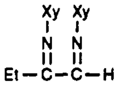
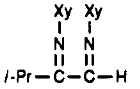
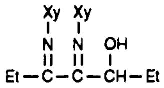
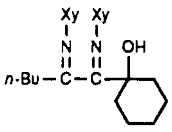
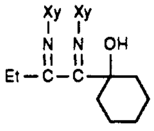
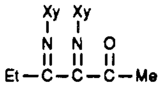
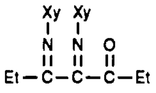
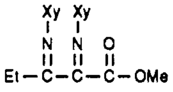
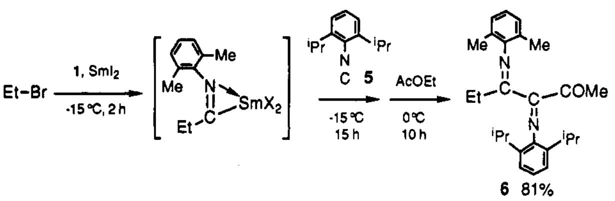
Table I. Reaction of 3 with Electrophiles[a]

entry	RBr	E, conditions	product	yield, %
1	EtBr	H_2O, 0 °C, 15 min	 $\mathrm{Et{-}C({=}NXy){-}C({=}NXy){-}H}$ **4a**	90
2	*i*-PrBr	H_2O, 0 °C, 15 min	 $\mathrm{\mathit{i}\text{-}Pr{-}C({=}NXy){-}C({=}NXy){-}H}$ **4b**	60[b]
3	EtBr	EtCHO, 0 °C, 12 h	 $\mathrm{Et{-}C({=}NXy){-}C({=}NXy){-}CH(OH){-}Et}$ **4c**	70
4	*n*-BuBr	cyclohexanone, 0 °C, 12 h	 **4d**	77
5	EtBr	cyclohexanone, 0 °C, 12 h	 **4e**	92
6	EtBr	AcOEt, 0 °C, 5 h	 $\mathrm{Et{-}C({=}NXy){-}C({=}NXy){-}C({=}O){-}Me}$ **4f**	83
7	EtBr	$EtCO_2Me$, 0 °C, 6 h	 $\mathrm{Et{-}C({=}NXy){-}C({=}NXy){-}C({=}O){-}Et}$ **4g**	79
8	EtBr	$MeOCO_2Me$, 0 °C, 20 h	 $\mathrm{Et{-}C({=}NXy){-}C({=}NXy){-}C({=}O){-}OMe}$ **4h**	63

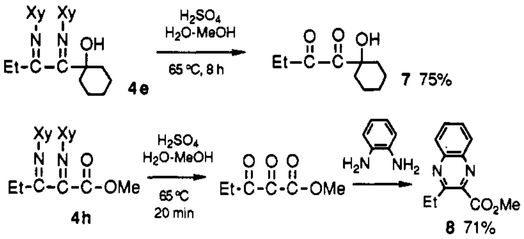
[a] Unless otherwise noted, alkyl bromide (1 equiv) was added to a mixture of 2,6-xylyl isocyanide (2.5 equiv), HMPA (5.8 equiv), and SmI_2 (0.1 M in THF, 2.0-2.5 equiv) at -15 °C. After stirring for 10 h, an electrophile (1.5 equiv) was added, and the reaction mixture was stirred under the conditions specified above. All products have been fully characterized by spectroscopic methods plus elemental analysis or HRMS. [b] Double insertion was carried out at 0 °C for 10 h.

Scheme II



6 81%

Scheme III



h at -15 °C. After the reaction with AcOEt, a cross double insertion product (6) was obtained in 81% yield based on 1. The homo double insertion product, which might arise from double insertion of two molecules of 1, was not detected. This finding suggested that the double insertion is irreversible and that the first insertion proceeds rather faster than the coupling with the second isocyanide.

The diimines thus obtained were hydrolyzed in acidic media to the corresponding polycarbonyl compounds[6] in good yields (Scheme III). Of particular interest was that this procedure provides a novel and convenient method for the construction of 1,2,3-tricarbonyl functionality, which has recently attracted a growing attention; 1,2,3-tricarbonyl system is a peculiar and pharmacologically interesting structural feature of the powerful immunosuppressant FK-506, whose synthetic study is currently being undertaken by several groups.[7] In addition, the synthetic utility of 1,2,3-tricarbonyl compounds for nitrogen-containing heterocycles has been reported.[8]

Application of the present methodology to the synthesis of 1,2,3-tricarbonyl segment of FK-506 is under progress in our laboratory.

Supplementary Material Available: Experimental details and spectroscopic and microanalytical data for 4 and 6-8 (4 pages). Ordering information is given on any current masthead page.

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[6] The tricarbonyl compound appeared to be in the hydrated form based on ^{13}C NMR of the crude product mixture and was trapped as the quinoxaline derivative (8) for isolation: Hoffman, R. V.; Kim, H.-O.; Wilson, A. L. *J. Org. Chem.* **1990**, *55*, 2820.

[7] Villalobos, A.; Danishefsky, S. J. *J. Org. Chem.* **1990**, *55*, 2776 and references cited therein.

[8] Wasserman, H. H.; Cook, J. D.; Vu, C. B. *J. Org. Chem.* **1990**, *55*, 1701.

Electroorganic Chemistry. 130.[1] A Novel Trifluoromethylation of Aldehydes and Ketones Promoted by an Electrogenerated Base

Tatsuya Shono,* Manabu Ishifune, Toshio Okada, and Shigenori Kashimura

Department of Synthetic Chemistry, Faculty of Engineering, Kyoto University, Yoshida, Sakyo, Kyoto 606, Japan

Received October 9, 1990

Summary: A base generated by the electroreduction of 2-pyrrolidone deprotonated trifluoromethane to form a trifluoromethyl anion equivalent. In the presence of hexamethyldisilazane, this species reacted with a variety of aldehydes and ketones to afford (trifluoromethyl)carbinols in high yield.

0022-3263/91/1956-0002$02.50/0

The unique chemical reactivity of electrogenerated bases, especially the one generated from pyrrolidone, was observed in our previous studies.[2-5] We now report that the base generated from pyrrolidone was remarkably effective in promoting the formation of a trifluoromethyl anion equivalent.

Although the trifluoromethyl anion, or its chemical equivalent, would obviously be valuable for the synthesis of organic compounds that incorporate CF_3 groups,[6] the generation of such a species is difficult, due to its low stability.[7,8] Its formation has so far been achieved by the reaction of dibromodifluoromethane[9,10] or iodotrifluoromethane[11-13] with Zn, under rather unusual reaction conditions. The recently reported[14] trifluoromethylation of carbonyl compounds involved the use of (trifluoromethyl)trimethylsilane[15] as the source of the trifluoromethyl anion.

We found that a trifluoromethyl anion equivalent could be efficiently formed by deprotonation of trifluoromethane with the base **2** (**2a**, R = Et; **2b**, R = *n*-Bu; **2c**, R = *n*-C_8H_{17}), generated from 2-pyrrolidone (**1**) by electrochemical reduction (Scheme I). The reaction of this species with aldehydes and ketones gave (trifluoromethyl)carbinols in fair to good yield.

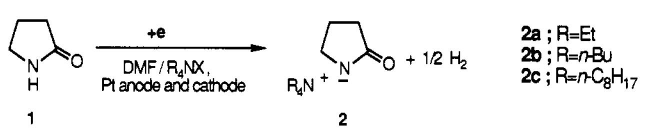
Because the formation of a trifluoromethyl anion by deprotonation of trifluoromethane has never been reported, the effect of a variety of bases was studied. The species generated was then allowed to react with benzaldehyde (**3a**) (Scheme II).

Although the trifluoromethyl anion could be formed by treatment of trifluoromethane with some common bases (Table I, runs 1 and 3), the yield of phenyl(trifluoromethyl)carbinol (**4a**) from the subsequent reaction was low.[16] On the other hand, the use of electrogenerated **2b** or **2c** as the base led to a remarkable increase in the yield of **4a** (Table I, runs 6 and 7).

Furthermore, the results shown in Table I clearly indicated that the structure of the counterion of the electrogenerated pyrrolidone anion had great influence on both the stability and reactivity of the anion equivalent (Table I, runs 5, 6, and 7).

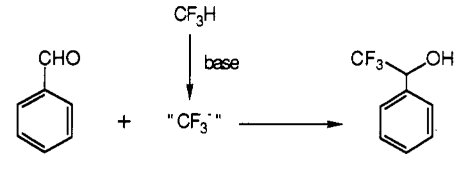
The trifluoromethylation of aromatic aldehydes promoted by electrogenerated **2b** (runs 1–3) gave good yields of (trifluoromethyl)carbinols (Table II). The trifluoromethylation of aliphatic ketones, however, did not give satisfactory results under the same reaction conditions (runs 4 and 8). After examining a variety of reaction conditions,[17] we found that the presence of hexamethyldisilazane (HMDS) in the reaction mixture brought about a remarkable increase in the yield of product (runs 5 and 9). The presence of HMDS[18] was also effective in pro-

Scheme I



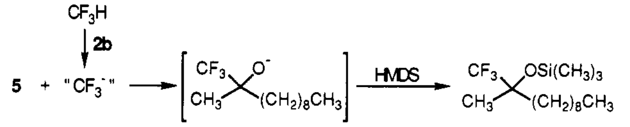
1 2

Scheme II



3a 4a

Scheme III



7 8

Table I. Trifluoromethylation of Benzaldehyde[a]

run	base	yield of **4a**,[b] %	run	base	yield of **4a**,[b] %
1	NaH	28	5	**2a**	34
2	LiH	0	6	**2b**	74
3	*t*-BuOK	40	7	**2c**	80
4	*n*-Bu_4NOH	0			

[a] All reactions were performed in DMF, using 1.5 equiv of base (based on **3a**). [b] Isolated yield.

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(1) Electroorganic Chemistry. 129. Submitted to *J. Org. Chem.*

(2) Shono, T.; Kashimura, S.; Ishizaki, K.; Ishige, O. *Chem. Lett.* **1984**, 1311.

(3) Shono, T.; Kashimura, S.; Nogusa, H. *J. Org. Chem.* **1984**, *19*, 2043.

(4) Shono, T.; Kashimura, S.; Ishige, O. *J. Org. Chem.* **1986**, *51*, 546.

(5) Shono, T.; Kashimura, S.; Sawamura, M.; Soejima, T. *J. Org. Chem.* **1988**, *53*, 907.

(6) Kitazume, T.; Ishikawa, N. *Nippon Kagaku Kaishi* **1984**, 1275.

(7) Pierce, O. R.; McBee, E. T.; Judd, G. F. *J. Am. Chem. Soc.* **1954**, *76*, 474.

(8) Haszeldine, R. N. *J. Chem. Soc.* **1954**, 1273.

(9) Burton, J. D.; Wiemers, D. M. *J. Am. Chem. Soc.* **1985**, *107*, 5014.

(10) Wiemers, D. M.; Burton, J. D. *J. Am. Chem. Soc.* **1986**, *108*, 832.

(11) The trifluoromethyl anion was formed by the electroreduction of iodotrifluoromethane with a Ni cathode and a sacrificial Zn anode. See: Stibille, S.; Mcharek, S.; Perichon, J. *Tetrahedron* **1989**, *45*, 1423.

(12) O'Reilly, N. J.; Maruta, M.; Ishikawa, N. *Chem. Lett.* **1984**, 517.

(13) Kitazume, T.; Ishikawa, N. *J. Am. Chem. Soc.* **1985**, *107*, 5186 and references cited therein.

(14) Prakash, G. K. S.; Krishnamurti, R.; Olah, G. A. *J. Am. Chem. Soc.* **1989**, *111*, 393.

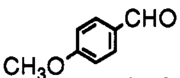
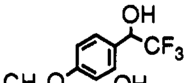
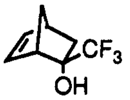
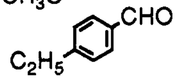
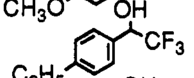
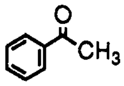
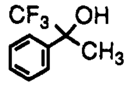
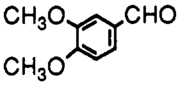
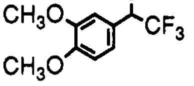
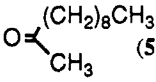
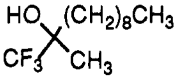
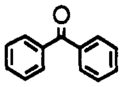
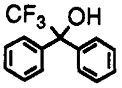
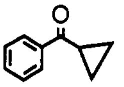
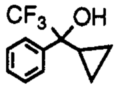
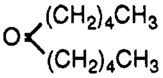
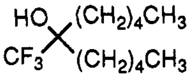
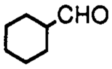
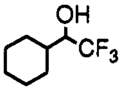
(15) Rupport, I.; Schlich, K.; Volbach, W. *Tetrahedron Lett.* **1984**, *25*, 2195.

(16) The use of NaH or *t*-BuOK as the base led to a mixture of benzyl alcohol and benzoic acid as the main products. They arose from the Cannizzaro reaction of **3a**.

(17) The presence of Ac_2O, Me_3SiCl, or H_2O in the reaction mixture, instead of HMDS, did not increase the yield of **6**.

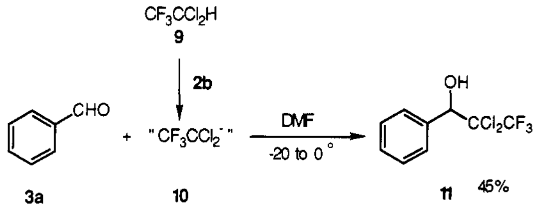
(18) A solution of electrogenerated base (**2a**, **2b**, **2c**) in DMF was prepared by the electroreduction of **1**, as previously described.[5] To a cold (−50 °C) solution of HMDS (18 mmol) and carbonyl compound (3 mmol) in DMF (5 mL) was added gaseous trifluoromethane (21 mmol, 1.5 g). A solution of **2b** (9 mmol) in 10 mL of DMF was then added, drop-by-drop, over 10 min. The reaction mixture was kept at −10 °C for 5 h. After the usual workup, the products (**4**, **6**, and **11**) were isolated by bulb-to-bulb distillation. The structures of **4b**, **4c**, **4d**, and **6** were determined from their spectra (IR; ^1H and ^{13}C NMR) and high-resolution mass spectrometry (HRMS) or elemental analysis. The structures of the other products in Table I (runs 6–12) and **4a**, and **11** were confirmed by comparison of their spectra with those of authentic samples.[14,19] **4b**: IR (neat) 3450, 1260, 1180, 1135, 825, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.67 (s, 1 H), 3.75 (s, 3 H), 4.93 (q, $J_{HCF} = 6.8$ Hz, 1 H), 6.75–7.42 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 55.48, 72.64 (q, $J_{CCF} = 31.8$ Hz), 114.39, 124.79 (q, $J_{CF} = 281.9$ Hz), 126.66, 129.22, 160.91; HRMS *m/e* 206.05547 [calcd for $C_9H_9F_3O_2$, 206.05436]. **4c**: IR (neat) 3400, 1280, 1180, 1135, 825, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.25 (t, $J = 7.8$ Hz, 3 H), 2.28 (s, 1 H), 2.70 (q, $J = 7.8$ Hz, 2 H), 5.00 (q, $J_{HCF} = 6.6$ Hz, 1 H), 7.20–7.52 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 15.46, 28.71, 73.01 (q, $J_{CCF} = 31.9$ Hz), 124.71 (q, $J_{CF} = 284.0$ Hz), 127.82, 128.59, 131.66, 146.32; HRMS *m/e* 204.07798 [calcd for $C_{10}H_{11}F_3O$, 204.07623]. **4d**: IR (KBr) 3460, 1260, 1235, 1150, 1120, 1070, 880, 860, 820, 715 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.65 (s, 1 H), 3.90 (s, 6 H), 4.95 (q, $J_{HCF} = 6.0$ Hz, 1 H), 6.87–7.12 (m, 3 H); ^{13}C NMR ($CDCl_3$) δ 56.07, 72.78 (q, $J_{CCF} = 31.5$ Hz), 110.56, 111.23, 120.70, 124.73 (q, $J_{CF} = 280.7$ Hz), 149.48, 150.32. Anal. Calcd for $C_{10}H_{11}F_3O_3$: C, 50.85; H, 4.69; F, 24.13. Found: C, 51.09; H, 4.65; F, 24.02. **6**: IR (neat) 3410, 2975, 2950, 2870, 1480, 1165 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.78–1.07 (m, 3 H), 1.08–1.42 (m, 14 H), 1.42–1.80 (m, 5 H), 1.83 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 14.16, 20.60, 22.78, 29.41, 29.63, 30.06, 32.02, 35.29, 73.99 (q, $J_{CCF} = 29.8$ Hz), 127.00 (q, $J_{CF} = 288.8$ Hz). Anal. Calcd for $C_{12}H_{23}F_3O$: C, 59.98; H, 9.65; F, 23.72. Found: C, 60.10; H, 9.88; F, 23.85.

Table II. Trifluoromethylation of Aldehydes and Ketones

run	carbonyl compound	method[a]	product	yield,[b] %	run	carbonyl compound	method[a]	product	yield,[b] %
1		A		(**4b**) 92	7		B		65
2		A		(**4c**) 60	8		A		trace
3		A		(**4d**) 78	9		B		60
4	 (5)	A		(**6**) 36	10		B		84
5		B		(**6**) 83	11		B		73
6		B		71	12		B		23

[a] All reactions were performed in DMF, using 3 equiv (based on carbonyl compound) of **2b**. Method A: no HMDS present. Method B: 6 equiv of HMDS present in the reaction mixture. [b] Isolated yield of pure compound.

Scheme IV



moting the trifluoromethylation of other ketones (runs 6–11).

It seems reasonable to assume that HMDS promoted the reaction by silylating the intermediate **7**, formed by the reaction of **5** with the trifluoromethyl anion equivalent (Scheme III). Silyl ether **8** was, in fact, detected in the reaction mixture.

We also found that the introduction of **2b** into a mixture of **3a** and trifluorodichloroethane (**9**) in DMF led to the formation of alcohol **11**[19] in fair yield (Scheme IV). This result was interesting because the formation of **11** indicated the involvement of an intermediate chemically equivalent to anion **10**, in which the negative charge is localized on the carbon atom α to the trifluoromethyl group. An anion of this type is highly unstable,[20–21] and hence reports of its nucleophilic addition to carbonyl compounds are rare.

Why the electrogenerated base was so effective in promoting the formation and subsequent reaction of the trifluoromethyl anion equivalent is not clear. However, it seems reasonable to assume that two factors—the use of a tetraalkylammonium counterion and the use of a highly aprotic reaction medium—were, at least in part, responsible for the observed stability of the trifluoromethyl anion equivalent.

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[19] Fujita, M.; Morita, T.; Hiyama, T. *Tetrahedron Lett.* **1986**, *27*, 2135.

[20] Yokozawa, T.; Nakai, T.; Ishikawa, N. *Tetrahedron Lett.* **1984**, *26*, 3987.

[21] Fuchigami, T.; Nakagawa, Y. *J. Org. Chem.* **1987**, *52*, 5276.

Stereoselective Addition Reactions of Chiral *N*-Benzylidene-*p*-toluenesulfinamides. Asymmetric Syntheses of *β*- and *γ*-Amino Acids

Duy H. Hua,*,† Shou Wu Miao, Jin Shan Chen, and Sadahiko Iguchi[1]

Department of Chemistry, Kansas State University, Manhattan, Kansas 66506

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Summary: Chiral *N*-benzylidene-*p*-toluenesulfinamides **2** were prepared by the reaction of benzonitrile with alkyllithium in ether followed by (–)-*l*-menthyl (*S*)-*p*-tolylsulfinate. Treatment of **2** with allylmagnesium bromide in ether at 0 °C gave the adducts (*R*)-**7** with excellent stereoselectivity. Pure chiral sulfinamides **7** were converted into chiral *β*- and *γ*-amino acids in four and five steps, respectively.

Racemic *N*-alkylidenearenesulfinamides were first reported by Davis[2] and Burger.[3] The optically active versions were prepared in 15–70% yields by Cinquini et al.[4] by the reaction of Grignard reagents with benzonitrile followed by (–)-*l*-menthyl (*S*)-*p*-toluenesulfinate (**1S**). As part of our continuing studies in the enantioselective addition reactions of α-sulfinyl ketimines,[5] the chemistry of

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† Fellow of the Alfred P. Sloan Foundation, 1989–1991.

[1] Ono Pharmaceutical Co., Osaka 618, Japan.

[2] (a) Davis, F. A.; Friedman, A. J.; Kluger, E. W. *J. Am. Chem. Soc.* **1974**, *96*, 5000. (b) Davis, F. A.; Friedman, A. J. *J. Org. Chem.* **1976**, *41*, 898. (c) Davis, F. A.; Kluger, E. W. *J. Am. Chem. Soc.* **1976**, *98*, 302. (d) Davis, F. A.; Friedman, A. J.; Nadir, U. K. *J. Am. Chem. Soc.* **1978**, *100*, 2844.

[3] Burger, K.; Albanbauer, J.; Kafig, F.; Penninger, S. *Liebigs Ann. Chem.* **1977**, 624.

[4] (a) Cinquini, M.; Cozzi, F. *J. Chem. Soc. Chem. Commun.* **1977**, 502. (b) *Ibid.* **1977**, 723. (c) Annunziata, R.; Cinquini, M.; Cozzi, F. *J. Chem. Soc., Perkin Trans. 1* **1982**, 339–43.

0022-3263/91/1956-0004$02.50/0