149.

Experimental details and spectral data (^{1}H, ^{13}C, and ^{19}F) (PDF)
HRMS data (PDF)
X-ray crystallographic data for **4a** (CIF)
X-ray crystallographic data for **6a** (CIF)

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Notes

The authors declare no competing financial interest.

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