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THE APPLICATION OF THE FRIEDEL-CRAFTS ALKYLATION TO ω-HALOALKANENITRILES. SYNTHESIS OF ω-ARYLALKANENITRILES

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Acrylonitrile plus hydrogen chloride and 3-chloropropionitrile have been used in Friedel-Crafts alkylations of highly activated aromatic substrates e.g. resorcinol,[1,2] orcinol,[1] phenol,[3] o-cresol,[4] p-cresol,[5] and anisole.[6]

Perhaps because of the expectation of rearrangements of the type shown by n-alkylhalides in Friedel-Crafts alkylations,[7-9] to my knowledge no studies have been carried out using ω-haloalkanenitriles with benzene or with ω-haloalkanenitriles longer than 3-chloropropionitrile with the exception of one compound prepared using 4-chlorobutyronitrile and resorcinol.[1] γ-Butryolactone has been reported to give a moderate yield (44%) of γ-phenylbutyric acid without rearrangement in the Friedel-Crafts reaction.[10] It has been stated that 5-chlorovaleric acid gives a better yield in the Friedel-Crafts reaction than valerolactone.[11]

In connection with other studies, a series of ω-arylalkanenitriles were synthesized by a 5-7 step procedure featuring a Friedel-Crafts acylation using succinic anhydride[12] or the half ester-half acid chloride of a dibasic acid.[13] With authentic samples of the desired compounds in hand, the direct (one step) Friedel-Crafts alkylation was investigated. It was felt that rearranged products could be easily detected by NMR spectroscopy and vapor phase chromatography. The NMR spectrum of s-butylbenzene clearly shows the unequal doublet for the α-CH_3 group centered at 1.20 PPM.[14] This area in the NMR spectra of the known ω-arylalkanenitriles shows only end absorption and the unequal doublet of any secondary type product should be clearly superimposed.

General Procedure

The ω-haloalkanenitrile[15] (0.4 mole) was dissolved in benzene (1 l.). The mixture was cooled to +6° and with stirring finely powdered anhydrous aluminum chloride (0.84 mole)[16] was rapidly added. The first half of the addition was mildly exothermic and the temperature rose to 15°. The mixture was warmed and became mostly homogeneous. The evolution of hydrogen halide began between 45-50°. After a 2 hr reflux period, the cooled mixture was poured on to a stirred mixture of ice cubes and 18% hydrochloric acid. The organic layer was separated and the aqueous solution was extracted with ether. After drying ($MgSO_4$) and concentration, the nitrile was purified by vacuum distillation.

4-Chlorobutyronitrile thus affords 4-phenylbutyronitrile (I)[17] (98%), b.p. 61-63°/0.3 mm, 144-145°/16 mm (reported[18] b.p. 142-145°/16 mm); infrared (film) 2250 cm^{-1} (C≡N). This compound showed superimposable NMR and IR spectra and identical VPC retention time in comparison with the compound prepared by earlier workers.[18] Mild alkaline hydrolysis of the nitrile (I) furnished γ-phenylbutyric acid (II) (95%) m.p. 50-52° (reported[18] m.p. 52°).

5-Bromovaleronitrile thus affords 5-phenylvaleronitrile (III) (98%), b.p. 87-89°/0.2 mm, 158-160°/17 mm (reported[18] b.p. 157-161°/17 mm); infrared (film), 2250 cm^{-1} (C≡N). This product was identical in all aspects with the compound prepared by the earlier method.[18] Conversion of the nitrile (III) using 15% H_2O_2 (excess) and a catalytic amount of NaOH solution furnished 5-phenylvaleramide (IV) (90%), m.p. 108-109° (reported[18] 109°).

6-Bromohexanenitrile thus affords the first evidence of rearrangement using an ω-halo-alkanenitrile in this reaction. This nitrile affords a mixture of 6-phenylhexanenitrile (V) and 5-phenylhexanenitrile (VI) (97%) b.p. 80-90°/0.15 mm. The amount of rearrangement is far less than that reported for n-alkylhalides[7-9] as the proportion of V-VI is 85-15 by VPC. This method is still synthetically useful since a vacuum distillation of the mixture of nitriles through a spinning band column yields V in 67% yield with greater than 98% purity (VPC). The presence of VI is shown in the mixture by the presence in the NMR spectrum of the typical doublet of the CH_3 group alpha to the phenyl and the distinct blurring of the fine structure of the remainder of the spectrum. The position of the CH_3 group was also demonstrated by alkaline hydrolysis of the mixture of nitriles to a mixture of 6-phenylhexanoic acid (VII) and 5-phenylhexanoic acid (VIII) followed by light catalyzed bromination. The expected benzylic bromination under these conditions results in a mixture of 6-bromo-6-phenylhexanoic acid (IX) and 5-bromo-5-phenylhexanoic acid (X) and the removal of the CH_3 doublet in the NMR spectrum of the mixture of brominated acids. In the same spectrum, a triplet appears centered at 4.95 PPM due to the 6-H in IX. Pure V has a b.p. 89-90°/0.15 mm, 163-164°/13 mm (reported[18] 160-164°/13 mm); infrared (film)

2250 cm^{-1} (C≡N). In one attempt at separating V and VI by preparing a crystalline derivative, the mixture of nitriles was treated with a slight excess of 15% H_2O_2 and a catalytic amount of NaOH solution. A VPC on the product showed a 75% conversion to the amides and complete resolution of the four component mixture. Trituration with cyclohexane gave 6-phenylhexanamide (XI) (50%) m.p. 91-93° (reported 90°[20] and 94°[21]). XI synthesized from V prepared by the earlier route[19] gave m.p. 91-93° (recrystallized from cyclohexane).

It was possible that the ratio of V-VI was dependent upon the reaction temperature. Therefore, 6-bromohexanenitrile was used in a variation of the general procedure. After the addition of the aluminum chloride, the reaction mixture was stirred between 10-15° for 4 hr and at 25° for 16 hr. After workup, V and VI were isolated in essentially the same ratio as with the general procedure. However, the yield was lowered to 77% and a higher boiling fraction was present. The room temperature procedure was repeated and the mixture allowed to stand 10 days before workup. The yield of V-VI was 59% and the yield of high boiling material was 36.8%. The latter was a three component mixture by VPC (8.3, 5.7, 86.). Redistillation gave a 27% yield of a 3-1-96 mixture. The major component has been assigned the structure, *m*-benzenedihexanenitrile (XII), based upon the NMR and IR spectra. These spectra have the aromatic pattern typical of a meta substituted benzene. The mass spectrum shows the parent peak at 268. The second component is tentatively assigned the structure 6-[*m*-(4-cyano-1-methylbutyl)phenyl]hexanenitrile (XIII) based upon the presence of a small amount of the unequal doublet of the CH_3 group in the NMR spectrum. The structures of XII and XIII are reasonable since it has been shown that redistribution of side chains under Friedel-Crafts conditions is time dependent[22] and occurs without rearrangement.[23]

These results show that Friedel-Crafts alkylation of benzene with ω-haloalkanenitriles is a high yield, simple, and fast alternative to previous methods of synthesis of ω-arylalkanenitriles. This method should be applicable to any aromatic substrate that has been successfully alkylated using alkyl halides and aluminum chloride.[7-9]

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(15) Commercial samples of these compounds vary between 70-100% and two to ten compounds by VPC analysis. The 4-chlorobutyronitrile and 5-bromovaleronitrile were commercially available at the 100% level and used as such. 6-Bromohexanenitrile was obtained (100%) by distillation through a spinning band column at reduced pressure.

(16) The use of a catalytic amount of aluminum chloride, i.e. 0.1 mole under otherwise identical conditions, resulted in the recovery of unreacted ω-haloalkanenitrile. The reaction proceeds if a catalytic amount of aluminum chloride in excess of an amount equivalent to the moles of ω-haloalkanenitrile is used, i.e., 0.5 mole, however the yield is slightly lower.

(17) All compounds described here gave expected elemental analyses and were 100% by VPC unless otherwise stated. No effort was made to analyze VII-X.

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