Generation and Reaction of (*N*-Aryltrifluoroacetimidoyl)zinc Halide

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Synopsis. (*N*-Aryltrifluoroacetimidoyl)zinc halides were easily generated at room temperature by the oxidative addition of imidoyl halides to activated zinc powder. [*N*-(2,6-Dichlorophenyl)- and *N*-(2,6-dimethylphenyl)trifluoroacetimidoyl]zinc halides react with aldehydes to give the corresponding alcohols smoothly in good to excellent yields. These adducts could be readily transformed to the α-amino ketones.

The requirement for trifluoromethylated organic compounds in the field of medicinal, agrochemical, and material sciences[1] has prompted us to develop a new methodology for the syntheses of trifluoromethylated synthetic blocks.[2] We have proposed that *N*-aryltrifluoroacetimidoyl halides (**1**, **2**, and **3**) are one of the promising synthetic blocks for trifluoromethylated nitrogen heterocycles and have developed an efficient synthetic method for them.[3] In the preceding papers, nucleophilic displacement of chloride **1** with nitrogen[4] and carbon[5] nucleophiles has been described for the syntheses of trifluoromethylated nitrogen heterocycles. Metalation of the imidoyl halides **1**—**3** is another part of our interests and would enable them to behave as carbanions that react with electrophiles. The method should further extend the utility of **1**—**3** for heterocycle syntheses. Palladation and lithiation have been examined so far. Thus, the highly covalent imidoyl palladiums **4** are stable enough to be used for alkynylation,[6] alkenylation,[6] and carbonylation[7] on the imino carbon at room temperature and even at 60 °C. In contrast, imidoyl lithiums **5** as a representative carbanion have been found so unstable, being in equilibrium with the carbene intermediate **7** (Chart 1), that they must be handled below −78 °C.[8] On this basis, the imidoyl zinc **6** is expected to be more stable than the imidoyl lithium **5** and thus could be handled at room temperature, because the Pauling percent ionicities of carbon–metal bonds are in the order of C–Pd (3%), C–Zn (19%), and C–Li (43%).[9] This paper describes the generation of the imidoyl zinc **6** and its reaction with aldehydes.

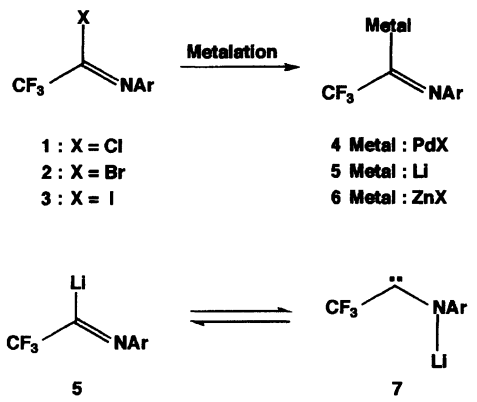


Chart 1.

Results and Discussion

The imidoyl iodide **3a** (Ar = 4-methylphenyl) was completely consumed by the action of activated zinc powder[10] in DMF–HMPA (1 : 1 v/v) within 60 min at room temperature. The reaction was accelerated in the presence of an equimolar amount of aluminum powder on the basis of that of zinc or by sonication for 30 min at 40—50 °C. In particular, the reaction of **3a** with benzaldehyde was brought to success within 10 min by use of aluminum powder under sonication, affording the unstable alcohol **8a** which could be isolated as its acetate form **9a** in 51% yield. Zinc–copper couple[11] was also applicable for the reaction, but the yield was less (15 min, 38%).

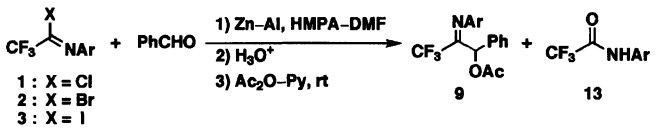
A mixture of DMF and HMPA (1 : 1) is the best choice of solvents so far as examined. The zinc reagent **6** could be generated in aprotic solvents such as THF, ether, acetonitrile, and dichloromethane, but the yield of the adducts was poor. The reaction of the chloride **1a** and the bromide **2a** took a longer time and gave **9a** in very poor yields (Entries 1 and 2 in Table 1). Both compounds with 2,6-dimethyl- and 2,6-dichlorophenyl groups would stabilize the zinc reagents of **6e**[12] and **6f** by the ortho substitution effect as observed in Table 1. Adducts **9e** and **9f** were obtained in excellent yields (94% and 64%) by increasing the amount of zinc (20.0 equiv).[13]

The alcohols **8** with a disubstituted phenyl group were stable and could be isolated with a flash column chromatography. The alcohols **8** were readily transformed to α-amino ketones **12** on heating them at 150 °C as shown in Table 2. The transformation of **8** to **12** can be explained by an imine–enamine equilibrium. Prototropy from the aminoenol intermediate **10** would result in the formation of α-amino ketone as a final product as shown in Scheme 1. In fact, the variable temperature ^{1}H and ^{19}F NMR study of the acetate **9e** (Ar=2,6-dimethylphenyl, R=Ph) showed that both imine **9** and enamine **11** forms exist as an equilibrium mixture in the ratio of 1 (**9**) : 3 (**11**) in $CDCl_3$.

Experimental

^{1}H and ^{19}F NMR spectra were recorded on a Varian VXR-200 operating at 200 and 188 MHz, respectively. Chemical shifts were reported in ppm down-field from TMS or C_6F_6.

Table 1. Reaction of Imidoyl Halides **1**—**3** with Benzaldehyde[a)]



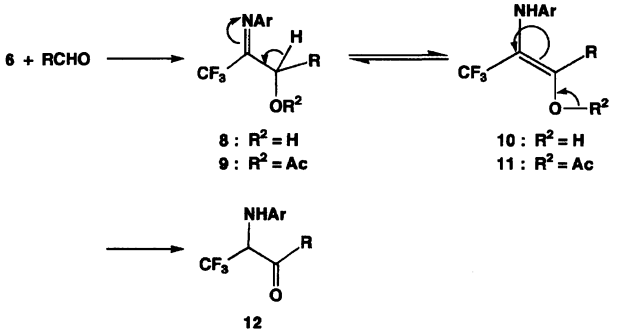
Entry	X	Ar	Zn	Solvent	Time	Yield of **9**	Yield of **13**
			equiv	ml	min	%	%
1	Cl	4-MeC_6H_4	3.0	0.1	120	**9a** (3)	**13a** (16)
2	Br	4-MeC_6H_4	3.0	0.1	840	**9a** (8)	**13a** (75)
3	I	4-MeC_6H_4	3.0	0.1	10	**9a** (51)	**13a** (5)
4	I	4-MeC_6H_4	7.2	0.1	10	**9a** (48)	**13a** (5)
5	I	3-MeC_6H_4	3.0	0.1	10	**9b** (21)	**13b** (4)
6	I	2-MeC_6H_4	3.0	0.1	15	**9c** (42)	**13c** (18)
7	I	2-MeC_6H_4	10.0	0.4	30	**9c** (37)	**13c** (23)
8	I	2-EtC_6H_4	3.0	0.1	15	**9d** (48)	**13d** (14)
9	I	2,6-$Me_2C_6H_3$	3.0	0.1	60	**9e** (38)	**13e** (trace)[d)]
10	I	2,6-$Me_2C_6H_3$	10.0	0.4	30	**9e** (54)	**13e** (trace)[d)]
11[c)]	I	2,6-$Me_2C_6H_3$	20.0[e)]	0.4	25	**9e** (94)	**13e** (0)
12[c)]	Br	2,6-$Cl_2C_6H_3$	20.0[e)]	0.4	120	**9f** (64)	**13f** (0)

a) A suspension of zinc powder and aluminum powder in HMPA was irradiated by ultrasound for 30 min at 40—50 °C, then benzaldehyde (2.0 equiv) and imidoyl halides (0.31 mmol) in DMF were added successively. b) Mixed solvent of HMPA–DMF (1 : 1 v/v). c) Imidoyl halides (0.15 mmol). d) Other by-product was 2,6-xylidine. e) See Ref. 12.

Table 2. Reaction of *N*-(2,6-Disubstituted phenyl)-imidoyl Halides with Aldehydes and Transformation of the Adducts **8** to α-Amino Ketone Derivatives **12**

Entry	X	Ar	R	Yield of **8**[a)]	Yield of **12**[b)]
				%	%
1	I	2,6-$Me_2C_6H_3$	Ph	**8e** (83)	**12e** (91)
2	I	2,6-$Me_2C_6H_3$	n-C_5H_{11}	**8e′** (60)	**12e′** (94)
3	I	2,6-$Cl_2C_6H_3$	Ph	**8f** (46)	**12f** (70)

a) Based on **3e** or **2f**. b) Based on **8**.



Scheme 1.

IR spectra were measured on a Hitachi 270-30 spectrophotometer.

DMF and HMPA were dried by distillation over calcium hydride. Aldehydes were commercially available and were distilled before use. Zinc powder was treated as described.[10)] The imidoyl halides **1**—**3** was prepared by using a previously reported procedure.[3)] All other chemicals were of commercial reagent grade and were used without further purification. Sonication was done in a Bransonic Model B 1200 ultrasonic generator (145 W, 47 kHz) (Yamato).

3, 3, 3- Trifluoro- 2- (2, 6- dimethylphenylimino)- 1-phenyl-1-propanol (8e). A suspension of activated zinc powder (399 mg, 6.11 mmol) and aluminum powder (165 mg, 6.11 mmol) in HMPA (0.2 ml) was irradiated by ultrasound under nitrogen at 40—50 °C (bath temp) for 30 min. Then, benzaldehyde (65 mg, 0.62 mmol) and a solution of the imidoyl iodide **3e** (100 mg, 0.31 mmol) in DMF (0.2 ml) were added successively to the suspension at room temperature. The imidoyl iodide **3e** was completely consumed within 25 min. The reaction mixture was quenched with wet ether and filtered. The filtrate was extracted with ether several times. The ether layer was washed with saturated solution of $NaHSO_3$ and brine. The ether layer was dried over anhydrous $MgSO_4$ and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel using a 50 : 1 mixture of hexane and ether as an eluent to give **8e** (78.0 mg, 83% yield) as a yellow oil: IR (neat) 3420 cm^{-1}; ^1H NMR ($CDCl_3$) δ=2.00 (s, 3H, CH_3), 2.06 (s, 3H, CH_3), 5.00 (d, J=4.9 Hz, 1H, OH), 5.63 (d, J=4.9 Hz, 1H, Ar-C<u>H</u>), 6.97—7.46 (m, 8H, ArH); ^{19}F NMR ($CDCl_3$) δ=95.4 (s). Found: C, 66.52; H, 5.26; N, 4.72%. Calcd for $C_{17}H_{16}F_3NO$: C, 66.44; H, 5.25; N, 4.56%.

1,1,1-Trifluoro-2-(2,6-dimethylphenylimino)-3-octanol (8e′): IR (neat) 3472 cm^{-1}; ^1H NMR (DMSO-d_6) δ=0.72 (t, J=6.6 Hz, 3H, CH_3), 0.88—1.67 (m, 8H), 1.92 (s, 3H, CH_3), 1.98 (s, 3H, CH_3), 3.91—4.08 (br s, 1H, Ar-C<u>H</u>), 5.85 (d, J=5.9 Hz, 1H, OH), 6.89—7.10 (m, 3H, ArH); ^{19}F NMR (DMSO-d_6) δ=96.5 (s). Found: C, 63.66; H, 7.52; N, 4.95%. Calcd for $C_{16}H_{22}F_3NO$: C, 63.77; H, 7.36; N, 4.65%.

3, 3, 3- Trifluoro- 2- (2, 6- dichlorophenylimino)- 1-phenyl-1-propanol (8f): IR (neat) 3456 cm^{-1}; ^1H NMR ($CDCl_3$) δ=4.57 (br s, 1H, Ar-C<u>H</u>), 7.02—7.10 (m, 1H,

ArH), 7.29—7.57 (m, 7H, ArH); ^{19}F NMR ($CDCl_3$) δ= 95.0 (s). Found: C, 51.91; H, 3.17; N, 3.84%. Calcd for $C_{15}H_{10}Cl_2F_3NO$: C, 51.75; H, 2.90; N, 4.02%.

3,3,3-Trifluoro-2-(4-methylphenylimino)-1-phenylpropyl Acetate (9a). The alcohol **8a** was so unstable that the crude **8a** was directly acetylated with acetic anhydride (0.15 ml, 1.60 mmol) in pyridine (0.5 ml) under stirring at room temperature overnight. The ether extract was washed with 10% HCl and brine, and dried over anhydrous $MgSO_4$. The solvent was removed in vacuo and the residue was purified by flash column chromatography on silica gel to give **9a** (54.6 mg, 51% yield) as a yellow oil: IR (neat) 1754 cm^{-1} (ester C=O); ^{1}H NMR ($CDCl_3$) δ=2.14 (s, 3H, Ac), 2.33 (s, 3H, CH_3), 6.71 (s, 1H, Ar-C<u>H</u>), 6.74—6.83 (m, 2H, ArH), 7.08—7.37 (m, 7H, ArH); ^{19}F NMR ($CDCl_3$) δ=94.6 (s). Found: C, 64.01; H, 5.00; N, 4.04%. Calcd for $C_{18}H_{16}F_3NO_2$: C, 64.47; H, 4.81; N, 4.18%.

3,3,3-Trifluoro-2-(3-methylphenylimino)-1-phenylpropyl Acetate (9b): IR (neat) 1754 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=2.12 (s, 3H, Ac), 2.30 (s, 3H, CH_3), 6.55—6.72 (m, 3H), 6.89—6.98 (m, 1H, ArH), 7.10—7.38 (m, 5H, Ph), 7.85—7.93 (m, 1H, ArH); ^{19}F NMR ($CDCl_3$) δ= 94.4 (s). Found: C, 64.02; H, 5.03; N, 4.02%. Calcd for $C_{18}H_{16}F_3NO_2$: C, 64.47; H, 4.81; N, 4.18%.

3,3,3-Trifluoro-2-(2-methylphenylimino)-1-phenylpropyl Acetate (9c): IR (neat) 1752 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=1.87 (s, 3H, CH_3), 2.11 (s, 3H, Ac), 6.47—6.80 (m, 2H), 6.97—7.23 (m, 5H, ArH), 7.23—7.42 (m, 3H, ArH); ^{19}F NMR ($CDCl_3$) δ=94.4 (s). Found: C, 64.77; H, 5.06; N, 4.20%. Calcd for $C_{18}H_{16}F_3NO_2$: C, 64.47; H, 4.81; N, 4.18%.

3,3,3-Trifluoro-2-(2-ethylphenylimino)-1-phenylpropyl Acetate (9d): IR (neat) 1754 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=1.07 (t, J=7.5 Hz, 3H, C<u>H</u>$_3$CH$_2$), 2.12 (s, 3H, Ac), 2.37 (q, J=7.5 Hz, 2H, CH$_3$C<u>H</u>$_2$), 6.48—6.82 (m, 2H), 7.04—7.39 (m, 8H, ArH); ^{19}F NMR ($CDCl_3$) δ= 94.5 (s). Found: C, 65.21; H, 5.38; N, 4.08%. Calcd for $C_{19}H_{18}F_3NO_2$: C, 65.32; H, 5.19; N, 4.09%.

3,3,3-Trifluoro-2-(2,6-dimethylphenylimino)-1-phenylpropyl Acetate (9e): IR (neat) 1756 cm^{-1}; ^{1}H NMR ($CDCl_3$, 55 °C) δ=2.05 (s, 3H, Ac), 2.11 (s, 6H, Ar-CH_3), 6.47 (s, 1H, Ar-C<u>H</u>), 6.83—7.47 (m, 8H, ArH); ^{19}F NMR ($CDCl_3$, 50 °C) δ=95.1 (s). Found: C, 65.22; H, 5.38; N, 4.21%. Calcd for $C_{19}H_{18}F_3NO_2$: C, 65.32; H, 5.19; N, 4.09%.

The ^{1}H NMR spectrum of **9e** ($CDCl_3$) recorded at 20 °C showed broadened signals generally and the ^{19}F NMR ($CDCl_3$) at this temperature had a singlet at δ=95.1 due to CF_3 of **9e** together with an additional singlet at δ=94.2 due to that of **11e** in the ratio of 1:3.

3,3,3-Trifluoro-2-(2,6-dichlorophenylimino)-1-phenylpropyl Acetate (9f): IR (neat) 1760 cm^{-1}; ^{1}H NMR ($CDCl_3$, 50 °C) δ=2.10 (s, 3H, Ac), 6.65 (s, 1H, Ar-C<u>H</u>), 6.89—7.07 (m, 2H, ArH), 7.17—7.44 (m, 6H, ArH); ^{19}F NMR ($CDCl_3$, 50 °C) δ=94.0 (s). Found: C, 52.88; H, 3.55; N, 3.55%. Calcd for $C_{17}H_{12}Cl_2F_3NO_2$: C, 52.38; H, 3.10; N, 3.59%.

3,3,3-Trifluoro-2-(2,6-dimethylanilino)-1-phenyl-1-propanone (12e). The alcohol **8e** was purified by a short flash column chromatography on silica gel by using hexane and ether (50:1). Compound **8e** (10 mg, 0.033 mmol) was heated at 150 °C for 2—4 h in an evacuated (air-free) sealed tube. The product was purified by a flash column chromatography on silica gel with hexane as an eluent to afford **12** (9.1 mg, 91% yield) as a yellow oil: IR (neat) 3392, 1696 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=2.39 (s, 6H, Ar-CH_3), 4.54 (d, J=11.2 Hz, 1H, NH), 5.31—5.52 (m, 1H, CF_3C<u>H</u>), 6.82—6.90 (m, 1H, ArH), 6.96—7.03 (m, 2H, ArH), 7.45—7.57 (m, 2H, ArH), 7.60—7.70 (m, 1H, ArH), 7.86—7.94 (m, 2H, ArH); ^{19}F NMR ($CDCl_3$) δ=91.3 (d, J_{H-F}=6.4 Hz, 3F, CF_3). Found: C, 66.07; H, 5.54; N, 4.45%. Calcd for $C_{19}H_{18}F_3NO_2$: C, 66.44; H, 5.25; N, 4.56%.

1,1,1-Trifluoro-2-(2,6-dimethylanilino)-3-octanone (12e′): IR (neat) 3392, 1734 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=0.79—0.97 (m, 3H), 1.11—1.43 (m, 6H), 2.31 (s, 6H, Me_2), 2.34—2.54 (m, 1H), 2.61—2.77 (m, 1H), 4.15—4.26 (br, 1H, NH), 4.34—4.54 (m, 1H, CF_3C<u>H</u>), 6.80—6.90 (m, 1H, ArH), 6.93—7.06 (m, 2H, ArH); ^{19}F NMR ($CDCl_3$) δ= 90.7 (d, J_{H-F}=7.0 Hz, 3F, CF_3). Found: C, 63.95; H, 7.44; N, 4.67%. Calcd for $C_{16}H_{22}F_3NO$: C, 63.77; H, 7.36; N, 4.65%.

2-(2,6-Dichloroanilino)-3,3,3-trifluoro-1-phenyl-1-propanone (12f): IR (neat) 3368, 1696 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=5.34 (d, J=11.2 Hz, 1H, NH), 6.17—6.37 (m, 1H, CF_3C<u>H</u>), 6.87 (dd, J_1=7.8 Hz, J_2=8.5 Hz, 1H, ArH), 7.22—7.30 (m, 2H, ArH), 7.48—7.74 (m, 3H, ArH), 7.96—8.06 (m, 2H, ArH); ^{19}F NMR ($CDCl_3$) δ=91.4 (d, J_{H-F}=6.4 Hz, 3F, CF_3). Found: C, 51.87; H, 3.11; N, 4.21%. Calcd for $C_{15}H_{10}Cl_2F_3NO$: C, 51.75; H, 2.90; N, 4.02%.

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10) Zinc powder was successively washed with aqueous

diluted HCl, H_2O, EtOH, and ether, then dried in vacuo for a few days, and milled for a while with a pestle and mortar immediately before use.

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12) The structure of the zinc reagent **6** was expected as shown by the referential paper, for example, concerning the formation of 3,3,3-trifluoroisopropenylzinc bromide: B. Jiang and Y. Xu, *J. Org. Chem.*, **56**, 7336 (1991). Further details of the structure in organic solvents are remained to be studied.

13) 2,6-Disubstitution to the *N*-phenyl ring much improved the product selectivity, but retarded the reaction. Increasing the amount of zinc to 20.0 equiv solved the problem.