Addition of α-Halo-substituted Carbonitriles to and Aldehydes/Ketones in the Presence of Iron Pentacarbonyl

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Abstract—Halo-substituted carbonitriles in the presence of iron pentacarbonyl react with aldehydes and ketones by Reformatsky reaction type. In contrast to halo-substituted esters the nitriles are considerably more reactive toward ketones than aldehydes. At the same time the structure and yield of products obtained from both nitriles and esters are strongly and similarly affected by the character of the para-substituents in the benzaldehyde.

We showed formerly [1], that the addition of α-halo-substituted carboxylic acids esters to aldehydes and ketones by Reformatsky reaction type can be performed in good yields in homogeneous medium in the presence of iron pentacarbonyl (heating at reflux of the reagents mixture in benzene for 2–3 h). This procedure furnished β-hydroxyacids esters or the corresponding derivatives of acrylic acids esters. Therewith the reaction with aldehydes was found to occur very efficiently, and with ketones more difficult. It was shown besides that reactions with para-substituted benzaldehydes were notably affected by the polar character of the substituents: the process with p-chlorobenzaldehyde proceeded like that with benzaldehyde or even better to give hydroxyacids esters whereas anisaldehyde either could not be involved into the reaction or affords only unsaturated products [2] (formally arising from hydroxysterols dehydration).

In this study we used for the first time an iron pentacarbonyl to effect reactions of α-halo-substituted nitriles with aldehydes and ketones by Reformatsky reaction type planning to obtain β-hydroxyacids and further aminoalcohols, synthons for preparation of a number of biologically active substances [3]. It turned out unexpectedly that behavior of nitriles in reactions involving Fe(CO)₅ was essentially unlike that of esters, in contrast to reactions of Reformatsky type carried out in the presence of cromium(II) salts [4].

We brought into the reaction of halonitriles I with carbonyl compounds substrates of dissimilar reactivity: acetonitriles substituted by iodine Ia and bromine Ib, dibromoacetonitrile Ic, and 2-bromopropionitrile Id. As carbonyl compounds II were applied 2-hexanone Ila, acetonophene IIb, cyclopentanone IIc, benzaldehyde IIId, p-chlorobenzaldehyde IIe, p-methoxybenzaldehyde IIff, and pivalaldehyde IIg.

Nitriles Ia, b with ketone Ila afforded hydroxynitrile III. Therewith at the use instead of the highly reactive iodide Ia less active bromide Ib the yield of product III decreased from 70 to 23%. The reaction proceeds along the scheme:

\[
XCH₂CN + \overset{\text{O}}{\text{Fe(CO)₅}} \rightarrow \overset{\text{CN}}{\text{OH}}
\]

\[
\text{Ia, b} \quad \text{IIa} \quad \text{III}
\]

I. X = I (a), Br (b).

These reactions proceeded in the same manner with acetonophene IIb although the yield was low even with the active iodide Ia. As a result were obtained 3-hydroxy-3-phenylbutyronitrile IV and a product of acetonophene aldol condensation. The addition of benzaldehyde IIId occurred unexpectedly inefficiently affording the corresponding hydroxynitrile Va in a low yield (5–8%).

The process involving aldehyde IIe occurred selectively and gave adduct Vb in a high yield whereas with anisaldehyde (IIff, Y = OMe) under the same conditions only the product of a formal dehydration, 3-(p-methoxyphenyl)acrylonitrile VI, was obtained in a yield as low as 12%.

\[
XCH₂CN + Y\text{C}_{6}\text{H}_{5}\text{CHO} \xrightarrow{\text{Fe(CO)₅}} \text{Y}\text{C}_{6}\text{H}_{5} \overset{\text{CN}}{\text{OH}}
\]

\[
\text{Ia, b} \quad \text{IIld, e} \quad \text{Va, b}
\]

II. Y = H (d), Cl (e); V, Y = H (a), Cl (b).
The most reactive of the nitriles studied, dibromoacetanitrile \( \text{Ic} \), afforded the target products in good yield both with benzaldehyde \( \text{IId} \) and methyl butyl ketone \( \text{IIa} \), in somewhat lesser yield with cyclopentanone \( \text{IIc} \). However the reactants carried out at 60°C resulted only in unsaturated compounds (due to elimination of Br and OH). In particular, from benzaldehyde cynamonitrile VII, and from ketone \( \text{IIa} \) 3-methyl-2-heptenylcyanide VIII were obtained. Only at room temperature we succeeded to prepare in plausible yield benzaldehyde adduct IX.

Reactions with \( p \)-chloro- and \( p \)-methoxybenzaldehyde gave rise to \( p \)-chloro VIIa and \( p \)-methoxy VIIb derivatives of nitrile VII.

We believe that in reaction with cyclopentanone the intermediated formed adduct X loses BrOH and the arising cyclopentylideneacetonitrile XI rearranges with a double bond migration into the ring to afford unsaturated adduct XII whose structure is proved by the spectral data.

The difference and similarity in the behavior of haloesters [1] and the corresponding halonitriles studied here is the most clearly seen by an example of reactions between 2-bromopropionitrile \( \text{Id} \) with aldehydes and ketones. Nitrile \( \text{Id} \) reacts both with ketone \( \text{IIa} \) providing hydroxynitrile XIII and with aldehyde \( \text{IId} \) giving adduct XIV, but in the former case the hydroxynitrile yield is twice as large as in the latter.

The situation in analogous reactions of methyl bromopropionate [1] is quite the opposite: the yield with benzaldehyde is considerably higher than with methyl butyl ketone.

With the sterically hindered carbonyl compounds, acetophenone \( \text{Iib} \) and pivalaldehyde \( \text{Ilg} \), both bromopropionitrile \( \text{Id} \) and methyl bromopropionate [1] are approximately equally reactive furnishing adducts XV and XVI in about 30% yield. A similar behavior of esters and nitriles is also observed in reactions with the para-substituted benzaldehydes. In reactions of haloacetonitriles \( \text{Ia, b} \) and of bromopropionitrile \( \text{Id} \) with \( p \)-chlorobenzaldehyde \( \text{IIId} \) the yield of hydroxynitriles \( \text{Vb} \) and XVII attained about 60–90%, whereas with \( p \)-methoxybenzaldehyde \( \text{IIe} \) formed only the corresponding derivatives of acrylonitrile VI or of adduct XVIII in 12–30% yield.

The probable reason of the different behavior demonstrated by nitriles and esters in the reactions under study lies in the analogy with a mechanism we suggested previously [2] that involves the reaction between halonitrile and iron pentacarbonyl to form a radical followed by its reduction to carbanion; the latter in the transition state of A type attacks the C=O group of the electrophile.

Inasmuch as the cyano group is considerably stronger electron-acceptor than alkoxy carbonyl group the reaction site of nitrile is more electron-deficient and naturally should react better with the electrophile possessing higher relative electron density on its reaction site, namely, with ketone.

To the same result should lead the probable change in the reaction mechanism towards prevalence of the radical.