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A Facile, General Synthesis of 3,4-Difluoro-6-substituted-2-pyrones

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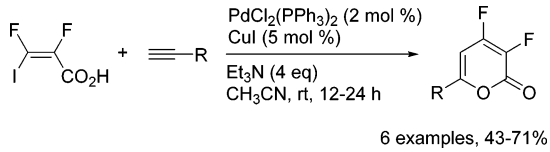

Reaction of (2*E*)-2,3-difluoro-3-iodoacrylic acid with a variety of terminal acetylenes under cocatalysis of $PdCl_2(PPh_3)_2$ and CuI gave difluorinated 2-pyrones as the sole product in good yields.

Introduction

Fluorinated organic compounds have attracted the interest of pharmaceutical chemists and agrochemists.[1] Replacement of hydrogen atoms by fluorine atoms in organic molecules causes a relatively small steric perturbation but leads to major changes in lipophilicity and polarity factors; thus, it often leads to enhanced biological activity. 2-Pyrones[2] are found in numerous natural products that display important biological activities such as anti HIV,[3] telomerase inhibition,[4] antimicrobial,[5] antifungal,[6] cardiotonic,[7] pheromonal,[8] androgen-like,[9] and phytotoxic effects.[10] Consequently, much attention has been paid to the synthesis of 2-pyrones by traditional methods,[11] transition-metal-catalyzed procedures,[8,12] or nucleophilic phosphine catalysis of allenoates and butynoates.[13] However, to the best of our knowledge, there is only one report of the preparation of 3,4-difluoro-6-substituted-2-pyrones. England and co-workers re-

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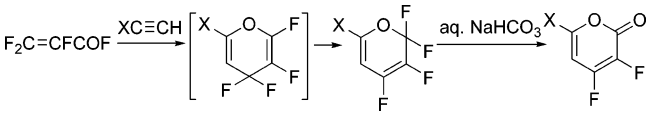
SCHEME 1



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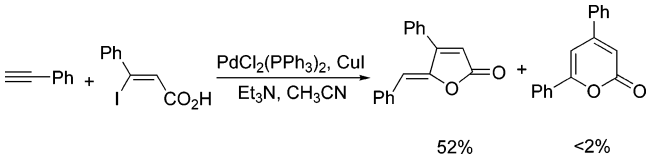
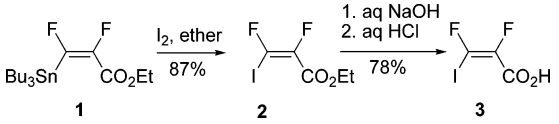


SCHEME 3. Preparation of 3



ported a synthetic route to this class of compounds via the Diels−Alder reactions of perfluoroacryloyl fluorides with monosubstituted acetylenes, followed by isomerization of the adducts and hydrolysis in aqueous $NaHCO_3$ (Scheme 1).[14]

Unfortunately, by this methodology, most of the fluorinated 2-pyrones derivatives were obtained in poor yields. Herein, we wish to report a more efficient and general route to this class of compounds.

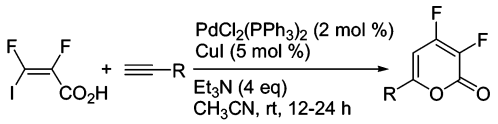
Results and Discussion

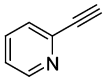
Recently, c*is*-*β*-haloacrylic acids have been utilized for the highly stereoselective synthesis of *γ*-(*Z*)-alkylidenebutenolides and/or 2-pyrones under cocatalysis of palladium and copper(I),[15] Ag(I),[16] Hg(II),[17] and Zn(II).[16] In most of these cases, the 2-pyrones were observed only as the major side products. Negishi and co-workers reported a convenient synthesis of *γ*-(*Z*)-alkylidenebutenolides; however, the 2-pyrone was obtained as a minor product (Scheme 2).[17]

Since we have recently reported the preparation of ethyl (*E*)-2,3-difluoro-3-(tributylstannyl)acrylate **1** and studied its reaction with organic halides[18] and acid chlorides,[19] it occurred to us that **1** might be a possible precursor to the fluorinated c*is*-*β*-haloacrylic acid, which could be further utilized to prepare the corresponding fluorinated analogue of *γ*-(*Z*)-alkylidenebutenolides and/or 2-pyrones. Treatment of **1** with iodine in ether afforded the iodoester **2**,[19] which underwent saponification and subsequent acidification to give the *cis*-iodo acid **3** (Scheme 3).

With acid **3** in hand, we investigated the possibility of the synthesis of difluorosubstituted *γ*-alkylidenebutenolides under the reported reaction conditions. Under the cocatalysis of $PdCl_2(PPh_3)_2$ (2 mol %) and CuI (5 mol %), reaction of **3** with phenylacetylene occurred very smoothly at room temperature, and ^{19}F NMR spectroscopy indicated there was a sole product after the reaction was completed. To our surprise, the product was found to be 3,4-difluoro-6-phenyl-2*H*-pyran-2-one **4** after comparison of its NMR data with those in England's report.[14] A variety of acetylenes were employed under similar reaction conditions, and only the 2-pyrone product was formed in each case. These results are summarized in Table 1.

TABLE 1. Synthesis of 3,4-Difluoro-6-substituted-2-pyrones



entry	R	time (h)	product	yield[a] (%)
1	C_6H_5	24	**4**	62
2	*n*-C_5H_{11}	24	**5**	59
3	$C_6H_5CH_2CH_2$	24	**6**	64
4	4-$CF_3C_6H_4$	12	**7**	69
5	4-$MeOC_6H_4$	16	**8**	71
6		24	**9**	43

[a] Isolated yield based on **3**.

Both aromatic (entries 1, 4, and 5) and aliphatic acetylenes (entries 2 and 3) worked well, as well as a heterocyclic acetylene (entry 6). The presence of neither an electron-withdrawing group (entry 4) nor an electron-donating group (entry 5) on the aromatic rings affected the yield of the products. The relative low yield in entry 6 was due to incomplete reaction even after 24 h at room temperature. Spectroscopic data of **4** are identical to those reported by England and co-workers, and the assignment of 2-pyrone was further confirmed by its single-crystal X-ray diffraction.[20]

On the basis of our observed results, the following mechanism is proposed to explain the formation of the 2-pyrone products (Scheme 4). The Pd(0) is first formed in the presence of phenylacetylene. In the first catalytic cycle, the iodoacid **3** reacts with the alkyne under the catalysis of Pd(0) to produce the ynenoic acid. Pd(0) species is regenerated after the first cycle and is readily converted into Pd(II) in the solution containing an acid moiety HX (X could be I^-, Cl^-, and/or (*E*)-CFI═$CFCO_2^-$). In the second catalytic cycle, the ynenoic acid is further transformed into the final product under the catalysis of Pd(II). Upon reductive elimination, the Pd(0) is regenerated to yield **4**.

At this point, the reason for the exclusive formation of the fluorinated 2-pyrone is not clear. It is nevertheless tempting to attribute the selectivity to the strong electronegativity of fluorine.[21] The presence of two fluorine atoms on the double

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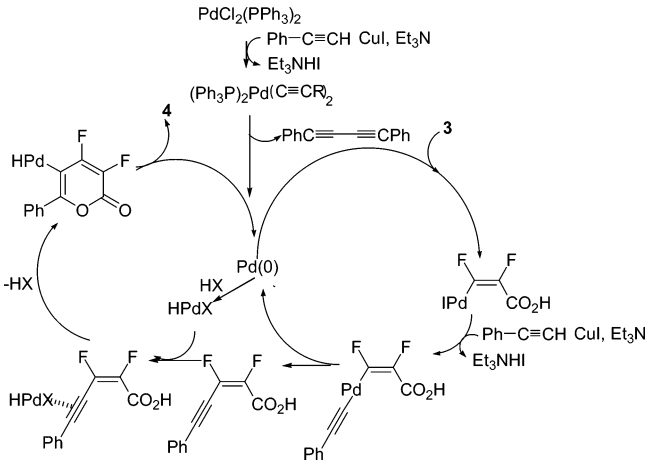
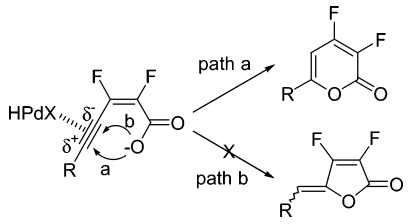
(20) CCDC 299095 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK.; fax: +44 1223 336033. Also see the Supporting Information.

(21) In ref 1d, pp 1−23.

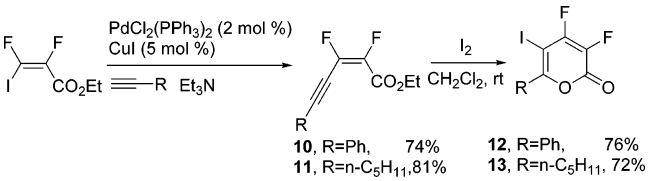
SCHEME 4. Proposed Mechanism of the Formation of 4



SCHEME 5. Exclusive Formation of 2-Pyrones



SCHEME 6



bond makes the triple bond partially polarized. The carboxylic anion would attack the partially positive charged carbon to give the 2-pyrone (via path a) rather than the other carbon on the triple bond to give the γ-alkylidenebutenolide (via path b) as illustrated in Scheme 5.

As an extension of this work, we were able to prepare 3,4-difluoro-5-iodo-6-substituted-2-pyrones via the electrophilic cyclization work developed by Larock and co-workers.[11d] Treatment of **2** with alkynes (Sonogashira reaction[22]) under the cocatalysis of $PdCl_2(PPh_3)_2$ (2 mol %) and CuI (5 mol %) afforded enynes **10** and **11**, respectively. The reaction of **10** and **11** with I_2 in CH_2Cl_2 gave the corresponding 5-iodo-2-pyrones **12** and **13**, respectively (Scheme 6).

Formation of 6-iodo-2-pyrones presumably follows the mechanism proposed by Larock and co-workers[11d] (Scheme 7). Nucleophilic attack by the oxygen of carbonyl group on the triple bond activated by coordination to I^+ is followed by S_N2 attack of the iodide.

Confirmation of the structure of the 5-iodo-2-pyrones rather than iodo-substituted butenolides was verified by subsequent reduction of the enynes. Treatment of **12** and **13** in the presence of zinc dust in acetic acid[23] yielded **4** and **5** in 67% and 66% yield, respectively.

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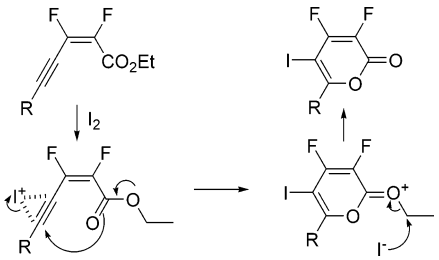
SCHEME 7



Conclusion

In conclusion, difluorinated 2-pyrones were readily prepared in a one-pot reaction from iodo acid **3** with a variety of terminal alkynes. Cyclization of enynes with I_2 afforded 5-iodo-6-substituted 2-pyrones, which could be further utilized to synthesize more functionalized fluorinated 2-pyrones (via transition-metal-catalyzed coupling reactions). These methods should find application in the synthesis of fluorinated natural products.

Experimental Section

Preparation of (2*E*)-2,3-Difluoro-3-iodoacrylic Acid (3). To a solution of **2** (0.23 g, 0.88 mmol) in THF (3 mL) was added aqueous sodium hydroxide (1 mL, 3 M) dropwise at 0 °C. After 3 h at room temperature, the reaction was treated with aqueous HCl until the pH was ∼1. Then the mixture was extracted with 25 mL of ethyl acetate. The organic layer was washed with brine (5 mL), dried over anhydrous Na_2SO_4, and concentrated by rotary evaporation. The crude acid was recrystallized from hexane to yield 0.16 g of a white solid (yield 78%): mp 95−96 °C; ^{19}F NMR ($CDCl_3$) δ −70.4 (d, J = 10.6 Hz, 1 F), −130.0 (d, J = 10.5 Hz, 1 F); ^{1}H NMR ($CDCl_3$) δ 11.8 (br s); ^{13}C NMR ($CDCl_3$) δ 165.0 (dd, J = 28.4, 7.9 Hz), 140.0 (dd, J = 264.2, 15.2 Hz), 108.8 (dd, J = 336.5, 24.4 Hz); HRMS calcd 233.8989 for $C_3HF_2IO_2$, found 233.8990.

General Procedure for the Preparation of 3,4-Difluoro-6-substituted-2-pyrones. A round-bottomed flask was charged with a stirring bar and nitrogen tee, (2*E*)-2,3-difluoro-3-iodoacrylic acid **3** (0.23 g, 1 mmol), CuI (10 mg, 0.05 mmol), $PdCl_2(PPh_3)_2$ (14 mg, 0.02 mmol), and 5 mL of MeCN. Et_3N (0.56 mL, 4 mmol) and alkyne (1.1 mmol) were added sequentially under N_2. After the reaction was completed (the reaction progress was monitored by TLC), the reaction mixture was diluted with ether (25 mL). The mixture was filtered, and the filtrate was concentrated by rotary evaporation. The crude residue was purified on silica gel (hexane/ethyl acetate = 10:1), and the pure product was obtained.

Preparation of 3,4-Difluoro-6-phenyl-2*H*-pyran-2-one (4). The reaction mixture of **3** (0.23 g, 1 mmol), CuI (10 mg, 0.05 mmol), $PdCl_2(PPh_3)_2$ (14 mg, 0.02 mmol), Et_3N (0.56 mL, 4 mmol), and phenylacetylene (0.12 mL, 1.1 mmol) in 5 mL of MeCN was stirred under N_2 at room temperature for 24 h. Column chromatography with a mixture of hexane and ethyl acetate (10:1) afforded 0.13 g of a yellow solid: mp 130−132 °C; ^{19}F NMR ($CDCl_3$) δ −118.0 (dd, J = 16.5, 8.5 Hz, 1 F), −163.9 (dd, J = 16.5, 4.6 Hz, 1 F); ^{1}H NMR ($CDCl_3$) δ 7.78−7.76 (m, 2 H), 7.54−7.46 (m, 3 H), 6.64 (dd, J = 8.5, 4.6 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 157.3 (dd, J = 22.9, 10.3 Hz), 157.0 (dd, J = 11.6, 7.5 Hz), 156.7 (dd, J = 271.8, 9.6 Hz), 133.3 (dd, J = 252.0, 9.7 Hz), 131.6 (d, J = 0.6 Hz), 129.7 (dd, J = 3.3, 1.5 Hz), 129.2, 125.6 (d, J = 1.0 Hz), 95.2 (dd, J = 25.4, 3.2 Hz); HRMS calcd 208.0336 for $C_{11}H_6F_2O_2$, found 208.0336.

Preparation of Ethyl (2*Z*)-2,3-Difluoro-5-phenylpent-2-en-4-ynoate (10). A round-bottomed flask was charged with a stirring bar and nitrogen tee, $PdCl_2(PPh_3)_2$ (14 mg, 0.02 mmol), CuI (10 mg, 0.05 mmol), and 4 mL of CH_3CN. Ethyl (2*E*)-2,3-difluoro-3-iodoacrylate **2** (0.26 g, 1 mmol), phenylacetylene (0.12 mL, 1.1 mmol), and Et_3N (0.21 mL, 1.5 mmol) were added subsequently

under N_2. After 12 h, the mixture was diluted with ether (25 mL) and filtered. The filtrate was concentrated, and the crude product was purified on silica gel (hexane/ethyl acetate = 20:1) and a yellow oil was obtained (0.17 g, 74%): ^{19}F NMR ($CDCl_3$) δ −113.6 (d, J = 9.9 Hz, 1 F), −139.0 (d, J = 9.9 Hz, 1 F); ^{1}H NMR ($CDCl_3$) δ 7.58−7.54 (m, 2 H), 7.44−7.38 (m, 3 H), 4.37 (q, J = 7.1 Hz, 2 H), 1.37 (t, J = 7.1 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 159.6 (dd, J = 28.0, 7.0 Hz), 142.6 (dd, J = 263.6, 23.2 Hz), 138.8 (dd, J = 250.9, 24.4 Hz), 132.0 (dd, J = 2.6, 1.3 Hz), 130.3, 128.6 (2C), 120.5 (dd, J = 2.8, 1.6 Hz), 102.7 (dd, J = 8.1, 5.1 Hz), 62.1, 14.2; HRMS calcd 236.0649 for $C_{13}H_{10}F_2O_2$, found 236.0655.

Preparation of 3,4-Difluoro-5-iodo-6-phenylpyran-2-one (12). In a round-bottomed flask charged with a stirring bar and nitrogen tee was stirred a solution of 2,3-difluoro-5-phenylpent-2-en-4-ynoic acid ethyl ester (0.14 g, 0.59 mmol) and iodine (0.18 g, 0.71 mmol) in 10 mL of CH_2Cl_2 under N_2 at room temperature for 2 h. The reaction mixture was then diluted with 50 mL of ether, washed with 20 mL of aq $Na_2S_2O_3$, and dried over Na_2SO_4. The solvent was evaporated under vacuum, and the product was purified on silica gel (hexane/ethyl acetate = 10:1) to give a yellow solid (0.15 g, 76%): mp 93−94 °C; ^{19}F NMR ($CDCl_3$) δ −97.3 (d, J = 15.2 Hz, 1 F), −159.5 (d, J = 15.2 Hz, 1 F); ^{1}H NMR ($CDCl_3$) δ 7.73−7.70 (m, 2 H), 7.52−7.48 (m, 3 H); ^{13}C NMR ($CDCl_3$) δ 157.7 (dd, J = 7.8, 5.3 Hz), 156.5 (dd, J = 23.1, 10.3 Hz), 155.5 (dd, J = 267.9, 10.1 Hz), 132.4 (dd, J = 257.8, 13.2 Hz), 132.1 (d, J = 2.7 Hz), 131.5, 129.5, 128.4, 62.1 (dd, J = 28.3, 4.0 Hz); HRMS calcd 333.9302 for $C_{11}H_5IF_2O_2$, found 333.9303.

Reduction of 12. In a round-bottomed flask charged with a stirring bar and nitrogen tee was added zinc dust (0.07 g, 1.1 mmol) to a solution of 3,4-difluoro-5-iodo-6-phenylpyran-2-one (0.17 g, 0.51 mmol) in 3 mL of HOAc at room temperature. After the mixture was refluxed under N_2 for 2 h, it was cooled to room temperature and diluted with ether (25 mL). The organic layer was washed with aq $NaHCO_3$ (5 mL) and brine (5 mL), dried, and concentrated. The product was purified on silica gel (hexane/ethyl acetate = 10:1) to give a yellow solid (0.07 g, 67%): mp 130−132 °C. ^{1}H and ^{19}F NMR spectroscopic data were identical to those for **4**.

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Supporting Information Available: Experimental procedure for the synthesis of **5**−**9**, **11**, and **13** and their characterization by ^{1}H, ^{19}F, and ^{13}C NMR and HRMS; copies of ^{1}H, ^{19}F, and ^{13}C NMR of compounds **3**−**13**. Complete X-ray crystallographic data of compound **4** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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