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A Selective Synthesis of 3-Alkynyl Perfluoroalkyl Ketones by the Trifluoroborane Etherate Mediated 1,4-Addition Reaction of (1-Alkynyl)diisopropoxyboranes to α,β-Unsaturated Ketones

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ABSTRACT

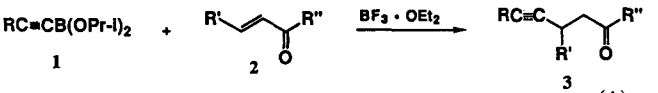
A variety of 3-alkynyl perfluoroalkyl ketones were prepared by a trifluoroborane etherate mediated 1,4-addition reaction of (1-alkynyl)diisopropoxyboranes to α,β-unsaturated ketones substituted by a perfluoroalkyl group. The undesired side reaction, such as 1,2-addition of alkynyl groups, could be avoided completely and the products were obtained in high yields.

INTRODUCTION

Fluorinated compounds have been of great interest to synthetic and medicinal chemists due to the unique physical and biological properties imparted by fluorine [1]. Among them, fluorinated ketones are the subject of renewed interest by organic chemists because of their roles as the key intermediates in the preparation of more complex molecules as well as their own biological properties as enzyme inhibitors [2].

The 1,4-addition reaction of organometallic compounds to fluorinated α,β-unsaturated ketones is an efficient method for the synthesis of fluorinated ketones having the desired structures. However, the strong electron-withdrawing character and the lability of a fluoroalkyl group attached to the unsaturated ketones restricted their application for the reaction with organometallic compounds, such as organocopper reagents [3]. The introduction of alkynyl groups is difficult, because alkynyl copper derivatives fail to undergo 1,4-addition reaction to α,β-unsaturated ketones [4].

Recently, we reported that (1-alkynyl)diisopropoxyboranes (**1**) react with α,β-unsaturated ketones (**2**) in the presence of trifluoroborane etherate to give 3-alkynyl ketones (**3**) selectively [5] (Equation 1).



(1)

Because the trifluoroborane etherate mediated 1,4-addition reaction of alkynyldiisopropoxyboranes proceeded under mild conditions and the formation of undesired 1,2-addition products was avoided, we decided to apply this method to the reaction with α,β-unsaturated ketones substituted by a perfluoroalkyl group directed toward the development of a new synthetic route to fluorinated ketones.

RESULTS

A mixture of **1**, a 1-alkenyl perfluoroalkyl ketone **4**, and trifluoroborane etherate was stirred in di-

Dedicated to Professor Yao-Zeng Huang on the occasion of his eightieth birthday.

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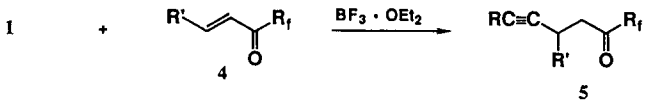
chloromethane at room temperature or under reflux for 4–20 hours. The reaction was monitored by GLPC. After the complete consumption of each compound **4** was confirmed, the corresponding 1,4-addition product (**5**) was isolated (Equation 2). Although each reaction was slow, it gave only **5** in excellent yield without any formation of the undesired 1,2-addition product. The representative results are shown in Table 1. The yields of **5** are higher than those of **3** [5]. Namely, the substitution of perfluoroalkyl groups on the carbonyl carbon evidently improves the yield of **5**. This effect may be due to the strong electron-withdrawing character of perfluoroalkyl groups which attract electrons from the carbonyl group and stabilize the unstable α,β-unsaturated ketones under the reaction conditions [2].



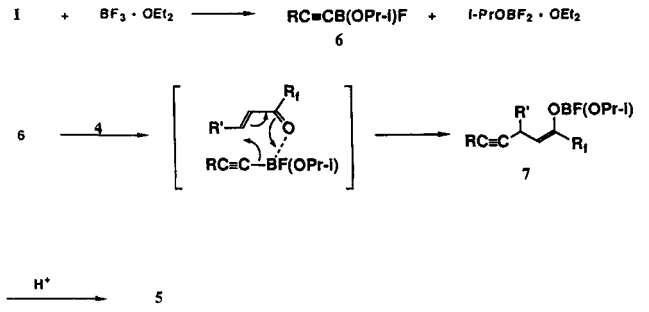
(2)

The starting alkynylboranes (**1**) were readily prepared from 1-lithio-1-alkynes and triisopropoxyborane and isolated by distillation [6]. When 1-alkynes having functional groups such as **8** were used, the corresponding diisopropoxyborane derivatives were difficult to isolate by distillation. In such cases, they were employed for this reaction without isolation. Thus, the diisopropoxyborane derivative was prepared from **8**, triisopropoxyborane, and anhydrous HCl. After removal of the generated solid, the filtrate was concentrated under reduced

TABLE 1 Reaction of (1-Alkynyl)diisopropoxyboranes with 1-Alkenyl Perfluoroalkyl Ketones

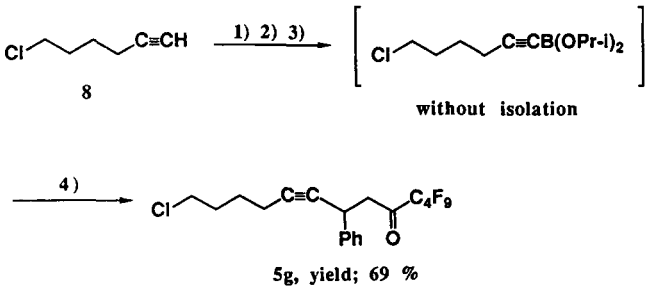
Borane	Enone	Reaction conditions	Product	Yield, %[a]
BuC≡CB(OPr-i)$_2$ **1a**	Ph, C_4F_9, O **4a**	room temp. 6h	BuC≡C, C_4F_9, Ph, O **5a**	99
1a	Me, C_8F_{17}, O **4b**	room temp. 20h	BuC≡C, C_8F_{17}, Me, O **5b**	91
1a	Ph, CF_3, O **4c**	40 °C, 12h	BuC≡C, CF_3, Ph, O **5c**	94
C≡CB(OPr-i)$_2$ **1b**	Ph, C_4F_9, O **4a**	room temp. 3h	C≡C, C_4F_9, Ph, O **5d**	98
PhC≡CB(OPr-i)$_2$ **1c**	Ph, C_4F_9, O **4a**	40 °C, 4h	PhC≡C, C_4F_9, Ph, O **5e**	98
1c	Ph, CF_3, O **4c**	40 °C, 2h	PhC≡C, CF_3, Ph, O **5f**	98

[a]Isolated yield based on ketone used.



SCHEME 1

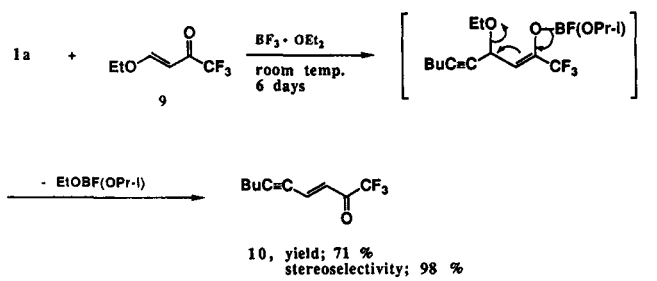
pressure and the residue was dissolved in dichloromethane to use directly for the reaction with **4a** (Equation 3). This method is effective when the alkyne has a functional group or high boiling point.



(3)

The reaction seems to proceed as follows. At first, an isopropoxy group on boron is displaced by fluorine of the trifluoroborane etherate [7]. The resulting monofluorinated borane (**6**), possessing higher Lewis acidity than **1**, coordinates more readily to the carbonyl oxygen of **4**. Through the cyclic transition state shown in Scheme 1 [8], the alkynyl group of **6** adds to **4** via a 1,4-addition to give the adduct **7**, the hydrolysis of which gives the product (**5**).

When ethoxyvinyl trifluoromethyl ketone (**9**) was used instead of **4**, the elimination of the ethoxy group from the boron enolate generated by the addition of the alkynyl group occurred to provide the 1-alken-3-ynyl ketone (**10**) stereoselectively (the stereochemistry of the generated double bond in **10** is *E* (= 98%)) (Equation 4).



(4)

Further application of this method for the synthesis of fluorinated ketones and more complex molecules is now under investigation.

EXPERIMENTAL

The ^{1}H NMR spectra were taken on a Hitachi R-90H FT spectrometer (90 MHz) or measured at the NMR laboratory, Faculty of Engineering, Hokkaido University, by using a Bruker NSL-400 spectrometer (400 MHz) in $CDCl_3$, employing TMS as an internal standard. The IR spectra were taken on a Hitachi 260-10 IR spectrophotometer in the form of a film. High resolution mass spectra were taken at the Center for Instrumental Analysis, Hokkaido University. Merck silica gel 60 Art 7747 was used for the preparative TLC and Art 7734 for the column chromatography. Dichloromethane was distilled from calcium hydride and kept over 4A molecular sieves. Trifluoroborane etherate was distilled under a nitrogen atmosphere before use. (1-Alkynyl)diisopropoxyboranes (**1**) were prepared from 1-alkynes and triisopropoxyborane according to the literature [6]. Perfluoroalkyl alkenyl ketones (**4a** [9], **4b** [10], **4c** [10], and **9** [11]) were also prepared according to published procedures.

General Procedure for the Preparation of **5** from **1** and **4**

At room-temperature trifluoroborane etherate (2 mmol) was added to a mixture of **1** (2 mmol) and **4** (1 mmol) in dichloromethane (10 ml), and the mixture was stirred at the temperature prescribed for 3–20 hours (reaction time is shown in Table 1). The reaction was monitored by GLPC, and when the consumption of **4** was confirmed, the product was extracted with ether. The organic phase was washed with aqueous sodium bicarbonate and water, dried over magnesium sulfate, and concentrated under reduced pressure. Purification of the residue by column chromatography (silica gel/hexane:ether = 95:5) gave **5**.

Preparation of **5g** from **8** and **4a**

A hexane solution of butyllithium (1.9 mL of 1.6 M solution, 3 mmol) was added at −78°C to a THF solution (10 mL) of **8** (345 mg, 3 mmol), and then the mixture was stirred at this temperature for 30 minutes. After the addition of triisopropoxyborane (564 mg, 3 mmol), the mixture was stirred for 2 hours at −78°C. Anhydrous hydrogen chloride in ether (2 mL of 1.5 M solution, 3 mmol) was added at −78°C, and then the mixture was stirred at room temperature overnight. The volatile part was removed under reduced pressure, and hexane (10 mL) was added. The precipitate was removed by filtration through the filter cell and washed repeatedly with hexane. The filtrate was concentrated under reduced pressure, and the residue was dissolved in

a dichloromethane (10 mL) solution containing **4a** (350 mg, 1 mmol). To prevent the hydrolysis of **4a**, the operation should be carried out as fast as possible and its exposure to air without solvent must be minimized. After the addition of trifluoroborane etherate (0.123 mL, 1 mmol) at room temperature, the mixture was stirred for 3 days. The product was extracted with ether, and the organic layer was dried over magnesium sulfate and concentrated under reduced pressure. Purification of the product by preparative TLC (silica gel/hexane:ether = 95:5) gave 326 mg of **5g** (70% yield).

Spectral Data of **5**

5a: n_D^{20} = 1.4260. IR (film): 1768 cm^{-1} (C=O). ^1H NMR (90 MHz $CDCl_3$): 7.27 (s, $5H_{arom}$); 4.33–4.08 (m, ≡C—C*H*(Ph)—CH_2—); 3.47–2.81 (m, ≡C—CH(Ph)—C*H*$_2$—); 2.31–2.06 (m, —CH_2—C*H*$_2$—C≡); 1.61–1.22 (m, CH_3—C*H*$_2$—C*H*$_2$—CH_2—C≡); 0.89 (t, J = 6.3 Hz, C*H*$_3$—CH_2—CH_2—CH_2—C≡). HRMS calcd for $C_{19}H_{17}F_9O$ 432.1136, found 432.1117.

5b: n_D^{20} = 1.3568. IR (film): 1772 cm^{-1} (C=O). ^1H NMR (90 MHz $CDCl_3$): 3.14–2.64 (m, ≡C—C*H*(Me)— and ≡C—CH(Me)—C*H*$_2$—); 2.19–1.98 (m, —C*H*$_2$—C≡C—); 1.50–1.33 (m, —C*H*$_2$—C*H*$_2$—CH_2—C≡C—), 1.20 (d, J = 6.3 Hz, ≡C—CH(C*H*$_3$)—); 0.88 (t, J = 6.3 Hz, C*H*$_3$—CH_2—CH_2—CH_2—C≡C—). HRMS calcd for $C_{18}H_{15}F_{17}O$ 570.0852, found 570.0842.

5c: n_D^{20} = 1.4779. IR (film): 1780 cm^{-1} (C=O). ^1H NMR (90 MHz $CDCl_3$): 7.27 (s, $5H_{arom}$); 4.33–4.08 (m, ≡C—C*H*(Ph)—CH_2—); 3.38–2.81 (m, ≡C—CH(Ph)—C*H*$_2$—); 2.31–2.06 (m, —CH_2—C*H*$_2$—C≡); 1.61–1.22 (m, CH_3—C*H*$_2$—C*H*$_2$—CH_2—C≡); 0.89 (t, J = 6.3 Hz, C*H*$_3$—CH_2—CH_2—CH_2—C≡). HRMS calcd for $C_{16}H_{17}F_3O$ 282.1232, found 282.1223.

5d: n_D^{20} = 1.4357. IR (film): 1768 cm^{-1} (C=O). ^1H NMR (90 MHz $CDCl_3$): 7.32 (s, $5H_{arom}$); 5.2–5.11 (m, *H*$_2$C=C); 4.33 (t, J = 6.8 Hz, ≡C—C*H*(Ph)—CH_2—); 3.50–2.90 (m, ≡C—CH(Ph)—C*H*$_2$); 1.85 (s, CH_2=C(C*H*$_3$)—). HRMS calcd for $C_{18}H_{13}F_9O$ 416.0823, found 416.0822.

5e: n_D^{20} = 1.4772. IR (film): 1765 cm^{-1} (C=O). ^1H NMR (90 MHz $CDCl_3$): 7.47–7.17 (m, $10H_{arom}$); 4.47 (t, J = 6.87 Hz, ≡C—C*H*(Ph)—CH_2—); 3.61–3.00 (m, ≡C—CH(Ph)—C*H*$_2$—). HRMS calcd for $C_{21}H_{13}F_9O$ 452.0823, found 452.0813.

5f: n_D^{20}: 1.5333. IR (film): 1775 cm^{-1} (C=O). ^1H NMR (90 MHz $CDCl_3$): 7.47–7.17 (m, $10H_{arom}$); 4.47 (t, J = 6.87 Hz, ≡C—C*H*(Ph)—CH_2—); 3.50–2.94 (m, ≡C—CH(Ph)—C*H*$_2$—). HRMS calcd for $C_{18}H_{13}F_3O$ 302.0919, found 302.0941.

5g: n_D^{20} = 1.4432. IR (film): 1770 cm^{-1} (C=O). ^1H NMR (90 MHz $CDCl_3$): 7.29 (s, $5H_{arom}$); 4.32–4.16 (m ≡C—C*H*(Ph)—CH_2—), 3.50 (t, J = 6.25 Hz, Cl—C*H*$_2$—); 3.36–2.83 (m, ≡C—CH(Ph)—C*H*$_2$); 2.32–2.18 (m, —C*H*$_2$—C≡C—); 1.93–1.48 (m, —C*H*$_2$—C*H*$_2$—CH_2—C≡C—). HRMS calcd for $C_{19}H_{16}ClF_9O$ 466.0747, found 466.0756.

Preparation of **10** from **1a** and **9**

At room temperature trifluoroborane etherate (0.123 mL, 1 mmol) was added to a dichloromethane solution (10 mL) of **1a** (420 mg, 2 mmol) and **9** (168 mg, 1 mmol), and the mixture was stirred at this temperature for 6 days. The product was extracted with ether, and the organic layer was washed with aqueous sodium bicarbonate and water. The separated organic layer was dried over magnesium sulfate and concentrated under reduced pressure. The purification of the product by preparative TLC (silica gel/hexane: dichloromethane = 9:1) gave 155 mg of **10** (76% yield). n_D^{20} = 1.4457. IR (film): 2220 (C≡C), 1730 (C=O) cm^{-1}. ^1H NMR (400 MHz $CDCl_3$): 7.03 (d, t, J = 15.6 Hz, J = 2.2 Hz, ≡C—C*H*=CH—C); 6.69 (d, J = 15.6 Hz, ≡C—CH=C*H*—C); 2.47–2.42 (m, —C*H*$_2$—C≡C—); 1.61–1.53 (m, —C*H*$_2$—CH_2—C≡C—); 1.48–1.39 (m, —C*H*$_2$—CH_2—CH_2—C≡C—); 0.94 (t, J = 7.3 Hz, C*H*$_3$—CH_2—CH_2—CH_2—C≡C—). HRMS calcd for $C_{10}H_{11}F_3O$ 204.0762, found 204.0744.

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