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Preparation of 1-Aryl- or 1-Alkenyl-2-(perfluoroalkyl)acetylenes[1)]

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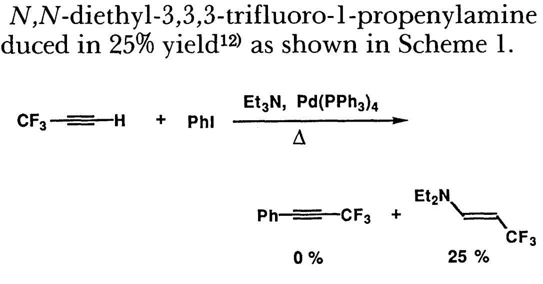
Synopsis. 1-Aryl- or 1-alkenyl-2-(perfluoroalkyl)acetylenes were produced in high yields by the coupling reaction of aryl or alkenyl iodides with (perfluoroalkynyl)zinc compounds prepared from the corresponding (perfluoroalkyl)acetylenes in the presence of Pd catalyst.

Fluoro-organic compounds are of increasing interest, because of their use as medicinals, as tools in medical diagnosis, and in fundamental studies of biologically active products.[2)] Synthesis of fluoro-organic compounds from fluorine-containing molecules is a useful methodology for the specific introduction of fluorine into a variety of types of organic substrates. (Perfluoroalkyl)acetylenes are expected to be such a useful fluorine-containing molecules for the synthesis of fluoro-organic compounds, and some studies have been reported.[3—9)] We have also previously reported[1)] on the synthesis of 1-aryl-2-(perfluoroalkyl)acetylenes using (perfluoroalkyl)acetylenes by the use of the Negishi reaction.[10)]

We now wish to report some extended work on the cross-coupling reactions of aryl halides[1,7)] or alkenyl halides with (perfluoroalkynyl)zinc compounds, which are derived from the corresponding (perfluoroalkyl)acetylenes, to prepare 1-aryl- or 1-alkenyl-2-(perfluoroalkyl)acetylenes in good yields using palladium (Pd) catalyst.

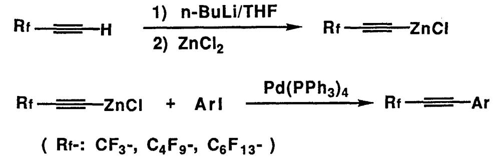
Results and Discussion

Since ethynylarenes are known to be produced by the reaction of aryl halides in the presence of Pd catalyst,[11)] we first examined the reaction of 3,3,3-trifluoropropyne (**1**) with iodobenzene (**2**) using tetrakis(triphenylphosphine)-palladium ($Pd(PPh_3)_4$) (**3**) and diethylamine for 4—6 h at 120—160 °C. However, we could not obtain the corresponding ethynylarene yet *N,N*-diethyl-3,3,3-trifluoro-1-propenylamine was produced in 25% yield[12)] as shown in Scheme 1.



Scheme 1.

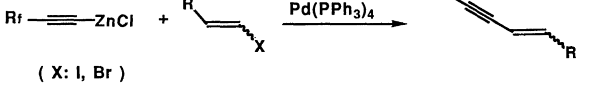
The titled compounds, on the other hand, were produced by the reaction of aryl iodides with (perfluoroalkynyl)zinc compounds in the presence of Ph catalyst as shown in Scheme 2. Some results are summarized in Table 1. The conditions determined as optimum for the preparation of (trifluoro-1-propynyl)benzene (**4**) in the reaction of **2** with **1** were as follows. The temperature that produced (trifluoro-1-propynyl) zinc chloride (**5**) was −78 °C or lower. The ratio of **5** to **2** is two equivalent. The amount of **3** is 5 mol%. The coupling reaction temperature and time is 50 °C and 4 h.



Scheme 2.

As seen in the Table 1, iodobenzenes (ArI) gave the corresponding **4** in high yields independing on whether ArI has an electron-withdrawing or -donating substituent. The position of substituents on the aromatic ring also had no effect on the reactivity of ArI as was observed in the reaction of methyliodobenzenes. (Perfluorobutyl)- or (perfluorohexyl)acetylenes were less reactive than **1**, so that it required somewhat more severe conditions (THF reflux, 6 h or longer) to afford the corresponding 1-aryl-2-(perfluoroalkyl)acetylenes. However, the reaction was difficult to bring about for aryl halides (ArX X: Cl, Br) other than ArI.

Benzoyl chloride did not afford the cross-coupling reaction product with **5** but gave benzoic acid butyl ester under THF reflux conditions. The reaction of heteroaromatic iodides with (perfluoroalkyl)acetylenes was sluggish, although the reaction with alkylacetylenes was known to proceed readily affording the corresponding coupling reaction products in fairly good yields.[10)] On the other hand, as shown in Scheme 3, the reaction of alkenyl halides with (perfluoroalkyl) acetylene zinc chlorides was successfully carried out using Pd catalyst to produce the corresponding ene-yne compounds containing perfluoroalkyl groups with retention of configuration. Representative results are also shown in Table 1.



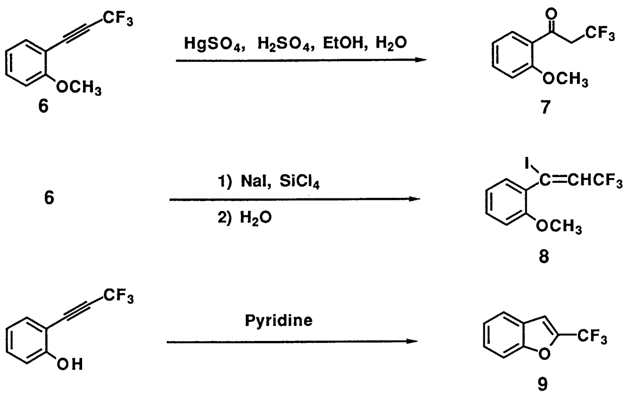
Scheme 3.

These 1-aryl-2-(perfluoroalkyl)acetylenes could be converted readily to other fluoro-organic compounds such as (**7**), (**8**), and (**9**) as shown in the following Scheme. The methoxyl group is known to convert to the hydroxyl group by the reaction of NaI and $SiCl_4$, followed by the treatment of H_2O.[13)] However,

Table 1. The Reaction of (Perfluoroalkyl)acetylenes with Aryl or Alkenyl Iodides[a)]

Acetylene	Aryl or Alkenyl halide	Yield of product[b)]/%[c)]
CF_3-C≡C-H	Iodobenzene	96
	Bromobenzene	Trace
	o-Methoxyiodobenzene	98
	m-Chloroiodobenzene	94
	m-Nitroiodobenzene	85
	(*E*)-4-Iodo-3-butene-2-ol[d)]	60(90)
C_4F_9-C≡C-H	*o*-Methyliodobenzene	78
	m-Methyliodobenzene	96
	p-Methyliodobenzene	98
	1-Iodonaphthalene	80
	(*E*)-1-Iodo-1-octene	73(98)
	(*Z*)-1-Iodo-1-octene	67(90)
	(*E*)-1-Iodo-3,3-dimethyl-1-butene	74(98)
	(*E*)-1-Iodo-2-Phenylethene	70(98)
	(*Z*)-1-Bromo-2-phenylethene	35(98)
C_6F_{13}-C≡C-H	*o*-Methyliodobenzene	90
	m-Nitroiodobenzene	94
	1-Iodo-1-cyclohexene	72
	(*E*)-1-Bromo-1-octene	35(98)

a) See reaction conditions in the text. b) Aryl- or alkenyl-(perfluoroalkyl)acetylenes. c) Isolated yields. Parentheses are purity of the stereoisomer determined by GC. d) The hydroxyl group is protected as OTHP before the reaction.



Scheme 4.

interestingly, *o*-(3,3,3-trifluoropropynyl)anisole (**6**) did not give the corresponding phenol but afforded *o*-(3,3,3-trifluoro-1-iodo-1-propenyl)anisole (**8**) under similar conditions.

Experimental

Materials. (Perfluoromethyl, -butyl, and -hexyl)acetylenes were obtained from Nippon Halon Co. The halobenzenes and vinyl halids employed were commercial reagents and used for the reaction without further purification. Pd catalysts were prepared according to the literature.[14)]

The Representative Procedure for the Reaction of (Perfluoroalkyl)acetylenes with Iodobenzenes. Two mmol of **1** (gas; ca. 46 cm^3) in a glass made 50 cm^3 syringe was bubbled into a dry 5 cm^3 THF at −78 °C placed in a flame-dried 25 cm^3 Pyrex vessel equipped with reflux condenser. To this solution was added 2 mmol of *n*-BuLi in THF and the mixture was stirred at −78 °C for 30 min. Then $ZnCl_2$ (6 mmol) in THF (6 ml) was added and the resultant solution was allowed to warm slowly (for 3 h) to room temperature by removing the cooling bath (Dry Ice-acetone). After another 30 min stirring at room temperature, the reaction vessel was immersed in an ice water bath and 57 mg of $Pd(PPh_3)_4$ (5 mol%) and 0.238 g of *m*-chloroiodobenzene (1 mmol) were added respectively under an argon atmosphere. The resultant solution was stirred for 30 min at room temperature and then allowed to warm at 50 °C for 4 h in an oil bath. After cooling, 5 ml of water was added and the resulting mixture was extracted with 5 ml of ether. The ether solution was dried ($MgSO_4$), filtered, and concentrated in vacuo to obtain crude products. The products were separated from the crude mixture by column chromatography on silica gel with 2:1 hexane/dichloromethane as an eluant. All pure products were fully characterized by infrared spectra, recorded on a Hitachi 260-10 Spectrophotometer, ^1H NMR taken on a Hitachi R-22 (90 MHz) spectrometer, and mass spectra analysis which were carried out at the Center for Instrumental Analysis, Hokkaido University. Analytical GC was performed on a SE 30 1 m, Silicone OV-17 2 m on Uniport 20%, or PEG 20M capillary column 25 m.

Preparation of *o*-(1-Oxo-3,3,3-trifluoropropyl)anisole (7). To 10 cm^3 ethanol in a 25 cm^3 round bottle was added to 1 ml H_2O, one drop of concentrated H_2SO_4, 2 mg of $HgSO_4$ and 0.2 g of 6 (1 mmol) at room temperature. The resultant solution was stirred under ethanol reflux overnight, and another 5 ml of water and 5 ml of benzene were added. The benzene solution was then dried over ($MgSO_4$), filltered and evaporated in vacuo. Compound **7** (0.168 g) was separated by TLC with hexane/CH_2Cl_2 (1:1) eluent (Yield 76%). ^1H NMR ($CDCl_3$) δ=3.88(q, *J*=10 Hz, 2H), 3.94(s, 3H), and 6.94—7.86(m, 4H), Found: *m/z* 218.0558. Calcd for $C_{10}H_9O_2F_3$ 218.0565.

Preparation of *o*-(3,3,3-Trifluoro-1-iodo-2-propenyl)anisole (8). To a solution of CH_2Cl_2 (5 cm^3) and CH_3CN (5 cm^3) 0.2 g of 6 (1 mmol), 0.225 g of NaI and 0.172 cm^3 (1.5 mmol) of $SiCl_4$ were added at room temperature and refluxed at CH_2Cl_2 (38 °C) overnight. Next 5 ml of water and 5 ml of ether were added to extract organic compounds. The ether solution was treated in the usual manner to obtain product **8** in a yield of 89%. ^1H NMR ($CDCl_3$) δ=3.88 (s, 3H), 6.62 (q, *J*=7 Hz, 1H), and 6.82—7.41 (m, 4H). Found: *m/z* 327.9585, Calcd for $C_{10}H_8O_2F_3I$ 327.9586.

Preparation of 2-(Trifloromethyl)benzofuran (9). The solution of *o*-(3,3,3-trifluoro-1-propynyl)phenol (1 mmol) and pyridine (6 ml) in a 25 cm^3 round bottle was stirred at reflux temperature for 4 h. Ether was added, and the solution washed ten times with 50 ml of water of remove the pyridine. The ether solution was then dried over $MgSO_4$, filtered and evaporated in vacuo. The crude product was treated in the usual way to obtain the pure product **9** in a yield of 30%. ^{1}H NMR ($CDCl_3$) δ=6.84—7.81 (m, 4H) and 8.52—8.72 (m, 1H). MS *m/z* 186 (M^+).

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