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AN IMPROVED METHOD FOR THE PREPARATION OF FLUORINE-SUBSTITUTED AROMATIC AMINES

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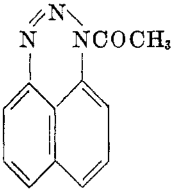
The usual method for the preparation of fluoro-substituted aromatic amines consists in the diazotization of nitro-substituted aromatic amines, precipitation and decomposition of the diazonium borofluorides (Schiemann reaction), and reduction of the nitro group in the nitrofluoro compounds obtained. However, the decomposition of these diazonium borofluorides is "tempestuous and unorderly, and special methods are required for handling them" (1). In addition, the over-all yields in this reaction are generally unsatisfactory; they range from 5 to 50%. Following occasional observations in the literature (2), the behavior of monoacetyl diamines in the diazotization and the Schiemann reaction was investigated. It was found that the *m*- and *p*-representatives of this series can be diazotized easily, without loss of the acetyl group, and that the Schiemann reaction can be applied to the diazonium compounds formed. Decomposition of the diazonium borofluorides proceeds smoothly and gives the N-acetyl derivatives of the desired fluoroaromatic amines in satisfactory yield. Thus, the following compounds have been prepared (the figures in parenthesis indicate the over-all yield): *p*-fluoroacetanilide from *N*-acetyl-*p*-phenylenediamine (82%); *m*-fluoroacetanilide from *N*-acetyl-*m*-phenylenediamine (75%); 4-fluoro-4′-acetamidobiphenyl from *N*-acetylbenzidine (62%); 4-fluoro-4′-acetamido-3,3′-dimethoxybiphenyl from *N*-acetyl-*o*-dianisidine (37%); 4′-fluoro-2-acetamidobiphenyl from 4′-amino-2-acetamidobiphenyl (59%); 4-fluoro-1-acetamidonaphthalene from *N*-acetyl-1,4-naphthylenediamine (69%); 5-fluoro-1-acetamidonaphthalene from *N*-acetyl-1,5-naphthylenediamine (55%).

It is believed (1) that all diazonium borofluorides are insoluble in water; however, we have found that this rule does not apply generally to the acetamino substituted borofluorides. Of the above-mentioned cases, *p*- and *m*-acetamidobenzene (the latter is somewhat less soluble) and 5-acetamidonaphthalene diazonium borofluoride proved soluble in water. This, however, did not impede the applicability of the method, as their aqueous solutions decomposed smoothly at room temperature in the presence of catalytic quantities of copper powder in the expected manner (time required 3–5 hours). In all those cases in which the diazonium borofluorides were insoluble, they were subjected to the usual thermal decomposition, which proceeded without difficulty.

As far as we are aware, the preparation of aromatic fluorine compounds by decomposition of the corresponding diazonium borofluorides in *aqueous solution* has not yet been reported. Starkey (3) observed that aqueous solutions of *o*- and *p*-nitrobenzene diazonium borofluorides containing sodium nitrite gave *o*- and *p*-dinitrobenzene, respectively, upon addition of copper powder.

The reaction described is not applicable to *ortho* diamines. *N*-Acetyl-*o*-phenylenediamine gave only the acetylbenzotriazole (4), when diazotized even in presence of fluoroboric acid, and from *N*-acetyl-1,8-naphthylenediamine, the analogous N^1-acetyl-1,2,3-triazaphenalene is obtained (5–8). Similar reactions have been observed with N^1-phenyl-, N^1-(2,4-dinitrophenyl)-, and N^1-benzenesulfonyl-1,8-diaminonaphthalene (9, 10).



It appeared possible to avoid this complication if the *N*,*N*-diacyl derivatives of *ortho* diamines were used. Indeed, the N^1-phthaloyl derivatives of 1,2-phenylenediamine and of 4′-methoxy-1,2-phenylenediamine, as well as $N^4,N^{4'}$-diphthaloyl-3,3′-diaminobenzidine could be converted smoothly by diazotization and subsequent Schiemann reaction into the *N*-phthaloyl derivatives of 2-fluoroaniline, 4-methoxy-2-fluoroaniline, and 3,3′-difluorobenzidine in over-all yields of 61, 36, and 25%, respectively. As the phthalimido group in the final products can easily be removed by treatment with hydrazine hydrate (11) or phenylhydrazine (12), this modification of the above reaction does not present any undue difficulties. It should be noted that in this series, too, one water-soluble diazonium borofluoride was observed, *viz.* that derived from N^1-phthaloyl-4-methoxy-1,2-phenylenediamine.

The method described here is the more promising as the arylene diamines which are necessary as starting materials, can easily be *mono*acetylated, due to the different basicity of their amino groups (13, 14). It appears, however, still simpler to start from the appropriate acyl-substituted nitro compounds and to reduce the nitro group catalytically. Using Raney nickel or palladium-charcoal as catalyst, this has been possible for the benzene and naphthalene derivatives reported here with yields ranging from 83 to 98%, and also 2-acetamido-4′-nitrobiphenyl has been reduced in this manner in a yield of 91%, and 3,3′-dinitro-4,4′-diphthalimidobiphenyl in a yield of 85%.

EXPERIMENTAL

N-Acetyl-p-phenylenediamine. 1. *p*-Nitroacetanilide (15 g.) in ethanol (250 ml.) was reduced catalytically at room temperature and a pressure of 3 atmospheres, using Raney nickel (3 g.) as catalyst. The reaction required 40 minutes. Yield, 95–98%; m.p. 161°. The reduction with iron and acetic acid (15) gives only a 75% yield.

2. *p*-Phenylenediamine (10.8 g.) was refluxed 3 hours with glacial acetic acid (50 ml.). To the filtered solution there was added hydrochloric acid (*d.* 1.12) (15.5 ml.) and the heating was continued for one hour. After dilution with water (50 ml.), the product was neutralized with concentrated sodium carbonate solution and extracted thoroughly with ether. The ether residue was crystalline and melted at 160°, after recrystallization from alcohol. Yield, 12 g. (80%).

p-Fluoroacetanilide. To finely powdered *N*-acetyl-*p*-phenylenediamine (15 g.) and some pieces of ice in a mortar, was added slowly 2 *N* hydrochloric acid (150 ml.); the mixture was kneaded until a clear solution was obtained (in order to prevent hydrolysis of the acetyl

TABLE I

N-ACETYLDIAMINES

Compound	Method of preparation	Yield, %	Recryst. from	M.p., °C.	Ref.
Monoacetylbenzidine	Benzidine and Ac_2O in chloroform	71	Dil. alcohol	199	19
Monoacetyl-*o*-dianisidine	Same	74	Chloroform	114	15, 22
4′-Amino-2-acetamidobiphenyl	Catalytic reduction of 4′-nitro-2-acetamidobiphenyl[a]	91	Petroleum ether	119[b]	
4-Amino-1-acetamidonaphthalene	Catal. red.[c] of 4-nitro-1-acetamidonaphthalene[d]	93	Dil ethanol	212	25
5-Amino-1-acetamidonaphthalene	Catal. red.[e] of 5-nitro-1-acetamidonaphthalene[f]	88	Dil. ethanol	162	29
Monoacetyl-*o*-phenylenediamine	Catal. red.[g] of *o*-nitroacetanilide (30); *o*-phenylenediamine and Ac_2O in ethyl acetate[h]	96 80	Dilute alcohol	131	
8-Amino-1-acetamidonaphthalene	Catal. red.[i] of 8-nitro-1-acetamidonaphthalene[k]	86	Ethanol	201–203[l]	

[a] In alcoholic solution; 10% palladium-charcoal as catalyst; time required 10 minutes. [b] *Anal.* Calc'd for $C_{14}H_{14}N_2O$: C, 74.4; H, 6.2; N, 12.4. Found: C, 74.5; H, 6.0; N, 12.2. [c] In alcoholic solution; 10% palladium-charcoal as catalyst; time required 7 minutes. [d] From 4-nitro-1-naphthylamine (24) by acetylation according to Liebermann (25). [e] In alcoholic solution; 10% palladium-charcoal as catalyst; time required 8 minutes. [f] Prepared according to Beilstein and Kuhlberg (27) from 5-nitro-1-naphthylamine (28). [g] In alcoholic solution; Raney nickel as catalyst; time required 20 minutes. [h] From 10.8 g. of *o*-phenylenediamine in 250 ml. of ethyl acetate with 10 ml. of acetic anhydride in 50 ml. of the same solvent. 5°; 20 minutes. [i] In alcoholic solution; 10% palladium-charcoal as catalyst. [k] From 8-nitro-1-naphthylamine (10, 27, 31) according to the literature (31, 32). [l] *Anal.* Calc'd for $C_{12}H_{12}N_2O$: N, 14.0. Found: N, 14.0. *Hydrochloride*, from alcohol, m.p. 260–261° (dec.). *Anal.* Calc'd for $C_{12}H_{13}ClN_2O$: N, 11.8. Found: N, 11.9.

group). To this solution, there was added dropwise and with vigorous agitation successively 20% sodium nitrite solution (35 ml.), the temperature being kept at 0°, and 40% fluoroboric acid (30 ml.). *The diazonium borofluoride did not precipitate.* Copper powder (1 g.) was, therefore, added and the mass was stirred at room temperature for 3 hours. The filtered solution was extracted with ether; evaporation of the extract left a crystalline residue, m.p. 147°. After recrystallization from benzene, the m.p. rose to 151–152°. Yield, 12.5 g. (82%) [lit. (16) m.p. 150–151°].

N-Acetyl-m-phenylenediamine. 1. *m*-Nitroacetanilide was reduced as described above. Yield, 93–96%; m.p. 70°.

2. *m*-Phenylenediamine (10.8 g.) was refluxed for 4 hours with a mixture of glacial acetic acid (12 ml.) and hydrochloric acid (*d.* 1.12; 15.5 ml.) and the product, after dilution with water (until a clear solution resulted) was neutralized with sodium carbonate solution and extracted with ether. The oily residue crystallized upon scratching; after recrystallization from benzene, the product had m.p. 68–70°. Yield, 12 g. (80%) (17).

m-Fluoroacetanilide. At 0°, an aqueous solution of the foregoing compound (15 g.) and sodium nitrite (7.5 g.), was added to 2 *N* hydrochloric acid (200 ml.). After 15 minutes, 40% fluoroboric acid (30 ml.) was added and the stirring was continued for another half hour. The solid borofluoride was filtered (filtrate A), washed with ice-cold dilute borofluoric acid, alcohol and ether, and dried. Yield, 15 g. (60%); the product decomposed at 102°.

TABLE II

N-ACETYLFLUOROAMINES

Compound	Diazonium Borofluoride			M.p., °C.	Recrystallized from	Yield, %	Remarks
	Dec. pt., °C.	Yield, %	Dec. car. out, °C.				
4-Fluoro-4′-acetamidobiphenyl	133–135	77	140	202	Ethanol	80	Ref. 21[a]
4-Fluoro-4′-acetamido-2,2′-dimethoxybiphenyl	195–200	67	200	73–74	Petroleum ether	55	Rhombic plates[b]
4′-Fluoro-2-acetamidobiphenyl	120	77	125	120	Petroleum ether	78	Ref. 19[c]
4-Fluoro-1-acetamidonaphthalene	160–162	93	170	170	Petroleum ether	73	Needles[d]
5-Fluoro-1-acetamidonaphthalene	Soluble in water		In water, Cu-powder[e]	190–191	Petroleum ether	55	[f]
N-Phthalyl-2-fluoroaniline	180	83	180	216	Alcohol	73	[g]
N-Phthalyl-2-fluoro-4-methoxyaniline	Soluble in water		In water, Cu-powder[h]	57	Alcohol	36	[i]
3,3′-Difluoro-4,4′-diphthalimidobiphenyl	275–280	60[k]	280	218	Alcohol	42	[l]

[a] De-acetylation (of 2.3 g.) with hot concentrated hydrochloric acid gave 4-fluoro-4′-aminobiphenyl, m.p. 119° (from dilute alcohol) (1.5 g.; 80%) (21). [b] *Anal.* Calc'd for $C_{16}H_{16}FNO_3$: N, 4.8. Found: N, 5.1. [c] *Anal.* Calc'd for $C_{14}H_{12}FNO$: C, 73.4; H, 5.2; N, 6.1. Found: C, 73.8; H, 5.6; N, 5.6. [d] *Anal.* Calc'd for $C_{12}H_{13}FNO$: C, 70.9; H, 4.9; N, 6.1. Found: C, 70.7; H, 4.8; N, 6.7. [e] Diazotization of 2 g.; 0.5 g. of copper powder; 5 hours at room temperature. [f] *Anal.* Calc'd for $C_{12}H_{10}FNO$: C, 70.1; H, 4.9; N, 6.9. Found: C, 70.6; H, 5.3; N, 6.5. [g] *Anal.* Calc'd for $C_{14}H_8FNO_2$: C, 70.1; H, 3.3; N, 5.8. Found: C, 70.1; H, 3.6; N, 5.8. [h] The solution of 2.5 g. of *N*¹-phthaloyl-4-methoxy-1,2-phenylenediamine in 2.5 ml. of concentrated sulfuric acid was diazotized with 0.7 g. of sodium nitrite in 8 g. of concentrated sulfuric acid at 0° with agitation, diluted with ice-water, filtered, and treated with 15 ml. of 40% fluoroboric acid. Decomposition of the clear solution was with 1 g. of copper powder at room temperature; 3 hours. [i] *Anal.* Calc'd for $C_{15}H_{10}FNO_3$: C, 66.4; H, 3.7; N, 5.2. Found: C, 66.1; H, 3.9; N, 5.0. [k] Diazotization with nitrosyl sulfate (see *h*). [l] *Anal.* Calc'd for $C_{28}H_{14}F_2N_2O_4$: C, 70.0; H, 2.8; N, 5.8. Found: C, 69.8; H, 3.2; N, 5.9.

The product was decomposed at 105° in the usual manner (1) and the residue was extracted with ether. The ether, upon evaporation, left a product which was recrystallized from dilute alcohol and then had m.p. 84°. Yield, 6.5 g.

Copper powder (0.5 g.) was added to filtrate A and the part of the diazonium borofluoride which had remained in solution was allowed to decompose, as described above. Thus, a second crop (5.0 g.) of *m*-fluoroacetanilide was obtained; m.p. 82°. Total yield, 11.5 g. (75%) [lit. m.p. (18) 84.6°, (19) 84°, (20) 83°].

The data concerning the other *N*-acetyl diamines prepared in this investigation are summarized in Table I, and those referring to the *N*-acetyl fluoroamines in Table II.

N-Acetylbenzotriazole. When monoacetyl-*o*-phenylenediamine was diazotized and treated in the manner described for the *m*- and *p*-isomer, only *N*-acetylbenzotriazole was obtained. M.p. 49°. [lit. (3) m.p. 51°]; yield, 84%.

N^1-Phthaloyl-1,2-phenylenediamine. A solution of 3 g. of *N*-phthalimido-*o*-nitroaniline (33) in 200 ml. of warm ethanol was reduced catalytically in the presence of 0.1 g. of 10% Pd-charcoal catalyst. Reduction time: 1 hour. After recrystallization from alcohol, the product melted at 189° (34). Yield: 2.5 g. (93.5%).

N-Phthalyl-2-fluoroaniline was also prepared, for the sake of comparison, from *2-fluoroaniline* (2.2 g.) (35) and *phthalic anhydride* (3 g.) at 160–170° (30 minutes). The solid product crystallized from ethanol in colorless needles; m.p. and mixture m.p. 216°. Yield, 3.7 g. (77%).

For the preparation of *2-fluoroaniline*, 4.8 g. of the phthalimido compound was dissolved in 50 ml. of ethanol, and after addition of 15 g. of hydrazine hydrate refluxed for two hours. Then the solvent was removed, 100 ml. of 2 *N* hydrochloric acid was added, and the heating was continued for 1 hour. The phthalyl hydrazide formed was filtered off and the solution made alkaline and extracted with ether. The yellow oil so obtained was identified as its acetyl derivative; m.p. and mixture m.p. with an authentic sample 80°. Yield, 1.7 g. (77%).

N-Phthaloyl-2-nitro-4-methoxyaniline. A mixture of 8.4 g. of 2-nitro-4-methoxyaniline (36) and 7.4 g. of phthalic anhydride was heated for 3 hours at 170–180°. Recrystallization of the solid product from ethanol gave slightly brownish rhombic plates; m.p. 146°. Yield, 10.9 g. (73%).

Anal. Calc'd for $C_{15}H_{10}N_2O_5$: C, 60.4; H, 3.6; N, 9.4.
Found: C, 59.8; H, 3.4; N, 9.3.

N^1-Phthaloyl-4-methoxy-1,2-phenylenediamine. To a solution of 3 g. of *N*-phthaloyl-2-nitro-4-methoxyaniline in 150 ml. of warm ethyl acetate, there was added 0.1 g. of 10% Pd-charcoal. The hydrogenation was complete in 12 minutes. After recrystallization from ethyl acetate, the product melted at 288°. Yield, 2.5 g. (92.5%).

Anal. Calc'd for $C_{15}H_{12}N_2O_3$: C, 67.1; H, 4.5; N, 10.4.
Found: C, 66.9; H, 4.8; N, 10.4.

3,3'-Dinitrobenzidine. For the preparation of this substance, its *N,N'*-diacetyl derivative (37–39, 39a) was hydrolyzed with concentrated sulfuric acid. Contrary to the results of Hodgson and Gorowara (40) this was achieved easily as follows: 3,3'-dinitro-*N,N*-diacetylbenzidine (30 g.) and concentrated sulfuric acid (150 ml.) were heated for 30 minutes at 130–140°, cooled, and poured into ice water. After drying, the dark red precipitate had the correct m.p. of 278-279° [lit. m.p. 275° (37); 281-282° (39)].

3,3'-Diamino-4,4'-diphthalimidobiphenyl. A solution of 4 g. of 3,3'-dinitro-4,4'-diphthalimidobiphenyl (41) in 150 ml. of hot dimethylformamide was catalytically reduced in the presence of 0.1 g. of 10% Pd-charcoal. The reaction product was a yellowish powder, which melted after recrystallization from aqueous pyridine at 231°. Yield, 3 g. (84.5%).

Anal. Calc'd for $C_{28}H_{18}N_4O_4$: C, 70.9; H, 3.8; N, 8.5.
Found: C, 71.1; H, 3.9; N, 8.4.

The carbon-hydrogen determinations in the fluorine-containing compounds were carried out according to Bodenheimer and Goldstein (42).

SUMMARY

Monoacetyl derivatives of aromatic *meta-* and *para*-diamines can be converted into the corresponding *N*-acetyl fluoroamines, *via* the diazonium fluoroborates. The starting materials can be prepared by partial acetylation of the diamines or by catalytic reduction of the *N*-acetyl nitroamines. The over-all yields are satisfactory.

In the case of *ortho* diamines, the diazotization of the monoacetyl derivatives leads to the formation of cyclic compounds, containing three nitrogen atoms in the rings. Application of the above method to the monophthaloyl derivatives of the *ortho* diamines leads smoothly to the *o*-fluoroamines.

Some of the diazonium fluoroborates encountered in this investigation have

proven soluble in water. Their decomposition to the corresponding fluoroaryl compounds has been achieved at room temperature by adding copper powder to the aqueous solution.

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