Pergamon

Tetrahedron Letters 40 (1999) 1459–1462

TETRAHEDRON
LETTERS

Reaction of Diethyl Dibromomalonate with Methoxide: Evidence for a Novel Bromophilic Attack

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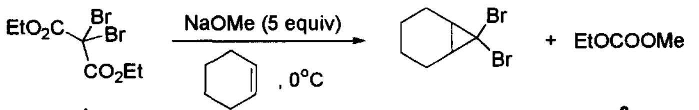
Received 10 November 1998; revised 21 December 1998; accepted 22 December 1998

Abstract: Reaction of diethyl dibromomalonate (**1**) with sodium methoxide in cyclohexene yields dibromonorcarane (**2**) as the major product. This product forms *via* the capture of dibromocarbene (**4**) by cyclohexene. Dibromocarbene, in turn, is generated from ethyl tribromoacetate (**6**) which evidence suggests arises via a bromophilic attack between the carboethoxydibromomethyl carbanion (**7**) and diethyldibromomalonate (**1**). © 1999 Elsevier Science Ltd. All rights reserved.

Nucleophilic substitution reactions are among the most-studied and well-established of all organic chemical reactions.[2] Although the center at which this reaction takes place is almost invariably a carbon atom, there is a growing interest in nucleophilic attacks at atoms other than carbon.[3] Of particular interest has been nucleophilic substitutions at halogens. Known as halophilic reactions, these reactions have been observed in a variety of substrates including halogenated aliphatic nitro-compounds,[4] perhaloalkanes,[5] N-halo-acetanlides[6] and succinimides,[7] and α-halosulfones.[8] Nucleophiles employed in these halophilic reactions have included α-sulfonyl carbanions,[8a] thiolates,[8b,9] sulfinates,[8b] amines,[5d,6] carbanions,[5a,5f,5g,5h] phosphonium ylides,[5e] alkoxides,[5c] and phenoxides.[5b,5c] At first glance, the polarization of the carbon-halogen bond should make halophilic attack unfavorable. Generally, halophilic attacks are observed only when the nucleophile is polarizable (soft) and the leaving group (usually carbon) is particularly stabilized as the anion.[3]

Our own interest in this area was sparked from an unexpected result in our attempt to prepare bromocarboethoxycarbene[10] *via* the reaction of sodium methoxide with diethyldibromomalonate (**1**) in cyclohexene. Thus, when **1** was reacted with an excess of sodium methoxide suspended in cyclohexene (eq 1), the major product isolated was dibromonorcarane (**2**). The only other product detected (GC) was ethyl methyl carbonate (**3**). Dibromonorcarane (**2**) was obtained in 60% yield[11] under optimized reaction conditions which consisted of running the reaction at 0°C and using 5 equiv of sodium methoxide. There was no sign of dibromonorcarane (**2**) in the complex product mixture that resulted when methanol was included in the reaction.[12]



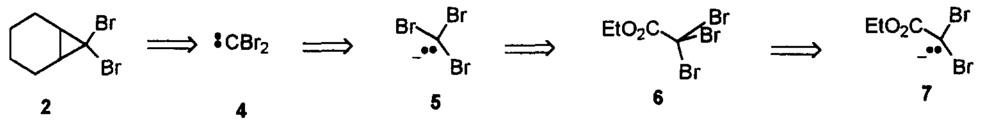
(eq 1)

1 **2** **3**

PII: S0040-4039(99)00024-6

As to the origin of **2**, we reasoned that it most likely resulted from the capture of dibromocarbene (**4**) by cyclohexene (Scheme 1). It seemed unlikely to us that **4** formed through a base-promoted decomposition of **1** by a concerted mechanism or *via* a concerted decomposition of carbanion 7 (the expected initial intermediate in the reaction of **1** and methoxide ion) into **4**, carbon monoxide, and ethoxide ion.[13] Knowing that dihalocarbenes are readily generated from trihalomethyl carbanions by loss of a halide ion we postulated that **4** could have come from tribromomethyl carbanion **5**. In turn, we felt that carbanion **5** could have originated from ethyl tribromoaceatate (**6**) which should readily undergo carbonate cleavage with methoxide in to give ethyl methyl carbonate and **5**. Finally, it seemed plausible to us that ethyl tribromoacetate could be formed through a novel bromophilic reaction between **1** and ethyl dibromoacetate carbanion 7, a likely intermediate in the reaction between **1** and methoxide ion.

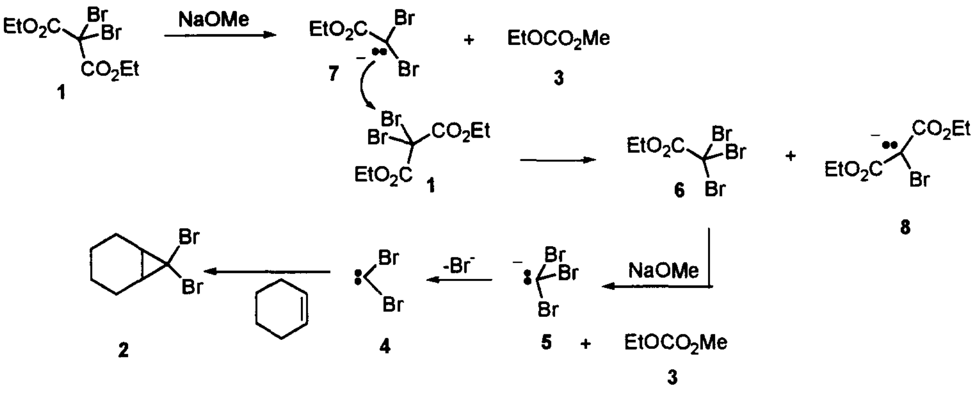
Scheme 1



Our proposed multi-step mechanism for the reaction in eq. 1 is outlined in Scheme 2. In order to gain evidence in support of our mechanistic scheme we first attempted to trap any carbanionic intermediates such as 5,7, and **8** which may be formed in the reaction. We chose p-nitrobenzaldehyde as our trapping agent since this aldehyde has been shown to readily react with trichloromethyl carbanion to give 1-(p-nitrophenyl)-2,2,2-trichloroethanol.[14] Reaction of a cyclohexene/ethylene glycol dimethyl ether solution of **1** with sodium methoxide in the presence of p-nitrobenzaldehyde gave a mixture which could not be separated by silica gel column chromatography. Nevertheless, the ^{1}H-NMR of the mixture was similar in many respects to the spectrum of an authentic sample of 1-(p-nitrophenyl)-2,2,2-tribromoethanol. Although this result suggested that we may have trapped the tribromomethyl carbanion **5**, we were interested in a more definitive experiment. As seen in Scheme 2, formation of **2** by our proposed mechanism requires two equiv of methoxide. Thus, we reasoned that if **1** was reacted with a limited amount of sodium methoxide we should be able to stop the reaction after the bromophilic attack. Stopping the reaction after the bromophilic attack would give ethyl tribromoacetate (**6**). Indeed, when we reacted **1** with 0.5 equiv of sodium methoxide in cyclohexene we found in addition to recovered starting material (63%), ethyl tribromoaceate (**6**) and ethyl dibromoaceatate in 28% and 11% yields, respectively.

Further compelling evidence for bromophilic attack in our reaction was obtained when we showed that **6** is formed when **1** is reacted with carbanion 7 which was prepared independent of step 1 in Scheme 2. Carbanion 7 was prepared by treating ethyl dibromomalonate with sodium hydride in THF at 0^{o}C.[5f] The addition of a THF solution of **1** yielded ethyl tribromoacetate (**6**) and diethyl bromomalonate as the only product.[15] Not only does this finding support bromophilic attack on **1** by 7, this result effectively eliminates an alternate mechanism for the formation of ethyl tribromoaceate (**6**) which involves bromination of 7 by methoxy hypobromite[16] which in turn could be generated by bromophilic attack of **1** by methoxide ion. Although methoxide is probably "too hard"[17] to attack a bromine on **1** we felt we had to consider this possibility in light of recent reports demonstrating halophilic attack on carbon-halogen bonds by oxygen nucleophiles.[18]

Scheme 2



In our reaction we propose a two-electron S_N2-type mechanism with bromine attack. An alternate mechanism exists and involves single electron transfer from carbanion 7 to a bromine in 1 to initiate a radical chain process. This single electron transfer (SET) mechanism has been proposed for some halophilic reactions.[3] With the objective of eliminating the possibility that our reaction involves a radical chain process, we repeated the experiment in the presence of the radical chain-inhibitor nitrobenzene.[8b] We observed no alterations in the yield of dibromonorcarane (**2**) with the added nitrobenzene,[19] thus suggesting that our reaction is most likely a polar reaction involving a two-electron attack of carbanion 7 on a bromine in **1**.

To the best of our knowledge, this is the first reported example of bromophilic attack on diethyl dibromomalonate (**1**) by a carbon anion. It is interesting to note that bromophilic attack on **1** has been implicated in the reactions of **1** with tertiary stibines[20] and tertiary phosphines.[21] The shift of the center of S_N2 attack from carbon to bromine in these reactions is apparently due to the carboethoxy groups. These strong electron-withdrawing groups polarize the carbon-bromine bonds, giving the bromine atoms a partial positive charge. Simultaneously, these groups also stabilize the carbanion which results from removal of one of the bromines as a cation. The range of nucleophiles capable of undergoing a bromophilic reaction with **1** is currently being investigated.

Acknowledgments. We acknowledge the Grote Chemistry Fund and the UC Foundation for financial support. Support from the National Science Foundation ILI Program to purchase a Gemini 300 NMR instrument is also gratefully acknowledged.

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(11) Yield based on our mechanism which requires two moles of **1** for each one mole of **2** formed.

(12) Although the complex product mixture obtained from this experiment was not fully characterized, the ^{1}H-NMR spectrum of the mixture was consistent with products reported by others in the reaction of **1** with alkoxides in alcohol solutions; see Wakui, T.; Otsuji, Y.; Imoto, E. *Nippon Kagaku Kaishi* 1974, *9*, 1686-1690.

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(15) Ethyl tribromoacetate (**6**) was formed in 75% yield after a suitable work-up and correction for recovered starting material.

(16) Hypohalites are known to halogenate carbanions; for example see Anbar, M.; Dostrovsky, I.; Samuel, D.; Yoffee, A. P. *J. Chem. Soc.* 1954, 3603-3611.

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