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Synthesis and reactions of 2-hydroxy-4-oxo-4-(2,3,5,6-tetrafluoro-4-methoxyphenyl)-but-2-enoic acid methyl ester

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Abstract

2-Hydroxy-4-oxo-4-(2,3,5,6-tetrafluoro-4-methoxyphenyl)-but-2-enoic acid methyl ester (**1**) was synthesized by the reaction of pentafluoroacetophenone with dimethyl oxalate in the presence of sodium methylate. Subsequently, reactions of compound **1** with aniline, *o*-phenylenediamine, and *o*-aminophenol were investigated. In addition, the thermal cyclization of ester **1** was studied and led to the formation of 5,6,8-trifluoro-7-methoxy-4-oxo-4H-chromene-2-carboxylic acid methyl ester (**6**) due to nucleophilic substitution of the 3-fluoro group. Hydrolysis of compound **1** and subsequent cyclization by treatment with $SOCl_2$ gave 5-(2,3,5,6-tetrafluoro-4-methoxyphenyl)-furan-2,3-dione (**3**). Thermal decarbonylation of compound **3** under mild conditions resulted in the formation of 3-(2,3,5,6-tetrafluoro-4-methoxyphenyl)-propene-1,3-dione (**4**) which dimerized to pyranone 5.

Keywords: 2-Hydroxy-4-oxo-4-(2,3,5,6-tetrafluoro-4-methoxyphenyl)-but-2-enoic acid methyl ester; 5-(2,3,5,6-Tetrafluoro-4-methoxyphenyl)-furan-2,3-dione; 3-(2,3,5,6-Tetrafluoro-4-methoxyphenyl)-propene-1,3-dione

1. Introduction

Pyruvic acid is a natural metabolite, which plays an important role in biochemistry. In addition, substituted benzoylpyruvic acids and their derivatives are convenient synthons for the synthesis of various acyclic and heterocyclic compounds [1–5]. For example, they have been utilized by Andreichikov et al. [2] for the synthesis of highly reactive five member 2,3-dioxoheterocylic compounds such as furandiones [3], pyrrolediones [4], and pyrazolediones [5].

Substituted benzoylpyruvic acids and their derivatives are also known as an important source of biologically active compounds. The analgesic activity of aroylpyruvic acids has been widely studied [6–8]. Substituted benzoylpyruvic acids and their derivatives have also demonstrated antiviral [9], antibacterial [10,11], and anti-inflammatory [7,9,12] activity.

As the result of our previous work several novel derivatives of benzoylpyruvic acids were found to be active against *Mycobacterium tuberculosis* [13] and human myeloma (ATCC CCL155) [14].

The goal of this research was to provide a novel synthesis of 2-hydroxy-4-oxo-4-(2,3,5,6-tetrafluoro-4-methoxyphenyl)-but-2-enoic acid methyl ester (**1**) and to prepare novel derivatives by thermal cyclization and by reaction with aniline, *o*-phenylenediamine, and *o*-aminophenol.

2. Results and discussion

As previously mentioned, substituted benzoylpyruvic acids and their derivatives have been of interest due to their biological activity. Therefore, this research has two goals: to provide a novel synthetic route to new synthons by the introduction of aroyl fragments containing four fluorine atoms at C-3, which would provide opportunities to produce additional synthons due to the ease of nucleophilic substitution of fluorine atoms that are *ortho* to acyl groups; to use this synthetic route to provide additional analogs for further biological studies.

As shown in Scheme 1, pentafluoroacetophenone underwent condensation with dimethyl oxalate in the presence of sodium methylate (ratio 1:1:2) to give compound **1**. This occurred due to a Claisen reaction that was accompanied by nucleophilic substitution of the fluorine atom at position 4 by a methoxy group which resulted in the formation of

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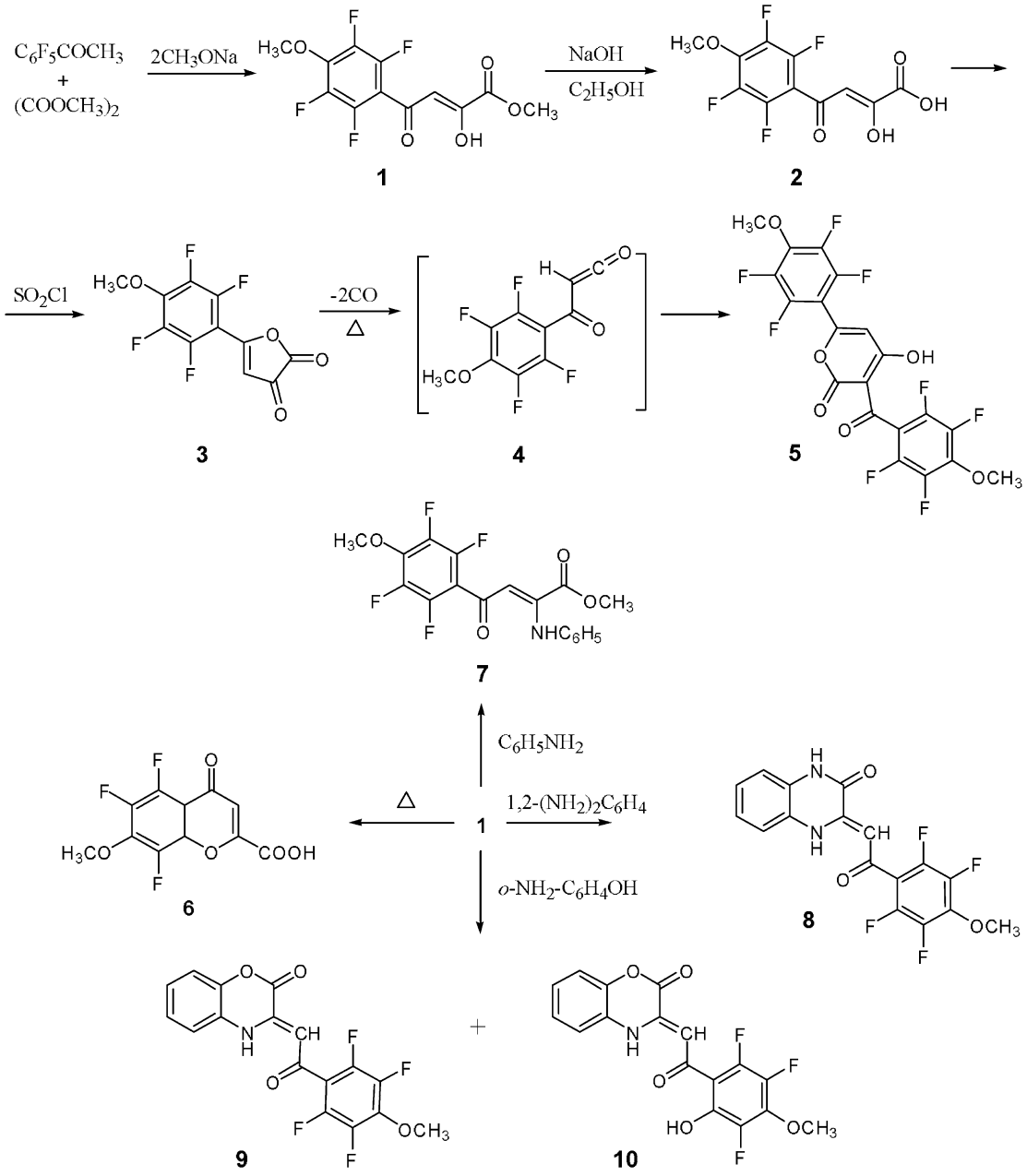

Scheme 1.

2-hydroxy-4-oxo-4-(2,3,5,6-tetrafluoro-4-methoxyphenyl)-but-2-enoic acid methyl ester (**1**). The structure of compound **1** was confirmed by elemental analysis, IR, and ^{1}H and ^{19}F NMR spectroscopy. 2-Hydroxy-4-oxo-4-(2,3,5,6-tetrafluoro-4-methoxyphenyl)-but-2-enoic acid (**2**) was prepared by hydrolysis of ester **1** with a solution of sodium hydroxide in ethanol. Acid **2** underwent cyclization in a manner analogous to non-fluorinated substituted benzoylpyruvic acids [2,3] into 5-(2,3,5,6-tetrafluoro-4-methoxyphenyl)-furan-2,3-dione (**3**) by heating at 50–60 °C with $SOCl_2$. Thermal decarboxylation of **3** at temperatures greater than 65 °C resulted in the formation of a 3-(2,3,5,6-tetrafluoro-4-methoxyphenyl)-propene-1,3-dione **4** which underwent dimerization due to a [4+2] cycloaddition reaction to give 4-hydroxy-3-(2,3,5,6-tetrafluoro-4-methoxybenzoyl)-6-(2,3,5,6-tetrafluoro-4-methoxyphenyl)-pyran-2-one (**5**).

Compounds **1** and **2** exist in the 1,3-ketoenol forms, which is stabilized by intramolecular hydrogen bonds and is typical for substituted benzoylpyruvic acids and their ester derivatives [1,4,15]. This allows for the thermal cyclization of ester **1** into 5,6,8-trifluoro-7-methoxy-4-oxo-4H-chromene-2-carboxylic acid methyl ester (**6**) due to the nucleophilic substitution of the fluorine atom that is *ortho* to the 1,3-diketone enol group as was observed earlier for pentafluorobenzoylpyruvic acids and their esters [16,17]. However the ability of the fluorine atom to undergo nucleophilic substitution is considerably reduced when *meta* to the methoxy

group. Therefore cyclization of **1** into **6** proceeds only by heating in DMSO at temperature 100 °C.

Under mild conditions ester **1** reacts with aniline to give (*Z*)-4-oxo-2-phenylamino-4-(2,3,5,6-tetrafluoro-4-methoxyphenyl)-but-2-enoic acid methyl ester (**7**). The reaction of ester **1** with *o*-phenylenediamine and *o*-aminophenol results in the formation of (*Z*)-3-[2-oxo-2-(2,3,5,6-tetrafluoro-4-methoxyphenyl)-ethylidene]-3,4-dihydro-1H-quinoxalin-2-one (**8**) and the mixture of (*Z*)-3-[2-oxo-2-(2,3,5,6-tetrafluoro-4-methoxyphenyl)-ethylidene]-3,4-dihydrobenzo[1,4]oxazin-2-one (**9**), and (*Z*)-3-[2-oxo-2-(2,3,5-trifluoro-6-hydroxy-4-methoxyphenyl)-ethylidene]-3,4-dihydrobenzo[1,4]oxazin-2-one (**10**), respectively.

Formation of products analogous to compounds **8–10** is typical for non-fluorinated and pentafluorinated benzoylpyruvic acids [1,16–18]. Evidence that compounds **8–10** are in the *Z*-form is the deshielding in the NMR spectrum of the NH proton due to intermolecular hydrogen bonding with the NH proton.

In summary, the Claisen reaction of pentafluoroacetophenone with dimethyl oxalate and the sodium methylate as the condensing agent leads to 2-hydroxy-4-oxo-4-(2,3,5,6-tetrafluoro-4-methoxyphenyl)-but-2-enoic acid methyl ester (**1**) instead of the expected pentafluorobenzoylpyruvic acid or its esters. The ease of substitution of the fluorine atom which is *ortho* to the 1,3-diketone enol group in this compound is reduced in comparison with pentafluorobenzoylpyruvic acids and their esters due to the presence of a *para* methoxy group. This is confirmed by the fact that more severe conditions are required for the thermal cyclization of ester **1** to compound **6**. In reactions of compounds **1** and **2** with mono- and dinucleophiles the C-2 carbonyl group is attacked preferentially to the C-4 carbonyl group. Cyclization of acid **2** by $SOCl_2$ and its further decarboxylation leads to 3-(2,3,5,6-tetrafluoro-4-methoxyphenyl)-propene-1,3-dione (**4**) is an effective way of generation of polyfluorinated arylketenes. Further dimerization of compound **4** leads to the formation of 4-hydroxy-3-(2,3,5,6-tetrafluoro-4-methoxy-benzoyl)-6-(2,3,5,6-tetrafluoro-4-methoxyphenyl)-pyran-2-one (**5**).

3. Experimental

3.1. General experimental procedures

Infrared spectra (Nujol oil) were obtained on UR-20 spectrometer, ^{1}H NMR spectra were recorded on a Bruker AC-300 (300 MHz) referenced to tetramethylsilane. ^{19}F NMR spectra were obtained on Bruker WP 80 SY at 75.398 MHz, where a C_6F_6 internal standard has been utilized. All δ values are given relative to $CFCl_3$.

3.1.1. 2-Hydroxy-4-oxo-4-(2,3,5,6-tetrafluoro-4-methoxyphenyl)-but-2-enoic acid methyl ester (*1*)

A solution of sodium methylate, prepared from 0.46 g (20 mmol) of sodium and 30 ml absolute methanol, was added in small portions to a mixture of 6.35 g (10 mmol) pentafluoroacetophenone and 3.54 g (10 mmol) of dimethyl oxalate. The reaction was maintained at room temperature for 24 h and then was stirred with 50 ml of water and acidified with a solution of HCl (1:4). The resulting ester **1** was extracted with ether (240 ml), washed by a solution of soda and water, and then dried with anhydrous Na_2SO_4. The solvent was removed in vacuum and solid **1** was crystallized from methanol to obtain 2.25 g (73% yield) of colorless crystals with mp 92–93 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.87 (s, 3H, CO_2CH_3), 4.19 (s, 3H, CH_3O), 6.68 (s, 1H, CH), 13.24 (s, 1H, OH). ^{19}F NMR ($CDCl_3$): δ 156.27 (dd, 2F, $J = 13$ Hz), 136.49 (dd, 2F, $J = 13$ Hz). IR: ν 1732, 1645, 1610 cm^{-1}. Anal. Calcd for $C_{12}H_8F_4O_5$: C, 46.77; H, 2.62. Found: C, 46.83; H, 2.83.

3.1.2. 2-Hydroxy-4-oxo-4-(2,3,5,6-tetrafluoro-4-methoxyphenyl)-but-2-enoic acid (*2*)

To a solution of 3.08 g (10 mmol) of ester **1** in absolute ethanol (10 ml) a saturated solution of NaOH in ethanol was added with stirring. After 1 h the reaction mixture was diluted with water and acidified with H_2SO_4 (10%) to obtain a pH of 1–2. The resulting precipitate of **2** was filtered and recrystallized from toluene to give 2.38 g (81% yield) in the form of white–yellow crystals, mp 155–156 °C (decomp.). ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.15 (s, 3H, CH_3O), 6.66 (s, 1H, CH), 10.40 (s, 1H, OH). ^{19}F NMR (DMSO-d_6): δ 157.95 (dd, 2F), 143.54 (dd, 2F). IR: ν 3500–3400, 3100–3000, 1730, 1650, 1630 cm^{-1}. Anal. Calcd for $C_{11}H_6F_4O_5$: C, 44.92; H, 2.06. Found: C, 45.03; H, 1.83.

3.1.3. 5-(2,3,5,6-Tetrafluoro-4-methoxyphenyl)-furan-2,3-dione (*3*)

A solution of 5.88 g (20 mmol) of acid **2** and 1.51 ml (21 mmol) of $SOCl_2$ in absolute benzene (8 ml) and absolute hexane (4 ml) was heated on a water bath at a temperature of 50–60 °C for 1 h. The solution was cooled and the resulting precipitate of **3** was filtered and recrystallized from absolute benzene–hexane (1:1) to give 1.93 g (35% yield) of orange crystals, mp 113–114 °C (decomp.). ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.19 (s, 3H, CH_3O), 6.31 (s, 1H, CH). IR: ν 1830, 1722, 1645, 1590 cm^{-1}. Anal. Calcd for $C_{11}H_4F_4O_4$: C, 47.85; H, 1.46. Found: C, 48.03; H, 1.53.

3.1.4. 4-Hydroxy-3-(2,3,5,6-tetrafluoro-4-methoxy-benzoyl)-6-(2,3,5,6-tetrafluoro-4-methoxyphenyl)-pyran-2-one (*5*)

A solution of 1.38 g (5 mmol) of furandione **3** in absolute toluene (10 ml) was refluxed for 2 h, cooled and the precipitate was filtered and recrystallized from toluene to give 0.88 g (71% yield) of colorless crystals **5**, mp 204–205 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 4.20 + 4.26 (2s, 6H, $2CH_3O$), 7.15 (s, 1H, CH). IR: ν 3085, 1765, 1650, 1630 cm^{-1}. Anal. Calcd for $C_{20}H_8F_8O_6$: C, 48.41; H, 1.62. Found: C, 48.49; H, 1.23.

*3.1.5. 5, 6,8-Trifluoro-7-methoxy-4-oxo-4H-chromene-2-carboxylic acid methyl ester (**6**)*

A solution of 1.54 g (5 mmol) of ester **1** in DMSO (5 ml) was heated at reflux on a water bath for 20 min, cooled, and the resulting solid (**5**) was filtered to give 1.27 g (88% yield) of colorless crystals, mp 154–156 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.92 (s, 3H, CH_3COO), 4.20 (s, 3H, CH_3O), 6.87 (s, 1H, CH). ^{19}F NMR (DMSO-d_6): δ 156.43 (d, 1F, $J = 22$ Hz), 154.36 (dt, 1F, $J = 17$ Hz), 146.51 (dd, 1F, $J = 22$ Hz). IR: ν 3044, 1742, 1656 cm^{-1}. Anal. Calcd for $C_{12}H_7F_3O_5$: C, 50.01; H, 2.45. Found: C, 50.09; H, 2.57.

*3.1.6. (Z)-4-Oxo-2-phenylamino-4-(2,3,5,6-tetrafluoro-4-methoxyphenyl)-but-2-enoic acid methyl ester (**7**)*

A solution of 1.54 g (5 mmol) of ester **1** and 0.47 ml (5 mmol) aniline in 10 ml benzene was refluxed for 2 h. The solvent was removed and the residue was recrystallized from CCl_4 to give 1.90 g (99% yield) of yellow crystals **7**, mp 115–116 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.59 (s, 3H, CH_3COO), 3.99 (s, 3H, CH_3O), 5.76 (s, H, CH), 7.12 (m, 5H, C_6H_5), 11.59 (s, 1H, NH). IR: ν 3200, 1740, 1650 cm^{-1}. Anal. Calcd for $C_{18}H_{13}F_4NO_4$: C, 56.40; H, 3.42; N, 3.65. Found: C, 56.08; H, 3.18; N, 3.52.

*3.1.7. (Z)-3-[2-Oxo-2-(2,3,5,6-tetrafluoro-4-methoxyphenyl)-ethylidene]-3,4-dihydro-1H-quinoxalin-2-one (**8**)*

To a solution of 0.62 g (2 mmol) of ester **1** in 5 ml benzene a solution of 0.25 g (2 mmol) *o*-phenylenediamine in 10 ml benzene was added. The reaction mixture was maintained for 24 h at room temperature and the resulting solid was filtered and recrystallized from $CHCl_3$ to give 0.72 g (98% yield) of orange crystals (**8**), mp 259–260 °C (decomp.). ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.89 (s, 3H, CH_3O), 6.69 (s, 1H, CH), 7.08 (m, 4H, C_6H_4), 8.56 (s, 1H, NHCO), 13.03 (s, 1H, NH). IR: ν 1690, 1615 cm^{-1}. Anal. Calcd for $C_{17}H_{10}F_4N_2O_3$: C, 55.75; H, 2.75; N, 7.66. Found: C, 55.83; H, 2.88; N, 7.94.

*3.1.8. (Z)-3-[2-Oxo-2-(2,3,5,6-tetrafluoro-4-methoxyphenyl)-ethylidene]-3,4-dihydro-benzo[1,4]oxazin-2-one (**9**) and 3-[2-oxo-2-(2,3,5-trifluoro-6-hydroxy-4-methoxyphenyl)-ethylidene]-3,4-dihydro-benzo[1,4]oxazin-2-one (**10**)*

A solution of 3.08 g (10 mmol) of ester **1** and 1.09 g (10 mmol) of *o*-aminophenol in 30 ml ethanol was refluxed for 30 min and cooled to give compound **9** which was filtered and recrystallized from ethyl acetate to give 3.13 g (85% yield) of orange crystals, mp 183–184 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 4.15 (s, 3H, CH_3O), 6.40 (s, 1H, CH), 7.20 (m, 3H, C_6H_3), 7.70 (d, 1H, C^5–H), 12.52 (s, 1H, NH). IR: ν 1750, 1630, 1610 cm^{-1}. Anal. Calcd for $C_{17}H_9F_4NO_4$: C, 55.60; H, 2.47; N, 3.81. Found: C, 56.03; H, 2.53. MS (70 eV), *m/z* (%): 367 (11) [M^+], 325 (16), 207 (91) [*p*-$CH_3OC_6F_4CO$], 187 (16), 160 (100) [M^+-207], 159 (63) [M^+-207-H], 132 (45).

Solvent was evaporated in vacuo and the resulting material was recrystallized from ethanol to yield 0.083 g (2% yield) of compound **10** in the form of yellow crystals, mp 230–232 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 4.13 (s, 3H, CH_3O), 6.77 (s, 1H, CH), 7.20 (m, 4H, C_6H_3), 7.65 (d, 1H, C^5–H), 12.56 (brs, 2H, NH, OH). IR: ν 3200, 1760, 1635 cm^{-1}. Anal. Calcd for $C_{17}H_{10}F_3NO_5$: C, 55.90; H, 2.76; N, 3.83. Found: C, 55.79; H, 2.85; N, 3.90.

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