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Short communication

A preparation of 3,3-difluoropyruvate from trifluoroacetic anhydride

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ABSTRACT

Difluoropyruvate was prepared from trifluoroacetic anhydride via 3 steps (Friedel–Crafts type addition, reductive defluorination, and ozonolysis) in 30% yield.

The importance of fluorinated synthetic building blocks for preparation of biologically active compounds would need no repeated description here [1]. Trifluoropyruvate is commercially available and one of the well-studied fluoro-building blocks for preparation of trifluoromethylated amino acids and heterocycles [2]. In contrast, there has been reported only a few reactions of difluoropyruvates [3–5]. The poor chemistry of the difluoropyruvate would be due to its low availability.

Conventionally, difluoropyruvates were prepared by reduction of trifluoropyruvates followed by dehydrofluorination [3], reductive enolization of trifluoropyruvates followed by defluorosilylation [4], or oxidative fluorination of the corresponding fluoroenols [5]. Drawbacks of these preparations are the use of expensive substrates. Therefore, a new preparation of difluoropyruvates from cheaper starting material has been demanded.

Here we report a laboratory scale synthesis of methyl difluoropyruvate 5 from commercially available trifluoroacetic anhydride. Optimized synthetic route is illustrated in Scheme 1. Preparation of the 2-trifluoroacetyl-5-methylfuran **1** and the magnesium promoted defluorination of the furan **1** to difluoroacetyl furan **2** were described in our previous report [6].

Successive oxidation of the furan **2** was the key-step of this preparation. Because of low lying HOMO of the molecule, fluorinated compounds would need strong oxidant for its oxidation [1]. Meanwhile, the C–C bond between the carbonyl carbons of the pyruvate is easily cleaved by a strong oxidant. Actually, the Ru-catalyzed oxidation with NMO oxidant (TPAP oxidation), which was a successful oxidation in the preparation of difluorolactate [6], resulted in cleavage of C–C bond to give difluoroacetic acid. Among examined oxidations, ozonolysis in MeOH at low temperature gave the methyl difluoropyruvate hemiacetal **3** with its derivatives (**4** and **5**) in the best yield [7]. Here, a slightly excess amount of O_3 depress the over oxidation, of which amount could be observed by the slightly greenish yellow color of the reacting solution. Use of excess amount of O_3 with blue colored solution resulted in over oxidation to give difluoroacetic acid.

Further esterification and hydrolysis of the hemiacetal **3** in MeOH with sulfuric acid gave the acetal **4** in ca. 55% yield from the difluoroacetylfuran **2** (3 stages). Ketonization of acetal unit with P_2O_5 gave the methyl 3,3-difluoropyruvate **5** in ca. 84% yield. The total yield of the difluoropyruvate **5** from the trifluoroacetic anhydride was 30% (3 steps, 6 stages).

A similar procedure produced trifluoropyruvate by ozonolysis of trifluoroacetylfuran **1** followed by esterification, hydrolysis, and ketonization in 41% yield from trifluoroacetic anhydride.

This laboratory scale preparation of the difluoropyruvate **4** enables the compound to use in preparation of biologically active compounds, such as difluoromethyl-amino acids and difluoromethyl-heterocycles with its application to the reactions instead of trifluoropyruvates [2].

1. Experimental

1.1. General

1.1.1. Spectroscopic measurements

1.1.1.1. NMR spectra. All NMR spectra were recorded as $CDCl_3$ solutions. ^1H, and ^{19}F NMR spectra were recorded at 300 and 282 MHz respectively with Varian MERCURY 300 instrument. The

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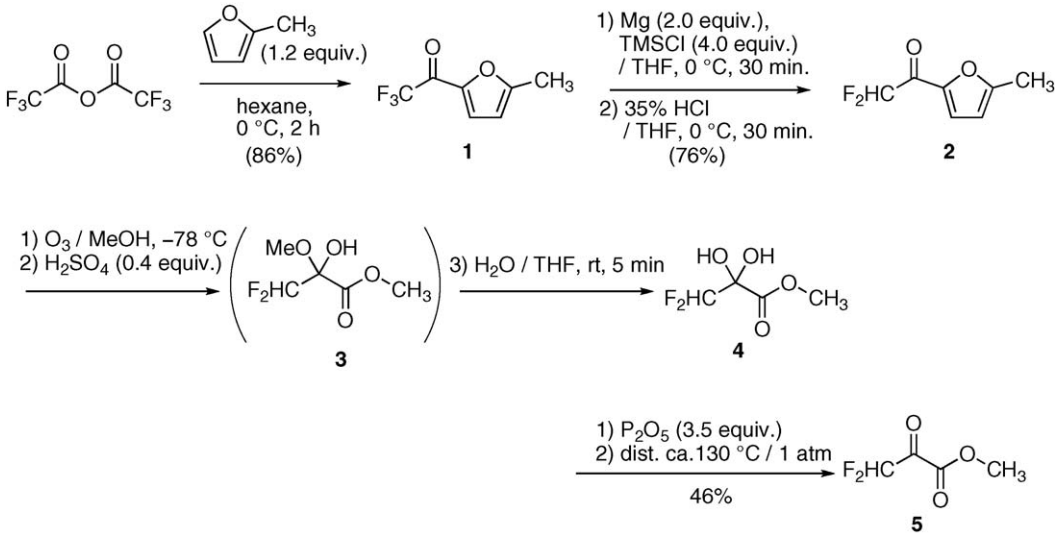

Scheme 1.

chemical shifts are reported in δ (ppm) related to the $CHCl_3$ (7.26 ppm for ^1H NMR) and C_6F_6 (0 ppm for ^{19}F NMR: the relative chemical shift of C_6F_6 to $CFCl_3$ is −162.2 ppm). Coupling constants (J) are reported in hertz (Hz).

1.1.1.2. IR spectra. Infrared spectra were recorded on a Hitachi 270-30 spectrometer. Only selected absorbances are reported (ν in cm^{-1}).

1.1.1.3. MS analysis. MS analyses were performed on a Shimadzu GCMS-QP5050A.

1.1.2. Chemicals

Hexane was dried over MS 4A for 1 day and used without further purification. THF was dried over benzophenone Na ketyl and distilled just prior to use. Trifluoroacetic anhydride (TFAA: Aldrich) was distilled and stored in Schlenk tube. 2-Methylfuran (Aldrich) was used without further purification. Chlorotrimethylsilane (TMSCl: TCI) was distilled and stored in a glass tube. Mg turnings for Grignard reagent grade (Nacalai) were used without further treatment.

Ozone (O_3) was prepared from pure O_2 by ED-OG-R2+ Ozone Gas Generator equipped with SD-158-11 Silent Electric Discharge Tube (Eco Design Co.).

Preparations of 2-trifluoroacetyl-5-methylfuran **1** and 2-difluoroacetyl-5-methylfuran **2** were reported in our previous report [6].

*1.1.3. Ozonolysis of 2-difluoroacetyl-5-methylfuran (**2**)*

In a 200 ml flask, 2-difluoroacetyl-5-methylfuran 2 (3.87 g, 24 mmol), was dissolved in MeOH (120 ml) and cooled to −80–100 °C. The O_3/O_2 gas (0.15 L/min) was bubbled into the solution for 90 min (until the solution became greenish yellow). The excess O_3 was purged by 10 min of Ar bubbling. The solution was added by sulfuric acid (0.5 ml) and stirred for 20 min at −50 °C, followed by addition of MS 3A (1.5 g) and 15 h refluxing. Removal of sulfuric acid by filtration through silica gel, followed by evapolation of MeOH under a reduced pressure, and difluoroacetic acid was removed by silica gel column chromatography to give crude hemiacetal of methyl difluoropyruvate **3**, which was submitted for hydrolysis without further purification. Further removal of MeOH gave a mixture of **3** and **5**.

*1.1.4. Hemiacetal of methyl difluoropyruvate (**3**)*

[^{19}F] NMR (282 MHz, $CDCl_3$) δ 31.6 (dd, J = 235, 54 Hz, 1F), 24.2 (dd, J = 235, 54 Hz, 1H) (lit. δ 32.6 (dd, J = 299, 55 Hz, 1F), 25.1 (dd, J = 299, 55 Hz, 1H) ppm [5]); GC–MS m/z (rel. Int.) 153 (2), 119 (5), 111 (100), 91 (24), 63 (43), 51 (42).

Hemiacetal 3 was mixed with THF/H_2O (=1/1, 90 ml) and stirred. The solution was added by saturated brine (15 ml), separated, and extracted by ethyl ether (80 ml). Combined organic layer was dried over $MgSO_4$, and concentrated under a reduced pressure to give crude hydrate of difluoropyruvate **4**. When the product was submitted to GC–MS, it converted completely to methyl difluoropyruvate in vaporizing chamber.

*1.1.5. Hydrate of methyl difluoropyruvate (**4**)*

[^{19}F] NMR (282 MHz, $CDCl_3$) δ 26.4 (d, J = 54 Hz, 2F) (lit. δ 27.4 (d, J = 55 Hz, 2F) [5]); ^1H NMR (300 MHz, $CDCl_3$) δ 5.87 (t, J = 54.6 Hz, 1H), 3.94 (s. 3H) (lit. δ 5.88 (t, J = 54.7 Hz, 1H) (no description of chemical shift of methyl group in literature) [5]).

Hydrate 4 was mixed with P_2O_5 (6.5 g) then sonicated for 5 min. Distillation gave methyl difluoropyruvate 5 (1.54 g, 11.1 mmol) in 46% yield from the difluoroacetylfuran 2.

*1.1.6. Methyl difluoropyruvate (**5**)*

[^{19}F] NMR (282 MHz, $CDCl_3$) δ 31.1 (d, J = 54 Hz, 2F) (lit. δ 32.0 (d, J = 53 Hz, 2F) [5]); ^1H NMR (300 MHz, $CDCl_3$) δ 6.40 (t, J = 52.8 Hz, 1H), 3.98 (s. 3H) (lit. δ 6.40 (t, J = 52.7 Hz, 1H), 3.99 (s, 3H) [5]); GC–MS m/z (rel. Int.) 94 (1), 81 (10), 79 (5), 59 (57), 51 (100), 44 (2), 43 (18).

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