Reactivity of the Perhalogenoalkanes CF_2BrX (X = Cl, Br) with Nucleophiles. Part 4.[1] Condensation with Carbanions

By **Isabelle Rico, Danielle Cantacuzene,** and **Claude Wakselman,*** C.N.R.S.–C.E.R.C.O.A., 2 rue H. Dunant, 94320 Thiais, France

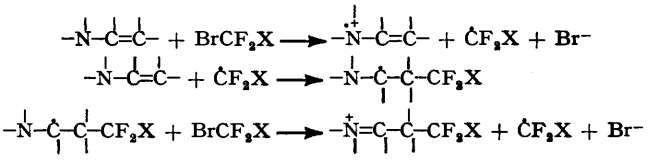
The condensation of CF_2BrX (X = Cl, Br) with different carbanions is described. CF_2BrX reacts with lithium acetylides and with substituted, active methylene compounds. The limits of reactivity of this reagent as well as the mechanism involved in the condensation are examined.

RECENTLY, we showed that perhalogenoalkanes CF_2BrX (X = Cl, Br) can react *via* two types of mechanism with nucleophiles. In the condensation with phenates ($Nu^- = ArO^-$) and thiophenates ($Nu^- = ArS^-$) we have postulated an ionic chain mechanism which involves the difluorocarbene $:CF_2$ [1a,1b] (Scheme 1). That hydrogenated by-products ($ArYCF_2H$; Y = O, S) were produced and that only the bromo-derivatives ($ArYCF_2Br$; Y = O, S) were obtained with CF_2BrCl indicate this mechanism.

$$Nu^- + BrCF_2X \longrightarrow NuBr + CF_2X^-$$
$$CF_2X^- \longrightarrow :CF_2 + X^-$$
$$Nu^- + :CF_2 \longrightarrow NuCF_2^-$$
$$NuCF_2^- + BrCF_2X \longrightarrow NuCF_2Br + CF_2X^-$$
$$NuCF_2^- + {}^{\prime}H{}^{\prime}_{solvent} \longrightarrow NuCF_2H$$

SCHEME 1

However, in the condensation of CF_2BrX with enamines a different mechanism is involved.[1c] That no hydrogenated by-products were observed and that only the chloro-derivative (CCF_2Cl) was obtained with CF_2BrCl indicate a radical chain mechanism similar to the one proposed by Kornblum [2] and later by Bunnett [3] (Scheme 2). This type of mechanism could also be involved with anions as shown in Scheme 3.



SCHEME 2

$$Nu^- + BrCF_2X \longrightarrow Nu + \dot{C}F_2X + Br^-$$
$$\dot{C}F_2X + Nu^- \longrightarrow NuCF_2X^{-\cdot}$$
$$NuCF_2X^{-\cdot} + BrCF_2X \longrightarrow NuCF_2X + \dot{C}F_2X + Br^-$$

SCHEME 3

In this paper we present the results obtained from the condensation of CF_2BrX with some carbanions. We show the limits of reactivity of this reagent and discuss the ionic (Scheme 1) or radical (Scheme 3) nature of the mechanism involved.

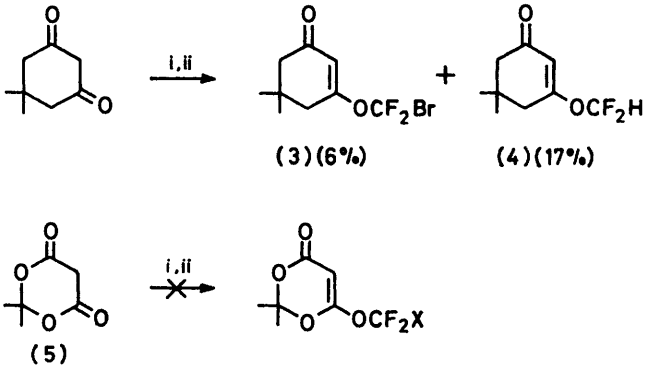
Few examples of condensation of CF_2BrX with carbanions are known. CF_2Br_2 reacts with alkyl-lithium to give olefins,[4] but no fluorinated products are obtained. However, with the substituted derivatives of aminoacids bromodifluoromethyl and difluoromethyl groups have been introduced with success.[5] On the other hand, substituted difluoromethylmalonates have been obtained with chlorodifluoromethane (CHF_2Cl) through carbene insertion.[6]

Condensation of CF_2BrX *with Lithium Acetylides.*—Lithium acetylides of propiolic acid and phenylacetylene react with dibromodifluoromethane, at 0 °C in tetrahydrofuran (THF), to give the corresponding bromodifluoromethane derivatives (1) and (2), respectively (Scheme 4). In the condensation of the same acetylides with CF_2BrCl, only the bromo-derivatives (1) and (2) were obtained and not the chlorodifluoromethylacetylenic compounds $R{-}C{\equiv}C{-}CF_2Cl$. This indicates an ionic chain mechanism (Scheme 1), though no hydrogenated by-products, such as $R{-}C{\equiv}C{-}CF_2H$, were observed.

$$HO_2C{-}C{\equiv}C{-}H \xrightarrow{2\times\ i,\ ii} HO_2C{-}C{\equiv}C{-}CF_2Br \quad (1)\ (25\%)$$
$$Ph{-}C{\equiv}C{-}H \xrightarrow{i,\ ii} Ph{-}C{\equiv}C{-}CF_2Br \quad (2)\ (35\%)$$

SCHEME 4 *Reagents*: i, BuLi; ii, CF_2Br_2

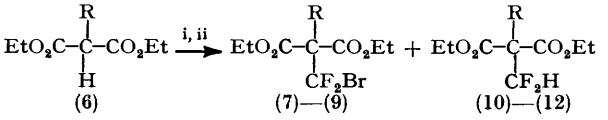
Condensation of CF_2Br_2 *with the Potassium Salt of* 5,5-*Dimethylcyclohexane*-1,3-*dione.*—CF_2Br_2 condenses with the potassium salt of 5,5-dimethylcyclohexanedione under phase-transfer conditions. In this case, only the *O*-alkylated derivatives (3) and (4) were obtained (Scheme 5). Several attempts to prepare the *C*-alkylated products were unsuccessful. It is noteworthy that with Meldrum's acid (5) no condensation occurred.



SCHEME 5 *Reagents*: i, KOH (50%)–$CHCl_3$, benzyltriethylammonium chloride (BTEA); ii, CF_2Br_2

Other β-diketones were tried (*e.g.* cyclohexane-1,3-dione and pentane-2,4-dione). However, though condensation was shown to have occurred by ^{19}F n.m.r. spectroscopy, it was not possible to isolate the *O*-alkylated derivatives, which were too unstable. With the enolate of cyclohexanone, a highly exothermic reaction occurred, but no fluorine was incorporated into the molecule.

Sodium Salts of Malonates.—The sodium salt of malonate does not condense with CF_2Br_2. However, the substituted diethyl malonates (6) reacted easily with CF_2Br_2 (as they did with CHF_2Cl) [6] to give the expected malonates (7), (8), and (9), as well as the difluoromalonates (10), (11), and (12) (Scheme 6). CF_2BrCl condensed with



(6) (7)—(9) (10)—(12)

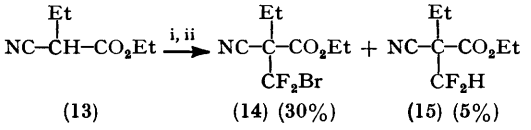
R = Me (7) (35%) (10) (5%)
R = Et (8) (45%) (11) (5%)
R = Ph (9) (20%) (12) (5%)

SCHEME 6. *Reagents*: i, NaH, THF; ii, CF_2Br_2, 0 °C

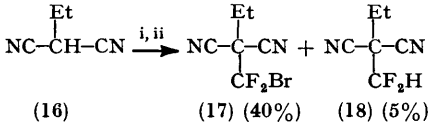
substituted malonates to give the same bromodifluoromethyl derivatives (7), (8), and (9) as well as the difluoromethylmalonates (10), (11), and (12) which again indicates an ionic chain mechanism.

Sodium Salts of Cyanoacetate and Malononitrile.—The reactions of unsubstituted cyanoacetate and malononitrile carbanions with CF_2Br_2 were observed by ^{19}F n.m.r. spectroscopy. However, the products of condensation could not be isolated because of their high instability.

The substituted cyanoacetate (13) and malononitrile (16) condensed easily with CF_2Br_2 to give respectively, the bromocyanodifluoroacetate (14) and the malononitrile (17) (Scheme 7).



(13) (14) (30%) (15) (5%)



(16) (17) (40%) (18) (5%)

SCHEME 7 *Reagents*: i, NaH, THF; ii, CF_2Br_2, 0 °C

The results presented here show that CF_2BrX can react with different types of carbanions. However, with unsubstituted, active methylene compounds no condensation products could be isolated. This may be due to the instability of the difluoromethyl derivatives (as in the case of malononitrile and cyanoacetate) or to decomposition of the intermediate due to a second metallation of the remaining hydrogen atom (as in the case of cyclohexanone).* In some cases (malonate itself or Meldrum's acid) no reaction seems to take place.

The mechanism of condensation of CF_2BrX with carbanions is an ionic chain mechanism as for the phenates and thiophenates (Scheme 1), since hydrogenated by-products are usually obtained and since CF_2BrCl gives bromodifluoromethyl derivatives.

EXPERIMENTAL

^1H N.m.r. spectra were recorded on a Perkin-Elmer R24A at 60 MHz. ^{19}F N.m.r. spectra were recorded on a Jeol C60HL. Chemical shifts are given in p.p.m. relative to internal $SiMe_4$ for ^1H n.m.r. data and relative to external $CFCl_3$ for ^{19}F n.m.r. data (solvent: $CDCl_3$). Mass spectra were obtained on an AEI MS30 spectrometer at 70 eV. I.r. spectra were obtained with a Perkin-Elmer 167.

Bromodifluoromethylpropiolic Acid (1).—Propiolic acid (3.5 g, 0.05 mol) was dissolved in dry THF (100 ml) and the mixture was flushed with argon and cooled to −20 °C. BuLi (1.4M; 70 ml, 0.1 mol), was added as drops. The solution was warmed to 0 °C and dibromodifluoromethane (10.5 g, 0.05 mol) was added. The mixture was stirred at room temperature for 4 h. Water was added after evaporation of the THF and the aqueous phase was extracted with diethyl ether. The diethyl ether phase was washed with dil. HCl and water, and dried ($MgSO_4$). Distillation of the mixture gave the *acid* (1) (2.5 g, 25%), b.p. 130 °C at 2 mmHg, m.p. 25 °C; δ 8 (s, CO_2H); δ (^{19}F) 43 (s, CF_2Br); *m/e* 198—200 (M^+) (Found: C, 24.3; F, 18.5. $C_4HBrF_2O_2$ requires C, 24.1; F, 19.0%).

Bromodifluoromethylphenylacetylene (2).—The same procedure as described above was used. From phenylacetylene (5 g, 0.05 mol), BuLi (1.4M; 35 ml, 0.05 mol), and CF_2Br_2 (10.5 g, 0.05 mol), pure *bromodifluoromethylacetylene* (2) was obtained after two distillations (3.8 g, 35%), b.p. 50 °C at 1 mmHg; δ 7 (s, Ph); δ (^{19}F) 42.9 (s, CF_2Br); *m/e* 230—232 (M^+) (Found: C, 46.6; H, 2.2; F, 16.2. $C_9H_5BrF_2$ requires C, 46.8; H, 2.2; F, 16.5%). *N.B.* With CF_2BrCl the same procedure was used and compound (2) was obtained in a 20% yield.

The 5,5-Dimethylcyclohexane-1,3-dione Enol Ethers (3) *and* (4).—5,5-Dimethylcyclohexane-1,3-dione (4.2 g, 0.03 mol) was dissolved in $CHCl_3$ (80 ml). Benzyltriethylammonium chloride (300 mg) was added as well as 50% KOH (60 ml). Under vigorous stirring CF_2Br_2 (12 g, 0.06 mol) was added as drops in 0.5 h. The organic phase was separated off and the water phase extracted with $CHCl_3$. The different organic phases were combined, washed with water, and dried ($MgSO_4$). A bulb-to-bulb distillation (at 0.01 mmHg) gave a mixture of compounds (3) and (4) (1.9 g) which was purified by thin layer chromatography [pentane–diethyl ether, 1 : 1)]. *Compound* (3) (500 mg, 6%) gave δ 1.08 (3 H, s, Me), 2.22 (2 H, s, CH_2), 2.35 (2 H, s, CH_2), and 5.8 (1 H, s, CH=); δ (^{19}F) 16.7 (d, CF_2Br, $^5J_{HF}$ 2 Hz); $\nu_{max.}$ (CCl_4) 1 686—1 646 cm^{-1} (Found: C, 40.5; H, 4.4. $C_9H_{11}BrF_2O_2$ requires C, 40.2; H, 4.1%). *Compound* (4) (960 mg, 17%) gave δ 1.10 (3 H, s, Me), 2.20 (2 H, s, CH_2), 2.33 (2 H, s, CH_2), 5.4 (1 H, s, CH=), and 6.42 (1 H, t, CF_2H, $^2J_{HF}$ 69 Hz); δ (^{19}F) 84 (d, CF_2H $^2J_{FH}$ 69 Hz); $\nu_{max.}$ (CCl_4) 1 674—1 642 cm^{-1} (Found: C, 57.2; H, 6.4. $C_9H_{12}F_2O_2$ requires C, 56.8; H, 6.4%).

* As simple enolates do not give any condensation products with CF_2Br_2 it is better to use enamines to synthesize α-bromodifluoromethyl ketones (ref. 1*c*).

Diethyl α-Bromodifluoromethyl-α-methylmalonate (7).—Sodium hydride (50% in oil, 4.8 g, 0.1 mol) was added to dry THF (150 ml) under nitrogen. Diethyl α-methylmalonate (17.5 g, 0.1 mol) was added as drops at room temperature. The mixture was cooled to 0 °C and CF_2Br_2 (21 g, 0.1 mol) was added as drops. After being warmed to room temperature for 2 h, water (20 ml) was added. The organic phase was separated off and dried (sodium carbonate). THF was evaporated off and the mixture was distilled with a spinning band column. In the first fractions of the distillate some diethyl α-difluoromethyl-α-methylmalonate (10) appeared but it was not possible to isolate the pure product. Then the pure *malonate* (7) was obtained (10.5 g, 35%), b.p. 99 °C at 12 mmHg; δ 1.3 (3 H, t, CO_2CH_2-*Me*), 1.7 (3 H, s, C=*Me*), and 4.3 (2 H, q, CO_2CH_2Me); δ (^{19}F) 41.7 (s, CF_2Br) (Found: C, 35.2; H, 4.3; Br, 26.3. $C_9H_{13}BrF_2O_4$ requires C, 35.6; H, 4.3; Br, 26.3%).

Diethyl α-Bromodifluoromethyl-α-ethylmalonate (8).—The same procedure as described above was used. From diethyl α-ethylmalonate (18.9 g, 0.1 mol), the *malonate* (8) was obtained after spinning band distillation (13.5 g, 45%), b.p. 104 °C at 15 mmHg; δ 1.2 (6 H, 2t, CO_2CH_2Me, C–CH_2Me), 2.2 (2 H, q, C–CH_2Me), and 4.3 (2 H, q, CO_2CH_2Me); δ (^{19}F) 41.5 (s, CF_2Br) (Found: C, 37.6; H, 4.8; Br, 25.05. $C_{10}H_{15}BrF_2O_4$ requires C, 37,8; H, 4.8; Br, 25.2%). *N.B.* With CF_2BrCl the same procedure was used to give compound (8) in a 35% yield.

Diethyl α-Bromodifluoromethyl-α-phenylmalonate (9).—From diethyl α-phenylmalonate (23.6 g, 0.1 mol), the pure *α-phenylmalonate* (9) was obtained (7.2 g, 20%), b.p. 175 °C at 15 mmHg; δ 1.2 (3 H, t), 4.3 (2 H, q), and 7.3 (5 H, s); δ (^{19}F) 41.7 (s, CF_2Br) (Found: C, 46.2; H, 4.1; Br, 21.8. $C_{14}H_{15}BrF_2O_4$ requires C, 46.0; H, 4.1; Br, 21.9%).

Ethyl α-Bromodifluoromethyl-α-cyano-α-ethylacetate (14).—Sodium hydride (50% in oil, 4.8 g, 0.1 mol) was added to dry dimethylformamide (DMF) (150 ml) under nitrogen. Ethyl cyanoacetate (11.3 g, 0.1 mol) was added as drops. After the addition was completed, EtBr (11 g, 0.1 mol) was added and the mixture was stirred at room temperature for 20 h. 15% HCl (100 ml) was added, the aqueous phase was extracted with diethyl ether, and the organic phase was dried (sodium carbonate). Diethyl ether was evaporated and the residue distilled to give cyano-α-ethylacetate (13) (8.7 g, 60%), b.p. 55 °C at 0.02 mmHg. To a suspension of sodium hydride (1 g, 0.02 mol) in THF (50 ml) was added, at 0 °C and under nitrogen, the cyanoacetate (13) (2.8 g, 0.02 mol). When the addition was complete (dissolution of the salt), CF_2Br_2 was added as drops (8.4 g, 0.04 mol). After the usual work-up (see above) the *cyanoacetate* (14) was obtained by distillation (1.5 g, 30%), b.p. 45 °C at 0.02 mmHg; δ 1.0 (6 H, 2t, CO_2CH_2Me, C–CH_2Me), 1.5 (2 H, q, C–CH_2Me), and 4.5 (2 H, q, CO_2CH_2Me); δ (^{19}F) 54.2 (2 F, CF_2Br, J_{AB} 19.7 Hz); $\nu_{max.}$ (CCl_4) 2 260—1 740 cm^{-1}; *m/e* 269—271 (M^+) and 224—226 (M − Et). The instability of the product allowed no elemental analysis to be made.

α-Bromodifluoromethyl-α-ethylmalononitrile (17).—The same procedure as above was used to obtain α-ethylmalononitrile (16) (35%), b.p. 55 °C at 0.5 mmHg. To a suspension of sodium hydride (1.2 g, 0.025 mol) in THF (100 ml) was added, at 0 °C under nitrogen, α-ethylmalononitrile (16) (2.5 g, 0.025 mol). CF_2Br_2 (10.5 g, 0.05 mol) was then added as drops. After the usual work-up and distillation the *malononitrile* (17) was obtained (1.2 g, 40%), b.p. 45 °C at 0.5 mmHg; δ 1 (3 H, t) and 1.5 (2 H, q); δ (^{19}F) 50.9 (s, CF_2Br); $\nu_{max.}$ (CCl_4) 2 280 cm^{-1}; *m/e* 243 (M − Br). The instability of the product allowed no elemental analysis to be made.

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