# CYANATION OF HALO DERIVATIVES BY ACETONE CYANOHYDRIN

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*A preparative method is proposed for the synthesis of substituted acetonitriles by the cyanation of halo derivatives by acetone cyanohydrin in the presence of base and phase transfer catalysts.*

The cyanation of halo derivatives (I) by alkali metal cyanides is one of the major methods for the preparation of the corresponding nitriles (II) [1]. However, the use of this method both under laboratory conditions and on an industrial scale is complicated by the high toxicity of the cyanides.

In the present work, we report the cyanation of (I) by acetone cyanohydrin (ACH), which is less toxic and more convenient for use as a reagent. This reaction proceeds upon a heating of a mixture of (I), ACH, and a base taken in 1.0:1.1:0.5-1.0 mole ratio in the presence of 0.5-1.0% phase transfer catalyst (PTC) in a solvent or without solvent and is accompanied by the distillation of acetone. The release of gaseous HCN was not observed during the reaction. This was established according to Houben-Weyl [2]

$$\underset{\text{(I)}}{\mathrm{RR'CHX}} + \mathrm{Me_2C(OH)CN} \xrightarrow[-\mathrm{Me_2CO}]{\text{base, PTC/80-100°C}} \underset{\text{(II)}}{\mathrm{RR'CHCN}}$$

$$\underset{\text{(Ih)}}{\text{4-}\mathrm{ClCH_2C_6H_4CH_2Cl}} + \mathrm{Me_2C(OH)CN} \rightarrow \underset{\text{(IIh)}}{\text{4-}\mathrm{NCCH_2C_6H_4CH_2CN}}$$

$R = Et$, $R' = H$, $X = Br$ (a); $R = 3\text{-}PhOC_6H_4$, $R' = H$, $X = Cl$ (b); $R = 3\text{-}PhOC_6H_4$, $R' = H$, $X = Br$ (c); $R = 2\text{-}MeOC_6H_4$, $R' = H$, $X = Cl$ (d); $R = H_2C = CH$, $R' = H$, $X = Br$ (e); $R = Ph$, $R' = H$, $X = Cl$ (f); $R = R' = Ph$, $X = Cl$ (g), $R = 4\text{-}ClCH_2C_6H_4$, $R' = H$, $X = Cl$ (h).

The yields of (II) depend on the base and PTC used (see Table 1) and reach a maximum of 93-97% using powdered $K_2CO_3$ and dibenzo-18-crown-6 (DB-18-C-6), 18-crown-6 (18-C-6), or 18-C-6 with acetonitrile (18-C-6-AN) as the PTC. $Na_2CO_3$ and $NaHCO_3$ proved less effective. The yield of (II) did not exceed 70% when these salts were used. The cyanation of (I) did not proceed in the presence of organic bases such as $Et_3N$. Strong bases such as NaOH and KOH in combination with crown ethers give virtual complete conversion of (I) to tarry products. However, the formation of (II) is observed in the presence of $Bu_4N^+Br^-$ but the yields do not exceed 30-35% in this case. The use of acetonitrile or benzene as the solvent has virtually no effect on the yield of (II) but markedly facilitates the separation of the liquid products from the solid salts.

Thus, ACH permits us to replace highly toxic cyanides in the preparation of (II) by the cyanation of (I).

## EXPERIMENTAL

The gas-liquid chromatographic analysis was carried out on a Chrom-5 chromatograph with a flame ionization detector on a 200 × 0.2-cm column packed with Chromaton AW-DMCS at 185°C and 30 ml/min as the helium carrier gas flow rate. The course of the reaction was monitored by thin-layer chromatography on Silufol UV-254 plates with 1:1 hexane-benzene as the eluent.

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TABLE 1. Yields of Nitriles RR′CHCN (II) under Conditions for the Cyanation of Halo Derivatives RR′CHX (I) by ACH at 90°C (the (I):ACH mole ratio was 1.0:1.1*)

| R | R′ | X | Base, mole % | Catalyst, % | Solvent | Time, h | Yield of (II), % |
|---|---|---|---|---|---|---|---|
| Et | H | Br | $K_2CO_3$ (50) | DB-18-C-6 (0.8) | Benzene | 5 | 46 |
| 3-$PhOC_6H_4$ | H | Cl | $K_2CO_3$ (100) | 18-C-6 AN (0.7) | MeCN | 6 | 96.5 |
| 3-$PhOC_6H_4$ | H | Br | $K_2CO_3$ (100) | 18-C-6-AN (0.7) | » | 5 | 97 |
| 2-$MeOC_6H_4$ | H | Cl | $K_2CO_3$ (100) | 18-C-6 (1.0) | – | 6 | 95 |
| $H_2C{=}CH$ | H | Br | $K_2CO_3$ (50) | DB-18-C-6 (1.0) | Benzene | 7 | 85 |
| Ph | H | Cl | $K_2CO_3$ (100) | DB-18-C-6 (0.7) | » | 7 | 93 |
| Ph | H | Cl | $K_2CO_3$ (50) | DB-18-C-6 (0.7) | » | 7 | 85 |
| Ph | H | Cl | $K_2CO_3$ (100) | 18-C-6 (1.0) | – | 6 | 94 |
| Ph | H | Cl | $K_2CO_3$ (100) | 18-C-6-AN (0.7) | MeCN | 5 | 97 |
| Ph | H | Cl | $NaHCO_3$ (100) | DB-18-C-6 (0.7) | – | 6 | 64 |
| Ph | H | Cl | $Na_2CO_3$ (100) | 18-C-6 (1.0) | – | 6 | 66 |
| Ph | H | Cl | NaOH (100) | $Bu_4N^+Br^-$ (0.5) | Benzene | 6 | 35 |
| Ph | H | Cl | KOH (100) | $Bu_4N^+Br^-$ (0.5) | » | 6 | 30 |
| Ph | Ph | Cl | $K_2CO_3$ (100) | 18-C-6 (1.0) | MeCN | 6 | 91 |
| 4-$ClCH_2C_6H_4$ | H | Cl | $K_2CO_3$ (200) | DB-18-C-6 (1.0) | » | 10 | 87 |

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*A 2.2-fold excess of ACH was used in the cyanation of (Ih).

**3-Phenoxybenzyl Cyanide (IIb).** A mixture of 26.3 g (0.1 mole) (Ic), 9.35 g (0.11 mole) ACH, 14 g (0.1 mole) $K_2CO_3$, 0.14 g (0.7%) 18-C-6-AN, and 40 ml acetonitrile was heated at reflux for 5 h. The acetone formed was distilled off. The reaction course was monitored by thin-layer chromatography relative to the disappearance of the spot with $R_f$ 0.35. The mixture was cooled at the end of the reaction, filtered, diluted with 50 ml water, and extracted thrice with 40 ml ether. The combined extracts were dried over $MgSO_4$ and evaporated. The residue was distilled in vacuum to give 20.3 g (97%) (IIb), bp 186-190°C (10 mm) [3].

Analogous procedures gave (IIa), bp 115-117°C, $n_D^{20}$ 1.3835 [4], (IId), bp 143°C (15 mm), $n_D^{20}$ 1.5458 [5], (IIe), bp 117-119°C, $n_D^{20}$ 1.4047 [6], (IIf), bp 234°C, $n_D^{20}$ 1.5207 [7], (IIg), mp 71-72°C [8], and (IIh), mp 95-96°C [9].

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