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Synthesis of substituted α-methylene-γ-butyrolactones from chloroformates *via* palladium catalysed cyclisation–anion capture

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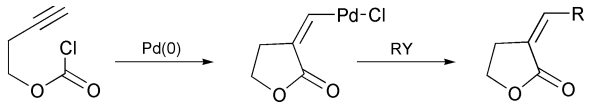
Cyclisation of chloroformates onto proximate alkyne functionality in the presence of a Pd(0) catalyst followed by anion capture affords α-methylene-γ-butyrolactone derivatives in moderate to good yields.

α-Methylene-γ-butyrolactones constitute an important group of natural products possessing a range of biological activities.[1] Their biological profiles are based on the specific reactivity of the α,β-unsaturated functionality acting, in most cases, as a Michael acceptor in reactions with biological nucleophiles.[2] The importance of this class of compounds has led to a number of synthetic procedures for the preparation of α-methylene-γ-butyrolactone derivatives.[2,3] Our approach is based on our palladium catalysed cascade cyclisation–anion capture methodology, (Scheme 1).[4] In the current context cyclisation of appropriate chloroformates onto the alkyne functionality in the presence of a Pd-catalyst would produce a vinylpalladium moiety suitable for further functionalisation by an anion-capture reagent.



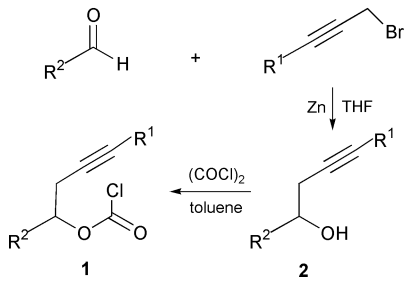
Scheme 1

Compared to the existing Pd-based methodology[5] for the preparation of α-methylene-γ-butyrolactones this approach allows direct access to β-substituted derivatives of this important class of compounds. In a recent communication we report similar methodology for the preparation of oxindole derivatives.[6]

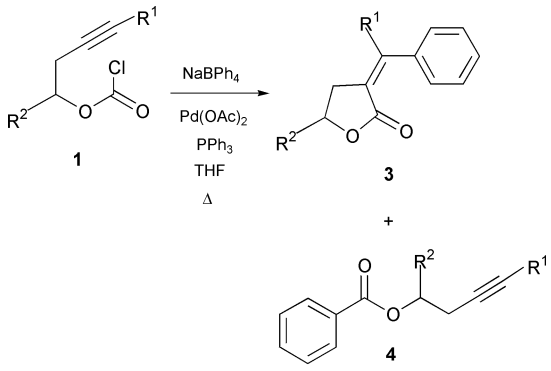
The required chloroformates **(1)** were readily prepared from homopropargylic alcohols **2** by stirring the alcohol with excess of $COCl_2$ in toluene at rt for 16 h, (Scheme 2). These alcohols, if not commercially available, were easily prepared using a standard propargylation procedure of aldehydes in the presence of activated zinc (Scheme 2).

The cyclisation reactions (Scheme 3, Table 1) of chloroformates in the presence of an equimolar amount of $NaBPh_4$ as the anion capture reagent were performed in THF at 65–70 °C (oil bath temperature) in the presence of $Pd(OAc)_2$ (10 mol%)–PPh_3 (20 mol%). In cases of terminally unsubstituted alkyne functionality the expected γ-butyrolactones were isolated in moderate to good yields (Table 1, entries a–e) as the only product. The stereochemistry of all the γ-butyrolactones described in this communication was established from NOE data. The presence of a terminal substituent on the alkyne moiety of the chloroformates (Table 1, entries f and g) resulted in formation of the expected product together with the direct capture product **4**. It is likely that sterically induced slower cyclisation due to the presence of a terminal substituent caused the formation of the direct capture products **4**.

The (*Z*-)-lactone isomer formed in the above reactions can be easily isomerised *via* Michael addition–retro Michael to produce the (*E*)-isomer in almost quantitative yield by heating in the presence of excess of a secondary amine (Scheme 4). The opening of the lactone ring was not observed in this reaction.



Scheme 2

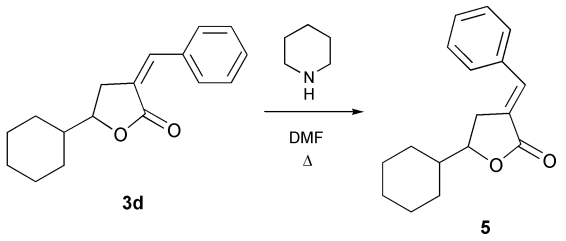


Scheme 3

Table 1

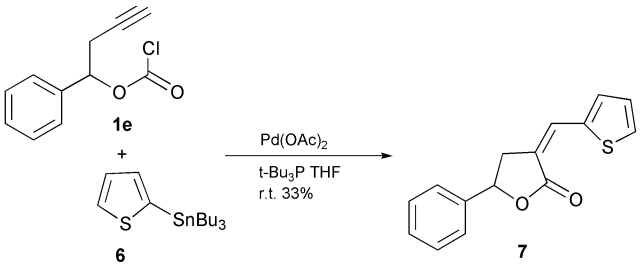
Entry	Chloroformate (**1**)	Lactone (**3**)	Benzoate (**4**)	Yield (%)[a]
a	R^1 + H, R^2 = H	R^1 = H, R^2 = H	—	51
b	R^1 = H, R^2 = CH_3	R^1 = H, R^2 = CH_3	—	51
c	R^1 = H, R^2 = CH_3CH_2	R^1 = H, R^2 = CH_3CH_2	—	55
d	R^1 = H, R^2 = C_6H_{13}	R^1 = H, R^2 = C_6H_{13}	—	73
e	R^1 = H, R^2 = Ph	R^1 = H, R^1 = Ph	—	49
f	R^1 = CH_3, R^2 = H	R^1 = CH_3, R^2 = H	R^1 = CH_3, R^2 = H	64[b]
g	R^1 = CH_3CH_2, R^1 = H	R^1 = CH_3CH_2, R^2 = H	R^1 = CH_3CH_2, R^2 = H	65[c]

[a] Isolated yields. [b] Combined yield, ratio 1:1. [c] Combined yield, ratio 1.3:1.



3d 5

Scheme 4



1e + **6** → **7**

Scheme 5

We briefly investigated the application of organostannanes as anion-capture reagents, (Scheme 5). Stirring the chloroformate **1e** and **6** in the presence of $Pd(OAc)_2$ and *t*-Bu_3P at rt afforded the lactone **7** in 33% yield. This reaction remains to be optimised but indicates possible further applications of organostannanes in these processes.

In summary, we have developed a simple procedure for the preparation of (*Z*)-isomers of α-methylene-γ-butyrolactone derivatives from homopropargyl chloroformates. The reaction affords the lactones in good yield but the presence of a terminal substituent on the alkyne induces formation of the direct capture product as well. Isomerisation of the α,β-double bond is possible in the presence of a secondary amine providing access to the (*E*)-stereoisomer. Chloroformates and carbamoyl chlorides constitute new starter species for our wide ranging catalytic cascade cyclisation–anion capture methodology.[4] Further studies involving the application of other anion-capture reagents and the application of this methodology to the synthesis of some naturally occurring lactones are in progress.

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Notes and references

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