Pergamon

Tetrahedron Letters 40 (1999) 3481–3484

TETRAHEDRON LETTERS

Chromium-Mediated β-Lactone Synthesis Using Ultrasonication

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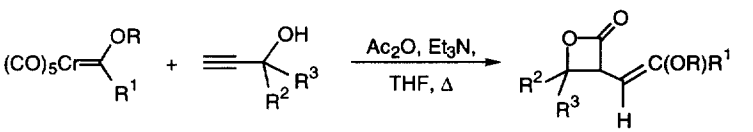
Received 26 January 1999; accepted 23 February 1999

Abstract: The reaction of chromium aryl(alkoxy)carbenes with propargylic alcohols has been investigated under dry state adsorption and ultrasound conditions. When compared to the corresponding thermal processes, the developed sonication reactions afford good yields of β-lactone products over generally shorter reaction times. Dry state adsorption affords diene products which are also obtained from the corresponding β-lactones.

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

Following our recent discovery and development of the facile synthesis of β-lactones from the reaction of chromium carbene complexes with propargylic alcohols under thermal conditions (Scheme 1),[2] further investigations have been carried out in our laboratory to optimise and extend the scope of this novel cyclisation reaction.



Scheme 1

Prior to the β-lactonisation discovery we had shown how the Dötz annulation reaction of α,β–unsaturated chromium carbene complexes and alkynes, to afford functionalised benzenoid systems, can be accelerated and the product yields enhanced by the application of ultrasound and dry state techniques.[2b,3] In this respect, it is believed that these conditions promote the benzannulation reaction by facilitating the loss of a carbon monoxide ligand from the metal centre of the chromium carbene complex; this has been shown to be the first and rate determining step of the Dötz cyclisation.[4] Our previous studies on the formation of β-lactones from the reaction of chromium carbenes and propargylic alcohols had supported a mechanism which followed that of the Dötz annulation to form a vinyl ketene intermediate; subsequent nucleophilic attack of the hydroxyl group onto the carbonyl of the vinyl ketene affords our β-lactone products while cyclisation through the vinyl moiety affords Dötz products.[2] Thus, as dry state adsorption and ultrasound conditions had promoted the Dötz reaction, it was proposed that the formation of β-lactone products by our cyclisation strategies would also be enhanced by using similar techniques.

On application of the established dry state adsorption methods to the reaction of complex **1** with 1-ethynyl-1-cyclohexanol **2**, disappointingly, no β-lactone product was observed;[5] the only organic compound isolated from this reaction was the diene **3** (Scheme 2). At this point it was considered possible that this diene

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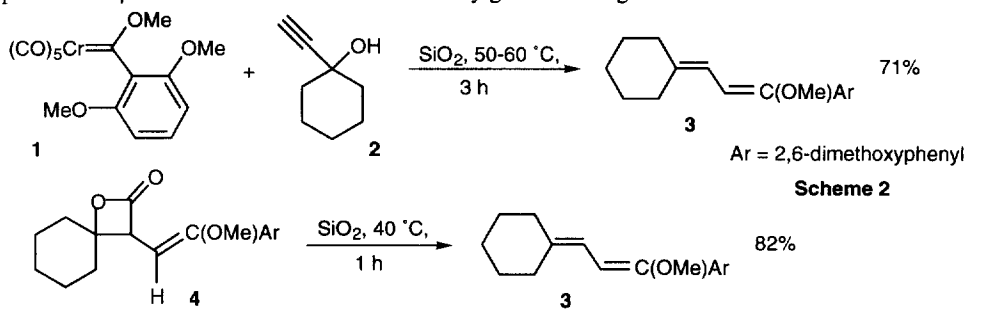
0040-4039/99/$ - see front matter
PII: S0040-4039(99)00429-3

was being formed *via* the expected β-lactone followed by decarboxylation under the dry state conditions employed. Indeed, this pathway was supported when diene **3** was formed in 82% yield following adsorption of the pre-formed β-lactone **4**[2a] onto silica followed by gentle heating to 40 °C.



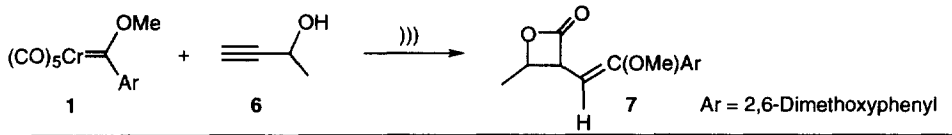
Scheme 2

Despite this unexpected result under dry state methods, we proceeded to the application of ultrasound conditions. Following the outcome of previous studies, which showed that complex **1** afforded higher yields of β-lactone products over the phenyl(methoxy)carbene complex **5**,[2a] our preliminary investigations were carried out using complex **1** with the propargylic alcohol **6**; these substrates had previously been shown to react under our optimised thermal conditions to afford β-lactone **7** in a yield of 48% following a reaction time of 3.5 hours.[2a] The reaction was carried out using a titanium horn ultrasound source[6] and employing three different sonication solvents: THF was used in order to provide a direct comparison with our previously obtained optimum thermal yield, *n*-Bu_2O was applied as this had previously been employed in the ultrasound promoted Dötz cyclisation reactions,[3] while benzene was used as a non-coordinating sonication solvent. Furthermore, a range of reaction conditions were explored in which the quantities of triethylamine and acetic anhydride additives (the previously employed thermal reaction promoters) were varied.

In reactions with THF as solvent the use of triethylamine/acetic anhydride was completely ineffective and led only to the return of unreacted starting materials. On the other hand, when no additives were employed with THF β-lactone **7** was obtained in a good 55% yield to improve on the previous optimum thermal cyclisation (Table 1). With *n*-Bu_2O cyclisation yields were generally poor. However, it was observed that the use of Et_3N and Ac_2O in benzene led to a pleasing 72% yield. Furthermore, in the presence of Et_3N (3 equiv.) alone, in the same solvent, our optimum sonication conditions were realised and cyclisation proceeded to provide an excellent 89% yield of β-lactone **7**.[7,8]

With this short ultrasound study having proven successful we moved on to apply our optimised sonication conditions to the reaction of complex **1** with a range of alternative propargylic alcohols, which we had previously shown to react under thermal conditions.[2a] As shown in Table 2, the expected β-lactones were formed in good yields (Entries 1-4) and, when compared to the thermal processes, over generally shorter reaction times. Furthermore, propargyl alcohol (Entry 5) also performed more efficiently than in the corresponding thermal process[2a] and, notably, with no benzannulation side-products.[11] Following the general success of our sonication conditions with complex **1** we proceeded to investigate reactions with the parent phenyl complex **5**. Pleasingly, the same β-lactonisation process was achieved (Table 2, Entries 6-8). In contrast, and consistent with our previous thermal studies, this unhindered complex performed less efficiently than the optimum dimethoxyphenyl species **1**.

Table 1. Ultrasound Promoted Reactions of Complex **1** with Alcohol **6**.[9]

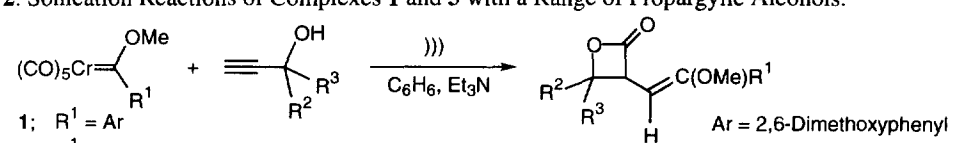


1 **6** **7** Ar = 2,6-Dimethoxyphenyl

Entry[10]	Solvent	Additives	Reaction Time (h)	Yield (%)[a]
1	THF	-	3	55
2	THF	Et_3N (3 equiv.)	3	0[b]
3	THF	Ac_2O (1.5 equiv.)	4	0[b]
4	THF	Et_3N (3 equiv.), Ac_2O (2 equiv.)	3	0[b]
5	*n*-Bu_2O	-	1	29
6	*n*-Bu_2O	Et_3N (3 equiv.)	1	27
7	*n*-Bu_2O	Ac_2O (1.5 equiv.)	3	0[c]
8	*n*-Bu_2O	Et_3N (3 equiv.), Ac_2O (2 equiv.)	1.5	25
9	C_6H_6	0	3	20
10	C_6H_6	Et_3N (3 equiv.)	3	89
11	C_6H_6	Ac_2O (1.5 equiv.)	1	0[c]
12	C_6H_6	Et_3N (3 equiv.), Ac_2O (2 equiv.)	2.5	72

[a]β-Lactone product **7** was isolated as a mixture of >2 isomers. [b]No reaction occurred; only starting materials remained by TLC analysis and no β-lactone product was observed by FTIR. [c]Decomposition occurred; no β-lactone product was observed by TLC or FTIR analysis.

Table 2. Sonication Reactions of Complexes **1** and **5** with a Range of Propargylic Alcohols.[9]



1; R^1 = Ar
5; R^1 = Ph

Ar = 2,6-Dimethoxyphenyl

Entry[10]	Complex	R^2	R^3	Reaction Time (h)	Yield (%)[a]
1	**1**	-$(CH_2)_5$-		3	79[b]
2	**1**	CH_3	CH_3	3	67[c]
3	**1**	$CH(CH_3)_2$	H	3.5	77[d]
4	**1**	CH_3	H	3	89[d]
5	**1**	H	H	4.5	45[e]
6	**5**	-$(CH_2)_5$-		1.5	36[f]
7	**5**	CH_3	CH_3	1.5	35[g]
8	**5**	$CH(CH_3)_2$	H	3	20[d]

[a]See ref. 2a for yields and reaction times for thermal reactions. [b]Isolated as a 7:3 mixture of isomers (around the enol ether double bond). [c]3:1 Mixture of isomers. [d]>2 Isomers. [e]Single isomer. [f]9:1 Mixture of isomers. [g]4:1 Mixture of isomers.

In conclusion, by the development and application of ultrasound techniques we have now improved the overall efficiency of these strategies for heavily functionalised β-lactone formation from aryl chromium carbene complexes and propargylic alcohols. Additionally, dry state adsorption conditions, although anticipated as providing the β-lactone *in situ*, afford the corresponding decarboxylated diene product. Both processes are the subject of on-going studies in our laboratory.

Acknowledgements. We gratefully acknowledge financial support from the EPSRC for studentships (J. P. A. H. & S. McK.), from the Carnegie Trust for a postgraduate scholarship (J. J. C.) and from Glaxo Wellcome Research and Development.

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4. Fischer, H.; Mühlemeier, J.; Märkl, R.; Dötz, K. H. *Chem. Ber.* **1982**, *115*, 1355.
5. Under our thermal reaction conditions this optimum ("blocked") 2,6-dimethoxyphenyl complex **1** has been shown to give a 74% yield of β-lactone **4** when reacted with 1-ethynyl-1-cyclohexanol **2**.[2a]
6. A Vibracell™ VC 50 titanium horn (50W/20kHz) operating at 50% output was used.
7. Yamashita and co-workers established the use of Ac_2O and Et_3N as reaction promoters for the Dötz benzannulation process when more sensitive (alkyne) substrates are employed: (a) Yamashita, A.; Toy, A. *Tetrahedron Lett.* **1986**, *27*, 3471. (b) Yamashita, A. J. *Am. Chem. Soc.* **1985**, *107*, 5823. (c) Yamashita, A.; Scahill, T. A.; Toy, A. *Tetrahedron Lett.* **1985**, *26*, 2969. (d) Flitsch, W.; Lauterwein, J.; Micke, W. *Tetrahedron Lett.* **1989**, *30*, 1633.
8. In the related Dötz benzannulation reactions Boger and Jacobson have also noted that the use of individual reaction promoters has led to optimum yields of reaction products: (a) Boger, D. L.; Jacobson, I. C. *J. Org. Chem.* **1991**, *56*, 2115. (b) Boger, D. L.; Jacobson, I. C. *J. Org. Chem.* **1990**, *55*, 1919. (c) Boger, D. L.; Jacobson, I. C. *Tetrahedron Lett.* **1989**, *30*, 2037.
9. All new compounds exhibited satisfactory analytical and spectral data.
10. **Typical Experimental Procedure**: A solution of pentacarbonyl(methoxy(2,6-dimethoxyphenyl)methylene)chromium(0) **1** (19 mg, 0.051 mmol), 3-butyn-2-ol **6** (8 mg, 0.114 mmol) and triethylamine (0.02 ml, 0.143 mmol) in dry benzene (5 ml) was sonicated for 3 hours. After this time the solvent was evaporated *in vacuo* and the crude product purified by flash column chromatography (eluant: petrol/ether, 2/1) to afford 4-methyl-3-(2-methoxy-2-(2,6-dimethoxyphenyl)ethenyl)oxetan-2-one **7** (12.7 mg, 89%) as a mixture of >2 isomers.
IR(CH_2Cl_2): 1816 (s, C=O), 1600 (m, C=C) cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$): δ 1.11; 1.41 (3H, 2xd, J = 6.0 Hz; 6.4 Hz, CH_3), 3.25-3.29 (1H, m, CH), 3.62-3.82 (9H, m, $ArOCH_3$, OCH_3), 3.36-3.47; 3.89-4.00; 4.23-4.32; 4.45-4.62; 4,77-5.03 (2H, 5xm, CH, C=CH), 6.46-6.54 (2H, m, ArH), 7.18-7.26 ppm (1H, m, ArH). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 16.60, 19.65, 29.01, 41.01, 42.72, 53.30, 55.40, 55.47, 55.68, 55.76, 56.00, 56.01, 56.12, 56.99, 73.37, 76.30, 90.77, 93.68, 102.10, 103.70, 103.80, 104.11, 104.40, 112.67, 130.42, 130.56, 131.02, 131.12, 154.16, 155.12, 157.99, 158.17, 158.27, 158.53, 159.12, 171.25, 172.40 ppm. HRMS (CH_2Cl_2): *m/z* Calc. for $C_{15}H_{18}O_5$ (M^+): 278.1423. Found 278.1402 (6.7).
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