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Note

Efficient synthesis of spirolactones from cyclic anhydrides via an allylation/alkylation-RCM sequence

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Abstract

Starting from cyclic anhydrides the diallyl or dibutenyl lactones were obtained. The ring closing metathesis reaction of these using the Grubbs catalyst provided the corresponding spirolactones in good yields. With diallyl δ-lactone **2h**, RCM occurred only in the presence of titanium tetraisopropoxide.

Keywords: Spirolactones; Cyclic anhydrides; Allylation/alkylation-RCM

1. Introduction

Spirobicyclic cores display an important role in the field of the development of new bioactive substances [1]. Molecules containing this moiety have often been proposed as substitute of linear structure to reduce the conformational stability and to increase their stability towards metabolism pathway. Among these, spirobicyclic lactones compounds have not received great attention from a synthetic point of view and most of the described methods are based on lactonisation reactions [2]. In this field, we recently described a 'one pot' procedure leading to the formation of spiro-(2,5-divinyl)-cyclopentanyl lactones from cyclic anhydrides through a double allylation with 1,8-bis-(trimethylsilyl)-octa-2,6-diene (BISTRO) [3]. In addition, since Grubbs' and Schrock's groups have described new alkenylidene–ruthenium and molybdenum catalysts, olefin metathesis has attracted increased attention [4]. Ring closing metathesis reaction (RCM) under these catalysts activation has especially been studied and syntheses of numerous cyclic structures (from five membered rings to large rings) have been reported [5]. As a part of an ongoing research program on the use of (divinyl)-cyclopentanyl-lactone in the total synthesis of novel steroid [6], we were interested in the possibility of performing via metallo carbene metathesis versatile synthesis of spirolactones which cannot be obtained through BISTRO chemistry. Moreover, recent reports prompted us to report results in this field [7].

In this paper, we disclose the preparation of a series of novel spirolactones using a sequence involving allylation or alkylation of cyclic anhydrides followed by ring closing metathesis.

2. Results and disscussion

Synthesis of diallyl lactones were obtained using the following routes (Scheme 1). Diallyl lactones **2a**–**h** were synthesised by the titanium tetrachloride promoted double allylation reaction of cyclic anhydrides with allyltrimethylsilane in a mixture of dichloromethane and nitromethane [8]. Dibutenyl lactones **2i**–**j** were prepared through Grignard alkylation of anhydrides, with butenyl magnesium bromide in THF, according to a procedure described in the literature [9]. (Scheme 1)

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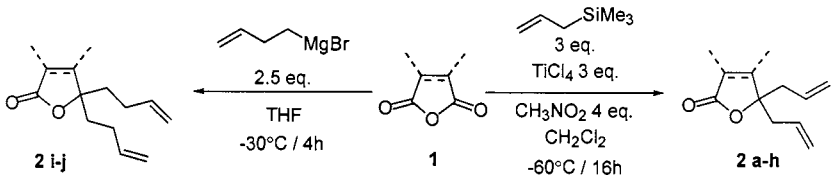


Scheme 1.

Next, attention was directed to the intramolecular ring closing metathesis reaction. The RCM reaction was performed using 5 mol% of Grubbs' ruthenium catalyst [$(Cy_3P)_2Cl_2Ru$=CH–Ph]. After stirring in CH_2Cl_2 or $CHCl_3$ at 40–70°C under Ar atmosphere during 5 h, the cyclised products were isolated in high yield (Scheme 2).

The results are summarised in the Table 1. All the RCM products gave consistent spectral and analytical data (see Table 2). The formation of the five-membered ring occurred as the sole pathway even in the case where the lactone ring contains an olefin moiety (entries 3–7). We also found that the reaction occurred in fair to good yield with 5,5-dibutenyllactones to afford a seven-membered ring but with a slight increase in the reaction time (8 h). With six-membered ring lactones (entry 8), our first attempt to perform a cyclisation reaction failed. This non-reactivity could be attributed to the formation of a chelate between the oxygen atom of carbonyl function and the ruthenium centre preventing the chelation of the second double bond and therefore the formation of metallocyclobutane involved in the Chauvin mechanism [10]. This problem was solved using titanium tetraisopropoxyde (one equivalent) as preconcieved by Fürstner [11]. As an explanation for the difference in reactivity between γ- and δ-lactones (Scheme 3), we think that the chelation of the ruthenium atom is only possible with the oxygen atom of the carbonyl function of the δ-lactone (complex **A**) while steric constraint due to planarity of γ-lactone ring prevents the formation of this type of chelate (complex **B**).

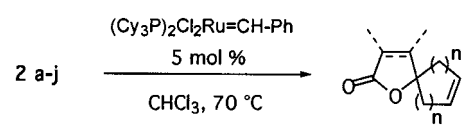
Finally, we decided to submit the diene derivatives of himic anhydride **4a**–**b** to the metathesis reaction in order to examine the selectivity of the three possible metathesis pathways. Due to their strained structures, lactones **4** could lead to compounds either resulting in ring closing process, ring opening polymerisation metathesis [12] or the combination of ring closing and ring opening metathesis as described by Blechert [13]. The reaction of **4a** or **4b** with 5 mol% of Grubbs catalyst yields 82 and 85% of the spiro cyclopentenyl and spiro cycloheptenyl lactones **5a** and **5b**, respectively (Scheme 4). No products resulting from the other possibilities were detected. In order to promote ring opening of the norbornyl moiety, an identical attempt conducted on **4b** was performed with 1.5 equivalents of allyltrimethylsilane; nevertheless, only the seven-membered cyclisation pathway occurred after 5 h at r.t. These reactions demonstrated the kinetic preference of ring closing processes over the ring opening of strained olefins.

In conclusion, under Grubbs' ruthenium complex catalysis, diallyl or dibutenyl lactones react via a ring closing metathesis to selectively provide spirolactones. Studies to extend this reaction to other heterocyclic structures are currently underway and will be reported in due course.

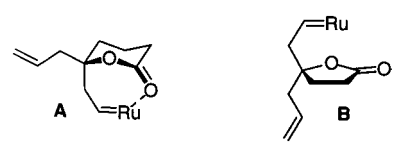
3. Typical procedure to obtain diallyl and dihomoallyl lactones

*3.1. 5,5-Diallyl-5H-furan-2-one (**2c**)*

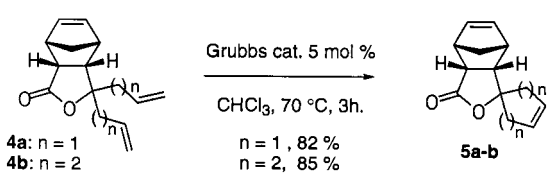
A solution of maleic anhydride (10.0 mmol) in dichloromethane (10 ml) was added at −60°C under argon atmosphere, to titanium tetrachloride (30.0 mmol) and nitromethane (40.0 mmol) in anhydrous dichloromethane (20 ml). The reaction mixture was then cooled to −90°C, before the addition through a syringe of allyltrimethylsilane (30.0 mmol) in dichloromethane (10 ml). The reaction mixture was



Scheme 2.

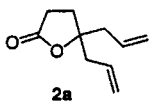
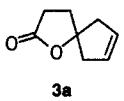
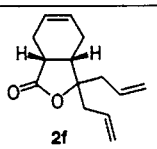
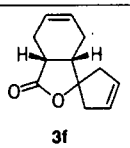
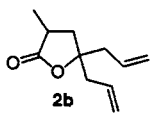
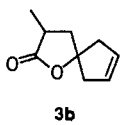
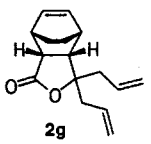
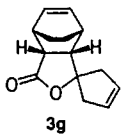
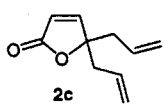
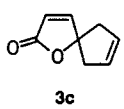
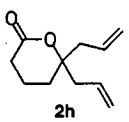
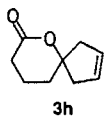
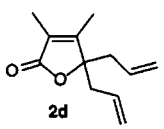
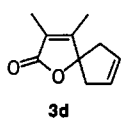
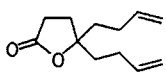
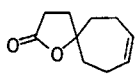
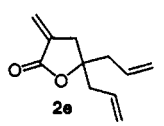
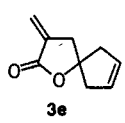
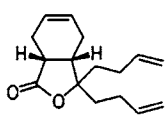
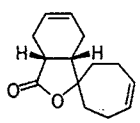


Scheme 3.



Scheme 4.

Table 1
Synthesis of spiro bicyclic lactones [a]

entry	2	3	yield (%)	entry	2	3	yield (%)
1			94	6			71
2			56	7			65
3			67	8[a]			79
4			54	9			78
5			65	10			85

[a] Reaction was carried out with one equivalent of $Ti(O\text{-}i\text{-}Pr)_4$ in CH_2Cl_2.

stirred at -90°C during 0.5 h, and warmed to -60°C. The mixture was stirred during 16 h at this temperature and was hydrolysed with a saturated ammonium chloride solution. The organic layer was extracted with dichloromethane, washed with brine and dried over magnesium sulfate. After removal of the solvent, the crude product was chromatograph with 50:50 petroleum ether–ether to afford the 5,5-diallyl-5*H*-furan-2-one (**2c**) in a 95% yield.

*3.2. 5,5-Diallyl-4-oxa-tricyclo[5.2.1.0^{2,6}]dec-8-en-3-one (**4a**)*

Magnesium (0.250 g) in suspension in anhydrous tetrahydrofurane (10 ml) was placed in a 500 ml round-bottomed flask, with one iode crystal. Then 1,2-dibromoethane (0.05 ml) was added. When the reaction had begun, allylchloride (0.2 mol) in anhydrous tetrahydrofurane (100 ml) was added dropwise. The solution was stirred overnight and himic anhydride (75.0 mmol) in anhydrous tetrahydrofurane (100 ml) was added. After 3 h, the reaction was hydrolysed with a 10% hydrochloric solution and was heated at 40°C during 0.5 h. The mixture was then extracted with diethylether, washed with brine and dried over magnesium sulfate. After removal of the solvent, the residue was chromatograph with 50/50 petroleum ether–ether to afford the 5,5-4-oxa-tricyclo[5.2.1.0^{2,6}]dec-8-en-3-one (**4a**) in 66% yield.

4. Typical procedure to obtain cyclopentenic lactones and cycloheptenic lactones

*4.1. 1-Oxa-spiro[4.4]non-3,7-dien-2-one (**3c**)*

Grubbs catalyst (5.10^{-2} mmol) in anhydrous dichloromethane (3 ml) was added to 5,5-diallyl-5*H*-furan-2-one (1.0 mmol) in anhydrous dichloromethane (3 ml) under argon atmosphere. The reaction mixture was refluxed for 6 h then the solvent was removed under vacuum and the residue was chromatograph with petroleum ether–ether (50:50) to afford the 1-oxa-spiro[4.4]non-3,7-dien-2-one (**3c**) in 94% yield.

*4.2. 6-Oxa-spiro[4.5]dec-2-en-7-one (**3h**)*

Titanium isopropylate (2.0 mmol) was added to 6,6-tetrahydropyran-2-one (1.0 mmol) in anhydrous

Table 2
NMR data

	^{1}H-NMR (200 MHz, $CDCl_3$) δ	^{13}C-NMR (50 MHz, $CDCl_3$) δ
3a	2.18 (t, $J = 8.6$ Hz, 2H), 2.44 (t, $J = 8.6$ Hz, 2H), 2.46 (d, $J = 16.5$ Hz, 2H), 2.63 (d, $J = 16.5$ Hz, 2H), 5.59 (s, 2H).	29.6, 33.7, 45.1, 92.7, 128.0, 176.5.
3b	1.24 (d, $J = 7.0$ Hz, 3H), 1.92 (m, $J = 12.0$ Hz, 2H), 2.39–2.83 (m, 5H), 5.66 (s, 2H).	15.6, 36.4, 42.8, 45.7, 46.1, 92.8, 128.4, 128.6, 172.9.
3c	2.57 (d, $J = 16.5$ Hz, 2H), 2.69 (d, $J = 16.5$ Hz, 2H), 5.72 (s, 2H), 5.95 (d, $J = 5.4$ Hz, 1H), 7.44 (d, $J = 5.4$ Hz, 1H).	42.4, 94.1, 120.0, 128.2, 159.1, 172.5.
3d	1.75 (s, 3H), 1.88 (s, 3H), 2.56 (d, $J = 17.9$ Hz, 2H), 2.61 (d, $J = 17.9$ Hz, 2H), 5.72 (s, 2H).	8.5, 11.2, 42.0, 93.7, 122.8, 128.4, 146.7, 173.8.
3e	2.53 (d, $J = 16.2$ Hz, 2H), 2.81 (d, $J = 16.2$ Hz, 2H), 3.00 (t, $J = 2.6$ Hz, 2H), 5.62 (t, $J = 2.6$ Hz, 1H), 5.71 (s, 2H), 6.23 (t, $J = 2.6$ Hz, 1H).	39.9, 46.0, 84.2, 121.6, 128.2, 138.0, 165.0.
3f	1.61–1.81 (m, 1H), 2.02–2.22 (m, 1H), 2.23–2.68 (m, 7H), 2.88 (dd, $J = 7.4$, 2.9 Hz, 1H), 5.56–5.74 (m, 4H).	21.8, 22.2, 38.5, 39.8, 40.0, 44.8, 94.1, 124.2, 124.6, 127.6, 128.1, 178.0.
3g	1.12–1.20 (m, 5H), 2.38–2.92 (m, 6H), 3.00 (dd, $J = 9.6$, 3.8 Hz, 1H), 5.69 (m, 2H), 6.23 (m, 2H).	23.1, 25.3, 32.3, 32.8, 41.9, 47.3, 47.4, 49.7, 95.9, 128.0, 129.1, 133.2, 133.6, 177.9.
3h	1.17–1.38 (m, 4H), 2.20–2.32 (m, 2H), 2.59 (d, $J = 15.9$ Hz, 2H), 2.91 (d, $J = 15.9$ Hz, 2H), 5.63 (s, 2H).	17.3. 29.1, 32.4, 46.2, 90.9, 127.6, 172.4.
3i	1.64–2.18 (m, 6H), 2.32 (m, 4H), 2.57 (t, $J = 8.0$ Hz, 2H), 5.75 (s, 2H).	23.6, 29.3, 34.1, 38.6, 90.5, 132.0, 177.3.
3j	1.62–2.65 (m, 13H), 3.12 (dt, $J = 8.0$, 3.9 Hz, 1H), 5.75 (s, 2H), 5.78 (s, 2H).	21.6, 22.4, 22.9, 23.4, 33.3, 36.3, 37.8, 40.2, 90.1, 125.3, 125.8, 130.7, 131.2, 178.7.
5a	1.40 (d, $J = 8.3$ Hz, 1H), 1.68 (dt, $J = 8.3$,1.6 Hz, 1H), 2.49–2.68 (m, 4H), 3.00 (dd, $J = 9.0$, 4.0 Hz, 1H), 3.10 (m, 1H), 3.26 (m, 1H), 3.40 (dd, $J = 9.0$, 4.0 Hz, 1H), 5.65 (s, 2H), 6.14 (dd, $J = 5.3$, 2.6 Hz, 1H), 6.21 (dd, $J = 5.3$, 2.6 Hz, 1H).	42.0, 45.5, 46.5, 49.8, 49.9, 50.0, 52.0, 93.1, 127.4, 128.2, 134.3, 135.9, 177.1.
5b	1.05–2.50 (m, 10H), 2.80 (dd, $J = 8.7$, 3.5 Hz, 1H), 3.03 (m, 1H), 3.25 (m, 1H), 3.42 (dd, $J = 8.9$, 4.8 Hz, 1H), 5.71 (s, 2H), 6.21 (s, 2H).	23.4, 23.7, 34.7, 41.9, 45.4, 45.5, 49.0, 51.8, 53.2, 89.7, 131.3, 131.8, 135.0, 136.4, 177.9.

dichloromethane (3 ml). The solution was stirred during 0.5 h under argon atmosphere then Grubbs catalyst (5×10^{-2} mmol) in anhydrous dichloromethane (3 ml) was added. The reaction mixture was refluxed for 6 h. The solvent was removed under vacuum and the residue was chromatograph with a mixture of petroleum 50:50 ether–ether to afford the 6-oxa-spiro[4.5]dec-2-en-7-one (**3h**) in 79% yield.

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