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Formation of Cyclopropanes from 2-Bromo-1-phenylalkylidene-malononitriles and Nucleophiles

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The reaction of the title compounds with selected nucleophiles was studied. With cyanide and hydride (from sodium borohydride) ions, substituted cyclopropanes were obtained in good yields. With alkoxide ions, cyclopropanes were formed only when the bromide was tertiary.

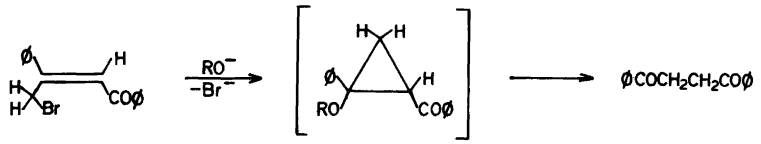
The reaction of dimethyl 2-bromo-2-methylpropylidenemalonate[1] and dimethyl (1-bromocyclohexyl)methylidenemalonate[2] with sodium methoxide or potassium cyanide in methanol gave cyclopropane derivatives in high yields. Later on it was shown that the former compound gave good yields of cyclopropanes with sulfur nucleophiles, and that it gave a cyclopropane with sodium borohydride indicating that hydride ion formally acts as a nucleophile.[3]

When the more reactive (1-bromocyclohexyl)-methylidenemalononitrile and 2-bromo-2-methylpropylidenemalonitrile were treated with sodium methoxide in methanol, high yields of Δ^2-pyrrolines were obtained in reactions involving cyclopropane intermediates.[4] In contrast, the latter upon reaction with a large excess of sodium borohydride gave a mixture of 2,2-dimethyl-1,1-cyclopropanedicarbonitrile (46 %) and *t*-butylmalononitrile (54 %), the latter product most likely arising from ring cleavage by further attack of hydride ion.[5] In this report it will be shown that cyanide ion will produce an excellent yield of 3,3-dimethyl-1,1,2-cyclopropanetricarbonitrile from 2-bromo-2-methylpropylidenemalononitrile.

It has been reported that the base-induced conversion of E-4-bromo-1,3-diphenyl-2-butene-1-one (*trans*-γ-bromodypnone) into 1,2-dibenzoylethane possibly involves a cyclopropane intermediate (Scheme 1).[6] It is thus of interest to see how the introduction of a phenyl group (with its conjugative capacity) would influence the reaction of allylic halides carrying electronegative substituents in the γ position with selected nucleophiles. Thus 2-bromo-1-phenylalkylidenemalononitriles *1*–*5* were treated with MeO^-, CN^- or $H^-(NaBH_4)$ (Table 1).

Treatment of allylic bromides *1*–*5* with potassium cyanide in 80–85 % acetone–water at room temperature gave cyclopropanes *6*–*10* in good yields.

In the same manner, treatment of *1*, *4* and *5* with sodium borohydride (1.25 molar equiv.) in ethanol



Scheme 1.

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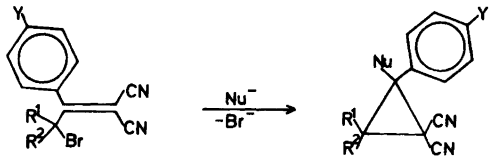
Table 1. Formation of cyclopropanes *6–16* from allylic bromides *1–5*.



1–5 *6–16*

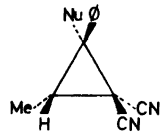
				Nu = CN		Nu = BH_4	
No.	R_1	R^2	Y	No.	Yield %	No.	Yield %
1	H	H	H	*6*	73	*11*	[a]
2	H	H	Br	*7*	65		
3	H	H	OMe	*8*	58		
4	Me	H	H	*9*	92	*12*	60
5	Me	Me	H	*10*	68	*13*	55
5	Nu = MeO			*14*	89		
5	Nu = EtO			*15*	68		
5	Nu = i-PrO			*16*	71		

[a] See Experimental.

gave cyclopropanes *11*, *12* and *13*. No ring cleavage products were observed from *4* and *5*, while the existence of such products from *1* cannot be excluded as the reaction product was an intractable oil, from which only *11* could be obtained in reasonably pure state (see Experimental).

Cyclopropanes *9* and *12* may exist as a mixture of isomers (the methyl groups *cis* or *trans* to phenyl). However, as only one signal was detected for the methyl group in *9* and *12* by ^{1}H NMR spectrometry, while *10* and *13* gave well separated signals for the geminal methyl groups, it can be concluded that only one single isomer of *9* and *12* is formed.

Due to the anisotropy of the phenyl ring, *cis*-methyl protons are shielded while *trans*-methyl protons are deshielded in phenylcyclopropane derivatives.[7,8] The chemical shifts for the methyl protons in *9* and *12* are close to those found at lowest field in *10* and *13*. Accordingly, cyclopropanes *9* and *12* most likely have the *trans*-configuration.



9 Nu = CN
12 Nu = H

On addition of an equivalent amount of sodium methoxide, sodium ethoxide or sodium isopropoxide to an alcoholic solution of *1* or *4* at room temperature, the reaction mixture became strongly coloured. Work-up by the usual procedure gave only glassy products with the exception of the reaction between *4* and sodium methoxide which caused a precipitation of an organic compound in about 10 % yield. Its molecular weight of *ca.* 410 (vapour pressure osmometric measurements) indicated a dimer. This reaction has not been studied in detail, but it should be mentioned that reaction of the related (1-bromocyclohexyl)methylidenemalononitrile with sodium methoxide gave a Δ^2-pyrroline in high yield.[4]

On the other hand, treatment of the allylic bromide *5* with sodium methoxide, sodium ethoxide or sodium isopropoxide gave cyclopropanes *14–16* in high yields.

Dimethyl 2-bromoethylidenenalonate and dimethyl 2-bromopropylidenemalonate reacted with sodium methoxide to give dimethyl 2,2-dimethoxyethylmalonate and dimethyl 2,2-dimethoxy-1-methylethylmalonate, respectively,[9] while dimethyl 2-bromo-2-methylpropylidenemalonate gave dimethyl 2-methoxy-3,3-dimethyl-1,1-cyclopropanedicarboxylate in high yield.[1]

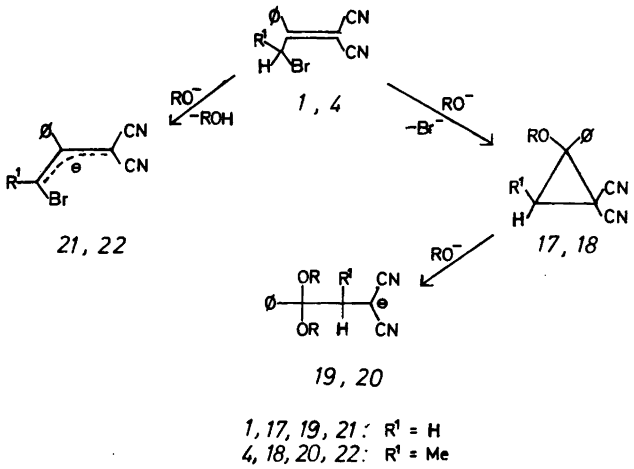
Thus, the reason why no cyclopropane derivatives could be isolated when allylic bromide *1* or *4* was treated with sodium alkoxides may be reactions initiated by a rapid ring cleavage of an intermediate cyclopropane by alkoxide (Scheme 2). The anions created, *19* and *20*, may participate in further reactions:

(i) Addition to the cyano group in the initially formed cyclopropanes *17* or *18* with the possibility of yielding Δ^2-pyrrolines.[4]

(ii) As alkylidenemalonitriles are more reactive than alkylidenemalonates in Michael reactions, anions *19* and *20* may be expected to add to the carbon-carbon double bond in *1* and *4* respectively, initiating dimerization or polymerization.

(iii) An initially formed cyclopropane may also be opened by attack of anion *19* or *20*.

The reaction between dimethyl 2-bromo-1-phenylpropylidenemalonate and sodium methoxide in methanol at room temperature gave among other products dimethyl 2-bromo-1-phenyl-1-propenylmalonate,[10] readily explained by invoking abstraction of an allylic proton in the substrate



Scheme 2. Possible intermediates in the reaction between *1* and *4* with sodium alkoxides.

followed by isomerization. A similar reaction on bromides *1* and *4* would create the allylic anions *21* and *22* which may initiate a lot of different reaction pathways giving rise to dimerization and polymerization reactions (Scheme 2).

EXPERIMENTAL

General. Melting points (uncorrected) were determined on a micro hot-stage. IR spectra were recorded on a Perkin-Elmer 457 Grating Infrared Spectrophotometer, ^{1}H NMR spectra on a Varian A-60A spectrometer, mass spectra on an AEI MS 902 instrument and the UV spectra on a Cary 14 spectrophotometer. Elemental analyses were performed by I. Beetz, West-Germany.

3,3-Dimethyl-1,1,2-cyclopropanetricarbonitrile. 2-Bromo-2-methylpropylidenemalononitrile[4] (3.55 g, 17.9 mmol) was dissolved in acetonitrile (80 ml). A potassium cyanide (1.16 g, 17.9 mmol) solution in water (20 ml) was added dropwise. After 1.5 h the acetonitrile was evaporated and dichloromethane added. Evaporation of the organic phase gave 2.3 g (85 %) essentially pure product (^{1}H NMR). M.p. 125–126 °C (90 % MeOH). Anal. $C_8H_7N_3$: C, H. ^{1}H NMR ($CDCl_3$): δ 2.50 (1H, s), 1.64 (3H, s), 1.57 (3H, s). ^{13}C NMR ($CDCl_3$): δ 112.3–111.6–110.6 (3 × C≡N), 35.2(C3), 27.5(C2), 22.0–19.2 (2 × CH_3), 17.7(C1). IR (KBr): 3025, 2240 cm^{-1}.

Preparation of allylic bromides 1–5. The bromides *1*–*5* were made by condensation of the ketones with malononitrile[11] followed by bromination with *N*-bromosuccinimide (NBS) (*1*–*3*) or 1,3-dibromo-5,5-dimethylhydantoin (Dibromantin) (*4* and *5*) in carbon tetrachloride using dibenzoyl peroxide or 2,2′-azobis(2-methylpropionitrile) as a catalyst. The reaction mixtures were irradiated with UV light during the whole reaction period.

2-Bromo-1-phenylethylidenemalononitrile (*1*), yield yield 56 %, m.p. 122 °C (EtOH). Found: C 54.07; H 2.96. Calc. for $C_{11}H_7BrN_2$: C 53.46; H 2.84. MS: *m/e* 246/248 (M^+). ^{1}H NMR ($CDCl_3$): δ 7.60 (5H, s), 4.53 (2H, s). IR (KBr): 2220, 1590, 1580, 1565 and 1470 cm^{-1}. UV (dioxane): λ_{max} 305 nm, ε 10600.

2-Bromo-1-(p-bromophenyl)ethylidenemalononitrile (*2*), yield 65 %, m.p. 80–84 °C (MeOH). Found: C 40.06; H 1.93. Calc. for $C_{11}H_6Br_2N_2$: C 40.51; H 1.84. ^{1}H NMR ($CDCl_3$): δ 7.68 (2H, d, *J* 12.0 Hz), 7.48 (2H, d, *J* 12.0 Hz), 4.51 (2H, s). IR (KBr): 2250 cm^{-1}. UV (dioxane): λ_{max} 315 nm, ε 12990.

2-Bromo-1-(p-methoxyphenyl)ethylidenemalononitrile (*3*), yield 39 %, m.p. 106–108 °C (MeOH). Found: C 52.18; H 4.00. Calc. for $C_{12}H_9BrN_2O$: C 52.55; H 3.28. ^{1}H NMR ($CDCl_3$): δ 7.72 (2H, d, *J* 9.0 Hz), 7.05 (2H, d, *J* 9.0 Hz), 4.55 (2H, s), 3.90 (3H, s). IR (KBr): 2250 cm^{-1}. UV (dioxane: λ_{max} 353 nm, ε 14580.

2-Bromo-1-phenylpropylidenemalononitrile (*4*), yield 69 %, m.p. 104.5–105.5 °C (MeOH). Anal. $C_{12}H_9BrN_2$: C, H. MS: *m/e* 181 (M^+–Br). ^{1}H NMR ($CDCl_3$): δ 7.50 (5H, s), 5.41 (1H, q), 1.68 (3H, d). IR (KBr): 2220 cm^{-1}. UV (dioxane): λ_{max} 297 nm, ε 5350.

2-Bromo-2-methyl-1-phenylpropylidenemalononitrile (*5*), yield 46 %, m.p. 91–92 °C (benzene). Found: C 57.16; H 4.16. Calc. for $C_{13}H_{11}BrN_2$: C 56.73; H 4.00. MS: *m/e* 195 (M^+–Br). ^{1}H NMR

($CDCl_3$): δ 7.1 – 7.6 (5H, m), 2.05 (6H, s). IR ($CHCl_3$): 2210 cm^{-1}. UV (dioxane): λ_{max} 280 nm, ε 4060.

Reactions of allylic bromides *1–5* with potassium cyanide

General procedure. Potassium cyanide (1 – 1.1 molar eqv.) was added to a solution of the bromide in 80 – 85 % acetonitrile – water, dioxane – water or acetone – water. The mixture was stirred for 1.5 – 2 h and the solvent evaporated. The residue was added to water and the cyclopropane extracted into chloroform. The organic layer was dried over $MgSO_4$. After removal of the solvent, the products were recrystallized.

2-Phenyl-1,1,2-cyclopropanetricarbonitrile (*6*), yield 73 %, m.p. 175.0 – 175.5 °C (ethanol – acetone). Anal. $C_{12}H_7N_3$: C, H. ^1H NMR [$(CD_3)_2CO$]: δ 7.4 – 8.0 (5H, m), 3.27 (1H, d, *J* 8.0 Hz), 3.13 (1H, d, *J* 8.0 Hz). IR (KBr): 2250 cm^{-1}.

2-[4-Bromophenyl]-1,1,2-cyclopropanetricarbonitrile (*7*), yield 65 %, m.p. 170 – 172 °C (ethanol – acetone). MS: *m/e* 272/270 ($M^+ - 1$). ^1H NMR [$(CD_3)_2CO$]: δ 7.78 (4H, s), 3.33 (1H, d, *J* 8.0 Hz), 3.18 (1 ×, d, *J* 8.0 Hz). IR (KBr): 2250 ym^{-1}.

2-[4-Methoxyphenyl]-1,1,2-cyclopropanetricarbonitrile (*8*), yield 58 %, m.p. 134 – 135 °C (ethanol – acetone). MS: *m/e* 223 (M^+), $C_{13}H_9NO_3$. ^1H NMR [$(CD_3)_2CO$]: δ 7.69 (2H, d, *J* 9.0 Hz), 7.08 (2H, d, *J* 9.0 Hz), 3.85 (3H, s), 3.19 (1H, d, *J* 8.0 Hz), 3.06 (1H, d, *J* 8.0 Hz). IR (KBr): 2250 cm^{-1}.

3-Methyl-2-phenyl-1,1,2-cyclopropanetricarbonitrile (*9*), yield 92 %, m.p. 110 – 111 °C (MeOH). Found: C 75.06; H 4.80. Calc. for $C_{13}H_9N_3$: C 75.36; H 4.35. MS: *m/e* 207 (M^+). ^1H NMR [$(CD_3)_2CO$]: δ 7.50 (5H, s), 3.37 (1H, q, *J* 6.0 Hz), 1.77 (3H, d, *J* 6.0 Hz). IR ($CHCl_3$): 2230 cm^{-1}.

3,3-Dimethyl-2-phenyl-1,1,2-cyclopropanetricarbonitrile (*10*), yield 68 %, m.p. 183 – 184 °C (methanol – acetone). Anal. $C_{14}H_{11}N_3$: C, H. MS: *m/e* 221 (M^+). ^1H NMR ($CDCl)_3$: δ 7.47 (5H, s), 1.87 (3H, s), 1.40 (3H, s). IR ($CDCl_3$): 2235 cm^{-1}.

Reactions of allylic bromides *1*, *4* and *5* with sodium borohydride

General procedure. A solution of the bromide (8 mmol) in ethanol (30 ml) was added to a suspension of sodium borohydride (10 mmol) in ethanol (10 ml). In the case of allylic bromide *1*, the temperature during the addition was kept below 45 °C, while for *4* and *5* the temperature was in the range 15 – 25 °C. The mixture was stirred for 3 h at room temperature. Excess sodium borohydride was destroyed by addition of acetic acid (1.8 M) and the pH adjusted to pH = 6. After addition of some water, the cyclopropane was extracted into chloroform. The organic layer was dried over $MgSO_4$ and the solvent removed.

2-Phenyl-1,1-cyclopropanedicarbonitrile (*11*). The crude product was a black oil. An analytical sample (light yellow liquid) was obtained by column chromatography on neutral aluminium oxide (activity 1) with methylene chloride as the eluent, MS: *m/e* 168 (M^+). ^1H NMR (CCl_4): δ 7.1 – 7.6 (5H, m), 3.17 (1H, t, *J* 8.5 Hz, the middle line is broad), 2.09 (2H, d, *J* 8.5 Hz). IR (film): 2240 cm^{-1}.

3-Methyl-2-phenyl-1,1-cyclopropanedicarbonitrile (*12*), yield 60 %, b.p. 100 °C/0.05 mmHg. Anal. $C_{12}H_{10}N_2$: C, H. MS: *m/e* 182 (M^+). ^1H NMR (CCl_4): δ 7.0 – 7.5 (5H, m), 2.8 (1H, d, *J* 8.0 Hz), 2.1 – 2.6 (1H, m), 1.52 (3H, d, *J* 6.0 Hz). IR (film): 2230 cm^{-1}.

3,3-Dimethyl-2-phenyl-1,1-cyclopropanedicarbonitrile (*13*), yield 55 %, m.p. 78 – 79 °C (MeOH). Anal. $C_{13}H_{12}N_2$: C, H. MS: *m/e* 196 (M^+). ^1H NMR (CCl_4): δ 7.34 (5H, s), 3.01 (1H, s), 1.65 (3H, s), 1.33 (3H, s). IR ($CHCl_3$): 2230 cm^{-1}.

Reactions of allylic bromide *5* with sodium methoxide, sodium ethoxide and sodium isopropoxide

2-Methoxy-3,3-dimethyl-2-phenyl-1,1-cyclopropanedicarbonitrile (*14*). A solution of sodium methoxide in methanol (15.7 ml, 0.46 mol) was added dropwise in 0.5 h at room temperature to a suspension of bromide *5* (2.0 g, 7.3 mmol) in methanol (5 ml). The bromide dissolved. The solution was stirred at room temperature for 0.5 h and extracted with chloroform after addition of water. The organic layer was washed with water and dried over $MgSO_4$. The solvent was removed to give *14*, yield 1.5 g (89 %), m.p. 84 – 85 °C (MeOH). Anal. $C_{14}H_{14}N_2O$: C, H. MS: *m/e* 226 (M^+). ^1H NMR ($CDCl_3$): 7.47 (5H, s), 3.25 (3H, s), 1.68 (3H, s), 1.22 (3H, s). IR (KBr): 2230 cm^{-1}.

2-Ethoxy-3,3-dimethyl-2-phenyl-1,1-cyclopropanedicarbonitrile (*15*). Use of the same procedure as above gave *15*, yield 68 %, m.p. 106 – 107 °C (MeOH). Anal. $C_{15}H_{16}N_2O$: C, H. MS: *m/e* 240 (M^+). ^1H NMR ($CDCl_3$): δ 7.47 (5H, s), 3.1 – 3.9 (2H, m), 1.70 (3H, s), 1.21 (3H, s), 1.14 (3H, t, *J* 7.0 Hz).

2-Isopropoxy-3,3-dimethyl-2-phenyl-1,1-cyclopropanedicarbonitrile (*16*). A 0.2 M solution of sodium isopropoxide in isopropyl alcohol was used. Use of the same procedure as above gave *16*, yield 71 %, m.p. 128.0 °C (MeOH). Anal. $C_{16}H_{18}N_2O$: C, H. MS: *m/e* 105 (ϕCO^+, 100). ^1H NMR ($CDCl_3$): δ 7.47 (5H, s), 3.80 (1H, m), 1.67 (3H, s), 1.30 (3H, d, *J* 6.5 Hz), 1.20 (3H, s), 0.77 (3H, d, *J* 6.5 Hz).

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