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Regioselective cyclization of α,ω-alkynoic acids catalysed by TpRu complexes: synthesis of endocyclic enol lactones [Tp = hydrotris(pyrazolyl)borate]†

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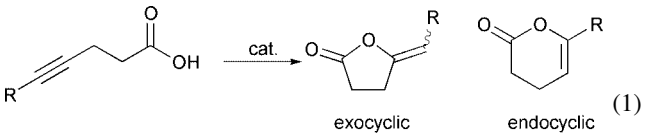
The σ-enynyl complex [TpRu{C(Ph)=C(Ph)C≡CPh}(P-Me^{i}Pr$_2$)] efficiently catalyses the regioselective cyclization of α,ω-alkynoic acids to yield endocyclic enol lactones having ring size up to 12 atoms.

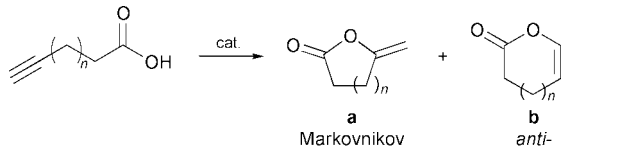
Enol lactones are present in a number of biologically active natural products. Whereas some compounds contain the exocyclic enol lactone substructure,[1] other natural products contain an endocyclic enol lactone ring, *e.g.* eresmofarfugin A,[2] and all products containing the isocoumarin ring system.[3,4] Endocyclic enol lactones are useful intermediates in the synthesis of more complex natural products such as the alkaloid (−)-aspidospermidine.[5] The cyclization of α,ω-acetylenic acid precursor represents one effective synthetic approach to enol lactone systems.[6] Silver salts and mercuric salts have been used as catalysts, but their utility suffers from limited scope, drastic conditions and poor selectivity.[7] Transition metal complexes have shown to catalyse efficiently the cyclization of α,ω-alkynoic acids to give enol lactones of 5- and 6-member rings, with variable degree of regio- and stereoselectivity depending upon the catalyst used and the particular alkynoic acid [eqn. (1)].[8–11]



(1)

In the case of terminal alkynoic acids (R = H), the metal-catalysed cyclization reaction yields exclusively exocyclic enol lactones. This can be interpreted in terms of the regioselective Markovnikov addition of the carboxylic acid to the terminal alkyne.[12] Alternatively the *anti*-Markovnikov addition would produce the corresponding endocyclic enol lactone. However, *anti*-Markovnikov addition products have never been observed to any significant extent, hence the use of this synthetic route for the general preparation of enol lactones seems to be very limited. We have recently reported the σ-enynyl complexes [TpRu{PhC=C(R)C≡CPh}(PMe^{i}Pr$_2$}] [R = Ph, H; Tp = hydrotris(pyrazolyl)borate(1−)] and their ability to catalyse the dimerisation and even cross-coupling of alkynes.[13] We have now found that [TpRu{PhC=C(Ph)C≡CPh)(PMe^{i}Pr$_2$}] (**1**) catalyses the regioselective cyclization of HOOCCH$_2$(CH$_2$)$_n$C≡CH (*n* = 1, 2, 3, 7) to the corresponding endocyclic enol lactones. Results are shown in Table 1 (entries 1–4).‡ The cyclization takes place smoothly in refluxing toluene in 6 h, and 2% catalyst load. Analytical samples of the lactones were isolated by solvent removal followed by preparative HPLC. In the case of larger lactone rings, the catalyst load and reaction time were increased to 10% and 24 h respectively, diluting the substrate concentration to *ca.* 0.05 M in order to prevent the formation of linear oligomers. As shown in Table 1, endocyclic enol lactones were the only product generated when catalyst **1** was used. So far, our catalyst has proven to be able to cyclize ring systems of up to 12 atoms. This constitutes an efficient method for the synthesis of macrocyclic enol lactones, with the potential ability for accessing even larger cyclic systems. In these cases, the cyclization is not stereoselective, and mixtures of the endocyclic *Z*- and *E*-enol lactones are obtained (entry 4).§ The complex [TpRuH(PPh$_3$)$_2$] (**2**)[14] can also cyclize alkynoic acids to enol lactones (Table 1, entries 5–8). However, with pentynoic acid the only exception, the cyclization is not regioselective, and mixtures of endocyclic (*anti*-Markovnikov) and exocyclic (Markovnikov) enol lactones are obtained. Detailed studies carried out on rhodium and iridium complexes, supported by X-ray crystal structure determinations of some iridium model catalytic intermediates,[11] have led to a mechanistic proposal for the catalytic cyclization of alkynoic acids leading to exocyclic enol lactones.[10,11] Based upon these observations, we can propose in our case a similar catalytic cycle to account for the formation of exocyclic enol lactones (Scheme 1, pathway A). Compound **2** dissociates one PPh$_3$ molecule followed by insertion of the alkynoic acid into the Ru–H bond. The resulting alkenyl complex releases alkenoic acid (10-undecenoic acid has been isolated from runs

Table 1 Catalysed cyclization of alkynoic acids to enol lactones



Entry	Catalyst	*n*	Product ratio a:b	Total yield (%)
1	**1**	1	0:100	97
2	**1**	2	0:100	95
3	**1**	3	0:100	45[a]
4	**1**	7	0:100[b]	84
5	**2**	1	0:100	98
6	**2**	2	47:53	95
7	**2**	3	32:68	50[a]
8	**2**	7	13:87[c]	79

[a] The remaining yield corresponds to 7-oxoheptanoic acid. [b] As a mixture of *Z*/*E* isomers in the ratio 51:49. [c] As a mixture of *Z*/*E* isomers in the ratio 41:59.

† Electronic supplementary information available: selected spectral data for enol lactone derivatives. See http://www.rsc.suppdata/cc/b1/b106647c/

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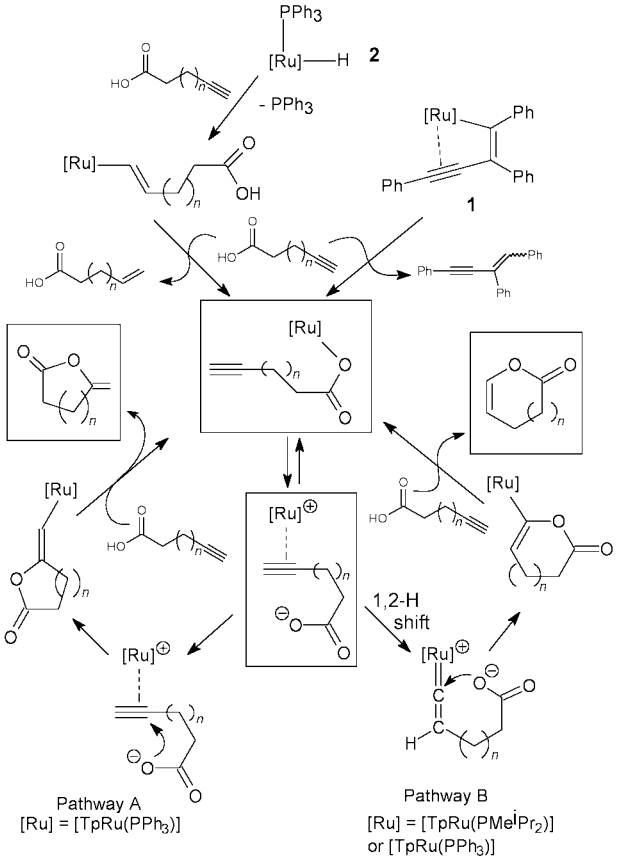

Scheme 1 Proposed mechanism for the cyclization of alkynoic acids to exocyclic enol lactones (pathway A) or endocyclic enol lactones (pathway B) catalysed by the complexes **1** and **2**.

involving undecynoic acid) upon reaction with another alkynoic acid molecule, furnishing a coordinatively unsaturated carboxylate complex which seems to be the actual catalytic species. An alternative pathway must be figured out in order to explain the regioselective formation of endocyclic enol lactones. Dixneuf and co-workers have developed ruthenium-based catalysts which can give either Markovnikov or *anti*-Markovnikov addition of acids or other organic substrates to terminal alkynes in a regioselective fashion.[12] The *anti*-Markovnikov addition takes place when the terminal carbon atom of the alkyne becomes electrophilic, this being feasible if a ruthenium–vinylidene intermediate species is generated at some stage during the catalytic process.[12] Therefore, we assume that in our case, a fast alkyne to vinylidene rearrangement takes place, most likely *via* a concerted 1,2-hydrogen shift (Scheme 1, pathway B).[15] In this fashion, the terminal carbon of the alkyne becomes electrophilic, and hence the carboxylate group attacks at this position. Ring closure yields an endocyclic alkenyl complex. As in pathway A, reaction with another alkynoic acid molecule releases the enol lactone and regenerates the coordinatively unsaturated carboxylate complex. It appears that the fast isomerization to vinylidene prior to carboxylate attack is the key step in the regioselective formation of endocyclic enol lactones. In the case of catalyst **1**, the presence of highly basic phosphine PMe^iPr_2 prompts the fast alkyne to vinylidene tautomerisation. In fact, we have already observed that facile alkyne to vinylidene rearrangement takes place at the $\{[TpRuCl(PMe^iPr_2)]\}$ moiety furnishing neutral vinylidene complexes $[TpRu{=}C{=}CHR(Cl)(PMe^iPr_2)]$ (R = Ph, Bu^t, $SiMe_3$).[13] For catalysts **2**, the alkyne to vinylidene rearrangement possibly occurs at a slower rate, similar to that of the attack of the carboxylate on the π-alkyne, so both pathways A and B of Scheme 1 might operate simultaneously. Further investigations are currently in progress in order to expand the applicability of these catalytic reactions, and in order to find additional information in support of our proposal for the reaction sequence in the catalytic cycle.

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Notes and references

‡ *General procedure*. A round bottom flask fitted with a condenser was loaded with 0.02 equiv. of the catalyst and dry toluene (5 mL), and the mixture was heated at 100 °C under argon. Then, 1 equiv. of alkynoic acid dissolved in dry toluene (2 mL) was added. The reaction mixture was refluxed for 6 h and then allowed to cool to rt. Cyclohexane (5 mL) was added and the solvent removed using reduced pressure. In the case of octynoic and undecynoic acids, the catalyst load and reaction time were increased to 10% and 24 h respectively, diluting the substrate concentration to *ca*. 0.05 M in order to prevent the formation of linear oligomers. The ratio of the different products present in the crude was established by integration of the signals in the ^{1}H NMR spectrum. Pure samples of the lactones were obtained by preparative HPLC.

§ There is evidence for the formation of *Z*- and *E*-stereoisomers also in case of the 8-membered lactone ring, but the *E*-stereoisomer is strained, and tends to open up during the purification process yielding 7-oxoheptanoic acid (Table 1, entry 3).

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