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Friedel–Crafts Acylation with *N*-(Trifluoroacetyl)-α-amino Acid Chlorides. Application to the Preparation of β-Arylalkylamines and 3-Substituted 1,2,3,4-Tetrahydroisoquinolines

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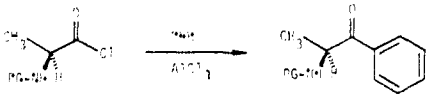
Several *N*-(trifluoroacetyl)-α-amino acid chlorides have been reacted with benzene, anisole, and veratrole in the presence of $AlCl_3$ or $SnCl_4$ to produce the corresponding aromatic ketones in fair to high yields. The products are reducible under neutral or acidic conditions to the corresponding *N*-(trifluoroacetyl)-β-hydroxy-β-arylalkylamines or *N*-(trifluoroacetyl)-β-arylalkylamines. The latter can be readily detrifluoroacetylated by mild basic hydrolysis and thence converted to the corresponding 3-substituted 1,2,3,4-tetrahydroisoquinolines by condensation with formaldehyde.

The common natural and synthetic amino acids are attractive starting materials for the preparation of more complex amines. One goal in this area has been the utilization of N-protected amino acid chlorides in Friedel–Crafts acylations to produce dissymmetric aromatic amino ketones. Buckley and Rapoport[1] have recently reviewed the literature of largely unsuccessful efforts toward this end and reported a significant step forward in the reaction of benzene with L-*N*-(ethoxycarbonyl)alanyl chloride (**1a**) and $AlCl_3$ to produce the optically pure keto carbamate, eq 1. The process failed with anisole, however. These



(1)

1a PG = EtOCO
b PG = MeOCO
c PG = p-$C_7H_7SO_2$
d PG = CF_3CO

authors at the same time found the tosyl function in derivative **1c** to provide ineffective protection of the amino group under the conditions of eq 1. McClure and coworkers concurrently acylated benzene with the L-*N*-methoxycarbonyl analogue, **1b**, with 3–4% racemization.[2a] They have since obtained fair yields with the corresponding reagents from leucine and proline plus benzene (the enantiomeric product composition was not determined) but found the process to fail starting with valine or isoleucine.[2b] Several groups have reported successful intramolecular acylations of aromatic rings within N-protected amino acids.[2,3]

Pines and co-workers in 1967[4] recorded a single Friedel–Crafts acylation using (trifluoroacetyl)-protected L-alanyl chloride, **1d**, with an apparently high degree of configurational preservation, eq 1. We report here results that demonstrate *N*-(trifluoroacetyl)amino acid chlorides to be broadly advantageous reagents for the Friedel–Crafts synthesis of aryl *N*-(trifluoroacetyl)aminoalkyl ketones. We describe also the reduction and hydrolysis of these products to the corresponding β-hydroxy-β-arylalkylamines and β-arylalkylamines and conversion of the latter by Pictet–Spengler cyclocondensation with formaldehyde to 3-substituted 1,2,3,4-tetrahydroisoquinolines. The stereochemistry of these reactions will be addressed in ensuing papers.

Results

Friedel–Crafts Acylations. The parent reaction of the study was conducted between *N*-(trifluoroacetyl)glycyl

(1) (a) Buckley, T. F., III; Rapoport, H. *J. Am. Chem. Soc.* **1981**, *103*, 6157. See also: (b) Knudsen, C. G.; Rapoport, H. *J. Org. Chem.* **1983**, *48*, 2260. (c) Buckley, T. F., III; Rapoport, H. *Ibid.* **1983**, *48*, 4222. (d) Buckley, T. F., III; Rapoport, H. *J. Am. Chem. Soc.* **1980**, *102*, 3056.

(2) (a) McClure, D. E.; Arison, B. H.; Jones, J. H.; Baldwin, J. J. *J. Org. Chem.* **1981**, *46*, 2431. (b) McClure, D. E.; Lumma, P. K.; Arison, B. H.; Jones, J. H.; Baldwin, J. J. *Ibid.* **1983**, *48*, 2675.

(3) (a) Zhao, Y.-F.; Xi, S.-K.; Tian, Y.-F; Song, A.-T. *Tetrahedron Lett.* **1983**, *24*, 1617. (b) Rebek, J.; Shue, Y. K. *J. Am. Chem. Soc.* **1980**, *102*, 5426. (c) Reifenrath, W. G.; Bertelli, D. J.; Micklus, M. J.; Fries, D. S. *Tetrahedron Lett.* **1976**, 1959. (d) Koo, J. *J. Org. Chem.* **1963**, *28*, 1134. (e) Braunholtz, J. T.; Mann, F. G. *J. Chem. Soc.* **1957**, 4166.

(4) Pines, S. H.; Chemerda, J. M.; Kozlowski, M. A.; Weinstock, L. M.; Davis, P.; Handelsman, B.; Grenda, V. J.; Lindberg, G. W. *J. Med. Chem.* **1967**, *10*, 725.

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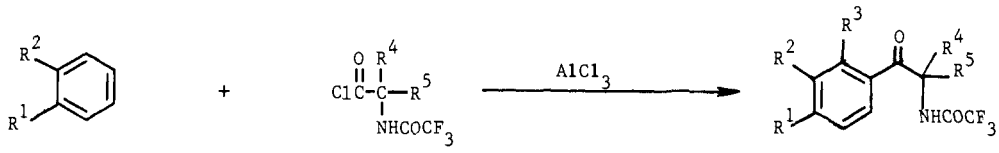
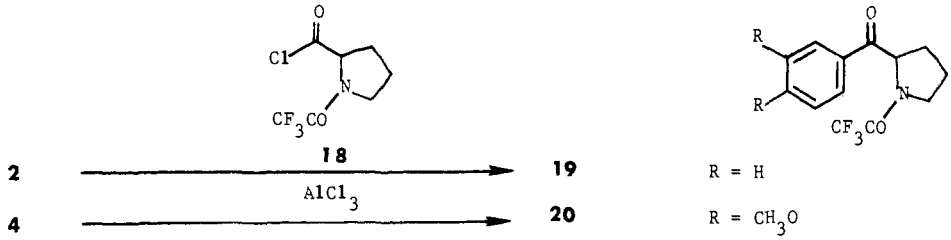
Scheme I. Preparation of Aryl *N*-(Trifluoroacetyl)-α-aminoalkyl Ketones by Friedel-Crafts Acylation



	R^1	R^2		R^4	R^5		R^1	R^2	R^3	R^4	R^5	Method	% Yield
2	H	H	**5**	H	H	**9**	H	H	H	H	H	B (A)	77 (43)
3	CH_3O	H	**6**	H	CH_3	**10**	H	H	CH_3O	H	H	A	30[a]
4	CH_3O	CH_3O	**7**	CH_3	CH_3	**11**	CH_3O	H	H	H	H	A	30[a]
			8	H	$CH(CH_3)_2$	**12**	CH_3O	CH_3O	H	H	H	A	38
						13	H	H	H	H	CH_3	A	69
						14	CH_3O	CH_3O	H	H	CH_3	A	37
						15	H	H	H	CH_3	CH_3	B (A)	67 (55)
						16	CH_3O	CH_3O	H	CH_3	CH_3	B[b]	22
						17	H	H	H	H	$CH(CH_3)_2$	A	32

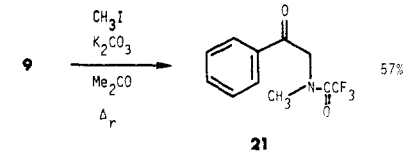


2	**19**	R = H	A 87
4	**20**	R = CH_3O	A 65

[a] Ortho/para ratio (10/11) = 1.33. [b] $SnCl_4$ used in place of $AlCl_3$.

chloride[5] (*N*-TFAglycyl chloride) (**5**) and benzene (**2**) in CH_2Cl_2 in the presence of 2.1 equiv of anhydrous $AlCl_3$ under dry N_2 with efficient stirring (Scheme I). Standard workup and recrystallization produced *N*-(trifluoroacetyl)-α-aminoacetophenone (**9**) in 77% yield. The acid chloride was generated from *N*-(trifluoroacetyl)glycine[6a,b] by reaction with oxalyl chloride and a catalytic amount of $HCONMe_2$ in CH_2Cl_2 as described by Buckley and Rapoport[1a] for the production of (ethoxycarbonyl)-protected alanyl chloride, **1a**. In like manner ketones **10**–**17**, **19**, and **20** were prepared from *N*-TFAglycyl (**5**), -(±)-alanyl[6c] (**6**), -α-aminoisobutyryl (**7**), -(±)-valyl (**8**), and -(±)-prolyl[7] (**18**) chlorides in reaction with benzene (**2**), anisole (**3**), and veratrole (**4**), as outlined in Scheme I. In the reactions with anisole and veratrole, 1.1 equiv of $AlCl_3$ was employed in accordance with Buckley and Rapoport's demonstration of retarding effects of large excesses of aluminum halides in other acylations of methoxy-substituted benzenes.[1c] $SnCl_4$ was used instead with fair success in the preparation of **16**. Yields were better when the acid chlorides were produced by the method above (method B) than in earlier experiments when benzene and pyridine were used as the solvent and catalyst, with evaporation of the benzene prior to reaction with another aromatic substrate (method A). The TFA amino acids were prepared from the amino acids by reaction with CF_3CO_2Et in MeOH containing Et_3N[8] or, to better effect in the case of **7** and **18**,[9] 1,1,3,3-tetramethylguanidine.[10]

N-Alkylation of (Trifluoroacetyl)amino Ketones. In a representative alkylation of the (trifluoroacetyl)amino function,[5a,11] ketone **9** was converted to its *N*-methyl derivative **21** by reaction with anhydrous K_2CO_3 and CH_3I in boiling dry acetone.



21

Ketone Reductions. Reductions of several of the (trifluoroacetyl)amino ketones were investigated under five different reaction conditions, with a primary view toward complete deoxygenation of the keto function to a methylene group. The results are summarized in Scheme II.

Parent ketone **9** could be reduced with triethylsilane in trifluoroacetic acid[12a] to the (trifluoroacetyl)amino alcohol

(5) (a) Nordlander, J. E.; Payne, M. J.; Balk, M. A.; Gress, J. L.; Harris, F. D.; Lane, J. S.; Lewe, R. F.; Marshall, S. E.; Nagy, D.; Rachlin, D. J. *J. Org. Chem.* **1984**, *49*, 133. (b) Weygand, F.; Leising, E. *Chem. Ber.* **1954**, *87*, 248.

(6) (a) Weygand, F.; Csendes, E. *Angew. Chem.* **1952**, *64*, 136. (b) Schallenberg, E. E.; Calvin, M. *J. Am. Chem. Soc.* **1955**, *77*, 2779. (c) Weygand, F.; Geiger, R. *Chem. Ber.* **1956**, *89*, 653.

(7) Bonner, W. A. *J. Chromatogr. Sci.* **1972**, *10*, 159.

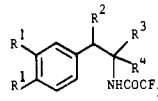
(8) Curphey, T. J. *J. Org. Chem.* **1979**, *44*, 2805.

(9) (a) Horiba, M.; Kitahara, H.; Murano, A. *Agric. Biol. Chem.* **1977**, 10, 2003. (b) Tomida, I.; Kuwahara, T. *Agric. Biol. Chem.* **1978**, *42*, 1059. (c) Tomida, I.; Matsuzaki, M. *Agric. Biol. Chem.* **1979**, *43*, 925. (d) Panetta, C. A. *Org. Synth.* **1977**, *56*, 122. (e) Isralli, Z. H.; Smissman, E. E. *J. Chem. Eng. Data* **1977**, 22, 357.

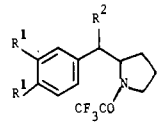
(10) Steglich, W.; Hinze, S. *Synthesis* **1976**, *399*.

(11) Gribble, G. W.; Soll, R. M. *J. Org. Chem.* **1981**, *46*, 2433.

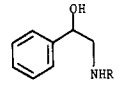
Scheme II. Reductions of Aryl *N*-(Trifluoroacetyl)-α-aminoalkyl Ketones



							% Yield
9	A	22	H	OH	H	H	50
9	C						86
9	B	23	H	H	H	H	78
9	D						83
12	A	24	CH_3O	H	H	H	74
12	C	25	CH_3O	OH	H	H	72
14	A	26	CH_3O	H	H	CH_3	88
15	A	27	H	OH	CH_3	CH_3	72
15	C						97
16	B	28	CH_3O	H	CH_3	CH_3	78



					% Yield
19	D	29	R^1 = H	R^2 = H	85
20	B	30	R^1 = CH_3O	R^2 = H	88



					% Yield
9	E	31	R = H		25
21	E	32	R = CH_3		97

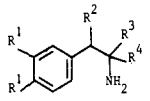
[a] Reagents: A, Et_3SiH/CF_3CO_2H; B, $Et_3SiH/BF_3{\cdot}Et_2O$; C, $H_2/Pd/EtOH$; D, $H_2/Pd/HCl/EtOH$; E, $NaBH_4/EtOH$.

22, but not beyond. Since acetophenone has been found to be readily reduced to ethylbenzene under the same conditions,[12a] the (trifluoroacetyl)amino group is seen to inhibit the dehydroxylation step, presumably by inductive destabilization of a requisite carbenium ion. Alcohol **22** was also produced from **9** by ordinary hydrogenation over 10% Pd/C.[1a] Complete deoxygenation was effected, on the other hand, by treatment of **9** with triethylsilane in neat $BF_3{\cdot}Et_2O$[12b] or by catalytic hydrogenation in the presence of HCl,[1a] yielding **23**.[13]

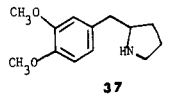
Ketones **12** and **14**, in contrast, were reduced by Et_3SiH in CF_3CO_2H smoothly to the methylene compounds, **24**[14] and **26**, respectively, doubtless due to the carbenium-ion-stabilizing *p*-methoxy substituents. Phenyl ketone **15** accordingly afforded only the alcohol **27** on reaction with this reagent pair. Neutral catalytic hydrogenation of **12** and **15** again gave the expected alcohols **25** and **27**, respectively, while **19** underwent hydrogenolysis under strongly acidic conditions to produce **29**. Activated ketones **16** and **20** were deoxygenated with Et_3SiH in $BF_3{\cdot}Et_2O$ to furnish **28** and **30**, respectively.

Reduction of trifluoroacetamido ketones **9** and **21** with $NaBH_4$ in EtOH occurred at both functional sites, as expected,[15] to give 2-phenylethanolamine[16a] (**31**), a vasoconstrictor,[16b] and the alkaloid halostachine[17] (**32**), respectively.

Scheme III. Basic Hydrolysis of Trifluoroacetamides

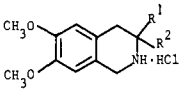


							% Yield
22	$K_2CO_3/MeOH/H_2O/\Delta_r$	31	H	OH	H	H	25
24	"	33	CH_3O	H	H	H	63
26	"	34	CH_3O	H	H	CH_3	70
27	"	35	H	OH	CH_3	CH_3	60
28	"	36	CH_3O	H	CH_3	CH_3	57

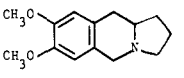


30	"	37	83

Scheme IV. Preparation of 3-Substituted 1,2,3,4-Tetrahydroisoquinolines



				% Yield
34	CH_2O, HCl	38	R^1 = CH_3 R^2 = H	56
36	CH_2O, HCl, EtOH	39	R^1 = R^2 = CH_3	55



37	CH_2O, HCl, EtOH	40	55

Hydrolysis of Trifluoroacetamides. Weakly basic hydrolysis[5a] of trifluoroacetamides **22**, **24**, **26–28**, and **30** yielded the corresponding amines **31**[16] and **33–37**,[18–20] respectively, as shown in Scheme III. Dimethoxyamphetamine **34** has received attention as a mild hallucinogen[19] and as a metabolite of *p*-chloroamphetamine.[19]

3-Substituted 1,2,3,4-Tetrahydroisoquinolines. The preceding reactions provide a convenient pathway to the otherwise difficultly accessible 3-alkyl-1,2,3,4-tetrahydroisoquinolines through Pictet–Spengler ring closure.[21]

(12) (a) West, C. T.; Donnelly, S. J.; Kooistra, D. A.; Doyle, M. P. *J. Org. Chem.* **1973**, *38*, 2675. (b) Doyle, M. P.; West, C. T.; Donnelly, S. J.; McOsker, C. C. *J. Organomet. Chem.* **1976**, *117*, 129. See also: (c) Adlington, M. G.; Orfanopoulos, M.; Fry, J. L. *Tetrahedron Lett.* **1976**, 2955. (d) Fry, J. L.; Orfanopoulos, M.; Adlington, M. G.; Dittman, W. R., Jr; Silverman, S. B. *J. Org. Chem.* **1978**, *43*, 374.

(13) (a) Joullié, M. M.; Day, A. R. *J. Am. Chem. Soc.* **1954**, *76*, 2990. (b) Pailer, M.; Huebsch, W. J. *Monatsh. Chem.* **1966**, *97*, 1541.

(14) (a) O'Donnell, J. P.; Azzaro, A. J.; Urquilla, P. R. *J. Pharm. Sci.* **1980**, *69*, 149. (b) Gray, R. W.; Dreiding, A. A. *Helv. Chim. Acta* **1980**, *63*, 315.

(15) Weygand, F.; Frauendorfer, E. *Chem. Ber.* **1970**, *103*, 2437.

(16) (a) Dornow, A.; Theidel, H. *Chem. Ber.* **1955**, *88*, 1267. (b) Roth, H. J. *Arch. Pharm. (Weinheim, Ger.)* **1959**, *292*, 76.

(17) (a) Prakash, D.; Raj, K.; Kapil, R. S.; Popli, S. P. *Indian J. Chem., Sect. B* **1980**, *19*, 533. (b) Menshikov, G. P.; Rubinshtein, M. M. *J. Gen. Chem. U.S.S.R.* **1943**, *13*, 801.

(18) Compound **33**: (a) Boulton, A. A. *Nature (London)* **1971**, *231*, 22. (b) Friedhoff, A. J.; Park, S.; Schweitzer, J. W.; Burdock, E. I.; Armour, M. *Biol. Psychiatry* **1977**, *12*, 643. (c) Knoll, E.; Wisser, H.; Emrich, H. M. *Clin. Chim. Acta* **1978**, *89*, 493. (d) Hempel, H.; Ulrich, H.; Philippe, G. *Biol. Psychiatry* **1982**, *17*, 49. (e) Pummangura, S.; Nichols, D. E.; McLaughlin, J. L. *J. Pharm. Sci.* **1977**, *66*, 1485. (f) Doetsch, P. W.; Cassady, J. M.; McLaughlin, J. L. *J. Chromatogr.* **1980**, *189*, 79.

(19) Compound **34**: (a) Ho, B. T.; McIsaac, W. M.; An, R.; Tansey, L. W.; Walker, K. E.; Englert, L. F., Jr.; Noel, M. B. *J. Med. Chem.* **1970**, *13*, 26. (b) Harris, R. A.; Snell, D.; Loh, H. H. *J. Pharmacol. Exp. Ther.* **1978**, *204*, 103. (c) Midha, K. K.; Bailey, K.; Cooper, J. K.; Hubbard, J. W. *Xenobiotica* **1979**, *9*, 485. (d) Cannon, J. G.; Perez, Z.; Long, J. P.; Rusterholz, D. B.; Flynn, J. R.; Costall, B.; Fortune, D. H.; Naylor, R. J. *J. Med. Chem.* **1979**, *22*, 901. (e) Glennon, R. A.; Liebowitz, S. M.; Anderson, G. M., III. *J. Med. Chem.* **1980**, *23*, 294.

(20) Compound **36**: Renger, B. *Arch. Pharm. (Weinheim, Ger.)* **1983**, *316*, 193.

Three examples using formaldehyde are presented in Scheme IV. 7,8-Dimethoxy-1,2,3,5,10,10a-hexahydropyrrolo[1,2-*b*]isoquinoline[22] (**40**) has recently been synthesized by a longer route and reported to be a uterine stimulant.

Discussion

The present results establish the general effectiveness of Friedel–Crafts acylation reactions of N-trifluoroacetylated amino acid chlorides with benzene and electron-rich aromatics. For amino protection under such highly acidic conditions, the strongly electronegative trifluoroacetyl group is clearly superior to other acyl and sulfonyl functions that have been explored[1a] and is easily attached and removed. This development opens a new avenue to a wide variety of aryl aminoalkyl ketones and derived structures, including many of biological interest.

It is notable that no decarbonylation was observed in the present Friedel–Crafts reactions. Decarbonylation is a rapid reaction of α-tertiary amino acid chlorides[23] and even N-sulfonylated α-amino acid chlorides in the presence of Lewis acids at room temperature.[24] The other significant synthetic finding here is that the intermediate ketones can be readily deoxygenated under acidic conditions without cleavage of the trifluoroacetamido function. This allows N-monoalkylation,[5a,11] if desired, before deprotection of the amine by basic hydrolysis.

The synthetic value of the present reactions will be much enhanced if the enantiomeric purity of chiral amino acid reactants can be preserved. Pines' original observation with **1d** was encouraging to this prospect, which has been strengthened by further results in our laboratory. Detailed information will be reported shortly.

Experimental Section

General Methods. Capillary melting points are uncorrected. Infrared spectra were obtained with a Beckman IR-8 or IR-10 spectrophotometer. ^{1}H NMR spectra were recorded at 60 MHz on a Varian EM-360A spectrometer and at 200 MHz on a Varian XL-200 Fourier-transform spectrometer using $CDCl_3$ as solvent and Me_4Si as internal standard unless otherwise noted; 2,2-dimethyl-2-silapentane-5-sulfonate (DSS) was employed as internal standard when the solvent was D_2O. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, TN.

For the preparation of compounds **9**–**17** and **19**–**40**, below, yields are given in Schemes I–IV and recrystallization solvents and melting points in Table I. See paragraph at the end of paper about supplementary material.

***N*-(Trifluoroacetyl)amino Acids.** *N*-(Trifluoroacetyl)glycine, -(±)-alanine, and -(±)-valine were prepared from the amino acids by using CF_3CO_2Et and Et_3N in MeOH as described by Curphey.[8] *N*-(Trifluoroacetyl)-(±)-proline and -α-aminoisobutyric acid were prepared likewise by using 1,1,3,3-tetramethylguanidine as base, according to Steglich and Hinze,[10] rather than Et_3N.

***N*-(Trifluoroacetyl)amino Acid Chlorides.** Two methods were used to prepare the corresponding acid chlorides.

Method A.[5a] Oxalyl chloride (4.8 mL, 55 mmol) was added dropwise over 5 min to a stirred suspension of 50 mmol of the *N*-(trifluoroacetyl)amino acid in 50 mL of dry benzene containing 3 drops of dry pyridine. The mixture was heated under reflux for 15 min and allowed to cool to room temperature, and the benzene and excess reagent were removed by rotary evaporation, yielding the crude acid chloride as a clear yellow liquid.

Method B.[1a] To a magnetically stirred solution of the *N*-(trifluoroacetyl)amino acid (0.10 mol) in 300 mL of CH_2Cl_2 under nitrogen at 0 °C was added 0.5 mL of $HCONMe_2$ and 10 mL (14.6 g, 0.12 mol) of oxalyl chloride (Aldrich) in one portion. The reaction mixture was allowed to warm to room temperature and was stirred for an additional 2 h to give the acid chloride, which was used in solution without further purification.

***N*-(Trifluoroacetyl)-α-aminoacetophenone (9).** *N*-TFAglycyl chloride (**5**), prepared by method A above from 4.0 g (23 mmol) of *N*-TFAglycine, was dissolved in 50 mL of dry benzene, and 3.4 g (26 mmol) of anhydrous $AlCl_3$ was added to the stirred solution over a 10-min period. The mixture was boiled under reflux under N_2 for 3 h, allowed to cool, and poured into 40 mL of cold 6 M HCl. The layers were separated, and the aqueous layer was extracted with 2 × 40 mL of benzene. The combined organic layers were washed with 50 mL of saturated $NaHCO_3$ solution, dried over anhydrous $MgSO_4$, and concentrated by rotary evaporation to yield a brown solid, which was recrystallized to afford pure **9**.

Alternatively, **5** prepared by method B above from 14.4 g (84.4 mmol) of *N*-TFAglycine was diluted with 130 mL of CH_2Cl_2 and 1 L of benzene and cooled to −15 °C. In one portion 24.0 g (180 mmol) of anhydrous $AlCl_3$ was added, and stirring was continued at −15 °C for 12 h. The solution was quenched with 250 mL of cold 1 N HCl and diluted with 150 mL of cold water. The phases were separated, and the organic layer was washed successively with 2 × 150 mL of cold 1 N HCl, 250 mL of water, and 2 × 150 mL of saturated $NaHCO_3$ solution, dried over $MgSO_4$, and concentrated by rotary evaporation to afford a brown solid, which was recrystallized to give ketone **9**.

***N*-(Trifluoroacetyl)-α-amino-*o*-methoxyacetophenone (10) and -*p*-methoxyacetophenone (11).** To a three-necked, round-bottomed flask fitted with an efficient mechanical stirrer

Table I. Melting Points and Recrystallization Solvents

compd	mp, °C	solvent(s) of recrystallization
9[a]	108.5–110	$EtOH/H_2O$
10[a]	107.5–108	$EtOH/H_2O$
11[a]	73–74	$EtOH/H_2O$
12[a]	123–124	$PhCH_3$/hexanes
13	62–63[b]	petroleum ether
14[a]	109–110	$PhCH_3$/hexanes
15[a]	92–94	$PhCH_3$/heptane
16[a]	178–179	PhH/Et_2O
17[a]	125–127	hexanes
19[a]	79–82	$PhCH_3$/heptane
20[a]	122–124	$PhCH_3$/heptane
21[a]	53–55	petroleum ether
22[a]	77–79	$PhCH_3$/heptane
23	55–56[c]	heptane
24	83–85[d]	$PhCH_3$/heptane
25	oil	
26	103–104	$PhCH_3$/hexanes
27[a]	108–110	$PhCH_3$/heptane
28[a]	82–84	$PhCH_3$/heptane
29	oil	
30	oil	
31	55[e]	H_2O/EtOH/petroleum ether
32	74–75[f]	Et_2O/petroleum ether
33	155–156[g]	$EtOH/Et_2O$
34	oil	
35[a]	101–103	$PhCH_3$/heptane
36	oil	
37	oil	
38	245–247[h]	H_2O/EtOH/Et_2O
39[a]	241–242.5	$EtOH/Et_2O$
40	126–127[i]	heptane

[a] Satisfactory elemental analysis (±0.4%) obtained for C, H, N. [b] Usin; L-alanine, lit.[4] mp 50–51 °C. [c] Lit.[13] mp 56–57 °C. [d] Lit.[14] mp 84 °C. [e] Lit.[16a] mp 57–59 °C. [f] Lit.[17] mp 75–77 °C. [g] Compound made from free base also had mp 155–156 °C. [h] Lit.[26] mp 245 °C. [i] Lit.[22] mp 120–122 °C.

(21) (a) Kametani, T.; Kigasawa, K.; Hiiragi, M.; Ishimaru, H. *J. Chem. Soc. C* 1971, 2632. (b) Soerens, D.; Sandrin, J.; Ungemach, F.; Mokry, P.; Wu, G. S.; Yamanaka, E.; Hutchins, L.; DiPierro, M.; Cook, J. M. *J. Org. Chem.* **1979**, *44*, 535. (c) Ungemach, F.; DiPierro, M.; Weber, R.; Cook, J. M. *J. Org. Chem.* **1981**, *46*, 164.

(22) Gaur, S. P.; Jain, P. C.; Anand, N. *Indian J. Chem.* **1982**, *21B*, 46.

(23) (a) Dean, R. T.; Padgett, H. C.; Rapoport, H. *J. Am. Chem. Soc.* **1976**, *98*, 7448. (b) Mannich, C.; Kuphal, R. *Ber.* **1912**, *45*, 314. (c) Clemo, G. R.; Perkin, W. H. *J. Chem. Soc.* **1925**, 2297. (d) Proctor, G. R.; Thomson, R. H. *J. Chem. Soc.* **1957**, 2302. (e) Mortes, M. P.; Borne, R. F.; Hare, L. F. *J. Org. Chem.* **1968**, *33*, 133.

(24) (a) Von Braun, J.; Blessing, G.; Cahn, R. S. *Ber.* **1924**, *57*, 908. (b) Von Braun, J.; Wirz, K. *Ber.* **1927**, *60*, 102.

and reflux condenser were added *N*-(TFA)glycyl chloride prepared from 4.0 g (23 mmol) of *N*-(trifluoroacetyl)glycine by method A, 2.5 mL (2.52 g, 23 mmol) of anisole, and 100 mL of CH_2Cl_2. Aluminum chloride (3.43 g, 26 mmol) was slurried in 25 mL of CH_2Cl_2 and added in portions to the stirred solution at 0 °C. The resulting mixture was boiled under reflux under N_2 for 48 h and then allowed to cool to room temperature. The dark mixture was poured into 60 mL of cold 6 M HCl, the layers were separated, and the aqueous layer was extracted twice with 50-mL portions of CH_2Cl_2. The combined organic layers were washed with 10% K_2CO_3, dried over $MgSO_4$, and concentrated by rotary evaporation to give a brown solid. ^1H NMR analysis of this crude product mixture indicated an ortho/para ratio of 1.33. Recrystallization from 70% aqueous EtOH gave a first crop at room temperature and a second crop on cooling to 0 °C. Recrystallization of the first crop from toluene/hexane afforded 1.03 g (4.0 mmol) of the pure ortho product **10**, and recrystallization of the second crop likewise gave 0.77 g (3.0 mmol) of pure para product **11**. The products were differentiated by their distinctive ^1H NMR spectra in the aromatic region.

***N*-(Trifluoroacetyl)-α-amino-3,4-dimethoxyacetophenone (12), *N*-(trifluoroacetyl)-α-aminopropiophenone (13),[4] *N*-(trifluoroacetyl)-α-amino-3,4-dimethoxypropiophenone (14), *N*-(trifluoroacetyl)-α-aminoisobutyrophenone (15), *N*-(trifluoroacetyl)-α-amino-3,4-dimethoxyisobutyrophenone (16), *N*-(trifluoroacetyl)-α-aminoisovalerophenone (17), *N*-(trifluoroacetyl)prolylbenzene (19), and *N*-(trifluoroacetyl)-3,4-dimethoxyprolylbenzene (20)** were prepared from the reactants shown in Scheme I by methods analogous to those described for the preparation of **9–11**.

***N*-Methyl-*N*-(trifluoroacetyl)-α-aminoacetophenone (21).** Ketone **9** (2.00 g, 8.66 mmol) was dissolved in 48 mL of dry acetone (freshly distilled from oven-dried K_2CO_3). Anhydrous K_2CO_3 (2.41 g, 17.4 mmol) and 2.17 mL (3.32 g, 34.9 mmol) of CH_3I were added. The mixture was boiled under reflux under N_2 for 48 h. The volatiles were removed by rotary evaporation, and 3 mL of H_2O was added to the residue, which was extracted into 3 × 40 mL of Et_2O, dried over anhydrous $MgSO_4$, and concentrated by rotary evaporation. The resulting solid was recrystallized to afford pure **21**.

Ketone Reductions. Ketones **9**, **12**, **14–16**, and **19–21** were reacted under five types of reducing conditions as described below. The individual methods used are shown in Scheme II.

Method A. To a stirred solution of the carbonyl compound (7 mmol) in 12 mL (156 mmol) of freshly distilled trifluoroacetic acid was added 3.8 mL (24 mmol) of distilled triethylsilane.[12a] The resulting solution was boiled under reflux under N_2 for 2 h and then stirred overnight at room temperature. Saturated $NaHCO_3$ solution was added cautiously until the solution was alkaline, and the product was extracted with 3 × 30 mL of Et_2O. The combined Et_2O layers were dried over $MgSO_4$ and concentrated by rotary evaporation to afford the product, which was washed with hexanes. Solid products were recrystallized, while oils were used without further purification.

Method B. Triethylsilane[12b] (0.6 mL, 3.8 mmol) was added to a solution of the ketone (0.94 mmol) in 2.32 mL (19.0 mmol) of freshly distilled $BF_3{\cdot}Et_2O$. The solution was stirred under N_2 for 40 h and then treated with 1 mL of saturated NaCl solution. The aqueous layer was extracted with 2 × 10 mL of Et_2O, the ether layers were combined and dried ($MgSO_4$), and the volatiles were removed by rotary evaporation.

Method C. A solution of the ketone (1.93 mmol) in 50 mL of absolute ethanol and 75 mg of 10% Pd/C were shaken under 44 psig of H_2 for 12 h. The mixture was filtered, and the ethanol was evaporated to give the product.

Method D. To a solution of the ketone (1.73 mmol) in 5 mL of absolute EtOH was added 600 μL of saturated ethereal HCl and 5 mg of 10% Pd/C, and the mixture was shaken under 55 psig of H_2 for 4 h.[1a] The mixture was filtered and concentrated to yield the product.

Method E. To a solution of the ketone[15] (0.87 mmol) in 10 mL of absolute EtOH was added 0.20 g (5.2 mmol) of $NaBH_4$. The mixture was stirred under nitrogen for 12 h. To obtain amino alcohol **31**, the mixture was rotary evaporated to dryness, and the resulting solid was triturated sequentially with 95%, 97%, and 100% EtOH. To obtain amino alcohol **32**, the EtOH was rotary evaporated and the resulting solid dissolved in 2 mL of H_2O. The product was extracted with Et_2O. The Et_2O was dried and rotary evaporated to afford a light yellow solid which was recrystallized to give pure **32**.

Hydrolysis of Trifluoroacetamides. Cleavage of the trifluoroacetamido function for compounds **22**, **24**, **26–28**, and **30** proceeded as follows.[5a] In a 100-mL, round-bottomed flask fitted with a reflux condenser and magnetic stirrer were placed 3.6 mmol of the trifluoroacetamide, 1.5 g (11 mmol) of K_2CO_3, 30 mL of MeOH, and 1.5 mL of H_2O. The mixture was boiled under reflux for 2 h (54 h for **28**) and allowed to cool to room temperature, and the solid K_2CO_3 was removed by filtration. The majority of the MeOH was rotary evaporated, and the residue was treated with saturated ethereal HCl to precipitate the amine as the hydrochloride salt, which was recrystallized. Alternatively, the residue was dissolved in 2 mL of H_2O and extracted with 3 × 30 mL of $CHCl_3$, and the combined $CHCl_3$ fractions were dried over anhydrous K_2CO_3 and concentrated to afford the free amine.

3-Methyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline Hydrochloride (38). Formaldehyde (0.27 mL of a 37% solution, 3.6 mmol) was added to 0.45 g (2.3 mmol) of crude amine **34**, and the solution was heated on an oil bath at 90 °C for 1 h.[25] A 4-fold excess of 23% HCl was added, and the solution was concentrated to a solid under reduced pressure. Recrystallization provided pure **38**.

6,7-Dimethoxy-3,3-dimethyl-1,2,3,4-tetrahydroisoquinoline Hydrochloride (39). A solution of 360 mg (1.72 mmol) of amine **36**, 4.4 mL of EtOH, and 4.4 mL of 37% formaldehyde was acidified with 370 μl of concentrated HCl and boiled under reflux for 12 h. The volatiles were removed by rotary evaporation, and the resulting solid was recrystallized to afford pure tetrahydroisoquinoline **39**.

7,8-Dimethoxy-1,2,3,5,10,10a-hexahydropyrrolo[1,2-*b*]isoquinoline (40). A solution of 1.06 g (4.79 mmol) of amine **31**, 12.4 mL of EtOH, and 12.4 mL of 37% formaldehyde was acidified with 1.04 mL of concentrated HCl and boiled under reflux for 6 h. The volatiles were distilled under reduced pressure, and the residue was diluted with 10% HCl. The aqueous layer was washed with Et_2O, basified with 28% ammonia, and extracted with $CHCl_3$. The solvent was evaporated, and the resulting solid was recrystallized to give pure **40**.

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Registry No. **2**, 71-43-2; **3**, 100-66-3; **4**, 91-16-7; **5**, 383-69-7; **5** (acid), 383-70-0; (±)-**6**, 1597-19-9; (±)-**6** (acid), 1597-49-5; **7**, 91994-48-8; **7** (acid), 2707-93-9; (±)-**8**, 92076-91-0; (±)-**8** (acid), 1978-55-8; **9**, 91994-49-9; **10**, 91994-50-2; **11**, 91994-51-3; **12**, 91994-52-4; (±)-**13**, 91994-53-5; (±)-**14**, 91994-54-6; **15**, 91994-55-7; **16**, 91994-56-8; (±)-**17**, 91994-57-9; (±)-**18**, 92076-92-1; (±)-**18** (acid), 92076-93-2; (±)-**19**, 91994-58-0; (±)-**20**, 91994-59-1; **21**, 57052-65-0; **22**, 91994-60-4; **23**, 458-85-5; **24**, 13230-71-2; **25**, 91994-61-5; (±)-**26**, 91994-62-6; **27**, 91994-63-7; **28**, 91994-64-8; (±)-**29**, 91994-65-9; (±)-**30**, 91994-66-0; **31**, 7568-93-6; (±)-**32**, 68579-60-2; **33**, 120-20-7; (±)-**34**, 2936-29-0; **35**, 34405-42-0; **36**, 75561-47-6; (±)-**37**, 91994-67-1; (±)-**38**, 91994-68-2; **39**, 37462-24-1; (±)-**40**, 91994-69-3.

Supplementary Material Available: Full details for preparation of (trifluoroacetyl)amino ketones **12–17**, **19**, and **20**, complete ^1H NMR spectral data for compounds **9–17** and **19–40**, and IR spectral data for compounds **9–17**, **19–22**, **26–30**, **35–37**, and **40** (6 pages). Ordering information is given on any current masthead page.

(25) Buck, J. S. *J. Am. Chem. Soc.* **1934**, *56*, 1769.
(26) Ide, W. S.; Buck, J. S. *J. Am. Chem. Soc.* **1940**, *62*, 425.