Synthesis and study of new derivatives of 6-[methoxy(phenyl)methyl]-2-(nitroamino)pyrimidin-4(3*H*)-one

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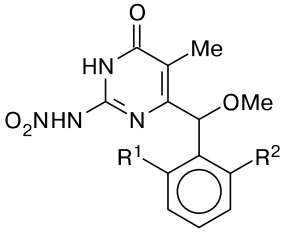
New 6-[(2,6-dihalophenyl)(methoxy)methyl]-5-methyl-2-(nitroamino)pyrimidin-4(3*H*)-ones were synthesized by an original and efficient method involving regioselective O,O´-dimethylation of substituted mandelic acids in superbasic medium. The compounds obtained can serve as precursors to a novel series of non-nucleoside HIV-1 replication inhibitors.

Key words: 6-[methoxy(phenyl)methyl]-2-(nitroamino)pyrimidin-4(3*H*)-ones, 2-(2,6-dihalophenyl)-2-hydroxyacetic acids, 3-oxo esters, nitroguanidine.

As a next step in our previous investigations into the synthesis of novel non-nucleoside derivatives of 6-(arylmethyl)pyrimidin-4(3*H*)-one and study of their antiviral properties,[1] we obtained new functionalized derivatives of this series (**1a—c**) that contain the methoxy group in the α-position of the benzyl radical.



1a—c

$R^1 = R^2 = F$ (**a**); $R^1 = F$; $R^2 = Cl$ (**b**); $R^1 = R^2 = Cl$ (**c**)

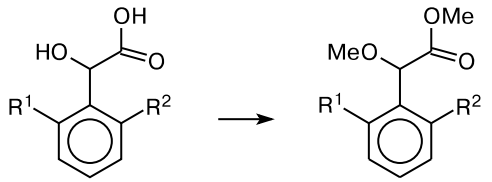
These compounds were synthesized as possible precursors to the corresponding 2-(dialkylamino)-6-[(2,6-dihalophenyl)(methoxy)methyl]-5-methylpyrimidin-4(3*H*)-ones, analogs of the highly efficient anti-HIV-1 agents obtained earlier.[2,3] Since conformationally hindered derivatives of this series exhibit higher antiviral activity, we found it expedient to study how the antiviral properties of a compound vary with the hydrophilic-lipophilic balance of its molecule (when moving from 6-[1-(2,6-dihalophenyl)ethyl]-5-methylpyrimidin-4(3*H*)-ones to the corresponding methoxylated analogs).

The earlier reported synthesis of 6-benzylisocytosine derivatives by aminolysis of appropriate 6-benzyl-2-(methylsulfanyl)pyrimidin-4(3*H*)-ones is not versatile: good results were achieved with primary amines in 2-ethoxyethanol[4] and 2-(ethoxyethoxy)ethanol,[5,6] while the use of secondary aliphatic amines decreases the yields of the target products and makes their isolation in the individual state more difficult.[3] To increase the yield and purity of the corresponding derivatives, we proposed 2-(nitroamino)pyrimidin-4(3*H*)-ones[7] as the starting materials.

Results and Discussion

2-(Nitroamino)pyrimidines were synthesized from mandelic acid derivatives, *viz.*, 2-(2,6-difluorophenyl)-2-hydroxyacetic acid (**2a**),[8] 2-(2-chloro-6-fluorophenyl)-2-hydroxyacetic acid (**2b**),[9] and 2-(2,6-dichlorophenyl)-2-hydroxyacetic acid (**2c**).[10] These starting compounds were transformed into the corresponding 2-methoxylated analogs according to a procedure described earlier[11] for the conversion of 2-hydroxy-3-methylbutanoic acid into methyl 2-methoxy-3-methylbutanoate: compounds **2a—c** were alkylated with MeI in the superbasic system $MeS(O)CH_2Li—Me_2SO$ (Scheme 1). The target products (>95% purity) were obtained in high yields and isolated simply by extraction of the reaction mixture.

Scheme 1



2a—c **3a—c**

Reagents and conditions: $MeI/MeS(O)CH_2Li$; Me_2SO.

2, **3:** $R^1 = R^2 = F$ (**a**); $R^1 = F$; $R^2 = Cl$ (**b**); $R^1 = R^2 = Cl$ (**c**)

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GC-MS analysis in the EI mode (70 eV) failed to detect the molecular ions of the compounds obtained; yet this was done by applying chemical ionization. The mass spectrum of each ester features the corresponding α-methoxybenzyl cation.

The IR spectra of these compounds show a band at 1769 cm^{-1}, which is not very typical of the ester CO group. Such a band is known to be more characteristic of carboxylic acid anhydrides, imidazolides, and chlorides. Obviously, this is due to the influence of the methoxy group in the α-position relative to the carbonyl and is reflected in the high hydrolability of the corresponding esters.

Basic hydrolysis of esters **3a**—**c** followed by acidification of the reaction mixture afforded the corresponding acids employed in further transformations without purification.

Interestingly, attempted synthesis of esters **3a**—**c** by methylation of appropriate mandelic acids in the presence of K_2CO_3[12] was not very successful. We obtained complex mixtures of methylation products, which made isolation of the target compounds laborious and inefficient.

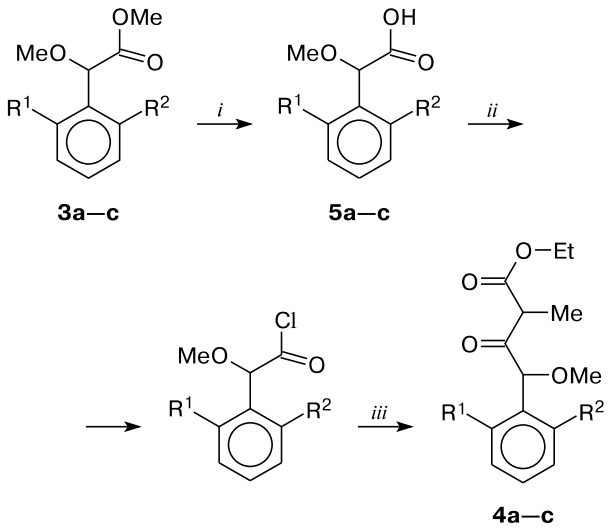
In the study of the synthesis of ethyl 4-(2,6-dihalophenyl)-4-methoxy-2-methyl-3-oxobutanoates **4a**—**c**, we demonstrated that these esters are highly thermolabile and decompose when purified by distillation under reduced pressure. In addition, ionization of these compounds produces no molecular ions, either by electron impact (the α-methoxybenzyl cation is detected) or by chemical reagents (the fragmentation ion $[M - OMe]^+$ is detected). To avoid purifying these compounds by column chromatography, we developed a synthetic approach by modifying our previous method.[13] Acids **5a**—**c** were transformed into the corresponding acid chlorides by reactions with $SOCl_2$ at room temperature (because the α-methoxybenzyl moiety is unstable when exposed to strong Lewis acids). The resulting acid chlorides were used without further purification for the synthesis of the corresponding 3-oxo esters **4a**—**c** (Scheme 2).

It should be noted that high-purity 3-oxo esters **4a**—**c** were obtained in good yields and isolated simply by extraction. GC-MS analysis revealed that these compounds containing two chiral centers exist as two pairs of diastereomers in dynamic equilibrium. The latter phenomenon arises from possible changes (due to keto-enol tautomerism) of the configuration of the chiral C(2) center.

The target 2-(nitroamino)pyrimidin-4(3*H*)-ones **1a**—**c** were obtained by cyclocondensation of 3-oxo esters **4a**—**c** with nitroguanidine in the presence of a solution of KOEt in anhydrous EtOH and isolated in the individual state by precipitation with AcOH from aqueous basic solutions (Scheme 3).

To sum up, we proposed a convenient route to new 6-[(2,6-dihalophenyl)(methoxy)methyl]-5-methyl-2-(nitroamino)pyrimidin-4(3*H*)-ones, precursors to a novel series of non-nucleoside HIV-1 replication inhibitors. This method allows isolation of both the target products and intermediates in the individual state without using laborious and inefficient techniques of purification. The yields of the key intermediates, *viz.*, methyl 2-(2,6-dihalophenyl)-2-methoxyacetates and ethyl 4-(2,6-dihalophenyl)-4-methoxy-2-methyl-3-oxobutanoates, are nearly quantitative.

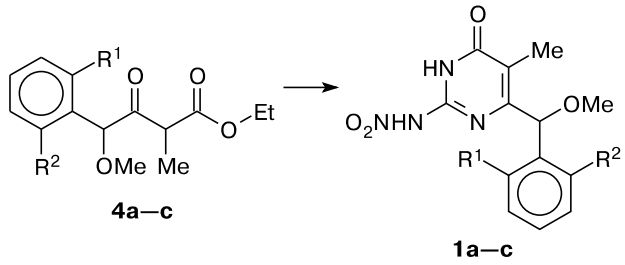
Scheme 2



Reagents and conditions: *i*. 1) KOH—H_2O; 2) HCl—H_2O. *ii*. $SOCl_2$. *iii*. 1) $(BrMgO)_2C{=}C(Me)COOEt$/THF; 2) HCl—H_2O.

3—5: $R^1 = R^2 = F$ (**a**); $R^1 = F$; $R^2 = Cl$ (**b**); $R^1 = R^2 = Cl$ (**c**)

Scheme 3



Reagents and conditions: 1) $H_2NC(NH)NHNO_2$/KOEt—EtOH; 2) AcOH—H_2O.

1, 4: $R^1 = R^2 = F$ (**a**); $R^1 = F$; $R^2 = Cl$ (**b**); $R^1 = R^2 = Cl$ (**c**)

Experimental

GLC-MS analysis was performed on a Varian Saturn 2100 instrument. For esters **3a,b** and **4a**—**c**, *m/z* values are cited only for molecular ions and fragmentation ions containing ^{35}Cl isotopes. ^1H NMR spectra were recorded on a Varian Mercury 300 BB instrument (300 MHz); chemical shifts are referenced to HMDS as

the internal standard. IR spectra were recorded on a Specord M-82 spectrometer (Nujol). Melting points were determined on a Fisher—Jones hot stage (Cole Palmer) at a heating rate of 10°C min^{-1}. TLC analysis was carried out on POLYGRAMSILG/UV_{254} plates (aluminum substrate coated with silica gel, MACHEREY-NAGEL GmbH&Co. KG) with C_6H_{14}—THF—MeOH (12 : 3 : 1, v/v) as an eluent; spots were visualized under UV light. Reaction mixtures and extracts were concentrated on a Heidolph Laborota 4000 rotary evaporator (~20 Torr). Organic extracts were dried with $MgSO_4$. All the starting reagents were purchased from Aldrich, Acros, or Lancaster Synthesis. Solvents were additionally purified and dried according to known procedures.[14] Samples prepared for physicochemical studies, as well as nitroguanidine containing ballast water, were dried in high vacuum over P_2O_5 for 20 h at 25—110 °C, depending on the melting point of the sample.

Methyl 2-(2-chloro-6-fluorophenyl)-2-methoxyacetate (3b). A 2.5 *M* solution of Bu^nLi (137.5 mmol) in hexane (55 mL) was slowly added under dry nitrogen to anhydrous DMSO (90 mL) while stirring and cooling it. Stirring was continued for another 5—10 min. Then a solution of acid **2b** (13.46 g, 65.8 mmol) in anhydrous DMSO (90 mL) was added dropwise with stirring and cooling. The mixture was stirred at room temperature for 2.5 h and cooled again, whereupon MeI (9.4 mL, 21.41 g, 150.8 mmol) was added dropwise with stirring. The stirring was continued for another ~1.5 h. The reaction mixture was left at room temperature for 16 h and poured into water (500 mL). Organic materials were extracted with Et_2O (3×150 mL). The combined organic extracts were washed with brine (3×75 mL), dried, filtered, and concentrated. The yield of crude ester **3b** (95.2% purity, GLC-MS) was 97%. This product was distilled to give ester **3b** (14.65 g, 86%) with 98.8% purity (R_t = 11.268 min, GLC-MS), n^{20}_D = 1.5116, b.p. 109—111 °C (2 Torr). Found (%): C, 51.60; H, 4.39; Cl, 15.14; F, 8.27. $C_{10}H_{10}O_3FCl$ (M = 232.64). Calculated (%): C, 51.63; H, 4.33; Cl, 15.24; F, 8.17. MS (EI, 70 eV), *m/z*: 173.2 $[M - COOMe]^+$ (100). MS (CI), *m/z*: 233.0 $[M + 1]^+$ (100), 173.0 $[M - COOMe]^+$ (35).

Methyl 2-(2,6-difluorophenyl)-2-methoxyacetate (3a) was obtained as described above for ester **3b** from acid **2a**. Yield 86%, purity 96.0% (R_t = 9.197 min, GLC-MS). Found (%): C, 55.60; H, 4.70; F, 17.48. $C_{10}H_{10}O_3F_2$ (M = 216.18). Calculated (%): C, 55.56; H, 4.66; F, 17.58. MS (EI, 70 eV), *m/z*: 157.1 $[M - COOMe]^+$ (100). MS (CI), *m/z*: 217.0 $[M + 1]^+$ (100), 157.1 $[M - COOMe]^+$ (36).

Methyl 2-(2,6-dichlorophenyl)-2-methoxyacetate (3c) was obtained as described for ester **3b** from acid **2c**. Yield 92%, purity 99.4% (R_t = 13.159 min, GLC-MS), m.p. 95—96 °C (from hexane). Found (%): C, 48.20; H, 4.00; Cl, 28.50. $C_{10}H_{10}O_3Cl_2$ (M = 249.09). Calculated (%): C, 48.22; H, 4.05; Cl, 28.47. MS (EI, 70 eV), *m/z*: 248.8 $[M]^+$ (7), 191.0 $[M - COOMe]^+$ (100). MS (CI), *m/z*: 250.0 $[M + 1]^+$ (100), 189.1 $[M - COOMe]^+$ (62).

2-(2,6-Difluorophenyl)-2-methoxyacetic acid (5a). Ester **3a** (10 g, 46.2 mmol) was refluxed with 10% aqueous NaOH (7.4 g, 185.0 mmol) until a transparent solution formed. On cooling, the product was extracted with diethyl ether (2×50 mL). The extracts were mixed with Et_2O (250 mL) and acidified with conc. HCl to pH 1. The organic phase was separated, washed with water (to pH 5), dried, and filtered. The solvent was removed to give pure acid **5a** (^{1}H NMR). Yield 9.19 g (98%). Found (%): C, 53.51; H, 3.99; F, 18.81. $C_9H_8O_3F_2$ (M = 202.15). Calculated (%): C, 53.47; H, 3.99; F, 18.80. ^{1}H NMR ($CDCl_3$), δ: 3.40 (s, 3 H, OMe); 5.14 (s, 1 H, CH); 6.86—6.93 (m, 2 H, $H_{Ar}(3)$, $H_{Ar}(5)$), 7.25—7.33 (m, 1 H, $H_{Ar}(4)$); 9.00 (br.s, 1 H, COOH).

2-(6-Chloro-2-fluorophenyl)-2-methoxyacetic acid (5b) was obtained as described for acid **5a** from ester **3b**. Yield 93%. Found (%): C, 49.41; H, 3.70; Cl, 16.20; F, 8.74. $C_9H_8O_3FCl$ (M = 218.61). Calculated (%): C, 49.45; H, 3.69; Cl, 16.22; F, 8.69. ^{1}H NMR ($CDCl_3$), δ: 3.39 (s, 3 H, OMe); 5.32 (s, 1 H, CH); 7.19 (t, 1 H, $H_{Ar}(4)$, *J* = 8.8 Hz); 7.26 (d, 2 H, $H_{Ar}(3)$, $H_{Ar}(5)$, *J* = 8.3 Hz); 8.07 (br.s, 1 H, COOH).

2-(2,6-Dichlorophenyl)-2-methoxyacetic acid (5c) was obtained as described for acid **5a** from ester **3c**. Yield 98%, m.p. 120—122 °C (from cyclohexane). Found (%): C, 46.01; H, 3.45; Cl, 30.20. $C_9H_8O_3Cl_2$ (M = 235.06). Calculated (%): C, 45.99; H, 3.43; Cl, 30.16. ^{1}H NMR ($CDCl_3$), δ: 3.39 (s, 3 H, OMe); 5.60 (s, 1 H, CH); 6.94 (t, 1 H, $H_{Ar}(4)$, *J* = 9.7 Hz); 7.16—7.25 (m, 2 H, $H_{Ar}(3)$, $H_{Ar}(5)$); 10.62 (s, 1 H, COOH).

Ethyl 4-(2-chloro-6-fluorophenyl)-4-methoxy-2-methyl-3-oxobutanoate (4b). Thionyl chloride (100 mL, 165.5 g, 1.39 mol) was added to acid **5b** (11.11 g, 50.8 mmol). Then several drops of anhydrous DMF were added. The reaction mixture was stirred at room temperature for 24 h and concentrated. Toluene (2×75 mL) was added to the residue and then distilled off. The resulting crude acid chloride was not purified prior to subsequent transformations.

A solution of Pr^iMgBr prepared from metallic Mg (6.79 g, 279.2 mg-atom) and Pr^iBr (24 mL, 31.44 g, 255.6 mmol) in anhydrous THF (150 mL) was added dropwise to a cooled and stirred solution of EtOOCCH(Me)COOH (14.85 g, 101.6 mmol) in anhydrous THF (75 mL). The mixture was stirred for another 20 min and cooled to −8 °C. Then a solution of the crude acid chloride in anhydrous THF (50 mL) was added dropwise at 0 °C over 1 h, while keeping the reaction mixture stirred. Stirring was continued at 0 °C for 1 h and then at room temperature for 1 h. The reaction mixture was poured into a stirred mixture of conc. HCl (35 mL) and crushed ice (70 g) and stirring was continued until the ice melted completely. The product was extracted with diethyl ether (3×200 mL). The combined extracts were washed with water (to pH 4—5), 5% aqueous K_2CO_3 (when acidified, these extracts return up to 80% of the excess EtOOCCH(Me)COOH), again water to a neutral reaction, and brine (3×100 mL). The washed organic solution was dried, filtered through a short (5—7 mm) column with silica gel for TLC, and concentrated. The yield of the target ester **4b** was 15.30 g (99%). The content of the title component was 95.0% (two pairs of diastereomers with R_t = 15.101 min (51.0%) and R_t = 15.422 min (44.0%), GLC-MS). Found (%): C, 55.60; H, 5.30; Cl, 11.72; F, 6.28. $C_{14}H_{16}O_4FCl$ (M = 302.73). Calculated (%): C, 55.55; H, 5.33; Cl, 11.71; F, 6.28. MS (EI, 70 eV), *m/z*: 173.2 $[M - C(O)CH(Me)COOC_2H_5]^+$ (100). MS (CI), *m/z*: 271.0 $[M - OMe]^+$ (100).

Ethyl 4-(2,6-difluorophenyl)-4-methoxy-2-methyl-3-oxobutanoate (4a) was obtained as described for 3-oxo ester **4b** from acid **5a**. Yield 94%. Found (%): C, 58.80; H, 5.61; F, 13.30. $C_{14}H_{16}O_4F_2$ (M = 286.27). Calculated (%): C, 58.74; H, 5.63; F, 13.27. The content of the title component was 98.5% (two pairs of diastereomers with R_t = 13.376 min (59.6%) and R_t = 13.713 min (38.9%), GLC-MS). MS (EI, 70 eV), *m/z*: 157.0 $[M - C(O)CH(Me)COOC_2H_5]^+$ (100). MS (CI), *m/z*: 254.8 $[M - OMe]^+$ (100).

Ethyl 4-(2,6-dichlorophenyl)-4-methoxy-2-methyl-3-oxobutanoate (4c) was obtained as described for 3-oxo ester **4b** from

acid **5c**. Yield 98%. Found (%): C, 52.71; H, 5.10; Cl, 22.25. $C_{14}H_{16}O_4Cl_2$ (M = 319.18). Calculated (%): C, 52.68; H, 5.05; Cl, 22.22. The content of the title component was 96.4% (two pairs of diastereomers with R_t = 16.722 min (38.9%) and R_t = 17.052 min (57.5%), GLC-MS). MS (EI, 70 eV), *m/z*: 191.0 $[M - C(O)CH(Me)COOC_2H_5]^+$ (100). MS (CI), *m/z*: 287.3 $[M - OMe]^+$ (100).

6-[(2,6-Dichlorophenyl)(methoxy)methyl]-5-methyl-2-(nitroamino)pyrimidin-4(3*H*)-one (1c). Nitroguanidine (3.26 g, 31.3 mmol) and ester **4c** (10 g, 31.3 mmol) were added to a solution of KOEt prepared from metallic potassium (2.44 g, 62.6 mg-atom) and anhydrous EtOH (250 mL). The reaction mixture was refluxed with stirring for 18 h and concentrated. The residue was dissolved in water (300 mL). Organic materials were extracted with diethyl ether (3×75 mL). The aqueous phase was neutralized with AcOH with stirring. The precipitate that formed was filtered off, washed with water (3×75 mL), cold EtOH (50 mL), and Et_2O (3×25 mL), squeezed on the filter, and dried to a constant weight. The yield of the target product **1c** was 3.71 g (33%), crystalline powder, m.p. 230.5—231.0 °C, R_f 0.26. Found (%): C, 43.55; H, 3.41; Cl, 19.80; N, 15.70. $C_{13}H_{12}N_4O_4Cl_2$ (M = 359.16). Calculated (%): C, 43.47; H, 3.37; Cl, 19.74; N, 15.60. ^{1}H NMR (DMSO-d_6), δ: 1.42 (s, 3 H, Me); 3.44 (s, 3 H, OMe); 6.20 (s, 1 H, CH); 7.51 (t, 1 H, $H(4)_{Ar}$, J = 6.7 Hz); 7.61 (d, 2 H, $H_{Ar}(3)$, $H_{Ar}(5)$, J = 6.7 Hz); 12.71 (s, 1 H, NH); 12.91 (s, 1 H, NH).

6-[(2,6-Difluorophenyl)(methoxy)methyl]-5-methyl-2-(nitroamino)pyrimidin-4(3*H*)-one (1a) was obtained as described for compound **1c** from 3-oxo ester **4a**. Neutralization of the aqueous solution resulted in oil formation. The oil was extracted with EtOAc (3×150 mL). The combined organic extracts were washed with water (4×75 mL) and brine (3×100 mL), dried, filtered, and concentrated. The residue was purified by recrystallization from MeOH with activated charcoal (1 g). Yield 25%, m.p. 282—284 °C (decomp.), R_f 0.22. Found (%): C, 47.80; H, 3.70; F, 11.70; N, 17.24. $C_{13}H_{12}N_4O_4F_2$ (M = 326.26). Calculated (%): C, 47.86; H, 3.71; F, 11.65; N, 17.17. ^{1}H NMR (DMSO-d_6), δ: 1.65 (s, 3 H, Me); 3.43 (s, 3 H, OMe); 5.92 (s, 1 H, CH); 7.21 (t, 2 H, $H_{Ar}(3)$, $H_{Ar}(5)$, J = 9.7 Hz); 7.52—7.62 (m, 1 H, $H_{Ar}(4)$); 12.60 (s, 1 H, NH); 12.88 (s, 1 H, NH).

6-[(2-Chloro-6-fluorophenyl)(methoxy)methyl]-5-methyl-2-(nitroamino)pyrimidin-4(3*H*)-one (1b) was obtained as described for compound **1c** from 3-oxo ester **4b**. Yield 26%, m.p. 201.5—202.5 °C (decomp.), R_f 0.25. Found (%): C, 45.61; H, 3.60; Cl, 10.42; F, 5.54; N, 16.42. $C_{13}H_{12}N_4O_4FCl$ (M = = 342.71). Calculated (%): C, 45.56; H, 3.53; Cl, 10.34; F, 5.54; N, 16.35. ^{1}H NMR (DMSO-d_6), δ: 1.56 (s, 3 H, Me); 3.45 (s, 3 H, OMe); 6.00 (s, 1 H, CH); 7.33 (t, 1 H, $H_{Ar}(4)$, J = 10.0 Hz); 7.52—7.59 (m, 2 H, $H_{Ar}(3)$, $H_{Ar}(5)$); 12.64 (s, 1 H, NH); 12.91 (s, 1 H, NH).

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