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Synthesis of a Precursor of the Antiviral Agent A-315675

V. A. Egorov[a] and F. A. Gimalova[a],*

[a] *Ufa Institute of Chemistry, Ufa Federal Research Center, Russian Academy of Sciences, pr. Oktyabrya 71, Ufa, Bashkortostan, 450054 Russia*
**e-mail: fangim@anrb.ru*

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Abstract—Ethyl 2-(acetylamino)-3-methoxy-3-methylhexanoate, a key precursor of the known pyrrolidine antiviral agent A-315675, was synthesized starting with the readily available acetoacetic ester.

Keywords: neuraminidase inhibitors, A-315675, antiviral activity, acetoacetic ester, allyl bromide, precursors, synthesis

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Antiviral drugs are used for prevention and treatment of seasonal influenza epidemics, and are considered as an economically effective way to reduce the risk of rapid spread of pandemic disease [1, 2]. The main antiviral drugs include M2 ion channel protein inhibitors (adamantane derivatives [3, 4]) and more active neuraminidase inhibitors [5, 6], such as Relenza (Zanamivir) [7], Tamiflu (Oseltamivir) [8], and Peramivir [9].

Fairly recently, researchers from the Abbott have discovered new pyrrolidine neuraminidase inhibitors **1** (A-192558) and **2** (A-315675) [10, 11], which proved quite potent antiviral agents (Scheme 1).

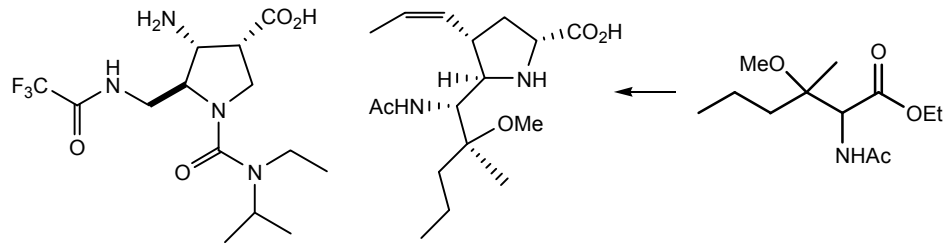
In the present work, searching for synthetic approaches to precursors of compound **2**, we prepared compound **3** starting with acetoacetic acid. Compound **3** was intended to be further used in the synthesis of A-315675 by the [C+NC+CC] coupling scheme [12].

The first step involved the synthesis of oxime **4** from acetoacetic ester by a known procedure. The subsequent reduction of oxime **4** in acetic acid and one -pot acylation in the presence of acetic anhydride gave amide **5** [13] (Scheme 2).

Further on we suggested to prepare hydroxy ester **6** by the Reformatsky reaction of compound **5** with propyl bromide and Zn in DMF. However, the reaction took an unusual pathway to form azirine **7** in a low yield, rather than the expected tertiary alcohol **6** (Scheme 2). The structure of compound **7** was confirmed by NMR spectroscopy and mass spectrometry. We also failed to prepare compound **6** by the reaction of keto ester **5** with propylmagnesium bromide in THF.

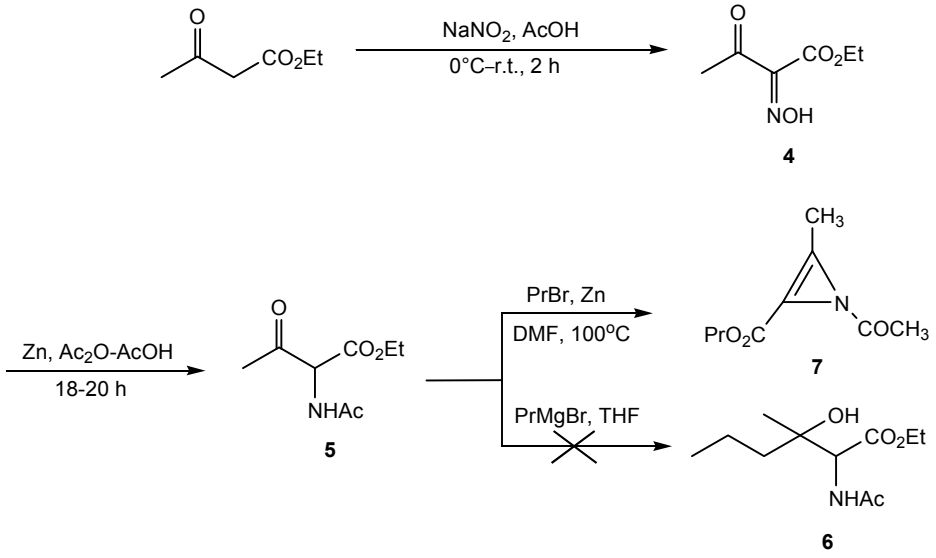
In view of the failure to synthesize compound **3** by the reaction with *n*-PrBr, we chose an alternative version of the Reformatsky reaction (Scheme 3). The reaction of compound **5** with allyl bromide and Zn in DMF formed adduct **8** as a mixture of diastereomers in a good total yield. Compound **8** was then hydrogenated with hydrogen in MeOH in the presence of 10% Pd/C

Scheme 1.



1 (A -192558) **2** (A-315675) **3**

Scheme 2.



to obtain hydroxy ester **6** in a quantitative yield. The methylation of the tertiary OH group in the latter under the action of MeI in DMF in the presence of NaH and catalytic quantities of $Bu_4N^+I^-$ gave the target ester **3** in a moderate yield.

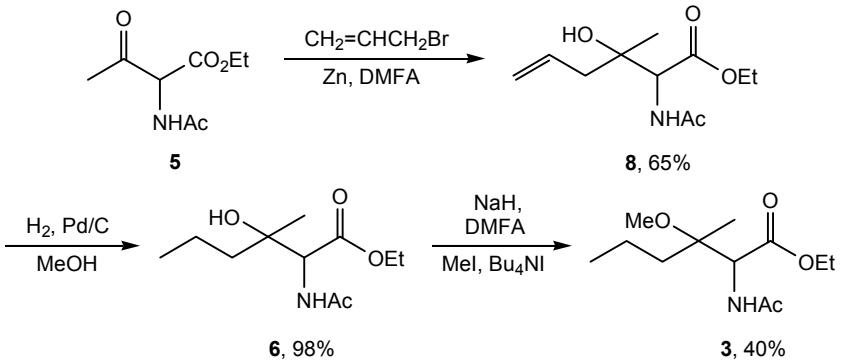
Thus, starting with the readily available acetoacetic ester, we synthesized a key precursor of the known pyrrolidine antiviral agent A-315675, which has all necessary functional groups for further assembly of the target structure.

EXPERIMENTAL

The IR spectra were obtained on a Shimadzu IR-Prestige-21 spectrometer in thin films. The ^1H and ^{13}C NMR spectra were recorded on a Bruker AM-300 spectrometer at 300.13 and 75.47 MHz, respectively, and a Bruker AVANCE-500 spectrometer at 500.13 and 125.77 MHz, respectively, internal reference TMS. The mass spectra were run on a Shimadzu LCMS-2010EV and a Thermo Finnigan MAT 95XP instruments (ionizing voltage 70 eV). Elemental analysis was performed on a EuroVector EURO EA-3000 CHNS analyzer. Reaction progress was monitored by TLC on Sorbfil plates (Russia), development by heating or treatment with alkaline potassium permanganate. The synthesized compounds were isolated by column chromatography on silica gel (Macherey−Nagel, Germany; 30−60 g/g compound).

Ethyl 2-(acetylamino)-3-methoxy-3-methylhexanoate (3). To a cold (0°C) solution of 0.1 g (0.43 mmol) compound **6** in 1.0 mL of DMF, we added 31 mg (0.65 mmol) of 50% NaH and then 0.05 mL (0.86 mmol) of CH_3I and 19.4 mg (0.086 mmol) of Bu_4NI. The mixture was stirred for 48 h and decomposed with NH_4Cl. The aqueous layer was extracted with CH_2Cl_2

Scheme 3.



(3 × 15 mL). The combined organic extracts were dried over $MgSO_4$ and evaporated to isolate 42 mg (40%) of product **6** as oil. Found, %: C 58.43, H 9.67, N 5.58. $C_{12}H_{23}NO_4$. Calculated, %: C 58.75, H 9.45, N 5.71. Mass spectrum, *m/z* (I_{rel}, %): 246 $[M + H]^+$ (2), 228 $[M + H - H_2O]^+$ (100), 214 $[M - OCH_3]^+$ (2), 187 $[M + H - OEt]^+$ (36).

Major isomer. ^{1}H NMR spectrum ($CDCl_3$, 500 MHz), δ, ppm: 0.87 t (3H, CH_3, *J* 7.3 Hz), 1.27 t (3H, CH_3, *J* 7.1 Hz), 1.44 s (3H, CH_3), 1.67 m (4H, CH_2), 2.12 s (3H, CH_3), 3.19 s (3H, OCH_3), 4.18 q (2H, OCH_2, *J* 7.1 Hz), 5.37 s (1H, CH). ^{13}C NMR spectrum ($CDCl_3$, 125 MHz), δ, ppm: 14.16 (CH_3), 14.87 (CH_3), 17.18 (CH_2), 21.01 (CH_3), 21.80 (CH_3), 39.09 (CH_2), 60.99 (C^2), 60.74 (OCH_2), 79.88 (C^3), 172.28 (NHC=O), 170.40 ($\underline{C}O_2Et$).

Minor isomer. ^{1}H NMR spectrum ($CDCl_3$, 500 MHz), δ, ppm: 0.93 t (3H, CH_3, *J* 7.2 Hz), 1.13 s (3H, CH_3), 1.27 t (3H, CH_3, *J* 7.1 Hz), 1.67 m (4H, CH_2), 2.12 s (3H, CH_3), 3.24 s (3H, OCH_3), 4.19 q (2H, OCH_2, *J* 7.0 Hz), 5.54 s (1H, CHN). ^{13}C NMR spectrum ($CDCl_3$, 125 MHz), δ, ppm: 14.11 (CH_3), 14.68 (CH_3), 18.03 (CH_2), 20.28 (CH_3), 21.74 (CH_3), 38.25 (CH_2), 59.01 (C^2), 60.65 (OCH_2), 80.25 (C^3), 170.40 (NHC=O), 172.28 ($\underline{C}O_2Et$).

Ethyl 2-(acetylamino)-3-oxobutanoate (5) was prepared as described in [13]. Yield 70% (after two stages). ^{1}H NMR spectrum ($CDCl_3$, 500 MHz), δ, ppm: 1.22 t (3H, CH_3, *J* 7.1 Hz), 1.99 s (3H, CH_3), 2.30 s (3H, CH_3), 4.18 q (2H, OCH_2, *J* 7.2 Hz), 5.21 d.d (1H, CH, *J* 3.8, 6.6 Hz), 6.97 m (1H, NH). ^{13}C NMR spectrum ($CDCl_3$, 125 MHz), δ, ppm: 13.86 (CH_3), 22.41 (CH_3) 28.01 (CH_3), 62.52 (OCH_2), 63.05 (CHN), 166.12 (NHCO), 170.25 ($\underline{C}O_2Et$), 198.83 (C=O).

Ethyl 2-(acetylamino)-3-hydroxy-3-methylhexanoate (6). To a solution of 0.61 g (2.66 mmol) of compound **8** in 20 mL of MeOH, we added 0.3 g of 10% Pd/C, and the mixture was stirred under hydrogen for 48 h. The catalyst was filtered off, and the filtrate was evaporated to isolate 0.61 g (98%) of product **6** as an oil. Mass spectrum, *m/z* (I_{rel}, %): 232 $[M + H]^+$ (100), 214 $[M + H - H_2O]^+$ (39), 187 $[M + H - OEt]^+$ (36).

Major isomer. ^{1}H NMR spectrum (methanol-d_4, 500 MHz), δ, ppm: 0.92 t (3H, CH_3, *J* 7.2 Hz), 1.23 s (3H, CH_3), 1.28 t (3H, CH_3, *J* 7.2 Hz), 1.49 m (4H, CH_2), 2.03 s (3H, CH_3), 4.19 m (2H, OCH_2), 4.43 s (1H, NCH). ^{13}C NMR spectrum ($CDCl_3$, 125 MHz), δ, ppm: 13.50 (CH_3), 16.44 (CH_2), 21.05 (CH_3), 22.60 (CH_3), 41.66 (CH_2), 59.76 (C^2), 60.79 (OCH_2), 72.72 (C^3), 170.65 (NHC=O), 171.97 ($\underline{C}O_2Et$).

Minor isomer. ^{1}H NMR spectrum (methanol-d_4, 500 MHz), δ, ppm: 0.93 t (3H, CH_3, *J* 7.0 Hz), 1.20 s (3H, CH_3), 1.30 t (3H, CH_3, *J* 7.1 Hz), 1.49 m (4H, CH_2), 2.03 s (3H, CH_3), 4.19 m (2H, OCH_2), 4.48 s (1H, NCH). ^{13}C NMR spectrum ($CDCl_3$, 125 MHz), δ, ppm: 13.09 (CH_3), 16.44 (CH_2), 21.05 (CH_3), 22.32 (CH_3), 41.63 (CH_2), 59.72 (C^2H), 60.79 (OCH_2), 73.11 (C^3), 170.65 (NHC=O), 171.91 ($\underline{C}O_2Et$).

Propyl 1-acetyl-3-methyl-1*H*-azirene-2-carboxylate (7). To a stirred solution of 0.2 g (1.07 mmol) of keto ester **5** and 0.14 mL (1.55 mmol) of propyl bromide in 5 mL of DMF, we added in portions over the course of 15 min 0.105 g (1.61 mmol) of Zn dust. The mixture was stirred for 2 h at 100°C. After cooling to room temperature, 5 mL of saturated aqueous NH_4Cl was added, and the mixture was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were dried over $MgSO_4$, the solvent was evaporated, and the residue was subjected to column chromatography (EtOAc–petroleum ether, 1 : 1) to isolate 50 mg (25%) of compound **7** as an oil. ^{1}H NMR spectrum ($CDCl_3$, 500 MHz), δ, ppm: 0.99 t (3H, CH_3, *J* 7.2 Hz), 1.78 sextet (2H, CH_2, *J* 7.2 Hz), 2.39 s (3H, CH_3), 2.57 s (3H, CH_3), 4.26 t (2H, CH_2, *J* 7.0 Hz). ^{13}C NMR spectrum ($CDCl_3$, 125 MHz), δ, ppm: 10.42 (CH_3), 11.92 (CH_3), 13.70 (CH_3), 22.05 (CH_2), 66.36 (OCH_2), 127.41 (C^3), 155.92 (C^2), 159.43 ($\underline{C}O_2Pr$), 162.51 (NC=O). Mass spectrum, *m/z* (I_{rel}, %): 184 $[M + H]^+$ (100), 225 $[M + H + CH_3CN]^+$ (83%), 142 $[M + H - C_3H_7]^+$ (11%).

Ethyl *N*-acetyl-3-allyl-3-methylserinate (8). To a vigorously stirred solution of 1.0 g (5.34 mmol) of keto ester **5** and 0.686 (8.02 mmol) of allyl bromide in 5 mL of DMF, we added in portions over the course of 15 min 1.10 g (17.0 mmol) of Zn dust. Active reaction accompanied by heat release was observed. After 2 h, the reaction mixture was acidified with saturated aqueous NH_4Cl and extracted with CH_2Cl_2 (3 × 20 mL). The organic layer was dried over $MgSO_4$, the solvent was evaporated, and the residue was subjected to column chromatography (EtOAc–petroleum ether, 1 : 1) to isolate 0.77 g (65%) of product **8** as an oil. IR spectrum, ν, cm^{-1}: 3342, 3338, 3078, 2982, 2939, 1731, 1648, 1603, 1534, 1518, 1446, 1375, 1341, 1296, 1259, 1206, 1157, 1132, 1026, 924. Mass

spectrum, *m/z* (I_{rel}, %): 230 $[M + H]^+$ (70), 212 $[M - OH]^+$ (100%), 187 $[M + H - CH_3CO]^+$ (24).

Major isomer. ^{1}H NMR spectrum ($CDCl_3$, 500 MHz), δ, ppm: 1.20 s (3H, CH_3), 1.28 t (3H, CH_3, *J* 7.0 Hz), 2.19 s (3H, CH_3), 2.26 m (2H, CH_2), 3.04 d (1H, OH, *J* 19.7 Hz), 4.22 m (2H, OCH_2), 4.53 d (1H, CH, *J* 8.7 Hz), 5.13 m (2H, $=CH_2$), 5.83 m (1H, =CH), 7.11 d (1H, NH, *J* 8.9 Hz). ^{13}C NMR spectrum ($CDCl_3$, 125 MHz), δ, ppm: 14.06 (CH_3), 23.20 (CH_3), 23.94 (CH_3), 43.55 (CH_2), 58.83 (CHN), 61.88 (OCH_2), 73.44 (C^3), 120.04 ($=CH_2$), 132.10 (=CH), 170.95 ($\underline{C}O_2Et$), 173.01 (NHC=O).

Minor isomer. ^{1}H NMR spectrum ($CDCl_3$, 500 MHz), δ, ppm: 1.20 s (3H, CH_3), 1.29 t (3H, CH_3, *J* 7.0 Hz), 2.19 s (3H, CH_3), 2.26 m (2H, CH_2), 3.08 d (1H, OH, *J* 18.3 Hz), 4.22 m (2H, OCH_2), 4.56 d (1H, CH, *J* 8.9 Hz), 5.13 m (2H, $=CH_2$), 5.83 m (1H, =CH), 7.07 (1H, NH, *J* 8.2 Hz). ^{13}C NMR spectrum ($CDCl_3$, 125 MHz), δ, ppm: 14.03 (CH_3), 23.20 (CH_3), 23.71 (CH_3), 43.85 (CH_2), 59.27 (CHN), 61.93 (OCH_2), 73.81 (C^3), 119.64 ($=CH_2$), 132.29 (=CH), 170.90 ($\underline{C}O_2Et$), 173.01 (NHC=O).

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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