EurJOC
European Journal of Organic Chemistry

A Journal of
ChemPubSoc Europe

Accepted Article

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To be cited as: *Eur. J. Org. Chem.* 10.1002/ejoc.201900649

Link to VoR: http://dx.doi.org/10.1002/ejoc.201900649

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10.1002/ejoc.201900649

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FULL PAPER

Regioselective synthesis of 4,5-dihydro-6*H*-oxepino[3,2-*c*]chromene-2,6(3*H*)-diones via palladium-catalyzed intramolecular alkoxycarbonylation of 3-allyl-4-hydroxycoumarins

D. Oliver Sosa,[a] Karla Almaraz[a] and Manuel Amézquita-Valencia*[a]

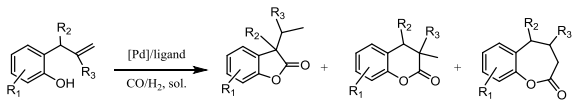
Abstract: Seven-membered ring lactones fused to coumarin scaffolds were obtained via a palladium-catalyzed regioselective intramolecular alkoxycarbonylation under a CO atmosphere. Cyclocarbonylation of 3-allyl-4-hydroxycoumarin derivatives was accessed in the absence of hydrogen gas, acidic conditions, or any other additives. The results of the control experiments revealed the importance of pKa of the substrate for initiating the reaction.

Introduction

The combination of heteroatoms and heterocyclic compounds occupies a significant position in heterocyclic chemistry, extending the exploration of new compounds with a variety of properties. In particular, coumarins are among the most privileged frameworks found in numerous bioactive organic materials, pharmaceuticals, and natural products.[1] The synthesis of coumarin derivatives has emerged as a potent platform for the discovery of new compounds.[2-3] In general, this heterocycle has been functionalized with five and six ring sizes, which have presented a wide range of applications.[4] Accordingly, several approaches have been developed for the synthesis of these compounds.[5]. However, many of these methods are limited to the synthesis of six-membered ring lactones. Despite the importance of medium-size lactones, protocols for the synthesis of 4,5-dihydro-6*H*-oxepino[3,2-*c*]chromene-2,6(3*H*)-diones are limited.

Seven-membered ring lactones are important structural motifs that occur in numerous bioactive natural and synthetic compounds.[6] This core has presented interesting biological activities such as antimalarial,[7] antimicrobial, antitumor, antifungal, and as potential therapeutic agents for the treatment of inflammatory diseases.[8] Therefore, the construction of seven-membered ring lactones fused to other skeletons holds great promise for the preparation of significant molecules that will be important in chemistry and biology.

Palladium-catalyzed carbonylation reactions represent one of the most useful tools in the synthesis of medium size carbonyl derivatives.[9] Various medium to large-sized ring lactams and lactones can be synthesized by choosing the appropriate substrate. For example, 2-(2-iodophenoxy)anilines[10] and 2-(2-ethynylphenoxy)anilines[11] were suitable substrates to form seven-, eight-, nine- and ten-membered ring lactams via palladium-catalyzed intramolecular cyclocarbonylation under a CO atmosphere. Baylis-Hillman acetates were appropriate precursors to submit to cyclocarbonylation reactions.[12] 2-Iodobenzyl alcohol and 2-iodophenetyl alcohol in the presence of internal alkynes and CO as a building block produced seven- and eight-membered ring lactones.[13] In particular, this class of heterocycles also can be formed utilizing 2-allylphenol. In 1996, Alper and co-workers demonstrated that this substrate under certain conditions affords a mixture of five-, six-, and seven-membered ring lactones (Scheme 1). To control the regioselectivity of the process, the palladium source, phosphine ligand, solvent, temperature, the relative pressure and ratio of the gases (CO/H_2) must be taken into consideration.[14] For example, five-membered ring lactones are predominately formed by using of $[Pd(PCy_3)_2(H)(H_2O)]^+BF_4^-$ and dppb under 600 psi of pressure (1:5, CO/H_2). An appropriate monodetate ligand and syngas conditions change the selectivity, resulting in the formation of six-membered ring lactones.[15] Using $Pd(OAc)_2$ as catalyst and bidentate ligand under 300 psi of CO and 300 psi of H_2 affords seven-membered ring lactones.[14] Therefore, we reasoned that this approach could be an excellent option for fusing lactones and coumarins.



Scheme 1. Cyclocarbonylation of 2-allylphenols

Usually, the methodologies previously described to achieve the carbonylation product and catalytic turnover demanded one series of additives such as hydrogen gas (H_2) or acidic conditions to help generate the palladium hydride species, which are responsible for initiating the cyclization reaction. Here, we reported the results for the synthesis of seven-membered ring lactones fused to the coumarin scaffold from 3-allyl-4-hydroxycoumarin derivatives through palladium-catalyzed intramolecular alkoxycarbonylation using only CO in an additive-free manner.

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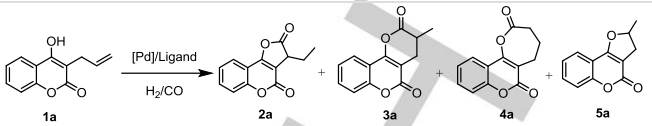
Results and Discussion

We began our investigation by examining the intramolecular cyclocarbonylation with 3-allyl-4-hydroxycoumarin (**1a**) as the model substrate. The reaction was carried out in presence of H_2 and CO in a 1:1 ratio (600 psi) at 120 °C, with $Pd(OAc)_2$ as a palladium precursor and 1,4-bis-(diphenylphosphino)butane (dppb) as a ligand (Table 1, entry 1). This led to 2,3-dihydro-2-methyl-4*H*-furo[3,2-*c*][1]benzopyran-4-one (**5a**) in 86% yield, because of a C-O coupling promoted by the palladium catalyst.[16] This result was quite opposite to the desired product. A similar outcome was obtained using dichloromethane (DCM) as a solvent, but in this case, small amounts of the cyclocarbonylation products were observed (Table 1, entry 2). Encouraged by this result, different solvents, temperatures, and palladium sources were tested. We observed that both temperature and the solvent played important roles in obtaining the carbonylation product. When the reaction was carried out at 105 °C in DCM, six- and seven-membered ring lactones were obtained in a low conversion and moderate selectivity of 30% and 70% for (**3a/4a**), respectively (Table 1, entry 3). If the reaction was dissolved in toluene, the seven-membered ring lactone (**4a**) was obtained in good selectivity 90% (Table 1, entry 4). Lowering the temperature to 90 °C resulted in low conversion (Table 1, entry 5). Further screening of solvents such as dichloroethane (DCE), tetrahydrofuran (THF) and acetonitrile (MeCN) decreased the catalytic activity (Table 1, entries 6-8). The use of other palladium sources as catalytic precursors was ineffective for the reaction (Table 1, entries 9-11).

Then, we studied the impact of the ligand on the selectivity. The obtained result indicated that dppp showed excellent conversion, but low selectivity (Table 1, entry 12). In the cases of Xantphos and dppf, no product formation was observed, which indicated that dppb is the best option (Table 1, entries 13-14). An extra reaction was carried out using 300 psi of H_2/CO to check the influence of the pressure. Even though the conversion was affected, the selectivity for the seven-membered ring lactone (**4a**) was increased remarkably (Table 1, entry 15). To our delight, by using of only CO at 300 psi in DCM as a solvent, seven-membered ring lactone (**4a**) was obtained in excellent yield of 90% with a fine selectivity of 100% (Entries 16-18). Here, the increase of the yield under CO atmosphere can be explained by the decreased yield of the double bond hydrogenation.

With the optimal reaction conditions established [$Pd(OAc)_2$, dppb, 300 psi of CO, 105 °C and 20 h], we next investigated the generality of the scope of cyclocarbonylation reaction of 3-allyl-4-hydroxycoumarin derivatives. As depicted in Scheme 2, the transformation of various substrates (**1**) proceeded smoothly and delivered the corresponding oxepino[3,2,*c*]chromene derivatives (**4**) in moderate to good yields. Both electron-donating and electron-withdrawing groups were well tolerated. NO_2 or F substituents could be used to give the corresponding lactone in good yield (**4b** and **4c**). Methyl, *t*-butyl and methoxy substituents in the 6´ and 7´ positions were well tolerated (**4d-4h**). The structure of oxepino[3,2,*c*]chromene (**4d**) was further confirmed by X-ray crystallography (Figure 1).[17]

Table 1 Optimizations of reaction conditions[a]



Entry	[Pd]	Solvent	Conv.[b] (%)	Selectivity[b] 2-3-4-5
1	$Pd(OAc)_2$	PhMe	100	0-0-0-92(86)[c]
2	$Pd(OAc)_2$	DCM	100	3-8-19-70
3[d]	$Pd(OAc)_2$	DCM	53	0-30-70-0
4[d]	$Pd(OAc)_2$	PhMe	64	0-10-90(71)[c]-0
5[e]	$Pd(OAc)_2$	PhMe	10	traces
6[d]	$Pd(OAc)_2$	DCE	58	0-42-58-0
7[d]	$Pd(OAc)_2$	THF	8	traces
8[d]	$Pd(OAc)_2$	MeCN	4	traces
9[d]	$Pd(PPh_3)_4$	PhMe	20	traces
10[d]	$Pd(cod)Cl_2$	PhMe	NR[h]	-
11[d]	PdI_2	PhMe	NR[h]	-
12[d,f]	$Pd(OAc)_2$	PhMe	100	0-41-59-0
13[d,g]	$Pd(OAc)_2$	PhMe	NR[h]	-
14[d,i]	$Pd(OAc)_2$	PhMe	NR[h]	-
15[d,j]	$Pd(OAc)_2$	PhMe	70	0-0-100-0
16[d,k]	$Pd(OAc)_2$	PhMe	NR[h]	-
17[d,k]	$Pd(OAc)_2$	DCM	99	0-0-100(90)[c]-0
18[d,l]	$Pd(OAc)_2$	DCM	99	0-0-100(60)[c]-0

[a]Reaction conditions: Substrate **1a** (0.25 mmol), 2.0 mol % of [Pd], 2.0 mol % of dppb as a ligand, 5.0 mL of solvent, H_2 (300 psi) and CO (300 psi), 120 °C, 20 h. [b]The conversion and ratio of **2a**,**3a**,**4a**, **5a** were determined by ^{1}H-NMR spectroscopy of the crude reaction mixture. [c]Isolated yield is shown in brackets. [d]Reaction at 105°C. [e]Reaction at 90°C. [f]dppp (2.0 mol%) was used. [g]Xantphos (2.0 mol%) was used. [h]No reaction. [i]dppf (2.0 mol%) was used. [j]300 psi of H_2/CO (1:1 ratio) was used. [k]300 psi of CO was used. [l]200 psi of CO was used.

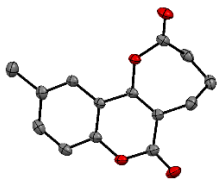
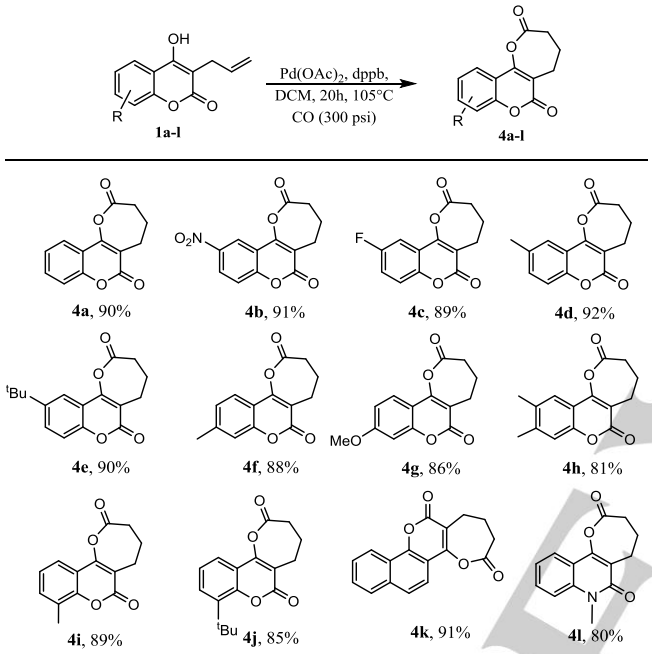


Figure 1. ORTEP representation of **4d** with the thermal ellipsoids set at 50% probability level, all hydrogen atoms are omitted for clarity.

A similar result was obtained with a substituent in the 8´ position (**4i** and **4j**). Fused aromatics such as the naphthalene derivative also afforded the corresponding lactone in good yield (**4k**). The replacement of the coumarin scaffold by methylquinolinone (**1l**) failed to produce the desire product. However, quinolinone fused to a seven-membered ring lactone (**4l**) could be obtained when the reaction was carried out using a mixture of H_2/CO (Ratio 1:1, 600 psi) in the presence of $Pd(PPh_3)_4$, dppb as a ligand in THF at 110 °C for 48 h. Here, hydrogen is necessary to promote the generation of the hydride palladium [Pd-H] and to achieve the catalysis.



Scheme 2. Scope of coumarins **1**. Reaction conditions: **1a-k** (0.5 mmol), $Pd(OAc)_2$ (2.0 mmol %), dppb (2.0 mmol %), 10 mL of dichloromethane, 300 psi of CO, 105 °C, 20 h. Yields refer to pure products after purification.

A mixture of CO/H_2 is well known to generate a high concentration of palladium hydride species [Pd-H], which can promote double bond isomerization. Under syngas conditions, six-membered ring lactones from coumarin (**1a**) and methylquinolinone (**1l**) were obtained in poor yields and low selectivities of 44% and 55%, respectively (Figure. 2). Several reactions were carried out to improve the selectivity towards six- or five-membered ring lactones, but all attempts were fruitless. Alper and co-workers demonstrated that the selectivity in the cyclocarbonylation reaction was very sensitive to both the ratio and the pressure of gases (H_2/CO), with regioselectivity continuing to be a challenge.[14]

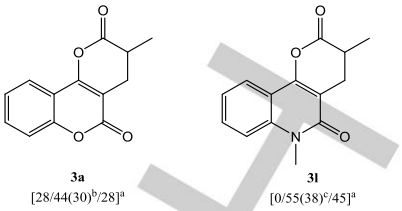
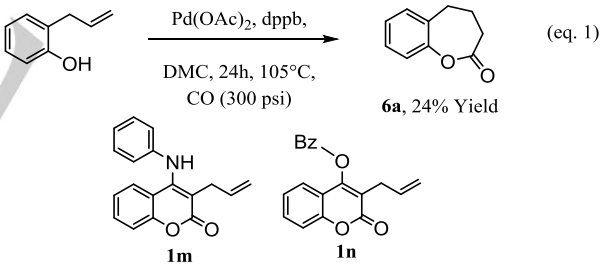


Figure 2. Reaction conditions for **3a**: PdI_2 (2.0 mol%), PPh_3 (4.0 mol%), toluene (10 mL), H_2/CO (1:5, 600 psi), 110 °C, 20h. For **3l**: $Pd(PPh_3)_4$ (2.0 mol%), dppb (2.0 mol%), DCE (10 mL), H_2/CO (1:1, 600 psi), 110°C, 24h. [a]The conversion and ratio were determined by 1H-NMR spectroscopy. [b]Isolated yield of the mixture of isomers. [c]Isolated yield is shown in brackets.

In contrast, seven-membered ring lactones (**4a-4k**) from 3-allyl-4-hydroxycoumarins could be formed in high selectivity using only CO and without the need to use hydrogen (H_2) or acidic conditions, as a shown in the Scheme 2. We believed that this behavior would be influenced by the acidic character of the hydroxy group on the substrate (pKa ≈ 4.16).[18] To confirm our hypothesis, 2-allylphenol (pKa = 10.88)[19] was treated under standard reaction conditions, and the lactone (**6a**) was obtained in 24% yield along with starting material (Scheme 3, eq. 1). This outcome is unlike the reaction enriched with hydrogen (300/300 psi of H_2/CO) which afforded lactone (**6a**) in good yield, demonstrating the need for the hydrogen for initiating the catalytic turnover. Likewise, utilizing a more nucleophilic substrate such as 3-allyl-4-(phenylamino)-2*H*-chromen-2-one (**1m**), no cyclocarbonation product was found (Scheme 2).

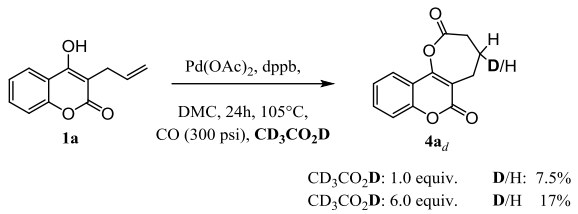


Scheme 3. Control experiments.

On the other hand, when 3-allyl-4-hydroxycoumarin was used as a substrate containing a protected hydroxy group (**1n**), the cyclocarbonylation was not possible. These results may indicate that the first step in the reaction is the generation of the hydride species [Pd-H] through O-H activation. Huang´s group reported a palladium-catalyzed hydroaminocarbonylation of 2-vinylbenzylamines in the absence of acidic or any other additives and demonstrated that the palladium hydride species comes from N-H bond activation from the substrate.[20] Rationalizing this possibility, a reaction was carried out between 1.0 equivalent of palladium precursor and substrate (**1a**). In the first instance, 1H NMR analysis indicated that the signal of the hydrogen at the hydroxyl group disappeared rapidly (1 min approximately). Then, signals corresponding to the allyl arm became broad and shifted

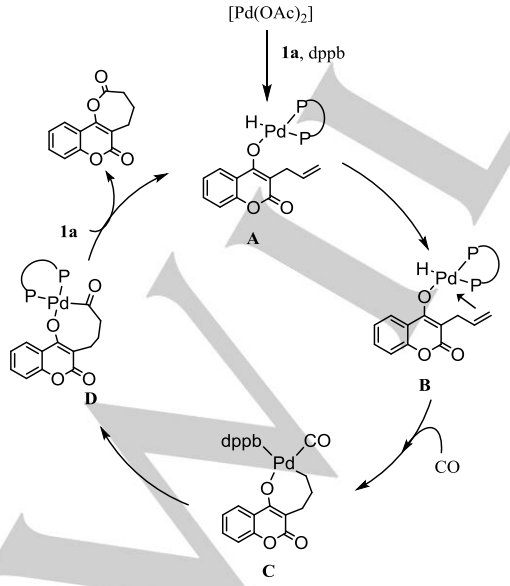
down field. This behavior is associated with the formation of a π-allylpalladium intermediate.[21] Subsequent FAB^+ mass spectroscopy analysis of a similar solution showed a peak at m/z 307 [M^+], which agreed with the palladium-hydride intermediate.

To check the participation of the acetate ion, isotopic labeling experiments using deuterated acetic acid (d-4, 99.9%) were performed. The 1H NMR analysis of the pure product showed the incorporation of the deuterium atom was only 7.5% at the 12-position of 4,5-dihydro-6H-oxepino[3,2-*c*]chromene-2,6(3*H*)-diones (**4a**$_d$) (Scheme 4). Even when acetic acid was used in excess (6.0 equivalents), the incorporation of deuterium was minimal. The above experimental results suggested the poor participation of the acetate ion for the protonation or deprotonation process that could help in obtaining the desired product.



Scheme 4. Carbonylation reaction in presence of CD_3CO_2D.

Based on the previous literature reports and the experimental results,[22] a tentative catalytic cycle is proposed in Scheme 5. The reaction begins with the generation of palladium hydride species **A** from the reaction of [$Pd(OAc)_2$]/dppb and substrate.[20] Next, π coordination of the olefin to Pd **B**, followed by the intramolecular hydropalladation with concomitant coordination of CO could form **C**. Subsequent insertion of CO into the alkyl-palladium bond affords the acyl palladacyclic complex **D**. Finally, the intramolecular cyclization leads to the desired product and regenerates the species **A** for the next catalytic cycle.



Scheme 5. Proposed catalytic cycle.

Conclusions

In summary, palladium-catalyzed cyclocarbonylation for the regioselective synthesis of coumarin fused to seven-membered ring lactones from 3-allyl-4-hydroxycoumarin has been elaborated. The protocol does not involve hydrogen (H_2) or acidic conditions. The control experiments suggest that the pKa of the substrate is a key feature in the process. The catalytic system provides a straightforward route to the synthesis of interesting coumarin derivatives in good yield.

Experimental Section

General procedure for the Pd-catalyzed intramolecular cyclocarbonylation of 3-allyl-4-hydroxycoumarin derivatives

A mixture of substituted 3-ally-4-hydroxylcoumarin (0.15 mmol), $Pd(OAc)_2$ (2.0 mmol%), dppb (2.0 mmol%), and dichloromethane (10 mL) was placed in a 45 mL autoclave with a magnetic stirring bar. The autoclave was flushed three times with CO and pressurized with CO to 300 psi at room temperature. The autoclave was then immersed in an oil bath preheated at 105 °C for 20 h. Excess CO was discharged at room temperature. The reaction mixture was purified by washes with hexane cool, and ethyl acetate cool to give the corresponding oxepino[3,2,*c*]chromene derivatives in good yield.

4,5-Dihydro-2H-oxepino[3,2-c]chromene-2,6(3H)-dione (4a): Colorless solid, 27.1 mg, m.p. 181-182 °C, 90% yield. ^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm): 7.76 (dd, J = 7.9, 1.5 Hz, 1H), 7.58 (ddd, J = 8.8, 7.4, 1.6 Hz, 1H), 7.40–7.29 (m, 2H), 2.91 (t, J = 7.4 Hz, 2H), 2.69 (t, J = 7.2 Hz, 2H), 2.34 (p, J = 7.3 Hz, 2H). ^{13}C{^{1}H}-NMR (100 MHz, $CDCl_3$, δ ppm): 168.4, 162.1, 157.7, 152.4, 132.6, 124.6, 122.9, 116.7, 114.9, 112.1, 32.5, 26.5, 21.5. IR (ATR)/cm-1: 1762, 1700, 1640. MS (EI) m/z 230 [M^+]. HRMS (EI) calculated for $C_{13}H_{10}O_4$ 230.0579 found 230.0507.

10-Nitro-4,5-dihydro-6H-oxepino[3,2-c]chromene-2,6(3H)-dione (4b): Colorless solid 27.3 mg, m.p. 120-122 °C, 91% yield. ^{1}H NMR (500 MHz, $CDCl_3$, δ ppm): 8.63 (d, *J* = 2.6 Hz, 1H), 8.38 (dd, *J* = 9.1, 2.7 Hz, 1H), 7.45 (d, *J* = 9.1 Hz, 1H), 2.90 (t, *J* = 7.4 Hz, 2H), 2.69 (t, *J* = 7.2 Hz, 2H), 2.34 (q, *J* = 7.4, 7.2 Hz, 2H). ^{13}C{^{1}H}-NMR (126 MHz, $CDCl_3$, δ ppm): 167.2, 160.6, 156.4, 155.6, 144.3, 127.3, 119.4, 118.0, 115.4, 113.9, 32.6, 26.4, 21.2. IR (ATR)/cm^{-1}:1771, 1720, 1634. MS (DART) *m/z* 276 [M+1]. HRMS (DART) calculated for $C_{13}H_9O_6$ 276.0429 found 276.0431.

10-Fluoro-4,5-dihydro-6H-oxepino[3,2-c]chromene-2,6(3H)-dione (4c): Colorless solid, 26.7 g, m.p. 190-191 °C 89% yield. ^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm): 7.44 (dd, *J* = 8.1, 2.7 Hz, 1H), 7.37–7.25 (m, 2H), 2.91 (t, *J* = 7.4 Hz, 2H), 2.69 (t, *J* = 7.2 Hz, 2H), 2.42–2.29 (m, 2H). ^{13}C{^{1}H}-NMR (100 MHz, $CDCl_3$, δ ppm): 167.9, 161.7, 160.1 (d, $^1J_{CF}$ = 243 Hz), 156.8 (d, $^4J_{CF}$ = 3.0 Hz), 148.5 (d, $^4J_{CF}$ = 2.0 Hz), 120.3-120.0 (d, $^2J_{CF}$ = 25.0 Hz), 118.5-118.4 (d, $^3J_{CF}$ = 9.0 Hz), 117.3, 113.0, 108.9-108.6 (d, $^2J_{CF}$ = 26.0 Hz), 32.5, 26.4, 21.7. IR (ATR)/cm^{-1}: 1782, 1691, 1610. MS (EI) *m/z* 248 [M^+]. HRMS (EI) calculated for $C_{13}H_9O_4F$ 248.0485 found 248.0478.

10-Methyl-4,5-dihydro-6H-oxepino[3,2-c]chromene-2,6(3H)-dione (4d): Colorless solid 27.6 mg, m.p. 187-189 °C, 92% yield. ^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm): 7.52 (s, 1H), 7.36 (d, *J* = 8.4 Hz, 1H), 7.22 (d, *J* = 8.5

Hz, 1H), 2.88 (t, *J* = 7.4 Hz, 2H), 2.67 (t, *J* = 7.2 Hz, 2H), 2.38 (s, 3H), 2.35–2.28 (m, 2H). $^{13}C\{^1H\}$-NMR (100 MHz, $CDCl_3$, δ ppm): 168.6, 162.3, 157.6, 150.6, 134.5, 133.6, 122.5, 116.4, 114.5, 112.0, 32.4, 26.5, 21.5, 20.8. IR (ATR)/cm^{-1}: 1775, 1705, 1632. MS (EI) *m/z* 244 [M^+]. HRMS (EI) calculated for $C_{14}H_{12}O_4$ 244.0736 found 244.0733.

10-(*tert*-Butyl)-4,5-dihydro-6H-oxepino[3,2-c]chromene-2,6(3H)-dione (4e): Colorless solid 27.1 mg, m.p. 177-179 °C, 90 % yield. ^1H NMR (500 MHz, $CDCl_3$, δ ppm): 7.69 (dd, J = 7.9, 1.6 Hz, 1H), 7.61 (dd, J = 7.8, 1.6 Hz, 1H), 7.29 (m, 1H), 2.96 (t, J = 7.4 Hz, 2H), 2.74 (t, J = 7.2 Hz, 2H), 2.39 (p, J = 7.4 Hz, 2H), 1.55 (s, 9H). $^{13}C\{^1H\}$-NMR (126 MHz, $CDCl_3$, δ ppm): 168.7, 161.6, 158.2, 151.1, 138.0, 130.2, 124.1, 121.0, 115.3, 111.4, 35.0, 32.5, 29.8, 26.6, 21.3. IR (ATR)/cm^{-1}: 1770, 1710, 1636. MS (DART) *m/z* 287 [M^+]. HRMS (DART) calculated for $C_{17}H_{18}O_4$ 287.1283 found 287.1280.

9-Methyl-4,5-dihydro-6H-oxepino[3,2-c]chromene-2,6(3H)-dione (4f): Colorless solid 26.4 g, m.p. 187-189 °C, 88% yield. ^1H-NMR (400 MHz, $CDCl_3$, δ ppm): 7.67 (d, *J* = 8.0 Hz, 1H), 7.24–7.11 (m, 2H), 2.93 (t, *J* = 7.4 Hz, 2H), 2.72 (t, *J* = 7.2 Hz, 2H), 2.50 (s, 3H), 2.37 (p, *J* = 7.3 Hz, 2H). $^{13}C\{^1H\}$-NMR (100 MHz, $CDCl_3$, δ ppm): 168.6, 162.4, 157.9, 152.6, 144.1, 125.8, 122.6, 116.8, 112.4, 110.9, 32.5, 26.6, 21.8, 21.4. IR (ATR)/cm^{-1}: 1765, 1708, 1619. MS (DART) *m/z* 245 [M+1]. HRMS (DART) calculated for $C_{14}H_{12}O_4$ 245.0736 found 245.0735.

9-Methoxy-4,5-dihydro-6H-oxepino[3,2-c]chromene-2,6(3H)-dione (4g): Colorless solid 25.8 mg, m.p. 138-139 °C, 86% yield. ^1H NMR (500 MHz, $CDCl_3$, δ ppm) 7.69 (d, J = 8.8 Hz, 1H), 6.92 (dd, J = 8.8, 2.4 Hz, 1H), 6.88 (d, J = 2.4 Hz, 1H), 3.92 (s, 3H), 2.92 (t, J = 7.3 Hz, 2H), 2.72 (t, J = 7.3 Hz, 2H), 2.36 (p, J = 7.3, Hz, 2H). $^{13}C\{^1H\}$-NMR (126 MHz, $CDCl_3$, δ ppm) 168.7, 163.5, 158.1, 154.3, 124.0, 112.8, 108.8, 108.1, 100.7, 55.8, 32.5, 26.6, 21.3. IR (ATR)/cm^{-1}: 1762, 1704, 1614. MS (DART) *m/z* 261 [M+1]. HRMS (DART) calculated for $C_{14}H_{13}O_5$ 261.07630 found 261.07672.

9,10-Dimethyl-4,5-dihydro-6H-oxepino[3,2-c]chromene-2,6(3H)-dione (4h): Colorless solid, 24.3 mg, m.p. 197-198 °C, 81% yield. ^1H-NMR (400 MHz, $CDCl_3$, δ ppm): 7.48 (s, 1H), 7.13 (s, 1H), 2.88 (t, *J* = 7.4 Hz, 2H), 2.66 (t, *J* = 7.2 Hz, 2H), 2.39–2.24 (m, 8H). $^{13}C\{^1H\}$-NMR (100 MHz, $CDCl_3$, δ ppm): 168.8, 162.5, 157.9, 150.9, 142.9, 133.6, 122.7, 117.2, 112.4, 110.9, 32.5, 26.6, 21.4, 20.3, 19.2. IR (ATR)/cm^{-1}: 1769, 1708, 1608. MS (EI) *m/z* 258 [M+1]. HRMS (EI) calculated for $C_{15}H_{14}O_4$ 258.0892 found 258.0877.

8-Methyl-4,5-dihydro-6H-oxepino[3,2-c]chromene-2,6(3H)-dione (4i): Colorless solid 26.7 mg, m.p. 187-189 °C, 89% yield. ^1H-NMR (400 MHz, $CDCl_3$, δ ppm): 7.55 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.40–7.31 (m, 1H), 7.16 (t, *J* = 7.7 Hz, 1H), 2.86 (t, *J* = 7.3 Hz, 2H), 2.63 (t, *J* = 7.2 Hz, 2H), 2.41 (s, 3H), 2.33-2.23 (m, 2H). $^{13}C\{^1H\}$-NMR (100 MHz, $CDCl_3$, δ ppm): 168.6, 162.1, 158.0, 150.8, 133.9, 126.2, 124.1, 120.5, 114.6, 111.8, 32.5, 26.6, 21.5, 15.5. IR (ATR)/cm^{-1}: 1750, 1691, 1625. MS (DART) *m/z* 245 [M+1]. HRMS (DART) calculated for $C_{14}H_{12}O_4$ 245.0736 found 245.0735.

8-(*tert*-Butyl)-4,5-dihydro-6H-oxepino[3,2-c]chromene-2,6(3H)-dione (4j): Colorless solid 25.5 mg, m.p. 127-129 °C, 85% yield. ^1H NMR (500 MHz, $CDCl_3$/DMSO-d_6, δ ppm) 7.59 (d, *J* = 2.4 Hz, 1H), 7.53 (dd, *J* = 8.7, 2.4 Hz, 1H), 7.20 (d, *J* = 8.7 Hz, 1H), 2.80 (t, *J* = 7.4 Hz, 2H), 2.62 (t, *J* = 7.2 Hz, 2H), 2.24 (p, *J* = 7.3 Hz, 2H), 1.24 (s, 9H). $^{13}C\{^1H\}$-NMR (126 MHz, $CDCl_3$/DMSO-d_6, δ ppm) 168.6, 162.1, 157.8, 150.3, 147.8, 130.2, 118.7, 116.1, 114.0, 111.6, 34.6, 32.4, 31.2, 26.5, 21.4. IR (ATR)/cm^{-1}: 1783, 1698, 1635. MS (DART) *m/z* 287 [M+1]. HRMS (DART) calculated for $C_{17}H_{18}O_4$ 287.1283 found 287.1281.

8,9-Dihydro-6H-benzo[h]oxepino[3,2-c]chromene-6,10(7H)-dione (4k): Colorless solid 27.3 mg, m.p. 198-200 °C, 91% yield. ^1H NMR (500 MHz, $CDCl_3$, δ ppm): 8.60 (m, 1H), 7.93 (m, 1H), 7.78 (m, 2H), 7.71 (m, 2H), 3.02 (t, J = 7.4 Hz, 2H), 2.77 (t, J = 7.2 Hz, 2H), 2.42 (p, J = 7.3 Hz, 2H).$^{13}C\{^1H\}$-NMR (126 MHz, $CDCl_3$, δ ppm): 168.5, 162.2, 158.7, 150.0, 135.2, 129.1, 128.0, 127.5, 124.7, 122.7, 122.4, 118.2, 111.4, 110.3, 32.6, 30.9, 26.6, 21.6. IR (ATR)/cm^{-1}: 1780, 1699, 1609. MS (DART) *m/z* 281 [M+1]. HRMS (DART) calculated for $C_{17}H_{12}O_4$ 281.0813 found 281.0813.

7-Methyl-3,4,5,7-tetrahydrooxepino[3,2-*c*]quinolone-2,6-dione (4l): Colorless solid, 24 mg, m.p. 181-182 °C, 80% yield. ^1H-NMR (500 MHz, $CDCl_3$, δ ppm): 7.95 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.65 (ddd, *J* = 8.7, 7.2, 1.6 Hz, 1H), 7.43 (d, *J* = 8.5 Hz, 1H), 7.33 (ddd, *J* = 8.2, 7.2, 1.0 Hz, 1H), 3.80 (s, 3H), 3.06 (t, *J* = 7.4 Hz, 2H), 2.65 (t, *J* = 7.2 Hz, 2H), 2.35 (p, *J* = 7.3 Hz, 2H). $^{13}C\{^1H\}$-NMR (126 MHz, $CDCl_3$, δ ppm): 169.9, 162.3, 154.3, 138.8, 131.4, 123.2, 122.5, 117.3, 115.3, 114.1, 32.2, 30.1, 26.7, 21.3. IR (ATR)/cm^{-1}: 1688, 1631, 1605, 1564. MS (DART) *m/z* 244 [M+1]. HRMS (DART) calculated for $C_{14}H_{13}NO_3$ 244.0974 found 244.0973.

4,5-Dihydro-2H-oxepino[3,2-c]chromene-2,6(3H)-dione (4a) and 3-Methyl-3,4-dihydro-2H,5H-pyrano[3,2-c]chromene-2,5-dione (3a): Colorless solid, 9.2 mg, 30% yield. ^1H-NMR (500 MHz, $CDCl_3$, δ ppm): 7.87 (dd, J = 7.9, 1.6 Hz, 1H), 7.81 (dd, J = 8.0, 1.6 Hz, 1H), 7.62 (ddt, J = 8.9, 7.3, 1.5 Hz, 2H), 7.43–7.34 (m, 4H), 3.19 (dd, J = 17.1, 7.2 Hz, 1H), 3.01–2.90 (m, 3H), 2.74 (t, J = 7.2 Hz, 2H), 2.65 (dd, J = 17.1, 12.2 Hz, 1H), 2.39 (p, J = 7.3 Hz, 2H), 1.48 (d, J = 6.8 Hz, 3H). $^{13}C\{^1H\}$-NMR (126 MHz, CDCl3, δ ppm): 168.49, 168.42, 162.1, 161.2, 157.7, 157.3, 153.0, 152.4, 132.66, 132.63, 124.65, 124.61, 122.9, 122.4, 116.9, 116.7, 114.9, 113.6, 112.1, 103.2, 33.5, 32.5, 26.6, 26.1, 21.5, 15.4. IR (ATR)/cm-^{1}: 1774, 1699, 1651, 1610. MS (DART) m/z 231 [M+1].

3,6-Dimethyl-4,6-dihydro-2H-pyrano[3,2-c]quinolin-2,5(3H)-diona (3l): Colorless solid, 11,4 mg, m.p. 139-141 ºC, 38% yield. ^1H NMR (500 MHz, DMSO, δ ppm) 7.99 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.60 (ddd, *J* = 8.6, 7.1, 1.5 Hz, 1H), 7.48 (d, *J* = 8.3 Hz, 1H), 7.28–7.24 (m, 1H), 3.59 (s, 3H), 3.03–2.85 (m, 1H), 2.84–2.65 (m, 1H), 1.04 (d, *J* = 6.8 Hz, 3H). $^{13}C\{^1H\}$-NMR (126 MHz, DMSO, δ ppm): 178.3, 163.2, 157.2, 138.9, 130.9, 123.5, 121.7, 116.5, 114.7, 109.3, 38.0, 29.5, 28.1, 16.9. MS (DART): *m/z* 244 [M+1]. HRMS (DART) calculated for $C_{14}H_{13}NO_3$ 244.0973 found 244.0973.

4,5-Dihydro-2H-oxepino[3,2-c]chromene-2,6(3H)-dione-12-*d* (4a$_d$): Colorless solid, 27.6 mg, 90% yield. ^1H-NMR (500 MHz, $CDCl_3$, δ ppm): 7.72 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.57–7.50 (m, 1H), 7.36–7.24 (m, 3H), 2.87 (t, *J* = 7.3 Hz, 2H), 2.69–2.59 (t, 2H), 2.30 (p, *J* = 7.4 Hz, 1.6H). $^{13}C\{^1H\}$-NMR (126 MHz, $CDCl_3$, δ ppm): 168.5, 162.3, 157.7, 152.5, 132.6, 124.6, 122.9, 116.7, 115.0, 112.0, 32.4, 29.7, 21.4. MS (EI) *m/z* 232 [M+1]. HRMS (DART) calculated for $C_{13}H_9DO_4$ 232.0720 found 232.0722.

4,5-Dihydro-3H-benzo[*b*]oxepin-2-one (6a):[15] Yellow oil, 21,4 mg, yield 24%. ^1H NMR (500 MHz, $CDCl_3$, δ ppm) 2.17 (q, *J* =7.2 Hz, 2H), 2.46 (t, *J* =7.2 Hz, 2H), 2.81 (t, *J* =7.3 Hz, 2H), 7.07 (d, *J* =7.9 Hz, 1H), 7.20-7.11 (m, 2H), 7.28-7.23 (m, 1H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$, δ ppm) 26.5, 28.2, 31.1, 119.3, 125.9, 128.3, 129.6, 130.1, 151.8, 171.6.

2-Methyl-2,3-dihydro-4H-furo[3,2-c]chromen-4-one (5a): Colorless solid, 25.5 mg, 86% yield. ^1H NMR (500 MHz, $CDCl_3$, δ ppm): 7.58 (dd, J = 7.8, 1.7Hz, 1H), 7.48 (td, 8.8, 7.3, 1.6 Hz, 1H), 7.31 (m, J = 8.6, 1.0 Hz, 1H) 7.22 (td, J = 7.8, 1.7 Hz, 1H), 5.21 (dd, 9.7, 7.3, 6.4, 1H), 3.26 (dd, J = 15.0, 9.7 Hz, 1H), 2.72 (dd, J = 15.0, 7.3 Hz, 1H), 1.51 (d, J = 6.3 Hz, 3H). $^{13}C\{^1H\}$-NMR (126 MHz, $CDCl_3$, δ ppm): 166.4, 160.9, 154.9, 132.2, 123.8, 122.7, 116.9, 112.7, 101.8, 84.1, 33.9, 22.0. MS (EI) *m/z* 202 [M^+].

Acknowledgments

We gratefully acknowledge the financial support from DGAPA-UNAM (PAPIIT IA201818) and CONACyT (626716 Fellowship). We also thank A. Toscano, M. Paz Orta, R. Patiño, S. Hernández-Ortega, J. Pérez, M. C. García, L. Velasco, C. Márquez, L. Rios, E. García, G. Cortés (UCTIC), H. Rios, E. Huerta, M. A. Peña, M. León (LANCIC-IQ-UNAM), B. Quiroz (LURMN-IQ-UNAM) for the excellent technical support.

Keywords: Coumarin, cyclocarbonylation, medium-size lactones, alcoxycarbonylation, 3-Allyl-4-hydroxycoumarin

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10.1002/ejoc.201900649

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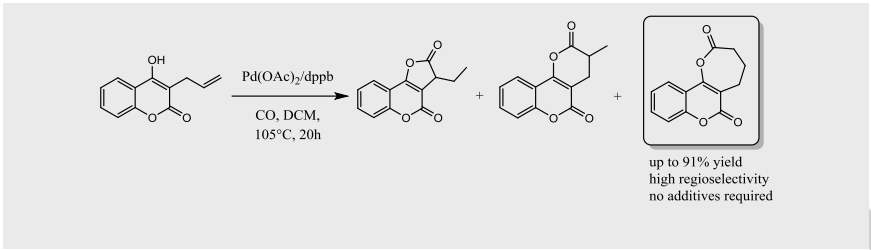

This work presents a regioselective route to synthesize of seven-membered ring lactones fused to coumarin scaffold. The protocol presents good yields and high regioselectivity. Additionality, the carbonylation reaction is in the absence of acidic or any other additive as hydrogen (H_2).

*Cyclocarbonylation, coumarin

Cyclocarbonylation Reaction*

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