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N-ALKYLATION OF AROMATIC AMINES WITH TRIS(TRIFLUOROETHYL)PHOSPHATE*

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SUMMARY

Results of a study of the use of tris(trifluoroethyl)phosphate for the alkylation of aromatic amines are reported. Tris(trifluoroethyl)phosphate is a satisfactory reagent for introducing a trifluoroethyl group into aromatic amines, except for those containing N-alkyl, hydroxyl, or alkoxyl substituents and for those containing strongly electron-withdrawing groups such as nitro and carboxyl.

INTRODUCTION

Aromatic amines bearing fluoroalkyl groups on the nitrogen are of interest as intermediates in the preparation of various dyes and medicinals. Compounds of this class have been made by direct alkylation of the desired amine with a fluoroalkyl alcohol or iodide.[1-3] These reactions require more drastic conditions and generally afford lower yields than similar alkylations performed with hydrocarbon alkylating agents.

One type of alkylating agent that has been used successfully in the hydrocarbon series but that does not appear to have been used to introduce

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fluoroalkyl groups is a trialkylphosphate.[4-6] This report describes the first application of this type of alkylating agent to the fluoroalkylation of derivatives of aniline.

Tris(trifluoroethyl)phosphate has been prepared by the action of trifluoroethanol on phosphorous oxychloride or phosphorous pentachloride.[7-9] For this work, we prepared it by the latter method[7] in 81 to 96% yields, and purified it by distillation (bp 93°-94°C at 10 mm, d_{21} 1.580 g/cm^3, n_D^{21}1.3195).

RESULTS AND DISCUSSION

Table 1 shows the relative reaction rate of a number of aniline derivatives at 200° compared to that of aniline. An electron-donating substituent in the meta or para position enhances the reactivity; an

TABLE 1

Relative reactivity at 200°C of substituted anilines.[a]

Substituent	Reactivity
m-methoxyl	5.1
p-methyl	2.3
p-fluoro	1.6
2,4,5-trimethyl	1.1
none	1.0
3,5-dimethyl	0.8
o-fluoro	0.4
N-methyl	0.3
o-methyl	0.01
p-carboxyl	0
p-nitro	0

[a] Ratio of product to starting material was determined by GC after a 40-h reaction period.

electron-withdrawing substituent strongly inhibits it. Substituents in the *ortho* position or on the nitrogen being alkylated also exhibit an inhibiting effect that is related to their steric requirements. Anilines containing alkyl substitutents on oxygen or nitrogen tend also to suffer alkyl migration;

TABLE 2

Optimum conditions and yield.

Substituent	Time (h)	Temperature (°C)	Yield (%)
none	40	220	50
o-methyl	60	220	49
p-methyl	40	200	60
3,5-dimethyl	40	200	24
2,4,5-trimethyl	40	200	51
m-methoxy	40	200	5.7[a]
o-fluoro	60	220	69
p-fluoro	40	200	30

[a] Plus 1.6% of N-methyl-N-trifluoroethyl-m-anisidine.

e.g., m-anisidine yields not only the desired product, but also N-methyl-m-anisidine, N,N-dimethyl-m-anisidine, and N-methyl-N-trifluoroethyl-m-anisidine. Phenols must also be formed by cleavage of the methoxyl, but they were not isolated. N-methylaniline yields more N-trifluoroethylaniline than the expected N-methyl-N-trifluoroethylaniline. This side reaction both lowers the yield and complicates purification, so this method is not very satisfactory in those cases where alkyl migration can occur.

Table 2 shows the optimum set of reaction conditions and the isolated yield for each of the aniline derivatives successfully alkylated. The survey

TABLE 3

Physical and chromatographic properties.

Substituent	Boiling point (°C)[a]	Density/temp. $\frac{g/cm^3}{°C}$	n_D/temp. (/°C)	GC retention time[b] (min at 170°C)
none[c]	180.7	1.274/21	1.4267/22	5.0
o-methyl	195.4	1.238/21	1.4637/21	4.1
p-methyl	207.5	1.239/24	1.4505/25	6.3
3,5-dimethyl	207.4		1.4480/22	7.3
2,4,5-trimethyl	d			7.5
m-methoxy[e]	242.0		1.4962/22	7.5[f]
o-fluoro	181.5	1.383/21	1.4139/21	3.2
p-fluoro	202.3	1.359/20	1.4285/20	6.3

[a] At 747 ± 3 mm, taken on a Mettler Model FP1 at 0.2 °C/min. (Reference to a company or product name does not imply approval or recommendation of the product by the University of California or the U. S. Energy Research and Development Administration to the exclusion of others that may be suitable.)

[b] 0.32cm by 2-m stainless steel column packed with 20% Carbowax 20M on 70/80 mesh Gaschrom R, injector temp. 230°C, detector temp. 270°C, thermal conductivity detector at 175 mA, helium carrier gas at 38 ml/min.

[c] Ref. 3: n_D 1.4825, bp 84-85°C at 15 mm.

[d] mp 87.0°C (corrected) after two recrystallizations from aqueous ethanol.

[e] Isolated by preparative scale GC.

[f] At 200°C.

Table 4 footnotes, cont'd.

ethyl group. The NH resonance was identified by its shift on addition of hydrogen bonding agents.

[f] The integrator was not able to resolve these three resonances. Their sum corresponded to 5 as expected.

TABLE 4

nmr spectral properties.[a]

Substituent	δ (ppm)					$J(CH_2,CF_3)$
	CF_3CH_2	NH	ring H	CH_3	OCH_3	(Hz)
none[b]	Q3.55(2)	Qi4.33(1)	M - (5)			9
o-methyl	Q3.68(2)	Qi4.26(1)	M - (4)	S2.10(3)		9
p-methyl	Q3.51(2)	Qi4.17(1)	M - (4)	S2.13(3)		8.5
3,5-dimethyl	Q3.57(2)	Qi4.25(1)	S6.10(2)	S2.13(6)		8
			S6.25(1)			
2,4,5-trimethyl	Q3.57(2)	M3.3(1)[c]	S6.20(1)	S1.97(6)		9
			S6.57(1)	S2.03(3)		
m-methoxy[d,e]	Q3.623[f]	M4.20(1)	M6.19(3)		S3.69[f]	9.0
	Q3.505[f]		M7.07(1)			
o-fluoro[b]	Q3.68(2)	Qi4.45(1)	M - (4)			8.5
p-fluoro	Q3.82(2)	Qi4.56(1)	M - (4)			9

[a] Varian EM360; 25-50% in CCl_4 solvent except as noted; shifts are given relative to internal TMS; S = singlet, Q = quartet, Qi = quintet, M = complex multiplet, The value in parentheses is the relative area.

[b] No solvent.

[c] The shift in this resonance is caused by it having been measured in a dilute solution. The low solubility prevented measurements at concentrations comparable to those used for the other measurements. The other compounds also exhibited similar NH shifts in a dilute solution.

[d] Solvent was $CDCl_3$. The shifts for this compound were measured on an in-house spectrometer built mainly from Varian components. The integrals are from a separate run on the EM360.

[e] The F^{19} spectrum shows one triplet at +72.79 ppm relative to external $CFCl_3$, with a coupling constant of 9.0 Hz. The two quartets for the CH_2 and the complexity of the NH resonance indicate hindered rotation of the trifluoro-

of conditions was not exhaustive, so further improvement in yields may very well be possible. Table 3 contains the physical and chromatographic properties of the N-trifluoroethylanilines prepared, and Table 4 gives nmr spectral data.

EXPERIMENTAL

Alkylation procedure

The aniline to be alkylated (6.9 mmole) and tris(trifluoroethyl)phosphate (1.0 ml, 4.6 mmole) were heated in a Carius tube (0.8 cm i.d. by 10 cm). Temperatures between 140 and 240°C and times up to 60 h were investigated. The optimum conditions found in each case are given in Table 2. The maximum feasible temperature was found to be near 220°C. Experiments run at 240°C usually resulted in exploded tubes. After cooling to room temperature, the tube was opened, and its contents were dissolved in 5 ml of diethyl ether. The solution was washed twice with 2.5-ml portions of 0.8*N* aqueous sodium hydroxide, once with 1 ml of water, dried over anhydrous magnesium sulfate, centrifuged, and analysed by gas chromatography (GC). Several reaction mixtures were combined, washed with 1*N* aqueous hydrochloric acid until the washes remained acidic, washed with water, redried over magnesium sulfate, centrifuged, and evaporated to leave a liquid residue. The residue was distilled at room temperature and 0.1-Pa pressure into a liquid-nitrogen-cooled trap. Analytical samples were purified by preparative GC using a 0.95-cm column and conditions similar to those for the analyses (Table 3, footnote b).

N-Trifluoroethyl-o-methylaniline (n.c.)

This compound was prepared as described in the above procedure. The GC analysis indicated a purity of better than 98%.

Analysis: Calculated for $C_9H_{10}F_3N$: C, 57.14; H, 5.33; N, 7.40%

Found: C, 57.41; H, 5.54; N, 7.22%

N-Trifluoroethyl-p-methylaniline (n.c.)

This compound was prepared as described in the above procedure. The GC analysis indicated a purity of better than 99%.

Analysis: Calculated for $C_9H_{10}F_3N$: C, 57.14; H, 5.33; N, 7.40%

Found: C, 57.25; H, 5.35; N, 7.32%

N-Trifluoroethyl-3,5-dimethylaniline (n.c.)

This compound was prepared as described in the above procedure. The GC analysis indicated a purity of 99.7%.

Analysis: Calculated for $C_{10}H_{12}F_3N$: C, 59.11; H, 5.96; N, 6.89%

Found: C, 58.83; H, 6.07; N, 7.19%

N-Trifluoroethyl-2,4,5-trimethylaniline (n.c.)

In the preparation of this compound, by the procedure above, the evaporation of the ether left a solid residue, which was recrystallized from aqueous ethanol; mp 87.0°C (corrected).

Analysis: Calculated for $C_{11}H_{14}F_3N$: C, 60.82; H, 6.50; N, 6.45%

Found: C, 60.70; H, 5.96; N 6.12%

N-Trifluoroethyl-m-methoxyaniline (n.c.)

This compound was produced only in a poor yield and could not be isolated from the reaction mixture by distillation. It was obtained in a pure state by preparative GC in a 5.7% yield.

Analysis: Calculated for $C_9H_{10}F_3NO$: C, 52.68; H, 4.91; N, 6.83%

Found: C, 52.39; H, 4.82; N, 6.74%

N-Trifluoroethyl-o-fluoroaniline (n.c.)

This compound was prepared as described in the above procedure. The GC indicated a purity of 99.6%.

Analysis: Calculated for $C_8H_7F_4N$: C, 49.75; H, 3.65; N, 7.25%

Found: C, 49.67; H, 3.74; N, 7.41%.

N-Trifluoroethyl-p-fluoroaniline (n.c.)

This compound was prepared as described in the above procedure. The GC indicated a purity of 99.8%.

Analysis: Calculated for $C_8H_7F_4N$: C, 49.75; H, 3.65; N, 7.25%

Found: C, 49.50; H, 3.60; N, 7.30%

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