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Nucleophilic Reactions of *o*-Halomethylbenzylidenemalonates, Cyano Esters and Malononitriles

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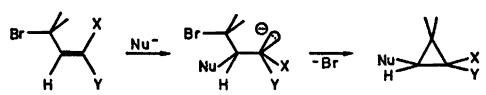
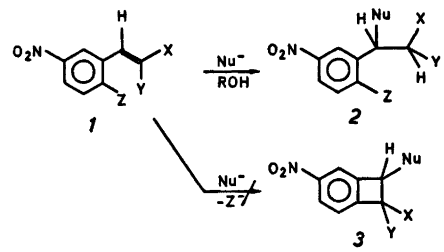
The reaction between selected nucleophiles and the title compounds has been studied. With methoxide and cyanide ion substituted indans were formed while other nucleophiles (Br^-, I^-, SCN^-, PhO^-, AcO^-, NO_3^-) gave normal substitution products.

In previous reports we have shown that nucleophilic attack on allylic halides carrying electronegative groups at the γ-carbon takes place on the β-carbon (giving substituted cyclopropanes) rather than on the α-carbon (S_N1 or S_N2) or on the γ-carbon (S_N1' or S_N2').[1,2] The kinetics of the reaction are shown to be of second order, first order in halide and nucleophile, respectively, and may be formulated as a β-S_N2'-process.[1,2] The details of the reaction mechanism are not known. Thus two main possibilities exist, *viz.* a concerted or a stepwise process. In the latter either of the two steps outlined in Scheme 1 may be rate limiting.



Scheme 1. X and Y = CN or CO_2Me; Nu = CN^- or MeO^-.

In a stepwise process, the intermediate carbanion acts as a nucleophile in the last step. With this in mind, we tried to extend the scope of the reaction to formation of larger rings by gradually moving the halide atom away from the double bond. Halides on aromatic rings can be displaced by nucleophiles provided activating groups for such reactions are present. Thus we prepared compounds *1* and subjected them to nucleophiles capable of forming cyclopropanes.[1,2] However, only the Michael addition products *2* and not the benzocyclobutanes *3* were formed (Scheme 2).



Scheme 2. 1a, X = Y = CO_2Me, Z = Cl; *1b*, X = CO_2Me, Y = CN, Z = F; *1c*, X = Y = CN, Z = Cl; *2a*, Nu = OMe, X = Y = CO_2Me, Z = Cl; *2b*, Nu = CN, X = Y = CO_2Me, Z = Cl; *2c*, Nu = CN, X = CO_2Me, Y = CN, Z = F.

Compounds *4*, which may be regarded as vinylogous allylic halides, were prepared as described in the experimental section. When reacted with nucleophiles, either *5* or *6* were obtained in very good yields (Scheme 3).

The structures of the substituted indans *5* were established mainly by spectroscopic methods. Thus, the IR spectra lacked the carbon-carbon double bond stretching frequency, the conjugated chromophore of *4* (and *6*) was missing in the UV spectra, and in the ^1H NMR spectra the benzylic methylene group (R = H) gave AB quartets with $J = 15-17$ Hz, consistent with a ring structure.

When the aromatic ring had a nitro substituent (*4f*) no indan was obtained. Instead several products were observed, which could not be separated. The UV maximum changed

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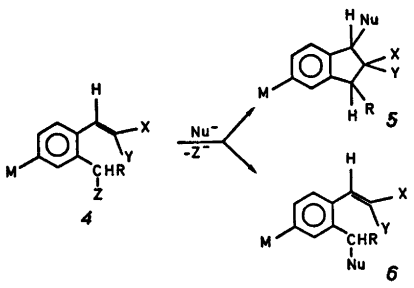

Scheme 3. *4a*, M = R = H, X = Y = CO_2Me, Z = Cl; *4b*, M = R = H, X = Y = CO_2Me, Z = Br; *4c*, M = R = H, X = Y = CO_2Me, Z = I; *4d*, M = OMe, R = H, X = Y = CO_2Me, Z = Br; *4e*, M = Cl, R = H, X = Y = CO_2Me, Z = Br; *4f* M = NO_2, R = H, X = Y = CO_2Me, Z = Br; *4g*, M = H, R = Me, X = Y = CO_2Me, Z = Br; *4h*, M = R = Y = H, X = CO_2Me, Z = Br; *4i*, M = R = Y = H, X = CN, Z = Br; *4j*, M = R = H, X = CO_2Me, Y = CN, Z = Br; *4k*, M = R = H, X = Y = CN, Z = Br; *5a*, M = R = H, Nu = CN, X = Y = CO_2Me; *5b*, M = R = H, Nu = MeO, X = Y = CO_2Me; *5c*, M = Cl, Nu = CN, R = H, X = Y = CO_2Me; *5d*, M = OMe, Nu = CN, R = H, X = Y = CO_2Me; *5e*, M = H, Nu = CN, R = Me, X = Y = CO_2Me (*cis* and *trans*); *5f*, M = R = H, Nu = Y = CN, X = CO_2Me; *5g*, M = R = H, Nu = OMe, X = CO_2Me, Y = CN; *6a*, M = R = H, Nu = SCN, X = Y = CO_2Me; *6b*, M = R = H, Nu = Oϕ, X = Y = CO_2Me; *6c*, M = R = H, Nu = OAc, X = Y = CO_2Me; *6d*, M = R = H, Nu = ONO_2, X = CO_2Me, Y = CN; *6e*, M = R = Y = H, Nu = CN, X = CO_2Me; *6f*, M = R = Y = H, Nu = X = CN.

slowly from 294 nm (substrate) to 285 nm, indicating a substitution of bromide by cyanide and thus preventing ring formation due to the low-leaving group reactivity of the latter.

From the experimental data it can be derived that the following requirements must be fulfilled to yield the indans *5*:

1. The leaving group must be better than or equal to chloride in reactivity.

2. Neither X nor Y can be hydrogen.

3. Only MeO^- or CN^- were effective as nucleophiles.

With nucleophiles like Br^-, I^-, SCN^-, PhO^-, AcO^-, $NO_3^-(Ag^+)$ substitution products were obtained.

EXPERIMENTAL

IR spectra were recorded on a Perkin Elmer Model 459 spectrophotometer, UV data on a Cary 16 spectrophotometer, ^1H NMR data on a Varian A60A spectrometer and mass spectra on an AEI MS902 spectrometer.

Melting points are not corrected.

Compounds *1*

were synthesized according to standard literature procedures [3] by condensation of the appropriate benzaldehydes with either dimethyl malonate, methyl cyanoacetate or malononitrile (Knoevenagel condensation) using either Amberlite IR45 [4] or piperidine as catalyst. Water was azeotropically removed using a Dean-Stark condenser. In one case (*1a*), the elimination of water was not successful. However, treatment of the addition product with cold concentrated H_2SO_4 yielded the condensation product *dimethyl 2-chloro-5-nitrobenzylidenemalonate* (*1a*) in 43 % overall yield, m.p. 96–97 °C (MeOH). Anal. $C_{12}H_{10}ClNO_6$: C, H. IR (KBr): 1720 (s). ^1H NMR (60 MHz, $CDCl_3$): 3.83 (3 H, s), 3.88 (3 H, s), 7.62 (1 H, d, *J* 8.0 Hz), 7.95 (1 H, s), 8.15 (1 H, dd, *J* 2.5 Hz and 8.0 Hz), 8.30 (1 H, d, *J* 2.5 Hz). *Methyl 2-fluoro-5-nitrobenzylidenecyanoacetate* (*1b*): Yield 64 %, m. p. 114–115 °C (MeOH). Anal. $C_{11}H_7FN_2O_4$: C, H. *2-Chloro-5-nitrobenzylidenemalononitrile* (*1c*): Yield 75 %, m.p. 121–122 °C (EtOH). Anal. $C_{10}H_4ClN_3O_2$: C, H. Spectroscopic parameters for the latter two compounds were as expected and analogous to those of *1a*.

Addition products *2*

1a was treated with equimolar quantities of KCN in 80 % aqueous MeOH. Evaporation of MeOH and extraction with $CHCl_3$ gave *methyl 2-cyano-1-methoxycarbonyl-2-[2-chloro-5-nitrophenyl] propanoate* (*2b*) in 65 % yield, m.p. 125–126 °C (MeOH). Anal. $C_{13}H_{11}ClN_2O_6$: C, H. ^1H NMR (60 MHz, $CDCl_3$): δ 8.55 (1 H, d, *J* 3 Hz), 8.30 (1 H, dd, *J* 3 Hz and 9 Hz), 7.70 (1 H, d, *J* 9 Hz), 5.18 (1 H, d, *J* 7 Hz), 4.30 (1 H, d, *J* 7 Hz), 3.92 (3 H, s), 3.85 (3 H, s).

1b, when treated likewise, gave the two diastereoisomers of *2c*, which were not isolated and characterized.

1a was treated with equimolar quantities of NaOMe in MeOH. The same work-up procedure as for the cyanide reaction gave *methyl 2-methoxy-1-methoxycarbonyl-2-[2-chloro-5-nitrophenyl]propanoate* (*2a*) in 81 % yield, m.p. 69–70 °C (MeOH). Anal. $C_{13}H_{14}ClNO_7$: C, H. MS (IP 70eV): 333–331 (M^+). ^1H NMR (60 MHz, $CDCl_3$): δ 8.63 (1 H, d, *J* 3Hz), 8.40 (1 H, dd, *J* 3 Hz and 9 Hz), 7.82 (1 H, d, *J* 9 Hz), 5.52 (1 H, d, *J* 7 Hz), 4.02 (1 H, d, *J* 7 Hz), 3.91 (3 H, s), 3.77 (3 H, s), 3.41 (3 H, s).

Compounds 4

The nonhalogenated *4* (Z=H) were synthesized analogously to *1*.

Dimethyl 2-bromomethylbenzylidenemalonate (*4b*) was obtained by reaction of the nonhalogenated analogue with *N*-bromosuccinimide (NBS), in refluxing CCl_4 using dibenzoyl peroxide as catalyst, yield 95 %, m.p. 82–84 °C (MeOH). Anal. $C_{13}H_{13}BrO_4$: C, H. IR (KBr): 1720 (s), 1625 (m). ^{1}H NMR (60 MHz, $CDCl_3$): δ 3.67 (3 H, s), 3.84 (3 H, s), 4.42 (2 H, s), 7.3 (4 H, m), 8.04 (1 H, s). MS (IP 70eV): 283–281 (M^+–MeO). UV (DMSO; log ε): 284 (4.1).

Compounds 4d–k were obtained in yields ranging from 45 % (*4h*) to 95 % (*4j*) by similar reactions with NBS. Elemental analysis were satisfactory for all compounds and the spectroscopic parameters as expected for these compounds, except that in the ^{1}H NMR spectra of *4j* and *4k* one aromatic proton is shifted 0.6–0.7 ppm downfield from the other three protons.

Dimethyl 2-chloromethylbenzylidenemalonate (*4a*) was made by heating a solution of the nonhalogenated analogue (16 g, 0.068 mol), *N*-chlorosuccinimide (11 g, 0.085 mol) and dibenzoyl peroxide (1 g) in 15 ml CCl_4 at 150 °C (oil-bath) for 12 h. Conventional work-up gave *4a* (61 %), m.p. 66–67 °C (MeOH). Anal. $C_{13}H_{13}ClO_4$: C, H. Spectroscopic parameters similar to those of *4b*.

Dimethyl 2-iodomethylbenzylidenemalonate (*4c*) was made from *4b* (0.01 mol) by refluxing for 2 h with NaI (0.033 mol) in acetone/water (80/20 ml). Yield 70 %, m.p. 92–93 °C (MeOH). Anal. $C_{13}H_{13}IO_4$: C, H. Spectroscopic parameters were similar to those of *4a* and *4b*.

Compounds 5

Indans 5a, 5c–f were prepared by dissolving halides *4* in MeOH, adding equimolar amounts of KCN dissolved in water (keeping the concentration of MeOH/H_2O about 4:1) and stirring at room temperature for 12 h. After evaporation of methanol, extraction with $CHCl_3$ gave the products in yields ranging from 77 % (*5c*) to 82 % (*5a*) after recrystallization from MeOH.

1-Cyano-2,2-dimethoxycarbonylindan (*5a*), m.p. 96–97 °C. Anal. $C_{14}H_{13}NO_4$: C, H. MS (IP 70eV): 259 (M^+). IR (KBr): 2240 (w), 1745 (s), 1725 (s). ^{1}H NMR (60 MHz, $CDCl_3$): δ 3.81 (3 H, s), 3.57–3.80 (2 H, 2d, AB-system, J_{AB} 17 Hz), 5.00 (1 H, s), 7.25–7.4 (4 H, m).

5-Chloro-1-cyano-2,2-dimethoxycarbonylindan (*5c*) m.p. 105–106 °C. Anal. $C_{14}H_{12}ClNO_4$: C, H. *1-Cyano-2,2-dimethoxycarbonyl-5-methoxyindan* (*5d*) m.p. 113–115 °C. Anal. $C_{15}H_{15}NO_5$: C, H. *5e* was obtained as a mixture of diastereoisomers which was not separated. *1,2-Dicyano-2-methoxycarbonylindan* (*5f*), m.p. 106–107 °C. Anal. $C_{13}H_{10}N_2O_2$: C, H. The spectroscopic parameters for *5c–f* were similar to those of *5a*.

Indans 5b *and* 5g were prepared by dissolving halides *4* in MeOH, adding equimolar quantities of sodium methoxide, and after 12 h at room temperature the solution was worked up as for *5a*. Yields 79 % (*5b*) and 97 % (*5g*) after recrystallization from MeOH. *2,2-Dimethoxycarbonyl-1-methoxyindan* (*5b*), m.p. 71–72 °C. Anal. $C_{14}H_{16}O_6$: C, H. *2-Cyano-1-methoxy-2-methoxycarbonylindan* (*5g*) m.p. 88–89 °C. Anal. $C_{13}H_{13}NO_3$: C, H. Spectroscopic parameters were similar to those of *5a*, except that in the ^{1}H NMR spectra the MeO-protonsignals (originated from the nucleophile) were observed at δ 3.45 (*5b*) and 3.57 (*5g*).

Substitution products 6

were obtained by treating halides *4* with the nucleophiles (Nu) in 80 % MeOH/H_2O, and after 12 h at room temperature the solution was worked up as for *5a*. Yields obtained ranged from 61 % (*6e*) to 84 % (*6b*) after recrystallization from MeOH.

Dimethyl 2-thiocyanomethylbenzylidenemalonate (*6a*), m.p. 87–88 °C. Anal. $C_{14}H_{13}NO_4S$: C, H. IR (KBr): 2150 (s), 1720 (s), 1625 (s). ^{1}H NMR (60 MHz, $CDCl_3$): δ 3.68 (3 H, s), 3.85 (3 H, s), 4.25 (2 H, s), 7.3–7.45 (4 H, m), 8.03 (1 H, s). *Dimethyl 2-phenoxymethylbenzylidenemalonate* (*6b*) m.p. 59–60 °C. Anal. $C_{19}H_{18}O_5$: C, H. *Dimethyl 2-acetoxymethylbenzylidenemalonate* (*6c*) m.p. 62–63 °C. Anal. $C_{15}H_{16}O_6$: C, H. *Methyl 2-nitrooxymethylbenzylidenecyanoacetate* (*6d*) m.p. 95–96 °C. Anal. $C_{12}H_{10}N_2O_5$: C, H. *Methyl 2-cyanomethylcinnamate* (*6e*), m.p. 73–74.5 °C. Anal. $C_{12}H_{11}NO_2$: C, H. *2-Cyanomethylcinnamonitrile* (*6f*), m.p. 132–133 °C. Anal. $C_{11}H_8N_2$: C, H. The spectroscopic parameters for compounds *6b–f* were similar to those of *6a* except that absorption signals in IR and/or ^{1}H NMR for the substituting group were also observed.

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