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Reaction of substituted alkynols with alkoxycarbene complexes of chromium: a facile synthesis of substituted α,β-unsaturated-γ-butyrolactones

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ABSTRACT

Substituted α,β-unsaturated-γ-butyrolactones, were synthesized from Fischer chromium carbenes and substituted alkynols in a two-step sequence. This method demonstrates a novel and mild route for the synthesis of this class of molecules.

α,β-Unsaturated-γ-butyrolactones are key structural subunits belonging to a number of molecules with pronounced biological activity. These range from (−)-*Arctigenins*, a bisbenzylobutyrolactone that exhibits *anti*-HIV properties[1] to *Asimicin*[2] and *Bullatacin*[3], two diastereomeric members of the Annonaceous acetogenins which are not only known for their anti-tumor activity but also known for being potent anti-malarial, immunosuppressive, pesticidal, and anti-feedant agents. Their profound biological activity led to various strategies for the synthesis of these compounds.[4–13]

In the late 1990s, Kerr and Mori had described reactions of alkoxy Fischer chromium carbenes with terminal alkynols toward the synthesis of 4–7-membered lactones.[14,15] Taking a cue from their work we have developed a novel approach toward the synthesis of substituted α,β-unsaturated-γ-butyrolactones by rearrangement of γ-methylenebutyrolactones derived from alkoxy Fischer chromium carbene complexes **1a**,**b** and substituted alkynols **2a–j** (Table 1).

The alkoxy Fischer chromium carbene complexes **1a–b** and alkynes **2a–j** used in the reaction were prepared using standard literature procedures.[16–18]

The key reaction between alkoxy Fischer chromium carbenes and substituted alkynols was performed under thermal conditions in the presence and absence of solvents. While the reactions in solvents (viz THF, toluene, and o-xylene) gave poor yields (17–58%), the solvent-free reaction conditions generated the butyrolactones in decent yields. The reaction time was considerably reduced (from 8 to 0.5 h) (Table 1). However these γ-methylenebutyrolactones (other than **3k**) are unstable. We observed that these molecules start converting to α,β-unsaturated-γ-butyrolactones (**4**) within 15–20 min of isolation. Hence we could only obtain the weight of the isolated product and a quick $^{1}H/^{13}C$ NMR for these molecules.

It is also known from the literature that γ-methylenebutyrolactones such as **3** undergo rearrangement in the presence of TsOH to furnish α,β-unsaturated-γ-butyrolactones.[19] Hence to facilitate the conversion of **3** to **4**, we further treated the intermediate γ-methylenebutyrolactones (**3a–k**) with methanesulfonic acid (MSA) in aq.THF to generate the desired α,β-unsaturated-γ-butyrolactones. All but **3k** were converted successfully to the desired α,β-unsaturated-γ-methylenebutyrolactones **4a–j** (Table 2). In the case of **3k**, we could only isolate the unreacted starting material.

To improve the procedure we have performed a one-pot synthesis of α,β-unsaturated-γ-butyrolactone from the corresponding carbene and alkynol. As an example, carbene **2f** was reacted with **1a**. Once the carbene was consumed the crude reaction mixture was further treated with MSA and water and stirred for 2–3 days. The desired product **4f** was obtained as colorless oil after column purification (isolated yield 37%).

The structures of compounds **3a–j** and **4a–j** were clearly distinguished from the ^{1}H NMR spectra. The ^{1}H NMR of **3a** showed a singlet at δ 4.40 corresponding to the benzylic proton, which was missing in **4a**, also the ethereal alkyl group present in **3a** was absent in **4a** (Scheme 1).

A plausible mechanism for the formation of the intermediate γ-methylenebutyrolactones (**3a–j**) is depicted in Scheme 2. This mechanism is based on the work by Solà and co-workers.[20]

In conclusion, we have described a facile synthesis of substituted racemic butyrolactones via Fischer chromium carbenes and substituted alkynols. Work is in progress toward understanding the mechanism for conversion of **3a–j** to **4a–j** and toward

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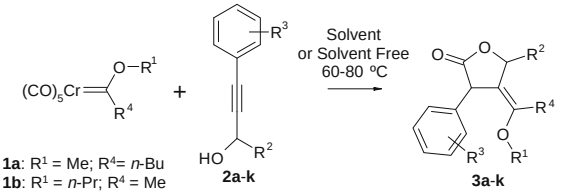
Table 1
Reactions of alkoxy Fischer chromium carbenes with alkynols



Compound	R^4	R^1	R^2	R^3
2a / 3a	*n*-Bu	Me	Me	*p*-Me
2b / 3b	*n*-Bu	Me	Me	*p*-OMe
2c / 3c	*n*-Bu	Me	H	*o*-Me
2d / 3d	*n*-Bu	Me	Et	*p*-Me
2e / 3e	*n*-Bu	Me	Et	*p*-OMe
2f / 3f	*n*-Bu	Me	H	*p*-OMe
2g / 3g	*n*-Bu	Me	H	*p*-Me
2h / 3h	*n*-Bu	Me	H	H
2i / 3i	*n*-Bu	Me	H	*p*-F
2j / 3j	Me	*n*-Pr	H	*p*-*t*-Bu
2k / 3k	*n*-Bu	Me	H	*p*-TBS

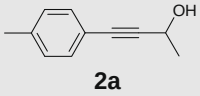
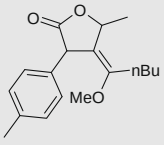
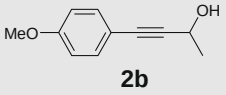
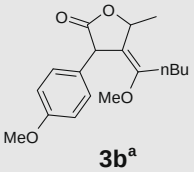
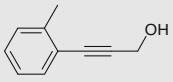
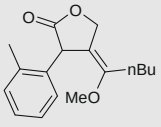
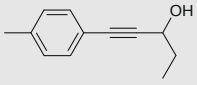
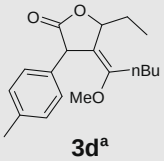
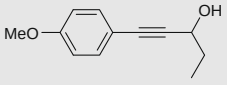
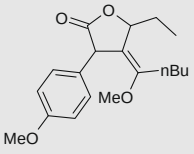
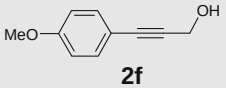
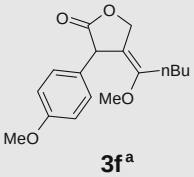
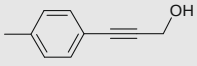
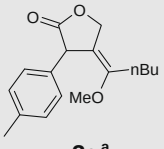
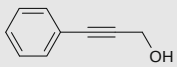
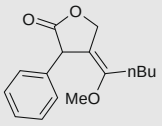
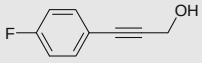
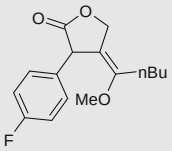
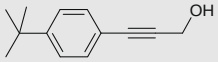
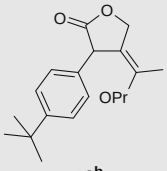
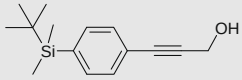
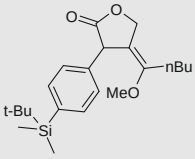
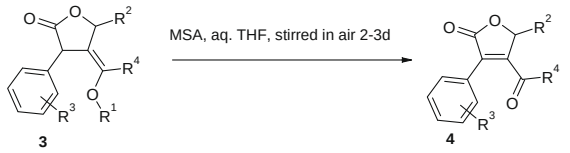
Entry	Alkynol	γ-Methylenebutyrolactone	Yields (%) (solvents)[c]	Yield (%) (solvent free)
1	 **2a**	 **3a**[a]	17 (THF/toluene)	45
2	 **2b**	 **3b**[a]	20 (THF/toluene)	48
3[b]	 **2c**	 **3c**[a]	15 (THF/toluene)	62
4	 **2d**	 **3d**[a]	21 (THF/*o*-xylene)	63
5	 **2e**	 **3e**[a]	20 (THF, toluene and *o*-xylene)	68
6	 **2f**	 **3f**[a]	25 (THF)	45
7	 **2g**	 **3g**[a]	21 (THF/toluene)	49

Table 1 (*continued*)

Entry	Alkynol	γ-Methylenebutyrolactone	Yields (%) (solvents)[c]	Yield (%) (solvent free)
8	 **2h**	 **3h**[a]	22 (THF/toluene)	59
9	 **2i**	 **3i**[a]	23 (THF, toluene and *o*-xylene)	51
10	 **2j**	 **3j**[b]	28 (THF/toluene)	49
11	 **2k**	 **3k**[a]	56 (THF)	72

[a] **1a** Fischer chromium carbenes were used.
[b] **1b** Fischer chromium carbenes were used.
[c] Temperatures for reaction in solvents are as follows: 60 °C (THF), 80 °C (toluene) and 135 °C (*o*-xylene).

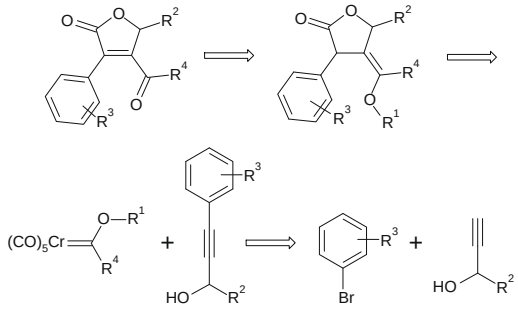
Table 2
Conversion of butyrolactones to butenolides



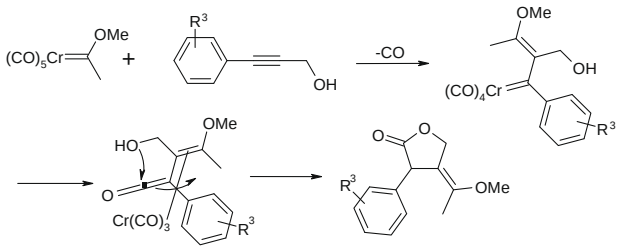
3 **4**

Substrate	Product	Yield (%)
3a	4a	84
3b	4b	83
3c	4c	80
3d	4d	83
3e	4e	84
3f	4f	82
3g	4g	82
3h	4h	81
3i	4i	85
3j	4j	82
3k	4k	0

the synthesis of their optically active analogues. These preliminary results establish a foundation to expand this methodology and demonstrate its utility in the synthesis of biologically significant molecules and provide for diversity in the preparation of compounds for structure–activity relationship (SAR) studies.



Scheme 1. Synthetic strategy.



Scheme 2. Mechanism for the conversion of alkoxy Fischer chromium carbenes to butyrolactones.

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Supplementary data

Supplementary data (synthesis of α-methylenebutyrolactones **3a**–**k** and α,β-unsaturated-γ-butyrolactones **4a**–**j**) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.06.076.

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