Polar fraction b eluted with hexane–ether and yielded 0.345 g (77%) of a diastereomeric mixture of (±)-1-(4-(dimethyl-*tert*-butylsiloxy)-2,2,6,6-tetramethylcyclohexylidene)-2,3-dihydroxy-3-methyl-2-phenylbutane (**16**) as a viscous oil: IR (film) 3500, 3070 (w), 3050 (w), 3025 (w), 2900 (m), 1940 (w), 1870 (w), 1800 (w), 1600, 1470 (m), and 1400–725 cm^{-1}; ^1H NMR δ 0.07 (s, 3 H), 0.08 (s, 3 H), 0.75, 0.80 (2 s, 3 H, in the ratio of 1:3), 0.90, 0.91 (2 s, 9 H), 1.10–1.90 (m, 23 H, including several CH_3 singlets), 3.02, 3.28 (2 br s, 1 H, OH), 4.04 (m, 1 H), 6.22, 6.30 (2 s, 1 H, in the ratio of 3:1), and 7.18–7.50 (m, 5 H).

Anal. Calcd for $C_{27}H_{46}O_3Si$: C, 72.64; H, 10.31. Found: C, 72.61; H, 10.31.

Cross-Coupling Reaction between (*S*)-(+)-7 and Acetone at Refluxing Temperatures. (*S*)-(+)-(4-(Dimethyl-*tert*-butylsiloxy)-2,2,6,6-tetramethylcyclohexylidene)acetophenone (**7**) (0.386 g, 1 mmol), $[\alpha]^{29}_D$ +40.31 ± 0.20°, 37.52% ee) and acetone (0.232 g, 4 mmol) in 30 mL of THF was allowed to reflux with 20 mmol of Ti(0) reagent for 20 h. Workup and separation as described earlier gave 0.35 g (85%) of (±)-1-(4-(dimethyl-*tert*-butylsiloxy)-2,2,6,6-tetramethylcyclohexylidene)-3-methyl-2-phenyl-2-butene (**15**) and a mixture of polar fractions (0.06 g).

Low Valent Titanium Reaction of (+)-1-(4-(Dimethyl-*tert*-butylsiloxy)-2,2,6,6-tetramethylcyclohexylidene)-2,3-dihydroxy-3-methyl-2-phenylbutane (16). The title compound glycol **16** (0.223 g, 0.5 mmol) and Ti(0) reagent (10 mmol) in 15 mL of dry THF was stirred at 0 °C for 5 h. Workup and separation gave only a trace of less polar fraction and 0.20 g (90%) of recovered starting material **16**.

Notes

1,1,1-Trifluoro-2-penten-4-one as a Building Block of Trifluoromethyl-Substituted Compounds

Hisanobu Ogoshi,* Hiromoto Mizushima, Hiroo Toi, and Yasuhiro Aoyama

Department of Material Science, Technological University of Nagaoka, Kamitomioka, Nagaoka, Niigata 949-54, Japan

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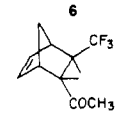
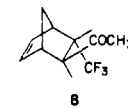
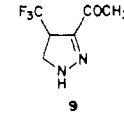
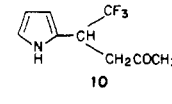
Partially fluorinated organic molecules are receiving increasing attention from the viewpoint of biological activity. Much effort has recently been paid to the development of trifluoromethylation, or perfluoroalkylation in general, of organic compounds.[1-6] An alternative general method involves chemical conversion of a simple CF_3-containing building block.[7] This approach would be more suited for the selective CF_3 functionalization of complicated organic molecules. Thus, reactions of CF_3-containing olefins[8-10] and carbonyl compounds[11-16] have been under active investigation. In the present work we have taken up a β-CF_3-α,β-unsaturated ketone and found that it is an excellent building block for the preparation of a variety of CF_3-containing compounds.

Table I. Reactions of 1,1,1-Trifluoro-2-penten-4-one (1) with Various Reagents

reagnt [solv]	condn	product	yield (%)
$(C_2H_5)_2NH$ $[(C_2H_5)_2NH]$	room temp 1 min	$F_3CCHCH_2COCH_3$ | $N(C_2H_5)_2$ **2**	56
CH_3NO_2, Na_2CO_3 $[CH_3NO_2$–$H_2O]$	60 °C 1 h	$F_3CCHCH_2COCH_3$ | CH_2NO_2 **3**	86
CH_3CH_2MgI $[(C_2H_5)_2O]$	room temp 1 h	$F_3CCHCH_2COCH_3$ | C_2H_5 **4**	13
CH_3CH_2MgI $[(C_2H_5)_2O]$	room temp 1 h	$F_3CCH{=}CHCC_2H_5$ (CH$_3$, OH) **5**	48
$(n\text{-}C_4H_9)_2CuLi$ $[(C_2H_5)_2O]$	room temp 1 h	$F_3CCHCH_2COCH_3$ | $C_4H_{9}\text{-}n$ **6**	44
cyclopentadiene [benzene]	80 °C 1 h	 **7**	62
cyclopentadiene [benzene]	80 °C 1 h	 **8**	18
CH_2N_2 $[(C_2H_5)_2O]$	room temp 1 min	 **9**	91
pyrrole $[CH_2Cl_2]$	40 °C 7 h	 **10**	65

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1,1,1-Trifluoro-2-penten-4-one (1), bp 89–91 °C, was prepared in 87% yield by the Wittig reaction of (acetylmethylene)triphenylphosphorane and trifluoroacetaldehyde (1.5 equiv) in ether at room temperature (eq 1).[17-18] The isomer ratio was determined by gas chro-

(1)

matography coupled with ^1H NMR analysis; E/Z = 95.5/4.5. The conjugate or Michael addition of nucleophiles to 1 was first examined. The addition of diethylamine to give 2 was almost instantaneous, that of nitromethane also took place readily under weakly basic condition (Na_2CO_3) and gave 3. 2-Penten-4-one, on the other hand, reacted with diethylamine and nitromethane anion to give the corresponding 1,4-adducts in rather poor yields (25 and 27%, respectively) under conditions identical with those for 1. The reaction of ethyl Grignard reagent with 1 gave a considerable amount of 1.4-adduct 4, although the major product was the 1,2-adduct 5. A lithium dialkylcuprate reagent led to the 1,4-addition product 6 exclusively. This was not a foregone conclusion, since reduction of a fluorine atom could have been competitive. The reaction conditions and yields of the products are summarized in Table I. The Diels–Alder reaction of 1 and cyclopentadiene afforded norbornene derivatives, in which the ratio of *endo*-acetyl 7 to *exo*-acetyl 8 isomers was 79:21. A facile 1,3-dipolar cycloaddition reaction of 1 with diazomethane gave 2-pyrazoline derivative 9, which may result from the isomerization of 1-pyrazoline derivative as the initial product. Such an isomerization is well-known to take place at room temperature when there is an electron-withdrawing group at the 3-position.[19]

Interestingly, the reaction of 1 with pyrrole gave rise to a substituted pyrrole 10. Formally, its formation involves an electrophilic attack on pyrrole of the electron-deficient β-carbon bearing the CF_3 group. A similar reaction, although very slow, was also observed with furan at −5 °C,[20] while at 40 °C it reacted with 1 to give the Diels–Alder adduct. An attempted reaction of 2-penten-4-one with pyrrole did not lead to the substitution product corresponding to 10.

A survey of the reactivities of 1 as presented here indicates its synthetic utility as a building block. As a Michael acceptor or dienophile, it seems to be considerably more reactive than the nonfluorinated analogue, leading to better yields of products and a choice of milder reaction conditions. As a fluorine-containing compound, its C–F bond is stable toward Grignard and dialkylcuprate reagents. As an electrophile, it gives unusual products of electrophilic substitution on heterocycles.

Experimental Section

Melting points are uncorrected. ^1H NMR spectra were taken for $CDCl_3$ solutions with a JEOL JNM-GX 270 or a JNM-PMX 60 instrument. IR spectra were obtained for neat liquids (2–8) or KBr disks (9 and 10) on a Hitachi 260-10 IR spectrophotometer. Mass spectra were recorded on a Shimadzu GCMC 6020S or a Hitachi M-60 spectrometer. Gas chromatography was performed with a Shimadzu GC-4C gas chromatography on columns of poly(ethylene glycol) 20M or silicone DC QF-1. Wakogel C-200 was used for column chromatography. Silica gel 60 F_{254} (Merck) was used for thin-layer chromatography. Elemental analyses were performed at the Microanalysis Center of Kyoto University.

1,1,1-Trifluoro-2-penten-4-one (1). This compound was prepared by a modification of the procedure of Molines and Wakselmann.[17] Into a suspension of (acetylmethylene)triphenylphosphorane (105 g, 0.33 mol) in ether (400 mL) was introduced, under nitrogen at room temperature in a period of 2 h, gaseous trifluoroacetaldehyde generated by the dropwise addition of trifluoroacetaldehyde ethyl hemiacetal (71.3 g, 0.50 mol) to polyphosphoric acid (100 mL) at 150–180 °C. The reaction mixture was further stirred for 1 h at room temperature. Triphenylphosphine oxide which separated was removed by filtration. Distillation of the filtrate at 89–91 °C afforded 1 (39.6 g, 87%). The stereoisomers were separated by preparative gas chromatography. *E* isomer (95.5%): ^1H NMR δ 6.82 (d, 1 H, J_{H-H} = 16.2 Hz), 6.69 (octet, 1 H, J_{F-H} = 6.0 Hz), 2.50 (s, 3 H); IR 1710 and 1694 (C=O), 1663 (C=C), 1305, 1245, and 1140 cm^{-1} (C–F). *Z* isomer (4.5%): ^1H NMR δ 6.56 (d, 1 H, J_{H-H} = 12.9 Hz), 5.97 (octet, 1 H, J_{F-H} = 8.0 Hz), 2.50 (s, 3 H). All reactions of 1 as described below were carried out under nitrogen.

5,5,5-Trifluoro-4-(diethylamino)pentan-2-one (2). Into diethylamine (4.24 g, 58 mmol) was added 1 (1.09 g, 7.9 mmol) at room temperature. The reaction was complete within 1 min. Excess diethylamine was removed, and the residue was distilled in vacuo to give 2 (0.97 g, 58%) as a colorless oil: R_f 0.74 (CH_2Cl_2); ^1H NMR δ 3.90 (m, 1 H), 2.63 (m, 6 H), 2.20 (s, 3 H), 1.04 (t, 6 H); IR 1720 (C=O), 1270 and 1100 cm^{-1} (C–F); MS, *m/e* 211 (M^+). Anal. Calcd for $C_9H_{16}ONF_3$: C, 51.18; H, 7.63; N, 6.63; F, 26.98. Found: C, 51.04; H, 7.89; N, 6.58; F, 27.10.

5,5,5-Trifluoro-4-(nitromethyl)pentan-2-one (3). A mixture of 1 (4.5 g, 33 mmol) and a mixed solvent of nitromethane (40 mL) and water (10 mL) containing Na_2CO_3 (0.5 g) was heated under reflux for 1 h. After having been cooled down, the mixture was extracted with chloroform. Workup and chromatography on silica gel with chloroform as eluant gave 3 (5.65 g, 86%) as a colorless oil: R_f 0.34 ($CHCl_3$); ^1H NMR δ 4.60 (m, 2 H), 3.68 (m, 1 H), 2.85 (m, 2 H), 2.25 (s, 3 H); IR 1720 (C=O), 1560 and 1380 (NO_2), 1260, 1170, and 1120 cm^{-1} (C–F); MS, *m/e* 184 ($M^+ - CH_3$).

4-(Trifluoromethyl)hexan-2-one (4) and 1,1,1-Trifluoro-4-methyl-4-hydroxyhex-2-ene (5). A solution of 1 (1.65 g, 12 mmol) in ether (19 mL) was added dropwise to an ether solution (15 mL) of ethylmagnesium iodide (1.5 equiv). The mixture was stirred for 1 h. Excess Grignard reagent was decomposed with concentrated HCl, and, after neutralization with $NaHCO_3$, the mixture was extracted with ether. Usual workup followed by distillation in vacuo afforded a mixture of 4 and 5 (1.23 g, 61%, in a ratio of 21:79 by gas chromatography) as a colorless oil, which was separated by means of preparative gas chromatography. 4: R_f 0.74 (CH_2Cl_2); ^1H NMR 3.74 (m, 1 H), 2.65 (d, 2 H), 2.22 (s, 3 H), 1.33 (m, 2 H), 0.96 (t, 3 H); IR 1720 (C=O), 1260 and 1170 cm^{-1} (C–F); MS, *m/e* 168 (M^+). 5: R_f 0.60 (CH_2Cl_2); ^1H NMR δ 6.45 (d, 1 H), 6.03 (m, 1 H), 1.56 (q, 2 H), 1.45 (s, 1 H), 1.35 (s, 3 H), 0.91 (t, 3 H); IR 3400 (O–H), 1310 and 1110 cm^{-1} (C–F); MS, *m/e* 153 ($M^+ - CH_3$).

4-(Trifluoromethyl)octan-2-one (6). A solution of 1 (1.65 g, 12 mmol) in ether (80 mL) was added dropwise in 30 min at 0 °C to a solution of lithium di-*n*-butylcuprate prepared from *n*-butyllithium (64 mmol, 40 mL of 15% hexane solution) and cuprous ioide (32 mmol) in ether (120 mL) at 0 °C. The mixture was stirred at room temperature for 1 h, poured into 1.2 N HCl (800 mL) with vigorous stirring, and extracted with ether. Workup and chromatography on silica gel with chloroform affrded 6 (1.04 g, 44%) as a colorless oil: R_f 0.66 (CH_2Cl_2), ^1H NMR δ 2.92 (m, 1 H), 2.62 (d, 2 H), 2.17 (s, 3 H), 1.46 (m, 6 H), 0.93 (t, 3 H); IR 1720 (C=O), 1170 and 1130 cm^{-1} (C–F); MS, *m/e* 196 (M^+).

5-*endo*-Acetyl-6-*exo*-(trifluoromethyl)norborn-2-ene (7) and 5-*exo*-Acetyl-6-*endo*-(trifluoromethyl)norborn-2-ene (8). A solution of 1 (0.966 g, 7 mmol) and cyclopentadiene (0.805 g, 12 mmol) in benzene (5 mL) in a sealed tube was heated at 80

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°C for 1 h. The solvent was removed, and the residue was chromatographed on silica gel. Elution with chloroform–hexane afforded a mixture of 7 and 8 (1.14 g, 80%, 78:12 by gas chromatography) as a colorless oil: R_f 0.70 ($CHCl_3$); IR 1710 (C=O), 1280 and 1130 cm^{-1} (C–F). Anal. Calcd for $C_{10}H_{11}OF_3$: C, 58.82; H, 5.43; F, 27.91. Found: C, 58.23; H, 5.30; F, 27.77. The isomeric mixture was separated by gas chromatography. 7: ^1H NMR δ 6.30 (m, 1 H), 6.15 (m, 1 H), 3.30 (m, 1 H), 3.10 (m, 2 H), 2.50 (m, 1 H), 2.30 (s, 3 H), 1.50 (m, 2 H); MS, *m/e* 204 (M^+). 8: ^1H NMR δ 6.25 (m, 1 H), 6.00 (m, 1 H), 3.26 (m, 1 H), 3.06 (m, 2 H), 2.58 (m, 1 H), 2.15 (s, 3 H), 1.78 (m, 1 H), 1.56 (m, 1 H); MS, *m/e* 204 (M^+).

3-Acetyl-4-(trifluoromethyl)-2-pyrazoline (9). To an ether solution (5 mL) of 1 (1.38 g, 10 mmol) was added a solution of CH_2N_2 (10 mmol) in ether (20 mL). The solvent was removed, and the residue was chromatographed on silica gel. Elution with dichloromethane afforded crude **9**, which was recrystallized from CH_2Cl_2–hexane to give yellow needles (1.64 g, 91%): mp 75–76 °C; R_f 0.29 (CH_2Cl_2); ^1H NMR δ 6.73 (br, 1 H), 4.00 (m, 3 H), 2.43 (s, 3 H); IR 1625 (C=O), 1520 (C=N), 1260, 1160, and 1130 cm^{-1} (C–F); MS, *m/e* 180 (M^+). Anal. Calcd for $C_6H_7ON_2F_3$: C, 40.00; H, 3.92; N, 15.55; F, 31.64. Found: C, 39.49; H, 3.84; N, 15.54; F, 31.62.

2-(1-(Trifluoromethyl)-3-oxobutyl)pyrrole (10). A solution of 1 (1.34 g, 9.7 mmol) and pyrrole (0.65 g, 9.7 mmol) in dichloromethane (10 mL) was refluxed for 7 h. The solvent was removed, and the residue was chromatographed on silica gel. Elution with dichloromethane afforded crude **10**, which was recrystallized from $CHCl_3$–hexane to give white needles (1.30 g, 65%): mp 59 °C; R_f 0.33 (CH_2Cl_2); ^1H NMR δ 8.42 (br, 1 H), 6.72 (q, 1 H), 6.33 (t, 2 H), 4.05 (m, 1 H), 3.03 (d, 2 H), 2.18 (s, 3 H); IR 3390 (N–H), 1715 (C=O), 1295, 1150, and 1095 cm^{-1} (C–F); MS, *m/e* 205 (M^+). Anal. Calcd for $C_9H_{10}NF_3$: C, 52.69; H, 4.91; N, 6.83; F, 27.99. Found: C, 52.61; H, 4.75; N, 6.73; F, 27.78.

Reaction of 1 with Furan. A solution of 1 (1.59 g, 12 mmol) and furan (1.65 g, 24 mmol) in dichloromethane (5 mL) was stirred at −5 °C for 1 h. The solvent was removed, and the residue was chromatographed on silica gel. Elution with dichloromethane afforded 2-(1-(trifluoromethyl)-3-oxobutyl)furan (ca. 40 mg) as an oil: R_f 0.55 (CH_2Cl_2); ^1H NMR δ 7.35 (q, 1 H), 6.35 (t, 2 H), 4.14 (m, 1 H), 3.05 (d, 2 H), 2.21 (s, 3 H). The same reaction was also carried out at 40 °C for 1 h. Chromatography followed by gel filtration with Sephadex LH-20 with methanol as eluant gave the Diels–Alder adduct, 5-acetyl-6-(trifluoromethyl)-7-oxanorborn-2-ene (0.42 g, 17%): R_f 0.75 (CH_2Cl_2); ^1H NMR δ 6.52 (m, 1 H), 6.31 (m, 1 H), 5.30 (m, 1 H), 5.13 (m, 1 H), 3.30 (m, 1 H), 2.72 (m, 1 H), 2.23 (s, 3 H); IR 1710 (C=O), 1275, and 1115 cm^{-1} (C–F); MS, *m/e* 206 (M^+).

Registry No. (*E*)-1, 101395-81-7; (*Z*)-1, 101518-49-4; 2, 101518-39-2; 3, 101518-40-5; 4, 101518-41-6; 5, 101518-42-7; 6, 101518-43-8; 7, 101518-44-9; 8, 101628-00-6; 9, 101518-45-0; 10, 101518-46-1; (acetylmethylene)triphenylphosphorane, 1439-36-7; trifluoroacetyl ethyl hemiacetal, 433-27-2; trifluoroacetaldehyde, 75-90-1; ethyl magnesium iodide, 10467-10-4; cyclopentadiene, 542-92-7; pyrrole, 109-97-7; furan, 110-00-9; 2-[(1-trifluoromethyl)-3-oxobutyl]furan, 101518-47-2; 5-acetyl-6-(trifluoromethyl)-7-oxonorborn-2-ene, 101518-48-3.

A General Method for the Synthesis of Glycerophospholipids

Karol S. Bruzik, Grzegorz Salamończyk, and Wojciech J. Stec*

Department of Bioorganic Chemistry, Centre of Molecular and Macromolecular Studies, Polish Academy of Sciences, 90-362 Lódź, Boczna 5, Poland

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The synthesis of phospholipids has been a subject of interest in various laboratories over many years, and numerous synthetic procedures have been reported to date.[1-4] The progress in this area has often relied upon the development of new methods originally designed for the synthesis of nucleic acid fragments.[5] Recently, the synthesis of phosphoric acid diesters has been improved with a procedure for the selective introduction of alkoxy functions at the phosphorus atom using phosphoroamidites.[6,7] Although this method is now being widely used for the synthesis of oligodeoxyribonucleotides on solid-phase support,[8] it has not yet been sufficiently exploited to prove its suitability for the synthesis of other groups of phosphodiesters, such as phospholipids and their analogues. Only a few syntheses of phospholipids have been published using the amidophosphite reagents.[9,10]

Lately, phosphorothioate analogues of glycerophospholipids have been shown to be useful in studies of the mechanisms of phospholipases[11-14] as well as nonperturbing probes of phospholipid bilayer organization.[15,16] The procedures described for the syntheses of these analogues involve repeated substitution of the chlorine atoms at the phosphorothioyl center such as in method of Vasilenko et al.,[15] or can be used for the preparation of phosphatidylcholines.[17] Both methods in practice are not reproducible with respect to yield and purity of the products.[18] Phosphorothioyl analogues of phospholipids are not easily accessible by the general routes described for the preparation of natural phospholipids such as the diester method of Aneja and Davies[5] or the alkylation procedures of Eibl[2] and Toccane et al.[19] The phosphoramidite method of phosphodiester synthesis involving trivalent phosphorus intermediates offers the advantage of a simple introduction of sulfur at the phosphorus atom, thus avoiding nucleophilic displacement steps at the phosphorothioyl center.[20] The phosphoramidite method is also applicable for the synthesis of phospholipids bearing an isotope label in their phosphate function due to the oxidation of P (III) intermediates with an oxygen-labeled water/iodine reagent.[21]

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