ORGANIC LETTERS

2011
Vol. 13, No. 11
2952–2955

Silver-Catalyzed Cycloisomerization of 1,n-Allenynamides

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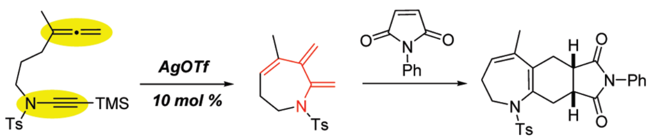
Received April 20, 2011

ABSTRACT



A variety of allenynamides can undergo cycloisomerization reactions in the presence of silver triflate thus leading to the formation of *N*-containing heterocycles incorporating cross-conjugated trienes. Access to new dienic 4-piperidinone and azepane motifs was achieved. An extension to one-pot tandem sequences involving silver-catalyzed cycloisomerization/Diels–Alder reaction was also examined.

Over the past decade, remarkable advances have been made in the field of ynamide chemistry. Numerous studies have illustrated the versatility of such a function in a range of reactions[1] featuring radical cascades, cycloadditions, ring closure metathesis, intramolecular carbopalladations, and cycloisomerization[2] transformations providing a diverse array of novel N-heterocyclic core structures for the synthesis of potential pharmacophores. For instance, in 2004, we showed that the $PtCl_2$-catalyzed ene-ynamide cycloisomerization can lead to original aza-1,3-dienes or aza-bicyclo compounds.[2a]

In this context, we decided to study the behavior of allenynamides in the presence of π-acid transition metals (M_T) such as copper(II), silver(I), platinum(II), and gold(I) salts. Considering that under π-acid catalysis allenynes react usually through initial triple bond activation,[3] we anticipated that the inherent polarization of the ynamide triple bond should allow a strong electrophilic activation by coordination of the metal and then trigger a nucleophilic attack from the allenic part to generate unusual reactive unsaturated piperidine allylic cation intermediates of type A (Scheme 1). The latter should evolve differently

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(1) (a) For recent reviews on ynamide chemistry, see: (a) DeKorver, K. A.; Li, H.; Lohse, A. G.; Hayashi, R.; Shi, Z.; Zhang, Y.; Hsung, R. P. *Chem. Rev.* **2010**, *110*, 5064. (b) Evano, G.; Coste, A.; Jouvin, K. *Angew. Chem., Int. Ed.* **2010**, *49*, 2840.

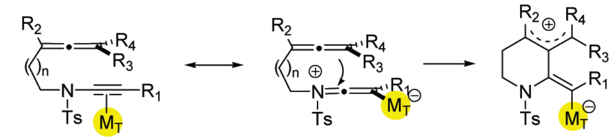
(2) (a) Marion, F.; Coulomb, J.; Courillon, C.; Fensterbank, L.; Malacria, M. *Org. Lett.* **2004**, *6*, 1509. (b) Marion, F.; Coulomb, J.; Servais, A.; Courillon, C.; Fensterbank, L.; Malacria, M. *Tetrahedron* **2006**, *62*, 3856. (c) Zhang, Y.; Hsung, R. P.; Zhang, X.; Huang, J.; Slater, B. W.; Davis, A. *Org. Lett.* **2005**, *7*, 1047. (d) Buzas, A.; Gagosz, F. *Org. Lett.* **2006**, *8*, 515. (e) Poloukhtine, A.; Popik, V. V. *J. Am. Chem. Soc.* **2007**, *129*, 12062. (f) Buzas, A.; Istrate, F.; Gagosz, F. *Tetrahedron* **2009**, *65*, 1889. (g) Hashmi, A. S.; Salathie, R.; Frey, W. *Synlett* **2007**, *11*, 1763. (h) Istrate, F. M.; Buzas, A. K.; Jurberg, I. D.; Odabachian, Y.; Gagosz, F. *Org. Lett.* **2008**, *10*, 925. (i) Lin, G.-Y.; Li, C.-W.; Hung, S.-H.; Liu, R.-S. *Org. Lett.* **2008**, *10*, 5059. (j) Hashmi, A. S.; Rudolph, M.; Bats, J.; Frey, W.; Rominger, F.; Oeser, T. *Chem.—Eur. J.* **2008**, *14*, 6672. (k) Yao, P.-Y.; Zhang, Y.; Hsung, R.; Zhao, K. *Org. Lett.* **2008**, *10*, 4275. (l) Dooleweerdt, K.; Ruhland, T.; Skrydstrup, T. *Org. Lett.* **2009**, *11*, 221. (m) Couty, S.; Meyer, C.; Cossy, J. *Angew. Chem., Int. Ed.* **2006**, *45*, 6726. (n) Couty, S.; Meyer, C.; Cossy, J. *Tetrahedron* **2009**, *65*, 1809.

(3) For a detailed review on transition-metal-catalyzed cycloisomerization of allenynes involving alkyne or allene activation, see: Aubert, C.; Fensterbank, L.; Garcia, P.; Malacria, M.; Simonneau, A. *Chem. Rev.* **2011**, *111*, 1954. For selected works of our group, see: (a) Cadran, N.; Cariou, K.; Hervé, G.; Aubert, C.; Fensterbank, L.; Malacria, M.; Marco-Contelles, J. *J. Am. Chem. Soc.* **2004**, *126*, 3408. (b) Zriba, R.; Gandon, V.; Aubert, C.; Fensterbank, L.; Malacria, M. *Chem.—Eur. J.* **2008**, *14*, 1482.

(4) For selected recent works on thermal [2 + 2] intramolecular isomerization of allenynes, see: (a) Cao, H.; Van Ornum, S. G.; Deschamps, J.; Flippen-Anderson, J.; Laib, F.; Cook, J. M. *J. Am. Chem. Soc.* **2005**, *127*, 933. (b) Brummond, K. M.; Chen, D. *Org. Lett.* **2005**, *7*, 3473. (c) Mukai, C.; Hara, Y.; Miyashita, Y.; Inagaki, F. *J. Org. Chem.* **2007**, *72*, 4454. (d) Jiang, X.; Ma, S. *Tetrahedron* **2007**, *63*, 7589. (e) Ohno, H.; Mizutani, T.; Kadoh, Y.; Aso, A.; Miyamura, K.; Fujii, N.; Tanaka, T. *J. Org. Chem.* **2007**, *72*, 4378. (f) Buisine, O.; Gandon, V.; Fensterbank, L.; Aubert, C.; Malacria, M. *Synlett* **2008**, 751. (g) Alcaide, B.; Almendros, P.; Aragoncillo, C. *Chem. Soc. Rev.* **2010**, *39*, 783.

10.1021/ol201041h
Published on Web 05/02/2011

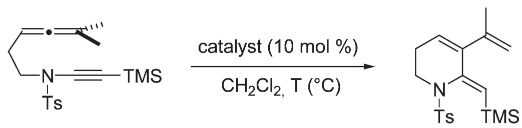
Scheme 1. Hypothesis on Reactivity of Allenynamides towards π-Acid Transition Metals (M_T)



according to the substitution pattern of both ynamide and allene partners.

We began our investigations with the 1,6-allenynamide **1a** containing a silylated ynamide (R_1 = TMS) and a trisubstituted allene (R_2 = H, R_3 = R_4 = Me). Control experiments confirmed that no reaction occurred under metal-free conditions.[4] Indeed, thermolysis of **1a** for 24 h at reflux in toluene resulted in a quantitative recovery of the starting material. Based on previous studies showing that allenynes can be cycloisomerized in the presence of platinum and gold salts,[3] we first selected $PtCl_2$ as well as AuCl as catalysts which rapidly proved to be inefficient (Table 1, entries 1−2). Conversely, the choice of the phosphine-coordinated gold complex, $AuClPPh_3$, in the presence or not of $AgSbF_6$ allowed access to the Alder-ene type cycloadduct **2a** showing a cross-conjugated triene moiety as a single diastereomer but in moderate yield and with incomplete conversion after 24 h under reflux in dichloromethane (Table 1, entries 3−4). The uncommon tetrahydromethylene vinylpyridine structure and the *Z*-configuration of the exocyclic double bond were both confirmed by X-ray analysis.[5] Yet, among the π-acid transition metals tested, silver salts were found to be the most efficient for the cycloisomerization[6] of **1a**. Total conversion was achieved with AgOTf after 24 h in dichloromethane at 25 °C and furnished **2a** in 61% isolated yield (Table 1, entry 6). Increasing the reaction temperature significantly reduced the reaction time but without improving the yield. Interestingly, the reaction can proceed with cheaper salts like $Cu(OTf)_2$, albeit in lower yield.

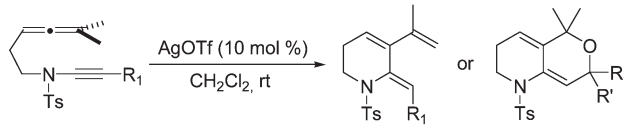
Table 1. Screening of Metal Salt Catalysts



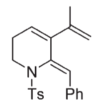
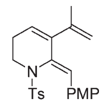
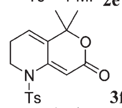
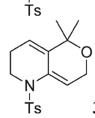
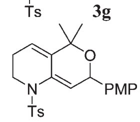
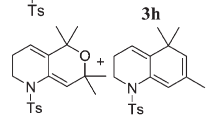
1a 2a

entry	catalyst	temp (°C)	time (h)	conv (%)	yield (%)
1	$PtCl_2$	reflux	48	0	0
2	AuCl	reflux	24	0	0
3	$AuClPPh_3$	reflux	24	80	40
4	$AuClPPh_3/AgSbF_6$	reflux	24	75	32
5	$AgSbF_6$	reflux	6	100	52
6	**AgOTf**	**25**	**24**	**100**	**61**
7	AgOTf	reflux	8	100	60
8	$Cu(OTf)_2$	25	2	100	52
9	$Cu(OTf)_2$	reflux	0.33	100	49

Table 2. Influence of the Ynamide Substitution



1 2 3

entry	R_1, substrate	time (h)	products	yield (%)
1	H, **1b**	24	-	-
2	Me, **1c**	24	-	-
3	Ph **1d**	2	 **2d**	90
4	PMP **1e**	2	 **2e**	95
5	C(O)OEt **1f**	2	 **3f**	99
6	CH_2OH **1g**	24	 **3g**	65
7	CH(PMP)OH **1h**	24	 **3h**	76
8	$C(Me)_2OH$ **1i**	24	 **3i** 1.9:1 **4**	53

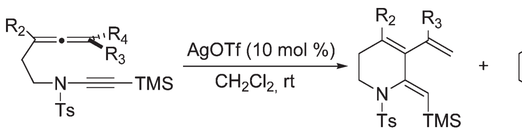
With these optimized reaction conditions in hand, we then examined the substrate scope by looking first at the influence of the substitution at the ynamide terminus. Unsubstituted and methyl-substituted ynamides **1b** and **1c** both gave a complex mixture of products (Table 2). While TMS compound **1a** required a long reaction time (24 h, see Table 1), an acceleration of the cycloisomerization process was evident when starting from allenynamide **1d** bearing a phenyl group. Indeed, within 2 h, a complete conversion toward the corresponding *Z*-Alder-ene product **2d** was observed. The introduction of a *para*-methoxy substituent to the aryl group (PMP) slightly improved the yield for a similar reaction time. Interestingly, performing the reaction with the ester-substituted substrate **1f** led to

(5) Crystallographic data deposited with the Cambridge Crystallographic Data Centre, Cambridge, UK (Reference CCDC 794305).

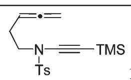
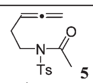
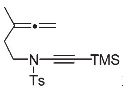
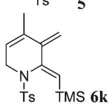
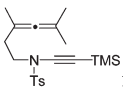
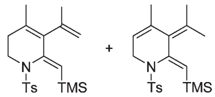
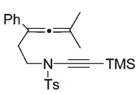
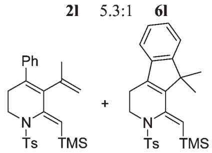
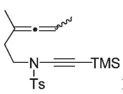
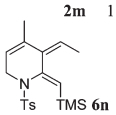
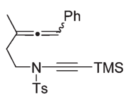
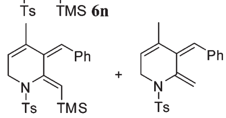
(6) (a) *Silver in Organic Chemistry*; Harmata, M., Eds.; John Wiley & Sons Inc.: 2010. For a recent review on silver-catalyzed cycloisomerization reactions, see: Belmont, P.; Parker, E. *Eur. J. Org. Chem.* **2009**, 6075.

the formation of the unexpected bicyclic lactone **3f** in an excellent yield after 2 h. The same feature was observed with propargylic alcohol moieties. The corresponding 2,3,5,7-tetrahydro-1*H*-pyrano[4,3-*b*]pyridine type compounds resulting from a tandem cycloisomerization and subsequent hydroxycyclization starting from **1g** and **1h** were isolated in moderate to good yields although a prolonged reaction time was required. Noteworthy, tertiary alcohol **1i** cyclized to **3i** accompanied with **4** resulting from a dehydrative cation-ene cyclization of **1i**.

Table 3. Influence of the Allene Substitution

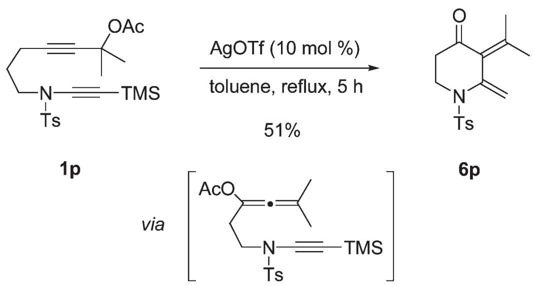


1 **2** **6**

entry	substrate	time (h)	products	yield (%)
1	 **1j**	18	 **5**	21
2	 **1k**	0.17	 **6k**	74
3	 **1l**	2	 **2l** 5.3:1 **6l**	85
4	 **1m**	24	 **2m** 1.2:1 **7**	70
5	 **1n**	0.17	 **6n**	79
6	 **1o**	3	 **6o** 3.3:1 **8**	75

The next parameter we investigated was the substitution of the allene function. Both the nature and the position of substituents proved to influence the cycloisomerization process. Thus, the unsubstituted TMS-allenynamide **1j** did not afford any cycloadduct. Instead, a slow and incomplete conversion to the corresponding acyclic acetamide **5** took place in dichloromethane at rt overnight (Table 3, entry 1).[7] As seen before, the presence of a *gem*-dimethyl group at the external allene carbon furnished the expected Alder-ene type compound **2a**. By contrast, a simple methyl substitution at the internal position generated the isomeric cross-conjugated triene **6k**[8] exhibiting an exocyclic 1,2-diene moiety potentially amenable to Diels–Alder reactions as shown later. Substitution at both extremities provided contrasted results. Indeed, permethylated allene **1l** subjected to the same reaction conditions gave a 5.3:1 mixture of isomeric trienes **2l** and **6l** in favor of the Alder-ene type product. By switching the internal group from methyl to phenyl, triene **2m** was formed in equal amounts along with the tricyclic pyridindene derivative **7** arising from a tandem Alder-ene type cycloisomerization/Friedel–Crafts process.[9] 1,3-Disubstitution at both internal and terminal positions provided exclusively compounds of type **6** whatever the nature of R_3 substituents (R_3 = Me or R_3 = Ph). The *Z,Z*-configuration of **6n** has been established by NOE experiments. When R_3 = Ph, both silylated and desilylated[10] adducts were formed in a 3.3:1 ratio.[11] Interestingly, shorter reaction times from 10 min to 3 h were observed with all substrates including a methyl at the internal position.

Scheme 2. Propargyl Acetate Rearrangement/Cycloisomerization Sequence



1p **6p**

Based on our experience on platinum and gold chemistry, one of the most attractive applications would be to combine, in a one-pot procedure, a silver-catalyzed propargyl acetate rearrangement to allenylester[12] with the cycloisomerization process. Gratifyingly, treatment of **1p** with 10 mol % of AgOTf in toluene at reflux during 5 h yielded the corresponding dienic 4-piperidinone system **6p** in 51% yield (Scheme 2).

(7) Due to the presence of water, formation of acetamide **5** from ynamide **1j** might take place first by TMS cleavage followed by the hydrolysis of the terminal ynamide. (a) For deprotection of trimethylsilyl acetylenes catalyzed by silver triflate, see: Orsini, A.; Viterisi, A.; Bodlenner, A.; Weibel, J.-M.; Pale, P. *Tetrahedron Lett*. **2005**, *46*, 2259. (b) For hydrolysis of ynamide, see: Zhang, X.; Li, H.; You, L.; Tang, Y.; Hsung, R. *Adv. Synth. Catal*. **2006**, *348*, 2437.

(8) The structure and the Z-configuration of the exocyclic double bond were both confirmed by X-ray analysis (Reference CCDC 794304).

(9) Lemière, G.; Gandon, V.; Agenet, N.; Goddard, J.-P.; de Kozak, A.; Aubert, C.; Fensterbank, L.; Malacria, M. *Angew. Chem., Int. Ed.* **2006**, *45*, 7596.

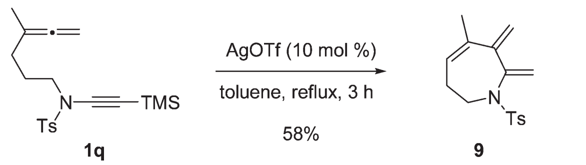
(10) Desilylation of the N-tosyl enamide motif presumably proceeds through a silver triflate activation of the double bond followed by a TMS cleavage of the intermediate **B** (Scheme 4).

(11) The *Z,Z* configuration of **6o** has been assigned by analogy with **6n**.

(12) For Ag-catalyzed [3,3] rearrangement of propargyl esters, see: (a) Saucy, G.; Marbet, R.; Lindlar, H.; Isler, O. *Helv. Chim. Acta* **1959**, *42*, 1945. (b) Schlossarczyk, H.; Sieber, W.; Hesse, M.; Hansen, H.-J.; Schmid, H. *Helv. Chim. Acta* **1973**, *56*, 875. (c) Oelberg, D. G.; Schiavelli, M. D. *J. Org. Chem.* **1977**, *42*, 1804. (d) Zhao, J.; Hughes, C. O.; Toste, F. D. *J. Am. Chem. Soc.* **2006**, *128*, 7436. (e) Cookson, R. C.; Cramp, M. C.; Parsons, P. J. *Chem. Commun.* **1980**, 197. (f) Bowden, B.; Cookson, R. C.; Davis, H. A. *J. Chem. Soc., Perkin Trans. 1* **1973**, 2634. (g) Sromek, A. W.; Kel'in, A. V.; Gevorgyan, V. *Angew. Chem., Int. Ed.* **2004**, *43*, 2280.

An extension of the cycloisomerization process to the formation of seven-membered rings was also envisaged. Homologation of the carbon chain of **1k** to **1q** provided azepane **9**, showing a desilylated cross-conjugated triene, in 58% yield when the reaction was carried out in toluene at reflux (3 h) (Scheme 3).[13]

Scheme 3. Application to Azepane Core Synthesis



The formation of the three classes of compounds, type **2**, **3** and **6**, can be rationalized mechanistically by first assuming a preliminary activation of the triple bond by the silver cation which promotes a 6-*exo*-dig cyclization. The transient intermediate can evolve along two different pathways depending on the stability of the allylic carbocation. Starting from terminal *gem*-disubstitued allenes, path **I** appears to be favored. In this case, when the ynamide is substituted by a nucleophilic alcohol or ester group, the cationic species $\mathbf{A_1}$ can be trapped intramolecularly to give the corresponding bicyclic compound **3** after protodemetalation;[14] otherwise a simple elimination/protodemetalation sequence can occur and furnish compound **(*Z*)-2**. Due to the steric hindrance between R_1 and R_3/R_4, the enamine double bond undergoes silver-catalyzed isomerization which justifies its *Z* configuration.[15] When the allene is substituted at the internal position, path **II** involving the formation of intermediate $\mathbf{A_2}$ and subsequent elimination/protodemetalation/isomerization operates preferentially to provide compound **6** (Scheme 4).

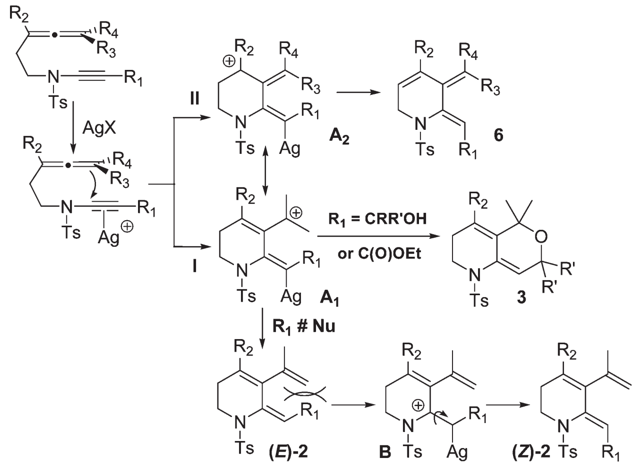
Finally, we tested the reactivity of trienes of type **6** and **9** toward dienophiles in a one-pot cycloisomerization/Diels–Alder sequence. To our delight, reaction of allenynamide **1k** in the presence of *N*-phenyl maleimide and 10 mol % silver triflate furnished tricycle **10** as the result of the expected tandem process. When performing the reaction in toluene at reflux rather than in CH_2Cl_2 at rt, homologous substrate **1q** followed the same trends and reacted with an appreciable 43% yield to form *endo*-desilylated 7,6,5-annulated heterocyclic system **11** (Scheme 5).

(13) Only 6% of cycloadduct were isolated when the reaction was performed at rt in CH_2Cl_2.

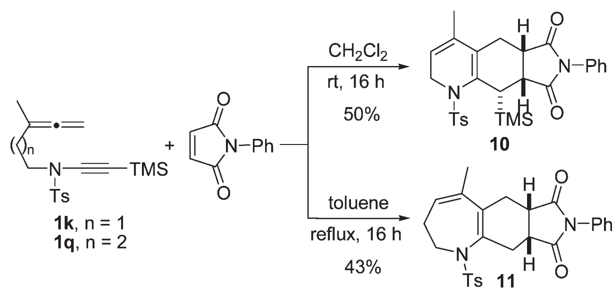
(14) It is noteworthy that formation of pyridindene derivative **7** follows the same pathway through an intramolecular Friedel–Crafts reaction.

(15) For *Z*/*E* isomerization of double bond promoted by silver triflate, see: (a) Goossen, L. J.; Ohlmann, D. M.; Dierker, M. *Green Chem.* **2010**, *12*, 197. (b) Zificsak, C. A.; Mulder, J. A.; Rameshkumar, C.; Wei, L.-L.; Hsung, R. P. *Tetrahedron* **2001**, *57*, 7575. (c) Himbert, G. In *Methoden Der Organischen Chemie (Houben-Weyl)*; Kropf, H., Schaumann, E., Eds.; Georg Thieme Verlag: Stuttgart, 1993; p 3267. (d) Ficini, J. *Tetrahedron* **1976**, *32*, 448.

Scheme 4. Proposed Reaction Mechanism



Scheme 5. Tandem Cycloisomerization/Diels–Alder Reactions



In summary, we have shown that cycloisomerization of allenynamides can take place in the presence of silver triflate. This efficient catalytic process provides the formation of novel isomeric tetrahydro pyridine-based trienes, 4-piperidinone, and also azepane motifs in good to excellent yields depending upon the substitution pattern of the allene moiety and the length of the side chain. Remarkably, formation of trienes in the presence of *N*-phenyl maleimide produces polycyclic ring systems *via* a cycloisomerization/Diels–Alder sequence. There is no doubt that such a method will be particularly appealing in the context of the total synthesis of alkaloids. Efforts along these lines are underway in our laboratory.

Acknowledgment. We thank UPMC, CNRS, IUF (M.M., L.F.), and Agence Nationale de la Recherche (Grant No. ANR-06-BLAN-03-02, "ALLENES").

Supporting Information Available. Experimental procedures, characterization data, X-ray data, and NMR spectra of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.