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Transition Metal Promoted Acetylene Isomerisation Reactions In Organic Synthesis

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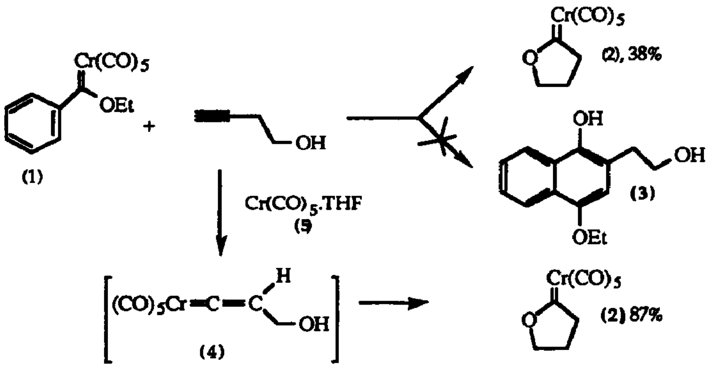
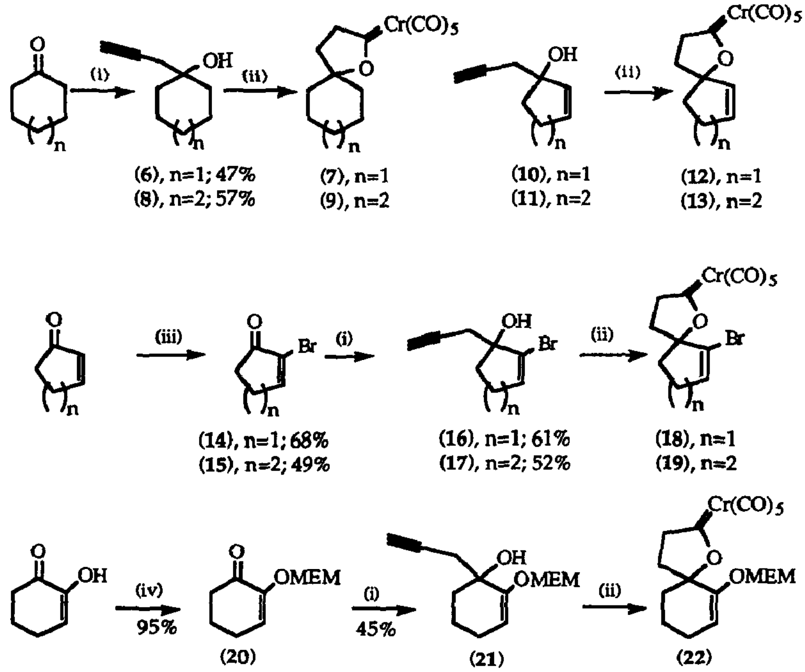
Abstract: *A transition metal mediated acetylene-vinylidene rearrangement has been developed for the synthesis of spirocyclic lactones*

During our recent investigations[1] into the use of the Dötz benzannulation reaction[2] for the synthesis of oxasteroidal analogues we noted that attempted benzannulation of the Fischer carbene complex (1) with butyn-1-ol afforded the cyclic carbene complex (2), in moderate yield (38 %), rather than the benzannulated product (3). We reasoned that the carbene complex (1) in this instance served as a source[3] of "$Cr(CO)_5$" which upon complexation with butyn-1-ol would effect an acetylene-vinylidene rearrangement[4] generating the highly electrophilic vinylidene complex (4). Intramolecular capture of (4) by the pendent hydroxyl group would then generate the carbene complex (2). This hypothesis was substantiated by reaction of butyn-1-ol with the readily available[5] complex $Cr(CO)_5$.THF (5), generating the complex (2) in 87 % isolated yield, **Scheme 1**.



Scheme 1

Whilst other workers[6] have observed similar reactions, synthetic applications of this process have not emerged[7]. Given the simplicity[8a] of the transformation and the synthetic potential[8b] of the cyclic carbene complexes (2) we decided to investigate the generality of the reaction sequence as outlined in **Scheme 2**. Reaction of cyclohexanone with propargyl magnesium chloride, as described by Viola[9], afforded the alcohol (6) in moderate yield (47%). Exposure of (**6**) to the labile σ-complex (**5**) (derived from the photolysis of $Cr(CO)_6$ in THF (500 W medium pressure Hg UV lamp)) in refluxing THF afforded the chromatographically stable spirocyclic carbene complex (**7**) in 78% yield. The carbinol (**8**) derived from cycloheptanone (in 57% isolated yield) similarly afforded the analogous carbene complex (**9**) in good isolated yield (64%). In order to gauge the effect of other functional groups upon the course of this reaction, a variety of acetylenic carbinols were subjected to the cyclisation sequence. The unsaturated carbinols (**10**) and (**11**), which are readily available from cyclohex-2-en-1-one and cyclopent-2-en-1-one, again afforded the spirocyclic carbene complexes (**12**) and (**13**) with only a slight diminution of yield (55 and 56% respectively).

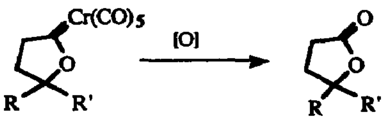


Reagents and conditions:- (i) C_3H_3MgBr, 1.1 eq.; Et_2O; -25°C; (ii) $Cr(CO)_5.THF$, 1.1 eq.; THF; 55°C (iii) Br_2, 1.1 eq.; Et_3N, 1.5 eq., CCl_4; 0°C to 20°C; (iv) (a) NaH, 1.2 eq; 0°C; (b) MEM-Cl, 1.1 eq.; THF; 0°C; 95%.

Scheme 2

Conversion of the vinyl bromides (**14**)[10] and (**15**)[11] into the carbinols (**16**) and (**17**) was readily accomplished and upon reaction with the preformed complex (**5**) afforded the halogenated carbene complexes (**18**) and (**19**) in moderate, unoptimised isolated yields of 30 and 59% respectively: the remainder of the mass balance was due to the presence of unreacted starting material. The MEM-ether (**21**), prepared from cyclohexane-1,2-dione, **Scheme 2**, likewise cyclised cleanly to the carbene complex (**22**), in moderate yield (49%).

Oxidative decomplexation of the cyclic carbene complexes to the respective lactones was investigated next, **Scheme 3**.



Scheme 3

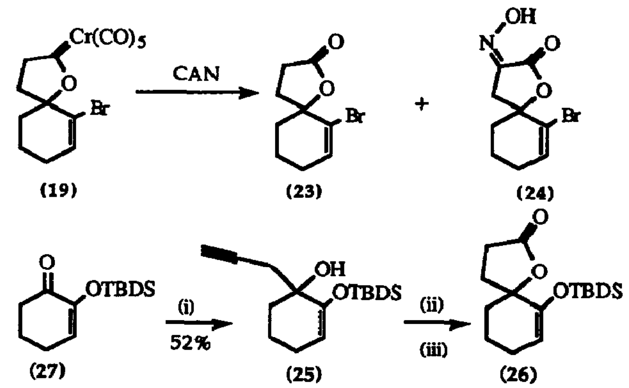
Whilst the carbene complexes appear to be stable towards oxidising agents such as DMSO[12] and polymer bound CrO_3, decomplexation with ceric ammonium nitrate[13] (CAN) proved to be successful in most cases, affording the desired lactones in good isolated yields (60-80%), **Table**.

Entry	Carbene† Complex	carbene yield	Oxidising agent	Lactone† yield
1	(7)	78%	CAN¶	81%
2	(9)	64%	CAN¶	77%
3	(12)	56%	CAN¶	16%*
4	(13)	55%	CAN¶	60%
5	(22)	49%	CAN¶	42%
6	(18)	57%	CAN¶	46%
7	(18)		PyNO§	72%
8	(19)	59%	CAN¶	9%
9	(19)		PyNO§	48%

† All new compounds were fully characterised by high resolution ^{1}H nmr, ir and mass spectrometry. ¶ CAN, 3 eq., acetone; 20°C 10 minutes. § Py-*N*-oxide, 3 eq.; CH_2Cl_2, 20°C; 3 hrs. * Isolated in low yield due to its' high volatility.

Table

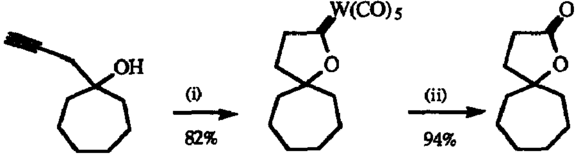
In certain instances, *e.g*. carbene complex (**19**), oxidation with CAN afforded the lactone (**23**) together with the oxime[14] (**24**) in poor isolated yield (9% and 4% respectively), suggesting that a more selective decomplexing agent should be employed. Further investigation revealed that pyridine-*N*-oxide is generally the reagent of choice for this transformation (e.g. **Table**, entries 7 and 9). Furthermore, the use of pyridine-N-



Reagents and conditions:-(i) C_3H_3MgBr, 1.1 eq.; Et_2O; -25°C; (ii) $Cr(CO)_5$.THF; 55°C; (iii) PyNO, 3 eq.; CH_2Cl_2.

Scheme 4

oxide in the decomplexation step is compatable with acid-labile functionality, as demonstrated by the preparation of the enol-lactone (**26**) in 38% overall yield from the alcohol (**25**), **Scheme 4**. We have also demonstrated that $W(CO)_5$.THF also promotes the acetylene-vinylidene rearrangement as exemplified by **Scheme 5**. In the few examples investigated so far, both the initial carbene generation and oxidative decomplexation steps appear to proceed in marginally higher yields in the tungsten series.



(8) (28) (27)

Reagents and conditions:- (i) $W(CO)_5$.THF, 1.0 eq.; THF; 55°C (ii) CAN, 3 eq.; acetone; 20°C; 10 mins.
Scheme 5

In conclusion we have developed a simple method for the construction of spirocyclic lactones utilising an acetylene-vinylidene rearrangement. Synthetic applications of this methodology are currently under investigation.

General Procedure

A suspension of chromium (or tungsten) hexacarbonyl in anhydrous THF was irradiated (500 Watt medium pressure Hg lamp) for 3 hours. The resulting orange-red solution of $Cr(CO)_5$.THF was transferred to a Schlenk tube and the acetylenic alcohol added. After stirring at 55°C for 16 hours the solution was concentrated *in vacuo* and chromatographed on silica gel. The carbene complex was dissolved in Analar® acetone and CAN (3 eq.) was added. After 10 minutes at 20°C, the solvent was removed *in vacuo* and the residue partitioned between ether/water. The organic layer was concentrated *in vacuo* , dried ($MgSO_4$) and the residue purified by "flash" chromatography to afford the lactone.

Acknowledgements

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