The Michael Reaction. Mechanism, Stereochemistry and a Synthetically Useful Modification

INGOLF CROSSLAND and SVEN IVAR HOMMELTOFT

Department of Organic Chemistry, The Technical University of Denmark, DK-2800 Lyngby, Denmark

Dimethyl malonate anions react with α,β-unsaturated aldehydes giving products with *trans* stereochemistry, Scheme 1. The enolate anions may be trapped with trimethylchlorosilane to give the enol ethers *4* with better than 95 % stereoselectivity. Triethylamine, trimethylchlorosilane and acrolein react similarly to give the enol ether *7* with the opposite, *i.e.* *cis*, stereochemistry. Dipole minimization in the transition states (Schemes 2 and 3) seems an obvious rationalization of the observed stereochemistry. The triethylamine catalyzed addition of dimethyl nitromalonate to atropaldehyde produces a stereoisomeric mixture of the enols *Z-5* and *E-5* as the initial product.

The mechanism of the Michael reaction is generally assumed to involve the formation of stereochemically non-specified enolate anions, subsequently protonated and tautomerizing to give the final adducts.[1-4] We present evidence substantiating this general scheme, but extended to provide information about the stereochemical course of the addition. Thus, the addition of a malonic ester anion to α,β-unsaturated aldehydes proceeds in a *trans* fashion with a stereoselectivity exceeding 95 %. "*trans*" here refers to the position of the methylene carbon atom relative to the enolic oxygen atom in the adducts *3* (Schemes 1 and 2).

The proposed configuration of the primary enolates *3* rests on trapping the enolate anions with trimethylchlorosilane (Scheme 1) and comparing the coupling constants of the resulting enol ethers *4* with literature values [5,6] (see Experimental). The reactions *1→3→4* (Scheme 1) are kinetically controlled. We conclude from these experiments that the stereochemistry of the C—C bonding step of the Michael reaction is nearly 100 % stereoselective and determined by stereoelectronic requirements of the transition state, rather than by steric effects. This is illustrated in Scheme 2, where the transition state is formulated such as to minimize the dipole moment. The stereoselectivities of the reactions *1a* and *1b* to *4a* and *4b*, respectively, are higher than those of the corresponding reactions of *1c* (*ca.* 95 %) and *1d*. This may be attributed to the better localized charge on anions of the unsubstituted (*1a*) or monoalkylated (*1b*) malonic esters, as compared to the anions of the more acidic esters *1c* and *1d*.
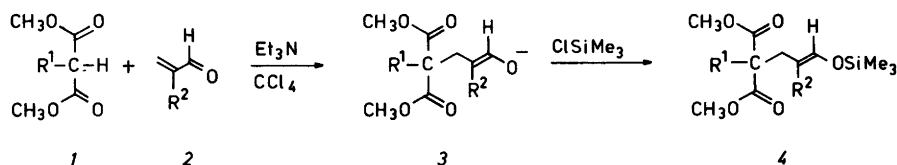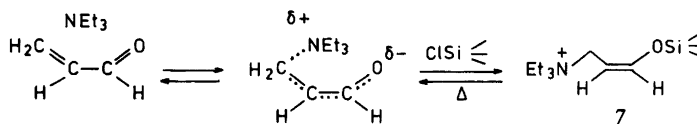

Scheme 1. Stereoselective formation of enolates and of silyl enol ethers.
a: $R^1 = R^2 = H$
b: $R^1 = E - CH_2CH = CH - OSi(CH_3)_3$, $R^2 = H$
c: $R^1 = NO_2$, $R^2 = C_6H_5$
d: $R^1 = CN$, $R^2 = C_6H_5$
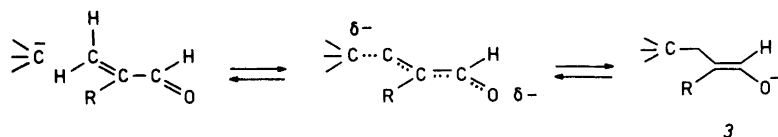
Scheme 2. Illustrates transoid transition state.

Scheme 3. Illustrates cisoid transition state.

The trimethyl silyl enol ether *Z-4d*, Scheme 1, is the thermodynamically least stable isomer. Upon heating for four hours at 150 °C it stereomutates to give a *ca.* 40:60 ratio of the *Z-4d* and *E-4d* isomers. Higher temperatures employed in a GLC analysis of the mixture resulted in still more advanced isomerization (see Experimental).

Addition of triethylamine to a mixture of acrolein and trimethylchlorosilane in petroleum ether gave the enol ether *7* with a stereochemistry opposite to that of the enol ethers formed by addition of the anionic nucleophiles. This observation supports the suggested mechanism, as illustrated in Scheme 3, where dipole minimization again predicts the observed stereochemistry. The polarity of the solvent is decisive: in light petroleum, the content of the *E*-isomer in the crude product was 3 %, in carbon tetrachloride 20 % and in deuteriochloroform about 50 %. The salt *7* hydrolyzes rapidly to acrolein and reacts with C-nucleophiles, such as the anions of *1a* and *1b*, to products of type *4*, demonstrating the reversibility of the reaction in Scheme 3.

Further details regarding the mechanism of the Michael reaction were obtained by following (^{1}H NMR) the triethylamine catalyzed reaction of dimethyl nitromalonate *1c* with atropaldehyde in carbon tetrachloride and benzene, see Fig. 1. The Michael adduct *6* was *not* the first to appear. A considerable (*ca.* 30 %) amount of enol *Z-5* was
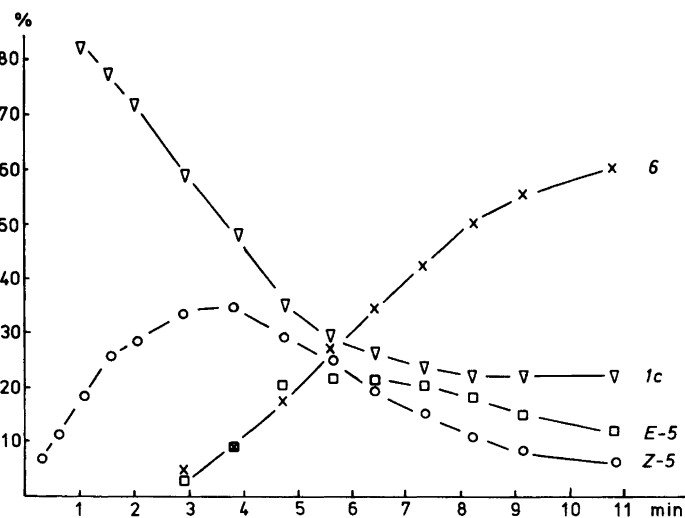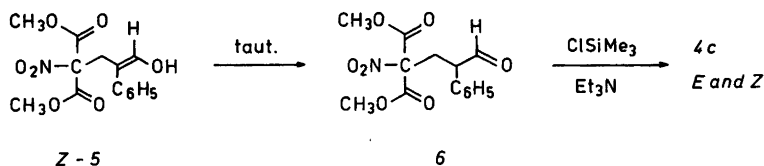

Fig. 1. Time course for the reaction of dimethyl nitromalonate ($\triangledown$) with atropaldehyde to enols *Z-5* ($\bigcirc$) and *E-5* ($\square$), and finally to Michael adduct *6* ($\times$). Percentages total 100%.

Scheme 4. Tautomerization of *Z-5* (*3c* protonated) to Michael adduct *6*, see Fig. 1.

formed before the concentrations of the isomeric enol *E-5* and the tautomer *6* could be observed. The delayed formation of the two latter products suggests that *Z-5* is the common precursor. Enol *E-5* could be detected for a longer time (*ca.* 5 min) than enol *Z-5*, suggesting that the tautomerization of the latter is fastest. Identification of the postulated enols *Z-5* and *E-5* relies on the observed resonances . of the ester groups and the simultaneous appearances and disappearances of resonances at δ-values matching those of the corresponding silyl ethers *Z-4c* and *E-4c*, respectively, see Experimental.

The modification of the Michael reaction described here has synthetic advantages as compared to the original and commonly employed version. It is experimentally simple and affords a protected aldehyde function, permitting further functionalization under basic conditions as illustrated in Scheme 1 (reaction *1b→4b*). Trimethylsilyl enol ethers are useful and versatile starting materials.[7-10] The scope of the reaction has not been studied in detail. Steric hindrance and/or low acidity may render the reaction synthetically useless: compare, for instance, the reaction conditions for *1a→4a* with those for *4a* (= *1b*)→*4b*.

A recent communication describes a Michael reaction sterically controlled by repulsion of negative charges on oxygen.[11]

$$(CH_3OOC)_2CH-CH\genfrac{}{}{0pt}{}{-OSi\leqq}{-CH=CH_2}$$
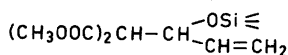
8

EXPERIMENTAL

Mass spectra were recorded on a VG Micromass 7070 F instrument, IP 70 eV. NMR spectra were obtained on Bruker WH-90, HXL-90, and HX-270 instruments. Solvent: CDCl$_3$. Acrolein (Ferak, "rein", stabilized) was kept at 0 °C. Trimethylchlorosilane (Fluka *purum*) contained *ca.*

10% hexamethylsiloxane (NMR). Triethylamine was kept over potassium hydroxide.

General procedure. To a mixture of the malonic ester derivative (100 mmol), acrolein (7.2 ml), and trimethylchlorosilane (24 ml) in carbon tetrachloride (100 ml), triethylamine (30 ml) was added at room temperature. The mixture was protected from moisture and refluxed (see below), cooled to −20 °C, and stirred with ice for 5 min. The water phase was washed twice with carbon tetrachloride, the combined organic phases dried (Na$_2$SO$_4$), concentrated *in vacuo* and distilled.

Methyl 2-carbomethoxy-5-trimeth-ylsilyloxy-4E-pentenoate, E-4a. Reaction time: 3 h at 77 °C (reflux). Slow distillation (20 cm by 2 cm Vigreux column) gave a forerun (see below) b.p. 38−84 °C/0.15 mmHg, and *4a*. Yield 11.1 g (43%), b.p. 84 °C −103 °C/0.15−0.3 mmHg. Redistillation gave b.p. 90 °C/0.25 mmHg. Anal. C$_{11}$H$_{20}$O$_5$Si: C, H. ^{1}H NMR: δ 0.17 (9H, s), 2.47 (2H, dt, *J* 1.1 and 7.5 Hz), 3.36 (1H, t, *J* 7.5 Hz), 3.71 (6H, s), 4.89 (1H, dt, *J* 12 and 7.5 Hz), 6.24 (dt, *J* 12 and 1.1 Hz). ^{13}C NMR [22.63 MHz]: δ −0.8 (q, CH$_3$Si), 27.0 (t, C3), 52.0 (q, CH$_3$O), 52.4 (d, C2), 106.5 (d, C4), 142.0 (d, C5), 168.9 (C=O).

Isomerization of 4a. E-4a (325 mg) in ether (0.8 ml) was irradiated for 22 h with UV light (quartz apparatus, Hanovia lamp 679A-36) at 25 °C. ^{1}H NMR showed a *ca.* 60% content of *Z-4a*: δ 0.18 (s), 2.67 (dt, *J* 1.5 and 7.5 Hz), 3.42 (t, *J* 7 Hz), 3.71 (s), 4.44 (dt, *J* 5.8 and 7.1 Hz), 6.17 (dt, *J* 5.8 and 1.5 Hz). None of this isomer was detected in *E-4a* prepared above.

The forerun (above) contained (NMR) dimethyl malonate (*ca.* 21 mmol), the enol silyl ether *4a* (*ca.* 13 mmol), and the silylated 1,2-adduct *8* (*ca.* 12 mmol). Fractionation of several foreruns gave *8*, b.p. 65−67 °C/0.2 mmHg. Anal. C$_{11}$H$_{20}$O$_5$Si: C, H. ^{1}H NMR: δ 0.10 (9H, s), 3.49 (d, *J* 9.2 Hz), 3.68 (3 H, s), 3.73 (3 H, s), 4.13 (1 H, dddd, *J* 9.2, 6.4, *ca.* 1, and *ca.* 1 Hz), 5.11 (1 H, ddd, *J* 10,0, *ca.* 2, and 1 Hz), 5.26 (1 H, ddd, *J* 17,0, *ca.* 2, and *ca.* 1 Hz), 5.84 (1 H, ddd, *J* 17.0, 10.0 and 6.4 Hz). ^{13}C NMR [22.63 MHz]: δ −0.2 (silyl), 52.0 (methoxy), 59.4 (C2), 72.6 (C3), 116.6 (C5), 137.5 (C4), 166.7 and 167.3 (diastereotopic C=O).

4,4-Dicarbomethoxy-1,7-di(trimethysiloxy)-1E-

6E-heptadiene **4b**. Enol ether *E-4a* (11.1 g, above) was refluxed (general procedure, above), for 22 h. Yield 6.62 g recovered **4a** (b.p. 80 – 123 °C/0.15 mmHg) and **4b**. Yield 5.90 g (38 %; 95 % based on consumed **4a**), b.p. 123 – 143 °C/0.15 mmHg, mainly 133 °C/0.15 mmHg. Anal. $C_{17}H_{32}O_6Si_2$: C, H. ^{1}H NMR: δ 0.17 (18 H, s), 2.46 (4 H, dd, *J* 8.0 and 1.2 Hz), 3.67 (6 H, s), 4.74 (2 H, dt, *J* 12 and 8.0 Hz), 6.18 (2 H, dt, *J* 12 and *ca.* 1 Hz). ^{13}C NMR [22.63 MHz]: δ – 0.7 (silyl), 30.7 (C3 and C5), 52.0 (methoxy), 58.5 (C4), 104.7 (C2 and C6), 142.4 (C1 and C7), 171.1 (C=O).

Methyl 2-carbomethoxy-2-nitro-4-phenyl-5-trimethylsilyloxy-4Z-pentenoate, **Z-4c**. Dimethyl nitromalonate[12] (1.5 ml), atropaldehyde[13] (1.0 g), and trimethylchlorosilane (1.4 ml) in carbon tetrachloride (5 ml) were cooled to 2 °C and triethylamine (2.0 ml) was added. The mixture was kept at 20 °C for a further 10 min. Work-up as above. The crude product could not be distilled (0.2 mmHg) without extensive decomposition. Crystallization from toluene – ligroin (6 ml, 1:1) at – 80 °C gave 1.9 g, m.p. 56 – 58 °C. Two recrystallizations from ether (10 ml) gave m.p. 61 – 62 °C. Anal. $C_{17}H_{23}NO_7Si$: C, H, N. ^{1}H NMR: δ 0.15 (9 H, s), 3.42 (6 H, s), 3.51 (2 H, broadened d, *J* 0.9 Hz), 6.38, (1 H, only partly resolved t, *J* < 1 Hz), 7.11 – 7.31 (5 H, m). A resonance at δ 0.19 suggests a maximum content of 4 % *E-4c* in a sample of crude **4c**. ^{13}C NMR [67.89 MHz]: δ 37.6 (C3), 53.3 (methoxy), 96.0 (C2), 112.3 (C4), 126.3, 127.5, 128.7, and 135.7 (phenyl), 141.0 (C5), 162.1 (C1), *J* (C3,H3) 134 Hz, *J* (C3,H5) 4 Hz, *J* (C5,H5) 177 Hz, *J* (C5,H3) 7 Hz. The 4 Hz coupling constant is consistent with a C3 *cis* to H5 configuration (1.7 × 4 = 6.8 Hz, *cf. J* (*cis*-protons) 5.8 Hz in *Z-4a*).[6] MS [*m/z* (% rel. int.)]: 381 (6, M), 336 (2), 303 (3), 217 (15), 207 (21), 205 (9), 199 (11), 179 (8), 173 (8), 171 (12), 115 (9), 113 (29), 105 (10), 75 (9), 73 (100, $(CH_3)_3Si$).

A mixture of *E-4c* and *Z-4c* was prepared for comparison. Dimethyl nitromalonate (1.53 g), atropaldehyde (1.0 g), ether (2.5 ml) and triethylamine (0.1 ml) were refluxed for 20 min, cooled, washed with water, dried ($MgSO_4$) and concentrated *in vacuo*. Yield 2.18 g of yellow oil, **6**. The product decomposed upon attempted distillation at 0.2 mmHg. ^{1}H NMR: δ 2.66 (dd, *J* 5.5 and 15 Hz), 3.60 (dd, *J* 5.5 and 15 Hz), 3.69 (s), 4.06 (broad t, *J* 5.5 Hz), 7.22 – 7.44 (m), 9.50 (d, *J* 0.5 Hz). The main impurity was triethylamine. MS [isobutane C.I.]: 310 (M + 1). The crude aldehyde (**6**, above, 0.30 g), trimethylchlorosilane (0.25 ml), carbon tetrachloride (3 ml), and triethylamine (0.3 ml) was stirred for 40 min at 20 °C. The mixture was diluted with light petroleum, washed with water, dried (Na_2SO_4) and concentrated *in vacuo*. ^{1}H NMR on the crude product showed *ca.* 30 % *Z-4c* (as above) and 70 % of the *E* isomer. δ 0.19 (s), 3.42

(s), 3.75 (s), 6.44 (s), 7.16 (s). ^{13}C NMR [67.89 MHz]: *J* (C3,H5) 6 Hz, *cf.* 4 Hz, above, suggesting C3 *trans* to H5.[6]

2,2-Dicarbomethoxy-4-phenyl-5-trimethylsilyloxy-4-Z-pentenonitrile **Z-4d**. Methyl cyanomalonate[14] (1.6 g), atropaldehyde[13] (1.3 g), trimethylchlorosilane (1.4 ml), and triethylamine (1.7 ml) were stirred at 40 – 47 °C for 40 min. Work-up as above gave 3.51 g of crude **4d**. ^{1}H NMR: δ 0.20 (9 H, s), 3.20 (2 H, partly resolved d, *J* < 1 Hz), 3.47 (6 H, s), 6.53 (1H, partly resolved t, *J* < 1 Hz) 7.00 – 7.42 (5H, m). A signal at δ 0.24 shows the presence of *ca.* 5 % of the *E* isomer. Distillation of the crude product (b.p. 155 – 172 °C/0.2 mmHg) resulted in *ca.* 15 % isomerization. The distillate was kept in an ampoule *in vacuo* at 148 – 152 °C for 4 h. ^{1}H NMR singlets at δ 0.24, 3.47, 3.51, 6.58, and 7.20 appeared and were assigned to the *E* isomer of **4d**. No splitting of the ester methyls was observed. Integration gave a 58:42 *E – Z* ratio. A GLC/MS analysis (1.5 m by 2 mm 5 % OV-101, 170 °C isothermal, injection temperature *ca.* 200 °C) showed an isomerization to an approximately 2:1 ratio of *E – Z* **4d**. MS [ip 70 eV; *m/z* (% rel. int. of *Z*; % rel. int. of *E*)]: 361 (M, 12; 14), 346 (M – 15, 3; 0), 205 (loss of cyanomalone ester, 86; 98), 73 ($Si(CH_3)_3$, 100).

N-3(Trimethylsilyloxy)allyl-N,N,N-triethylammonium chloride **Z-7**. Acrolein (0.63 ml), trimethylchlorosilane (1.4 ml), triethylamine (1.7 ml), and light petroleum (10 ml) were stirred for 30 min at 20 °C. The colorless crystals were washed with light petroleum and dried *in vacuo* to give crude salt **7**. ^{1}H NMR: δ 0.24 (9 H, s), 1.42 (9 H, t, *J* 7.2 Hz), 3.40 (6 H, q, *J* 7.2 Hz), 3.98 (2 H, d, *J* 8.0 Hz), 4.60 (1 H, dt, *J* 5.7 and 8.0 Hz), 6.64 (1 H, d, *J* 5.7 Hz). Resonances at δ 1.40 (t, *J* 7.3 Hz) and 3.13 (dq, *J* 4.7 and 7.3 Hz) show the presence of triethylammonium chloride (*ca.* 30 %), and at δ 6.94 (d, *J* 11.3 Hz) show the presence of the *E* isomer of **7** (*ca.* 3 %). The experiment was repeated (1:20 scale, in deuteriochloroform). ^{1}H NMR (after 2 min at 20 °C) showed the presence of **7** and of the *E* isomer of **7** (ratio 1:1). ^{1}H NMR: δ0.24 (s), 1.39 (t, broadened), 3.39 (q, *J* 7 Hz), 4.09 (d, *J* 8.0 Hz), 4.84 (dt, *J* 11.3 and 8.0 Hz), 6.94 (d, *J* 11.3 Hz). Unreacted acrolein and some hexamethyldisiloxane was also present. Salt **7** hydrolyzes readily to acrolein, hexamethyldisiloxane, and triethylammonium chloride.

Methyl 2-carbomethoxy-2-nitro-4-phenyl-5-hydroxy-4-pentenoate. Enols **Z-5** and **E-5**, Fig. 1 and Scheme 4. Atropaldehyde (85 mg), diethyl nitromalonate (**1c**, 140 mg), carbon tetrachloride (0.2 ml), and deuteriobenzene (0.1 ml) were cooled to *ca.* – 80 °C in an NMR tube. Triethylamine (10 μl) was added, the contents mixed rapidly and ^{1}H NMR spectra were recorded at intervals as

indicated in Fig. 1. Resonances at δ 3.62, 3.49, 3.33 and 3.30 were assigned the methoxy groups of dimethyl nitromalonate, the Michael adduct *6*, and the anols *E-5* and *Z-5*, respectively. Resonance heights normalized to 100% gave the product distributions plotted in Fig. 1. The accuracy of the measurements is low. The resonances of *E-5* and of *Z-5* are only partly resolved. Resonances at δ 3.44 and at 6.50[15] (broad and variable) increased and declined synchroneously with that of δ 3.30 and were assigned to the methylene and the vinylic protons of *Z-5*, respectively, *cf.* δ 3.51 and 6.38 for the corresponding protons of *Z-4c*. A resonance at δ6.72 (broad and variable) was assigned to the vinylic proton of *E-5*, *cf.* 6.44 for *E-4c*.[15] The variability of the vinylic protons may be due to exchange of enolic protons as the acidity of the medium changes.

REFERENCES

1. Bergmann, E. D., Ginsburg, D. and Pappo, R. *Org. React. 10* (1959) 179.
2. House, H. O. *Modern Synthetic Reactions,* Benjamin, Menlo Park, California 1972, p. 595.
3. Markisz, J. A. and Gettler, J. D. *Can. J. Chem. 47* (1969) 1965.
4. Cram, D. J. and Sogah, G. D. Y. *Chem. Commun.* (1981) 625.
5. House, H. O., Czuba, L. J., Gall, M. and Olmstead, H. D. *J. Org. Chem. 34* (1969) 2324.
6. Anderson, J. E. *Tetrahedron Lett.* (1975) 4079.
7. Rasmussen, J. K. *Synthesis* (1977) 91.
8. Fleming, I. *Chem. Soc. Rev. 10* (1981) 83.
9. Colvin, E. *Silicon in Organic Synthesis,* Butterworth, London 1981.
10. Miyashita, M., Yanami, T. and Yoshikoshi, A. *Org. Synth. 60* (1981) 117.
11. Stork, G., Shiner, C. S. and Winkler, J. D. *J. Am. Chem. Soc. 104* (1982) 310.
12. Arndt, F. and Rose, J. D. *J. Chem. Soc.* (1935) 1.
13. Crossland, I. *Org. Synth. 60* (1981) 6.
14. Cadogan, J. I. G., Hey, D. H. and Sharp, J. T. *J. Chem. Soc. C* (1966) 1743.
15. Capon, B., Rycroft, D. S., Watson, T. W. and Zucco, C. *J. Am. Chem. Soc. 103* (1981) 1761.