Pergamon

Tetrahedron Letters 42 (2001) 5459–5461

TETRAHEDRON
LETTERS

Direct synthesis of seven- and eight-membered lactones by ruthenium-catalyzed cyclocarbonylation of allenyl alcohols

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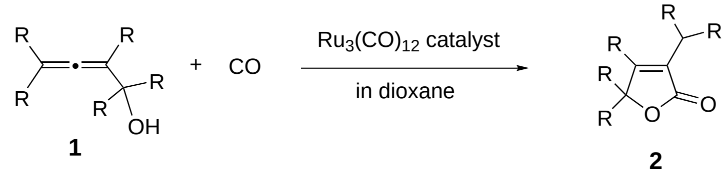
Received 8 May 2001; revised 4 June 2001; accepted 8 June 2001

Abstract—Carbonylation of 6-hydroxyhexa-1,2-dienes and 7-hydroxyhepta-1,2-dienes with a ruthenium catalyst in triethylamine quantitatively gave seven- and eight-membered lactones, respectively, in which the hydroxyl group of allenyl alcohols participated in the cyclization. © 2001 Elsevier Science Ltd. All rights reserved.

Development of an efficient method for preparation of medium-ring compounds continues to be a challenging subject in synthetic organic chemistry.[1] Medium-ring lactones are of special importance as biologically active compounds and generally are prepared by one of the following reactions: (1) iodolactonization of oct-7-enoic acids;[2] (2) reaction of ω-hydroxyalkynes with Fischer carbene complexes;[3] (3) ring-closing metathesis.[4] These reactions, however, are often unsatisfactory due to low product selectivity and/or the use of complicated starting materials. On the other hand, the cyclocarbonylation of unsaturated compounds provides an effective method for the synthesis of heterocyclic compounds such as furanones and indolones.[5] Recently, we showed a new cyclocarbonylation of allenes bearing a hydroxyl group which selectively produced five- or six-membered lactones (Scheme 1).[6] This cyclocarbonylation has great advantages because it offers a new direct and high-yield synthetic method for a variety of furanones from easily available starting materials.

We attempted to extend the carbonylation reaction to the synthesis of medium-ring lactones;[7] however, the reaction of 6-hydroxyhexa-1,2-diene **3a** did not give the expected seven-membered lactone under the same reaction conditions as those used for the carbonylation of 4-hydroxybuta-1,2-dienes **1**. The starting material **3a** was recovered almost quantitatively. Recent reports[8] on the transition metal-catalyzed carbonylation of unsaturated compounds have suggested strong dependence of the reaction on the kind of solvent used. Thus, we continued efforts to find the suitable reaction conditions, in particular, applicable solvents for the carbonylation of **3a**. Fortunately, we found that the use of a tertiary amine such as triethylamine and *N*-methylpiperidine as a solvent enables the formation of seven-membered lactone **4** by $Ru_3(CO)_{12}$-catalyzed cyclocarbonylation of allenyl alcohol **3** in good yields. (Scheme 2)

A mixture of 6-hydroxyhexa-1,2-diene **3a**[9] (1 mmol) and $Ru_3(CO)_{12}$ (0.03 mmol) in triethylamine (15 ml) was stirred at 100°C under 5 atm of carbon monoxide in a stainless steel autoclave. After 4 h, the solvent was evaporated, and the resulting residue was chromatographed on silica gel with ethyl acetate/hexane(1/1) to give **4a** in 71% yield as a colorless oil. The mass



Scheme 1.

Keywords: carbonylation; lactones; allenyl alcohols; cyclization; ruthenium catalyst.

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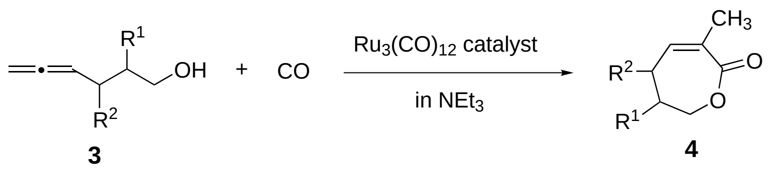
PII: S0040-4039(01)01018-8



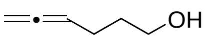
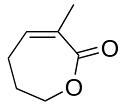
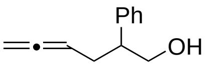
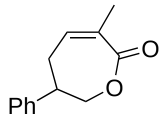
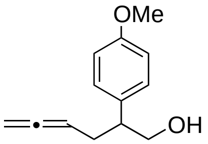
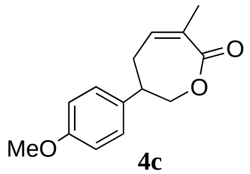
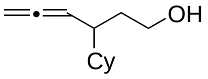
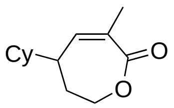
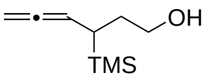
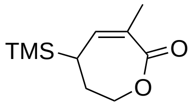
a: R^1=H, R^2=H
b: R^1=Ph, R^2=H
c: R^1=C_6H_4OMe-4, R^2=H
d: R^1=H, R^2=c-C_6H_{11}
e: R^1=H, R^2=$SiMe_3$

Scheme 2.

spectrum of **4a** showed an *m*/*z* of 126 (M^+) which corresponds to the sum of mass number 98 (**3a**) and 28(CO). The IR spectrum exhibited no absorption due to a hydroxyl group; instead, a characteristic absorption at 1714 cm^{-1} attributed to the carbonyl group of the lactone was observed. The ^1H NMR spectrum is fully consistent with that reported for 6-methyl-2*H*,3*H*,4*H*-oxepin-7-one **4a**.[10] Similar carbonylations of 6-hydroxyhexa-1,2-diene derivatives **3b–e** also proceeded smoothly to afford the corresponding seven-membered lactones in good yields. (Table 1)

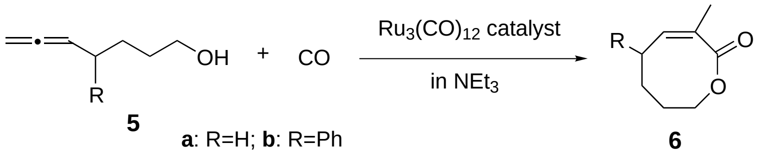
Stimulated by the above successful result, we investigated the synthesis of eight-membered lactones and found that the carbonylation of 7-hydroxyhepta-1,2-diene **5** affords eight-membered lactone **6** under the

Table 1. Carbonylation of 6-hydroxy-hexa-1,2-dienes **3**[a]

entry	substrate	solvent	product	yield (%)[b]
1	 **3a**	NEt_3	 **4a**	71
2		N-methylpiperidine		80
3	 **3b**	NEt_3	 **4b**	77
4	 **3c**	NEt_3	 **4c**	72
5	 **3d**	NEt_3	 **4d**	66
6	 **3e**	NEt_3	 **4e**	85

[a] Reaction conditions: substrate (1 mmol), CO (initial pressure 5 atm at 25 °C), $Ru_3(CO)_{12}$ (0.03 mmol), solvent (15 ml), at 100 °C for 4 h.

[b] Isolated yield.



Scheme 3.

same reaction conditions. (Scheme 3) Then, we examined the optimum reaction conditions for the synthesis of eight-membered lactones and found that tertiary amines such as triethylamine, tri-*n*-butylamine, and *N*-methylpiperidine are the best choice as a solvent, whereas primary and secondary amines such as diethyl amine, piperidine and *n*-butylamine are not suitable for the present cyclic carbonylation, giving several products with a low selectivity of **6**. The carbonylation of **5a** proceeded at 50°C to give **6a**, but the conversion of **5a** was 74% after 8 h. The best yield of **6a** was obtained when the reaction was carried out at 100°C, but higher reaction temperatures somewhat reduced the yield of **6a**. Even though the carbonylation of **5a** proceeded under an atmospheric pressure of CO, the conversion of **5a** was rather low. The pressure of 5 atm CO is sufficient for successful carbonylation. Thus, the reaction of **5a** in the presence of a $Ru_3(CO)_{12}$ catalyst (3 mol%) under carbon monoxide pressure (5 atm) at 100°C for 4 h in triethylamine gave 7-methyl-2*H*,3*H*,4*H*,5*H*-oxocin-8-one **6a** in an isolated yield of 81%. Similarly, 4-phenyl-7-hydroxyhepta-1,2-diene **5b** gave eight-membered lactone **6b** in an isolated yield of 72%.

It should be noted that ω-hydroxyhexa- and ω-hydroxyhepta-1,2-dienes **3** and **5** undergo cyclocarbonylation only in tertiary amines among the various solvents examined. Although 1,4-dioxane and tetrahydrofuran, which are good solvents for the cyclocarbonylation of 4-hydroxybuta-1,2-dienes **1**, are not suitable for **3** and **5**, the reaction of **3a** in a 1/1 mixture of 1,4-dioxane and triethylamine gave lactone **4a** in good yield, suggesting the important role of the amine in the cyclocarbonylation. The reaction mechanism is not clear at present; however, the basic amines might enhance the nucleophilicity of the hydroxyl group, and accelerate an intramolecular attack by an alkoxy anion to a Ru–COR intermediate resulting in the cyclization.[6]

In summary, we have found that ruthenium carbonyl catalyzes a novel cyclocarbonylation of allenyl alcohols to give seven- and eight-membered lactones in good yields. The present intramolecular reaction provides a new and efficient method for the selective synthesis of a variety of medium-ring lactones directly from allenyl alcohols and carbon monoxide.

Acknowledgements

This work was partially supported by Grant-in-Aid for Scientific Research from the Ministry of Education, Science, Sports and Culture. The authors are grateful for a JSPS Fellowship for Japan Junior Scientists to E.N.

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