"Reactivity pattern of α-bromo & α,α-dibromoderivative of carbonyl compounds"

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INTRODUCTION: The synthetic utility of α-halocarbonyl compounds is well known for more than a century. They have been widely used as versatile intermediates in organic synthesis. However, there has been considerable recent interest in the development of alternative approaches avoiding the use of these reagents because of their highly lachrymatory properties. In an important development, it has been shown that α,α-dihalocarbonyl compounds behave as synthetic equivalent of their corresponding α-halocarbonyl compounds.
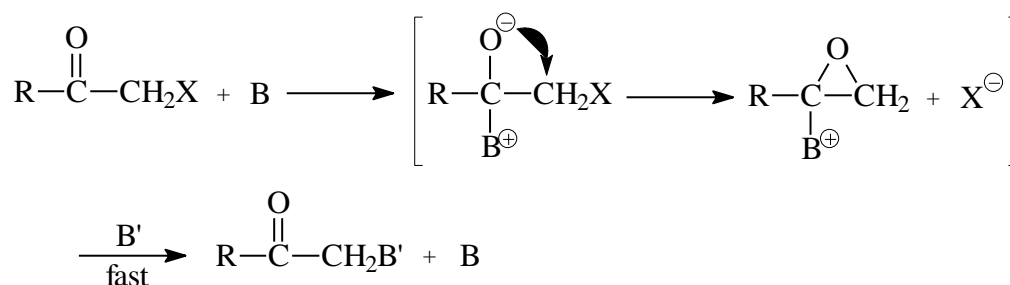
α-Haloketones (α-HK)

α-Haloketones (α-HK), first obtained and described as early as the end of the eighteenth century, have attracted increasing attention in view of their high reactivity as building blocks for the preparation of compounds of various classes due to their selective transformations with different reagents. A myriad of biologically active heterocyclic systems and a number of other useful organic compounds have been synthesized, starting from α-HK. The following description presents general considerations on the reactivity of α-HK with nucleophiles.

General Reactivity Pattern

The well-known reactivity of α-HK towards nucleophilic reagents has been the subject of several discussions. On treatment of an α-HK with various nucleophiles, the attack can take place at six possible electrophilic sites: The nucleophile is able to attack the carbon of the carbonyl function (position 1), the carbon atom carrying the halogen atom (position 2) and the halogen atom (position 3). In addition, due to the presence of two polar electron withdrawing groups, namely the carbonyl function and the halogen atom, the hydrogen atoms in the α-, α'- and β-positions also become susceptible to attack by nucleophiles (positions 4, 5, 6).

The interaction between the carbonyl group and the nucleophile is mainly electrostatic and the SN_2 reactivity is due to polarization interaction caused by smaller steric requirement of RCO as compared to RCH_2 (**eq 1.1**).

$$(1.1)$$

The high reactivity of α-halocarbonyl system has also been explained by proposing (i) enolate like transition state, **1** and (ii) bridging of the nucleophile between the α-carbon and the carbonyl carbon, **2**.

The isolation of moderately stable epoxides in the reaction of an α-HK with sodium methoxide and the evidence that these epoxides are reactive intermediates leading to other products of the reaction gives rise to another possible mechanism for the reaction of α-HK with bases (**eq 1.2**).

$$R-\overset{\overset{O}{\|}}{C}-CH_2X \; + \; B \; \longrightarrow \; \left[\; R-\overset{\overset{O^{\ominus}}{|}}{\underset{\overset{|}{B^{\oplus}}}{C}}-CH_2X \; \longrightarrow \; R-\overset{\overset{O}{|}}{\underset{\overset{|}{B^{\oplus}}}{C}}-CH_2 \; + \; X^{\ominus} \; \right]$$

$$\xrightarrow[\text{fast}]{B'} \; R-\overset{\overset{O}{\|}}{C}-CH_2B' \; + \; B$$

(1.2)

It is noteworthy that the reactivity of α-HK is due to the inductive effect of the carbonyl group, which enhances the polarity of the carbon-halogen bond by increasing the electron deficiency at the α-carbon atom. Also, the more polar the C-X bond, the faster the reaction with nucleophiles.

In majority of cases, initial reaction is the nucleophilic substitution of the α-halogen. The initially formed α-functionalized ketones may undergo further reactions intramolecularly or intermolecularly depending upon the structural features present in the α-functionalized ketones and also on the reaction conditions and reagents employed. One of the extremely useful and significant aspects of these reactions is to achieve the synthesis of a wide variety of heterocyclic compounds.

α,α-Dihaloketones (α,α-HK)

α,α-Dihaloketones (α,α-HK) have attracted increasing attention in view of their high reactivity and easy handling as compared to α-haloketones (α-HK). As α,α-dibromoketones (α,α-DK), devoid of lachrymatory property, can be conveniently prepared by bromination of the corresponding methyl ketones, it was thought of interest to investigate the reactivity of these compounds as masked α-bromoketone (α-BK) equivalents. A survey of literature revealed that this particular area has not been much explored. The following discussion presents the general considerations on the reactivity of α,α-DK with nucleophiles.

General Reactivity Pattern

There are certain discrepancies in the literature regarding the general reactivity pattern of α,α-DK mediated reactions as they behave similar to α-BK in some of their reactions while

in other they behave differently. On the basis of commonly accepted considerations and literature data, some possible explanation has been offered.

The literature reports reveal that the reactions of α,α-DK take place mainly in two steps. The first step involves the formation of α-monosubstituted α-haloketones *via* $SN_{(C)}$ mechanism, the second possibility in the first step is the formation of α-HK through $SN_{(X)}$ mechanism and then second step can give rise to various products depending upon several factors (**Scheme 1.1**).
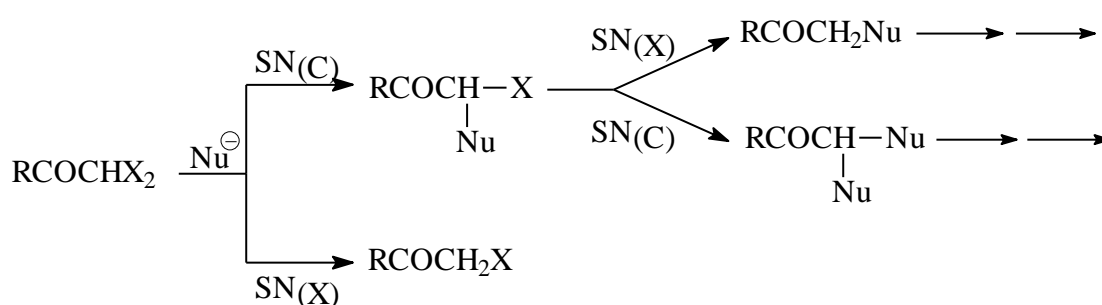

$SN_{(C)}$ = Nucleophilic attack on the Carbon
$SN_{(X)}$ = Nucleophilic attack on the Halogen

Scheme 1.1

It seems that a common step in all the reactions involving α,α-DK with all nucleophiles is the formation of α-substitution product by $SN_{(C)}$ mechanism. Subsequently, further reactions, which take place, depend upon the nature of the heteroatom that acts as a nucleophile, and reaction conditions, thereby giving different results.

Single Electron Transfer (SET) mechanism has also been suggested for α-monosubstituted products from the reaction of α,α-DK by Boeykens and Kimpe on the basis of some experimental evidence (**Scheme 1.2**).

SET = Single Electron Transfer
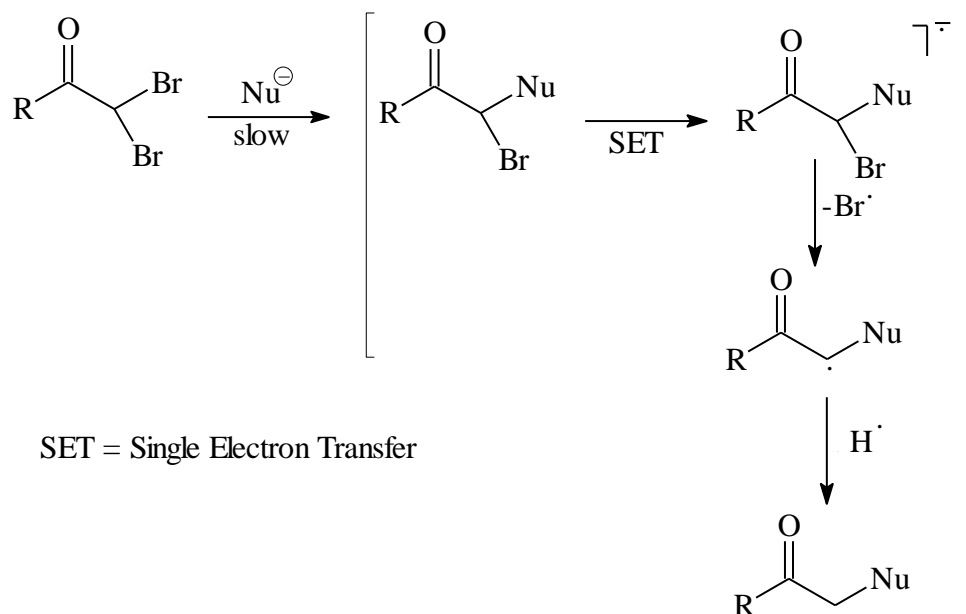
Scheme 1.2

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