Synthesis of 3-Substituted Ethyl 4,4,4-Trichloro-2-cyano-butanoates via Michael Addition to Ethyl 4,4,4-Trichloro-2-cyano-2-butenoate

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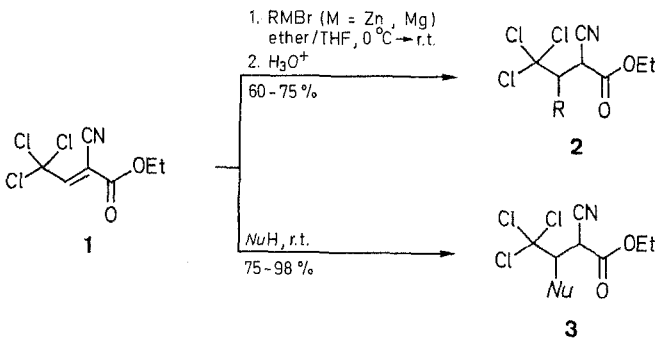
The title compounds **2** and **3** are easily synthesized in good to excellent yields and high stereoselectivity by addition of various nucleophiles, such as organometallic reagents, alcohols, thiols, phosphorus compounds and aniline, to ethyl 4,4,4-trichloro-2-cyano-2-butenoate.

In connection with our studies on the chemistry of diethyl 2,2,2-trichloroethylidenemalonate,[1] our attention has been attracted by the structurally similar ethyl 4,4,4-trichloro-2-cyano-2-butenoate (**1**). Except its preparation,[2,3] no reports have appeared in the literature concerning the synthetic applications of this compound. It is noteworthy that the yield of **1** prepared according to our method is higher. The ester **1** because of its higher electrophilicity, could be a good starting material for the preparation of 3-substituted butanoates. We report here a very simple and efficient synthesis of a series of new ethyl esters of 3-substituted 4,4,4-trichloro-2-cyano-butanoic acids by the addition of organometallic compounds and various nucleophilic reagents designated *Nu*H (alcohols, thiols, dimethyl phosphite, diphenylphosphine oxide, and aniline) to **1**.



1 **2** **3**

2	R	2	R
a	Ph[a]	**c**	$CH_2C(CH_3)=CH_2$
b	$CH_2CH=CH_2$	**d**	CH_2CO_2Et

[a] M = Mg

3	*Nu*	3	*Nu*
a	HO	**h**	EtS
b	CH_3O	**i**	*i*-PrS
c	EtO	**j**	PhS
d	*i*-PrO	**k**	$(MeO)_2P=O$
e	$PhCH_2O$	**l**	$(Ph)_2P=O$
f	$H_2C=CHCH_2O$	**m**	PhNH
g	$HC\equiv CCH_2O$		

The ester **1** reacts with allylzinc bromide and zinc/ethyl bromoacetate to give **2b–d** in good yields. In a similar manner phenylmagnesium bromide reacts to give ethyl 4,4,4-trichloro-2-

Table. Compounds **2** and **3** Prepared

Product	Reaction Time (h)	Yield[a] (%)	Ratio of *A* : *B*	bp (°C)/mbar mp (°C)[b] ($CHCl_3$/*n*-hexane)	Molecular Formula[c] or Lit. mp (°C)	Isomer	IR (KBr)[d] ν (cm^{-1})	^{1}H-NMR ($CDCl_3$/TMS)[e] δ, *J* (Hz)
2a	0.5	70	80 : 20	140–142/0.03	$C_{13}H_{12}Cl_3NO_2$ (320.6)	A	3350, 2300, 1750	1.16 (3H, t, J = 7.0); 4.16 (q, 2H, J = 7.0); 4.51 (d, H_α, J = 3.5); 4.66 (d, H_β, J = 3.5); 7.32–7.5 (m, 3H); 7.69 (m, 2H)
						B		1.05 (t, 3H, J = 7.1); 4.02 (q, 2H, J = 7.1)[h]
2b	0.5	70	100 : 0	105/0.05	$C_{10}H_{12}Cl_3NO_2$ (284.6)	A	2260, 1740, 1645	1.34 (t, 3H, J = 7.2); 2.76 (ddd, 2H, J = 15.0, 10.0, 3.0); 3.10 (br s, 1H, J = 15.0); 3.50 (m, H_β); 4.27 (q, 2H, J = 7.2); 4.40 (br s, H_α); 5.18 (d, 1H, J = 10.0); 5.42 (d, 1H, J = 16.0); 5.70 (m, 1H)
2c	0.5	75	100 : 0	115/0.07 59–60	$C_{11}H_{14}Cl_3NO_2$ (298.6)	A	2275, 1740, 1640	1.33 (t, 3H, J = 7.0); 1.76 (s, 3H); 2.84 (dd, 1H, J = 16.0, 12.0); 2.94 (br d, 1H, J = 16.0); 3.55 (m, H_β); 4.26 (m, 2H); 4.45 (br s, H_α); 4.90 (br s, 1H); 5.13 (br s, 1H)
2d	0.25	60	100 : 0	135/0.04	$C_{11}H_{14}Cl_3NO_4$ (330.6)	A	2280, 1740	1.29 (t, 3H, J = 7.2); 1.37 (t, 3H, J = 7.2); 3.02 (dd, 1H, J = 17.7, 9.2); 3.90 (dd, 1H, J = 17.7, 3.9); 3.90 (ddd, H_β, J = 1.5, 3.9, 9.2); 4.19, 4.20 (dq, 2H, J = 7.2); 4.35 (q, 2H, J = 7.2); 4.36 (d, H_α, J = 1.5)
				73–74	–	A	3350, 2270, 1740	1.39 (t, 3H, J = 7.1); 3.75 (br s, 1H); 4.31 (d, H_α, J = 1.8); 4.38 (q, 2H, J = 7.1); 4.87 (d, H_β, J = 1.8)
3a	15	98	90 : 10	–	45–47[3]	B		1.37 (t, 3H, J = 7.1); 4.1 (d, H_α, J = 6.5); 4.76 (d, H_β, J = 6.5)[h]
3b	3	98	> 95 : 5 (85 : 15)[f]	95–97	$C_8H_{10}Cl_3NO_3$ (274.5)	A	2250, 1740	1.39 (t, 3H, J = 7.2); 3.82 (s, 3H); 4.30 (d, H_α, J = 2.2); 4.37 (q, 2H, J = 7.2); 4.53 (d, H_β, J = 2.2)
						B		1.37 (t, 3H, J = 7.0); 3.77 (s, 3H); 4.0 (d, H_α, J = 7.1); 4.33 (d, H_β, J = 7.1)[h]
3c	3	98	90 : 10	99/0.07	$C_9H_{12}Cl_3NO_3$ (288.5)	A	2250, 1745	1.32 (t, 3H, J = 7.2); 1.39 (t, 3H, J = 7.0); 3.93, 4.05 (2q, 2H, J = 7.2); 4.28 (d, H_α, J = 2.5); 4.35 (q, 2H, J = 7.0); 4.60 (d, H_β, J = 2.5)
						B		1.22 (t, 3H, J = 7.0); 4.32 (d, H_α, J = 7.3); 4.49 (d, H_β, J = 7.3)[h]
3d	15	90	100 : 0	98–100/ 0.09	$C_{10}H_{14}Cl_3NO_3$ (302.6)	A	2275, 1750	1.27 (d, 3H, J = 6.6); 1.34 (d, 3H, J = 7.0); 1.40 (t, 3H, J = 7.0); 4.13 (m, 1H); 4.31 (d, H_α, J = 2.1); 4.38 (q, 2H, J = 7.0); 4.67 (d, H_β, J = 2.1)
3e	15	98	100 : 0	106/0.07 81–82	$C_{14}H_{14}Cl_3NO_3$ (350.6)	A	2310, 1750	1.30 (t, 3H, J = 7.2); 4.20 (q, 4H, J = 7.2); 4.30 (d, H_α, J = 1.9); 4.75 (d, H_β, J = 1.9); 4.91 (d, 1H, J = 11.4); 5.10 (d, 1H, J = 11.4); 7.35–7.4 (m, 5H)
3f	15	98	100 : 0	109/0.1	$C_{10}H_{12}Cl_3NO_3$ (300.5)	A	2280, 1750, 1650	1.38 (t, 3H, J = 7.1); 4.31 (d, H_α, J = 2.2); 4.35 (q, 2H, J = 7.1); 4.40 (dd, 1H, J = 12.3, 5.9); 4.54 (dd, 1H, J = 12.3, 5.6); 4.65 (d, H_β, J = 2.2); 5.28 (dd, 1H, J = 10.3, 1.5); 5.40 (dd, 1H, J = 17.2, 1.5); 5.95 (m, 1H)
3g	48	75	88 : 12	82–84[g]	$C_{10}H_{10}Cl_3NO_3$ (298.5)	A	3275, 2250, 2120, 1740	1.45 (t, 3H, J = 7.1); 2.61 (t, 1H, J = 2.2); 4.38 (d, H_α, J = 2.0); 4.42 (q, 2H, J = 7.2); 4.58 (d, 2H, J = 2.2); 4.86 (d, H_β, J = 2.0)
						B		1.43 (t, 3H, J = 7.0); 2.66 (t, 1H, J = 2.3); 4.12 (d, H_α, J = 7.0); 4.74 (d, H_β, J = 7.0)[h]
3h	48	98	100 : 0	120/0.07	$C_9H_{12}Cl_3NO_2S$ (304.6)	A	2300, 1740	1.39 (t, 3H, J = 7.2); 1.31 (t, 3H, J = 7.4); 2.97 (dq, 2H, J = 7.4); 4.21 (d, H_α, J = 1.9); 4.37 (dq, 2H, J = 7.2); 4.60 (d, H_β, J = 1.9)
	3	98	40 : 60			B		1.37 (t, 3H, J = 7.2); 1.34 (t, 3H, J = 7.4); 2.94 (q, 2H, J = 7.4); 4.09 (d, H_α, J = 6.7); 4.15 (d, H_β, J = 6.7)[h]
3i	15	98	100 : 0	49–50	$C_{10}H_{14}Cl_3NO_2S$ (318.6)	A	2300, 1735	1.35 (d, 3H, J = 6.5); 1.36 (d, 3H, J = 6.5); 1.39 (t, 3H, J = 7.0); 3.36 (m, 1H); 4.24 (d, H_α, J = 2.0); 4.35 (m, 2H); 4.59 (d, H_β, J = 2.0)
3j	15	98	100 : 0	69–70	$C_{13}H_{12}Cl_3NO_2S$ (352.6)	A	2300, 1740	1.32 (t, 3H, J = 7.2); 4.24 (m, 2H); 4.61 (d, H_α, J = 2.0); 4.67 (d, H_β, J = 2.0); 7.32 (m, 3H); 7.63 (m, 2H)
3k	3	98	> 95 : 5	80–81	$C_9H_{13}Cl_3NO_5P$ (352.5)	A	2280, 1740, 1300	1.40 (t, 3H, J = 7.0); 3.85 (dd, H_α, J = 2.0, J_{HP} = 11.0); 3.65, 3.90 (2d, 6H, J_{HP} = 11.5); 4.24 (dd, H_β, J = 2.0, J_{HP} = 22.0); 4.32–4.44 (m, 2H)

Table. (continued)

Product	Reaction Time (h)	Yield[a] (%)	Ratio of *A* : *B*	bp (°C)/mbar mp (°C)[b] ($CHCl_3$/ *n*-hexane)	Molecular Formula[c] or Lit. mp (°C)	Isomer	IR (KBr)[d] ν (cm^{-1})	^{1}H-NMR ($CDCl_3$/TMS)[e] δ, *J* (Hz)
3l	0.5	98	20 : 80	–	$C_{19}H_{17}Cl_3NO_3P$ (444.7)	A		1.31 (t, 3H, J = 7.1); 4.16 (q, 1H, J = 7.1); 4.31 (q, 1H, J = 7.1); 4.91 (dd, H_α, J = 1.5, J_{HP} = 9.0)[h]
				149–150		B	2300, 1740, 1290	1.29 (t, 3H, J = 7.2); 4.23 (q, 1H, J = 7.2); 4.26 (q, 1H, J = 7.2); 4.53 (dd, H_β, J = 1.8, J_{HP} = 21.0); 5.02 (dd, H_α, J = 1.8, J_{HP} = 13.0); 7.55 (m, 6H); 7.90–8.20 (m, 4H)
3m	5 min	98	0 : 100	97–98	$C_{13}H_{13}Cl_3N_2O_2$ (335.6)	B	3340, 2260, 1740	1.25 (t, 3H, J = 7.0); 4.26 (q, 2H, J = 7.0); 4.46 (d, H_α, J = 11.5); 4.56 (br s, 1H); 5.18 (d, H_β, J = 11.5); 6.81–6.92 (m, 3H); 7.22 (t, 2H)

[a] Yield of isolated product based on **1**. Remark concerning compounds **3c, d, f, h** is given in the experimental.
[b] The mp's uncorrected, measured in sealed capillary.
[c] Satisfactory microanalyses obtained: C ±0.30, H ±0.19, N ±0.16, Cl ±0.35, P ±0.19, S ±0.23.
[d] Recorded on a Perkin-Elmer R257 spectrophotometer.
[e] Recorded at 250 MHz on a Brucker WM spectrometer.
[f] See text.
[g] The mp of a 90 : 10 mixture of diastereoisomers, obtained by recrystallization.
[h] Values from the spectrum of the mixture of the two diastereoisomers.

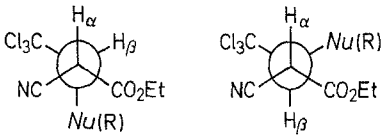
cyano-3-phenyl butanoate (**2a**). Under the same reaction conditions, ethylmagnesium bromide does not yield the corresponding substituted ethane.

The preparation of the derivatives **3a–l** does not require acidic or basic conditions and the addition proceeds at room temperature by simple mixing of **1** with an excess of the corresponding *Nu*H (with exception of dimethyl phosphite and diphenylphosphine oxide where an equimolecular mixture is used) in excellent yields (Table).

Our attempts to carry out this addition reaction with aliphatic or cyclic amines failed even at low temperature. On the contrary, at 0 °C, aniline adds quantitatively to **1** affording **3m**. No addition is observed with phenol.

Except compound **3a**,[3] all the products **2** and **3** have not been described in the literature. As seen from the Table, their structures are confirmed by their elemental analyses and spectral data. As these compounds have two asymmetric centres the formation of two diastereoisomers is possible. In most cases (**2b, 2c, 2d, 3d, 3e, 3f, 3i, 3j, 3k** and **3m**) only one isomer is present in the crude reaction product, in other (**2a, 3a, 3c** and **3l**), the formation of the two isomers is observed.

The cases of **3b** and **3h** will be discussed separately below. Only the major of these diastereoisomers is isolated in pure state. The isomer ratios are estimated from the ^{1}H-NMR spectra using the integration curves refering to the signals underlined in the Table. The ^{1}H-NMR data show, except for **3m** ($J_{H_\alpha H_\beta}$ = 11.5 Hz), a low vicinal methine proton coupling constant ($J_{H_\alpha H_\beta}$ = 1.5–3.5 Hz) for the preponderant (or the only obtained) diastereoisomer, while for the minor diastereoisomer this constant is higher ($J_{H_\alpha H_\beta}$ = 6.5–7.3 Hz). From a consideration of the three possible staggered conformations for each of the diastereoisomeric forms, the number of nonbonded group interactions, the relative bulk of these groups and the Karplus relationship, the configurations of the compounds **2** and **3** could be assigned as follow: *R*R** for **2a, 3a–g** and *R*S** for **2b–d, 3h–k** for the diastereoisomer with a low vicinal coupling constant characteristic for a conformation equilibrium with a marked predominance of the conformer with synclinal methine protons (type **I**) and *R*S** for **2a, 3a–c** and *R*R** for **3h, 3m** for the diastereoisomer with higher vicinal coupling constant in which the conformation with antiperiplanar protons is energetically favored (type **II**).



I **II**

As the configurations of the diastereoisomers of compounds **2** and **3** are assigned only on the basis of the ^{1}H-NMR data, we prefer to designate the respective isomers **A** (with lower $J_{H_\alpha H_\beta}$) and **B** (with higher $J_{H_\alpha H_\beta}$). A such assignement of configuration is not possible in the case of **3l**, because both the diastereoisomers have practically the same small vicinal coupling constants; the **A** and **B** designation is quite arbitrary. A theoretical study concerning the conformational equilibrium is in progress.

The following remarks can be made concerning the stereochemistry of the reaction leading to compounds **3b** and **3h**:

– When a three fold excess of ethanethiol is added to **1**, and after two minutes, at room temperature, the excess is removed *in vacuo*, a diastereoisomeric ratio **A/B** = 40 : 60 is observed; this ratio changes progressively to give in 48 hours only the thermodynamically more stable diastereoisomer **A**.

– In similar conditions, but with methanol (15 fold excess), after complete evaporation of methanol under reduced pressure, only the diastereoisomer with low coupling constant, **A**, is obtained (within limits of the ^{1}H-NMR precision). It is stable in crystalline state as well as in solution in solvents like chloroform, benzene and cyclohexane. The addition of traces of methanol, or another suitable catalyst able to provoke by deprotonation the isomerization (epimerization and reversibility), to a such solution is sufficient to achieve a 85 : 15 ratio always in favor of **A**. On the other hand, when the reaction is carried out in 0.4 M chloroform solution of equimolecular quantities of **1** and methanol a transformation of the ratio **A/B** from 70 : 30 to 85 : 15 is observed. Obviously **A/B** = 85 : 15 corresponds to the establishment in solution of the thermodynamic equilibrium between the two diastereoisomers. A slow crystallization of the product from this solution, by progressive removal of the solvent, affords pure **A**. It is known that where the diastereoisomers have a faster rate of isomerisation in the mother liquor than of crystallization, the equilibrium is shifted toward the less soluble diastereoisomer which can be obtained in pure state. Favorable conditions for

this so called "second-order" asymmetric transformation are realized in the case just described. It is usefull to underline that to obtain diastereoisomerically pure isomer **A** a complete removal of the methanol is necessary.

In conclusion, the merits of the present method for the synthesis of functionally substituted butanoic esters are simplicity of the procedure, mild reaction conditions, high yields, stereoselectivity, and ready availability of the starting materials.

Allylzinc reagents in THF[4] and Reformatsky reagent $BrZnCH_2CO_2Et$ in THF/Et_2O (1:4)[5] were prepared as reported in the literature. All *Nu*H employed are commercial products except Ph_2PO, which is prepared by hydrolysis of Ph_2PCl.[6]

Ethyl 4,4,4-Trichloro-2-cyano-2-butenoate (1):
To a stirred solution of ethyl cyanoacetate (11.3 g, 0.1 mol) and trichloroacetaldehyde (14.75 g, 0.1 mol) in dioxane (60 mL) under N_2 atmosphere and at ambient temperature is added diethylamine (0.8 g, 11 mmol) very slowly by keeping the reaction temperature below 50 °C and the stirring is continued over night at room temperature. The dioxane is removed *in vacuo* and the black residue is rapidly distilled (0.13 mbar) in the presence of $NaHSO_4$ (300 mg). Fractional distillation of this crude product gives **1**; yield: 14.5 g (60%); bp 80 °C/0.03 mbar.

Ethyl 4,4,4-Trichloro-2-cyano-3-phenylbutanoate (2a):
A solution of **1** (2.06 g, 8.5 mmol) in dry Et_2O (5 mL) is added during 5 min under N_2 to a stirred solution of C_6H_5MgBr (10 mmol) in dry Et_2O (10 mL) at − 50 °C. The cooling bath is then removed, the mixture is stirred for 25 min, then hydrolyzed with ice-cold H_2O (20 mL) containing conc. HCl (1 mL) and extracted with Et_2O (3 × 20 mL). The combined extracts are washed with H_2O (2 × 5 mL), dried ($MgSO_4$) and concentrated under reduced pressure to give **2a** which is purified by distillation (Table).

Ethyl 3-Substituted 4,4,4-Trichloro-2-cyanobutanoates 2b–d; General Procedure:
To a stirred solution of the organometallic reagent (10 mmol) in the respective solvent (8 mL) cooled to − 10 °C is added dropwise a solution of **1** (1.94 g, 8 mmol) in THF (5 mL) under a N_2 atmosphere. The cooling bath is then removed and the mixture is stirred at room temperature over a period of 15 or 30 min (Table). The crude products obtained are purified by vacuum distillation or recrystallization.

Ethyl 3-Substituted 4,4,4-Trichloro-2-cyanobutanoates 3; General Procedure:
The ester **1** (2.42 g, 10 mmol) is added to *Nu*H (12 mmol for **3a–j**, 10 mmol for **3k–m**) at ambient temperature (0 °C for **3m**). In the case of **3l**, Ph_2POH is dissolved in dry Et_2O (10 mL). The mixture is allowed to stand for a variable time (Table), then the excess of *Nu*H is removed *in vacuo*. Except for **3g**, yields are quantitative; the crude products being pure (as shown by ^1H-NMR spectra), the distillation of **3c, d, f, h** can be avoided, because it is accompanied by a slight decomposition leading to starting compounds due to the reversibility of the reaction.

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