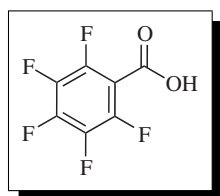


Pentafluorobenzoic Acid



[602-94-8] $C_7HF_5O_2$ (MW 212.08)
 InChI = 1/C7HF5O2/c8-2-1(7(13)14)3(9)5(11)6(12)4(2)10/h
 (H,13,14)/f/h13H
 InChIKey = YZERDTREOUSUHF-NDKGDYFDCD

(used to prepare partially fluorinated benzoic acid derivatives via regioselective nucleophilic aromatic substitution reactions or hydrodefluorination reactions;¹⁻¹³ pentafluorophenylation agent through decarboxylation¹⁴⁻¹⁶)

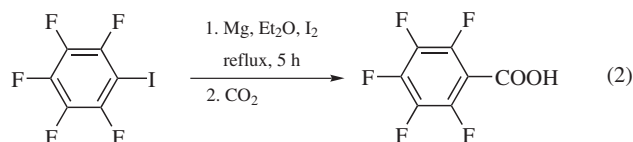
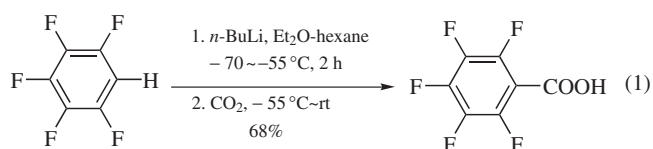
Physical Data: mp 106–107 °C; bp 220 °C; $d = 1.944$ (25 °C); $pK_a = 1.48$ (25 °C).¹⁷

Solubility: soluble in ethers, alcohols, toluene, petroleum ether, dichloromethane, and acetic acid.

Form Supplied in: colorless crystalline solid; often prepared from pentafluorophenyllithium (or pentafluorophenylmagnesium halide) and carbon dioxide.^{18,19}

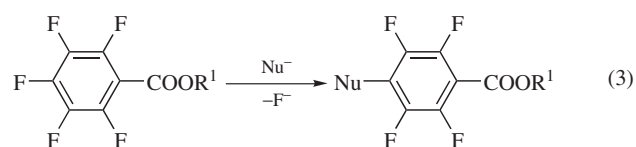
Handling, Storage, and Precautions: pentafluorobenzoic acid is a corrosive acid and has high reactivity with bases; readily reacts with strong nucleophiles such as alkoxides; avoid storing with reducing metals such as sodium, zinc; store under anhydrous, neutral conditions; use in a fume hood.

Preparation of Pentafluorobenzoic Acid. Pentafluorobenzoic acid is commonly prepared from the reactions of pentafluorophenyllithium (or pentafluorophenyl Grignard reagent) with carbon dioxide (eqs 1 and 2).^{18,19} Pentafluorophenyllithium and pentafluorophenyl Grignard reagent are usually prepared in situ from pentafluorobenzene, bromopentafluorobenzene, or iodopentafluorobenzene (eqs 1 and 2).^{18,19} Furthermore, oxidation of pentafluorophenylethylene with potassium permanganate also gives pentafluorobenzoic acid.²⁰ Crabtree and co-workers²¹ reported a magnesium anthracene ($MgC_{14}H_{10}$)-mediated preparation of pentafluorophenyl Grignard reagent directly from hexafluorobenzene or perfluorocyclohexane, and the in situ formed pentafluorophenyl Grignard reagent was quenched with carbon dioxide to give pentafluorobenzoic acid.

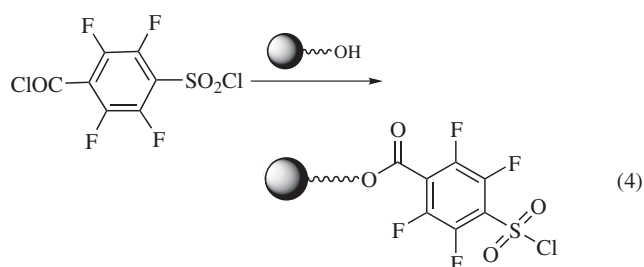
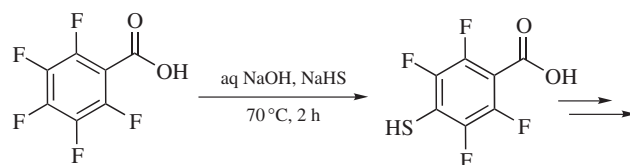


Direct fluorination of 2,4-difluorobenzoic acid using F_2/N_2 (10% v/v) in sulfuric acid at ambient temperature gives pentafluorobenzoic acid in 5% yield.²² Pentafluorobenzoic acid has also been prepared in 25% yield by sulfuric acid-induced hydrolysis of perfluorotoluene.²³

Nucleophilic Aromatic Substitution Reactions. Like other polyfluorinated aromatic compounds, pentafluorobenzoic acid and its esters readily undergo nucleophilic aromatic substitution reactions with various nucleophiles such as alkoxides,^{1,2} thiolates,³ and imidazoles⁴ (eq 3). The substitution reaction occurs mainly at the *para*-position of pentafluorobenzoic acid and its esters, and the corresponding 4-substituted-2,3,5,6-tetrafluorobenzoic acid or its esters are usually obtained in moderate to good yields (eq 3).¹⁻⁴ By using this *para*-substitution reaction, pentafluorobenzoic acid has been used to synthesize a novel solid-phase equivalent to the triflate group, which was applied to the traceless linking and cross-coupling-release strategies (eq 4).⁵



($R^1 = H, \text{alkyl group}$; $Nu^- = RO^-, OH^-, RS^-, N\text{-nucleophiles}$)

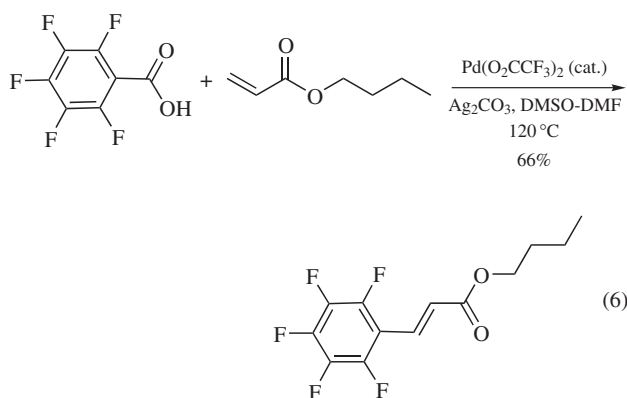
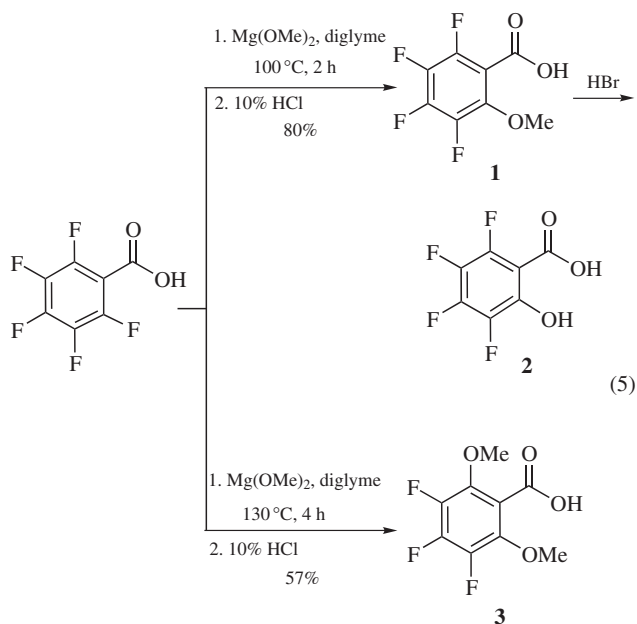


However, selective *ortho*-substitution reactions of pentafluorobenzoic acid has also been achieved using magnesium methoxide [$Mg(OCH_3)_2$] as the nucleophile (eq 5).⁶ This selective *ortho*-methoxylation provides a new synthetic approach to tetrafluorosalicylic acid (**2**) and its derivatives. Interestingly, even *ortho,ortho*-disubstituted product **3** could be obtained in 57% yield at elevated reaction temperature (eq 5).⁶

Similarly, pentafluorobenzoic acid reacts with benzyl(methyl)-magnesium halides to form *ortho*-substituted products.⁷

Decarboxylative Reactions. Pentafluorobenzoic acid is a good pentafluorophenyl synthon in the palladium-catalyzed decarboxylative Heck reaction (eq 6).¹⁴ The process can be viewed as an initial $Ar-S_E$ reaction, involving *ipso* attack of an electrophilic Pd(II) intermediate on pentafluorobenzoic acid to form pentafluorophenylpalladium(II) species with the loss of carbon

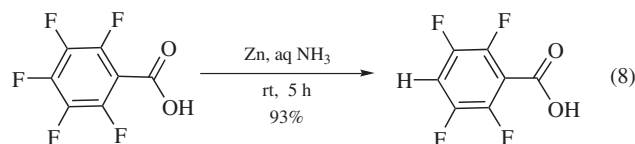
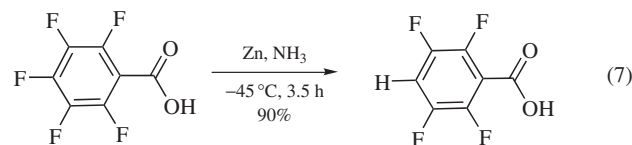
dioxide. The pentafluorophenylpalladium(II) intermediate is then proposed to react with an olefinic substrate by steps common to the Heck coupling process.¹⁴



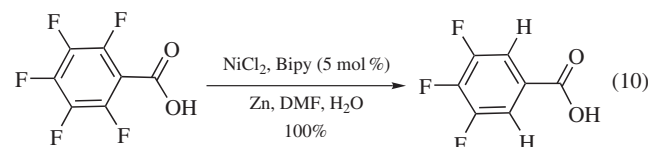
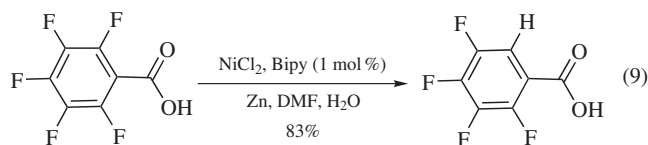
It was reported that the decarboxylative reactions of pentafluorobenzoic acid with 1,1,2-trifluoro-2-chloroethyldiethylamine gives pentafluorobenzene in 53% yield.¹⁵ Pentafluorobenzoic acid and its salts were also used to prepare the pentafluorophenyl-tin and -germanium compounds via decarboxylation process. For instance, reaction of bromotriphenylgermane with silver pentafluorobenzoate in boiling pyridine gave pentafluorophenyltri-phenylgermane.¹⁶

Reductive Hydrodefluorination Reactions. Partially fluorinated benzoic acids are highly useful compounds for drug synthesis, and these compounds are less accessible than pentafluorobenzoic acid. Therefore, regioselective reductive hydrodefluorination reaction of pentafluorobenzoic acid is a convenient way to prepare partially fluorinated benzoic acids and their derivatives. Shteingarts and co-workers reported that under the reduction of pentafluorobenzoic acid in liquid ammonia by zinc, only the product of *para*-defluorination was obtained in excellent yield (eq 7).⁸ Aqueous ammonia solution was later used to simplify the reaction conditions with no loss of the selectivity and yield

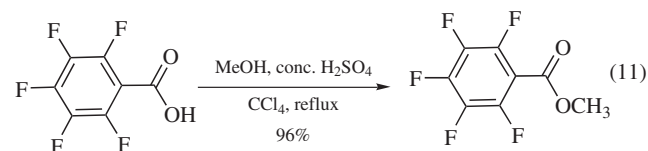
(eq 8).^{9,10} The reaction was viewed as a single-electron transfer process, followed by fragmentation of the radical anion of pentafluorobenzoate.¹¹

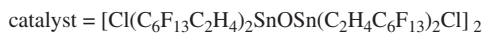
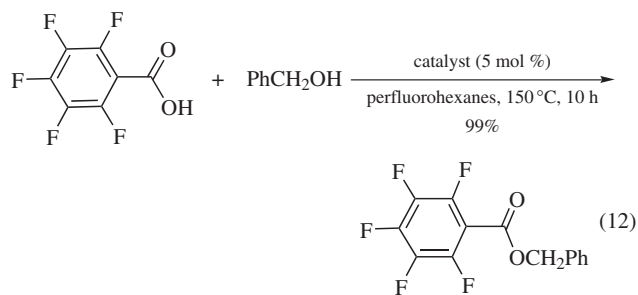


Interestingly, selective *ortho*-hydrodefluorination of pentafluorobenzoic acid can also be achieved by using zinc in the presence of NiCl₂-2'-bipyridine (or 1,10-phenanthroline) complexes, to give 2,3,4,5-tetrafluorobenzoic acid and 3,4,5-trifluorobenzoic acid in good yields (eqs 9 and 10).¹² Deacon et al. reported that pentafluorobenzoic acid reacted with YbCp₂(dme) to yield, after hydrolysis, 2,3,4,5-tetrafluorobenzoic acid.¹³ Conversion was near quantitative with activated magnesium as a coreductant and there was evidence for catalytic turnover in ytterbium on addition of a cyclopentadiene source.¹³



Esterification and Related Reactions. Pentafluorobenzoic acid can condense with alcohols under acid catalysis to give esters. For example, pentafluorobenzoic acid and methanol was heated with concentrated sulfuric acid in CCl₄ to give methyl pentafluorobenzoate in high yield (eq 11).²⁴ Pentafluorobenzoic acid can also react with benzyl bromide in the presence of cesium carbonate to give benzyl pentafluorobenzoate.²⁵ Otera and co-workers reported a fluorous biphasic esterification of pentafluorobenzoic acid with benzyl alcohol in the presence of fluoroalkyldistannoxane catalyst to give benzyl pentafluorobenzoate in quantitative yield (eq 12).²⁶





Pentafluorobenzoic anhydride has been readily prepared from pentafluorobenzoic acid and 1,3-dicyclohexylcarbodiimide (DCC) in high yield.²⁷ Pentafluorobenzoic acid can react with diphenylphosphinous chloride ($\text{Ph}_2\text{P}(\text{Cl})$) in water to give diphenyl-(2,3,4,5,6-pentafluorobenzyl)phosphine oxide in 88% yield.²⁸

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