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ELECTRON-CAPTURE DETECTION OF TERTIARY AROMATIC AMINES AFTER RING TRIFLUOROACETYLATION

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SUMMARY

Trifluoroacetyl substitution in the aromatic ring (C-acylation) of N,N-dimethylaniline and N,N-dimethyl-*p*-toluidine is described; the reaction is catalyzed by trimethylamine. The resulting trifluoroacetophenone derivatives elicit a high response from an electron-capture detector (3–4 $\times$ 10^{-16} mole/sec) and are well suited to quantitative determinations.

INTRODUCTION

Derivatization reactions have been frequently utilized for enhancing sensitivity by electron-capture detection. Numerous techniques have been reported for simple functional groups, *e.g.*, haloacyl derivatives of primary and secondary amines[1,2], alcohols[2,3] and phenols[4], pentafluorobenzyl derivatives of phenols[5] and carboxylic acids[6] and pentafluorophenylhydrazones of ketones[7] and aldehydes.

In the absence of such functional groups, other derivatization techniques have been attempted. Oxidation of diphenylmethane and hydrolysis of benzodiazepine structures, respectively, have yielded benzophenones[8,9]. N-Dealkylation followed by perfluoroacylation can provide a technique to determine tertiary amines[10], and conversion of tertiary amines into pentafluorobenzyl carbamates has recently been described[11].

This paper reports on trifluoroacetyl substitution in the aromatic ring (C-acylation) of tertiary aromatic amines to afford trifluoroacetophenone derivatives with high electron-capturing properties. Trifluoroacetyl substitution in an aliphatic carbon chain has earlier been reported[12,13].

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EXPERIMENTAL

Reagents

N,N-Dimethylaniline and N,N-dimethyl-*p*-toluidine were obtained from Eastman-Kodak (Rochester, N.Y., U.S.A.); their purity, as tested by non-aqueous titration and by gas chromatography, was better than 95%.

Trifluoroacetic anhydride was obtained from Pierce (Rockford, Ill., U.S.A.), and a 1 *M* solution of trimethylamine in benzene was prepared from trimethylamine base as supplied by Eastman-Kodak. Benzene and other solvents were of nanograde quality and were obtained from Mallinckrodt (St. Louis, Mo., U.S.A.). The dimethylformamide used was of Mallinckrodt spectrograde quality.

Preparation of derivatives

Macro. Solutions of N,N-dimethylaniline (0.4 g; 3 mmoles) and N,N-dimethyl-*p*-toluidine (0.4 g; 3 mmoles) in ethyl acetate (2 ml) were separately treated with trifluoroacetic anhydride (3 ml; 25 mmoles) at 50° overnight. The reaction mixtures were then shaken with 1 *M* carbonate buffer (pH 10), dried over anhydrous sodium sulphate and evaporated *in vacuo*, and the residues were recrystallized from ethanol–water. 4-Trifluoroacetyl-N,N-dimethylaniline gave yellow crystals (m.p. 74–75°); 2-trifluoroacetyl-N,N-dimethyl-*p*-toluidine gave yellow crystals (m.p. 71–72°).

Micro. Reaction conditions were investigated using the following derivatization procedure. N,N-Dimethylaniline and/or N,N-dimethyl-*p*-toluidine was dissolved (together with 1-bromonaphthalene as internal standard) in 200 μl of solvent; 25 μl of trifluoroacetic anhydride (0.2 mmoles) were added, and the reaction mixtures were heated at 50° for various periods. After cooling, the reaction mixtures were analyzed by using flame ionization detection and without removing the excess of reagent. The effects of five solvents, trimethylamine and trifluoroacetic acid on derivative formation were studied. Area ratios of derivative to internal standard were calculated, and the percentage yields of derivatives were obtained from a standard curve prepared from known amounts of synthetic derivatives and internal standard.

Quantitative analysis. To N,N-dimethylaniline and/or N,N-dimethyl-*p*-toluidine dissolved in 200 μl of benzene were added internal standard in benzene, 100 μl of 1 *M* trimethylamine in benzene (0.1 mmole) and 25 μl of trifluoroacetic anhydride (0.2 mmoles). The mixture was heated at 50° for 60 min, then cooled, and shaken with 0.5 ml of 0.5 *M* sodium hydroxide on a Vortex mixer for 30 sec to remove the excess of reagents; it was then centrifuged, and the benzene phase was used for gas chromatography (GC).

Mass (MS) and nuclear magnetic resonance (NMR) spectra of derivatives

4-Trifluoroacetyl-N,N-dimethylaniline. MS: *m/e* 217 (M^+, 90% relative intensity); *m/e* 148 ($M-CF_3$, 100%); and *m/e* 120 ($M-CF_3CO$, 5%). NMR: 2.87 ppm (s, 6 H), 6.50 ppm (d, 2 H) and 7.78 ppm (d, 2 H).

2-Trifluoroacetyl-N,N-dimethyl-p-toluidine. MS: *m/e* 231 (M^+, 60%); *m/e* 162 ($M-CF_3$, 100%); and *m/e* 134 ($M-CF_3CO$, 20%). NMR: 2.32 ppm (s, 3 H), 2.63 ppm (s, 6 H), 7.27 ppm (s, 2 H) and 7.50 ppm (s, 1 H).

Mass spectra were recorded at 20 eV using an LKB 9000 instrument. Only

ions characteristic of trifluoroacetyl substitution are reported. NMR spectra were recorded on a Varian T 60 instrument, using $CDCl_3$ solutions.

Gas chromatography

Reaction conditions were studied on a Varian Aerograph 204 equipped with a flame ionization detector.

Gas chromatographic and electron-capture detector (ECD) properties were studied on a Pye model 84 gas chromatograph equipped with a 10-mCi ^{63}Ni detector. A pulsed voltage was used (pulse amplitude 50 V, pulse period 500 μsec, pulse width 0.75 μsec. The detector-cell temperature was 140°.

Minimum detectable amounts of the derivatives were determined by analysis of known concentrations of synthetic products in benzene[2].

Both instruments were equipped with glass columns (150 cm × 2 mm I.D.) packed with 3% of OV-17 on Chromosorb W (80–100 mesh) silanized with dimethyldichlorosilane in pyridine[2]. The carrier gas (nitrogen) flow-rate was 35 ml/min, and the column temperature was 120°.

RESULTS AND DISCUSSION

Trifluoroacetic anhydride reacts with N,N-dimethylaniline to yield trifluoroacetyl substitution in the *para*-position (Fig. 1). GC–MS confirmed the trifluoroacetyl substitution, and NMR the position of substitution (see Experimental). The melting-point and NMR spectrum agreed well with the melting-point and NMR spectrum for the same compound prepared from *p*-fluorotrifluoroacetophenone and N,N-dimethylamine[14]. No *ortho*-substitution of N,N-dimethylaniline was observed.

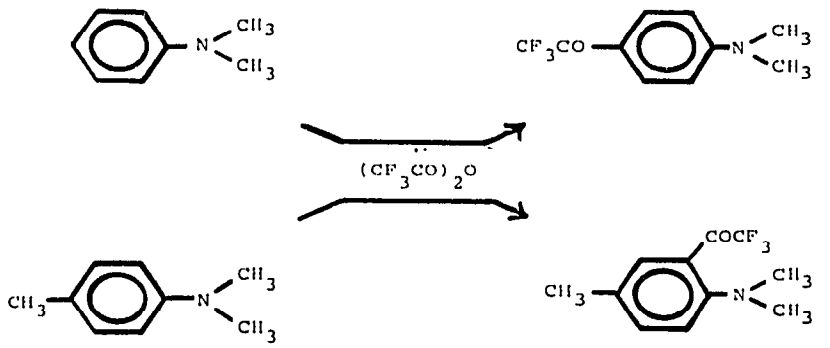

Fig. 1. Reaction mechanisms.

N,N-Dimethyl-*p*-toluidine, with the *para*-position blocked, was substituted in the *ortho*-position (Fig. 1). MS and NMR spectra support this structure (see Experimental).

The same products were obtained after synthesis of nanogram as well as milligram amounts as shown by GC–MS.

Reaction conditions

The rate of acylation is largely affected by the solvent used (Table I); only dimethylformamide gave quantitative reaction within 60 min at 50°. Trimethylamine, however, served as an excellent catalyst[2,4], giving quantitative reaction in both benzene and ethyl acetate. The presence of trifluoroacetic acid (formed during the acylation reaction) inhibited the reaction. An excess of trimethylamine to neutralize the acid is therefore required[2,15,16].

TABLE I

EFFECT OF SOLVENT ON TRIFLUOROACETYLATION OF N,N-DIMETHYLANILINE

Solvent	*Yield (% of the theoretical yield)*
Hexane	3
Benzene	8
Acetonitrile	8
Ethyl acetate	25
Dimethylformamide	100
Ethyl acetate or benzene + trimethylamine (0.1 mmole)	100
Ethyl acetate + trifluoroacetic acid (0.1 mmole)	5

The time course for the reaction between trifluoroacetic anhydride and N,N-dimethylaniline and N,N-dimethyl-*p*-toluidine, respectively, in benzene in the presence of trimethylamine is shown in Fig. 2. The reaction with N,N-dimethylaniline is complete in less than 10 min; with N,N-dimethyl-*p*-toluidine, it takes about 45 min.

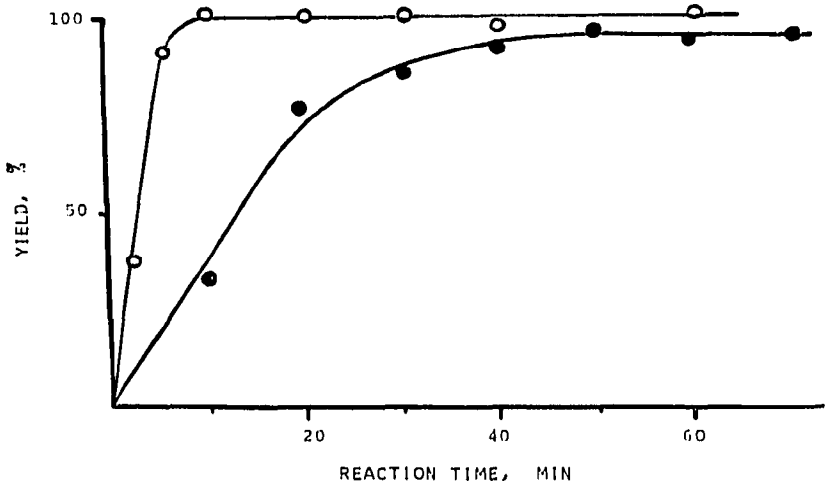

Fig. 2. Curves of derivative formation (as a percentage of the theoretical yield) against time for N,N-dimethylaniline (○—○) and N,N-dimethyl-*p*-toluidine (●—●). Conditions: benzene as solvent and trimethylamine catalysis according to Experimental.

Gas chromatographic properties

A gas chromatogram of the trifluoroacetyl derivatives of N,N-dimethylaniline and N,N-dimethyl-*p*-toluidine and 1-bromonaphthalene (internal standard) using electron-capture detection is shown in Fig. 3. The peak symmetry is excellent, and picogram amounts can easily be detected.

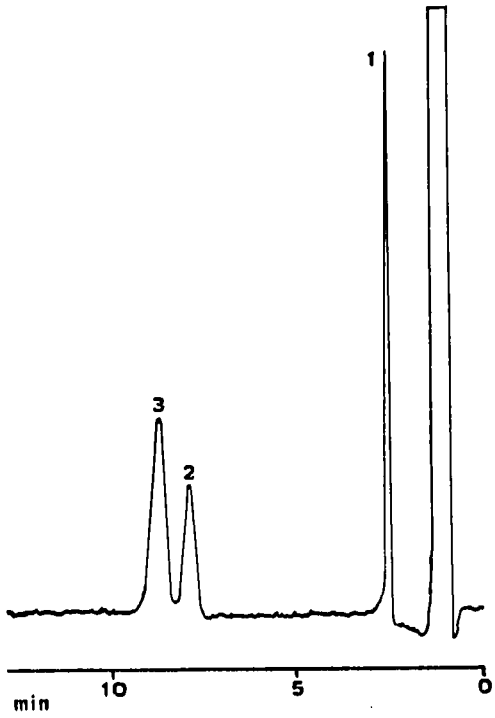

Fig. 3. Gas chromatographic analysis with electron-capture detection. 1 = 2-trifluoroacetyl-N,N-dimethyl-*p*-toluidine (65 pg); 2 = 1-bromonaphthalene (125 pg); 3 = 4-trifluoroacetyl-N,N-dimethylaniline (130 pg).

The relative retention of underivatized and derivatized amines and the ECD responses are summarized in Table II. The relative retention increases about ten times following *para*-trifluoroacetylation, whereas only a small increase takes place following *ortho*-trifluoroacetylation.

The ECD response is high and is the same for *para*- and *ortho*-substitution. Less than 1 pg can be detected on an efficient column.

Although the dimethylanilino-structure may contribute to the electron-capturing properties of the derivatives described, by far the most important electrophor is the trifluoroacetophenone structure, CF_3–CO–C_6H_5. It is therefore suggested that trifluoroacetyl substitution in aromatic rings will in general yield derivatives to which an ECD is highly sensitive.

The trifluoroacetyl substitution is not limited only to aromatic rings activated by tertiary amino groups. Aromatic rings activated in other ways can also be tri-

TABLE II

RELATIVE RETENTION AND ECD RESPONSE

Compound	*Relative retention**	*Minimum detectable amount*	
		*Mole/sec·10⁻¹⁶***	*Picogram****
N,N-Dimethylaniline	0.11	—	—
TFA-N,N-Dimethylaniline	1.1	3.0	0.4
N,N-Dimethyl-*p*-toluidine	0.16	—	—
TFA-N,N-Dimethyl-*p*-toluidine	0.20	3.9	0.5

* Relative to 1-bromonaphthalene (t_R = 8.14 min) on a 3% OV-17 column.
** A signal three times the background noise level[2].
*** At t_R = 3 min on a column with 3600 theoretical plates.

fluoroacetylated[17,18]. Perfluoroacylation of aromatic compounds in a Friedel–Craft type reaction has also been reported[19].

The ECD response of the derivatives is very sensitive to temperature changes (Fig. 4). An increase in detector-cell temperature from 140° to 280° decreases the sensitivity by a factor of about 270; this strong temperature dependency is consistent with a non-dissociative mechanism of electron attachment for these derivatives[20,21]. For the best sensitivity and reproducibility, the detector-cell temperature should be kept low and well-controlled.

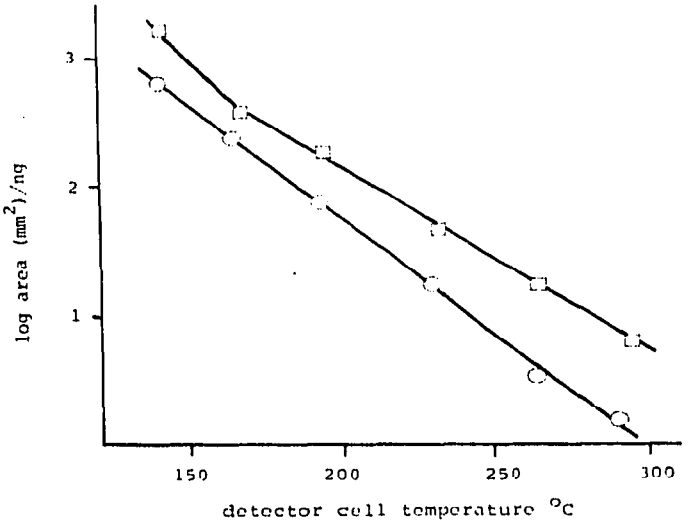

Fig. 4. Electron-capture response and detector-cell temperature. □—□ = 4-trifluoroacetyl-N,N-dimethylaniline; ○—○, = 2-trifluoroacetyl-N,N-dimethyl-*p*-toluidine.

Quantitative analysis

Quantitative analysis of small samples using an ECD requires removal of excess of reagent. With benzene as solvent, excess of trifluoroacetic anhydride and the acid formed during the reaction are easily removed by shaking the reaction mixture with 0.5 *M* sodium hydroxide. This principle of removing excess of reagent has been discussed elsewhere[2,4].

Repetitive derivatization and analysis of 20-ng samples of N,N-dimethylaniline and N,N-dimethyl-*p*-toluidine gave good recoveries and high precision, as shown in Table III.

Interference from the trifluoroacetic anhydride on the ECD is very small compared with the substantial interference obtained after acylation reactions using higher homologous perfluoroacyl anhydrides[12,22].

TABLE III

TRIFLUOROACETYLATION OF NANOGRAM AMOUNTS

Compound	*Nanograms per sample*	*Recovery (%)*	*n*
N,N-Dimethylaniline	20.0	98.9 ± 3.9	8
N,N-Dimethyl-*p*-toluidine	20.0	96.4 ± 5.1	7

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