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Radical Cyclization Cascade Involving Ynamides: An Original Access to Nitrogen-Containing Heterocycles

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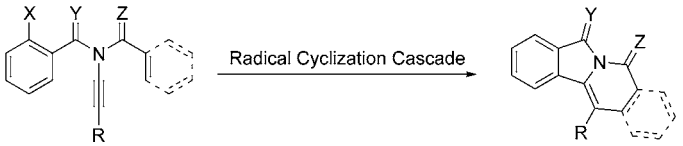
ABSTRACT



A radical cascade involving a *5-exo-dig* cyclization followed by a *6-endo-trig* radical trapping transforms ynamides into heterogeneous polycyclic compounds in good yields. This leads interestingly to the formation of isoindols, isoindolinones, and pyridoisoindolones.

In the past few years, interest in the chemistry of ynamides[1] has increased because of their greater stability as synthetic analogues of ynamines which were extensively studied in the 1970s.[1,2] Ynamides are easy to handle and their preparation is possible through several methods.[3] The reactivity of ynamides in metal catalyzed [2+2+1][4] and [2+2+2][5] cycloadditions, [2+2][6b] and [4+2][6] cycloadditions, metathesis,[7] and addition reactions[8] followed by palladium-catalyzed cross-coupling[9] or electrocyclic processes is now well-known and fully illustrates the synthetic power of these useful building blocks.

Although radical chemistry had proven to be a versatile tool for heterocycle synthesis,[11] to the best of our knowledge no radical process involving ynamides has been reported yet. Our group is deeply interested in radical cyclization cascades[12] and in the quest for new partners[12e,f] for radical chemistry. We report herein the first use of ynamides in radical cyclizations leading to polycyclic nitrogen hetero-

(1) For a recent review on ynamines and ynamides, see: Zificsak, C. A.; Mulder, J. A.; Hsung, R. P.; Rameshkumar, C.; Wei, L. *Tetrahedron* **2001**, *57*, 7575−7606.

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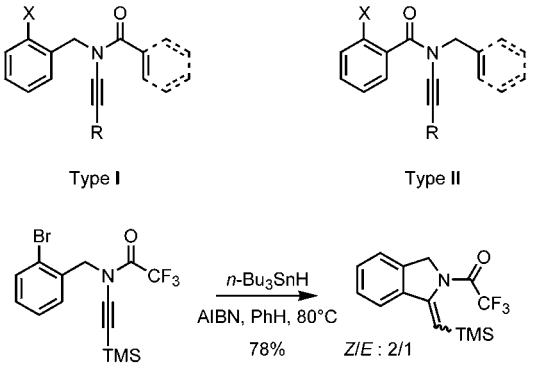
Scheme 1



cycles. The precursors were prepared according to Witulski's[3b] method, which involves the Michael addition of an amide to an alkynyliodonium salt. Desilylation[3b] and subsequent alkylation[3a] gave easy access to various substituted ynamides.

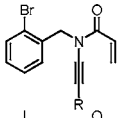
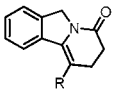
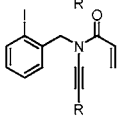
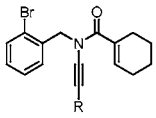
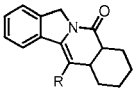
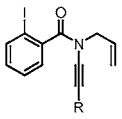
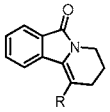
We were interested in the radical cyclization cascade of type **I** and **II** precursors (Scheme 1) for the synthesis of natural products. Toward this goal, we first examined the *5-exo-dig* cyclization with differently protected ynamides. First attempts to cyclize sulfonylynamides failed. The results could not be improved upon by changing the halogen atom or the nature of the sulfonyl group. These precursors reacted slowly and sluggishly to give only trace amounts of the *5-exo-dig* products in the case of the methanesulfonyl- and the trifluoromethanesulfonyl-protected ynamides.

Next we turned our attention to the trifluoroacetamide **1**, which cyclized in refluxing benzene in the presence of tin hydride and AIBN in 78% yield to give isoindol **2** as a mixture of two diastereomers on the double bond in a 2/1 ratio (Scheme 1). Noe experiments have shown that the *Z* diastereomer was the major compound, suggesting that the reduction of the vinylic radical was governed by its stability and therefore by allylic strain. The difference in reactivity between the sulfonamide and the carboxamide series could not be explained since radical cyclization of sulfonamide has been well studied in the literature.[11]

With this preliminary result in hand, we next assumed that the intermediate vinylic radical could be trapped by another unsaturation. Gratifyingly we could obtain a radical cyclization cascade with good yields when reacting type **I** precursors which contain an activated double bond (Table 1).

In the case of bromobenzyl precursors (**1**−**3** and **6**−**10**), the cyclization products could be observed only with silylated ynamides (**1**, **2**, and **6**−**8**). Slow addition of tin hydride was necessary to obtain the cascade products in good yields (**2** and **7**). For iodobenzyl compounds, the cyclization products were obtained in good yields without slow addition and in the case of silylated and terminal triple bonds (Table 1, **4** and **5**). This suggests that the addition of the tributylstannyl radical[13] is competitive with the bromine atom abstraction and is the major pathway when the ynamide is monosubstituted. The use of tristrimethylsilylsilane[14] as reductor to try to avoid this side reaction did not allow us to isolate any cyclization product in the case of the cyclohexenyl precursor (**8** and **10**). The observed products were issued from a radical cascade, which involves a 5-*exo-dig* cyclization followed by radical trapping in a 6-*endo-trig* mode for an activated terminal or endocyclic double bond. This cascade shows an excellent regioselectivity in the case of type **I** precursors which contain activated acceptors.

Table 1. Tandem Cyclization Leading to Nitrogen Heterocycles

entry	ynamide	product	R	yield[a]
type I				
1			TMS	42
2			TMS	70[b]
3			H	0[b]
4			TMS	83
5			H	54
6			TMS	45
7			TMS	75[b]
8			TMS	54[c]
9			H	0[b]
10			H	0[c]
type II				
11			TMS	90
12			H	78
13			Me	84
14			CO_2Et	45

[a] A benzene solution (15 mL) of ynamide (0.25 mmol), tin hydride (2 equiv), and AIBN (0.5 equiv) was refluxed until the strarting material disappeared. [b] Slow addition of the hydride was performed. [c] Tristrimethylsilylsilane was used as reductor.

The same *5-exo-dig*/*6-endo-trig* regioselectivity was observed when reacting type **II** compounds with nonactivated acceptors (Table 2). The substitution on the triple bond was also studied on type **II** compounds. To avoid the addition of tin on the triple bond we have chosen an iodine as the halogen atom. We obtained good yields for mono- and disubstituted ynamides. The yield decreased when the triple bond was activated with an ester group. The addition of tin then became possible and the yield could not be improved with slow addition of the hydride.

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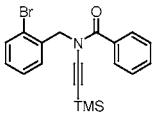
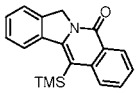
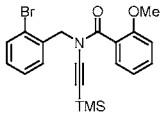
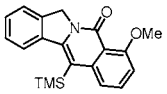
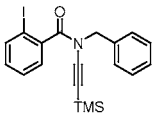
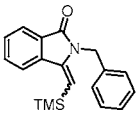
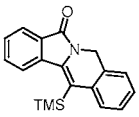
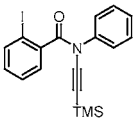
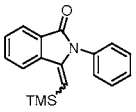
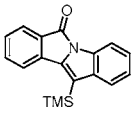
Table 2. Cyclization of Ynamides Bearing an Aromatic Terminator

entry	ynamide	product	*Z*/*E*	yield
type I				
1			-	67
2			-	54
type II				
3			1/1	57
4			-	46[a]
5			2/1	71
6			-	23
			-	62[a]

[a] Photolysis of hexabutylditin in toluene was used to perform the reaction.

Another part of this work concerns precursors of types **I** and **II** containing an aromatic acceptor (Table 2). In these cases, we observed two different reactivities for type **I** and type **II** compounds. We could isolate the product resulting from the trapping of the vinylic radical by the aromatic ring for type **I** compounds which gave the aromatized tetracyclic product in 67% (**1**) yield in 2 h using the standard cyclization conditions. No trace of the intermediate reduction product could be detected even when the aromatic ring was substituted by a methoxy group. In this case the cyclization yield and the reaction rate decreased slightly to 54% for 16 h (**2**) and no product issuing from an *ipso* cyclization[11d,15] followed by a rearrangement was isolated.

The carbonyl function plays an important role in the trapping rate. When reacting type **II** ynamides under the same conditions the major products isolated are the *iso*indolinones (**3** and **5**). The cascade cyclization products were only observed in less than 30% yield in the crude ^{1}H NMR even when slow addition of tin hydride was performed. When we carried out the reaction under atom transfer conditions to try to avoid the intermediate reduction products, type **II** precursors gave the tetracyclic products in 46% (40 h) and 62% (7 h) (**4** and **6**) yield. This suggests that the carbonyl influence in the radical trapping is due not only to an electronic effect but also to a steric factor.

We have demonstrated that ynamides are excellent partners for radical chemistry, we have described a new radical cyclization cascade that leads to isoindol, isoindolinones, and pyridoisoindolones in good yields. These results bring new perpectives for the development of ynamides and the application of their reactivity in the field of heterocyclic compound chemistry.

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Supporting Information Available: Experimental procedures and a description of spectroscopic and analytic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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