Comment on the Use of Dichloromethyl Methyl Ether as Formylating Agent

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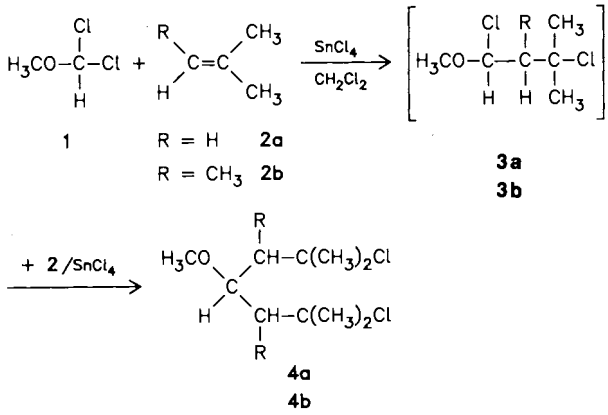
Received August 27, 1987

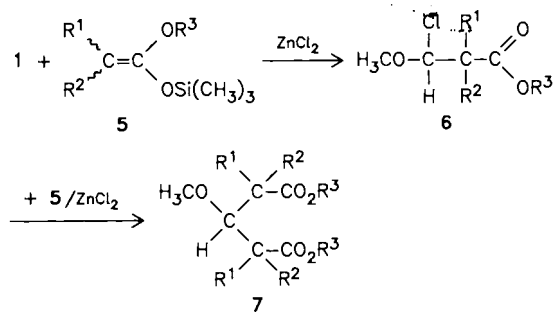
In contrast to normal alkenes, dialkylacetylenes can be formylated with dichloromethyl methyl ether (1) in the presence of 1.2 equivalents of boron trichloride. A rationalisation for the different behaviour of alkenes and alkynes arises from the NMR spectroscopic investigation of the reaction intermediates.

Dichloromethyl methyl ether (**1**) has been used for the formylation of aromatic compounds[1], but attempts to formylate isobutene **2a** and trimethylethylene **2b** gave only the 2:1 products **4**[2]. It has been concluded, therefore, that in electrophilic addition reactions to olefins the chloro ethers **3** are more reactive than **1**[2a].



1 R = H **2a**; R = CH_3 **2b** → **3a**, **3b** → **4a**, **4b**

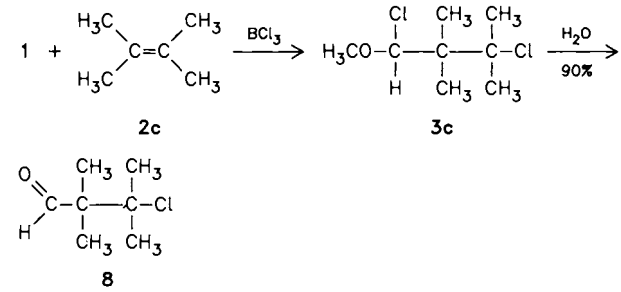
Analogously, the 1:1 products **6**, initially formed from **1** and ketene alkyltrimethylsilyl acetals **5**, have been reported to react far faster than the starting ether **1**[3]. Only when both R^1 and R^2 were alkyl groups, steric hindrance reduced the rate of formation of 2:1 products, and α-formylcarboxylic esters, hydrolysis products of **6**, were isolable in addition to **7**.



5 → 6 → 7

We have demonstrated recently that the relative electrophilicity of alkyl chlorides depends on the degree of ionisation. In predominantly unionised systems the more readily ionised compound is found to be more reactive, while the opposite is true when the competing alkylating agents are ionised to a large extent[4]. On this basis, we have now analysed formylations with the dichloromethyl methyl ether (**1**), though complications caused by anomeric stabilisation of **1** might be expected.

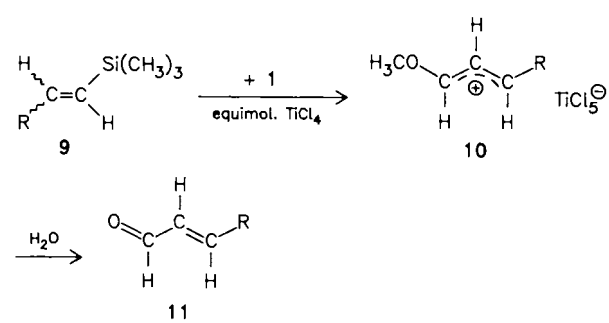
When compound **1** was treated with one or two equivalents of isobutene in the presence of 1.2 equivalents of BCl_3, only the 2:1 product **4a** was obtained, in accord with previous reports[2]. Under similar conditions, **1** and tetramethylethylene (**2c**) selectively gave the 1:1 product **8** after hydrolysis. Steric strain obviously inhibits the addition of **3c** to a second alkene molecule.



2c → **3c** → **8**

The termination of this addition at the stage of the 1:1 adduct **3c** allows to analyse the degree of ionisation of the reactants **1** and the 1:1 products **3**. The NMR spectrum of a solution of **1** and 1.2 equivalents of BCl_3 in CD_2Cl_2 showed that **1** is not ionised under these conditions. When compound **2c** was added to this solution, the ^{1}H-NMR spectrum showed singlets at δ = 3.49 (OCH_3) and at δ = 5.87 (CH) as expected for unionised **3c**. A fast exchange of Cl^- is indicated by the observation that the diastereotopic methyl group signals at δ = 0.94 and 1.01 and at δ = 1.46 and 1.52 (−100 °C) became equivalent when the sample was warmed up to −20 °C.

Since **3a**, **3b** can be expected to ionise to a similar degree as **3c**, the exclusive formation of 2:1 products – if strong steric effects are absent – can be explained on the basis of our general analysis: compounds **3** form better stabilised carbenium ions than **1** and are therefore more reactive in systems with a small degree of ionisation[4,5]. In principle, it should be possible to obtain 1:1 products by using stronger Lewis acids[4]. All attempts to formylate isobutene with **1** have failed until now, and 2:1 products in addition to polymers were obtained when an excess of $TiCl_4$, $SnCl_4$, or $AlCl_3$ was employed.



9 → 10 → 11

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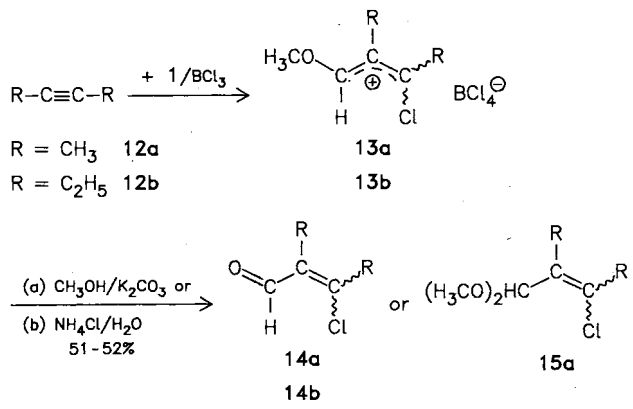
A different situation arises, when the 1:1 products give resonance-stabilised carbenium ions. It has been reported that vinylsilanes can be formylated by **1** in the presence of *equimolar* amounts of $TiCl_4$[6], while allylsilanes give only 2:1 products under these conditions[6c].

We interpret this finding by the low intrinsic reactivity of the cations **10** which are initially formed from **1** and vinylsilanes. Since similar types of 1:1 products may be formed by the addition of **1** to CC triple bonds, we investigated the formylation of alkynes under similar reaction conditions.

When the dialkylacetylenes **12a,b** were added to solutions of **1** and 1.2 equivalents of boron trichloride, the reactions terminate at the 1:1 product stage. Workup of the product obtained from 2-butyne (**12a**) with methanol/potassium hydrogencarbonate gave a mixture of **14a** and **15a** which was converted into pure **15a** by treatment with methyl orthoformate. Hydrolysis of the formylation product of 3-hexyne (**12b**) was carried out with aqueous ammonium chloride solution to yield the stereoisomeric aldehydes (*E,Z*)-**14b**.



The ionic character of the intermediates **13** was proven by ^{1}H-NMR spectroscopy. The spectrum taken after addition of 2-butyne to a mixture of **1** and BCl_3 in CD_2Cl_2 showed methyl resonances at δ = 2.04, 2.80, and 4.97 and a broad one-proton singlet at δ = 9.67, as expected for 1-alkoxyallyl cations[7]. Additional signals at δ = 1.34, 2.24, and 2.30 (1:1:2) are close to those reported for the tetramethylcyclobutadiene aluminium chloride complex (1.32, 2.29, 2.40)[8] and indicate that the BCl_3-initiated dimerisation of **12a** takes place as a side reaction. Lewis-acid-initiated oligomerisations of alkynes become dominant with terminal and aryl-substituted acetylenes, and attempts to formylate these types of compounds have not been successful.

Conclusion. Electrophilic formylations with dichloromethyl methyl ether (**1**) have previously been achieved with aromatic compounds and vinylsilanes and now with dialkylacetylenes. Since all these reactions require the use of at least 1 equivalent of strong Lewis acids and lead to the formation of intermediate delocalised carbenium ions of low intrinsic reactivity, it appears that these two conditions are needed for the use of **1** as formylating agent, in accordance with theoretical considerations[4]. Until now, appropriate conditions for the formylation of ordinary alkenes (very strong Lewis acids would be needed) have not yet been found, and **1** could only be used for the electrophilic formylation of alkenes, when the electrophilic centre of the formylation product was sterically shielded.

We thank Ms. *Roswitha Lammers* for experimental assistance and the *Deutsche Forschungsgemeinschaft* for financial support.

Experimental

General: NMR: XL 200 (Varian), chemical shifts are recorded with respect to internal TMS. – Mass spectra: 70–250 (VG-Instruments). – IR: IR-435 (Shimadzu).

3-Chloro-2,2,3-trimethylbutanal (**8**): A 1 M solution of BCl_3 in CH_2Cl_2 (36 ml) was added to a solution of **1** (3.45 g, 30.0 mmol) in 30 ml of CH_2Cl_2 at −78°C. A solution of 2,3-dimethyl-2-butene (**2c**) (5.40 g, 64.2 mmol) in 60 ml of CH_2Cl_2 was added dropwise within 30 min and allowed to react for 3 h at −78°C. The mixture was washed with 100 ml of 25% aqueous NH_4Cl solution, the aqueous layer extracted with two 20-ml portions of ether, and the combined organic layers were dried with $CaCl_2$. Evaporation of the solvents gave 4.01 g (90%) of spectroscopically pure **8**. – IR (neat): 2974 cm^{-1}, 1720, 1458, 1375, 1155, 1104, 829. – ^{1}H NMR ($CDCl_3$): δ = 1.21 (s, 6H, 2-CH_3), 1.63 (s, 6H, 3-CH_3), 9.83 (s, 1H, 1-H). – ^{13}C NMR ($CDCl_3$): δ = 18.95 (q, 2-CH_3), 28.90 (q, 3-CH_3), 52.87 (s, C-2), 73.68 (s, C-3), 204.41 (s, C-1). – 2,4-Dinitrophenylhydrazone of **8**: M.p. 141–143°C (methanol). – MS (70 eV): *m/z* (%) = 330 (3), 328 (10) [M^+], 252 (39), 251 (100).

$C_{13}H_{17}ClN_4O_4$ (328.8) Calcd. C 47.50 H 5.21
Found C 47.62 H 5.14

Dichloromethyl Methyl Ether (**1**) *and 2-Butyne* (**12a**): A 1 M solution of BCl_3 in CH_2Cl_2 (36 ml) was added to a solution of **1** (3.45 g, 30.0 mmol) in 30 ml of CH_2Cl_2 at −78°C. Compound **12a** (1.62 g, 30.0 mmol), dissolved in 60 ml of CH_2Cl_2, was added with stirring within 1 h to give a slightly yellow solution which became turbid 30 min after completion of the addition. After 2 h, 25.0 g of K_2CO_3 and 10 ml of anhydrous methanol were added, and stirring at −78°C was continued for another 15 min. The mixture was warmed at ambient temperature and washed with 30 ml of concentrated aqueous ammonia. The aqueous layer was extracted with two 20-ml portions of ether, the combined organic layers were dried with Na_2SO_4, and the solvent was evaporated to give a mixture of (*E,Z*)-**14a** and (*E,Z*)-**15a**. Complete acetalisation of **14a** was achieved by stirring this mixture with methanol (0.96 g, 30.0 mmol), methyl orthoformate (3.18 g, 30.0 mmol), and NH_4NO_3 (0.2 g) for 14 h. After alkalisation with diisopropylamine, 30 ml of ether was added. The mixture was filtered and distilled (64–66°C/25 mbar) to give 2.58 g (52%) of **15a** (2:1 mixture of stereoisomers).

(E,Z)-3-Chloro-1,1-dimethoxy-2-methyl-2-butene (**15a**): ^{1}H NMR ($CDCl_3$), major isomer: δ = 1.71 (m_c, 3H, 2-CH_3), 2.14 (m_c, 3H, 4-H), 3.39 (s, 6H, OCH_3), 5.27 (s, 1H, 1-H); minor isomer: δ = 1.80 (m_c, 3H, 2-CH_3), 2.21 (m_c, 3H, 4-H), 3.34 (s, 6H, OCH_3), 4.93 (s, 1H, 1-H). – ^{13}C NMR ($CDCl_3$), major isomer: δ = 12.19 (q, 2-CH_3), 22.23 (q, C-4, possibly other isomer), 54.90 (q, OCH_3), 103.91 (d, C-1), 128.76 (s, C-2), 130.96 (s, C-3); minor isomer: δ = 14.01 (q, 2-CH_3), 22.78 (q, C-4, possibly other isomer), 54.17 (q, OCH_3), 102.8 (d, C-1), 128.1 (s, C-2), 129.7 (s, C-3). – MS (70 eV): *m/z* (%) = 166 (0.23), 164 (0.73) [M^+], 135 (18), 133 (57), 129 (18), 97 (10), 75 (58), 31 (100).

$C_7H_{13}ClO_2$ (164.6) Calcd. C 51.07 H 7.96
Found C 51.67 H 7.81

Dichloromethyl Methyl Ether (**1**) *and 3-Hexyne* (**12b**): A 1 M solution of BCl_3 in CH_2Cl_2 (36 ml) was added to a precooled solution (−78°C) of **1** (3.45 g, 30.0 mmol) in 30 ml of CH_2Cl_2. A solution of **12b** (2.46 g, 30.0 mmol) in 60 ml of CH_2Cl_2 was added within 30 min and stirred for 2 h at −78°C. The mixture was poured onto 200 ml of aqueous NH_4Cl solution (25%), the aqueous layer was washed with two 30-ml portions of CH_2Cl_2, and the combined organic layers were dried with $CaCl_2$. Distillation at 65–80°C (bath)/32 mbar gave 2.24 g (51%) of *(E,Z)-3-chloro-2-ethyl-2-pen-*

tenal (**14b**) (≈2:1 mixture of stereoisomers) contaminated with small amounts (≈10%) of an unknown impurity. – Mixture of (*E,Z*)-**14b**: IR (neat): 1676 cm^{-1}, 1609. – ^1H NMR ($CDCl_3$): δ = 0.98 (t, *J* = 7.5 Hz, CH_3), 1.26 and 1.29 (2 t, *J* = 7.4 Hz, CH_3), 2.34, 2.44, 2.64, 2.93 (4 q, *J* = 7.5 Hz, CH_2), 10.01, 10.21 (2 s, ratio 2:1, CH=O). – ^{13}C NMR ($CDCl_3$): δ = 11.93, 11.98, 13.47 (3 q, CH_3), 19.47, 20.48 (2 t), 28.24, 30.59 (2 t), 139.40 (s, C-2), 154.82, 159.20 (2 s, C-3, assignment uncertain), 186.94, 191.21 (2 d, CHO). – MS (70 eV): *m/z* (%) = 148 (32), 146 (100) [M^+], 133 (3), 131 (8), 119 (9), 117 (24), 111 (37), 95 (36), 93 (17), 89 (20), 81 (36), 67 (76).

When the crude reaction product obtained from 30 mmol of **1** and **12b** was not distilled but treated with 2,4-dinitrophenylhydrazine[9], a mixture of stereoisomeric 2,4-dinitrophenylhydrazones (5.00 g, 51%) was obtained, which was separated by MPLC (30 × 2.5 cm LiChroprep Si 60, 15–25 μ, hexane:CH_2Cl_2 = 5:1, 12.5 ml/min) to give 2.47 g of an isomer I with R_t = 8.7 min and 0.89 g of an isomer II with R_t = 9.7 min. – 2,4-Dinitrophenylhydrazone of **14b** (isomer I): M.p. 147–148°C (hexane/CH_2Cl_2). – ^1H NMR ($CDCl_3$): δ = 1.14 (t, *J* = 7.5 Hz, 3H, CH_3), 1.24 (t, *J* = 7.4 Hz, 3H, CH_3), 2.60 (q, *J* = 7.5 Hz, 2H, CH_2), 2.63 (q, *J* = 7.4 Hz, 2H, CH_2), 11.26 (br. s, 1H, NH), aryl H as usual. – ^{13}C NMR ($CDCl_3$): δ = 12.63 (q), 13.90 (q), 21.51 (t), 29.91 (t), 116.6 (d), 123.5 (d), 129.4 (s), 130.0 (d), 132.3 (s), 138.2 (s), 144.3 (s), 144.8 (s), 147.2 (d).

$C_{13}H_{15}ClN_4O_4$ (326.7) Calcd. C 47.79 H 4.63
Found C 47.91 H 4.68

2,4-Dinitrophenylhydrazone of **14b** (isomer II): M.p. 154–156°C (hexane/CH_2Cl_2). – ^1H NMR ($CDCl_3$): δ = 1.13 (t, *J* = 7.5 Hz, 3H, CH_3), 1.26 (t, *J* = 7.5 Hz, 3H, CH_3), 2.70 (q, *J* = 7.5 Hz, 4H, 2 CH_2), 11.24 (br. s, 1H, NH), aryl H as usual. – ^{13}C NMR ($CDCl_3$): 12.41 (q), 13.47 (q), 22.65 (t), 29.03 (t), 116.7 (d), 123.5 (d), 129.3 (s), 130.1 (d), 133.8 (s), 138.2 (s), 144.5 (d), 144.8 (s), 146.1 (s).

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