Nucleophilic Displacements of Activated Fluorine in Aromatic Compounds

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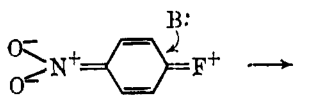
o- and *p*-fluoroaryl alkyl ketones were found to undergo facile nucleophilic displacements in dipolar aprotic solvents (DMSO and DMF) with aliphatic and alicyclic amines. This reaction was further extended to *p*-fluorobenzaldehyde, methyl *p*-fluorobenzoate, *p*-fluorobenzonitrile, *p*-fluorobenzotrifluoride, etc. Thus, a variety of substituted aromatic amines are readily obtained by these procedures.

The abundant amount of work on nucleophilic displacements in 4-halonitrobenzenes and in 1-halo-2,4-dinitrobenzenes established that, in these compounds, the order of reactivity of halogens is reversed from that observed in the monohalobenzenes.[1] The fluoro compounds undergo substitution by various nucleophiles at rates 100 to 1000 times faster than do their chloro analogs. The rate of displacement of fluorine was found to be further enhanced, in the order of 10^3 to 10^5, in dipolar aprotic solvents as compared with reactions in protic solvents.[2] Several recent papers were devoted to the examination and explanation of the effect of dipolar solvents and of the great difference in reactivity between fluorine and other halogens, and various hypotheses have been advanced.[2,3] The accepted sequence for aromatic bimolecular nucleophilic substitution[4] demonstrates the activating role of an *ortho* or *para* electron-withdrawing group.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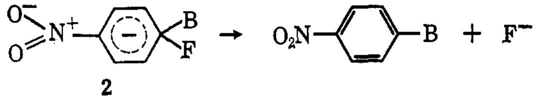
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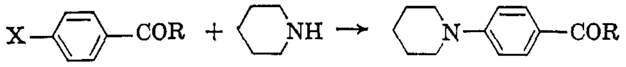
In previous investigations the nitro group was the main electron-withdrawing substituent which has been effective in causing a displacement such as described above. The only direct comparison between the nitro group and other electron-withdrawing groups was done in benzene solution. Thus, the displacement of the bromine by piperidine in 4-bromoacetophenone at 99° was found to be 770 times slower than the halogen displacement in 4-bromonitrobenzene under the same conditions[5]—a result which would not have encouraged its use as a preparative procedure.

It has now been found that 4-fluoroacetophenone does undergo very ready displacements of the halogen in aprotic dipolar solvents and affords in high yields the corresponding 4-amino derivatives, which are otherwise difficult to prepare. Attention was, therefore, directed to a further exploration of this finding with the purpose of ascertaining the optimum experimental conditions and with that of extending the reaction to electron-withdrawing substituents other than the acyl group.

The solvents used in this study were dimethylformamide (DMF) and dimethyl sulfoxide (DMSO) with potassium carbonate or an organic base added as an acid acceptor. Table I illustrates the influence of solvent, temperature, and the halogen on the yields of 4-piperidinoaryl alkyl ketones.

Table I

Reaction of 4-Haloaryl Alkyl Ketones with Piperidine



Expt	X	R	Solvent	Time, hr	Temp, °C	% Yield[a]
1	F	CH_3	DMSO	6	95	80[b]
2	F	CH_3	DMF	6	95	52[c]
3	F	CH_3	DMSO	6	150	70
4	F	C_2H_5	DMF	18	153	83
5	Cl	C_2H_5	DMF	18	153	20[d]
6	Br	C_2H_5	DMF	18	153	28[e]

[a] One equivalent of piperidine used. [b] 95% with 20% excess piperidine. [c] 77% with 20% excess piperidine. [d] 70% of 4-chloropropiophenone recovered. [e] 35% of 4-bromopropiophenone recovered.

The yields of products obtained in DMSO are higher than those obtained with DMF under comparable conditions (*cf.* 1 and 2). However, an equivalent yield can be obtained in DMF by extending the reaction time and increasing the temperature (4). A parallel can be drawn here with the order DMSO > DMF given for the rates of displacement of *p*-fluoronitrobenzene in the two solvents.[3b] However, the yields of the reactions carried out in DMF are also decreased by formation of additional by-products due to the presence of dimethylamine, such as formation of 4-dimethylaminoacetophenone (isolated in 4.3% yield) together with the 4-piperidinoacetophenone from the reaction of piperidine with 4-fluoroacetophenone (see Experimental Section).[6]

Increase of reaction temperature in a reaction using DMSO was of no benefit (*cf.* 3 and 1). Experiments 4–6 allow a comparison of the yields obtained under identical conditions by displacements of other halogens. Again, in keeping with the reaction rate studies established for the halonitrobenzenes,[1–3] a much higher yield was obtained with the fluoro than with the chloro or bromo compounds. The order of the latter two is

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(1) (a) N. B. Chapman and R. E. Parker, *J. Chem. Soc.*, 3301 (1951); (b) C. W. L. Bevan, *ibid.*, 2340 (1951); (c) A. L. Beckwith, J. Miller, and G. D. Leahy, *ibid.*, 3552 (1952); (d) J. Miller and K. W. Wong, *Australian J. Chem.*, **18**, 117 (1965); (e) for a comprehensive review, see R. E. Parker, *Advan. Fluorine Chem.*, **3**, 63 (1963).

(2) (a) J. Miller and A. J. Parker, *J. Am. Chem. Soc.*, **83**, 117 (1961); (b) A. J. Parker, *Quart. Rev.* (London), **16**, 163 (1962).

(3) (a) C. A. Kingsbury, *J. Org. Chem.*, **29**, 3263 (1964); (b) H. Suhr, *Chem. Ber.*, **97**, 3268, 3277 (1964); (c) P. E. Todesco, P. Vivarelli, and A. Ricci, *Tetrahedron Letters*, **No. 49**, 3703 (1964).

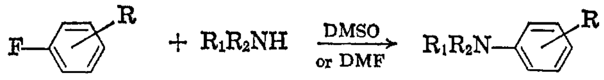
(4) J. F. Bunnett, *Quart. Rev.* (London), **12**, 1 (1958).

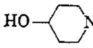
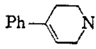
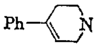
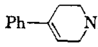
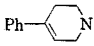
(5) J. F. Bunnett and A. Levitt, *J. Am. Chem. Soc.*, **70**, 2778 (1948).

(6) Note Added in Proof.—R. S. Asquith, W. M. Lord, A. T. Peters, and F. Wallace [*J. Chem. Soc.* (*C*), 95 (1966)] have similarly shown substitution of chlorine atoms by dimethylamino groups in refluxing dimethylformamide to occur with *p*-chloronitrobenzene (47% yield), 2-chloro-5-nitrobenzotrifluoride (7%), and 1-chloroanthraquinone (yield not stated).

TABLE II

PRODUCTS OF FLUORINE DISPLACEMENTS



Compd	R	R_1R_2NH	Yield,[a] %	Mp, °C	SC[b]	Formula	Carbon, % Calcd	Carbon, % Found	Hydrogen, % Calcd	Hydrogen, % Found	Nitrogen, % Calcd	Nitrogen, % Found
3	4-CH_3CO	$(CH_3)_2NH$	96	105–106[c]	H							
4	4-CH_3CO	Piperidine	95	87–88[d]	H	$C_{13}H_{17}NO$	76.81	76.40	8.43	8.30	6.89	6.70
5	2-CH_3CO	Piperidine	79	203 dec	I	$C_{13}H_{18}ClNO$[e]	65.12	64.84	7.57	7.45	5.85	5.88
6	4-C_2H_5CO	Piperidine	83[f]	198–199	I	$C_{14}H_{20}ClNO$[g]	66.26	66.30	7.96	8.10	5.52	5.30
7	4-CH_3CO		62	127–129	I	$C_{13}H_{17}NO_2$	71.20	71.30	7.82	7.42	6.39	6.28
8	2-CH_3CO		48	97–99	BH	$C_{19}H_{19}NO$	82.28	82.43	6.91	7.27	5.05	4.86
9	4-CHO	Piperidine	70	61–62	H	$C_{12}H_{15}NO$	76.15	76.35	7.99	8.14	7.40	7.24
10	4-CO_2CH_3	Piperidine	68[h]	92–95	H	$C_{13}H_{17}NO_2$	71.20	71.26	7.82	7.76	6.39	6.67
11	4-CO_2CH_3		75	159–161	B	$C_{19}H_{19}NO_2$	77.79	77.75	6.53	6.56	4.77	4.70
12	4-$CONH_2$	Piperidine	30	202–204	I	$C_{12}H_{16}N_2O$[i]	70.56	70.35	7.90	7.91	13.72	14.22
13	4-SO_2NH_2	Piperidine	42	150–152	B	$C_{11}H_{16}N_2O_2S$[j]	54.99	54.83	6.71	7.20	11.66	11.39
14	4-CN		90[k]	198–200	BH	$C_{18}H_{16}N_2$	83.04	83.16	6.20	6.17	10.76	10.79
15	4-CN	Piperidine	77	54–55	ME	$C_{12}H_{14}N_2$	77.38	77.32	7.58	7.60	15.04	15.10
16	4-CN	$PhCH_2NH_2$	95[l]	183–185	H	$C_{14}H_{13}ClN_2$[m]	68.70	68.57	5.36	5.22	11.45	11.84
17	4-CF_3	$PhCH_2NH_2$	36	165–167	I	$C_{12}H_{15}ClF_3N$[n]	54.24	54.15	5.69	5.87	5.27	5.18
18	4-CF_3		59[o]	171–173	BH	$C_{18}H_{16}F_3N$	71.27	71.51	5.32	5.39	4.62	4.65
19	4-SO_2CH_3	Morpholine	97[p]	175–177	A	$C_{11}H_{15}NO_3S$[q]	54.76	54.63	6.27	6.10	5.81	5.78

[a] All experiments were run for 6 hr at 85–95° in DMSO unless indicated otherwise. [b] Solvents of crystallization: A, ethanol; B, benzene; E, ethyl ether; H, *n*-heptane; I, 2-propanol; and M, methanol. [c] D. E. Pearson and J. D. Bruton [*J. Am. Chem. Soc.*, **73,** 864 (1951)] gave mp 102–104°. [d] G. Kresze and H. Goetz [*Chem. Ber.*, **90,** 2161 (1957)] gave mp 88.5–89.5° for the product obtained in a 20% yield by heating *p*-bromoacetophenone in excess of refluxing piperidine for 40 hr. [e] Hydrochloride. Calcd: Cl, 14.79. Found: Cl, 14.92. [f] 18 hr at 153° in DMF. [g] Hydrochloride. Calcd: Cl, 13.97. Found: Cl, 14.05. [h] reaction time 3-hr. [i] The hydrochloride, mp 235–240° dec (from ethanol–ether). Calcd for $C_{12}H_{17}ClN_2O$: C, 59.86; H, 7.12; Cl, 14.73; N, 11.63. Found: C, 59.94; H, 7.46; Cl, 14.65; N, 11.73. [j] The hydrochloride, mp 240–242° dec. Calcd for $C_{11}H_{17}ClN_2O_2S$: C, 47.74; H, 6.19; Cl, 12.81; N, 10.09; S, 11.59. Found: C, 48.26; H, 7.08; Cl, 12.70; N, 9.96; S, 10.43. [k] 150° reaction temperature. [l] 18 hr. at 100° in DMSO with 6 equiv of the fluoronitrile. [m] Hydrochloride. Calcd: Cl, 14.49. Found: Cl, 14.41. The free base, mp 78–79.5° (isolated from the hydrochloride). Calcd for $C_{14}H_{12}N_2$: C, 80.74; H, 5.81; N, 13.45. Found: C, 80.56; H, 6.13; N, 13.65. [n] Hydrochloride. Calcd: Cl, 13.34. Found: Cl, 13.29. [o] 135° for 24 hr. [p] 110° for 12 hr. [q] Calcd: S, 13.26. Found: S, 13.30.

reversed from that expected,[1-3] but this may be due to uneven losses incurred in recrystallization of the crude product.

The reaction of dimethylamine with *p*-fluoroacetophenone in DMSO gave 96% yield of *p*-dimethylaminoacetophenone. In this case, all the three isomeric amines are known and were specifically compared by two independent workers[7] as to their melting points, ultraviolet absorption, and other physical properties. Complete agreement with the data given for the *para* isomer (see Experimental Section) establishes that only one isomer is formed by displacement of fluorine. This finding, and the fact that only one isomer was isolated in all the reactions reported here, allows the assignment of all the aromatic amines as *para* (or *ortho*) products depending on the starting fluorine compound.

The scope of the reaction is illustrated by Table II. Compounds **3**–**8** are examples of the activating influence of the acyl group. An excellent yield of 4-dimethylaminoacetophenone **3** was obtained with dimethylamine by passing the gaseous amine through the hot solution of 4-fluoroacetophenone. Similar yields were obtained from the *p*- and the *o*-fluoroacetophenones (compounds **4** and **5**; see also **8**), but as expected the reaction did not take place with the *meta* isomer.

Very good yields of substitution products were obtained from 4-fluorobenzaldehyde (compound **9**) and from methyl 4-fluorobenzoate (**10** and **11**). However, no displacement occurred with 4-fluorobenzoic acid itself. The anion formed in presence of piperidine apparently decreases the electron-withdrawing character of the carbonyl group sufficiently to prevent reaction. On the other hand, 4-fluorobenzamide underwent a reaction with piperidine and yielded compound **12**. Similarly, 4-fluorobenzenesulfonamide could be converted to its 4-piperidino derivative **13**.

The cyano group was found to give as high yields of displacement products (**14**–**16**) as the acyl group. Somewhat lower yields were obtained with the *p*-trifluoromethyl substituent as the activating group (compounds **17** and **18**). On the other hand, methyl *p*-fluorophenyl sulfone was converted to the *p*-morpholino derivative (**19**) in a practically quantitative yield. It should be noticed, however, that no special effort was made to optimize the yields of individual compounds. Experimental conditions were kept within narrow limits so as to afford comparison of the influence of electron-withdrawing substituents.

No displacement products were detected when aniline, the sodium salt of aniline, or N-benzylaniline were heated in DMSO with 4-fluoroacetophenone.

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(7) (a) P. Grammaticakis, *Bull. Soc. Chim. France*, 93 (1953); (b) A. E. Lutskii and V. V. Dorofeev, *J. Gen. Chem. USSR*, **27**, 1059, 1064, 1303 (1957); *Chem. Abstr.*, **52**, 881, 882 (1958).

Similarly, the sodium salt of N-benzylaniline failed to react with 4-fluorobenzonitrile or with 4-fluorobenzotrifluoride. When the anion of acetanilide was employed with 4-fluoroacetophenone or the 4-fluorobenzonitrile, no desired substitution products were obtained. It will be noticed from Table II that benzylamine reacted only with one molecule of *p*-fluorobenzonitrile, even though a 6:1 ratio of fluoro compound to amine was used. Again, the intermediate benzylaniline is too poor a nucleophile to effect further displacement. *p*-Difluorobenzene, *p*-bromofluorobenzene and 2,4-dibromofluorobenzene were recovered unchanged from attempted displacement reactions with piperidine in DMSO.

Experimental Section[8]

The following examples illustrate the experimental procedures.

4-Piperidinobenzonitrile.—A mixture of 3.4 g (0.04 mole) of piperidine, 4.84 g (0.04 mole) of 4-fluorobenzonitrile, 5.52 g (0.04 mole) of anhydrous potassium carbonate, and 50 ml of dimethyl sulfoxide was stirred and heated at 95° for 6 hr. The mixture was cooled and washed with water. After drying, the crude solid (6.7 g, mp 46–52°) was recrystallized from *n*-heptane–diethyl ether: yield 5.8 g (77%), mp 54–55°.

4-Piperidinoacetophenone. A.—A mixture of 3.06 g (0.036 mole) of piperidine, 4.14 g (0.03 mole) of 4-fluoroacetophenone, 4.14 g (0.03 mole) of anhydrous potassium carbonate, and 10 ml of dimethylformamide was stirred and heated at 95° for 6 hr. After cooling to room temperature, the reaction mixture was poured into 300 ml of ice–water, and 4-piperidinoacetophenone (4.71 g; 76.6% theory), mp 75–79°, was removed by filtration. Recrystallization from *n*-heptane gave 4.3 g of solid, mp 87–88°, which showed an infrared absorption spectrum identical with that of the crude product.

The aqueous solution was extracted with ether, the dried extract was evaporated, and to the oily residue water and pentane were added, causing crystallization of 0.23 g (4.3% yield) of 4-dimethylaminoacetophenone, mp 98–101°, which after crystallization from pentane melted at 104–105° and was identical (infrared spectra and mixture melting point) with the authentic sample (see below).

B.—Under the same conditions, but using 10 ml of dimethyl sulfoxide instead of dimethylformamide, filtration of the solid from water gave 5.82 g (94.6% theory) of 4-piperidinoacetophenone, mp 86–88°.

4-Dimethylaminoacetophenone.—Dimethylamine gas was passed through a solution of 4.14 g (0.03 mole) of 4-fluoroacetophenone in 100 ml of dimethyl sulfoxide kept at 80° for 5 hr, by which time absorption of the gas ceased. The solution was poured into 600 ml of water, and the product was filtered and air dried, yielding 5.0 g (96.3% theory) of solid, mp 102–104.5°. Crystallization from *n*-heptane gave long needles: mp 105–106°; ultraviolet absorption, $\lambda_{max}^{95\%\ EtOH}$ 240 mμ (ε 6800) and 332 mμ (ε 27,700); lit. mp 102–104° (Table II, ref *c*), 106°;[7] $\lambda_{max}^{95\%\ EtOH}$ 240 mμ (ε 6300) and 333 mμ (ε 28,200).[7,9]

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[8] Melting points are corrected. Ultraviolet spectra were determined on a Beckman Model DK-2A ultraviolet spectrophotometer. Analyses were performed by Mr. Charles Pouchert of our Analytical Department.

[9] ε values quoted here (ref 7a) were read from the curve; ref 7b gives λ_{max}^{EtOH} 240.5 and 331.5 mμ. The same authors[7a,b] give, for the 3 isomer, mp 43°, λ_{max}^{EtOH} 241.7 (ε 22,400) and 360.5 mμ (ε 1800); and, for the 2 isomer, oil, λ_{max}^{EtOH} 267 mμ (ε 2200) and 349 mμ (ε 1800).

Nucleophilic Activity of the Phosphoryl Group. Oxygen-18 Transfer in Reactions of Phenyl Isocyanate with Labeled Phosphine Oxides[1a]

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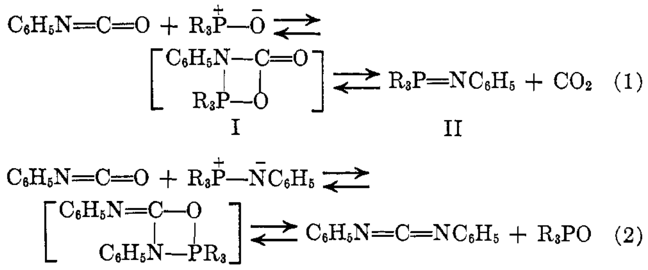
The proposed mechanism for the formation of carbodiimides from isocyanates using phosphine oxide catalysts has been tested using phosphine oxides labeled with oxygen-18. With both triphenylphosphine oxide-O^{18} and 3-methyl-1-phenyl-3-phospholene 1-oxide-O^{18} the carbon dioxide formed is enriched in oxygen-18. As the reaction progresses, the oxygen-18 content of the carbon dioxide formed decreases rapidly toward normal isotopic distribution while the second-order rate remains constant. The results demonstrate facile phosphorus–oxygen bond cleavage in the cyclic intermediate or transition state formed between isocyanate and phosphine oxide and provide strong support for the proposed mechanism.

The formation of carbodiimides from aryl isocyanates under the catalytic influence of the phosphoryl group is a convenient method for the preparation of these compounds in high purity under mild conditions.[2a]

A kinetic study of the reaction led to a proposed mechanism involving formation of an intermediate phosphinimide (II) followed by reaction of II with a second molecule of isocyanate to form the carbodiimide and regenerate the catalyst.[2b] Formation of the phosphinimide is believed to occur through the transition state or intermediate I formed by nucleophilic attack on the isocyanate carbonyl by the polarized oxygen of the phosphine oxide followed by cleavage of the phosphorus–oxygen bond. Nucleophilic activity of the phosphoryl group has been well demonstrated[3] but cleavage of the very stable phosphorus–oxygen bond is less well documented. Although evidence is available that this type of cleavage can occur under mild conditions,[3c] establishment of this point to support the proposed mechanism was essential to further study of the reaction.



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[1] (a) Presented at the 149th National Meeting of the American Chemical Society, Detroit, Mich., April 1965. (b) Taken from a portion of a thesis by J. M. in partial fulfillment of requirements for the M.S. Degree.

[2] (a) T. W. Campbell, J. J. Monagle, and V. S. Foldi, *J. Am. Chem. Soc.*, **84**, 3673 (1962); (b) J. J. Monagle, T. W. Campbell, and H. F. McShane, Jr., *ibid.*, **84**, 4288 (1962); (c) J. J. Monagle, *J. Org. Chem.*, **27**, 3851 (1962).

[3] (a) H. J. Harwood and D. W. Grisley, Jr., *J. Am. Chem. Soc.*, **82**, 423 (1960); (b) R. G. Laughlin, *J. Org. Chem.*, **27**, 1005 (1962); (c) M. Green and R. F. Hudson, *Proc. Chem. Soc.*, 217 (1962).