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α-AMINO-α-TRIFLUOROMETHYL-PHENYLACETONITRILE: A POTENTIAL REAGENT FOR ^{19}F NMR DETERMINATION OF ENANTIOMERIC PURITY OF ACIDS

by

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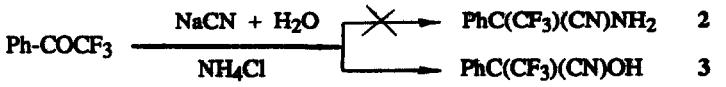
Abstract.- α-Amino-α-trifluoromethyl-phenylacetonitrile, $PhC(CF_3)(CN)NH_2$, **2**, in which the amino group is located on a crowded, chiral, quaternary carbon center, has been studied as a potential reagent for the ^{19}F NMR determination of enantiomeric purity of chiral acids by conversion to their corresponding diastereomeric amides. The differences in the ^{19}F NMR chemical shifts (Δδ) of the *R,R/S,S* versus *R,S/S,R* diastereomeric amides (**8a-j**) prepared from amine **2** and ten chiral acids range up to 0.266 ppm. Eight of the ten examples have Δδ in excess of the useful minimum of 0.02 ppm. These values are not notably superior to those of other known reagents.

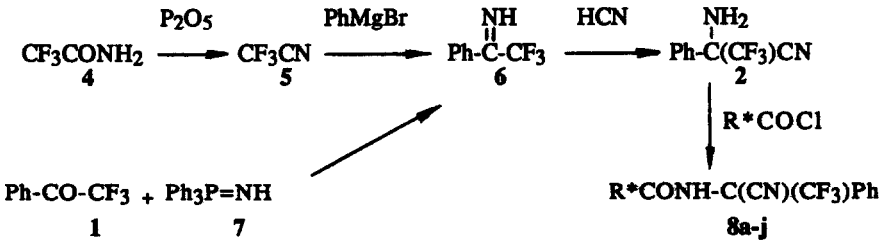
Introduction.- The determination of enantiomeric purity by NMR of diastereomeric derivatives has been reviewed[2,3]. α-Methoxy-α-trifluoromethyl-phenylacetic acid [MTPA, $PhC(OCH_3)(CF_3)COOH$][3,4] is a widely used chiral derivatizing agent for alcohols and amines by conversion to the diastereomeric esters and amides. Camphanic acid[5a] and the isocyanate of MTPA[5b] have also been used for this purpose. In such determinations ^{19}F NMR has inherent advantages over ^1H NMR for determination of enantiomeric purity by virtue of the generally larger chemical shift differences of ^{19}F resonances and the uncongested nature of the fluorine spectra. No generally accepted reagent such as MTPA is recognized for the equivalent determination of enantiomeric purity of chiral acids.[2a,6]. Methyl mandelate[2b] has been used for this purpose but has not been widely adopted. Amides containing fluorine, prepared from $PhCH(CF_3)NH_2$[6c] (**9**), $PhC(OCH_3)(CF_3)CH_2NH_2$[6a,b] (**10**) and $PhCHF(CH_2)NH_2$[6d] (**11**), have been studied recently for this purpose. These diastereomers also may be analyzed using separation by gas and liquid chromatographic methods [7-9].

We have undertaken a study of yet another trifluoromethyl-containing amine, α-amino-α-trifluoromethyl-phenylacetonitrile (**2**) which is a potential reagent for the determination of enantiomeric purity of chiral acids by conversion to diastereomeric amides. Thus amine **2** might serve the same role for acids that MTPA has served for alcohols and amines.. The rationale for this choice is that the highly crowded, chiral, quaternary carbon center, substituted with four very different groups, might lead to enhanced separations of ^{19}F resonance signals. In addition, the quaternary chiral center would not be susceptible to racemization. A possible disadvantage might be that the highly hindered, less basic, amine would not form amides readily.

The classical Strecker synthesis for preparation of this amine from phenyl trifluoromethyl ketone, as shown in **1** → **2**, failed under a variety of conditions; the cyanohydrin **3** and unreacted starting phenyl trifluoromethyl ketone, **1**, were isolated in reactions at -10 to 20°; only unidentified products were detected at higher temperatures (60-80°). The modification[9] using the bisulfite addition product of **1** was likewise unsuccessful.



However, the synthesis of **2** was accomplished in good yield by the addition of hydrogen cyanide to ketimine **6**, which in turn was made by the reaction of phenyl Grignard reagent with trifluoroacetonitrile **5**. We were aware of the stability of the trifluoromethyl ketimines from our prior study[10] on the action of phenyl and t-butyl Grignard reagents with **5**. Recent Russian studies[11-15] on trifluoromethyl ketimine derivatives have included the synthesis of **6**[14-16]. An alternate synthesis[11] of **6** via an aza Wittig reaction of triphenylphosphine imine **7**



with ketone **1** gave a much poorer yield than the Grignard method. Hydrogen cyanide addition to hexafluoroacetone ketimine[11] served as precedent for the reaction **6**→**2**.

Discussion.- Table 1 summarizes the ^{19}F NMR spectra of amides **8a-j** prepared from amine **2** and the ten different chiral acids shown. Useful chemical shift differences ($\Delta\delta$ greater than 0.02 ppm) are observed in the fluorine resonances for eight of the ten diastereomeric pairs tested (column 6, Table 1). In only three of these ten examples were the diastereomeric proton chemical shift differences sufficiently differentiated to permit accurate integration; namely, **8a**, 9-CH_3 and 10-CH, $\Delta\delta$ = 0.07 ppm; **8b**, OCH_3, and α-H, $\Delta\delta$ = 0.05 ppm; **8g**, t-butyl, $\Delta\delta$ = 0.08 ppm. Although the proton chemical shift differences are complementary to those of fluorine, the ^{19}F spectra are superior in most cases for the determination of enantiomeric purity[17] because of the generally larger $\Delta\delta$ values for ^{19}F versus ^{1}H. Two examples (Table 1, **8e** & **8h**) contain CF_3 groups in both the amine and acid moieties of the amide. The $\Delta\delta$ value for the diastereomeric CF_3 signals in the amine moiety of **8e** was 0.023 ppm and that for **8h** was 0.168 ppm, while for the CF_3 on the acid moiety these values were 0.140 and 0.178 ppm respectively.

The results with **2** are compared with the published results from **9**, **10** and **11** in the last three columns of Table 1. Amides derived from chiral amine **2** give substantially greater ^{19}F $\Delta\delta$ values than those obtained

from amides of α-trifluoromethyl-benzylamine[6c] [$PhCH(CF_3)NH_2$, **9**, Table 1, column 7]; however, the $\Delta\delta$ values are of the same magnitude as those reported for the amides of β-methoxy-β-trifluoromethyl-β-phenylethylamine[6a,b] [$PhC(OCH_3)(CF_3)CH_2NH_2$, **10**, column 8] and β-fluoro-β-phenylethylamine ($PhCHFCH_2NH_2$, **11**[6d], column 9). These limited data show that the $\Delta\delta$ values are as large or perhaps

Table 1: ^{19}F NMR Chemical Shifts of Diastereomeric Amides $\mathbf{8_{a-j}}$ of α-Amino-α-trifluoromethyl-phenylacetonitrile **2**, and Three Amino-fluorine-containing Compounds, **9**, **10**, **11**.

R*CONHC(CF_3)(CN)Ph	R*CO	δ_A [a]	δ_B [a]	$\Delta\delta_{AB}$ [b]	Literature Comparisons $\Delta\delta_{AB}$, ppm		
R*CO =	Config.	ppm[a]	ppm[a]	ppm[a]	**9**[6c]	**10**[6a,b]	**11**[6d]
8a	(1*S*)-(+)	0.534	0.302	0.232		0.599	
8b PhCH(OMe)CO	(*S*)-(+)	0.166	-0.100[c]	0.266	0.050	0.428	
8c PhCH(OCOMe)CO	(*R*)-(-)	0.024	-0.045[c]	0.069	0.070	-- 0 --	0.56
8d PhCH(C_2H_5)CO	(*R*)-(-)	0.021	0.021	-- 0 --		0.113	
8e PhCH(CF_3)CO[d]	(*S*)-(+)	0.846	0.823	0.023		0.041	
		8.883[e]	8.711[e]	0.172[e]			
8f [7-methoxy-2-naphthyl]-CH(Me)CO	(*S*)-(+)	0.117	0.063	0.053	0.088		
8g PhCH(t-Bu)CO[d]	(*R*)-(-)	0.267	0.124	0.143		0.198	
8h PhC(OMe)(CF_3)CO	(*R*)-(+)	0.174	0.006	0.168	0.087		
		7.053[e]	6.913[e]	0.148[e]			
8i (*l*-menthoxy)-CH_2CO	(*R*)-(-)	0.213	0.278	0.065	0.092	0.100	
8j C_2H_5CH(Me)CH_2CO	(*S*)-(+)	0.229	0.229	---0 ---		-- 0 --	
9 C_2H_5CH(Me)CO						0.054	0.10
10 PhCH(Me)CO					0.089	0.254	0.17
11 PhCH($CHMe_2$)CO					0.161		

a) δ_A refers to the ^{19}F chemical shift of one of the diastereomers and δ_B to the other; since racemic **2** was used, the specific diastereomer cannot be designated[17,18]. Spectra taken on Varian XL-400 MHz FT instrument at 376.3 Hz in $CDCl_3$ solvent. Resonance reported in ppm relative to TFA. b) $\Delta\delta_{AB}$ refers to the difference in the ^{19}F NMR signals for diastereomers A and B: i.e., $\Delta\delta = (\delta_A - \delta_B)$, with the designation of diastereomer A arbitrarily assigned to the low field signal. In $\mathbf{8_a}$ R*CO is (-)-camphanoyl and in $\mathbf{8_i}$ R*CO is menthoxyacetyl. c) The negative sign designates a signal upfield from TFA. d) Taken in deuteroacetone solvent. e) Resonance for the CF_3 group from the acid moiety.

larger when there is a single fluorine (**11**, column 9) rather than a CF_3 group substituted on the chiral α-carbon center[17]. Based on ^{19}F NMR alone, amine **2** is still a potential reagent which could be developed for the determination of enantiomeric composition of chiral acids. However, this requires amine **2** in enantiomerically pure form, an objective which has not yet been accomplished. Attempts to resolve amine **2** by crystallization of diastereomeric salts were unsuccessful since **2** proved to be such a weak base, by virtue of the strongly electron withdrawing CN and CF_3 groups, that it did not form crystallizable, stable salts even with camphor-10-sulfonic acid or 3-bromocamphor-8-sulfonic acid. The hydrochloride salt of **2** was prepared in anhydrous ether but it lost HCl on attempted isolation.

Amine **2** was hydrolyzed by sulfuric acid to amide **12** or by hydrochloric acid to give the amino acid **13**. Either **12** or **13** (or their derivatives) would be candidates for resolution; however, practical reconversion of either **12** or **13** to **2** seems problematic. Since amide derivatives of **2** did not have significantly larger ^{19}F Δδ

$$\underset{\mathbf{12}}{\text{Ph-C(NH}_2\text{)(CF}_3\text{)CONH}_2} \xleftarrow[H_2O]{H_2SO_4} \underset{\mathbf{2}}{\text{Ph-C(NH}_2\text{)(CF}_3\text{)CN}} \xrightarrow[H_2O]{HCl} \underset{\mathbf{13}}{\text{Ph-C(NH}_3^+\text{)(CF}_3\text{)COO}^-}$$

values than those described for β-methoxy-β-trifluoromethyl-β-phenyl-ethylamine[6a], **10**, which has already been resolved and whose absolute configuration is established, and also considering the likely difficulties in obtaining enantiomerically pure **2** in practical amounts, we have not pursued this aspect of the problem further.

In addition to these derivatives, the reaction of thiophenol and methanol with ketimine **6** gave adducts **14**, and **16**. The reaction of N,N-Dimethylhydrazine with ketone **1** gave adduct **15**.

The value of expanded high field ^1H NMR analysis of MTPA derivatives for configurtional determinations (in contrast to the determination of enantiomeric purity) has recently been demonstrated [19,20].

Experimental.- Fluorine NMRs were determined on a Varian XL-400 MHz FT instrument at 376.3 Hertz in $CDCl_3$ solvent. Phenyl trifluoromethyl ketone was used as internal standard with ^{19}F resonance set at 4.312 ppm (determined relative to trifluoroacetic acid at 0.00 ppm). Trifluoroacetic acid (TFA) was not used as a direct internal standard because it had a variable effect on the chemical shifts of the substrates depending upon its concentration[4b]. Proton NMR were determined on a Varian Gemini FT 200 MHz instrument in $CDCl_3$ solvent with chemical shifts reported in ppm relative to internal TMS at 0.00. Infrared spectra were recorded on a Perkin Elmer 1600 series FTIR instrument. Melting points were taken on an aluminum microscope hot stage with samples between thin cover glasses.

Phenyl trifluoromethyl ketimine **6**.- Trifluoroacetamide (**4**, 20 g) was dehydrated[10,14] with P_2O_5 to give trifluoroacetonitrile gas,[21] **5**, which was introduced (without isolation) directly into a phenylmagnesium bromide ether solution. After refluxing 1 h, standard work-up gave **6** (21 g, 69% overall yield from **4**, bp 52-56°, 13 torr; ^1H NMR: δ 10.69 and 10.78 (2s, 1H, *syn* and *anti* NH), 7.18-8.01 (m, 5H phenyl); ^{19}F NMR: δ 6.111 (s, CF_3); IR: cm^{-1} 3300 (NH); 1636 (= NH); 1151 (CF_3). Ketimine **6** was also prepared but in unsatisfactory yield by the aza-Wittig reaction:[11] **1** + **7** → **6**. Triphenylphosphine imine **7** was generated from its hydrosulfate (1.9 g, 5 mmole) by mixing with a suspension of $NaOCH_3$ (0.54 g, 10 mmole) in benzene (25 mL). To this solution was added **1** (0.87 g, 5 mmole). After 12 h at 20°, the mixture was worked up to give **6** (138 mg, 16% yield) with the same properties as those obtained for the product from the Grignard procedure.

Hydrochloride salt: Addition of **2** to a cooled, saturated, ethereal solution of HCl resulted in the slow formation of crystals which melted at 47-49° immediately after isolation; on standing at room temperature, these lost HCl and reverted to the liquid free amine. N-Acetyl derivative: Treatment of **2** with acetyl chloride in pyridine at 0-20° gave crystals (95% yield) which were recrystallized from ether, mp 174-175°; ^{1}H NMR: δ 7.45-7.61 (m, 5H, Ph), 6.57 (broad s, 1H, NH), 2.14 (s, 3H, CH_3); Anal. calcd for $C_{11}H_9F_3N_2O$: C, 54.55; H, 3.75; N, 11.57. Found: C, 54.79; H, 3.58; N, 11.79. N-Benzoyl derivative: Treatment of **2** with benzoyl chloride as above gave crystals, mp 128-129°; ^{1}H NMR: δ 7.45-7.88 (m, 10 H, 2 Ph), 6.86 (broad s, 1H, NH).

α-Amino-α-trifluoromethyl-phenylacetonitrile, **2**.- To ketimine **6** (6.92 g, 0.04 mole) at 0° was added liquid HCN[22] (**Caution!**, 1.20 g, 0.044 mole) followed by 2 drops of triethylamine. After 10 h at 10°, distillation gave **2**, 7.30 g, 85%, bp 49°, 0.06 torr, as a colorless oil which solidified, mp 27-28°; ^{1}H NMR: δ 7.42-7.79 (m, 5H. Ph), 2.40 (broad s, 2H, NH_2); ^{19}F NMR: δ 2.91 (s, CF_3); IR (neat) cm^{-1}: 3398, 3332, 1620 (NH_2), 2220 (weak CN). Anal. calcd for $C_9H_7F_3N_2$: C, 54.00; H, 3.53; N, 14.00. Found: C, 54.25; H, 3.35; N, 13.9.

General procedure for preparation of amides **8a-j**, Camphanic acid amide of **2**.- The acids for the preparation of the amides were commercially available (Aldrich Chem. Co.) with the exceptions of those for making **8e**[4c], **8g**[4c], **8j**[4f]. To dry pyridine (1.0 g in CCl_4, 1.2 mL) was added in the following order at *ca* 20°: acid chloride (0.55 mmole) and aminonitrile **2** (0.5 mmole, 100 mg). The mixture was then heated at 55-60° for 24 h, ether (25 mL) was added and the reaction worked up by successive extractions with cold 3% HCl (3 X 15 mL), cold saturated K_2CO_3 (2 X 15 mL), and cold saturated NaCl (3 X 15 mL). The ether extracts were dried ($MgSO_4$), decolorized (Norit A), filtered and evaporated to give the amides reported in Table 1 in crude yields of 60 to 90%. Several of the amides on cooling gave a crystalline mixture of diastereomers; *i.e.*, **8c** (mp 39-41°), **8d** (mp, 62-80°), **8f** (mp 157-158°); the camphanyl amide **8a** was recrystallized (hexane); mp 125-126°; Anal. calcd for $C_{19}H_{19}F_3N_2O_3$: C, 60.00; H, 5.04; N, 7.35. Found: C, 60.21; H, 5.03; N, 7.27.

α-Amino-α-trifluoromethyl-phenylacetamide, **12**.- Aminonitrile **2** (0.50g) was dissolved in H_2SO_4 (98%, 4.0 mL) and 5 drops of water added. After 15 h at 20°, the mixture was poured into 50 mL of ice water and the amide (**12**) obtained by neutralization, extraction, washing and drying: (0.47 g, 86%, mp 44-45°); ^{1}H NMR: δ 7.36 -7.69 (m, 5H, Ph), 6.80 and 6.27 (2 broad s, diastereomeric NH), 2.33 ppm (broad s, 2H, NH_2); ^{19}F NMR: δ 1.848 (s, CF_3). Anal. calcd for $C_9H_9F_3N_2O$: C, 49.55; H, 4.16; N, 12.84. Found: C, 49.51; H, 4.00; N,12.85.

α-Amino-α-trifluoromethyl-phenylacetic acid, **13**.- Aminonitrile **2** (250 mg) was refluxed with 30% HCl (2.5 mL) for 12 h. The mixture was poured into ice water, extracted with ether, and the water layer neutralized at 0° with pyridine. The solid which formed was separated, washed with water and recrystallized from ethanol-water to give amino acid **14** (222 mg, 81% yield); sublimes 250-260°; ^{1}H NMR (CD_3OD): δ 7.41-7.75 (m, 5 H, Ph), 4.90 (broad s, 3H, NH_3^+).

α-Phenylthio-α-trifluoromethyl-benzylamine,**14**.- Ketimine **6** (0.87 g), thiophenol (0.55 g) and triethylamine (0.51 g) were mixed with cooling. After warming to 20° and standing for 8 h, volatiles were removed under vacuum and the residue solidified, mp 52-59°; ^{1}H NMR: δ 7.15-7.84 (m, 10 H, Ph), 2.05 (broad s, 2H, NH_2); ^{19}NMR: δ 0.834 ppm (s, CF_3).

N,N-Dimethylhydrazone of phenyl trifluoromethyl ketone, **15**.- N,N-Dimethylhydrazine (0.31g) was added to ketone **1** (0.87 g) at 0° and then heated at 60° over night. Standard work-up and distillation gave hydrazone **15**;

bp 58-60°, 10 torr, 0.95 g (88%); ^{1}H NMR: δ 7.35-8.11 (m, 5H, Ph), 2.53 & 2.47 (2 s, 6H, 2 CH_3).

α-Methoxy-α-trifluoromethylbenzylamine, **16**.- Ketimine **6** (259 mg) was added to absolute methanol (3 mL) followed by triethylamine (3 drops). After 24 h at 60°, the methanol and triethylamine were vacuum evaporated leaving crude **16** (302 mg) as a colorless oil; ^{1}H NMR: δ 7.38-7.76 (m, 5H, Ph), 3.20 (s, 3H, OCH_3), 2.26 (broad, 2H, NH_2) ; ^{19}F NMR: δ -7.293 ppm (s, CF_3); Anal. Calcd for $C_9H_{10}ONF_3$: C, 52.68; H, 4.91; N, 6.83. Found: C, 52.56; H, 4.60; N, 5.98.

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17. From an analytical standpoint, if the magnitude of the NMR chemical shift differences is large enough for accurate integration of the two peaks (namely in excess of 0.02-0.03 ppm) then further separation of peaks is not important, depending upon the accuracy required. In addition, if Δδ is below this minimum, it is quite likely that Δδ may be enhanced by the use of a shift reagent[18] or possibly the addition of trifluoroacetic acid (see reference 5b under "NMR measurements"). Alternatively the analysis may be accomplished by use of HPLC or GLC methods[7,8]. Larger Δδ values are important for configuration correlations[19,20].
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