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Reductive Defluorination of Polyfluoroarenes by Zinc in Aqueous Ammonia.

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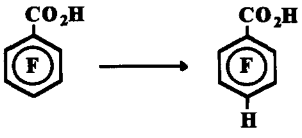
Abstract: Aqueous ammonia has been found to be a good and versatile medium for the reductive defluorination of polyfluoroarenes by zinc. Upon the reduction of pentafluorobenzoic acid, 2,3,4,5,6-pentafluorobenzyl alcohol, pentafluoropyridine and heptafluoro-2-naphthoic acid individual products derived from the removal of one fluorine atom have been obtained. © 1997 Elsevier Science Ltd.

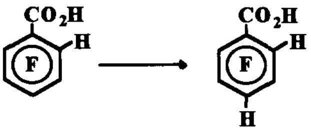
Perfluoroarenes can be easily obtained through displacement of chlorine or bromine in perhaloarenes by fluorine.[1-3] The reductive dehalogenation of these products is a potentially promising approach to partially fluorinated arenes which are valuable starting compounds for synthesis but significantly less accessible than perfluoroarenes. However, the synthetic utility of the reduction as applied to the replacement of fluorine by hydrogen is restrained by the scarcity of facile methods unlike hydrogen substitution for another halogens in arenes.[4,5] Among the various hydrodefluorination procedures of polyfluoroaromatics, the reductions by zinc (for example, hydrogenolysis of C-F bonds by Zn(Cu) in aqueous DMF[6,7] or the reductive defluorination by zinc of pentafluorobenzonitrile in aqueous solutions[8] and pentafluorobenzoic acid (**I**) in liquid NH_3[9]) are of particular interest due to both the cheapness of the reducing agent combined with the simplicity of the experiment and from a peculiarity of the mechanism which likely takes place through the intermediate formation of radical anions.[6,10,11] Therefore, the reductive defluorination by zinc is not only an access to partially fluorinated arenes but also provides the possibility to study the regioselectivity of the fragmentation of polyfluoroarene radical anions which is of special significance.[12] In this communication we focus our attention on the reductive defluorination of polyfluoroaromatics by using zinc in aqueous ammonia that is, to the best of our knowledge, the simplest and most versatile reductive system known.

The reduction of compound (**I**) by zinc in aqueous ammonia at room temperature[13] gave 2,3,5,6-tetrafluorobenzoic acid (**II**) quite rapidly as an only product after 1 hour. An increase of the reaction time to 5 hr led to practically complete conversion. The occurrence of the hydrodefluorination of compound (**I**) at the *para* position to the carboxylic group is in accordance with the previous reductions of the same compound,[6,9,14] particularly in liquid ammonia[9] but this experimental technique is essentially simplified.



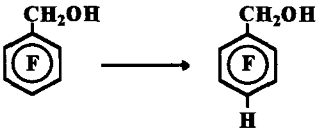
(I) (II)

The same regioselectivity was observed for the reduction of 2,3,4,5-tetrafluorobenzoic acid (III)[15] which produces 2,3,5-trifluorobenzoic acid (IV), but the removal of one fluorine from a starting molecule requires considerably increased reaction time (after 29 hr duration the conversion degree was only ~83 %).



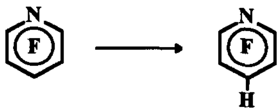
(III) (IV)

The reduction by zinc in aqueous ammonia was also successful for the less reactive compound - 2,3,4,5,6-pentafluorobenzyl alcohol (V)[16] which was almost completely converted to a product of *para*-defluorination - 2,3,5,6-tetrafluorobenzyl alcohol (VI). However, in this case the reaction time was essentially more prolonged as compared to the conversion of the acid (I). It should be noted that one of likely reasons of the difference in the reaction duration of compounds (I) and (V) is the difference in their solubilities in aqueous ammonia, which is obviously higher for the acid (I) that gives a benzoate on dissolving.



(V) (VI)

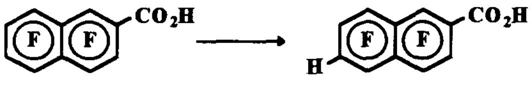
The reduction of pentafluoropyridine (VII) is worthy of particular emphasis due to the presence of a very nucleophilic fluorine atom in the γ-position[17] where it could be expected to react with ammonia to give 4-amino-2,3,5,6-tetrafluoropyridine. It has been found that the reduction of compound (VII) by zinc in aqueous ammonia at room temperature[18] gives an amino derivative only as a minor mixture (~5 %) which is easily separated from the only reduction product - 2,3,5,6-tetrafluoropyridine (VIII). Thus, under these conditions the reduction rate of compound (VII) is faster than that of the nucleophilic substitution reaction. Moreover, the reaction is remarkably rapid in spite of the small solubility of compound (VII) in water, after 5 hr the starting material underwent full conversion. The observed regioselectivity of defluorination is in accordance with the previous reductions of this compound by $LiAlH_4$[17] and Zn(Cu).[7]



(VII) (VIII)

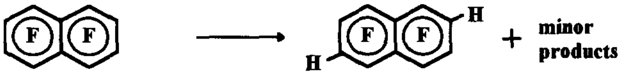
Thus, in all the above mentioned cases only one fluorine atom was lost from the position *para* to the non-fluorine substituent or heteroatom and the primary defluorination products were substantially unreactive under realized conditions. Therefore, polynuclear polyfluoroarenes are of interest owing to this peculiarity of the reactivity of mononuclear arene derivatives.

The reduction of heptafluoro-2-naphthoic acid (IX) by zinc in aqueous ammonia for 2 hr at room temperature[19] took place readily at position *6* and gave 1,3,4,5,7,8-hexafluoro-2-naphthoic acid (X) (this structure was assigned by ^{19}F NMR spectroscopy[19]). An increase of the reaction time resulted in the defluorination of compound (X).



(IX) (X)

However, the reductive defluorination of octafluoronaphthalene (XI)[20] is essentially more difficult than for compound (IX) to give immediately mainly the product of the removal of two fluorine atoms - 1,3,4,5,7,8-hexafluoronaphthalene (XII) with low conversion over 20 hr. The formation of compound (XII) is in accordance with the reduction of compound (XI) by $(C_5H_5)_2ZrCl_2$-Mg-HgCl$_2$ in THF.[21]



(XI) (XII)

Thus, aqueous ammonia is a pretty good medium allowing the possibility of carrying out the reductive defluorination of polyfluoroarenes by zinc in a highly selective manner to obtain either a valuable preparative outcome or mechanistically significant information concerning the regioselectivity of reductive fragmentation.

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13. Typical procedure: The compound (I) (1.06 g, 5 mmol) was added to zinc powder (1.30 g, 20 mmol) in aqueous ammonia (25 ml) and the mixture was stirred at room temperature for 5 hr. Unreacted zinc was separated and washed with water. The aqueous solution was acidified with hydrochloric acid and extracted with diethyl ether (3x30 ml). The combined ether extract was dried over $MgSO_4$. The solvent was removed by distillation to yield 0.90 g of compound (II) (yield 93 %), m.p. 150-152 ^{0}C. Lit. m.p. is 152-154 ^{0}C (see: Tamborski, C.; Soloski, E. J. *J. Org. Chem.* **1966**, *31*, 743-745). ^{1}H, ^{19}F NMR and IR spectra were identical to those of authentic specimen.

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15. According to the typical procedure (see ref. 13) the compound (III) (0.97 g, 5 mmol) was reduced by zinc powder at room temperature for 29 hr to give 0.82 g of a mixture containing ~83 % of compound (IV) and ~17 % of the starting compound (^{19}F NMR data).

16. According to the typical procedure (see ref. 13) the compound (V) (0.99 g, 5 mmol) was reduced by zinc for 60 hr to obtain 0.65 g of compound (VI) (yield 72 %), m.p. 31-32.5 ^{0}C. Lit. m.p. is 32-34 ^{0}C (see ref. 14). ^{1}H, ^{19}F NMR and IR spectra were in accordance with literature NMR (see ref. 14) and IR data (see: Aroskar, E. V.; Brown, P. J. N.; Plevey, R. G.; Stephens, R. *J. Chem. Soc., C* **1968**, 1569-1575).

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18. Typical procedure: The compound (VII) (4.22 g, 25 mmol) and zinc powder (5.85 g, 90 mmol) in aqueous ammonia (30 ml) were stirred at room temperature for 5 hr. The mixture was diluted with water and gradually heated to 95 ^{0}C. The compound (VIII) was collected in a Dean-Stark trap, separated from water and dried (yield ~70 %), b.p. 102 ^{0}C. Lit. b.p. is 102 ^{0}C (see ref. 17). ^{1}H, ^{19}F NMR spectra were identical to literature ones (see: Lee, J.; Orrell, K. G. *J. Chem. Soc.*, **1965**, 582-594).

19. Typical procedure: The compound (IX) (1.19 g, 4 mmol) (see: Osina, O. I.; Shteingarts, V. D. *Zh. Org. Khim.* **1974**, *10*, 329-334) was stirred with zinc powder (0.78 g, 12 mmol) in aqueous ammonia (30 ml) at room temperature for 2 hr. A crude product (the isolation see ref. 13) was crystallized from benzene to afford 0.96 g of compound (X) (yield 86 %), m.p. 187-189 ^{0}C. ^{1}H NMR (CD_3COCD_3/TMS) δ: 7.78 (dt, 1H, J=11 and 6 Hz), 7.99 (s, 1H). ^{19}F NMR ($CD_3COCD_3/CFCl_3$) δ: 116.8 (F-5; J=63.5 Hz), 117.6 (F-1; J=70 Hz), 134.9 (F-7), 139.9 (F-3), 147.5-148.3 (F-4,8; J=63.5, 70 Hz). Anal. calcl. for $C_{11}H_2F_6O_2$: C, 47.16; H, 0.72; F, 40.69. Found: C, 47.43; H, 0.82; F, 40.56.

20. According to the typical procedure (see ref. 13) the compound (XI) (0.82 g, 3 mmol) was reduced by zinc for 20 hr to obtain 0.58 g of a residue containing ~30 % of compound (XII), ~6 % of minor compounds and ~65 % of the starting compound (^{19}F NMR data).

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