

2-Methoxy-2-cyclohexen-1-one.—A solution of 11.2 g (0.1 mol) of **2** in 50 ml of 0.1 M sodium methoxide was allowed to stand at 20–25° for 40 hr. Neutralization of the reaction mixture, removal of excess solvent, and distillation yielded 3.1 g (25%) of product, bp 116–119° (18 mm).

The Synthesis of Amino-Substituted α,α,α -Trifluoroacetophenones

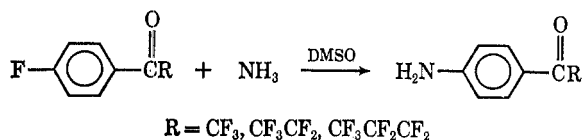
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In connection with other work in our laboratory, we were in need of a series of *meta*- and *para*-substituted perfluoroacyl ketones—especially substituted trifluoroacetophenones. Normal procedures for the preparation of substituted trifluoroacetophenones involve reaction of the appropriate Grignard reagents with trifluoroacetic acid,^{1,2} or bromination, nitration, etc., of the appropriate perfluoroacyl ketone to give some *meta* derivatives not available by the Grignard procedure. However, these procedures fail when substituents such as amino, dimethylamino, cyano, iodo, or bromo are present in the Grignard reagent.³ Consequently, substituents of this type cannot be introduced into the *para* position by these normal procedures.

Therefore, we have devised a new method for the introduction of such substituents. This procedure introduces a *p*-amino group into the appropriately substituted *p*-fluoro perfluoroacyl ketone (available *via* the Grignard method¹). The introduction of the amino group allows the preparation of other *para* substituents (such as CN, I, Br, etc.) *via* diazotization followed by a Sandmeyer reaction. Since all of the synthetic reactions of the amino-substituted ketones are carried out in acid solution, no haloform-type reaction of the ketones are observed. Similar substituents can be introduced into the *meta* position *via* diazotization of the *meta*-amino ketone (available *via* nitration of the parent ketones). For the sake of completeness these substituted ketones are also included.



Aryl carbon-fluorine bonds are significantly activated by the introduction of an electron-withdrawing group into the aromatic nucleus. In addition, fluorine atoms are relatively susceptible to displacement by nucleo-

philic species, much more so than other halogens.⁴ Bader and coworkers⁵ have found that dimethylamine displaces activated aryl fluorine atoms in both dimethyl sulfoxide (DMSO) and *N,N*-dimethylformamide (DMF) solvents. Therefore, we considered the displacement of activated fluorine by ammonia feasible. Indeed, it was found that in DMSO the conversion of *p*-fluorotrifluoroacetophenone (I)² into *p*-amino-trifluoroacetophenone (II) could be carried out by bubbling ammonia into the hot, well-stirred solution. The trifluoroacetyl group creates an activated aryl carbon-fluorine bond.⁶ The *p*-chloro ketone did not react under the same conditions. In addition, the conversion did not occur in other solvents such as dimethoxyethane, formamide, or DMF.

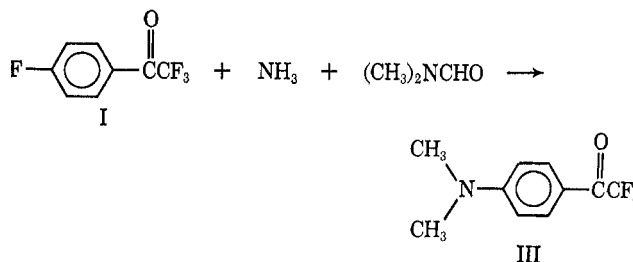
TABLE I

SUBSTITUTED TRIFLUOROACETOPHENONES *via* THE REACTIONS OF *m*- AND *p*-AMINOTRIFLUOROACETOPHENONE^a

Starting trifluoroacetophenone	Product trifluoroacetophenone	Yield, %	Reagents ^b
<i>p</i> -NH ₂	<i>p</i> -Cl	50	CuCl, HCl
<i>p</i> -NH ₂	<i>p</i> -Br	70	CuBr, HBr
<i>p</i> -NH ₂	<i>p</i> -I	74	KI, I ₂
<i>p</i> -NH ₂	<i>p</i> -CN	59	CuCN, KCN
<i>m</i> -NH ₂	<i>m</i> -I	71	KI, I ₂
<i>m</i> -NH ₂	<i>m</i> -CN	62	CuCN, KCN

^a Normal diazotization procedures which have been described in a general manner by Vogel⁹ were employed. ^b The cuprous salts used were freshly prepared. Best results were obtained if dilute sulfuric acid was used as the diazotization medium.

The use of DMF as solvent, ammonia, and I enabled the preparation of *p*-dimethylaminotrifluoroacetophenone (III). Apparently, when ammonia is bubbled into DMF, dimethylamine is produced. Dimethylamine is a stronger base than ammonia and must react much more rapidly to displace the aryl fluorine. Thus, as dimethylamine is consumed more is produced, and good yields of III are obtained.



(4) J. D. Roberts and M. C. Caserio, "Basic Principles of Organic Chemistry," W. A. Benjamin, Inc., New York, N. Y., 1965, p 847.

(5) H. Bader, A. R. Hansen, and F. J. McCarty, *J. Org. Chem.*, **31**, 2319 (1966).

(6) The trifluoroacetyl group is not a specific activator for this reaction, and the same aryl fluorine displacement by ammonia has been carried out with 1-(*p*-fluorophenyl)pentafluoropropanone and 1-(*p*-fluorophenyl)heptafluorobutanone (these ketones were prepared by the method of Dishart and Levine¹ using *p*-fluorophenylmagnesium bromide with pentafluoropropionic acid and heptafluorobutyric acid, respectively). The *p*-amino ketones produced (V and VI, respectively) showed ir, ¹H nmr, and ¹⁹F nmr spectra consistent with the expected structures. Data for V follow: ir 5.93 μ (C=O); ¹H nmr δ 4.40 (broad singlet, 2 H) and 6.67 and 7.95 (doublets, 4 H); ¹⁹F nmr 82.1 (singlet, 3 F) and 115.2 ppm (singlet, 2 F). Data for VI follow: ir 5.94 μ (C=O); ¹H nmr δ 4.38 (broad singlet, 2 H) and 6.67 and 7.92 (doublets, 4 H); ¹⁹F nmr 80.0 (3 F), 112.6 (2 F), and 125.1 ppm (2 F).

(1) K. T. Dishart and R. Levine, *J. Amer. Chem. Soc.*, **78**, 2268 (1956).

(2) F. E. Herkes and D. J. Burton, *J. Org. Chem.*, **32**, 1311 (1967).

(3) F. E. Herkes, Ph.D. Thesis, University of Iowa, 1966.

TABLE II
 PHYSICAL PROPERTIES OF SUBSTITUTED TRIFLUOROACETOPHENONES^a

Substituent	Registry no.	Bp, °C (mm)	Mp, ^b °C	Ir, μ (C=O)	n _D ²⁰	¹ H nmr ^c	¹⁹ F nmr ^d
<i>p</i> -NH ₂	23516-79-2	113 (0.5)	94.5-95.5	5.93		7.9, 6.6 (d, 4 H) 4.50 (br s, 2 H)	71.03
<i>m</i> -NH ₂	23516-80-5	82 (0.5)		5.85		7.3 (m, 4 H) 3.90 (s, 2 H)	71.54
<i>p</i> -N(CH ₃) ₂	2396-05-6		74-75 ^e	5.94		7.9, 6.6 (d, 4 H) 3.04 (s, 6 H)	70.84
<i>p</i> -Cl ^f	321-37-9	84 (23)		5.80	1.4901	7.78 (A ₂ B ₂ , 4 H)	72.03
<i>p</i> -Br	16184-89-7	95 (4)		5.80	1.5141	7.77 (A ₂ B ₂ , 4 H)	72.02
<i>p</i> -I	23516-84-9	89 (1)		5.80	1.5589	7.80 (A ₂ B ₂ , 4 H)	72.01
<i>p</i> -CN	23516-85-0	71 (0.2)	53-55	5.80		8.08 (A ₂ B ₂ , 4 H)	72.19
<i>m</i> -I	23516-86-1	89 (3)		5.81	1.5431	8.1, 7.3 (m, 4 H)	72.04
<i>m</i> -CN	23568-85-6	71 (0.2)		5.79		7.95 (m, 4 H) ^g	72.07 ^g

^a All compounds gave satisfactory C, H, N analyses with the exception of *m*-NH₂ (slightly impure). ^b All melting points are corrected. ^c In δ, parts per million, downfield from TMS; CDCl₃ solvent. ^d In parts per million upfield from CFCl₃; CDCl₃ solvent. The three fluorines appeared as a singlet in all cases. ^e Lit.⁷ mp 74.5-75.5°. ^f Also identified by comparison of ir spectra with an authentic sample. ^g A small amount of DMSO-*d*₆ was added to dissolve all of the material.

This preparation of III is superior to the one reported,⁷ since pure material can be obtained with a minimum of experimental difficulty.

The preparation of *m*-aminotrifluoroacetophenone (IV) was carried out by conventional means. That is, trifluoroacetophenone² was nitrated in the *meta* position according to the method of Stewart and Vander Linden,⁸ and reduced to the amine with tin and hydrochloric acid.

Both II and IV were readily diazotized and used to prepare other substituted ketones. General procedures for such diazotization reactions (Sandmeyer reactions) have been described.⁹ Table I indicates the ketones which were prepared from II or IV, the isolated yields, and reagents used. Table II lists the physical properties of all materials prepared.

Experimental Section

***p*-Aminotrifluoroacetophenone.**—Into a 1-l., three-necked flask equipped with a reflux condenser and gas inlet tube extending to the bottom of the flask were placed 61.6 g (0.32 mol) of *p*-fluorotrifluoroacetophenone (I)² and 200 ml of DMSO. The solution was stirred vigorously with a magnetic stirrer and heated to 135°. A large trap was inserted between the gas inlet tube and a tank of anhydrous ammonia, and ammonia was bubbled into the solution at a moderate rate for 24 hr. (The gas inlet tube had to be cleaned of solid formations several times during the reaction.) After cooling, the solution was poured into 1 l. of ice-water and stirred for several hours, and the dark precipitate was collected on a suction filter. The solid was air-dried and then melted and distilled under reduced pressure to yield 25.3 g (42%) of *p*-aminotrifluoroacetophenone (II).

***p*-Dimethylaminotrifluoroacetophenone.**—In the manner described previously, ammonia gas was bubbled into 57.5 g (0.30 mol) of *p*-fluorotrifluoroacetophenone (I) and 200 ml of DMF. The addition of ammonia continued for 12 hr while the reaction temperature was held at 150°. The mixture was cooled, poured over 1200 ml of water, and stirred overnight, and the precipitate was collected on a suction filter. The light green solid was recrystallized from a water-ethanol mixture. The crystals were dried over CaSO₄ at ca. 1-mm pressure. The yield was 36.2 g (55%).

***m*-Aminotrifluoroacetophenone.**—Into a 1-l., three-necked flask equipped with a reflux condenser and magnetic stirrer were

placed 36.0 g (0.30 g-atom) of tin granules and 34.0 g (0.16 mol) of *m*-nitrotrifluoroacetophenone,⁸ bp 131° (10 mm) [lit. bp 113° (12 mm)]. The mixture was stirred vigorously while 350 ml of concentrated hydrochloric acid was added in three portions. The reaction was moderated with a water bath. After the addition was completed, the solution was refluxed for 1 hr, cooled, and neutralized with aqueous sodium bicarbonate. The mixture was extracted twice with 200-ml portions of ether, and the extracts were washed with water. The ether was evaporated and the residue was distilled under reduced pressure to yield 11.5 g (39%) of *m*-aminotrifluoroacetophenone. Glpc analysis indicated 95% purity.

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Base-Catalyzed Reactions. XXXVIII.¹ Selected Lithium-Catalyzed Reactions of 4-Alkylpyridines with Olefins

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In previous papers of this series it was reported that sodium and potassium are catalysts for the side-chain alkylation,³ aralkylation,⁴ and alkenylation⁵ of alkyl aromatics. It was also reported that potassium cat-

(1) (a) For paper XXXVII, see W. M. Stalick and H. Pines, *J. Org. Chem.*, **35**, 422 (1970). (b) Paper IX of the series Alkylation of Heteroaromatics. (c) For part VIII see ref 1a.

(2) Taken in part from the Ph.D. thesis of W. M. Stalick, Northwestern University, Aug 1969.

(3) H. Pines and L. A. Schaap, *Advan. Catal.*, **12**, 117 (1960).

(4) (a) H. Pines and D. Wunderlich, *J. Amer. Chem. Soc.*, **80**, 6001 (1958); (b) H. Pines and J. Shabtai, *J. Org. Chem.*, **26**, 4220 (1961); (c) J. Shabtai, E. M. Lewicki, and H. Pines, *ibid.*, **27**, 2618 (1962).

(5) H. Pines and N. C. Sih, *ibid.*, **30**, 280 (1965).

(7) W. A. Sheppard, *J. Amer. Chem. Soc.*, **87**, 2410 (1965).

(8) R. Stewart and R. Vander Linden, *Can. J. Chem.*, **38**, 399 (1960).

(9) A. I. Vogel, "Elementary Practical Organic Chemistry," John Wiley & Sons, Inc., New York, N. Y., 1958.