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Platinum Dichloride-Catalyzed Cycloisomerization of Ene-ynamides

Frédéric Marion, Julien Coulomb, Christine Courillon, Louis Fensterbank,* and Max Malacria*

Laboratoire de Chimie Organique, Associé au CNRS, Université Pierre et Marie Curie, B. 229, 4 Place Jussieu, 75252 Paris Cedex 05, France

fensterb@ccr.jussieu.fr; malacria@ccr.jussieu.fr

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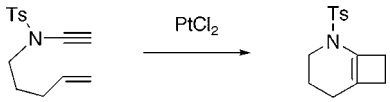
ABSTRACT



Various ene-tosylynamides react with platinum(II) chloride and lead to bicyclic nitrogenated heterocycles. This unprecedented and easily operated process can be coupled with a hydrolysis of the intermediate cyclic tosylenamides in a one-pot transformation, which provides cyclobutanones.

The transition metal-catalyzed cycloisomerization of enyne systems is a powerful synthetic tool that has witnessed intense development.[1] Nevertheless, there is still room for the implementation of new partners in this process. Among all potential candidates, ene-tosylynamides are highly appealing substrates that, to the best of our knowledge, have never been examined in this context.[2,3] Because of the presence of the nitrogen atom directly attached to the triple bond, one can anticipate charge-controlled processes.[3] This led us to the use of platinum(II) dichloride as a catalyst, since this versatile reagent is known to promote charge buildup on enyne systems.[4,5] In addition, the resulting products should incorporate valuable nitrogen heterocycles.

We have already demonstrated the synthetic potential of such an approach in the radical cascade field.[6] Herein, we describe our preliminary results of a versatile organometallic process that transforms different ene-tosylynamides, in the presence of $PtCl_2$, into bicyclic nitrogenated heterocycles.

Different methods have been reviewed in the literature describing the preparation of tosylynamides.[7] Direct alkylation of tosylamines with alkynyliodonium salts in the presence of a base has been notably reported by Witulski.[8] In our hands, the alkynyliodonium salts trick has always been efficient.[6] We have also followed Brückner's alternative transformation of formamides.[9] This procedure allowed us to obtain various ene-tosylynamides that are utilized in this work as precursors of original $PtCl_2$-catalyzed cycloisomerizations.

Our first attempt consisted of exposing ene-ynamide **1** to $PtCl_2$ (5 mol %) in toluene at 80 °C and led to the metathesis

(1) For a review: Aubert, C.; Buisine, O.; Malacria, M. *Chem. Rev.* **2002**, *102*, 813.
(2) For previous works in RCM, see: (a) Saito, N.; Sato, Y.; Mori, M. *Org. Lett.* **2002**, *4*, 803. (b) Huang, J.; Xiong, H.; Hsung, R. P.; Rameshkumar, C.; Mulder, J. A.; Grebe, T. P. *Org. Lett.* **2002**, *4*, 2417.
(3) For a review on transition metal-mediated cycloadditions of ynamides, see: Zificsak, C. A.; Mulder, J. A.; Hsung, R. P.; Rameshkumar, C.; Wei, L.-L. *Tetrahedron* **2001**, *57*, 7575. See also: Witulski, B.; Alayrac, C. *Angew. Chem., Int. Ed.* **2002**, *41*, 3281.
(4) (a) Chatani, N.; Kataoka, K.; Murai, S.; Furukawa, N.; Seki, Y. *J. Am. Chem. Soc.* **1998**, *120*, 9104. (b) Méndez, M.; Muñoz, M. P.; Nevado, C.; Cárdenas, D. J.; Echavarren, A. M. *J. Am. Chem. Soc.* **2001**, *123*, 10511. (c) Fürstner, A.; Szillat, H.; Gabor, B., Mynott, R. *J. Am. Chem. Soc.* **1998**, *120*, 8305. (d) Fürstner, A.; Stelzer, F.; Szillat, H. *J. Am. Chem. Soc.* **2001**, *123*, 11863. (e) Nevado, C.; Cárdenas, D. J.; Echavarren, A. M. *Chem. Eur. J.* **2003**, *9*, 2677. (f) For reviews, see: Méndez, M.; Mamane, V.; Fürstner, A. *Chemtracts* **2003**, *16*(7), 397. (g) Lloyd-Jones, G. C. *Org. Biomol. Chem.* **2003**, *1*, 215.
(5) Mainetti, E.; Mouriès, V.; Fensterbank, L.; Malacria, M.; Marco-Contelles, J. *Angew. Chem., Int. Ed.* **2002**, *41*, 2132. For the reactivity of allenyne systems, see: Cadran, N.; Cariou, K.; Hervé, G.; Aubert, C.; Fensterbank, L.; Malacria, M.; Marco-Contelles, J. *J. Am. Chem. Soc.* **2004**, *126*, 3408.
(6)) Marion, F.; Courillon, C.; Malacria, M. *Org. Lett.* **2003**, *5*, 5095.
(7) (a) Frederick, M. O.; Mulder, J. A.; Tracey, M. R.; Hsung, R. P.; Huang, J.; Kurtz, K. C. M.; Shen, L.; Douglas, C. J. *J. Am. Chem. Soc.* **2003**, *125*, 236. (b)Wie, L.-L.; Mulder, J. A.; Xiong, H.; Zificsak, C. A.; Douglas, C. J.; Hsung, R. P. *Tetrahedron* **2001**, *57*, 459.
(8) Witulski, B.; Stengel, T. *Angew. Chem., Int. Ed.* **1998**, *37*, 489.
(9) Brückner, D. *Synlett* **2000**, 1402.

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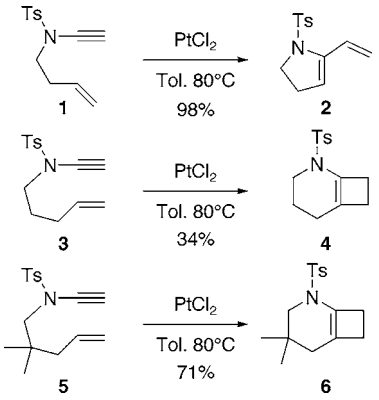
product **2** in 98% yield, whose structure was secured by comparison to Mori's data (Scheme 1). Mori has indeed

Scheme 1. Transformation of Ene-tosylynamides with $PtCl_2$

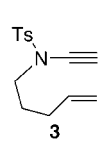
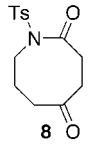
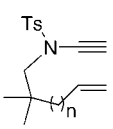
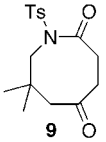


investigated the ring-closing metathesis transformation of **1** and found out that this reaction was accelerated in the presence of the second-generation Grubb's catalyst.[2] Moreover, she performed efficient ring-closing metathesis with several precursors bearing a different carbon tether between the amide function and the carbon−carbon double bond like precursors **3** and **5**. We show here a completely distinct and original reactivity of these substrates in the presence of platinum dichloride. Thus, in the case of ene-tosylynamide **3**, cyclization occurred and yielded the bicyclic[4.2.0] compound **4**.[10] This fragile structure, partially degrading during the purification process, was obtained in 44% yield, which we had some difficulty in reproducing since these reactions proved to be sensitive to moisture. The bicyclic derivative **6** was similarly obtained by reacting the *β*-dimethyl-substituted ene-ynamide **5** with 5−10 mol % equiv of $PtCl_2$ in 71% yield. The structural assignment for **4** and **6** was based on the following data: ^{1}H NMR spectra show no stereogenic center and ^{13}C NMR spectra display no CH signal, indicating that the double bond is shared by the two cycles. Quaternary carbon signals around 122 and 135 ppm confirm the structure of the bicyclic product. These platinum(II)-catalyzed cyclizations could not easily be monitored by TLC because of the close R_f values for the product and the starting material that, in addition, appear as faint spots. Therefore, we followed the consumption of the ene-ynamide by IR spectroscopy and checked the vanishing of the triple-bond band.

Because of the general lability of the final products,[11] we decided to transform the crude bicyclic products directly into more stable compounds through a second reaction in a one-pot process.

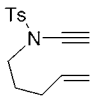
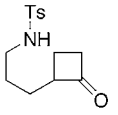
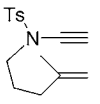
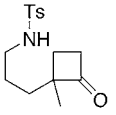
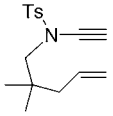
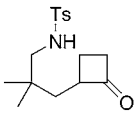
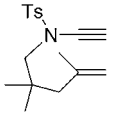
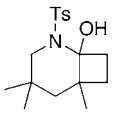
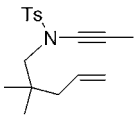
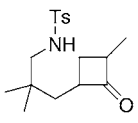
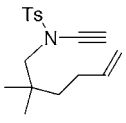
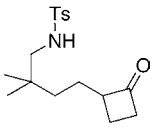
First, we performed ozonolysis, which provided easily isolable keto-lactams **8**−**10**, which could be useful building blocks in total synthesis of more complex alkaloid natural products.[12] Nevertheless, the moderate yields (Table 1), yet

Table 1. Ozonolysis

ynamides	keto-lactams	yield(%)
 **3**	 **8**	20
 n = 1 : **5**	 n = 1 : **9**	37
n = 2 : **7**	n = 2 : **10**	24

consistent with the literature,[13] drove us to switch to a hydrolysis reaction as the second step. Thus, after cycloisomerization reaction in the presence of 10 mol % $PtCl_2$, addition of a 1 M HCl solution to the crude cycloisomerized product gave cyclobutanones formed by hydrolysis of the intermediate enamines. The results of this cyclization−hydrolysis sequence are summarized in Table 2.

Table 2. Cyclization−Hydrolysis−Sequence

ynamides	cyclobutanones	ynamides	cyclobutanones
 **3**	 **11**(65%)	 **15**	 **16**(54%)
 **5**	 **12**(85%)	 **17**	 **18**(76%)
 **13**	 **14**(70%)	 **7**	 **19**(40%)

The four-atom-tethered substrates **3** and **5** are transformed in good yields into the corresponding cyclobutanones **11** and

(10) Isolation of cyclobutenes from metal-catalyzed [2 + 2] of enynes has been described, see: (a) Pd(II): Trost, B. M.; Yanai, M.; Hoogsten, K. *J. Am. Chem. Soc.* **1993**, *115*, 5294. (b) Trost, B. M.; Tanoury, G. J. *J. Am. Chem. Soc.* **1988**, *110*, 1636. In the latter case, the double bond is shifted to give a more stable cyclobutene product. (c) Pt(II): see ref 4d. (d) Pt(IV): Blum, J.; Beer-Kraft, H.; Badrieh, Y. *J. Org. Chem.* **1985**, *60*, 5567. In this particular case, the cyclobutene adduct reacts with O_2. (e) Ga(III): Chatani, N.; Inoue, H.; Kotsuma, T.; Murai, S. *J. Am. Chem. Soc.* **2002**, *124*, 10294.

(11) For a related report of instability, see: Smith, A. B., III; Cui, H. *Org. Lett.* **2003**, *5*, 587. See also ref 10d.

(12) Martin, S. F.; Chen, H.-J.; Courtney, A. K.; Liao, Y.; Pätzel, M.; Ramser, M. N.; Wagman, A. S. *Tetrahedron* **1996**, *52*, 7251.

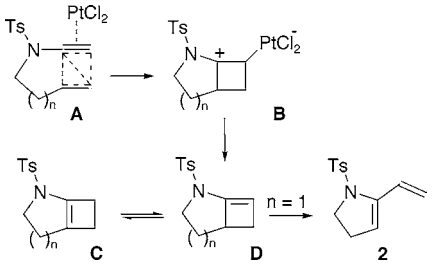
(13) (a) Strobel, M. P.; Morin, L.; Paquer, D. *New. J. Chem.* **1980**, *4*, 603. (b) Mahajan, J. R.; Ferreira, A. L.; Araújo, H. C.; Nunes, B. J. *Synthesis* **1976**, 112.

12. Alkyl substitution is tolerated both on the alkyne partner (precursor **13**) and on the alkene partner (precursors **15** and **17**). In the case of **17**, the nonopened bicyclic aminal **18** was obtained in 76% yield. As anticipated, introduction of a gem-dimethyl group in the tether resulted in improved yields (substrates **3** and **15** vs **5** and **17**).[14]

When the tether was lengthened to up to five atoms, corresponding to intermediate **7**, the 4-bicyclic adduct still gave a satisfactory yield of cyclobutanone **19**. In this case, some aminal could also be observed in the crude product but was not isolated after separation on silica gel.

The original results summarized in Scheme 1 and in both Tables 1 and 2 are consistent with the formation of bicyclic intermediates **C** and **D**, with the double bond either exo or endo at the ring junction. Following Fürstner's cationic manifold proposal,[4c,d,f] initial π-complexation of the alkyne partner would generate the nonclassical "homoallyl-cyclopropylmethyl-cyclobutyl" cation, best represented under the canonical form **B**.[15]

Scheme 2. $PtCl_2$-Catalyzed Cyclization Mechanism



Metal elimination from **B** then would produce **D**, which could isomerize to form **C** by proton-catalyzed process. The **C**:**D** ratio would be controlled by the ring strain associated with the bicyclic edifice. For $n = 1$, the double bond remains exo and cyclobutene **D** undergoes an electrocyclic ring opening leading to the metathesis adduct **2**. For $n = 2$ or 3, an intermediate of type **C** would be favored as demonstrated by the isolation of **4** and **6**. However, in the case of precursors **15** and **17**, intermediate **C** is not attainable. Instead, an intermediate of type **D**[16] could also lead to the hydrolysis products **14** and **16**.

In conclusion, we herein report the first use of ene-ynamides as versatile partners for $PtCl_2$-catalyzed cycloisomerization reactions. A formal [2 + 2] cycloaddition gives birth to versatile cyclobutenyl bicyclic substrates that we could ozonolyze to provide medium-sized nitrogen heterocycles and hydrolyze to give various cyclobutanone derivatives. In the latter case, the reaction corresponds to an intramolecular addition of a ketene on the alkene partner via a nitrogen tether. These preliminary elements of reactivity confirm the high synthetic potential of the introduction of ene-ynamides in organometallic chemistry and pave the way for important applications we will disclose in due course.

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Supporting Information Available: Experimental procedures and description of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) Jung, M. E.; Gervay, J. *J. Am. Chem. Soc.* **1991**, *113*, 224.

(15) Intermediacy of cyclopropylcarbene species is also conceivable; see ref 4e and references therein.

(16) Analysis of the crude cycloisomerization product from precursor **15** is consistent with the formation of an *exo*-cyclobutene intermediate.