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Short Communications

The Synthesis of 3-Bromo-2-fluoronitrobenzene and its Reduction by Copper(I)

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Many efforts were made by various methods to prepare 3-bromo-2-fluoronitrobenzene, which was desired for the purpose to study its reaction with copper(I) chloride.

An attempt to decompose thermally the 2-bromo-6-nitrobenzenediazonium fluoroborate, which was obtained in 59 % yield from 2-bromo-6-nitroaniline (available from previous work [1]) by the method of Lamm and Andersson,[2] was unsuccessful. The decomposition of the fluoroborate in aqueous acetone medium with copper(I) chloride following a description of Bergmann *et al.*[3] as well as the diazotization of 2-bromo-6-nitroaniline in anhydrous hydrogen fluoride followed by heating and decomposing according to Ferm and van der Werf [4] also failed to give the fluoro compound.

A halogen exchange of 3-bromo-2-chloronitrobenzene with potassium fluoride in dimethylformamide by a method described by Finger and Kruse [5] was found to be favourable and gave a yield of 76 % of the 3-bromo-2-fluoronitrobenzene. Finger and Kruse [5] reported that aryl halide-potassium fluoride exchanges are at least 10^3 times faster in a dipolar aprotic solvent (DMF) than in a protic one (methanol). Fluoride ion is much less solvated and thus more powerful as a nucleophile in dipolar aprotic solvents.

The reaction of 3-bromo-2-fluoronitrobenzene in aqueous hydrochloric acid-acetic acid with copper(I) chloride was carried out under an argon atmosphere at 90 °C as described in Ref. 1. After 23 h, 16 % of 3-bromo-2-fluoroaniline was obtained, as determined by GLC and mass spectrum, which had a 1:1 doublet at *m/e* 189 and 191. The remaining part was unreacted 3-bromo-2-fluoronitrobenzene. No fluorine-chlorine exchange products were detected. This is in full agreement with the observation of Bacon and Hill [6] who noticed "no reaction" between 1-fluoronaphthalene and copper(I) chloride in pyridine. In previous work [7] the copper(I) catalysed bromine-chlorine exchange in halonitrobenzenes was found to be about three times faster than the iodine-chlorine exchange. Bacon and Hill [6] give the following order of reactivity for 1-halonaphthalenes with copper(I) chloride in pyridine:
$ArI \approx ArBr > ArCl \gg ArF$.
This agrees with the tendency of different halide ions to formation of the copper(I) halide complexes in aqueous solution; the stability of the complexes increases with increasing atomic number of the halogen. Actually complex formation between copper(I) ion and fluoride ion is unknown. However, in our case, with the assumed approximately tetrahedral copper halide-aryl halide transition state, one must also consider the most favourable geometry.[1]

The observed reduction of the nitro group, which always occurs as a side reaction of about 2 – 3 % in all copper(I) catalysed bromine-chlorine and iodine-chlorine exchange reactions studied by the present author, will be more fully discussed in a following paper [8] concerning alkyl substituted bromonitrobenzenes and experiments with some free radical initiators and inhibitors. With the present compound, 3-bromo-2-fluoronitrobenzene, only one experiment was carried out: 1,4-dihydroxybenzene, known as an inhibitor, was added in equimolecular amount to the nitro compound in the reaction mixture, but no change in the degree of reduction was noticed. In the absence of copper(I) chloride in the dark, neither exchange nor reduction was observed. When the reaction mixture with copper(I) chloride present was irradiated at 30 °C for 2 h at 350 nm, the rate of reduction increased compared to the reduction at 30 °C in the dark. Mechanistic aspects of these results will be discussed in the following paper.[8]

Experimental. Melting points were determined with a Kofler Hot-Stage Microscope.

The GLC investigations were performed on a Perkin Elmer F 11 Hot Wire Gas Chromatograph with a 3 mm o.d. 2 m SE-30 column at 120 °C. Helium was carrier gas and the instrument was equipped with a Varian Model 480 Electronic Digital Integrator.

The ^{19}F NMR spectrum was recorded on a Varian XL-100-15 spectrometer at Instrumentstationen, The Chemical Center, University of Lund.

The irradiation was carried out in a photochemical reactor, Rayonet RPR-100.

The mass spectra were obtained on an LKB 9000 instrument at Crystallography group,

Mass Spectrometric Service at the University of Göteborg.

3-Bromo-2-chloronitrobenzene prepared from 2-bromo-6-nitroaniline by the same method as described for 2-chloro-3-fluoronitrobenzene,[9] gave a yield of 81 % after steam distillation and one recrystallization from hexane, m.p. 57.0 – 58.5 °C, lit.[1] 57.0 – 58.0 °C.

3-Bromo-2-fluoronitrobenzene. 3-Bromo-2-chloronitrobenzene (14.2 g, 0.06 mol, dried over P_2O_5) was boiled for 7 days at 150 °C with 6.95 g (0.12 mol) of commercial anhydrous potassium fluoride (which was heated before use in order to remove all moisture) in 25 ml of dimethylformamide, dried over molecular sieves (4 Å). The reaction was followed by GLC. After 7 days the reaction had gone to 96 – 97 % completion. The yield was 10.0 g (76 %) after steam distillation. After two recrystallizations from hexane and two from methanol, the yield was 2.4 g, m.p. 29.5 – 30.5 °C. 3-Bromo-2-fluoronitrobenzene has apparently not been described in the literature. The mass spectrum revealed a 1:1 doublet at *m/e* 219 and 221, as expected for the desired compound.

^{19}F NMR spectrum for 3-bromo-2-fluoronitrobenzene in $CDCl_3$: 111 ppm upfield from CCl_3F (octet). J_{F-H_5} 1.48 Hz, J_{F-H_4} 5.75 or 6.45 Hz and J_{F-H_6} 6.45 or 5.75 Hz.

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The Role of Oxaloacetate as Feed-back Inhibitor of Isocitrate Lyase in Baker's Yeast

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It has been shown that oxaloacetate competitively inhibits purified isocitrate lyase from *Chorella pyrenoidosa*,[1] *Brevibacterium flavum*,[2] and *Candida guillermondii*.[3] For oxaloacetate to function as a feed-back inhibitor of isocitrate lyase (EC 4.1.3.1) *in vivo*, it must inhibit the lyase in the conditions existing inside the cell. Because the Michaelis constant for *threo*-D_s-isocitrate of isocitrate lyase from *Chlorella* is smaller (23 μM) than the *in vivo* concentration of isocitrate, John and Syrett [1] concluded that the enzyme was normally saturated with its substrate, and therefore that oxaloacetate, a competitive inhibitor, cannot cause significant inhibition *in vivo*. However, the Michaelis constant is much higher (300 μM) for the enzyme from *C. guillermondii*, and Hildebrandt and Weide [3] have concluded that oxaloacetate may be an effective regulator of isocitrate lyase in this organism. For both enzymes inhibition constants are small (37 and 50 μM, respectively). We have investigated the inhibition of isocitrate lyase from baker's yeast, *Saccharomyces cerevisiae* by several intermediates of the TCA cycle. Our results are quite similar to those of Hildebrandt and Weide for *C. guillermondii*,[3] except in the case of oxaloacetate. Reaction rates were estimated by a method which prevented contact between the oxaloacetate and phenylhydrazine reagent used to estimate the product, glyoxylic acid.

Material and methods. A_4 growth-stage baker's yeast from Alko Yeast Factory, Rajamäki, was used. The culture has been described in detail elsewhere.[4] Sodium glyoxylate was from Fluka AG (Buchs, SG., Switzerland), trisodium-DL-isocitrate from the Sigma Chemical Company (St.Louis, Mo., USA) and oxaloacetate from C. F. Boehringer & Soehne GmbH (Mannheim, West-Germany). All other reagents were of analytical grade from E. Merck AG (Darmstadt, West-Germany).

Isocitrate lyase was purified as follows. 100 g baker's yeast was suspended in 250 ml 0.2 M potassium phosphate buffer pH 7.5 Ballotini beads (40 ml, No. 31/12, diameter 0.25 mm) were added to 25 ml fractions and the cells were treated for 6 min in a Mini-mill disintegrator (Gifford-Wood Co., New Jersey, USA) using a rotor speed of 3300 rpm. The cup of the apparatus was kept in an ice-bath during the disintegration.

The protamine sulfate and ammonium sulfate precipitations, dialysis, and chromatography on