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Synthesis of Seven-membered Lactones via Nickel- and Zinc-Catalyzed Highly Regio- and Stereoselective Cyclization of 2-Iodobenzyl Alcohols with Propiolates

Dinesh Kumar Rayabarapu and Chien-Hong Cheng*

Department of Chemistry, Tsing Hua University, Hsinchu, Taiwan 300

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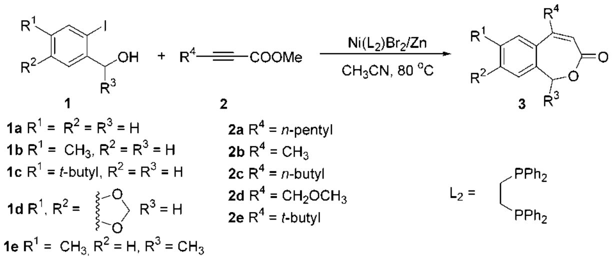
New methods for the synthesis of seven-membered ring compounds are attractive in view of the fact that a large number of these compounds have shown various interesting biological activities[1,2] and that they are difficult to prepare by conventional methods.[3] Recently, the use of *o*-iodobenzene derivatives and alkynes for the synthesis of five- or six-membered ring carbocycles[4,5] or heterocycles[6] catalyzed by palladium complexes has attracted great attention. Despite the synthetic significance of seven-membered ring lactones, only a few successful metal-catalyzed reactions for the synthesis are known.[7−10] Intramolecular cyclocarbonylations[11] of 2-allylphenols[8] catalyzed by Pd complexes and allenyl alcohols[9] catalyzed by a Ru complex were reported. For the intermolecular version, only a single example via cyclization of iodobenzyl alcohol, norbornene, and CO in the presence of Pd/TlOAc system was shown by Grigg et al.[10] In all reactions, CO gas was used. Our interest in the nickel-catalyzed[12−14] reactions encouraged us to investigate an alternative mild approach for the lactone synthesis via propiolate chemistry. Herein, we report a novel highly regio- and stereoselective cyclization of iodobenzyl alcohol with alkyl propiolates mediated by nickel complexes to afford seven-membered lactones. This new ring-closure reaction provides a convenient method to synthesize lactones in one pot from easily available starting materials. In addition, the catalytic mechanism for the cyclization is extremely interesting, requiring both nickel and zinc halides as the catalysts and involving an unusual *E*/*Z* isomerization of the carbon−carbon double bond prior to lactone formation.

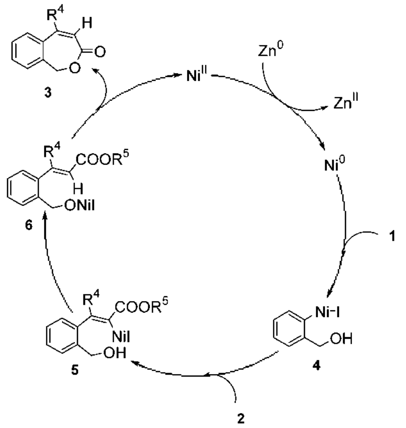
The reaction of 2-iodobenzyl alcohol (**1a**) and methyl 2-octynoate (**2a**) in the presence of Ni(dppe)Br$_2$ and zinc metal powder under N$_2$ in CH$_3$CN at 80 °C gave seven-membered lactone **3a** in 87% yield (Scheme 1 and Table 1). The structure of **3a** was confirmed by its ^{1}H, ^{13}C NMR, DEPT, and high-resolution mass data.

Similar to Ni(dppe)Br$_2$, several nickel complexes including Ni(PPh$_3$)$_2$Br$_2$, Ni(bipy)Br$_2$ Ni(dppm)Br$_2$, Ni(dppp)Br$_2$, Ni(dppf)Br$_2$, and Ni(dppe)Cl$_2$ showed substantial catalytic activity for the cyclization of **1a** with **2a** giving **3a** in 65−85% yield. Among the solvents examined, THF, toluene, DCM, and DMF afforded very low product yields or gave no desired product. CH$_3$CN appears to be the best choice of the solvents used for this catalytic reaction.

Scheme 1



Scheme 2



The cyclization can be successfully extended to other substituted propiolates. The results for the reaction of **1a** with various alkylpropiolates are summarized in Table 1. Thus, **1a** reacted with methyl 2-butynoate (**2b**) in the presence of Ni(dppe)Br$_2$ and Zn at 80 °C to afford lactone **3b** in 65% yield. Similarly, reaction of **1a** with propiolates **2c**−**e** afforded the corresponding seven-membered lactones in fair-to-good yields (Table 1, entries 3−5). To further explore the scope of the present catalytic reaction, iodobenzyl alcohols with substituents at the aromatic ring or at the carbon where the hydroxyl group is attached were employed for reaction with propiolates (Scheme 1). Thus, 3-methyl-2-iodobenzyl alcohol[15] (**1b)** underwent cyclization with **2a** and **2b** to give the corresponding lactones **3f** and **3g** in 68 and 62% yields, respectively. The reaction of **1c** and **1d** with a *tert*-butyl and dioxole substituent, respectively, on the aromatic ring with propiolates also proceeded smoothly in the presence of the nickel catalyst to give the corresponding seven-membered lactones **3h**−**k** in good yield. The cyclization involving **1d** as a reactant is interesting providing a convenient method for the synthesis of tricyclic products **3i**−**k** with five-, six- and seven-membered fused rings. Finally, the present methodology can also be applied to 2-iodobenzyl alcohols with a methyl group at the α-carbon. The reaction of **1e** with propiolate **2a**−**b** afforded the expected lactones **3l**−**m** in moderate yields (entries 12−13).

A possible catalytic cycle for the present nickel-catalyzed seven-membered lactone formation is shown in Scheme 2. This mechanism is proposed on the established nickel chemistry and the foregoing results. Reduction of Ni(II) to Ni(0) by Zn metal[17] likely initiates the catalytic cycle. Oxidative addition of 2-iodobenzyl alcohol to Ni(0) to generate organonickel (II) species **4** is followed by regioselective propiolate insertion to give intermediate **5**.[18] Subsequent protonation of **5** gives *E*-3-arylacrylate **6**. *E*/*Z* isomer-

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* To whom correspondence should be addressed. E-mail: chcheng@mx.nthu.edu.tw.

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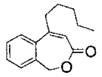
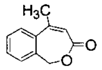
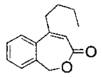
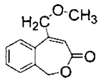
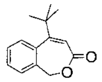
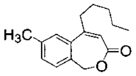
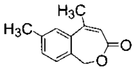
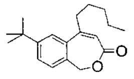
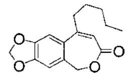
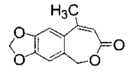
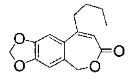
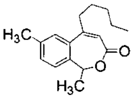
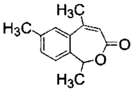
Table 1. Nickel-Catalyzed Cyclization of 2-Iodobenzyl Alcohols with Alkyl Propiolates[a]

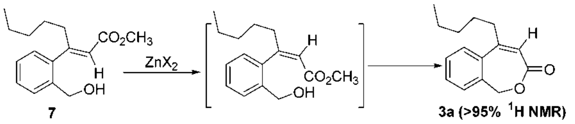
Entry	1	2	Product		Yield (%)[b]
1	**1a**	**2a**		**3a**	81
2	**1a**	**2b**		**3b**	65[c]
3	**1a**	**2c**		**3c**	74
4	**1a**	**2d**		**3d**	72
5	**1a**	**2e**		**3e**	44
6	**1b**	**2a**		**3f**	68
7	**1b**	**2b**		**3g**	62[c]
8	**1c**	**2a**		**3h**	76
9	**1d**	**2a**		**3i**	80
10	**1d**	**2b**		**3j**	69
11	**1d**	**2c**		**3k**	75
12	**1e**	**2a**		**3l**	67
13	**1e**	**2b**		**3m**	56[c]

[a] Unless stated otherwise, all reactions were carried out using an iodo alcohol (1.00 mmol), propiolate (1.50−2.00 mmol), Ni(dppe)Br_2 (0.0500 mmol), and Zn (2.75 mmol) in CH_3CN (3.0 mL) at 80 °C under N_2 for 16 h. [b] Isolated yields. [c] A small amount of cyclotrimerization product[16] of methyl-2-butynoate was found.

ization of the C−C double bond in **6** and ring closure then occurs to afford the final lactone product **3**.

An intriguing aspect of the mechanism is the formation of reductive coupling product **6** and its subsequent *E*/*Z* isomerization and ring closure. The reductive coupling step gains strong support from the isolation of product **7** in 42% yield from the reaction of **1a** with **2a** at room-temperature catalyzed by Ni(dppe)Br_2/Zn. No other stereoisomer was observed from the reaction. The *E* stereochemistry of **7** was carefully established by NOE experiments. This result is in agreement with the stereochemistry for alkyne insertion and then protonation.

Scheme 3



7

3a (>95% ^1H NMR)

The *E*/*Z* isomerization of **6** and subsequent ring closure in the proposed catalytic cycle is clearly evidenced by the readily cyclization of compound **7** in essentially quantitative yield in the presence of ZnI_2, $ZnBr_2$, or Ni(dppe)Br_2/Zn at 80 °C. (Scheme 3). No cyclization occurs if **7** was heated alone at 80 °C. It is noteworthy that *E*/*Z* isomerization of **7** is necessary prior to lactonization due to the unfavorable stereochemistry. The role of zinc halide in the ring closure of **7** is still unclear. A possible function of zinc halide, which is generated during the catalytic reaction, is to act as a Lewis acid assisting the *E*/*Z* isomerization and facilitating the cyclization.

In conclusion, we have demonstrated for the first time a bimetal-catalyzed regio- and stereoselective cyclization of 2-iodobenzyl alcohols with alkyl propiolates. This catalytic reaction provides a convenient and unique method for the synthesis of seven-membered lactones. The catalytic reaction involves an unusual *E*/*Z* isomerization of a carbon−carbon double bond prior to ring closure. Extension of the methodology to the synthesis of six- and eight-membered ring lactones is underway.

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Supporting Information Available: Experimental details and characterization data of **3a**−**3m** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) (a) Fung, S.; Siddall, J. B. *J. Am. Chem. Soc.* **1980**, *102*, 6581. (b) Anaatasia, M.; Allevi, P.; Ciuffreda, P.; Fiecchi, A.; Scala, A. *J. Org. Chem.* **1984**, *49*, 4297. (c) Donaubauer, J. R.; Greaves, A. M.; McMorris, T. C. *J. Org. Chem.* **1984**, *49*, 2834. (d) Mori, K.; Sakibara, M.; Okada, K. *Tetrahedron* **1984**, *40*, 1767. (e) Robertson, D. W.; Krushinski, J. H.; Utterback, B. G.; Kauffman, R. F. *J. Med. Chem.* **1989**, *32*, 1476. (f) Bjeldanes, L. F. *J. Org. Chem.* **1977**, *42*, 2333.

(2) (a) Corey, E. J.; Myers, A. G. *J. Am. Chem. Soc.* **1985**, *107*, 5574. (b) Corey, E. J.; Munroe, J. E. *J. Am. Chem. Soc.* **1982**, *104*, 6129. (c) Corey, E. J.; Nicolaou, K. C.; Melvin, L. S., Jr. *J. Am. Chem. Soc.* **1975**, *97*, 654.

(3) Collins, I. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1377.

(4) (a) Tao, W.; Silverberg, L. J.; Rheingold, A. L.; Heck, R. F. *Organometallics* **1989**, *8*, 2550. (b) Larock, R. C.; Doty, M. J.; Cachi, S. C. *J. Org. Chem.* **1993**, *58*, 4579. (c) Padwa, A.; Krumpe, K. E.; Gareau, Y.; Chiacchio, U. *J. Org. Chem.* **1991**, *56*, 2523.

(5) (a) Kadnikov, D. V.; Larock, R. C. *Org. Lett.* **2000**, *23*, 3643. (b) Catellani, M.; Chiusoli, G. P.; Fagnola, M. F.; Salari, G. *Tetrahedron Lett.* **1994**, *35*, 5923. (c) Larock, R. C.; Doty. M. J.; Han, X. *J. Org. Chem.* **1999**, *64*, 8770 and references therein. (d) Liao, H.-Y.; Cheng, C.-H. *J. Org. Chem.* **1995**, *60*, 3711.

(6) (a) Larock, R. C.; Tian, Q.; Pletnev, A. A. *J. Am. Chem. Soc.* **1999**, *121*, 3238. (b) Larock, R. C.; Yum, E. K. *J. Am. Chem. Soc.* **1991**, *113*, 6689. (c) Larock, R. C.; Zennerr, J. M. *J. Org. Chem.* **1995**, *60*, 482. (d) Larock, R. C.; Yum, E. K.; Doty, M. J.; Sham, K. K. C. *J. Org. Chem.* **1995**, *60*, 3270.

(7) (a) For review see Ali, B. E.; Alper, H. *Synlett* **2000**, 161. (b) Bringmann, G.; Hinrichs, J.; Henschel, P.; Peters, K.; Peters, E.-M. *Synlett* **2000**, 1822. (c) Hosmi F.; Rousseau, G. *J. Org. Chem.* **1998**, *63*, 5255.

(8) Ali, B. E.; Okura, K.; Vasapolla, G.; Alper, H. *J. Am. Chem. Soc.* **1996**, *118*, 4264.

(9) Yoneda, E.; Zhang, S. W.; Onitsuka, K.; Takahashi, S. *Tetrahedron Lett.* **2001**, *42*, 5459.

(10) Grigg, R.; Khalil, H.; Levett, P.; Virica, J.; Sridharan, V. *Tetrahedron Lett.* **1994**, *35*, 3197.

(11) For carbonylation, see: (a) Colqhoun, H. M.; Thompson, D. J.; Twigg, M. V. *Carbonylation*; Plenum Press: New York, 1991. (b) Negishi, E. T.; Conperet, C.; Ma, S.; Lion, S. Y.; Liu, F. *Chem. Rev.* **1996**, *96*, 365. (c) Ojima, I.; Tzamarionadki, M.; Li, Z.; Donovan, R. J. *Chem. Rev.* **1996**, *96*, 635.

(12) Rayabarapu, D. K.; Sambaiah, T.; Cheng, C.-H. *Angew. Chem., Int. Ed.* **2001**, *40*, 1286.

(13) Majumdar, K. K.; Cheng, C.-H. *Org. Lett.* **2000**, *2*, 2295.

(14) (a) Huang, D.-J.; Rayabarapu, D. K.; Li, L.-P.; Sambaiah, T.; Cheng, C.-H. *Chem. Eur. J.* **2000**, *6*, 3706. (b) Hsiao, T.-Y.; Santhosh, K. C.; Liou, K.-F.; Cheng, C.-H. *J. Am. Chem. Soc.* **1998**, *120*, 12232. (c) Sambaiah, T.; Huang, D.-J.; Cheng, C.-H. *J. Chem. Soc., Perkin Trans. 1* **2000**, 195. (d) Sambaiah, T.; Li, L.-P.; Huang, D.-J.; Lin, C.-H.; Rayabarapu, D. K.; Cheng, C.-H. *J. Org. Chem.* **1999**, *64*, 3663.

(15) Panetta, C. A.; Garlick, S. M.; Durst, C.; Longo, F. R.; Ward, J. R. *J. Org. Chem.* **1990**, *55*, 5202.

(16) Only one isomer of the cyclotrimerization of methyl-2-butynoate was observed among the two possible combinations.

(17) (a) Kende, A. S.; Liebeskind, L. S.; Braitsen, D. M. *Tetrahedron Lett.* **1975**, 3375. (b) Zembayashi, M.; Tamao, K.; Yoshida, J.; Kumada, M. *Tetrahedron Lett.* **1977**, 4089.

(18) For nickel oxametallacycles, see: (a) Kimura, M.; Matsuo, S.; Shibata, K.; Tamaru, Y. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 3386. (b) Sato, Y.; Takanashi, T.; Mori, M. *Organometallics* **1999**, *18*, 4891.

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