Notes

Electrolytic Transformation of Fluoroorganic Compounds. 5.[1] Anodic Cyanation of 2,2,2-Trifluoroethylamines

Akinori Konno, Toshio Fuchigami,* Yasushi Fujita, and Tsutomu Nonaka

Department of Electronic Chemistry, Graduate School at Nagatsuta, Tokyo Institute of Technology, Midori-ku, Yokohama 227, Japan

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Anodic nucleophilic substitution reaction of amines attracts much interest because of its synthetic utility. Various functional groups can be introduced into the α-position to the nitrogen atom in one step.[2] It is interesting that electrochemical reaction shows characteristic regiochemistry different from common homogeneous reaction in many cases. Anodic substitution usually takes place at a less substituted carbon atom preferably. For example, it is known that anodic methoxylation of *N*-ethyl-*N*-methylaniline occurs at the methyl group exclusively.[3] On the other hand, we have reported that the regioselectivity was dramatically changed in the case of anodic methoxylation of 2,2,2-trifluoroethylamines, i.e., the methoxylation preferably takes place at the α-position to the trifluoromethyl group.[4]

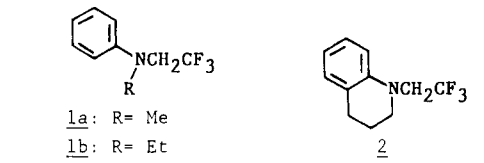
Although anodic cyanation of amines is expected to provide a promising method for the preparation of α-amino nitriles as versatile synthetic precursors, there are only a few reports on the anodic α-cyanation reaction of amines.[5] The regiochemistry of the oxidative α-cyanation of amines is important and interesting from synthetic and mechanistic aspects not only in electrochemistry but also in organic chemistry.[6] Our interest is therefore focused on the effects of the trifluoromethyl group both on the oxidation potentials of the amines and on the regiochemistry of the anodic cyanation reaction. We report here a remarkable difference in the regioselectivity between the anodic cyanation and methoxylation reactions of 2,2,2-trifluoroethylamines.

Results and Discussion

The oxidation potentials of 2,2,2-trifluoroethylamines were measured by cyclic voltammetry. These fluoroamines

Chart I

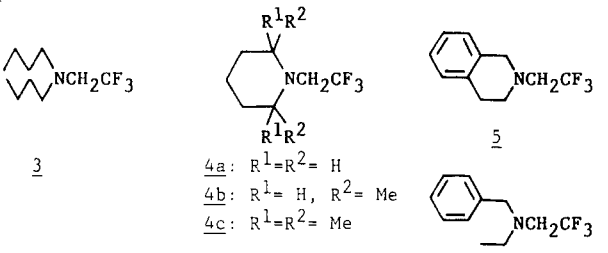
Aromatic Amines



1a: R= Me
1b: R= Et

2

Aliphatic Amines



3

4a: R^1=R^2= H
4b: R^1= H, R^2= Me
4c: R^1=R^2= Me

5

6

exhibited irreversible oxidation waves. The first half-peak oxidation potentials are summarized in Table I. Aromatic fluoroamines **1** and **2** were oxidized at less positive potentials than aliphatic ones **3–6** (Chart I). Cyclic aromatic amine **2** was found to be oxidized more easily than acyclic aromatic ones **1a** and **1b**, while no difference in oxidation potential between cyclic and open-chain aliphatic amines, **5** and **6**, was observed. The oxidation potentials of aniline derivatives **1** and **2** were positively shifted by 0.2–0.3 V compared with those of the corresponding unfluorinated anilines.[7] In the case of aliphatic amines **3–6**, the potential shift was rather small.[7] The potential shift can be explained by the electron-withdrawing effect of the trifluoromethyl group.

Electrolysis was conducted under conditions described in Table I. Results of the anodic cyanation are also given in Table I. The results can be classified into two types for aniline derivatives **1** and **2** and aliphatic amines **3–6** from the cyanated products.

In the electrolysis of the aniline derivatives, **1a** gave an α-cyanated product while **1b** did not by using Method A. On the contrary, **1b** provided α-cyanated one by using method B although the yield was rather low. Method B seems to be suitable for such cyanation since the total yield was also higher than method A. Regardless to the reaction method, cyanation and dimerization at the aromatic ring were main reactions while cyanation at the α-carbon to the nitrogen atom occurred very little. This fact suggests that ring cyanation and dimerization of the cation radical intermediates of **1** are faster than deprotonation from the α-carbon. In other words, the positive charge of the cation radical considerably delocalizes to the aromatic ring. Similar results have been observed by Weinberg and Reddy in the anodic methoxylation reaction of *N*,*N*-dimethylaniline.[8] In a basic medium, anodic methoxylation

(1) Part 4: Fuchigami, T.; Ichikawa, S.; Konno, A. *Chem. Lett.* **1989**, 1987. Electrochemical Generation of Reactive Nitrogen Species. 12.
(2) (a) Shono, T. *Tetrahedron* **1984**, *40*, 811. (b) Yoshida, K. *Electrooxidation in Organic Chemistry*; J. Wiley and Sons: New York, 1984. (c) Lines, R. In *Organic Electrochemistry*; Baizer, M. M., Lund, H., Eds.; Marcel Dekker: New York, 1983; Chapter 15, p 463. (d) Eberson, L.; Utley, J. H. P. In ref 2c; Chapter 23, p 775.
(3) Shono, T.; Matsumura, Y.; Inoue, K.; Ohmizu, H.; Kashimura, S. *J. Am. Chem. Soc.* **1982**, *104*, 5753.
(4) Fuchigami, T.; Nakagawa, Y.; Nonaka, T. *J. Org. Chem.* **1987**, *52*, 5489.
(5) (a) Andreades, S.; Zahnow, E. W. *J. Am. Chem. Soc.* **1969**, *91*, 4181. (b) Eberson, L.; Helgee, B. *Acta Chem. Scand.* **1975**, *B29*, 451. (c) Chiba, T.; Takata, Y. *J. Org. Chem.* **1977**, *42*, 2973.
(6) Recently the oxidative cyanation of tertiary amines using ClO_2 as a chemical oxidant has been reported. For a review some oxidative cyanation, see: Chen, C.-K.; Hortmann, A. G.; Marzabadi, M. R. *J. Am. Chem. Soc.* **1988**, *110*, 4829 and references cited therein.
(7) Oxidation potentials of related unfluorinated amines were also measured with cyclic voltammetry. The oxidation potentials of *N*,*N*-dimethylaniline, *N*,*N*-diethylaniline, triethylamine, and *N*-methylpiperidine are +0.71, +0.64, +0.96, and +1.10 V vs SCE, respectively.

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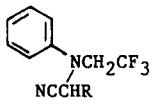
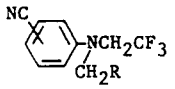
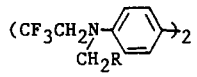
Table I. Oxidation Potentials and Anodic Cyanation Reactions of 2,2,2-Trifluoroethylamines 1–6



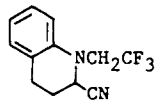
7a: R= H
7b: R= Me



8a: R= H
8b: R= Me



9a: R= H



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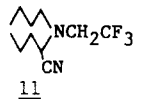

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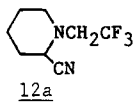
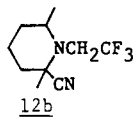
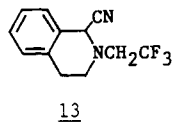


12a



12b



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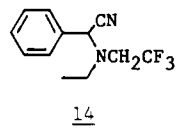

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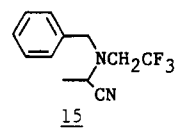

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run	substrate	$E_{p1/2}^{ox}$,[a] V vs SCE	method[b]	charge passed, F/mol	products[c] (yield, %)
1	**1a**	+0.95	A	2.0	**7a** (10), **8a** (16),[d] **9a** (17)[d]
2	**1b**	+0.94	A	2.0	**8b** (23)[d]
			B	2.0	**7b** (9), **8b** (34)[d]
3	**2**	+0.83	B	2.0	**10** (34)
4	**3**	+1.15	B	2.7	**11** (53)
5	**4a**	+1.18	B	3.8	**12a** (40)
6	**4b**	+1.17	B	4.0	**12b** (49)
7	**4c**	+1.24	B	2.2	polymeric products
8	**5**	+1.24	B	3.0	**13** (54)
9	**6**	+1.24	B	3.0	**14** (32), **15** (29)

[a] 2 mM of amines in 0.1 M $NaClO_4$/MeCN. Sweep rate: 100 mV s^{-1}. [b] Method A: amines (3 mmol) were electrolyzed at 0.5 A dm^{-2} of constant current using platinum anode (3 × 4 cm) and cathode in 0.4 M Et_4NCN/MeCN (30 mL) in an undivided cell. Method B: amines (2.6 mmol) were electrolyzed at 0.7 A dm^{-2} of constant current using platinum anode (3 × 4 cm) and cathode in 0.5 M NaCN/MeOH (26 mL in anode compartment) in an H-type divided cell. [c] Isolated yield. [d] The mixture of ortho and para isomers.

takes place, but only the dimerization proceeds in a neutral medium. Contrary to the cases of these amines **1**, cyclic aromatic amine **2** provided α-cyanated product **10** solely in a reasonable yield. However, in any cases, the cyanation did not take place at the α-position toward the trifluoromethyl group.

On the other hand, aliphatic amines underwent smoothly α-cyanation to give α-amino nitriles in good or reasonable yields. However, the cyano group was not introduced into the α-position to the trifluoromethyl group as observed in the case of aromatic amines. The cyanation took place exclusively at other α-carbons to the nitrogen atom. It is well known that anodic substitution generally takes place at a less substituted carbon more favorably. In this sense, it should be noticeable that *N*-(2,2,2-trifluoroethyl)-2,6-dimethylpiperidine (**4b**) was exclusively cyanated at the α-tertiary carbon atom efficiently although **4b** has an α-secondary carbon in the trifluoroethyl group. It is also noted that the anodic cyanation of **4c**, which has no α-proton to the nitrogen atom other than those in the trifluoroethyl group, did not give any isolable product.

These facts indicate the trifluoromethyl group completely inhibited the cyanation at the α-position to the trifluoromethyl group, regardless of the molecular structure of amines. From these results, it is clear that the trifluoromethyl group plays a role different from that in the methoxylation reaction. The main effect of the trifluoromethyl group is attributable to destabilization of the α-carbonium ion. Furthermore, it is also interesting that the benzylic cyanation took place predominantly in the case of cyclic amine **5**, while open-chain amine **6** provided two regioisomers **14** and **15** in almost equal yields.

In order to elucidate the reaction mechanism of the anodic cyanation, current–potential curves of the amines were measured. Figure 1 shows a typical example. The oxidation of the amine **4b** occurred at a much more cathodic potential than that of a NaCN–MeOH medium itself.

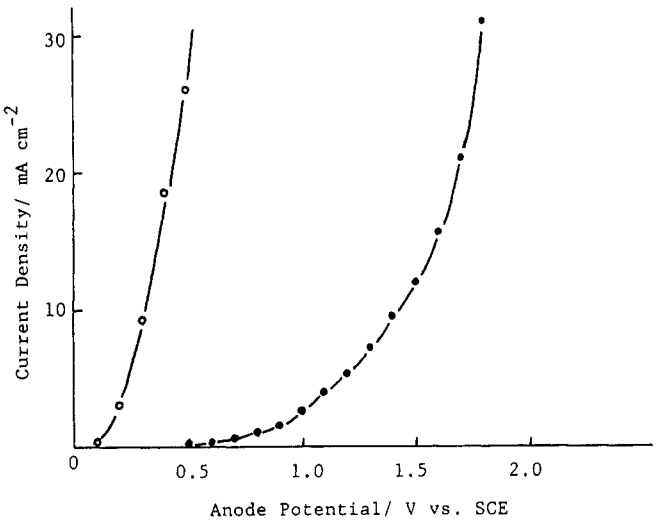
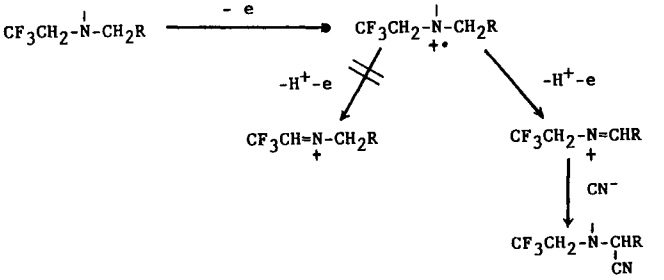


Figure 1. Current–potential curves: 0.5 M NaCN–MeOH solution (●); in the presence of 0.2 M **4b** (○).

Scheme I



This fact suggests that the anodic cyanation is initiated by direct oxidation of amines.

Considering the above results, the most reasonable mechanism at this stage is as follows. Deprotonation of cation radicals formed by initial oxidation of amines fol-

(8) Weinberg, N. L.; Reddy, T. B. *J. Am. Chem. Soc.* **1968**, *90*, 91.

lowed by effective reoxidation leads to imminium cation intermediates and successively the cyanation takes place (Scheme I). Since a trifluoromethyl group generally destabilizes α-cations, generation of such α-cations is quite difficult. Therefore, it is reasonable that the cyanation at the trifluoroethyl group was not observed.

However, at present it is not clear why the regiochemistry of the anodic cyanation is different from that of the anodic methoxylation. The difference in the reaction medium (electrolyte, pH, etc.) would influence on these reactions. The basicity and nucleophilicity of cyanide ions and of methoxide ions also should be considered. Detailed study for the reaction mechanism is now in progress.

Experimental Section

^{1}H NMR spectra were recorded at 60 MHz on a JEOL NMR spectrometer using $CDCl_3$ as solvent and Me_4Si as internal standard. ^{19}F NMR spectra were recorded at 60 MHz on a Hitachi R-24F NMR spectrometer using CF_3COOH as external standard. IR spectra were obtained with a Hitachi 295 infrared spectrometer. Mass spectra were obtained with a JEOL JMS-D100 mass spectrometer. High-resolution mass spectra were obtained with a Hitachi M-80B GC-mass spectrometer. Trifluoroethylamines (1-6) were synthetized similarly to the reported procedure.[4]

Electrolysis and Product Analyses. Electrolysis was carried out at a constant current using platinum plates as an anode and a cathode. Electrolytic conditions in each electrolysis are shown in Table I. After electrolysis, the electrolytic solution was concentrated, and the remaining crude liquid was treated with 20 mL of saturated potassium carbonate solution and extracted twice with 30-mL portions of ether. The combined ether layers were dried over anhydrous potassium carbonate, and the solvent was evaporated. The residue was separated and purified by preparative thin-layer chromatography (hexane–AcOEt as mobile phase).

***N*-(Cyanomethyl)-*N*-(2,2,2-trifluoroethyl)aniline (7a)**: ^{1}H NMR δ 3.83 (q, 2 H, CH_2CF_3, J = 9.0 Hz), 4.17 (s, 2 H, CH_2CN), 6.20–7.57 (m, 5 H, C_6H_5); ^{19}F NMR δ −7.50 (t, J = 9.0 Hz); MS m/e 214 (M^+), 145 ($M^+ - CF_3$), 77 (Ph^+); calcd for $C_{10}H_9F_3N_2$ m/e 214.0717, found 214.0735.

2-Cyano-*N*-methyl-*N*-(2,2,2-trifluoroethyl)aniline (8a, Isomer 1): ^{1}H NMR δ 3.13 (s, 3 H, CH_3), 4.03 (q, 2 H, CH_2CF_3, J = 9.0 Hz), 6.23–7.63 (m, 4 H, C_6H_4); ^{19}F NMR δ −9.70 (t, J = 9.0 Hz); MS m/e 214 (M^+), 145 ($M^+ - CF_3$); calcd for $C_{10}H_9F_3N_2$ m/e 214.0717, found 214.0694.

4-Cyano-*N*-methyl-*N*-(2,2,2-trifluoroethyl)aniline (8a, Isomer 2): ^{1}H NMR δ 3.13 (s, 3 H, CH_3), 3.93 (q, 2 H, CH_2CF_3, J = 9.0 Hz), 6.57–7.63 (m, 4 H, C_6H_4); ^{19}F NMR δ −8.15 (t, J = 9.0 Hz); MS m/e 214 (M^+), 145 ($M^+ - CF_3$); calcd for $C_{10}H_9F_3N_2$ m/e 214.0717, found 214.0718.

4,4′-Bis[*N*-methyl-*N*-(2,2,2-trifluoroethyl)amino]biphenyl (9a, Isomer 1): ^{1}H NMR δ 3.63 (s, 6 H, CH_3), 3.80 (q, 4 H, CH_2CF_3, J = 9.5 Hz), 6.60–7.47 (m, 8 H, C_6H_4); ^{19}F NMR δ −7.45 (t, J = 9.5 Hz); MS m/e 376 (M^+), 188 ($M^+/2$); calcd for $C_{18}H_{18}F_6N_2$ m/e 376.1373, found 376.1374.

2,4′-Bis[*N*-methyl-*N*-(2,2,2-trifluoroethyl)amino]biphenyl (9a, Isomer 2): ^{19}F NMR δ −7.60 (t, J = 9.5 Hz), −7.75 (t, J = 9.5 Hz); MS m/e 376 (M^+), 188 ($M^+/2$); calcd for $C_{18}H_{18}F_6N_2$ m/e 376.1373, found 376.1363.

***N*-(1-Cyanoethyl)-*N*-(2,2,2-trifluoroethyl)aniline (7b)**: ^{1}H NMR δ 1.51 (d, 3 H, $CHCH_3$, J = 7.0 Hz), 3.75 (q, 2 H, CH_2CF_3, J = 9.0 Hz), 4.25 (q, 1 H, $CHCH_3$, J = 7.0 Hz), 7.00–7.47 (m, 5 H, C_6H_5); ^{19}F NMR δ −7.70 (t, J = 9.0 Hz); MS m/e 228 (M^+), 213 (M^+ − Me), 159 ($M^+ - CF_3$); calcd for $C_{11}H_{11}F_3N_2$ m/e 228.0874, found 228.0915.

2-Cyano-*N*-ethyl-*N*-(2,2,2-trifluoroethyl)aniline (8b, Isomer 1): ^{1}H NMR δ 1.13 (t, 3 H, CH_2CH_3, J = 7.0 Hz), 3.47 (q, 2 H, CH_2CH_3, J = 7.0 Hz), 3.93 (q, 2 H, CH_2CF_3, J = 9.5 Hz), 6.27–7.70 (m, 4 H, C_6H_4); ^{19}F NMR δ −9.05 (t, J = 9.5 Hz); MS m/e 228 (M^+), 213 (M^+ − Me), 159 ($M^+ - CF_3$), 131 ($M^+ - CF_3 - C_2H_4$), 102 ($C_6H_4CN^+$); calcd for $C_{11}H_{11}F_3N_2$ m/e 228.0874, found 228.0916.

4-Cyano-*N*-ethyl-*N*-(2,2,2-trifluoroethyl)aniline (8b, Isomer 2): ^{1}H NMR δ 1.20 (t, 3 H, CH_2CH_3, J = 7.0 Hz), 3.53 (q, 2 H, CH_2CH_3, J = 7.0 Hz), 3.87 (q, 2 H, CH_2CF_3, J = 9.5 Hz), 6.53–7.57 (m, 4 H, C_6H_4); ^{19}F NMR δ −7.95 (t, J = 9.5 Hz); MS m/e 228 (M^+), 213 (M^+ − Me), 159 ($M^+ - CF_3$), 131 ($M^+ - CF_3 - C_2H_4$), 102 ($C_6H_4CN^+$); calcd for $C_{11}H_{11}F_3N_2$ m/e 228.0874, found 228.0888.

2-Cyano-*N*-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydroquinoline (10): ^{1}H NMR δ 2.15 (m, 2 H, CH_2CHCN), 2.97 (m, 2 H, $C_6H_4CH_2$), 3.83 (m, 2 H, CH_2CF_3), 4.35 (m, 1 H, $CHCN$), 6.46–7.17 (m, 4 H, C_6H_4); ^{19}F NMR δ −7.60 (t, J = 9.0 Hz); MS m/e 240 (M^+), 171 ($M^+ - CF_3$), 118 ($M^+ - CF_3 - CH_2CHCN$); calcd for $C_{12}H_{11}F_3N_2$ m/e 240.0874, found 240.0860.

***N*-(1-Cyanobutyl)-*N*-(2,2,2-trifluoroethyl)butylamine (11)**: ^{1}H NMR δ 0.96 (t, 3 H, CH_3), 1.00 (t, 3 H, CH_3), 1.13–1.80 (m, 8 H, $CH_3CH_2CH_2$), 2.73 (t, 2 H, CH_2N), 3.12 (double q, 2 H, CH_2CF_3), 3.60 (t, 1 H, NCHCN); ^{19}F NMR δ −7.33 (t, CF_3, J = 10.0 Hz); MS m/e 236 (M^+), 192 ($M^+ - CH_3CHCH_2$), 167 ($M^+ - CF_3$); calcd for $C_{11}H_{19}F_3N_2$ m/e 236.1499, found 236.1519.

2-Cyano-*N*-(2,2,2-trifluoroethyl)piperidine (12a): ^{1}H NMR δ 1.50–2.07 (m, 6 H), 2.60–2.90 (m, 2 H, NCH_2), 2.97 (double q, 2 H, CH_2CF_3), 3.87 (t, 1 H, NCHCN); ^{19}F NMR δ −6.80 (t, J = 10.0 Hz); MS m/e 192 (M^+), 123 ($M^+ - CF_3$); calcd for $C_8H_{11}F_3N_2$ m/e 192.0874, found 192.0853.

2-Cyano-2,6-dimethyl-*N*-(2,2,2-trifluoroethyl)piperidine (12b): ^{1}H NMR δ 1.19 (d, 3 H, $CHCH_3$, J = 6.0 Hz), 1.50 (s, 3 H, $CCNCH_3$), 1.69 (m, 7 H), 2.67 (m, 1 H, $NCHCH_3$), 3.14 (q, 2 H, CH_2CF_3), J = 9.0 Hz); ^{19}F NMR δ −9.25 (t, J = 9.0 Hz); MS m/e 220 (M^+), 205 ($M^+ - CH_3$), 151 ($M^+ - CF_3$), 122 ($M^+ - CF_3CH_2 - CH_3$); calcd for $C_{10}H_{15}F_3N_2$ m/e 220.1180, found 220.1218.

1-Cyano-*N*-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydroisoquinoline (13): ^{1}H NMR δ 2.55–3.17 (m, 4 H), 3.23 (double q, 2 H, CH_2CF_3, J = 9.2 Hz), 4.80 (s, 1 H, NCHCN), 7.10 (br s, 4 H, C_6H_4); ^{19}F NMR δ −7.45 (t, CF_3, J = 9.2 Hz); MS m/e 240 (M^+), 214 (M^+ − CN), 171 ($M^+ - CF_3$), 129 ($M^+ - CH_2NCH_2CF_3$); calcd for $C_{12}H_{11}F_3N_2$ m/e 240.0874, found 240.0853.

α-Cyano-*N*-ethyl-*N*-(2,2,2-trifluoroethyl)benzylamine (14): ^{1}H NMR δ 1.11 (t, 3 H, CH_2CH_3, J = 8.2 Hz), 2.69 (q, 2 H, CH_2CH_3, J = 8.2 Hz), 3.10 (double q, 2 H, CH_2CF_3, J = 9.0 Hz), 5.01 (s, 1 H, NCHCN), 7.14–7.60 (m, 5 H, C_6H_5); ^{19}F NMR δ −7.35 (t, CF_3, J = 9.0 Hz); MS m/e 242 (M^+), 227 ($M^+ - CH_3$), 173 ($M^+ - CF_3$), 116 ($C_6H_5CHCN^+$); calcd for $C_{12}H_{13}F_3N_2$ m/e 242.1030, found 242.1025.

***N*-(1-Cyanoethyl)-*N*-(2,2,2-trifluoroethyl)benzylamine (15)**: ^{1}H NMR δ 1.40 (d, 3 H, $CHCNCH_3$, J = 7.0 Hz), 3.12 (double q, 2 H, CH_2CF_3, J = 9.0 Hz), 3.57 (q, 1 H, NCHCN, J = 7.0 Hz), 3.65 (d, 1 H, $C_6H_5CH_2$, J = 13.0 Hz), 4.00 (d, 1 H, $C_6H_5CH_2$, J = 13.0 Hz), 7.17 (br s, 5 H, C_6H_5); ^{19}F NMR δ −7.32 (t, CF_3, J = 9.0 Hz); MS m/e 242 (M^+), 92 ($C_6H_5CH_3^+$); calcd for $C_{12}H_{13}F_3N_2$ m/e 242.1030, found 242.0997.

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A Convenient Regioselective Synthesis of Substituted Cycloheptenones

Chwang Siek Pak* and Sung Kee Kim

Korea Research Institute of Chemical Technology, P.O. Box 9, Daedeog-Danji, Chungnam, Korea

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Cycloheptenones are frequently prepared from bicyclo[3.2.0]heptane-1,6-diol monosulfonates by base-induced fragmentation[1-3] of the interannular bond, the position of

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