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TRAPPING OF THE TRIBROMOMETHYLANION BY ELECTRON POOR ALKENES

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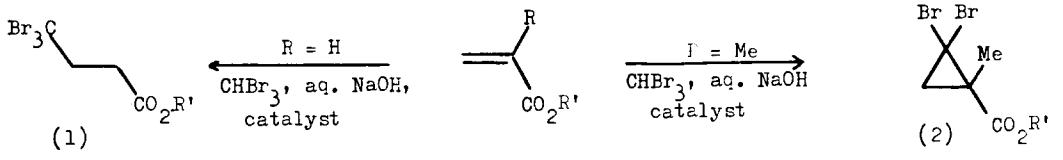
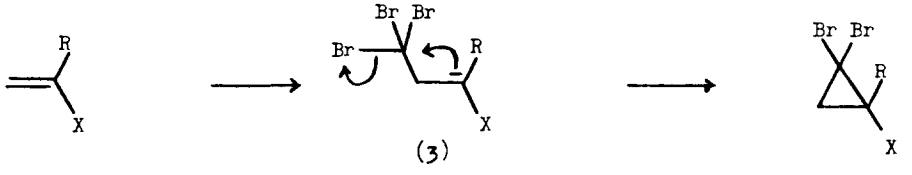
α-Bromoacrylates, α-bromoacrylonitrile and diethyl alkylidenemalonates all react with bromoform and base under phase transfer conditions to give dibromocyclopropanes. When a γ-bromine is present in a crotonate or an alkylidenemalonate, the intermediate derived by Michael addition of tribromomethylanion is trapped by cyclisation at that position to produce a (tribromomethyl)cyclopropane.

The reaction of a number of α- and β-alkylacrylates and acrylonitriles with bromoform or chloroform and aqueous base under phase transfer conditions is known to lead to dihalocyclopropanes, in a process which has been described as a dihalocarbene addition [1], whereas unsubstituted acrylates and acrylonitrile lead to products derived by Michael type addition of the trihalomethylanion, eg.:[2]



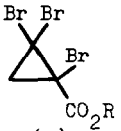
Although an α-methyl group is known to increase the rate of dihalocarbene addition to an alkene[3] and may be expected to reduce the rate of Michael addition of an anion, it is not clear that the combination of these effects would be sufficient to cause such a dramatic change in mechanism. An alternative possibility involves initial anion addition to produce (3), followed by elimination of halide ion and cyclisation to give (2):[4]

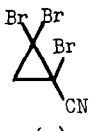


Though this route is well known in the cyclopropanation of electron poor alkenes by α-haloesters and base - where a relatively activated halogen is

lost in the final step,[5] it may be expected to be less favoured in the case of displacement of halogen from a trihalomethyl-group. However, we now provide evidence for this mechanism in the case of bromoform reactions.

The presence of ester, nitrile or halogen substituents on an alkene is known to dramatically reduce the rate of reaction with dihalocarbenes generated by thermolysis of phenyl trihalomethyl mercuries.[6] However, when ethyl or methyl α-bromoacrylates were treated with bromoform and 50% aq. sodium hydroxide in the presence of TEBA (benzyltriethylammonium chloride) for 4h at 20 °C the cyclopropanes (4, R=Me,Et) were obtained (40,21%); longer reaction times led to more complex products , including (4).[7] In the same way, treatment of α-bromoacrylonitrile with bromoform and base in the presence of TEBA led to (5)(39%).[8]


(4)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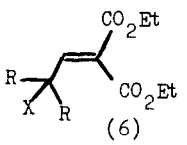
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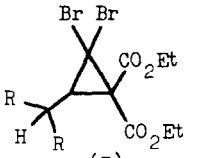
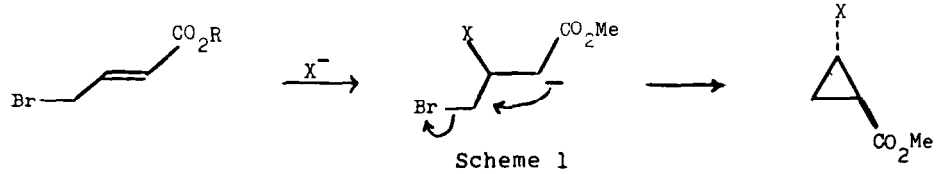

(7)


(8)

Perhaps more dramatic is the fact that alkylidenemalonates can also be cyclopropanated by treatment with bromoform and base. Thus, under the same conditions as described above, diethyl ethylidenemalonate (6,R=X=H) was converted to (7,R=H) [9](77%) in 1h at 20°C and diethyl iso-butylidenemalonate (6,R=Me,X=H)[10] gave (7,R=Me)(69%).[11] When these reactions were repeated with chloroform in place of bromoform the starting materials were consumed but only complex mixtures were obtained.[12] However, the reactions with bromoform-base were rapid compared to carbene addition to alkyl-substituted alkenes. When a 1:1 mixture of (6,R=X=H) and ethyl acrylate was treated with a deficiency of bromoform in the presence of aq.NaOH-TEBA, a 1:2 mixture of (1,R' = Et) and (7,R=H) was obtained; under the same conditions, competition between ethyl acrylate and 2,3-dimethylbut-2-ene in reaction with $CHBr_3$-base-TEBA led predominantly to (1, R' = Et) rather than (8) (ca. 26:1).

The rapid formation of the cyclopropanes (7) from alkenes having two ester groups at the 1-position seems unlikely to be the result of addition of the normally electrophilic species dibromocarbene. The simplest explanation is a Michael addition followed by cyclisation with displacement of bromide ion from the tribromomethyl group.

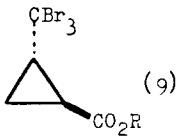
In order to prove the intermediacy of an anion in these reactions, γ-bromocrotonates were treated with haloform and base under phase transfer conditions. γ-Bromocrotonates are known to react with nucleophiles by initial Michael addition followed by cyclisation with loss of bromide ion:[13]



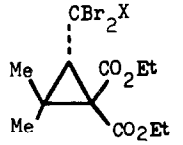
Scheme 1

Methyl γ-bromocrotonate was stirred for 6h at 20°C with one equivalent of

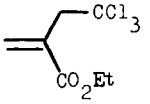
bromoform and excess 50% aq. NaOH in the presence of TEBA. A single product, (9,R=Me), was isolated (41%).[14] The two ring hydrogens adjacent to ester and tri- bromomethyl-groups (δ_H 2.2 and 2.9) each appeared as double double doublets with coupling constants of 4, 6, and 10Hz.Since each showed only one cis- coupling constant (10Hz) the overall stereochemistry has to be trans-. The geminal hydrogens appeared as an unresolved multiplet (δ_H 1.6) even at 300MHz.[14] In the same way ethyl γ-bromocrotonate led to (9, R=Et)(46%).[15] The formation of (9) is consistent with initial trapping of the tribromomethyl-anion by the γ-substituted alkene followed by displacement of bromide as in Scheme 1 ($X^- = Br_3C^-$). However, direct comparison with the non-brominated alkene methyl crotonate is not simple, as α,β-unsaturated esters with an α-hydrogen lead to very complex products on reaction with either chlorform or bromoform and base under phase transfer conditions[16]. Treatment of diethyl (2-bromo-2-methyl- propylidene)malonate (6, R=Me, X=Br)[17] with bromoform-aq.NaOH-TEBA for 3h at 20°C led to (10, X=Br)(43%).[18]



(9)



(10)



(11)

In this case the corresponding non-brominated alkene was dibromocyclo-propanated under the same conditions.

Although the above results implicate the tribromomethylanion in a number of cyclopropanations, the pattern of reactivity is apparently different from that observed in chloroform reactions. However, it is interesting to note that ethyl α-bromomethylacrylate is converted to (11) by reaction with chloroform and base under certain conditions. This has been described as a nucleophilic displacement of bromide ion by $^-CCl_3$,[19] but could equally represent a Michael addition of the anion followed by bromide loss.

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1. P.Weyerstahl, "Dihalocyclopropanes", in The Chemistry of Functional Groups, Eds. S.Patai and Z.Rappoport, Suppl.D.
2. E.V.Dehmlow, "Phase Transfer Catalysis", Verlag Chemie.
3. R.A.Moss in "Carbene Chemistry", Vol.1, Ed. W.M.Jones and R.A.Moss, Wiley.
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5. See eg., K.Nishiyama and Y.Inouye , Agric.Biol.Chem., 1982, 46, 1027; M.Joncla and J.le Brun,Tetrahedron Letters, 1985, 3001.
6. R.A.Moss and R.C.Munjal, Tetrahedron Letters, 1979, 4721.
7. Compound (4,R=Me) showed δ_H 1.95(1H, d, J 9.5Hz), 2.7(1H, d, J 9.5Hz), 3.8 (3H, s); δ_C 26.4, 36.1, 38.1, 54.0, 165.7.

8. Compound (5) showed δ_H 1.82 (1H, d, 7Hz), 2.55(1H, d, J 7Hz); δ_C 29.8, 31.8, 42.4, 126.4. When a mixture of α-bromoacrylonitrile and acrylonitrile was treated with a deficiency of bromoform in the presence of aq.base-TEBA, only the product from the latter, 4,4,4-tribromobutyronitrile, was observed.
9. Compound (7,R=H) showed δ_H 1.3(3H, d, J6.6Hz), 1.3(6H, d, J 7Hz), 2.55 (1H, q, J 6.6Hz), 4.2 (4H, m); δ_C 13.1, 14.0, 31.5, 35.2, 44.5, 61.9, 62.7, 163.0, 164.9. The presence of only nine signals in the ^{13}C n.m.r. spectrum was presumably due to accidental overlap of a pair of carbons (probably the carbons of the ester methyl groups , which appeared as a very large signal at δ14.0).
10. A.C.Cope, C.M.Hofmann, C.Wyckoff, and E.Hardenbergh, J.Amer.Chem.Soc., 1941, 63, 3452.
11. Compound (7,R=Me) showed δ_H 1.09 (3H, d,J 6.5Hz), 1.20 (3H, d,J 6.5Hz), 1.31(3H, t, J 7.1Hz), 1.33 (3H, t, 7.1Hz), 1.69 (1H, d.sept.,J 10.8, 6.5Hz), 2.22(1H, d, J 10.8Hz), 4.3(4H, m); δ_C 13.9, 14.0, 20.6, 20.7, 28.9, 29.6, 44.8, 47.4, 61.9, 62.7, 163.5, 165.4.
12. However, reaction of methyl α-methoxycrotonates with chloroform-aq.NaOH-TEBA led to the corresponding dichlorocyclopropane(47%). This has previously been prepared from the alkene and dichlorocarbene generated from phenyl trichloromethylmercury (T.Ando, A.Yamanaka, M.Matsumoto, T.Ishihara and H.Yamanaka,Chem.Lett., 1973, 1133).
13. R.Vehre, N.deKimpe, L.deBuyck, D.Courtheyn and N.Schamp, Bull.Soc.Chim.Belg., 1977, 86, 55; R.Vehre, Synthesis, 1978, 530; J.R.Dawson and R.D.Little, J.Amer.Chem.Soc., 1978, 100, 4607; J.A.Day, G.R.S.C.Thesis, Thames Polytechnic, 1981.
14. Compound (9,R=Me) showed δ_H 1.6(m,2H), 2.2(1H, ddd, J 10, 6, 4Hz), 2.9(1H, ddd, J 10, 6, 4Hz), 3.7(3H,s); δ_C 19.0, 25.2, 38.5, 45.0, 52.3, 171.5. When methyl γ-bromocrotonate and methyl methacrylate were treated with a deficiency of bromoform in the presence of aq.NaOH-TEBA, (9,R=Me) was formed and methyl methacrylate remained unreacted.
15. Reaction of either ethyl or methyl γ-bromocrotonates with chloroform-aq.base-TEBA led to intractible gums.
16. See eg., E.V.Dehmlow, Liebigs Ann. Chem., 1972, 758, 148; E.V.Dehmlow and G.Hofle, Chem.Ber., 1974, 107, 2760.
17. R.Vehre, N. De Kimpe, L.De Buyck, D.Courtheny, and N.Schamp, Bull.Soc. Chim.Belg., 1978, 87, 215.
18. Which showed δ_H 1.23 (3H, s), 1.29 (3H,t, J7.3Hz), 1.32 (3H,t, J7.3Hz), 1.78 (3H,s), 3.39 (1H, s), 4.1-4.3 (4H, m); δ_C 13.6, 14.1, 15.3, 24.0, 30.1, 35.0, 47.4, 55.0, 61.5, 62.2, 164.6, 166.9. Confirmation of this structural assignment was obtained by reduction to (10, X=H) by reaction with sodium borohydride in methanol; the product showed a characteristic doublet for the hydrogen of the dibromomethyl-group at δ 5.9 (J 11Hz).
19. W.M.P.Johnson and G.Holan, Aust.J.Chem., 1981, 34, 2461.

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