Niobium pentachloride-mediated novel homologation reactions using α-trialkylstannylmethyl-β-keto esters

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In the presence of niobium pentachloride ($NbCl_5$), an α-trialkylstannylmethyl-β-keto ester is homologated to the corresponding γ-keto ester in good yield; the reaction mechanism is discussed.

The treatment of stannyl carbonyl compounds with Lewis acids has been used in cyclisation,[1] cyclopropanation,[2] ring contraction[3] and a variety of other reactions.[4] The C–C bond cleavage of cyclopropanol in the presence of Lewis acid has also been discussed.[3]

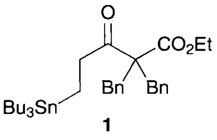
In the course of the study of stannyl compounds, we have investigated the treatment of a β-stannyl ketone **1** with a Lewis acid, which gave the cyclopropanol **2** or a corresponding ethyl ketone **3**.†

It became obvious that the ethyl ketone **3** was formed *via* the cyclopropanol intermediate. These results suggest that when a β-trialkylstannyl ketone with an electron-withdrawing substituent at the α-carbon atom, such as **4**, is treated with a suitable Lewis acid, it might be possible to control the regioselective C–C bond cleavage of the cyclopropanol ring.

Based on this consideration, we have discovered a novel homologation reaction in which α-trialkylstannylmethyl-β-keto esters were treated with $NbCl_5$ in dichloromethane to afford the corresponding γ-keto esters in good yields.

Initially, diethyl 2-trimethylstannylmethyl-3-oxopentane-1,5-diote **4** was treated with 1.2 equiv. of $NbCl_5$ in dichloromethane at −17 °C under nitrogen for 2 h (Scheme 1). The reaction mixture was then purified by silica gel column chromatography using an appropriate solvent to give diethyl 4-oxohexane-1,6-dioate **5** as a pale yellow oil in 76% yield. The diester **5** was hydrolysed and concentrated to afford a white solid which was recrystallised from acetone–light petroleum to give 3-oxohexane-1,6-dioic acid, mp 121–123 °C (lit.,[5] 121–123 °C).

When the amount of $NbCl_5$ was changed to 1.5 equiv., the yield of **5** increased to 82%. Compound **5** was also formed in 15% yield when **4** was treated with $TiCl_4$. However, none of the desired homologation product **5** was detected when $SnCl_4$, $ZrCl_4$ or $AlCl_3$ were used as the Lewis acid. In these cases the starting material **4** was mostly decomposed and only 8–13% of **4** was recovered. When triethyl aluminium was used as the Lewis acid, the homologation did not proceed and almost all of the starting material **4** was recovered.



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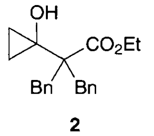

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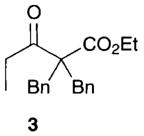

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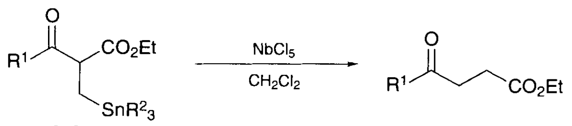


4, 6–9 **5, 10–13**

Scheme 1

Selection of the optimum reaction temperature was carried out using 1 mol of **4** and 1.2 equiv. of $NbCl_5$ in dichloromethane and the results are listed in Table 1.‡

Various 2-trialkylstannylmethyl-3-oxo esters **6–9** were examined and the homologation products **10–13** were obtained in good yields as listed in Table 2.§

Bis(tributylstannylmethyl) compound **14** was treated with $NbCl_5$ under the optimum conditions to give homologated product **15** in 61% yield. However, diethyl 2-(trimethylstannylmethyl)malonate **16** gave solely diethyl 2-(dimethylchlorostannylmethyl)malonate **17** in 51% yield.¶

The plausible reaction mechanism is shown in Scheme 2. In the presence of $NbCl_5$ in dichloromethane, compound **4** forms the corresponding cyclopropanol complex **18** which is immediately cleaved at a C–C bond of the cyclopropanol ring to give homologated γ-keto ester **5**.

Further applications of this homologation including bicyclic cyclopropane derivatives are now in progress.

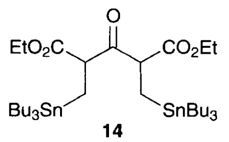
Table 1 Selection of optimum reaction temperature

Entry	T/°C	$NbCl_5$[a]/ equiv.	Yield (%)[b]
1	−73	1.2	54
2	−17	1.2	76
3	−17	1.5	82
4	0	1.2	74
5	35	1.2	55

[a] Amount of $NbCl_5$ for compound **4**. [b] Isolated yield.

Table 2 Synthesis of various homologated products

Compound	R^1	R^2	Yield (%)
5	CH_2CO_2Et	Bu	34
5	CH_2CO_2Et	Me	82
10	Me	Me	72
11	Ph	Me	51
12	CH_2CH_2Ph	Me	88
13	C_7H_{15}	Me	81



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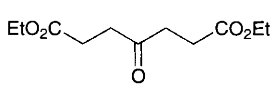

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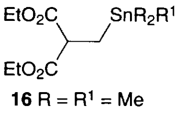
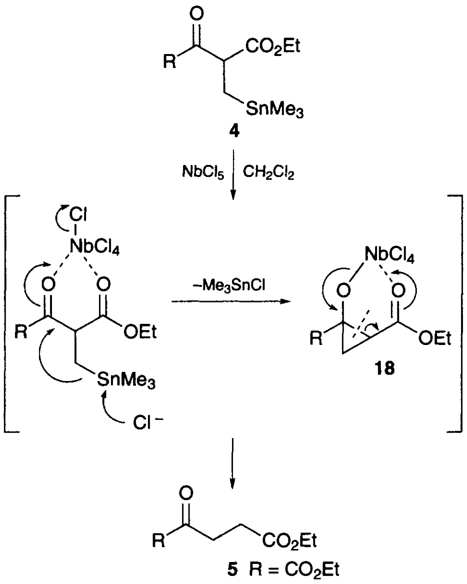


16 R = R¹ = Me
17 R = Me, R¹ = Cl



Scheme 2 Mechanism of the homologation

Footnotes

† Stannyl ketone **1** was treated with $TiCl_4$ in dichloromethane at room temperature for 2 h to give **2** in 79% yield. When $NbCl_5$ was used as the Lewis acid, **2** was also formed in 68% yield. However, ketone **1** gave **3** in 71% yield when $ZrCl_4$ was used as the Lewis acid. When the isolated **2** was treated with $ZrCl_4$, compound **3** was formed in 66% yield.

‡ Compound **4** was prepared as follows: in a two-necked round bottomed flask, ethyl acetoacetate and 1.1 equiv. of NaH in dry THF was stirred at room temperature for 1 h. To this mixture an equimolar amount of iodomethyltributyl tin in dry THF was added dropwise and the stirring was continued at 45 °C for 2 h. The reaction mixture was quenched with water, extracted with benzene, dried, concentrated and purified by silica gel column chromatography to give **4** in 85% yield. Compounds **6–9**, **14** and **16** were synthesised in a similar fashion.

§ All homologated compounds gave satisfactory spectral data. *Selected data* for compound **12**: ν(neat)/cm^{-1} 1737 and 1720; $\delta_H(CDCl_3)$ 1.26 (s, 3 H), 2.49–2.67 (m, 4 H), 2.77–3.03 (m, 4 H), 4.11 (q, 2 H) and 7.21 (s, 5 H); $\delta_c(CDCl_3)$ 13.96 (CH_3), 27.77 (CH_2), 29.47 (CH_2), 36.99 (CH_2), 44.00 (CH_2), 60.38 (CH_2), 125.9 (CH), 128.1 (CH × 2), 128.3 (CH × 2), 140.8 (C), 172.5 (CO) and 207.6 (CO); HRMS (FAB) Obs. 235.1334 (MH^+), calc. for $C_{14}H_{19}O_3$ 235.1329 (MH^+).

¶ This homologation reaction of **4** (R^1 = Me, R^2 = Bu) also proceeded when $Nb(OMe)_3Cl_2$ was used instead of $NbCl_5$. The yield of **5** was 17% accompanied with ethyl 2-methyl-3-oxobutanoate (45%). A mixture of $Nb(OMe)_5$[6] and $NbCl_5$ (3 : 2) was stirred at room temperature for 1 h and then **4** (R^1 = Me, R^2 = Bu) was added and stirred at 0 °C for 2 h.

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