ISSN 1070-4280, Russian Journal of Organic Chemistry, 2009, Vol. 45, No. 10, pp. 1531–1534. © Pleiades Publishing, Ltd., 2009.
Original Russian Text © A. Mai, M. Artico, D. Rotili, I.A. Novakov, B.S. Orlinson, M.B. Navrotskii, A.S. Eremiichuk, E.A. Gordeeva, 2009, published in Zhurnal Organicheskoi Khimii, 2009, Vol. 45, No. 10, pp. 1546–1549.

Stereoselective Synthesis of 2-Substituted 6-[1-(2,6-Difluorophenyl)ethyl]-5-methylpyrimidin-4(3*H*)-ones

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Received May 16, 2008

Abstract—A procedure has been proposed for the synthesis of 2-(cyclopentylsulfanyl)-6-[(1*R*)-1-(2,6-difluorophenyl)ethyl]-5-methylpyrimidin-4(3*H*)-one through intermediate (3*R*)-4,4-dimethyl-2-oxotetrahydrofuran-3-yl (2*R*)-2-(2,6-difluorophenyl)propanoate which was obtained from prochiral 2-(2,6-difluorophenyl)prop-1-en-1-one generated *in situ*. The proposed procedure may be regarded as stereoselective route to 6-[(1*R*)-1-(2,6-difluorophenyl)ethyl]-5-methylpyrimidin-4(3*H*)-one derivatives.

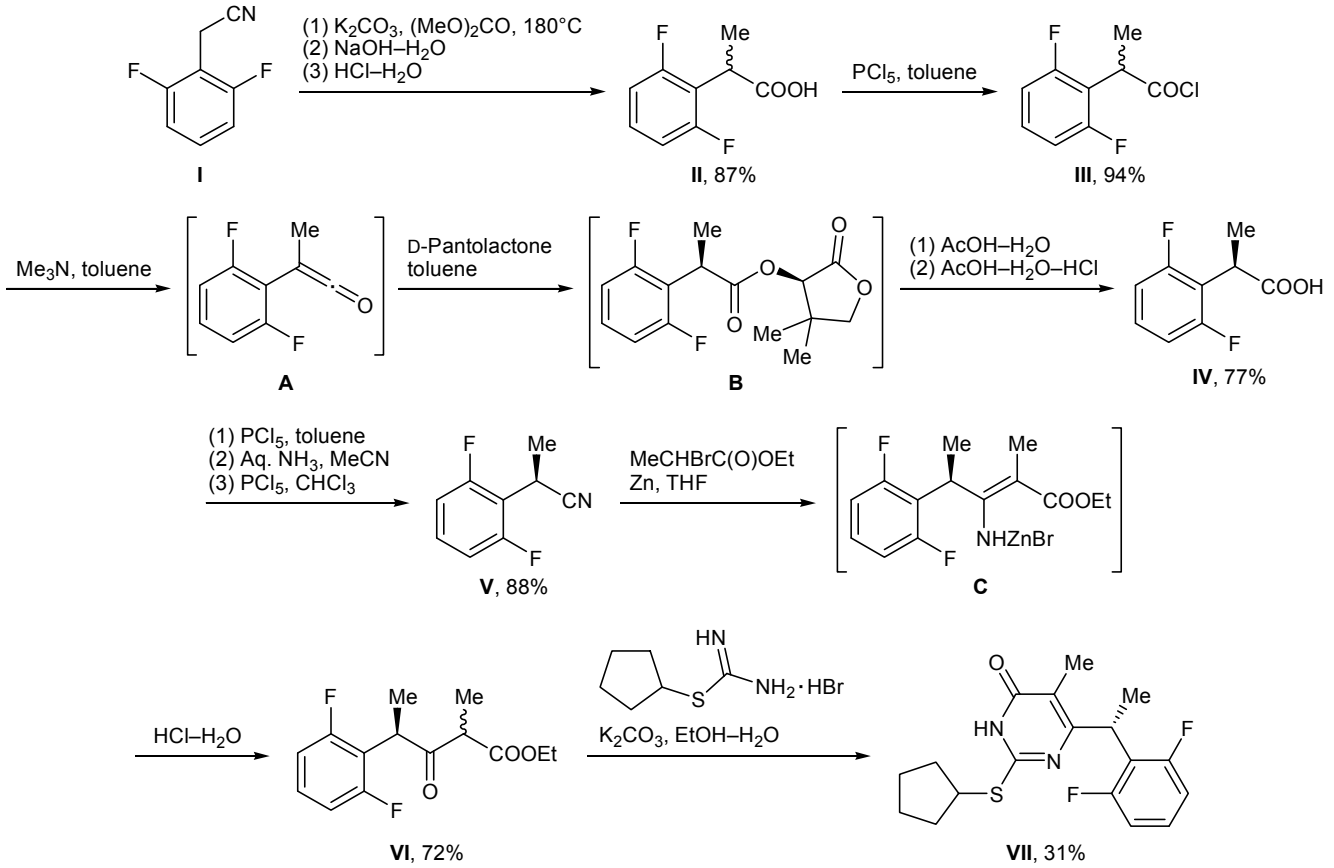
DOI: 10.1134/S1070428009100194

6-[1-(2,6-Difluorophenyl)ethyl]-5-methylpyrimidin-4(3*H*)-one derivatives having a cyclopentylsulfanyl [1], cyclopentylamino [2, 3], dimethylamino, or ethyl(methyl)amino group [4] in position *2* of the pyrimidine ring exhibit strong activity against HIV-1 in combination with low cytotoxicity. It was also found that the maximal antiviral activity in the above series of compounds is intrinsic to derivatives with *R* configuration of the benzylic carbon atom [5]. Up to now, the only procedure reported for the preparation of optically pure 2-(cyclopentylsulfanyl)-6-[(1*R*)-1-(2,6-difluorophenyl)ethyl]-5-methylpyrimidin-4(3*H*)-one is resolution by preparative chiral chromatography [5]. There are no published data on stereoselective synthesis of this compound. Therefore, development of stereoselective synthetic approaches to 2-(cyclopentylsulfanyl)-6-[(1*R*)-1-(2,6-difluorophenyl)ethyl]-5-methylpyrimidin-4(3*H*)-one and its analogs seems to be an important problem.

We have developed a novel strategy for stereoselective synthesis of 2-(cyclopentylsulfanyl)-6-[(1*R*)-1-(2,6-difluorophenyl)ethyl]-5-methylpyrimidin-4(3*H*)-one derivatives, which included the following transformations. 2-(2,6-Difluorophenyl)acetonitrile (**I**) was subjected to regioselective methylation at the α-carbon atom with dimethyl carbonate in the presence of potassium carbonate. Hydrolysis of 2-(2,6-difluorophenyl)propionitrile thus formed according to modified procedure [6] gave racemic acid **II** which was converted into acid chloride **III** by treatment with phosphorus(V) chloride in toluene [7]. Dehydrohalogenation of **III** with trimethylamine gave prochiral (2,6-difluorophenyl)methylketene **A** which acylated chiral D-(–)-pantolactone (by analogy with [8]). Optically active ester **B** was subjected (without isolation) to acid hydrolysis according to improved procedure [9], and chiral acid **IV** was converted into the corresponding amide through intermediate acid chloride (Schotten–Baumann reaction). Dehydration of the amide with phosphorus(V) chloride in chloroform afforded nitrile **V**, and Blaise reaction of the latter with ethyl 2-bromopropionate in the presence of zinc led (after acid hydrolysis of intermediate **C**) to the formation of optically active 3-oxo ester **VI**. Condensation of ester **VI** with *S*-cyclopentylisothiuourea hydrobromide in basic medium [10] gave crude target product **VII** which was purified by flash chromatography in a dry column, followed by recrystallization (Scheme 1). The properties of 2-(cyclopentylsulfanyl)-6-[(1*R*)-1-(2,6-difluorophenyl)ethyl]-5-methylpyrimidin-4(3*H*)-one (**VII**) were consistent with published data [1, 5].

Here, the Blaise organozinc synthesis [11, 12] of intermediate 3-oxo ester **VI** is more advantageous than alternative methods involving acylation of 1,3-dicarbonyl compounds with chiral acid chloride [13–16], which lead to the formation of racemic product

Scheme 1.



[through intermediate prochiral 2-(2,6-difluorophenyl)-prop-1-en-1-one] or the yield of the target 3-oxo ester is incomparably lower [17–19]. On the other hand, the Blaise synthesis in THF was accompanied by side formation of ethyl 2-methyl-3-oxopentanoate which can readily be separated from the target compound **VI** by fractional distillation under reduced pressure. In the stage of synthesis of optically active acid **IV** it is necessary to strictly follow conditions for hydrolysis of the ester group to avoid racemization.

EXPERIMENTAL

The ^{1}H NMR spectra were recorded on a Varian Mercury 300BB spectrometer using $CDCl_3$ as solvent and hexamethyldisiloxane as internal reference. The mass spectra (electron impact, 70 eV) were obtained on a Varian MAT 111 mass spectrometer with direct sample admission into the ion source. The melting points were determined on a Cole–Palmer melting point apparatus (corrected values are given).

(2*RS*)-2-(2,6-Difluorophenyl)propanoic acid (II). A mixture of 12.3 g (80.3 mmol) of 2-(2,6-difluorophenyl)acetonitrile, 111 ml of dimethyl carbonate, and 23.3 g (0.17 mol) of potassium carbonate was heated for 6.5 h in a steel high-pressure reactor under stirring at a bath temperature of 190–200°C. The mixture was filtered, the solvent was distilled off from the filtrate, and the residue was mixed with 100 ml of 2.5 M aqueous sodium hydroxide. The mixture was heated for 16 h at the boiling point under stirring, cooled, and extracted with diethyl ether (3×25 ml). The aqueous phase was acidified with 2 M hydrochloric acid to pH 1 and extracted with diethyl ether (3×100 ml), the extract was washed with water, dried over $MgSO_4$, and evaporated, and the residue was distilled under reduced pressure. Yield 13.0 g (87%), bp 90–95°C (2 mm). ^{1}H NMR spectrum, δ, ppm: 1.49–1.52 m (3H, CH_3), 4.07–4.18 m (1H, CH), 6.82–6.90 m (2H, 3-H, 5-H), 7.15–7.24 m (1H, 4-H), 7.95 s (1H, OH). Found, %: C 58.47; H 4.30; F 20.62. *m*/*z* 186 $[M]^+$. $C_{23}H_{29}N_3O$. Calculated, %: C 58.07; H 4.33; F 20.41. *M* 186.16.

(2*RS*)-2-(2,6-Difluorophenyl)propanoyl chloride (III). A mixture of 10 g (53.7 mmol) of acid **II**, 40 ml of anhydrous toluene, and 12.5 g (60.0 mmol) of freshly sublimed PCl_5 was kept with protection from

atmospheric moisture until vigorous evolution of hydrogen chloride ceased. The mixture was then heated for 2 h under reflux, the solvent was distilled under reduced pressure, and the residue was subjected to vacuum distillation. Yield 10.3 g (94%), bp 114–115°C (30 mm).

(2*R*)-2-(2,6-Difluorophenyl)propanoic acid (IV). A solution of 10 g (48.9 mmol) of freshly distilled acid chloride **III** in 100 ml of anhydrous toluene was added dropwise under dry argon to a solution of 9 g (152.3 mmol) of trimethylamine in 90 ml of anhydrous toluene. The mixture was stirred for 24 h at room temperature and cooled to –23°C (using a mixture of $CaCl_2 \cdot 6H_2O$ with ice as cooling agent), and 7 g (53.8 mmol) of D-(–)-pantolactone [(3*R*)-3-hydroxy-4,4-dimethyldihydrofuran-2(3*H*)-one] was added to the resulting suspension. The mixture was kept overnight at –20°C, washed with 10% aqueous citric acid and water (until neutral reaction), dried over $MgSO_4$, and evaporated under reduced pressure. The residue was dissolved in AcOH–H_2O (4:1 by volume), heated at 65–75°C under stirring, cooled to 10–15°C, and neutralized with 1 N aqueous sodium hydroxide under stirring. The product was extracted into diethyl ether (3×75 ml), and the extract was washed with water and dried over $MgSO_4$. The solvent was distilled off, the residue was heated at 80–90°C under stirring with a mixture of acetic acid and 2 M hydrochloric acid (5:2 by volume), and the mixture was cooled to room temperature, diluted with water, and extracted with diethyl ether (3×100 ml). The extract was washed with water and dried over $MgSO_4$, and the solvent was removed under reduced pressure. Vacuum distillation of the residue gave 7 g (77%) of acid **IV**, bp 74–78°C (1 mm). ^{1}H NMR spectrum, δ, ppm: 1.51–1.53 d (3H, CH_3), 4.10–4.21 q (1H, CH), 6.82–6.90 m (2H, 3-H, 5-H), 7.15–7.24 m (1H, 4-H), 7.96 s (1H, OH). Found, %: C 58.10; H 4.33; F 20.55. *m*/*z* 186 $[M]^+$. $C_{23}H_{29}N_3O$. Calculated, %: C 58.07; H 4.33; F 20.41. *M* 186.16.

(2*R*)-2-(2,6-Difluorophenyl)propanoyl chloride was synthesized from acid **IV** as described above for chloride **III**. Yield 7 g (91%), bp 100–101°C (18 mm).

(2*R*)-2-(2,6-Difluorophenyl)propionitrile (V). A solution of 7 g (34.2 mmol) of (2*R*)-2-(2,6-difluorophenyl)propanoyl chloride in 50 ml of anhydrous acetonitrile was added dropwise under stirring to 50 ml of 15 M aqueous ammonia, maintaining the temperature at –5 to 0°C. The resulting suspension was stirred for 1 h on cooling and for 1 h at room temperature, diluted with water, and filtered. The precipitate was dispersed in 100 ml of toluene, water was removed by distillation of toluene–water azeotrope, and the solvent was distilled off under reduced pressure. Anhydrous chloroform, 75 ml, and freshly distilled phosphorus(V) chloride, 8 g (38.4 mmol), were added to the redisue, and the mixture was heated for 16 h under reflux with protection from atmospheric moisture, washed with a saturated solution of sodium hydrogen carbonate and water, and dried over $MgSO_4$. The drying agent was filtered off, the filtrate was evaporated under reduced pressure, and vacuum distillation of the residue gave 5.1 g (88%) of compound **V**, bp 94–96°C (16 mm). Found, %: C 65.00; H 4.22; F 22.70; N 8.00. *m*/*z* 167 $[M]^+$. $C_{23}H_{29}N_3O$. Calculated, %: C 64.67; H 4.22; F 22.73; N 8.38. *M* 167.16.

Ethyl (4*R*)-4-(2,6-difluorophenyl)-2-methyl-3-oxopentanoate (VI). A small crystal of iodine and 100 mg of $HgCl_2$ were added to a mixture of 12 g (183.5 mol) of freshly prepared zinc turnings and 50 ml of anhydrous tetrahydrofuran. The mixture was heated under stirring until dark red color disappeared, several 0.1-ml portions of ethyl 2-bromopropionate were added until persistent green color (5–7 min), a solution of 5 g (29.9 mmol) of compound **V** in anhydrous THF was added in one portion, and 27.9 g (154.1 mmol) of ethyl 2-bromopropionate was slowly added dropwise under stirring. The mixture was heated for 30 min under reflux, the liquid phase was separated from excess zinc by decanting, the precipitate was washed with anhydrous THF, the solution was combined with the washings and concentrated under reduced pressure, and 150 ml of toluene and 80 ml of 12% hydrochloric acid were added. The mixture was vigorously stirred for 2.5 h, and the organic phase was separated, washed with water until neutral reaction, and dried over $MgSO_4$. The drying agent was filtered off through a layer of silica gel (Macherey–Nagel Kieselgel for TLC), the solvent was removed from the filtrate under reduced pressure, and the residue was subjected to fractional distillation under reduced pressure. After removal of EtC(O)CH(Me)C(O)OEt as by-product, crude ethyl (2*RS*,4*R*)-4-(2,6-difluorophenyl)-2-methyl-3-oxopentanoate was collected and subjected to repeated fractional distillation under reduced pressure. Yield 5.8 g (72%), bp 120–125°C (2 mm). ^{1}H NMR spectrum, δ, ppm: 1.14–1.24 m (6H, CH_3), 1.46–1.47 d (3H, CH_3), 3.47–3.61 d (1H, CH), 3.98–4.12 m (2H, CH_2), 4.23–4.29 q (1H, CH), 6.86–6.92 m (1H, 4-H), 7.19–7.28 (2H, 3-H, 5-H). Found, %: C 62.00; H 5.90;

F 14.37. *m*/*z* 270 $[M]^+$. $C_{23}H_{29}N_3O$. Calculated, %: C 62.22; H 5.97; F 14.06. *M* 270.27.

2-(Cyclopentylsulfanyl)-6-[(1*R*)-1-(2,6-difluorophenyl)ethyl]-5-methylpyrimidin-4(3*H*)-one (VII). A solution of 5.5 g (40.0 mmol) of potassium carbonate in 5.5 ml of water was slowly added to a mixture of 5 g (18.5 mmol) of compound **VI**, 9 g (40.0 mmol) of *S*-cyclopentylisothiourea hydrobromide, and 25 ml of 95% ethanol, maintaining the temperature at 10–15°C. The mixture was stirred for a week at room temperature, diluted with water, neutralized with acetic acid, and extracted with ethyl acetate (3×100 ml). The extracts were washed with water and a saturated aqueous solution of sodium chloride, dried over $MgSO_4$, and mixed with 50 g of silica gel (Macherey–Nagel Kieselgel). The solvent was removed under reduced pressure, and the sorbent was applied onto a dry column for flash chromatography charged with 150 g of silica gel (for TLC). The column was eluted with petroleum ether (bp 40–70°C)–diethyl ether (0–50 vol % of the latter). Fractions containing the target product were combined and evaporated under reduced pressure, and the residue was recrystallized from cyclohexane. Yield 2 g (31%), mp 196–197°C (from cyclohexane) [5]. The optical purity of the product was checked by HPLC using a chiral stationary phase according to the procedure described previously [5].

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