The Synthesis of Spirolactones Using Indium-Mediated Allylation of Cyclic Anhydrides and Ring-Closing Olefin Metathesis[1]

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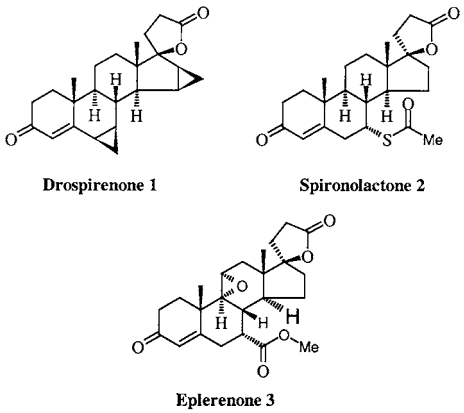
Received 7 August 2001

Abstract: A variety of spirolactones are prepared from cyclic anhydrides via indium-mediated allylation and ring-closing olefin metathesis (RCM) reaction as key steps.

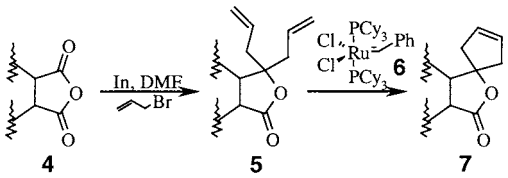
Key words: spirolactones, cyclic anhydrides, allylation, ring-closing metathesis

Spirolactones are important structural units because of their unique molecular geometry and interesting biological activity. This type of spiro system is present as key framework of numerous steroids[2,3] like Drospirenone **1**,[4] spironolactone **2**[5] and as well as in an antihypertensive drug Eplerenone **3**.[6] Construction of spirolactones can be achieved by intramolecular free radical cyclization,[7] oxidative cyclization of hydroxyalkenes,[8] SmI_2-induced reductive cross coupling of carbonyl compounds with α,β-unsaturated esters,[9] by oxidation of borinate esters[10] and other methods.[11] Ring-Closing Metathesis (RCM) has recently emerged as a powerful tool for the formation of a variety of ring systems[12] including spiroannelation.[13]



Figure

In 1989, Butsugan et al.[14] reported a novel example of gem-diallylation of the carbonyl group of acid anhydrides by indium-mediated allylation, which yielding gem-diallyl esters. We utilized this reaction to a variety of cyclic acid anhydrides, which provided diallylated butenolides and phthalides serving as substrates for RCM. In this context, we wish to report a novel and efficient methodology involving indium catalyzed allylation of cyclic anhydrides followed by ring closing metathesis reaction using Grubb's catalyst **6** for the key C–C bond formation reaction for the synthesis of a variety of novel spiro-γ-lactones (Scheme).



Scheme

Thus, the allylation reaction of cyclic acid anhydrides **4a**–**e** with allylbromide in DMF in the presence of indium metal resulted in the formation of 5,5-diallyl butenolides or 3,3-diallylphthalides **5a**–**e**[15] in good yields. The crucial ring closing reactions of the various dienes **5a**–**e** were performed in dichloromethane using 5 mol% of the Grubb's ruthenium carbene catalyst **6** at room temperature**.** All the reactions proceeded smoothly and were complete within 1 hour affording the corresponding spirolactones **7a**–**e**[15] in yields ranging from 52–92% (Table). It was further noted that, in the case of 4-fluorophthalic anhydride **4e**, allylation using indium afforded an inseparable mixture of two products. The ratio was found to be 1:1 mixture of isomers based on ^{1}H NMR spectral data and this mixture was further utilized for RCM reaction to give a mixture of spirolactones in 1:1 ratio as indicated by ^{1}H NMR data.

The structures of the diallyl products and spiro compounds were assigned based on IR, ^{1}H NMR, ^{13}C NMR spectroscopic and mass spectrometric data.

In conclusion, we have demonstrated a synthetic protocol utilizing indium-catalyzed allylation of cyclic anhydrides followed by ring-closing metathesis, which affords convenient access to γ-spirolactones. In addition to the reaction efficiency, reaction simplicity and generality, the present approach may find application in natural product synthesis and the presence of a double bond in the spiro compounds allows for further functionalization reactions.

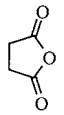
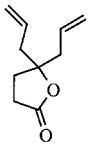
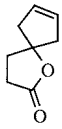
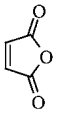
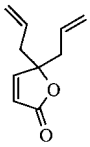
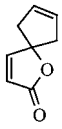
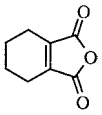
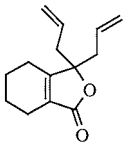
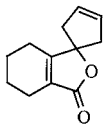
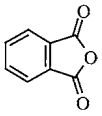
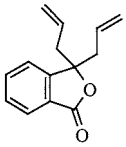
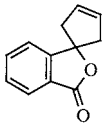
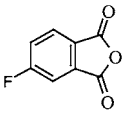
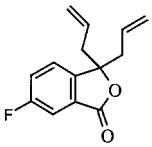
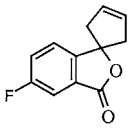
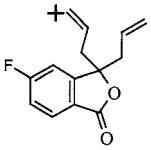
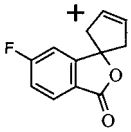
Acknowledgement

ChSR thank UGC and RSB thank CSIR, New Delhi for the award of fellowships.

Synlett 2001, No. 11, 26 10 2001. Article Identifier:
1437-2096,E;2001,0,11,1787,1789,ftx,en;D18101ST.pdf.

ISSN 0936-5214

Table Allylation of Cyclic Anhydrides and Ring-Closing Metathesis of Lactonedienes

Entry	Cyclic anhydride **4**	Lactone diene **5**	Spirolactone **7**
a		 71%	 83%
b		 64%	 87%
c		 57%	 52%
d		 80%	 92%
e		 83%[a]	 90%[a]
			

[a] Mixture of products were formed in 1:1 ratio.

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(14) Araki, S.; Katsumura, N.; Ito, H.; Butsugan, Y. *Tetrahedron Lett.* **1989**, *30*, 1581.
(15) **General Procedure for the Indium-mediated allylation:** A mixture of anhydride (1 mmol) and Indium (2 mmol) in anhyd DMF (2 mL) was added allylbromide (3 mmol) in DMF (1 mL) and the reaction mixture was stirred at r.t. for 1 h. After complete conversion as indicated by TLC, aq NH_4Cl was added and the product was extracted with Et_2O (3×10 mL). The combined organic layers were washed with brine, dried over anhyd Na_2SO_4 and concentrated in vacuo to yield crude product, which was purified by column chromatography using silica. The products **5a**–**e** were characterized by their IR and ^1H NMR spectral data. **General procedure for the preparation of the spirolactones (7a–e)using RCM:** To a solution of the ruthenium carbene catalyst **6** (5 mol%) in anhyd CH_2Cl_2 (1 mL) was added a solution of the diallyl compound (**5a**–**e**) (50 mg) in anhyd CH_2Cl_2 (1 mL). The resulting reaction mixture was stirred at r.t. for 1 h under N_2 atmosphere. After complete conversion as indicated by TLC, the solvent was removed in vacuo and the residue purified by silica column chromatography and eluting with EtOAc–Hexane (4:96) to give analytically pure products (**7a**–**e**).
Spectroscopic data: **5a:** ^1H NMR (200 MHz, $CDCl_3$) δ 2.03 (t, 2 H, *J* = 7.5 Hz, -CH_2), 2.28–2.45 (m, 4 H), 2.50 (t, 2 H, *J* = 7.5 Hz, -CH_2), 5.10–5.28 (m, 4 H, HC=CH_2), 5.65–5.90 (m, 2 H, HC=CH_2). **7a:** ^1H NMR (200 MHz, $CDCl_3$) δ 2.20 (t, 2 H, *J* = 4.9 Hz, -CH_2), 2.45 (d, 2 H, *J* = 9.8 Hz), 2.50 (t, 2 H, *J* = 4.9 Hz, -CH_2), 2.75 (d, 2 H, *J* = 9.8 Hz), 5.62 (s, 2 H, HC=CH). MS: *m/z* (%) = 138 (M^+), 110, 95, 83, 77, 55, 39. **5b:** ^1H NMR (400 MHz, $CDCl_3$) δ 2.42–2.58 (m, 4 H), 5.10–5.20 (m, 4 H, HC=CH_2), 5.60–5.70 (m, 2 H, HC=CH_2), 6.05 (d, 1 H, *J* = 8.1 Hz, -CH=CH-), 7.25 (d, 1 H, *J* = 8.1 Hz, -CH=CH-). **7b:** ^1H NMR (200 MHz, $CDCl_3$) δ 2.70 (s, 4 H, -CH_2), 5.80 (s, 2 H, HC=CH), 6.02 (d, 1 H, *J* = 5 Hz, -CH=CH-), 7.40 (d, 1 H, *J* = 5 Hz, -CH=CH-). **5c:** ^1H NMR (200 MHz, $CDCl_3$) δ 1.55–1.70 (m, 4 H), 2.45–2.49 (m, 4 H, -CH_2), 2.51–2.54 (m, 4 H), 5.01–5.52 (m, 4 H, HC=CH_2), 5.82–6.05 (m, 2 H, HC=CH_2). **7c:** ^1H NMR (200 MHz, $CDCl_3$)δ 1.48–1.60 (m, 4 H), 2.20–2.30 (m, 4 H, -CH_2), 2.42–2.55 (m, 4 H), 5.68 (s, 2 H, HC=CH). **5d:** IR (KBr): ν 1760 cm^{-1}, ^1H NMR (200 MHz, $CDCl_3$)δ 2.61–2.66 (dd,

2 H, *J* = 14.2, 6.8 Hz, -CH_2), 2.70–2.76 (dd, 2 H, *J* = 14.2, 6.8 Hz, -CH_2), 5.01–5.06 (m, 4 H, HC=CH_2), 5.49–5.59 (m, 2 H, HC=CH_2), 7.33 (d, 1 H, *J* = 7.8 Hz, ArH). **7d**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.00 (s, 4 H), 5.90 (s, 2 H, HC=CH), 7.45 (d, 1 H, *J* = 7.5 Hz, ArH), 7.53–7.68 (m, 2 H, ArH), 7.90 (d, 1 H, *J* = 7.5 Hz, ArH). ^{13}C NMR (400 MHz, $CDCl_3$) 46, 92, 121, 125, 128, 129, 134, 153, 169. MS: *m/z* (%) = 185 (M–1, 100%), 172, 157, 144, 128, 114, 103, 90, 75, 40. **5e:** ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.65–2.80 (dd, 2 H, *J* = 14.0, 7.5 Hz, -CH_2), 2.82–2.90 (dd, 2 H, *J* = 14.0, 7.5 Hz, -CH_2), 4.97–5.15 (m, 4 H, HC=CH_2), 5.40–5.60 (m, 2 H, HC=CH_2), 7.28 (d, 1 H, *J* = 7.5 Hz, ArH), 7.48 (m, 1 H, ArH), 7.65 (d, 1 H, *J* = 7.5 Hz, ArH). **7e:** ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.83 (d, 1 H, *J* = 16 Hz, -CH_2), 3.12 (d, 2 H, *J* = 17 Hz, -CH2), 5.89 (s, 2 H, HC=CH), 7.30 (m, 1 H, ArH), 7.51 (m, 1 H, ArH), 7.70 (d, 1 H, *J* = 7.4 Hz, ArH).

There is an erratum or addendum to this paper.
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