MOL2NET, International Conference Series on Multidisciplinary Sciences
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A more efficient catalyst for the cycloisomerization of alkynoic acids

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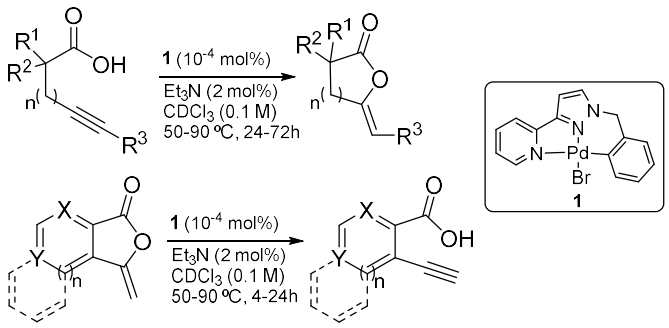
Graphical Abstract



Abstract.

A number of terminal and internal alkynoic acids with different substitution patterns have been efficiently cycloisomerized to the corresponding exocyclic enol lactones in the presence of low amounts of a non-symmetric NNC palladium complex and a catalytic amount of triethylamine.

Introduction

According to atom economy, the cycloisomerization of alkynoic acids is an advantageous option to synthesize γ or δ-alkyliden lactones, structures present in several natural products, biologically active compounds[1] and valuable synthetic intermediates.[2]. A number of transition metals have been employed as catalysts in this reaction.[3] However, relatively high catalyst loadings (10-0.01 mol%), prolonged reaction times and/or high temperatures are often required. In this context, the development of more efficient catalysts that overcome the above limitations has attracted much attentiont.[4] Herein we report the application of non-symmetrical NNC pincer complex **1** (Figure 1) to the cycloisomerization reaction of alkynoic acids.

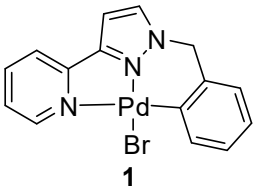


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Figure 1. Structure of the NNC type palladium catalyst used in this study.

Materials and Methods

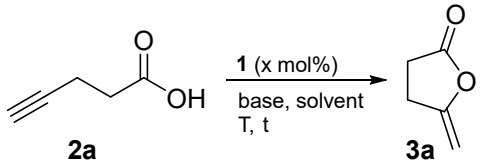
The alkynoic acid **2** (0.2 mmol), triethylamine (25 mL of a 0.16M solution in $CHCl_3$, $4x10^{-3}$ mmol), palladacycle 1 (50 mL of a $4x10^{-6}$M solution in $CHCl_3$, $2x10^{-7}$mmol) and $CDCl_3$ (2 mL) were placed in a screw-capped tube and heated in an oil bath at the indicated temperature for an appropriate time. The reaction mixture was subsequently filtered through a short plug of silica gel to remove triethylamine,

thus providing pure lactone **3**, or alternatively, purified by flash column chromatography using hexanes:EtOAc (7:3) in the referred cases. The progress of the reaction was monitored by ^{1}H NMR.

Results and Discussion

We began our research exploring the cycloisomerization of 4-pentynoic acid **2a** into 5-methylenedihydrofuran-2(3*H*)-one **3a**(Table 1). We used deuterated solvents in order to observe easily the formation of the target lactone in the reaction medium. We set the initial catalyst loading and reaction concentration at 10^{-2} mol% and 0.1 M. These initial assays shown that, on one hand, the presence of a base and, specifically, the presence of triethylamine was crucial to obtain the lactone (entry 1-6). Fortunately, a catalytic amount of this base was enough to achieve good results (entry 10). Moreover, moderate heating was necessary to obtain acceptable yields (entry 8 vs entry 5). On the other hand, deuterium chloroform shown to be a good solvent for this reaction since poor yields were obtained when dichloromethane was used (entry 8 vs 9). Finally, we probe that the use of palladium catalyst was indispensable to cycloisomerize the acid (entry 18,19). This catalyst shown to be highly efficient since just a 10^{-4}mol% provided the target lactone in excellent yield (entry 16, 17), although longer reaction times and higher temperatures were needed. Considering all studied parameters, we selected the conditions shown in Table 1, entry 14.

Table 1.Cycloisomerization of 4-pentynoic acid in the presence of palladium pincer complex **1**[a]



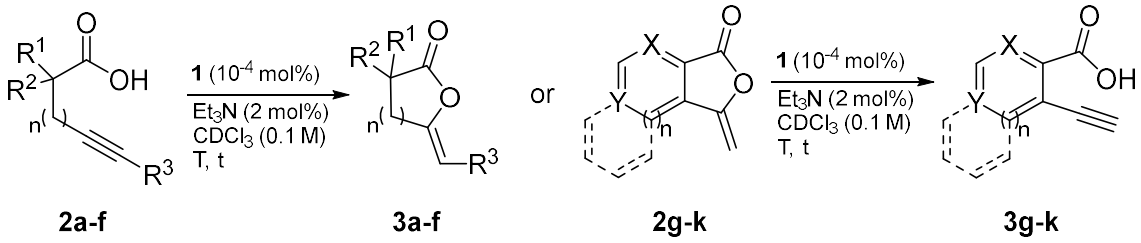
Entry	Solvent	**1** (mol%)	Base	T (ºC)	T (h)	Conversion (%)[b]
1	$CDCl_3$	10^{-2}	---	rt	2	---
2	CD_3COCD_3	10^{-2}	---	rt	2	---
3	$CDCl_3$	10^{-2}	K_2CO_3 (5 mol%)	rt	2	---
4	$CDCl_3$	10^{-2}	Et_3N (5 mol%)	rt	2	27
5	CD_3COCD_3	10^{-2}	Et_3N (5 mol%)	rt	2	---
6	$CDCl_3$	10^{-2}	KO-t-Bu (5 mol%)	rt	2	---
7	$CDCl_3$	10^{-2}	Et_3N (5 mol%)	90	12	99
8	$CDCl_3$	10^{-2}	Et_3N (5 mol%)	50	12	99
9	CH_2Cl_2	10^{-2}	Et_3N (5 mol%)	50	12	11
10	$CDCl_3$	10^{-2}	Et_3N (2mol%)	90	12	99
11	$CDCl_3$	10^{-2}	Et_3N (10mol%)	90	12	70
12	$CDCl_3$	10^{-2}	Et_3N (2mol%)	50	12	99
13	$CDCl_3$	10^{-3}	Et_3N (2 mol%)	50	24	99
14	$CDCl_3$	10^{-4}	Et_3N (2 mol%)	50	24	99
15	$CDCl_3$	10^{-5}	Et_3N (2 mol%)	50	24	83
16	$CDCl_3$	10^{-5}	Et_3N (2 mol%)	90	12	99
17	$CDCl_3$	10^{-4}	Et_3N (2 mol%)	50	12	72
18	$CDCl_3$	---	Et_3N (2 mol%)	50	24	---
19[c]	$CDCl_3$	10^{-4}	Et_3N (2 mol%)	50	24	---

[a]Reaction conditions: 4-pentynoic acid **x** (0.2 mmol), solvent (0.1M). [b]Conversion rate determined by ^{1}H NMR spectroscopy. [c]$Pd(OAc)_2$.

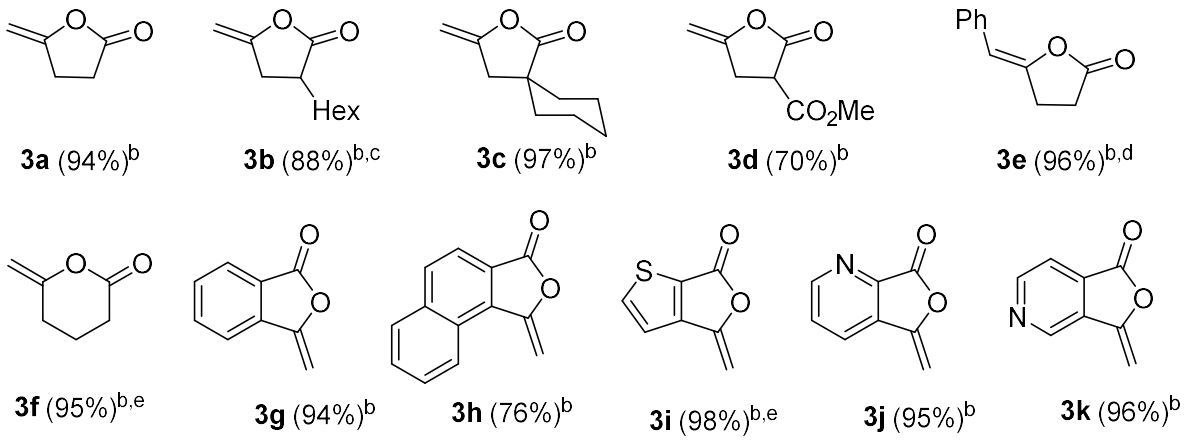
Employing mentioned conditions, we synthetized a series of enol lactones. As shown in Table 2, our protocol tolerated the presence of different substituents at the α-position to the carboxy group (compounds 3**b-3c**), although higher temperature were required. It is worth mentioning that benzylidenelactone**3e**was obtained with complete diastereoselectivity. On the other hand, rigid aromatic

and heteroaromatic 4-alkynoics acids (**acids 2g-2k**) were also cycloisomerized under optimized reaction conditions in excellent yields.

Table 2. Cycloisomerization of alkynoic acids in the presence of palladium complex **1**.[a]



2a-f **3a-f** **2g-k** **3g-k**



3a (94%)[b] **3b** (88%)[b,c] **3c** (97%)[b] **3d** (70%)[b] **3e** (96%)[b,d]

3f (95%)[b,e] **3g** (94%)[b] **3h** (76%)[b] **3i** (98%)[b,e] **3j** (95%)[b] **3k** (96%)[b]

[a] Reaction conditions: alkynoic acid **x** (0.2 mmol), palladium complex 1 (10^{-4}mol%), Et3N (2 mol%), $CDCl_3$ (2 mL), 50 ºC, 24h. [b] Isolated yields. [c] 70 ºC.[d] 72 h. [e] 90 ºC. [f] 4h.

Conclusions

In conclusion, γ- alkylidene lactones can be easily obtained through the cycloisomerization of the corresponding acetylenic acid in the presence of very low amounts (10^{-4}mol%) of palladium pincer complex **1**. This procedure shows tolerance to a variety of functional groups on the α position of the acetylenic acids.

References

1.See forexample: a) Y. Haga, M. Okazaki, Y. Shuto, *Biosci. Biotechnol. Biochem*. **2003**, *67*, 2183; b) R. Raju, R. Garcia, R. Mgller, *J. Antibiot*. **2014**, *67*, 725. c) F. von der Ohe, R. Bruckner, *New J. Chem*. **2000**, *24*, 659; d) M. Tori, K. Otose, H. Fukuyama, J. Murata, Y. Shiotani, S. Takaoka, K. Nakashima, M. Sono, M. Tanaka, Tetrahedron**2010**, *66*, 5235. e) H. R. Weiss, U.S. Patent 5,208,244, **1993**; f) S. Ibrahimi, G. Sauve, J. Yelle, E. M. Essassi, C. R. Chim. **2005**, *8*, 75; seealso: f) S. K. Kutty, B. Barraud, A. Pham, G. Iskander, S. A. Rice, D. S. Black, N. Kumar, J. Med. Chem. **2013**, *56*, 9517; g) A. Ghantous, A. Sinjab, Z. Herceg, N. Darwiche, Curr. DrugTargets**2013**, *18*, 894.

2.Some examples: a) C. Roussel, R. Fihi,K. Ciamala, J. Vebrel, T. Zair, *Org. Biomol. Chem*.**2003**, *1*, 2689; b) W. K. Goh, G. Iskander, S. S.Black, N. Kumar, *TetrahedronLett*. **2007**, *48*, 2287; c) E. C. Salo, K. R.Dayak, J. Huxford, P. H. Wei, N. J. Peraino, N. J. Kerrigan,*Arkivoc***2014**, *285*; d) Z. D. Dunn, W. J.Wever, N. J. Economou, A. A. Bowers, B. Li, *Angew.Chem*. **2015**, *127*, 5226; *Angew. Chem. Int. Ed.***2015**, *54*,5137; e) S.-S. Xie, X. Wang, N. Jiang, W. Yu, K. D. G.Wang, J.-S. Lan, Z.-R. Li, L.-Y. Kong, *Eur. J. Med.Chem*. **2015**, *95*, 153; f) C. Qu, P. Xu, W. Ma, Y. Cheng,C. Zhu, *Chem. Commun*. **2015**, *51*, 13508.

3. Seeforexample: a) B. M. Trost, A. McClory, *Angew. Chem*. **2007**, *119*, 2120; *Angew. Chem. Int. Ed*. **2007**, *46*, 2074; b) W. Dai, J. A. Katzenellenbogen, *J. Org. Chem*. **1993**, *58*, 1900; c) M. Jimenez-Tenorio, M. C. Puerta, P. Valerga, F. J.Moreno-Dorado, F. M. Guerra, G. M. Massanet, *Chem. Commun*. **2001**, 2324; d) M. M. Rammah, M. Othman, K. Ciamala, C. Strohmann, M. B. Rammah, *Tetrahedron***2008**, *64*, 3505; b) R. Nolla-Saltiel, E. Robles-Marin, S. Porcel, *TetrahedronLett*. **2014**, *55*, 4484; e) E. Genin, P. Y. Toullec, S. Antoniotti, C. Brancoukmr, J.-P. GenÞt, V. Michelet, *J. Am. Chem. Soc.***2006**, *128*, 3112; f) F. Neatu, Z. Li, R. Richards, P. Y. Toullec, J.-P. GenÞt, K. Dumbuya, J. M. Gottfried, H. P. Steinrgck, V. I. Prvulescu, V. Michelet, *Chem. Eur. J.***2008**, *14*, 9412; g) E. Tom#s-Mendivil, P. Y. Toullec, J. Díez, S. Conejero, V. Michelet,

V. Cadierno, *Org. Lett*. **2012**, *14*, 2520; h) T. L. Mindt, R. Schibli, *J. Org. Chem*. **2007**, *72*, 10247; i) M. E. Lopez-Reyes, R. A. Toscano, J. G. Lopez-Cortes, C. Alvarez-Toledano, *Asian J. Org. Chem*. **2015**, *4*, 545; j) F. Neatu, L. Protesescu, M. Florea, V. I. P.rvulescu, C. M. Teodorescu, N. Apostol, P. Y. Toullec, V. Michelet, *Green Chem*. **2010**, *12*, 2145; k) J. Garcia-Alvarez, J. Diez, C. Vidal, *Green Chem*. **2012**, *14*, 3190.

4. a) N. Nebra, J. Monot, R. Shaw, B.Martin-Vaca, D. Bourissou, *ACS Catal.***2013**, *3*, 2930; b) G. Hamasaka, Y. Uozumi, *Chem. Commun.***2014**, *50*,14516; c) N. Nebra, J. Monot, R. Shaw, B. Martin-Vaca,D. Bourissou, *ACS Catal*. **2014**, *4*, 3605; d) J. Monot, P.Brunel, C. E. Kefalidis, N. A. Espinosa-Jalapa, L.Maron, B. Martin-Vaca, D. Bourissou, *Chem. Sci*. **2016**,*7*, 2179.