Pergamon

Tetrahedron Letters 40 (1999) 3485–3486

TETRAHEDRON
LETTERS

Functionalised β-Lactones from Chromium Alkyl(alkoxy)carbene Complexes

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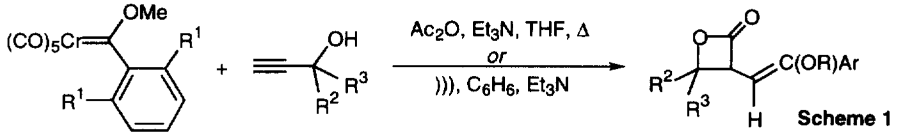
Received 26 January 1999; accepted 23 February 1999

Abstract: The reaction of chromium alkyl(alkoxy)carbenes with propargylic alcohols has been investigated under thermal and ultrasound conditions. Both sets of developed conditions provide rapid access to alkyl-substituted β-lactone products, which also possess enol ether functionality, from readily available starting materials.

Keywords: Alkynes; Chromium and compounds; Lactones; Sonochemistry.

Over the past few years we have established and optimised methods for the preparation of β-lactones from propargylic alcohols and Cr-aryl(alkoxy)carbene complexes[1] and, following our more recent application of ultrasound techniques to improve the overall efficacy of this class of transformation,[2] we planned to further extend the scope and flexibility of this organochromium-based chemistry (Scheme 1). More specifically, with a view to utilising this methodology to access biologically important alkyl-substituted β-lactone products, application of the practically more sensitive alkyl(alkoxy)carbene complexes[3] **1** and **2** was proposed.



Scheme 1

Both of the previously developed, thermal and sonication, techniques were utilised with a series of propargylic alcohols; whilst complexes **1** and **2** are less robust than their aromatic counterparts these alkyl carbenes do not have α,β-unsaturation and, thus, are not susceptible to competing Dötz benzannulation. In turn and pleasingly, when **1** and **2** were heated with the requisite alkynols, β-lactones were the sole organic products isolated. However, following a series of initial studies, it was observed that, in contrast to the aryl carbene complexes,[1] thermal reactions of **1** and **2** produced optimum yields of cyclised products when neither triethylamine nor acetic anhydride were present. In this respect, it is proposed that the additives may be causing excessive stabilisation of reaction intermediates from the alkyl complexes which, in turn, is enhancing the possibilities of decomposition.[4] Nonetheless, a range of β-lactones was readily accessed by the relatively simple thermal protocol with no additives (Table 1).

In due course, when ultrasound techniques were applied the reactions proceeded without complication to deliver the desired lactones in good to moderate yield (Table 1). Furthermore, the optimum conditions for the alkyl complexes (**1** and **2**) were equivalent to those used with the analogous aryl complexes (C_6H_6,))), approx. 2.4 equiv. Et_3N).[2] Additionally, as observed previously,[2] the sonication reactions provided a generally more effective protocol, especially in terms of gaining access to the less heavily substituted β-lactones (Entries 3-5).

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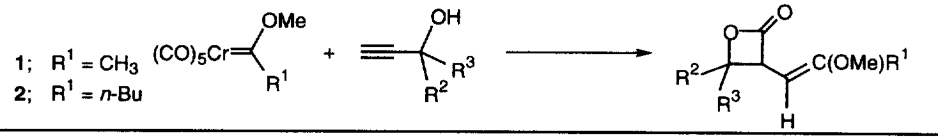
PII: S0040-4039(99)00430-X

Table 1. Thermal and Sonication Reactions of Complexes **1** and **2** with Propargylic Alcohols.[5]



Entry	Complex	R^2	R^3	Thermal Conditions[a]	Sonication Conditions[b]
1	**1**	-$(CH_2)_5$-		54% (6 h)[c]	56% (3 h)[c]
2	**1**	CH_3	CH_3	64% (4 h)[c]	59% (3 h)[c]
3	**1**	$CH(CH_3)_2$	H	33% (7 h)[c]	36% (5.5 h)[c]
4	**1**	CH_3	H	19% (6 h)[d]	32% (3.3 h)[e]
5	**1**	H	H	2% (5 h)[c]	34% (3 h)[c]
6	**2**	-$(CH_2)_5$-		65% (1 h)[c]	57% (1.5 h)[f]
7	**2**	CH_3	CH_3	42% (1.3 h)[g]	56% (0.6 h)[h]

[a] Yields of β-lactone after refluxing in THF and chromatographic purification; reaction times are shown in parentheses (see ref. 6 for a typical experimental procedure). [b] Yields after sonication in benzene with approx. 2.4 molar equiv. of Et_3N and chromatographic purification; reaction times are shown in parentheses (see ref. 2 for a typical experimental procedure). [c] Single isomer. [d] 6:1 Mixture of isomers. [e] >2 Isomers. [f] 3:1 Mixture of isomers. [g] 11.5:1 Mixture of isomers. [h] 9:1 Mixture of isomers.

As shown here we have now extended the scope and applicability of this novel Cr-mediated cyclisation reaction[7] to incorporate the use of generally less stable alkyl carbene complexes. In turn, β-lactones possessing alkyl enol ether (*i.e.* masked carbonyl) functionality can be rapidly accessed from readily available starting materials. The potential synthetic utility of these new techniques are now being explored within total synthesis programmes which are currently underway within our laboratory.

Acknowledgements. We gratefully acknowledge financial support from the EPSRC for a studentship (S. McK.) and from the Carnegie Trust for a postgraduate scholarship (J. J. C.). Furthermore, we are indebted to Zeneca Pharmaceuticals for Strategic Research Funding.

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4. When Et_3N/Ac_2O additives were used reaction work-up was also less routine.
5. All new compounds exhibited satisfactory analytical and spectral data.
6. **Typical Experimental Procedure**: A solution of pentacarbonyl(methoxybutylmethylene)chromium(0) **2** (353 mg, 1.21 mmol) and 1-ethynyl-1-cyclohexanol (243 mg, 1.96 mmol) in dry THF (100 ml) was heated to reflux for 1 hour. The solvent was removed *in vacuo* and the residue taken up in DCM, washed with a saturated solution of sodium bicarbonate, dried ($MgSO_4$) and the solvent evaporated *in vacuo*. The crude product was purified by flash column chromatography (eluant: petrol/ether, 3/1) to afford the pale yellow oil of 4-cyclohexanespiro-3-(2-methoxyhexen-1-yl)oxetan-2-one (198 mg, 65%) as a single isomer. IR (CH_2Cl_2): 1810 (s, C=O), 1659 (m, C=C) cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ 0.92 (3H, t, J = 7.2 Hz, CH_3), 1.20-2.00 (14 H, m, CyH, 2xCH_2), 2.12 (2H, t, J = 7.4 Hz, CH_2), 3.55 (3H, s, OCH_3), 3.89 (1H, d, J = 10.0 Hz, CH), 4.46 ppm (1H, d, J = 10.0 Hz, C=CH). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 13.93; 22.38; 22.44; 23.17; 24.83; 29.86; 30.50; 32.34; 37.05; 54.52; 57.00; 83.86; 85.46; 162.7; 172.16 ppm. HRMS (CH_2Cl_2): *m/z* Calc. for $C_{15}H_{25}O_3$ (MH^+) 253.1804. Found 253.1826 (16.4). Anal.: Calc. for $C_{15}H_{24}O_3$: C, 71.39; H, 9.59. Found C, 71.39; H, 9.86%.
7. During the completion of our experimental studies, a single and low yielding example of a β-lactone being formed by an analogous process was reported: Ishibashi, T.; Ochifuji, N.; Mori, M. *Tetrahedron Lett.* **1996**, *37*, 6165.