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Facile chromium carbene mediated synthesis of functionalised 5- to 7-ring lactones

Graham M. Good,[a] Mark I. Kemp[b] and William J. Kerr[a,*]

[a]*Department of Pure and Applied Chemistry, University of Strathclyde, Thomas Graham Building, Glasgow G1 1XL, UK*

[b]*Department of Discovery Chemistry, Pfizer Global Research and Development, Sandwich Laboratories, Ramsgate Road, Sandwich, Kent CT13 9NJ, UK*

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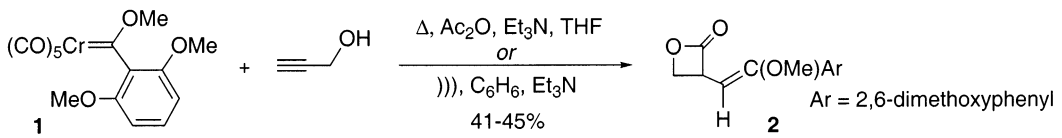
Abstract

The reaction of pentacarbonyl[methoxy(2,6-dimethoxyphenyl)methylene]chromium(0) with acetylenic alcohols has been investigated. Reaction protocols have been optimised for rapid and direct access to functionalised γ-, δ-, and ε-lactone products possessing enol ether (i.e. masked carbonyl) functionality.

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 chromium carbene complexes[1] and, more recently, our application of ultrasound techniques as well as the use of alkyl(alkoxy)carbene complexes have led to improvements in the overall efficacy, scope, and flexibility of this class of transformation.[2] Furthermore, our studies have also allowed us to report that the utilisation of complex **1** in this general protocol led to enhanced yields of β-lactones.[1a] We believe that this improvement in the efficiency of lactone formation is due to the methoxy groups at the 2- and 6-positions of the phenyl ring retarding any competing cyclisations. Indeed, reaction of propargyl alcohol with



Scheme 1.

* Corresponding author. Fax: 0141-548-4246; e-mail: cbas69@strath.ac.uk

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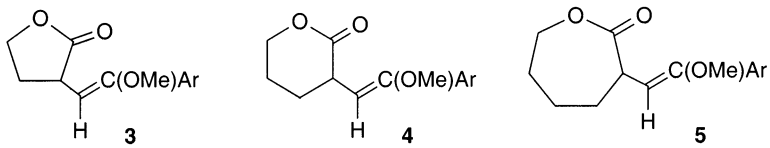
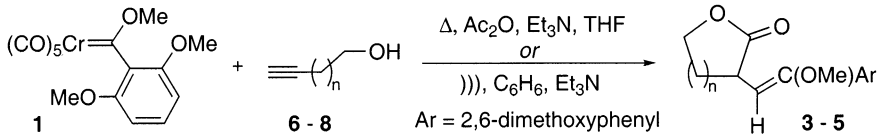
complex **1** gave the desired β-lactone **2** as the sole organic product (Scheme 1),[1a,2a] whereas Dötz has reported that when an analogous tolyl complex (where the 2- and 6-positions of the phenyl ring are unblocked) is reacted with propargyl alcohol, only the expected benzannulation product is obtained.[3]

Having shown that complex **1** can furnish β-lactone products by interrupting the Dötz annulation reaction, it was proposed that reaction of this complex with higher homologues of propargylic alcohols would lead to lactone products of larger ring size (i.e. **3**, **4**, and **5**) than the β-lactone products already accessed. This communication now describes our initial results in this area and our optimisation of this extended cyclisation protocol.



Based on our β-lactone protocols, the previously developed optimum thermal conditions (3 equiv. Et_3N, 2 equiv. Ac_2O, THF, reflux) were initially utilised. Accordingly, when complex **1** was heated with the requisite acetylenic alcohols **6**–**8**, the γ-, δ- and ε-lactones were formed in only low yield (Table 1).[4] In turn, application of our established sonication techniques (with Et_3N as an additive) considerably shortened the reaction time in each case. However, despite significant yield enhancements also being realised in the majority of cases, the efficiency of this cyclisation method remained only moderate. In this respect, it could be argued that formation of these larger ring lactones is thermodynamically more favoured than the previously optimised preparation of the more strained β-lactones. Consequently, the additives employed to this point

Table 1
Thermal and sonication reactions of complex **1** and acetylenic alcohols **6**–**8** in the presence of reaction additives



n	Substrate	Product	Thermal conditions[a]	Sonication conditions[b]
1	**6**	**3**	29% (3 h)[c]	33% (1.3 h)[f]
2	**7**	**4**	33% (3.5 h)[d]	59% (1.5 h)[g]
3	**8**	**5**	48% (2.5 h)[e]	58% (1 h)[h]

[a] Yields of lactone after refluxing in THF with 3 equiv. Et_3N and 2 equiv. Ac_2O and chromatographic purification; reaction times are shown in parentheses.

[b] Yields after sonication in benzene with 3 equiv. Et_3N and chromatographic purification; reaction times are shown in parentheses.

[c] 1.4:1 mixture of isomers.

[d] 5.8:1 mixture of isomers.

[e] 2.9:1 mixture of isomers.

[f] 1.8:1 mixture of isomers.

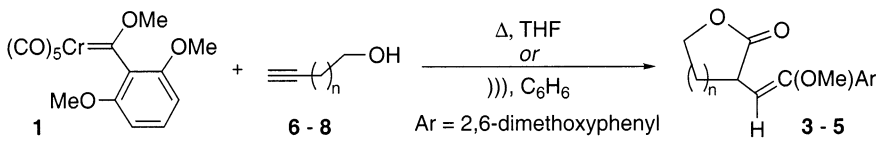
[g] Reaction carried out in toluene; 4.5:1 mixture of isomers.

[h] 3.2:1 mixture of isomers.

may then be causing over stabilisation of reaction intermediates and, in turn, enhancing the possibilities of decomposition.

On the basis of this rationale, modified reaction conditions were adopted. More specifically, under thermal conditions, optimum and consistently good yields of the functionalised higher lactone products were realised when the complex **1** and the acetylenic alcohols **6–8** were simply refluxed together in THF.[5] Indeed, this observation is somewhat analogous to that observed in our use of alkyl carbene complexes for the preparation of the similarly substituted β-lactones.[2b] The optimum results for access to the γ-, δ- and ε-lactones are presented in Table 2.

Table 2
Thermal and sonication reactions of complex **1** and acetylenic alcohols **6–8** in the absence of reaction additives



n	Substrate	Product	Thermal conditions[a]	Sonication conditions[b]
1	**6**	**3**	69% (3.25 h)[c]	62% (1.3 h)[f]
2	**7**	**4**	74% (4.75 h)[d]	65% (1.5 h)[g]
3	**8**	**5**	66% (2.75 h)[e]	55% (1 h)[f]

[a] Yields of 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 and chromatographic purification; reaction times are shown in parentheses (see Ref. 7 for a typical experimental procedure).

[c] 1.2:1 mixture of isomers.

[d] 3.5:1 mixture of isomers.

[e] 8.3:1 mixture of isomers.

[f] 2.7:1 mixture of isomers.

[g] 2.1:1 mixture of isomers.

In due course, when ultrasound techniques were applied the reactions proceeded without complication to again deliver the desired lactones in respectable yields (Table 2). It is worth noting here that, contrary to our previous observations,[2a,b] the sonication reactions were generally most efficient when performed in the absence of any amine additive. Nonetheless, consistent with our earlier results, use of ultrasound provided a simple and effective protocol, delivering the lactone products in reduced reaction time with yields which were comparable to those achieved in the optimised thermal process.

To conclude, we have now shown how complex **1** has been further used to extend our chromium carbene mediated lactonisation protocols. The optimised methods reported here now allow a series of functionalised 5- to 7-ring lactones to be directly and rapidly accessed from readily available alkynols. This general methodology is now being applied as the key transformation within total synthesis programmes currently underway in our laboratory.

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3. Dötz, K. H.; Sturm, W. *J. Organomet. Chem.* **1985**, *285*, 205.
4. All new compounds exhibited satisfactory analytical and spectral data.
5. It should also be noted that when Et_3N/Ac_2O additives were used, reaction work-up was also less routine.
6. **Typical experimental procedure for thermal reactions**: A solution of pentacarbonyl[methoxy(2,6-dimethoxyphenyl)-methylene]chromium(0) **1** (320 mg, 0.86 mmol) and 4-pentyn-1-ol **7** (144 mg, 1.71 mmol) in dry THF (60 ml) was heated to reflux for 4.75 hours. The solvent was removed in vacuo and the residue taken up in DCM. The crude product was purified by flash column chromatography (eluant: DCM to DCM/MeOH 1:1) to afford 3-[2-methoxy-2-(2,6-dimethoxyphenyl)ethenyl]tetrahydro-2(2*H*)-pyranone **4** (185 mg, 74%) as a 3.5:1 mixture of isomers. IR (CH_2Cl_2): 1739 (s, C=O), 1594 (m, C=C) cm^{-1}. ^1H NMR (400.13 MHz, $CDCl_3$): δ 1.60–1.96 (4H, m, $OCH_2(CH_2)_2$), 2.32 (0.22H, m, CHC=O), 2.82 (0.78H, q, $J=9.9$ Hz, CHC=O), 3.33 (0.64H, s, OCH_3), 3.68 (2.36H, s, OCH_3), 3.76 (6H, m, $ArOCH_3$), 4.11–4.17 (0.72H, m, OCH_2), 4.16–4.25 (0.74H, m, OCH_2), 4.34–4.38 (0.54H, m, OCH_2), 4.78 (0.22H, d, $J=8.0$ Hz, C=CH), 5.02 (0.78H, d, $J=9.3$ Hz, C=CH), 6.57 (2H, m, ArH), 7.27 ppm (1H, m, ArH). ^{13}C NMR (100.61 MHz, $CDCl_3$): δ 21.9, 26.1, 26.75, 37.1, 39.5, 55.5, 56.1, 56.25, 56.3, 67.95, 68.2, 99.8, 104.1, 104.2, 104.6, 107.55, 113.1, 130.4, 130.6, 151.5, 158.65, 159.2, 174.5 ppm. HRMS (CH_2Cl_2): m/z Calc. for $C_{16}H_{20}O_5$ (M^+) 292.1311. Found 292.1313. Anal. calc. for $C_{16}H_{20}O_5$: C, 65.74; H, 6.90. Found: C, 65.43; H, 6.93%. It should be noted that for compounds **3** and **5** chromatographic purification was carried out using neutral alumina.
7. **Typical experimental procedure for sonication reactions**: A solution of pentacarbonyl[methoxy(2,6-dimethoxyphenyl)methylene]chromium(0) **1** (28 mg, 0.07 mmol) and 3-butyn-1-ol **6** (11 mg, 0.16 mmol) in dry benzene (5 ml) was sonicated (using a Vibracell VC50 titanium horn operating at 50 W/20 kHz) for 1.3 hours. After this time the solvent was evaporated in vacuo, the crude product was taken up in DCM, pre-adsorbed onto neutral alumina, and purified by gravity column chromatography using neutral alumina (eluant: petrol/ether 1:1) to afford 3-[2-methoxy-2-(2,6-dimethoxyphenyl)ethenyl]dihydro-2(3*H*)-furanone **3** (13 mg, 62%) as a 2.7:1 mixture of isomers. IR (CH_2Cl_2): 1768 (s, C=O), 1595 (m, C=C) cm^{-1}. ^1H NMR (400.13 MHz, $CDCl_3$): δ 1.99–2.19 (1.73H, m, OCH_2CH_2), 2.66–2.68 (0.27H, m, OCH_2CH_2), 2.89–2.97 (0.73H, m, CHC=O), 3.38 (0.81H, s, OCH_3), 3.74 (2.19H, s, OCH_3), 3.80–3.86 (6.27H, m, $ArOCH_3$, CHC=O), 4.00–4.06 (0.72H, m, OCH_2), 4.23–4.36 (1.01H, m, OCH_2), 4.37–4.39 (0.27H, m, OCH_2), 4.68 (0.27H, d, $J=7.6$ Hz, C=CH), 4.94 (0.73H, d, $J=8.5$ Hz, C=CH), 6.50–6.64 (2H, m, ArH), 7.30–7.35 ppm (1H, m, ArH). ^{13}C NMR (100.61 MHz, $CDCl_3$): δ 30.7, 31.0, 37.2, 39.3, 55.6, 56.0, 56.2, 56.3, 65.6, 67.0, 97.8, 103.9, 104.0, 104.6, 105.4, 112.7, 113.3, 130.5, 130.8, 150.1, 153.4, 158.45, 158.6, 159.2, 178.9 ppm. HRMS (CH_2Cl_2): m/z Calc. for $C_{15}H_{18}O_5$ (M^+) 278.1154. Found 278.1155. Anal. calc. for $C_{15}H_{18}O_5$: C, 64.73; H, 6.52. Found: C, 64.80; H, 6.42%. It should be noted that for compound **4** chromatographic purification was carried out using silica.