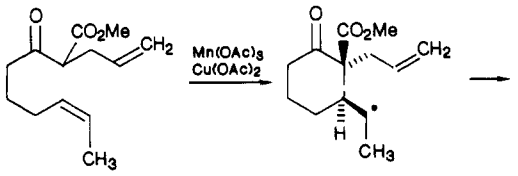

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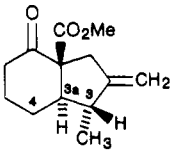

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applying it to total synthesis.

Acknowledgment. We thank the National Institutes of Health (GM-30528) for generous financial support.

Supplementary Material Available: Experimental procedures for the preparation of **1a** and **6a** and spectral data for **6b**, **9**, **16**, and **19** (3 pages). Ordering information is given on any current masthead page.

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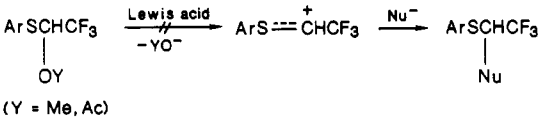
Electrolytic Transformation of Fluoroorganic Compounds. 3.[1] Highly Regioselective Anodic Methoxylation of *N*-(2,2,2-Trifluoroethyl)amines

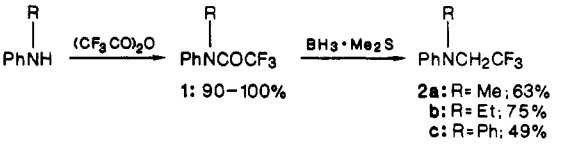
Summary: Anodic methoxylation of *N*-alkyl-*N*-(2,2,2-trifluoroethyl)anilines and *N*-(2,2,2-trifluoroethyl)diphenylamine places the methoxy group in the α-position (toward the trifluoromethyl group); these products are useful building blocks for the construction of a carbon–carbon bond at this α-position.

Sir: Although a great deal of recent interest has been focused on trifluoromethylated compounds because of their remarkable biological activities,[2] their preparative methods are limited in many cases.[3] For example, nucleophilic or electrophilic substitution at the α-positions of trifluoromethylated compounds generally occur with difficulty. Since the generation of a carbenium ion adjacent to a trifluoromethyl group is particularly difficult due to its strong electron-withdrawing effect,[4] attempts to prepare desired compounds bearing a trifluoromethyl group by S_N1 reaction via a trifluoroethyl carbenium ion have been unsuccessful so far.[5] Therefore, construction of a carbon–carbon bond α to the trifluoromethyl group is of current importance.

Scheme I



Scheme II



Scheme III

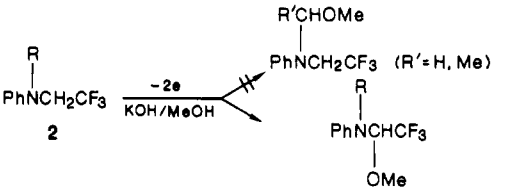


Table I. Oxidation Potentials (Half-Peak Potentials, $E^{ox}_{p_{1/2}}$) of *N*-(2,2,2-Trifluoroethyl)amines 2[a]

(trifluoroethyl)-amine 2	R	$E^{ox}_{p_{1/2}}$, V vs SCE
2a	Me	0.96
2b	Et	0.96
2c	Ph	1.05

[a] 2 mM of 2 in 0.1 M Et_4NOTs/MeCN. Sweep rate: 100 mV s^{-1}.

In our previous paper,[6] we reported the successful anodic methoxylation and acetoxylation of aryl 2,2,2-trifluoroethyl sulfides to give the corresponding α-methoxy and α-acetoxy sulfides, respectively, together with their synthetic utilization for fluoroorganic compounds. It was also found that nucleophilic substitution of these sulfides via cationic intermediates did not occur in the presence of Lewis acid (Scheme I), although nonfluorindated α-methoxy or α-acetoxy sulfides are known to easily generate cationic intermediates which can be trapped with various nucleophiles.[7]

In this paper, we wish to report highly regioselective anodic methoxylation of *N*-alkyl-*N*-(2,2,2-trifluoroethyl)-anilines **2a,b** and *N*-(2,2,2-trifluoroethyl)diphenylamine (**2c**) together with the first example of the generation of an α-trifluoromethylated iminium cation, which can be trapped with various carbon nucleophiles to give useful trifluoromethylated compounds.

The starting compounds **2** for the electrolysis were prepared by trifluoroacetylation of *N*-alkylanilines or diphenylamine followed by reduction with borane–dimethyl sulfide complex.[8] Trifluoroacetoanilides **1a,b** gave the corresponding *N*-(2,2,2-trifluoroethyl)aniline derivatives **2a,b** in good yields, while *N*-(trifluoroacetyl)diphenylamine (**1c**) provided the trifluoroethyl derivative **2c** in low yield

(1) Part 2: Fuchigami, T.; Nakagawa, Y. *J. Org. Chem.* **1987**, *52*, 5276. Electrochemical Generation of Reactive Nitrogen Species. 11. Part 10: Fuchigami, T.; Sato, T.; Nonaka, T. *J. Org. Chem.* **1986**, *51*, 366.

(2) (a) Carbon–Fluorine Compounds; A CIBA Foundation Symposium; Elsevier: Amsterdam, 1972. (b) Schlosser, M. *Tetrahedron* **1978**, *34*, 3. (c) Biomedical Aspects of Fluorine Chemistry; Filler, R., Kobayashi, Y., Eds.; Kodansha & Elsevier Biomedical: Tokyo, 1983.

(3) For example: Hudlicky, M. *Chemistry of Organic Fluorine Compounds*, 2nd ed.; Wiley: New York, 1976.

(4) Tidwell, T. T. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 20.

(5) For example: Umemoto, T.; Goto, Y. *J. Fluorine Chem.* **1986**, *31*, 231.

(6) Fuchigami, T.; Nakagawa, Y.; Nonaka, T. *Tetrahedron Lett.* **1986**, *27*, 3869.

(7) Torii, S.; Tanaka, H.; Saitoh, N.; Siroi, T. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 2185.

(8) *N*-Alkyl-*N*-(2,2,2-trifluoroethyl)-*m*-anisidine has been similarly prepared by using diborane: Johnson, F.; Subramanian, R. *J. Org. Chem* **1986**, *51*, 5041.

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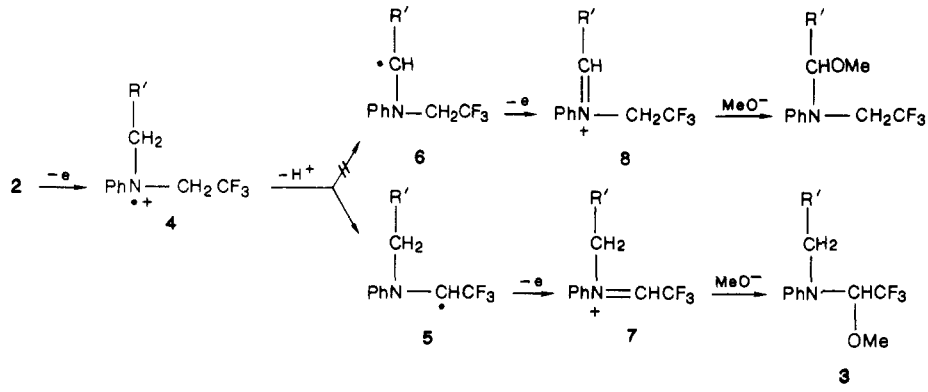
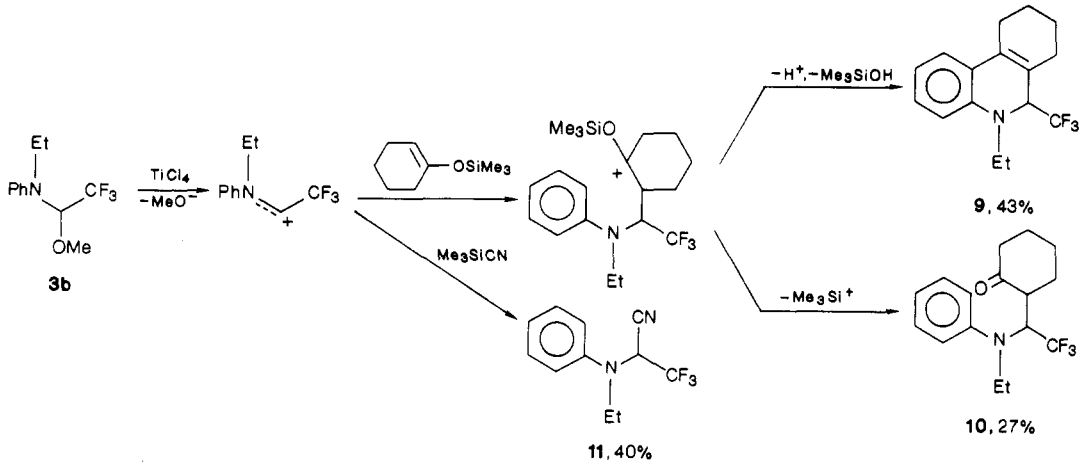
Scheme IV



Scheme V



due to competing reductive cleavage of a carbon–nitrogen bond of **1c** (Scheme II).

Anodic methoxylation of **2** was carried out at constant current in an alkaline methanol solution by using an undivided cell.[9] Highly regioselective methoxylation resulted; the methoxy group was exclusively introduced into the α-position toward the trifluoromethyl group of **2** as measured by NMR spectroscopy (Scheme III).[10]

It has been reported that anodic methoxylation occurs exclusively at the methyl group of *N*-ethyl-*N*-methylaniline.[11] Similar regioselectivity has been observed in the anodic methoxylation of carbamates[12] and amides.[13]

Thus, it should be noted that the trifluoromethyl group dramatically changed the regioselectivity of such anodic methoxylations. Thus, the trifluoromethyl group promotes anodic substitution at its α-position, which is also observed in the case of 2,2,2-trifluoroethyl sulfides.[6]

Next, the oxidation potentials of **2** were measured in anhydrous acetonitrile using a glassy carbon anode. As shown in Table I, the amines **2** exhibited their oxidation potentials (half-peak potentials) around +1.0 V vs SCE. *N*-(2,2,2-Trifluoroethyl)amines **2** were found to be oxidized at more positive than nonfluorinated amines.[14]

Since the cathodic shift was observed in the current–potential curves after addition of **2** into the electrolytic solution, this reaction appears to take place mainly by direct oxiation of **2**; however, another mechanism, the oxidation initited by anodically generated methoxy radicals, is not necessarily ruled out, because the anodic potential was not controlled in our experiments. The anodic methoxylation of **2** may proceed via electrogenerated cationic species **7** (Scheme IV), as is seen with nonfluorinated amines,[17] carbamtes,[12] and amides.[18] However, the regioselectivity of this anodic methoxylation does not seem to be governed by the stability of the cationic intermdiates **7** and **8** but by the rate of deprotonation of the radical cations **4** formed by one-electron oxidation of **2**.

(9) The electrolysis of **2** (10 mmol) was carried out at a carbon anode (6 × 2.4 cm) and a platinum cathode at room temperature in 0.34 M KOH–MeOH (35 mL). After a constant current (200 mA) was passed until **2** was completely consumed [monitored by GC (column: Apeazon Grease L)], the electrolytic solution was concentrated and the remaining oil was chromatographed on silica gel (hexane–AcOEt, 20:1–40:1) to provide α-methoxy products **3**.

(10) α-Methoxylated products **3**: satisfactory elemental analyses were obtained for **3a–c**. **3a**: ^{1}H NMR ($CDCl_3$) δ 2.87 (s, 3 H, CH_3N), 3.30 (s, 3 H, CH_3O), 5.05 (q, 1 H, CF_3CH, J_{H-F} = 6 Hz), 6.7–7.4 (m, 5 H, C_6H_5); ^{19}F NMR ($CDCl_3$, ext. CF_3CO_2H) δ −2.0 (d); MS, *m/e* 219 (M^+), 188 (M^+ − MeO), 150 (M^+ − CF_3), 135 (M^+ − CF_3 − Me), 106 ($PhNMe^+$), 77 (Ph^+). **3b**: ^{1}H NMR ($CDCl_3$) δ 1.10 (t, 3 H, CH_3CH_2, J_{H-H} = 7 Hz), 3.33 (s, 3 H, CH_3O), 3.45 (q, 2 H, CH_3CH_2, J_{H-H} = 7 Hz), 4.94 (q, 1 H, CF_3CH, J_{H-F} = 6 Hz), 6.7–7.3 (m, 5 H, C_6H_5); ^{19}F NMR ($CDCl_3$, ext. CF_3CO_2H) δ −1.8 (d); MS, *m/e* 233 (M^+), 202 (M^+ − MeOh), 164 (M^+ − CF_3), 104 ($PhN{=}CH^+$), 77 (Ph^+). **3c**: ^{1}H NMR ($CDCl_3$) δ 3.53 (s, 3 H, CH_3O), 5.30 (q, 1 H, CF_3CH, J_{H-F} = 6 Hz), 6.8–7.4 (m, 12 H, C_6H_5); ^{19}F NMR ($CDCl_3$, ext. CF_3CO_2H) δ −4.08 (d); MS, *m/e* 281 (M^+), 250 (M^+ − MeO), 212 (M^+ − CF_3), 168 (Ph_2N^+), 77 (Ph^+).

(11) Shono, T.; Matsumura, Y.; Inoue, K.; Ohmizu, H.; Kashimura, S. *J. Am. Chem. Soc.* **1982**, *104*, 5753.

(12) Shono, T.; Hamaguchi, H.; Matsumura, Y. *J. Am. Chem. Soc.* **1975**, *97*, 4264.

(13) Palasz, P.; Utley, J. H. P.; Hardstone, J. D. *J. Chem. Soc., Perkin Trans. 2* **1984**, 807; *Acta Chem. Scand., Ser. B* **1984**, *B38*, 281.

(14) For examples, the half-peak potentials of *N*,*N*-dimethylaniline,[15] diphenylamine,[16] and *N*-methyl-*N*,*N*-diphenylamine[15] are +0.71, +0.83, and +0.84 V vs SCE, respectively.

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That is, the regioselectivity may be rationalized as due to the ease of the deprotonation from **4**, since the stronger the acidity of the methyl or methylene hydrogen, the easier the deprotonation. In support of this, Kimura et al. have found that in the anodic oxidation of cyanomethyl sulfides in methanol, the electron-withdrawing cyano group facilitates deprotonation and methoxylation at their α-positions.[19] In addition, the stability of the radical intermediates **5** and **6** would aslo affect this regioselectivity. Most recently, Kubota et al. have found that the anodic oxidation of 3-hydroxy-2-(trifluoromethyl)propionic acid generated radicals α to the trifluoromethyl group, leading to their dimer almost quantitatively.[20] Their results and ours may suggest that the stabilizaion of the radical intermediate **5** by a sort of the captodative effect[21] also presumably contributes to this high regioselectivity.

In order to demonstrate the synthetic utility of the α-methoxylated products **3**, we generated α-trifluoromethylated iminium cations, which we trapped with various carbon nucleophiles. For example, treatment of **3b** with a Lewis acid, such as $TiCl_4$, in the presence of a silyl enol either efficiently provided a heterocyclic product **9** bearing a trifluoromethyl group together with an amino ketone **10** as shown in Scheme V.[22] A cyano group was similarly introduced to the α-position toward the trifluoromethyl group of **3b** to give α-amino nitrile **11** in reasonable yield (Scheme V).[23]

Thus, the α-methoxyanilines **3** were found to be highly useful building blocks for the construction of a carbon–carbon bond α to the trifluoromethyl group.

Acknowledgment. We thank Tsuyoshi Takiguchi and Yasushi Fujita for measurement of the anodic oxidation potentials of (trifluoroethyl)amines, Prof. Tomoya Kitazume of Tokyo Institute of Technology for obtaining ^{19}F NMR spectra, and Ajinomoto Co., Inc., Central Research Laboratories, and Dr. Toshio Kubota of Ibaragi University for measurement of the high-resolution mass spectra.

Registry No. 2a, 55204-33-6; **2b**, 55204-36-9; **2c**, 110972-14-0; **3a**, 110972-15-1; **3b**, 110972-16-2; **3c**, 110972-17-3; **9**, 110972-18-4; **10**, 110972-19-5; **11**, 110972-20-8; $Me_3SiOC{=}CHCH_2CH_2CH_2CH_2$, 6651-36-1; Me_3SiCN, 7677-24-9.

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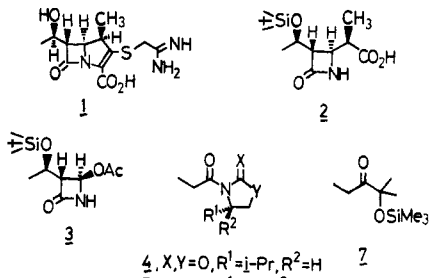
A New Approach to the Chiral Synthesis of the 1-β-Methylcarbapenem Key Precursor Using an Achiral Ketone Sn(II) Enolate

Summary: A highly stereoselective synthesis of the chiral 1-β-methylcarbapenem key precursor has been accomplished by the aldol-type reaction of the chiral 4-acetoxyazetidinone with a tin(II) enolate generated from 2-methyl-2-siloxy-3-pentanone.

Sir: Since the Merck group reported the enhanced chemical and metabolic stability of the 1-β-methylcarbapenem antibiotics such as **1**,[1] the chiral synthesis of the 1-β-methylcarbapenem key precursor (**2**) has been the subject of considerable synthetic activities.[2] The most extensively studied route to precursor **2** is based on the stereocontrolled aldol-type reaction of the readily available (+)-4-acetoxy-2-azetidinone (**3**)[3] with an appropriate equivalent



to the enolate of propionic acid, where the choice of the enolate equivalent is the key to success. Recently, efficient

(19) Kimura, M.; Koie, K.; Matsubara, S.; Sawaki, Y.; Iwamura, H. *J. Chem. Soc., Chem. Commun.* **1987**, 122.

(20) Kubota, T.; Aoyagi, R.; Sando, H.; Kawasumi, M.; Tanaka, T. *Chem. Lett.* **1987**, 1435.

(21) Viehe, H. G.; Janousek, Z.; Merenyi, R. *Acc. Chem. Res.* **1985**, *18*, 148.

(22) The reaction was carried out as follows. To a solution of 0.5 mmol of *N*-ethyl-*N*-(1-methoxy-2,2,2-trifluoroethyl)aniline (**3b**) in 0.5 mL of anhydrous dichloromethane was added dropwise a solution of 0.65 mmol of $TiCl_4$ in 0.77 mL at ca. −78 °C. After 5 min of stirring, a solution of 0.65 mmol of 2-cyclohexenyl trimethylsilyl ether in 0.5 mL of dichloromethane was added dropwise, and then the resulting solution was stirred for 0.5 h at the same temperature. To the reaction mixture, saturated aqueous potassium carbonate was added. The solution was repeatedly extracted with dichloromethane, washed with water, and then dried over anhydrous sodium sulfate. The extracts were concentrated under reduced pressure, and the remaining oil was chromatographed on silica gel (hexane–AcOEt, 20:1) to provide **9** and **10** as the first and second components, respectively. **1-Ethyl-2-(trifluoromethyl)-3,4-butano-1,2-dihydroquinoline (9)**: ^1H NMR ($CDCl_3$) δ 1.20 (t, 3 H, CH_3, J_{H-H} = 7 Hz), 1.6–2.7 (m, 8 H, CH_2CH_2), 3.22, 2.53 (q, 2 H, CH_3CH_2, J_{H-H} = 7 Hz), 4.03 (q, 1 H, CF_3CH, J_{H-F} = 7 Hz), 6.5–7.2 (m, 4 H, C_6H_4); ^{19}F NMR ($CDCl_3$, ext. CF_3CO_2H) δ −4.6 (d); MS, *m/e* 281 (M^+), 212 ($M^+ - CF_3$), 184 ($M^+ - CF_3 - C_2H_4$), 156 ($M^+ - CF_3 - 2C_2H_4$); calcd for $C_{16}H_{18}F_3N$ *m/e* 281.1391, found *m/e* 281.1296. ***N*-Ethyl-*N*-[1-(2-oxocyclohexyl)-2,2,2-trifluoroethyl]alanine (10)**: ^1H NMR ($CDCl_3$) δ 1.13, 1.20 (dt, 3 H, CH_3, J_{H-H} = 7 Hz), 1.0–2.7 (m, 8 H, CH_2), 3.22 (q, 1 H, CHCO), 3.45 (q, 2 H, CH_3CH_2, J_{H-H} = 7 Hz), 5.13 (quint, 1 H, CF_3CH, J_{H-F} = 9 Hz), 6.7–7.4 (m, 5 H, C_6H_5); ^{19}F NMR ($CDCl_3$, ext. CF_3CO_2H) δ −8.5 (d), −9.9 (d); IR 1730 (C=O), 1620, 1605 cm^{-1} (C=C); MS, *m/e* 299 (M^+), 230 ($M^+ - CF_3$), 202 ($M^+ - CF_3 - C_2H_4$), 174 ($M^+ - CF_3 - 2C_2H_4$), 120 (PhN^+Et), 77 (Ph^+); calcd for $C_{16}H_{20}F_3NO$ *m/e* 299.1497, found *m/e* 299.1502.

(23) The α-amino nitrile **11** was synthesized in the manner similar to the preparation of **9** and **10**, however, the reaction was not optimized. ***N*-(1-Cyano-2,2,2-trifluoroethyl)-*N*-ethylaniline (11)**: ^1H NMR ($CDCl_3$) δ 1.10 (t, 3 H, CH_3, J_{H-H} = 7 Hz), 3.43 (q, 2 H, CH_3CH_2, J_{H-H} = 7 Hz), 4.83 (q, 1 H, CF_3CH, J_{H-H} = 7 Hz), 6.7–7.4 (m, 5 H, C_6H_5); ^{19}F NMR (CCl_3, ext. CF_3CO_2H), δ −6.3 (d); MS, *m/e* 228 (M^+), 213 (M^+ – Me), 159 ($M^+ - CF_3$), 105 ($PhNCH_2^+$), 77 (Ph^+); calcd for $C_{11}H_{11}F_3N_2$ *m/e* 228.2165, found *m/e* 228.2186.

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