3,3,3-Trifluoro-1-nitropropene as a Novel Trifluoromethyl-Containing Building Block

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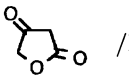
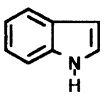
Synopsis. Additions of various carbanion nucleophiles to 3,3,3-trifluoro-1-nitropropene (**1**) proceeded regiospecifically at the C-2 position of **1** to give the corresponding adducts. The nitro group of the adducts, derived from the reactions with acetylacetone and ethyl acetoacetate, was reduced to the corresponding amines, which were cyclized in situ to the 3-(trifluoromethyl)pyrrole derivatives.

In the synthesis of fluorinated compounds, the regiospecific introduction of fluorine atom or fluoroalkyl group to the desired position is one of the problems to be clarified. For the purpose of the regiospecific introduction of the trifluoromethyl group, recently, many convenient synthetic methods using a trifluoromethyl-containing building block have been reported.[1—3] 1-Substituted 3,3,3-trifluoropropenes have been under the active research projects because of their high reactivity as Michael acceptors.[4] On the other hand, nitroalkanes have proven to be valuable intermediates because of their facile conversion into the corresponding amines, nitroaldol reactions, and reductive cleavage of the nitro groups.[5] In this connection, it is of interest to survey the reactivity of 3,3,3-trifluoro-1-nitropropene (**1**). We now wish to demonstrate utility of nitropropene **1** as a novel building block for the construction of trifluoromethylated compounds.

Nitropropene **1**, which was prepared by modifying the method of Shechter and his co-workers,[6] was reacted with various carbanion nucleophiles to give the regiospecific adducts formed by the nucleophilic additions to the 2-carbon of **1** (Scheme 1).[7] The reactions of **1** with acetylacetone, β-keto esters, diethyl malonate, and methyl cyanoacetate in the presence of a catalytic amount of sodium hydride gave the adducts **2a**—**d** and **3** in moderate yields (Table 1). Although the reaction with butyllithium did not give the adduct, those with some alkyl metal reagents such as ethylmagnesium bromide and lithium dibutylcuprate led to the corresponding adducts **4a** (44%) and **4b** (46%), respectively. Nitropropene **1** was reacted with pyrrole to give 2-substituted product **5** (70%), and with indole to give 3-substituted adduct **6** (56%).

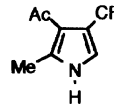
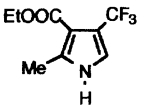
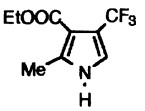
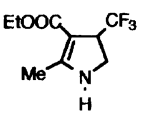
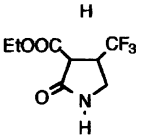
Trifluoromethyl-substituted pyrroles and pyrrolines were obtained by the reduction of the nitro group of **2a**, **2b**, and **2d** with iron-acetic acid (Table 2). Yields of pyrroles or pyrrolines are dependent on the activity of iron and reaction temperature. When *reduced* iron was used in ethanol–water at 70 °C, **2b** was converted to pyrrole **7b** in 21% yield, and heating in 1-butanol–water at 100 °C increased the yield to 47%. On the other hand, with iron itself, pyrroline **7b′** was formed in 36% yield. Thus obtained pyrroline **7b′** was dehydrogenated to pyrrole **7b** in 25% yield in boiling nitrobenzene. Treatment of **2a** and **2d** with *reduced* iron afforded pyrrole **7a** and 2-pyrrolidone **7d** in 27 and 67% yields, respectively.[8]

Table 1. Reactions of **1** with Carbanion Nucleophiles

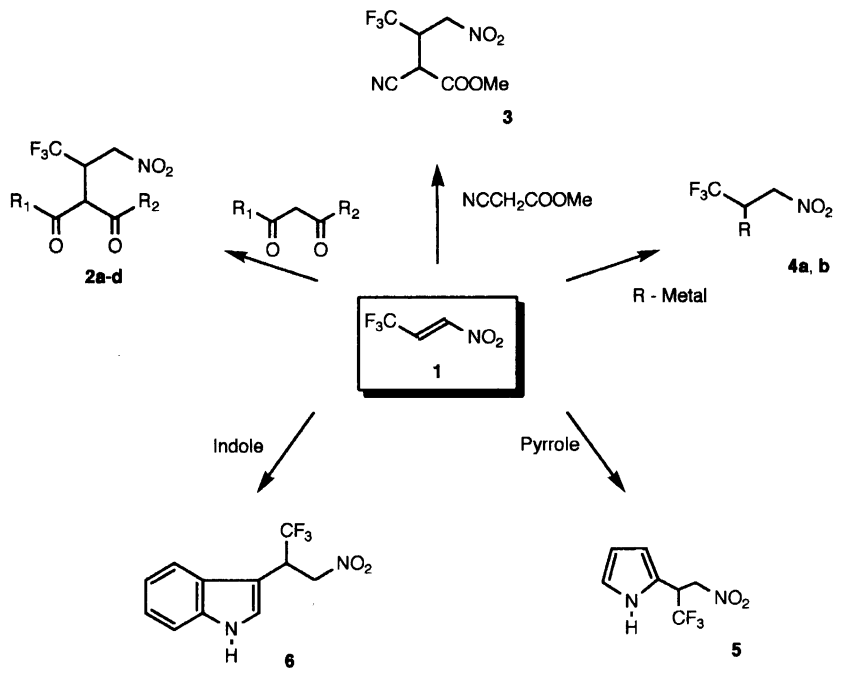
Nucleophile	Product	Yield/%[a]
$MeCOCH_2COMe$/NaH	**2a**	68[b]
$MeCOCH_2COOEt$/NaH	**2b**	74[c]
 /NaH	**2c**	64[d]
$CH_2(COOEt)_2$/NaH	**2d**	59
$NCCH_2COOMe$/NaH	**3**	67[e]
EtMgBr	**4a**	44
Bu_2CuLi	**4b**	46
	**5**	70
	**6**	56

a) Isolated Yield. b) A mixture of keto- and enol-forms. c) Ratio of diastereomers is 43/57. d) Enol-form. e) Ratio of diastereomers is 31/69.

Table 2. Reductions of the Adducts **2a**, **2b**, and **2d**

Adduct	Conditions	Product		Yield/%
2a	*reduced* Fe-AcOH/EtOH (70 °C)		**7a**	27
2b	*reduced* Fe-AcOH/EtOH (70 °C)		**7b**	21
	reduced Fe-AcOH/BuOH (100 °C)		**7b**	47
	Fe-AcOH/EtOH (70 °C)		**7b′**	36
2d	*reduced* Fe-AcOH/EtOH (70 °C)	 a)	**7d**	67

a) Isolated as one diastereomer.



Scheme 1.

In conclusion, it is found that trifluoronitropropene **1** is highly reactive as a Michael acceptor and the additions of carbanion nucleophiles take place at the C-2 carbon of **1** regiospecifically. The reduction of the adducts, derived from acetylacetone and ethyl acetoacetate, with *reduced* iron produced the corresponding 3-(trifluoromethyl)pyrroles. These results show synthetic utility of **1** as a building block for the construction of trifluoromethylated compounds.

Experimental

Melting points are uncorrected. Infrared spectra were recorded on a JASCO Report-100 spectrophotometer. ^{1}H and ^{19}F NMR spectra were taken on a JEOL JNM-GX270 (270 MHz) spectrometer, using TMS and trifluoroacetic acid as internal and external standards, respectively. The chemical shifts (δ) were given in deuteriochloroform. The elemental analyses were measured with a Yanaco MT-3 equipment. THF was freshly distilled from sodium benzophenone ketyl under nitrogen. Sodium hydride in oil was washed with hexane before use.

Preparation of 3,3,3-Trifluoro-1-nitropropene (1). A mixture of 1-ethoxy-2,2,2-trifluoroethanol (60.00 g, 0.417 mol), nitromethane (28.35 g, 0.465 mol), and anhydrous potassium carbonate (0.91 g) was stirred at 50—60 °C for 5 h. The reaction mixture was cooled, poured into water, and extracted with diethyl ether. The extracts were washed with brine and dried ($MgSO_4$). After removal of the solvent the residue was distilled under reduced pressure to give 41.60 g (63%) of 1,1,1-trifluoro-3-nitro-2-propanol; bp 60—63 °C (933 Pa) (lit,[6] 64—65 °C (933 Pa)).

A mixture of 1,1,1-trifluoro-3-nitro-2-propanol (41.60 g, 0.262 mol) and acetic anhydride (26.75 g, 0.262 mol) was stirred at 80—90 °C for 5 h in the presence of sulfuric acid (3 cm^3). The reaction mixture was washed with water and the obtained crude ester was used for the next reaction without further purification. The preparation of **1** was run in the vacuum distilling apparatus with dropping funnel. Anhydrous potassium carbonate (110 g) was placed in the 1 dm^3 flask which was heated at 140 °C (oil bath temperature) under reduced pressure (ca. 4 kPa). The crude ester (208.4 g, 1.037 mol) was added dropwise ***carefully***. The distillate (boiling range 30—65 °C), trapped with dry ice–acetone bath, was washed with water and dried ($MgSO_4$). The crude product was purified by distillation to give 90.18 g (62%) of a tearing pale yellow liquid **1**, bp 78—82 °C (lit,[6] 89 °C), which includes 2% of cis-isomer.

Reactions of 1 with Acetylacetone, β-Keto Esters, Diethyl Malonate, and Methyl Cyanoacetate. Reaction of 1 with Acetylacetone (Typical Procedure): To a suspension of THF (10 cm^3) containing sodium hydride (0.025 g, 1.0 mmol), a THF solution (5 cm^3) of acetylacetone (1.60 g, 16.0 mmol) was added dropwise at room temperature. Stirring was continued for 2 h, and then **1** (1.50 g, 10.6 mmol) was added dropwise to the reaction mixture. After stirred for 20 h at room temperature, the reaction mixture was quenched with saturated aqueous NH_4Cl solution, extracted with diethyl ether, washed with water and brine, and dried ($MgSO_4$). After removal of the solvent the residue was chromatographed on silica gel (eluent, hexane : ethyl acetate=2 : 1) to give 1.73 g (68%) of **2a** as a mixture of tautomers, which was further purified by preparative GLC; **2a (enol-form)**: White powder (hexane–ethyl acetate); mp 57.0—59.0 °C; IR (KBr) 3380 (OH), 1730, 1700 (C=O), 1560 (NO_2), 1175, and 1120 cm^{-1} (CF_3); ^{1}H NMR δ=2.0 (3H, d, J=1.2 Hz, CH_3), 2.2 (3H, s, CH_3), 4.1 (1H, ddq, J=7.2, 6.4, 8.6 Hz, CH), 4.4 (1H, dd, J=14.1, 7.2 Hz, CH_2), 4.6 (1H, dd, J=14.1, 6.4 Hz, CH_2), and 5.0 (1H, 2×q, J=1.2 Hz, OH).

Found: C, 40.08; H, 4.17; N, 5.58%. Calcd for $C_8H_{10}F_3NO_4$: C, 39.84; H, 4.18; N, 5.81%.

2a (keto-form): Pale orange oil; IR (neat) 1755, 1700 (C=O), 1555 (NO_2), 1200, 1175, 1155, and 1115 cm^{-1} (CF_3);

^{1}H NMR δ=2.3 (3H, s, CH_3), 2.4 (3H, s, CH_3), 3.9 (1H, dddq, J=6.4, 5.6, 2.6, 8.6 Hz, CH), 4.4 (1H, d, J=5.6 Hz, CH), 4.7 (1H, dd, J=14.9, 6.4 Hz, CH_2), and 4.8 (1H, dd, J=14.9, 2.6 Hz, CH_2).

Found: C, 40.02; H, 3.89; N, 5.66%. Calcd for $C_8H_{10}F_3NO_4$: C, 39.84; H, 4.18; N, 5.81%.

2b (74%): Colorless oil (a 43/57 mixture of two diastereomers); IR (neat) 1735, 1720 (C=O), 1555 (NO_2), 1190, 1175, 1150, and 1120 cm^{-1} (CF_3); ^{1}H NMR δ=1.2—1.4 (3H, 2×t, CH_3), 2.3 and 2.4 (3H, 2×s, CH_3), 4.1—4.4 (4H, m, 2×CH and 1×CH_2), 4.8—5.0 (2H, 2×dd, CH_2); ^{19}F NMR δ=6.0 (br s) and 8.3 (br s).

Found: C, 39.87; H, 4.59; N, 5.01%. Calcd for $C_9H_{12}F_3NO_5$: C, 39.86; H, 4.46; N, 5.16%.

2c (enol-form) (64%): White powder (hexane–ethyl acetate); mp 172.0—174.0 °C (decomp), IR (KBr) 3420 (OH), 1715 (C=O), 1640 (C=C), 1560 (NO_2), 1170, 1135, and 1120 cm^{-1} (CF_3); ^{1}H NMR δ=4.4 (1H, ddq, J=8.2, 5.6, 8.6 Hz, CH), 4.6 (2H, s, CH_2), 4.9 (1H, dd, J=14.0, 5.6 Hz, CH_2), and 5.2 (1H, dd, J=14.0, 8.2 Hz, CH_2).

Found: C, 34.80; H, 2.62; N, 5.86%. Calcd for $C_7H_6F_3NO_5$: C, 34.87; H, 2.51; N, 5.81%.

2d (59%): Colorless oil; IR (neat) 1750, 1730 (C=O), 1560 (NO_2), 1180, 1155, and 1125 cm^{-1} (CF_3); ^{1}H NMR δ=1.3 (6H, t, J=4.9 Hz, CH_3), 3.9 (1H, d, J=4.0 Hz, CH), 4.0 (1H, dddq, J=6.7, 4.0, 3.8, 8.6 Hz, CH), 4.3 (4H, q, J=4.9 Hz, CH_2), 4.8 (1H, dd, J=14.0, 6.7 Hz, CH_2), and 5.0 (1H, dd, J=14.0, 3.8 Hz, CH_2).

Found: C, 39.71; H, 4.67; N, 4.74%. Calcd for $C_{10}H_{14}F_3NO_6$: C, 39.87; H, 4.68; N, 4.65%.

3 (67%): Yellow oil (a 31/69 mixture of two diastereomers); IR (neat) 2255 (C≡N), 1750 (C=O), 1570 (NO_2), 1180, and 1135 cm^{-1} (CF_3); ^{1}H NMR δ=3.9 (3H, s, CH_3), 3.9—4.1 (2H, m, 2×CH), 4.7—4.9 (2H, m, CH_2); ^{19}F NMR δ=5.8 (br s) and 5.9 (br s).

Found: C, 35.16; H, 2.91; N, 11.93%. Calcd for $C_7H_7F_3N_2O_4$: C, 35.01; H, 2.94; N, 11.67%.

Reaction of 1 with Ethylmagnesium Bromide. An ethereal solution of ethylmagnesium bromide (3 mol dm^{-3}, 7 cm^3, 21.0 mmol) was added dropwise to a THF solution (20 cm^3) of **1** (2.00 g, 14.2 mmol) at ca. −100 °C. After stirred for 2 h at the same temperature, the reaction mixture was quenched with water at −30 °C, acidified to pH ca. 2 with dilute hydrochloric acid, extracted with diethyl ether, washed with water and brine, and dried ($MgSO_4$). After removal of the solvent the residue was distilled under reduced pressure to give 1.07 g (44%) of a pale yellow oil **4a**, which was further purified by preparative GLC; bp 70—74 °C (12.4 kPa); IR (neat) 1550 (NO_2), 1170, and 1140 cm^{-1} (CF_3); ^{1}H NMR δ=1.1 (3H, t, J=7.6 Hz, CH_3), 1.6 (1H, ddq, J=15.0, 7.4, 7.6 Hz, CH_2), 1.8 (1H, ddq, J=15.0, 6.3, 7.6 Hz, CH_2), 3.1 (1H, m, CH), 4.4 (1H, dd, J=13.5, 6.5 Hz, CH_2), and 4.6 (1H, dd, J=13.5, 5.6 Hz, CH_2).

Found: C, 35.19; H, 4.80; N, 7.99%. Calcd for $C_5H_8F_3NO_2$: C, 35.10; H, 4.71; N, 8.19%.

Reaction of 1 with Lithium Dibutylcuprate. To a diethyl ether suspension (70 cm^3) of copper(I) iodide (6.09 g, 32.0 mmol), a hexane solution of butyllithium (1.6 mol dm^{-3}, 40 cm^3, 64.0 mmol) was added dropwise in an ice bath. The mixture was stirred for 1 h in an ice bath, and then an ethereal solution (70 cm^3) of **1** (1.69 g, 12.0 mmol) was added dropwise to the reaction mixture. After stirred for 18 h at room temperature, the reaction mixture was acidified to pH ca. 1 with dilute hydrochloric acid and extracted with diethyl ether. Usual workup gave 1.09 g of a colorless oil **4b** (46%); IR (neat) 1560 (NO_2), 1175, and 1140 cm^{-1} (CF_3); ^{1}H NMR δ=0.9 (3H, t, J=7.3 Hz, CH_3), 1.3—1.9 (6H, m, CH_2), 3.1 (1H, m, CH), 4.4 (1H, dd, J=14.3, 6.2 Hz, CH_2), and 4.6 (1H, dd, J=14.3, 6.2 Hz, CH_2).

Found: C, 41.95; H, 5.72; N, 7.05%. Calcd for $C_7H_{12}F_3NO_2$: C, 42.21; H, 6.07; N, 7.03%.

Reaction of 1 with Pyrrole and Indole. To a dichloromethane solution (10 cm^3) of **1** (1.41 g, 10.0 mmol), a dichloromethane solution (5 cm^3) of pyrrole (0.67 g, 10.0 mmol) was added, and the reaction mixture was refluxed for 4 h. Usual workup gave 1.46 g of a pale yellow oil **5** (70%); IR (neat) 3400 (NH), 1560 (NO_2), 1175, and 1140 cm^{-1} (CF_3); ^{1}H NMR δ=4.4 (1H, ddq, J=8.6, 5.4, 8.6 Hz, CH), 4.8 (1H, dd, J=14.0, 8.6 Hz, CH_2), 4.9 (1H, dd, J=14.0, 5.4 Hz, CH_2), 6.2 (2H, m, 3-H and 4-H), 6.8 (1H, m, 5-H), and 8.3 (1H, br s, NH).

Found: C, 40.68; H, 2.99; N, 13.48%. Calcd for $C_7H_7F_3N_2O_2$: C, 40.39; H, 3.39; N, 13.46%.

The similar procedure to the above using indole gave white needles (hexane–diethyl ether) **6** (56%); mp 73.2—74.0 °C; IR (KBr) 3380 (NH), 1570 (NO_2), 1170, and 1110 cm^{-1} (CF_3); ^{1}H NMR δ=4.7 (1H, ddq, J=8.1, 6.8, 8.2 Hz, CH), 4.9 (1H, dd, J=13.2, 8.1 Hz, CH_2), 5.0 (1H, dd, J=13.2, 6.8 Hz, CH_2), 7.1—7.3 (4H, m, 2-H, 5-H, 6-H, and 7-H), 7.7 (1H, d, J=7.3 Hz, 4-H), and 8.4 (1H, br s, NH).

Found: C, 51.57; H, 3.54; N, 10.77%. Calcd for $C_{11}H_9F_3N_2O_2$: C, 51.17; H, 3.51; N, 10.85%.

Reduction of 2a, 2b, and 2d with *Reduced* Iron–Acetic Acid (General Procedure). After a suspension of 3.9 mmol of adduct **2a**, **2b**, or **2d**, 0.66 g(11.8 mmol) of *reduced* iron, and 1 cm^3 of acetic acid in 10 cm^3 of ethanol–water (1:4) was stirred at 70 °C for 8 h, the precipitate was filtered off. The filtrate was acidified to pH ca. 1 with dilute hydrochloric acid and extracted with diethyl ether. Usual workup gave 3-acetyl-2-methyl-4-(trifluoromethyl)pyrrole (**7a**), ethyl 2-methyl-4-(trifluoromethyl)pyrrole-3-carboxylate (**7b**), or ethyl 4-(trifluoromethyl)pyrrolidin-2-one-3-carboxylate (**7d**), respectively.

7a (27%): White powder (hexane–ethyl acetate); mp 176.0—178.0 °C; IR (KBr) 3160 (NH), 1620 (C=O), 1150, and 1105 cm^{-1} (CF_3); ^{1}H NMR δ=2.5 (6H, s, CH_3 and Ac), 7.0 (1H, s, CH), and 9.5 (1H, s, NH).

Found: C, 50.60; H, 4.47; N, 6.97%. Calcd for $C_8H_8F_3NO$: C, 50.27; H, 4.22; N, 7.33%.

7b (21%): Pale yellow needles (hexane–ethyl acetate); mp 124.0—125.0 °C; IR (KBr) 3230 (NH), 1665 (C=O), 1130, and 1105 cm^{-1} (CF_3); ^{1}H NMR δ=1.3 (3H, t, J=7.0 Hz, CH_3), 2.5 (3H, s, CH_3), 4.3 (2H, q, J=7.0 Hz, CH_2), 7.0 (1H, s, CH), and 8.3 (1H, s, NH).

Found: C, 48.75; H, 4.70; N, 6.34%. Calcd for $C_9H_{10}F_3NO_2$: C, 48.87; H, 4.56; N, 6.33%.

7d (68%): Colorless oil; IR (neat) 3230 (NH), 1730, 1710 (C=O), 1165, and 1120 cm^{-1} (CF_3); ^{1}H NMR δ=1.3 (3H, t, J=7.0 Hz, CH_3), 3.4—3.8 (4H, m, 2×CH and CH_2), 4.3 (2H, q, J=7.0 Hz, CH_2), and 6.4 (1H, br s, NH).

Found: C, 42.67; H, 4.58; N, 6.27%. Calcd for $C_8H_{10}F_3NO_3$: C, 42.67; H, 4.48; N, 6.22%.

Reduction of 2b with Iron–Acetic Acid. The similar reaction using **2b** and iron produced ethyl 2-meth-

yl-4-trifluoromethyl-2-pyrroline-3-carboxylate (**7b′**) (36%): Orange oil; IR (neat) 3250 (NH), 1630 (C=O), 1180, and 1130 cm^{-1} (CF_3); ^1H NMR δ=1.3 (3H, t, J=7.0 Hz, CH_3), 1.7 (1H, br s, NH), 2.0 (3H, s, CH_3), 3.3 (1H, ddq, J=9.2, 8.6, 8.8 Hz, CH), 3.9 (1H, ddq, J=14.6, 9.2, 2.7 Hz, CH_2), 4.2 (1H, ddq, J=14.6, 8.6, 1.7 Hz, CH_2), and 4.3 (2H, q, J=7.0 Hz, CH_2).

Found: C, 48.20; H, 5.71; N, 5.99%. Calcd for $C_9H_{12}F_3NO_2$: C, 48.43; H, 5.42; N, 6.28%.

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