A Simple and Efficient Synthesis of Chlorotetrolic Esters

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Treatment of propargyl chloride with methyl-lithium and an excess of alkyl chloroformate leads to chlorotetrolic esters in an average yield of 65%, in contrast with the previously reported three-step, low-yield synthesis of these biochemical reagents.

The synthesis[1] and properties[2–5] of chlorotetrolic esters, $ClCH_2–C{\equiv}C–CO_2R$, were described some years ago. Recently these compounds have gained a new importance since it was shown that they can be used as bifunctional reagents in protein[3,5] and nucleic acid[6] chemistry. However, the previously reported method for the preparation of these products (conversion of but-2-yne-1,4-diol into 4-chlorobut-2-yn-1-ol,[7] followed by chromic acid oxidation to the chlorotetrolic acid and esterification[1]) is rather long and has an overall yield of only *ca.* 10—15%. In view of the increasing importance of these compounds, a simpler and more efficient synthesis is desirable.

We have designed a rapid one-step method for the preparation of chlorotetrolic esters, starting from commercial propargyl chloride. One equivalent of methyl-lithium (1.55 M solution in diethyl ether) was added to a cold (−60 °C) diethyl ether solution of propargyl chloride. This mixture was treated with an excess of alkyl chloroformate at −50 °C, kept at −30 °C for 2 h, and worked up in the usual way.† The corresponding, analytically pure, chlorotetrolic esters were obtained in satisfactory yields (Table 1). The chlorotetrolic esters show the expected i.r. spectral data (film): 2267 (C≡C), 1725 (C=O), and 720 cm^{-1} (C–Cl). The use of butyl-lithium gave much lower yields (*ca.* 30%) and finely powdered sodium amide in diethyl ether suspension led to an insoluble solid material only, in agreement with previous observations.[8]

When propargyl bromide was treated with methyl-lithium and ethyl chloroformate, a 26% yield of ethyl bromotetrolate was obtained. Although this product had a remarkably constant boiling point (52 °C, 0.2 mmHg, n_D^{26} 1.4948) and

† Addition of water, extraction of the aqueous layer with diethyl ether, drying of the combined extracts over anhydrous magnesium sulphate, and distillation.

Table 1. Properties of the chlorotetrolic esters, $ClCH_2-C\equiv C-CO_2R$.

				Literature data (ref. 1)		
R	B.p./°C (mmHg)	n_D (t/°C)	Yield, %	B.p./°C (mmHg)	n_D (t/°C)	Yield, %
Me	82 (20)	1.4728 (22)	60	75.5 (11)	1.4700 (15)	10
Et	101 (14)	1.4675 (22.5)	60	86 (5)	1.4690 (17)	15
Bu[1]	62 (0.3)	1.4640 (22)	73		[a]	

[a] A satisfactory elemental analysis for this new product was obtained.

the correct i.r. spectrum (2267 and 1722 cm^{-1}, no allenic band), elemental analysis showed that it was somewhat impure, thus confirming the known difficulties in obtaining pure bromotetrolic esters.[9]

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