Stereoselective Synthesis of Tricyclic Pyranoxepin Derivatives by Ruthenium-Catalyzed Enyne Metathesis/Diels–Alder Reaction

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Abstract: Synthesis of tricyclic oxepin-annulated pyrone derivatives has been achieved by the ring-closing enyne metathesis using the first-generation Grubbs' catalyst under a nitrogen atmosphere. The Diels–Alder reaction of these cyclized products with the dienophile proceeded smoothly to afford the tricyclic compounds in excellent yield.

Key words: pyrone, oxepin, heterocycles, ruthenium, ring-closing metathesis, enyne metathesis, Diels–Alder reactions

The importance of pyran-2-ones as synthons in the field of synthetic and medicinal chemistry was recognized due to their unique structural features and diverse pharmacological properties.[1] Compounds of this ring system are widely present in naturally occurring physiologically active substances in the form of isolated or fused ring systems. This has encouraged research with regard to the development of procedures for the synthesis of this class of compounds. On the other hand, very little information is known about medium ring oxacycle fused pyrones, which may, in part, be due to the lack of general methods for the synthesis of such ring systems. There are no general syntheses of pyranoxepin derivatives. Bravo et al. have reported[2] the preparation of seven-membered annulated ring complexes by the treatment of suitably substituted pyran derivatives with amberlite-15. In recent years ring-closing metathesis (RCM) has been shown to be a highly effective and practical method in organic synthesis. It has emerged as an efficient strategy to prepare various functionalized carbocycles and heterocycles from acyclic diene precursors.[3] This success is based on the development of stable metal carbenes as olefin metathesis catalysts. An intramolecular enyne metathesis is a particularly interesting reaction, because the double bond of the enyne cleaves and the alkylidene part of the olefin migrates to the alkyne carbon to afford a cyclized product that has a diene moiety.[4] It appeared to us that a combination of the Claisen rearrangement and a ring-closing enyne metathesis (RCEM) process could be used to access various hitherto unknown medium-sized heterocycle-annulated heterocyclic systems of interest. In this communication, we wish to report some successful applications of this general approach towards the construction of the oxepin-annulated pyrones.

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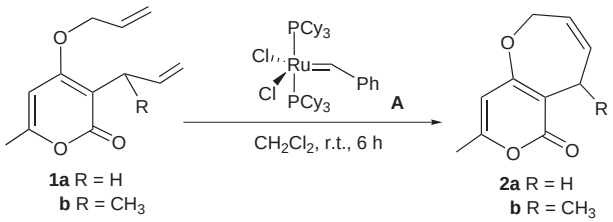
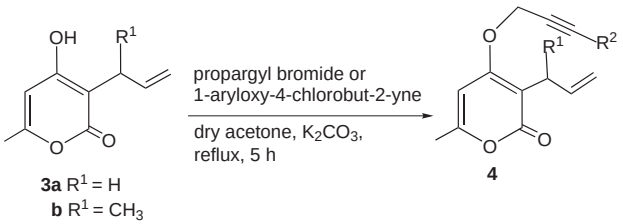
We planned the synthesis of oxepin derivatives from dienes connected to a pyrone moiety. To test this premise, dichloromethane solutions of derivatives **1a**,**b** and ruthenium carbene complex **A** (10 mol%)[5] were stirred at room temperature for six hours, leading to the formation of cyclized products **2a**,**b** in 80% and 78% yield, respectively (Scheme 1).



Scheme 1

The reaction was further extended to the synthesis of various seven-membered ring compounds connected with the pyrone ring by enyne bond reorganization. Compounds **3a**,**b** were prepared according to the earlier published procedure.[6] Straightforward alkylation of **3a**,**b** with the propargyl bromides in refluxing acetone in the presence of anhydrous K_2CO_3 for five hours gave **4a**,**b** in 72% and 70% yield, respectively. Similarly, the compounds **4c**–**e** were obtained from **3a**,**b** with 1-aryloxy-4-chlorobut-2-ynes in 75–80% yield (Table 1).

Table 1 Alkylation of Compounds **3**



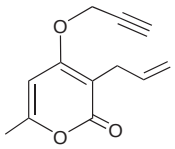
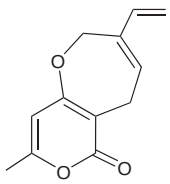
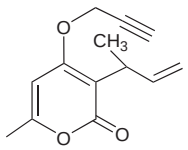
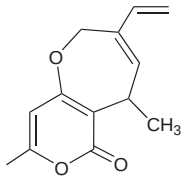
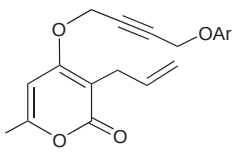
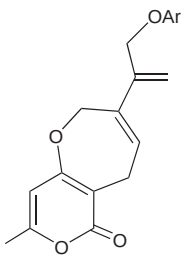
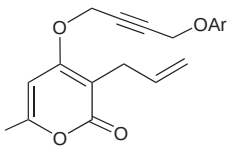
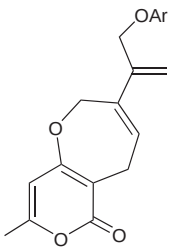
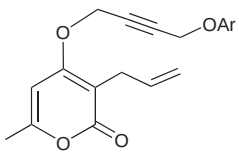
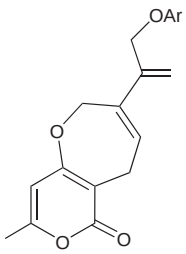
Compd **4**[a]	R^1	R^2	Yield (%)
a	H	H	72
b	CH_3	H	70
c	H	CH_2OAr	75
d	H	CH_2OAr	80
e	H	CH_2OAr	75

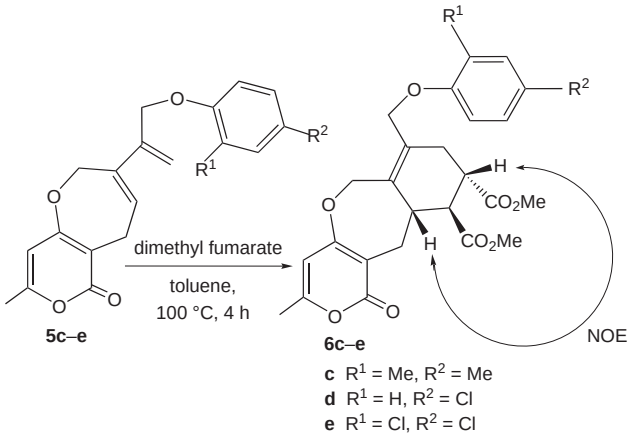
[a] Ar = 2,4-$Me_2C_6H_3$- (**4c**); Ar = 4-ClC_6H_4- (**4d**); Ar = 2,4-$Cl_2C_6H_3$- (**4e**).

We have successfully prepared some oxepin-annulated pyrone derivatives **5a**–**e**, possessing a diene unit, by using Grubbs' catalyst **A** and the enynes **4a**–**e**. Ring-closing enyne metathesis (RCEM) of **4a**–**e** with Grubbs' catalyst **A** in dichloromethane when stirred at room temperature for 5–8 hours delivered the desired products **5a**–**e** in 80–90% yield (Table 2). Better results were obtained with substituted propargyl aryl ethers, i.e. in the case of **4c**–**e**. Compounds **5c**–**e** were crystalline solids. However, compounds **5a**,**b** could not be solidified at room temperature. All the compounds **5a**–**e** were eluted by 25% ethyl acetate–petroleum ether and characterized from their elemental analyses and spectroscopic data.[7]

These diene derivatives **5a**–**e** can be useful substrates for subsequent Diels–Alder reactions. Several yne–ene cross-metathesis/cycloaddition sequences have recently been reported in the literature[8] in a stepwise manner. Sequential ring-closing metathesis/[4+2] cycloaddition have also been used for the preparation of several carbocyclic and heterocyclic systems.[9] This prompted us to explore the synthesis of tricyclic oxepin-annulated pyrones **6c**–**e** from our cyclized products **5c**–**e** by [π^4s + π^2s] cycloadditions. When a solution of **5d** and dimethyl fumarate (DMF) was stirred in benzene at 60 °C no reaction occurred even after 30 hours. When the compound **5d** was treated with dimethyl fumarate (DMF) in toluene at 100 °C, a single diastereoisomer **6d** was obtained within four hours in 95% yield. Other substrates **5c** and **5e** were also similarly treated with dimethyl fumarate to give single diastereoisomers **6c** and **6e** in 95% and 96% yield, respectively (Scheme 2). The formation of Diels–Alder products **6c**–**e** was confirmed by their elemental analyses and spectroscopic data.[10] The *cis* stereochemistry of the mentioned pair of hydrogens was confirmed by NOESY experiments.

Table 2 Ring-Closing Enyne Metathesis of **4a**–**e** with Grubbs' Catalyst

Entry	Substrate	Product		Time (h)	Yield (%)
1			**5a**	5	82
2			**5b**	6	80
3			**5c**	8	87
4			**5d**	8	90
5			**5e**	7	88



Scheme 2

We have been able to show that oxepin-annulated pyrone heterocycles having diene moieties can easily be synthesized by using ruthenium-catalyzed ring-closing metathesis of enynes. It was also demonstrated that the dienes are suitable substrates to prepare tricyclic compounds **6c**–**e**. In summary tricyclic compounds **6c**–**e** have been stereoselectively obtained by 'RCEM' in combination with a Diels–Alder cycloaddition process in excellent yield without any Lewis acidic promotion.

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(7) **Typical Procedure for the Enyne RCM.**
To a solution of substrate **4d** (68.9 mg, 0.2 mmol) in dry degassed CH_2Cl_2 (8 mL) under N_2 was added catalyst **A** (15 mg) and the reaction was stirred at r.t. for 8 h. After the removal of the solvent, the residue was purified by flash column chromatography on silica gel (PE–EtOAc, 4:1) to give **5d** in 90% yield.
Compound 5a: yield 82%; sticky liquid. IR (neat): ν_{max} = 1704, 1665, 1568 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.13 (s, 3 H), 3.47 (d, *J* = 6.55 Hz, 2 H), 4.99 (s, 2 H), 5.09 (d, *J* = 10.8 Hz, 1 H), 5.25 (d, *J* = 17.5 Hz, 1 H), 5.60 (s, 1 H), 6.24 (t, *J* = 6.55 Hz, 1 H), 6.29 (dd, *J* = 17.5 Hz, *J* = 10.8 Hz, 1 H). MS: *m/z* = 204 [M^+]. Anal. Calcd for $C_{12}H_{12}O_3$: C, 70.59; H, 5.88. Found: C, 70.73; H, 5.72%.
Compound 5d: yield 90%; light-yellow solid, mp 112 °C. IR (KBr): ν_{max} = 1698, 1658, 1568, 1491 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.13 (s, 3 H), 3.51 (d, *J* = 6.64 Hz, 2 H), 4.66 (s, 2 H), 5.07 (s, 2 H), 5.38 (s, 1 H), 5.41 (s, 1 H), 5.60 (s, 1 H), 6.39 (t, *J* = 6.64 Hz, 1 H), 6.82 (d, *J* = 8.88 Hz, 1 H), 7.21 (d, *J* = 8.88 Hz, 2 H). MS: *m/z* = 344, 346 [M^+]. Anal. Calcd for $C_{19}H_{17}O_4Cl$: C, 66.18; H, 4.93. Found: C, 65.98; H, 5.17%.

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(10) **Procedure for the Diels–Alder Reactions.**
A solution of **5d** (17.2 mg, 0.05 mmol) and dimethylfumarate (14.4 mg, 0.1 mmol) in toluene was heated at 100 °C for 4 h. After removal of the solvent the residue was purified by flash column chromatography on silica gel (PE–EtOAc, 3:1) to give **6d** in 95% yield.
Compound **6d**: yield 95%; white solid, mp 118–119 °C. IR (KBr): ν_{max} = 1736, 1703, 1655, 1580 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.15 (s, 3 H), 2.44–2.48 (m, 1 H), 2.58–2.69 (m, 3 H), 2.95–3.05 (m, 3 H), 3.67 (s, 3 H), 3.76 (s, 3 H), 4.39 (d, *J* = 11.2 Hz, 1 H), 4.47 (d, *J* = 11.2 Hz, 1 H), 4.79 (d, *J* = 13.6 Hz, 1 H), 5.04 (d, *J* = 13.6 Hz, 1 H), 5.65 (s, 1 H), 6.79 (d, *J* = 8.8 Hz, 2 H), 7.22 (d, *J* = 8.8 Hz, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 19.93, 27.11, 31.09, 41.86, 42.76, 47.74, 52.57, 52.69, 67.37, 69.49, 101.93, 102.54, 116.32, 126.79, 129.90, 130.79, 133.98, 157.35, 159.99, 166.12, 168.50, 174.01, 175.07. MS: *m/z* = 488, 490 [M^+]. Anal. Calcd for $C_{25}H_{25}O_8Cl$: C, 61.41; H, 5.12. Found: C, 61.68; H, 5.30%.
Compound **6e**: yield 96%; white solid, mp 125 °C. IR (KBr): ν_{max} = 1736, 1704, 1650, 1580 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.15 (s, 3 H), 2.41–2.47 (m, 1 H), 2.58–2.68 (m, 3 H), 2.93–3.02 (m, 3 H), 3.67 (s, 3 H), 3.76 (s, 3 H), 4.39 (d, *J* = 11.5 Hz, 1 H), 4.48 (d, *J* = 11.5 Hz, 1 H), 4.79 (d, *J* = 13.4 Hz, 1 H), 5.05 (d, *J* = 13.4 Hz, 1 H), 5.65 (s, 1 H), 6.78 (d, *J* = 8.6 Hz, 1 H), 7.21–7.25 (m, 2 H). MS: *m/z* = 522, 524, 526 [M^+]. Anal. Calcd for $C_{25}H_{24}O_8Cl_2$: C, 57.36; H, 4.59. Found: C, 57.66; H, 4.44%.