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.



Compared to the existing Pd-based methodology⁵ 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 NaBPh₄ 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%)– PPh₃ (20 mol%). In cases of terminally unsubstituted alkyne functionality the expected γ -butyrolactones were isolated in

Table 1

Chloroformate (1) Lactone (3) Benzoate (4) Yield (%)a Entry $\mathbf{R}^1 + \mathbf{H}, \, \mathbf{R}^2 = \mathbf{H}$ $\mathbf{R}^1 = \mathbf{H}, \mathbf{R}^2 = \mathbf{H}$ 51 а b $R^1 = H, R^2 = CH_3$ $\mathbf{R}^1 = \mathbf{H}, \, \mathbf{R}^2 = \mathbf{C}\mathbf{H}_3$ 51 $\mathbf{R}^1 = \mathbf{H}, \mathbf{R}^2 = \mathbf{C}\mathbf{H}_3\mathbf{C}\mathbf{H}_2$ $\mathbf{R}^1 = \mathbf{H}, \mathbf{R}^2 = \mathbf{C}\mathbf{H}_3\mathbf{C}\mathbf{H}_2$ 55 с $R^1 = H, R^2 = C_6 H_{13}$ d $R^1 = H, R^2 = C_6 H_{13}$ 73 $\mathbf{R}^1 = \mathbf{H}, \, \mathbf{R}^2 = \mathbf{P}\mathbf{h}$ $\mathbf{R}^1 = \mathbf{H}, \mathbf{R}^1 = \mathbf{P}\mathbf{h}$ 49 e $\mathbf{R}^1 = \mathbf{C}\mathbf{H}_3, \, \mathbf{R}^2 = \mathbf{H}$ f $R^1 = CH_3, R^2 = H$ $R^1 = CH_3, R^2 = H$ 64^{b} $R^1 = CH_3CH_2, R^1 = H$ $\mathbf{R}^1 = \mathbf{C}\mathbf{H}_3\mathbf{C}\mathbf{H}_2, \, \mathbf{R}^2 = \mathbf{H}$ $R^1 = CH_3CH_2, R^2 = H$ 654 ^a Isolated yields. ^b Combined yield, ratio 1:1. ^c Combined yield, ratio 1.3:1.

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

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

(COCI)₂ toluene

Scheme 2

Scheme 3

CI

NaBPh.

Pd(OAc)₂

PPh₃

THF

Δ

R

Zn | THF

ОН

R

2

4

opening of the lactone ring was not observed in this reaction.

The (Z-)-lactone isomer formed in the above reactions can be

the formation of the direct capture products 4.





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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