ISSN 1070-4280, Russian Journal of Organic Chemistry, 2008, Vol. 44, No. 2, pp. 288–291. © Pleiades Publishing, Ltd., 2008.
Original Russian Text © S.G. Ryazanov, S.I. Selivanov, D.V. Dar'in, P.S. Lobanov, A.A. Potekhin, 2008, published in Zhurnal Organicheskoi Khimii, 2008, Vol. 44, No. 2, pp. 292–295.

Chemoselective Cyclocondensation of α-Acylacetamidines with 2-Methylsulfanyl-4,6-dichloropyrimidine-5-carbaldehyde

S. G. Ryazanov, S. I. Selivanov, D. V. Dar'in, P. S. Lobanov, and A. A. Potekhin

St. Petersburg State University, St. Petersburg, 198504 Russia

Received March 14, 2007

Abstract—Cyclocondensation of α-acylacetamidine with 2-methylsulfanyl-4,6-dichloropyrimidine-5-carbaldehyde proceeds chemo- and regioselectively involving replacement by the α-carbon of the amidine of the chlorine in the aromatic ring and a reaction of the amino group with the formyl group.

DOI: 10.1134/S1070428008020176

The cyclocondensation of amidines with acceptor-substituted *ortho*-fluorobenzaldehydes is a simple and convenient procedure for the synthesis of 4-unsubstituted quinazolines. Benzamidines in this reaction behave like *N,N'*-dinucleophiles [1]. Yet it is known that amidines with an electron-withdrawing substituent (in particular, acyl moiety) in the α-position with respect to the amidine fragment may behave in reactions with 1,3-dielectrophiles also like N,C-dinucleophiles [2, 3]. We recently reported that some such amidines reacted with 5-nitro-2-fluorobenzaldehyde as N,C-dinucleophiles yielding predominantly 3-aminoisoquinolines [4, 5].

C-Nucleophilic nature of α-acylacetamidines **II** originates evidently from their existence partly or totally in a tautomer form of endiamines $(H_2N)_2C{=}CHCOR$ [5].

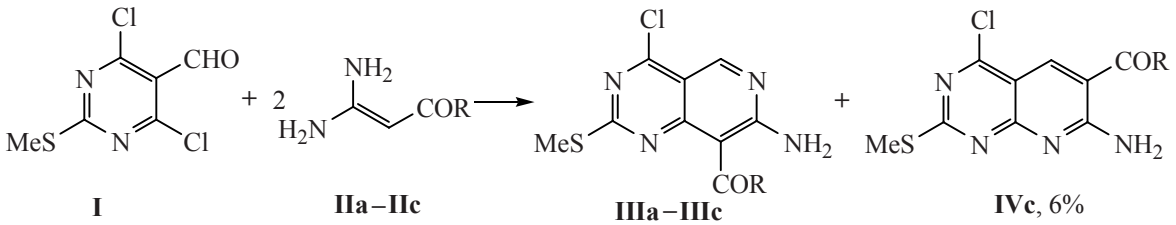
We investigated the possibility to involve into analogous cyclocondensation 2-methylsulfanyl-4,6-dichloropyrimidine-5-carbaldehyde (**I**) also including a labile halogen atom adjacent to the formyl group and studied the chemoselectivity of this reaction (the preliminary communication see [6]).

The reactions of amidines **IIa–IIc** with aldehyde **I** were carried out in anhydrous DMF in the presence of molecular sieves 4 E at room temperature and vigorous stirring. The amidine was taken in a two-fold excess. The attempts to use an equivalent amount of amidine in the presence of potassium carbonate or triethylamine as bases led to a considerable tarring and to reduced yield of the reaction products.

The main isolated reaction products were pyrido[4,3-*d*]pyrimidines **IIIa–IIIc** (Scheme 1). In reaction with amidine **IIc** in the NMR spectrum of the reaction mixture signals were observed belonging presumably to an isomeric compound **IVc**. The content of the compound in the reaction mixture amounted to about 10%, and we failed to isolate it. The structure of pyrido[4,3-*d*]-pyrimidines **III** were established by means of 1H and 13C NMR spectroscopy, applying also correlation spectra NOESY where cross-peaks were present between the signals of the protons of the methylsulfanyl group and the protons of the substituent at the carbonyl group.

Hence α-acylacetamidines **II** react with 2-methylsulfanyl-4,6-dichloropyrimidine-5-carbaldehyde (**I**) and

Scheme 1.



I **IIa–IIc** **IIIa–IIIc** **IVc**, 6%

R = $(CH_2)_2N(CH_2)_2$ (**a**, 51%), EtO (**b**, 86%), Ph (**c**, 57%).

5-nitro-2-fluorobenzaldehyde with the same chemoselectivity, namely: The α-carbon of the amidine replaces the chlorine in the aromatic ring and the amino group adds to the formyl group carbon.

Two cyclocondensation mechanisms are presumable for the reaction between α-acylacetamidines **II** with aldehyde **I**. They differ by the sequence of two stages where one is the nucleophilic substitution of the activated chlorine by the α-carbon of the amidine, and the other is the bond formation between the nitrogen of the amidine and the formyl group carbon (see Scheme 2).

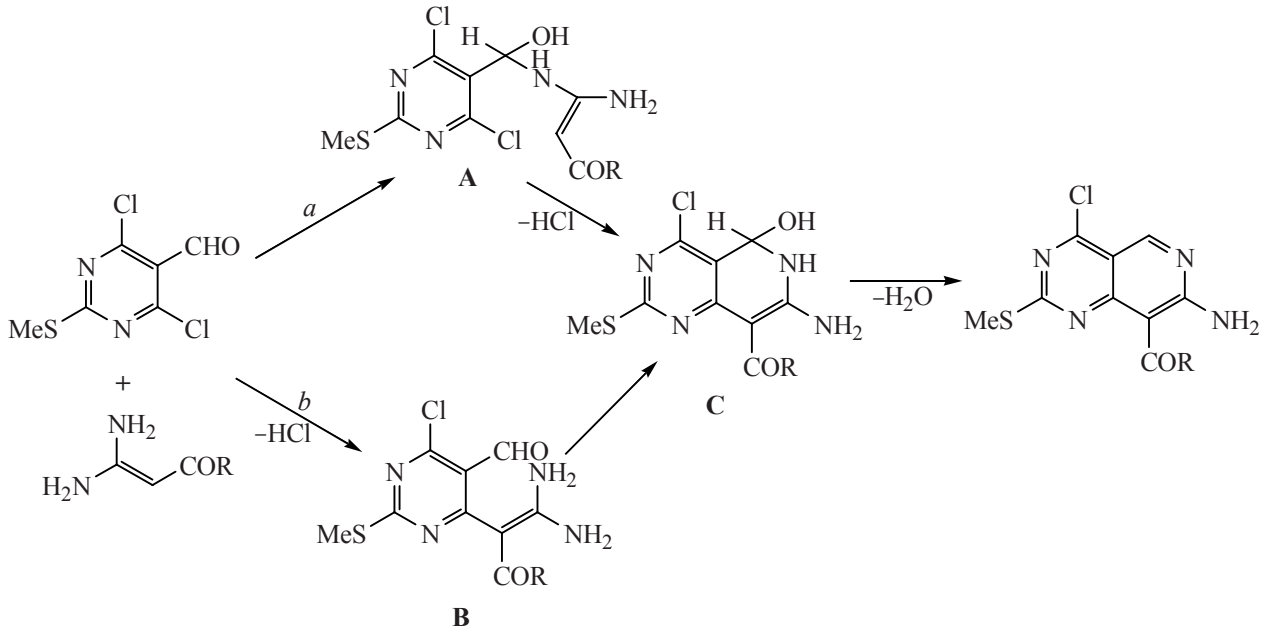
We attempted to establish the sequence of these two stages by performing the reaction in an NMR tube while intermittently registering the ^{1}H NMR spectra. We hoped that in event of considerably different rates of these stages we perhaps would be able to fix the spectra of intermediates **A** or **B**. Successful applications of this approach were described [7]. As the object of the study we selected the reaction of aldehyde **I** with amidine **IIb** for the reaction proceeded with the greatest yield, and the initial conpounds and the reaction products were well soluble. The reaction was carried out in DMSO-d_6 at 27°C.

The first spectrum was registered about 30 s after mixing the reagents. The main components of the reaction mixture at this instant proved to be intermediate **C** [δ 1.25 (3H, CH_3), 2.51 (3H, SCH_3), 4.15 (2H, CH_2), 5.76 (1H, OH), 6.39 (1H, CH), 8.33 ppm (1H, NH)] and ethoxycarbonylacetamidine hydrochloride. Besides small amounts of the initial compounds and of the cyclocondensation product **IIIb** were present. This data showed that at room temperature in DMSO within 30 s both stages preceding the formation of compound **C** were virtually completed, and we failed to fix the spectra of intermediate **A** or **B**. In the further spectra we observed the decrease in content of intermediate **C** and growth of the amount of pyrido[4,3-*d*]pyrimidine **IIIb**. Therefore it is possible to conclude that the limiting stage in the cyclocondensation of aldehyde **I** with amidine **IIb** is the water molecule elimination from the structure **C**, and the reaction as showed the last spectrum results in nearly quantitative yield. These experimental results cannot reveal the sequence of stages preceding the formation of intermediate **C**.

EXPERIMENTAL

^{1}H and ^{13}C NMR spectra were registered on a spectrometer Bruker DPX 300 at operating frequencies 300.130 (^{1}H) and 75.03 (^{13}C) MHz; solvent DMSO-d_6 or $CDCl_3$, as internal references served residual signals δ 7.26 ($CHCl_3$) and 2.50 ppm (DMSO-d_5) for ^{1}H nuclei and δ 77.7 ($CDCl_3$) and 39.7 ppm (DMSO-d_6) for ^{13}C nuclei. The coupling constants in the proton spectra were measured to the first approximation. Elemental analysis was carried out on a CHN-analyzer Hewlett-Packard 185B. The purity of compounds was checked

Scheme 2.



and the reaction progress was monitored by TLC on Silufol UV-254 plates.

(1-Pyrrolidinyl)carbonylacetamidine (IIa). To a mixture of 16 g (0.116 mol) 3-oxo-3-(1-pyrrolidinyl)-propionitrile, 6.45 g (0.14 mol) of ethanol, 2.1 g (0.116 mol) of water, and 15 ml of ethyl ether at room temperature while stirring was added dropwise within 45 min 9.5 ml (15.5 g, 0.13 mol) of thionyl chloride. The reaction mixture was left standing at room temperature for 12 h, then it was diluted with 100 ml of ethyl ether, the precipitated crystals were filtered off, mixed with 100 ml of ethyl acetate, the mixture was cooled, and a cold solution of 36 g (0.26 mol) of potassium carbonate in 100 ml of water was added thereto. The resulting mixture was thoroughly stirred, the organic layer was separated, the water layer was extracted with ethyl acetate, the combined organic solutions were dried with calcium chloride, and the solution was evaporated at a reduced pressure. The residue was dissolved in 120 ml of anhydrous ethanol, 6.32 g (0.12 mol) of ammonium chloride was added, and the reaction mixture was boiled for 13 h. Then it was cooled to room temperature, excess ammonium chloride was filtered off, the filtrate was evaporated to dryness, on the residue 200 ml of ethyl ether was poured, the mixture was thoroughly stirred, and the colorless crystals were filtered off. Yield of amidine **IIa** hydrochloride 12.4 g (56%), mp 130–140°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.70–1.95 m [4H, N(CH_2CH_2)$_2$], 3.30 m, 3.42 m [4H, N(CH_2CH_2)$_2$], 3.59 s (2H, CH_2), 8.80–9.00, 9.10–9.30 (4H, H_2N–C=NH_2Cl).

To a solution of sodium ethylate prepared from 0.84 g (36.5 mmol) of sodium metal in 100 ml of anhydrous ethanol was added a solution of 7.0 g (36.5 mmol) of amidine **IIa** hydrochloride in 150 ml of anhydrous ethanol, the mixture was cooled, and the precipitated crystals of sodium chloride were filtered off. The filtrate was evaporated at a reduced pressure to a volume of 30 ml (bath temperature not exceeding 40°C), the residue was cooled to 0°C, and the precipitated crystals were filtered off. Yield 3.51 g (62%) of amidine **IIa**, mp 168–169°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.61–1.92 m [4H, N(CH_2CH_2)$_2$], 3.05–3.25 m [4H, N(CH_2CH_2)$_2$], 3.83 s (1H, =CH), 9.10–9.30, 5.00–9.00 (4H, H_2N–C–NH_2).

Ethoxycarbonylacetamidine (IIb). To a solution of sodium ethylate prepared from 0.2 g (8.7 mmol) of sodium metal in 10 ml of anhydrous ethanol was added a solution of 1.5 g (9 mmol) of ethoxycarbonylacetamidine hydrochloride [8] in 25 ml of anhydrous ethanol, the mixture was cooled, and the precipitated crystals of sodium chloride were filtered off. The filtrate was evaporated at a reduced pressure (bath temperature not exceeding 40°C). To the residue 50 ml of ethyl ether was poured, the insoluble impurities were filtered off, the filtrate was evaporated at a reduced pressure to obtain 0.8 g (6.2 mmol, 70%) of amidine **IIb**, mp 78–79°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.09 t (3H, CH_3), 3.77 s (1H, =CH), 3.86 q (2H, CH_2), 5.60–5.90 (2H, NH_2), 6.00–7.50 (2H, NH_2).

7-Amino-2-methylsulfanyl-8-(pyrrolidin-1-yl-carbonyl)-4-chloropyrido[4,3-*d*]pyrimidine (IIIa). A solution of 0.3 g (1.3 mmol) of aldehyde **I** [9] in 3 ml of anhydrous DMF at room temperature while stirring was added dropwise within 30 min to a mixture of 0.42 g (2.8 mmol) of amidine **IIa** and 1 g of molecular sieves 4 E. The reaction mixture was maintained for 90 min at room temperature, the molecular sieves were filtered off, the filtrate was poured into 20 ml of water, extracted with chloroform, the organic layer was twice washed with water, dried with sodium sulfate, and the solvent was evaporated at a reduced pressure. The reaction product was purified by column chromatography (gradient elution with the mixture hexane–chloroform with chloroform content growing from 10 to 60%, then elution with the mixture hexane–chloroform–acetone, 3:6:1). Yield 0.22 g (51%), mp 225–230°C. A sample pure for analysis was obtained by recrystallization from acetonitrile. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.70–2.00 m [4H, N(CH_2CH_2)$_2$], 2.50 s (3H, SCH_3), 3.00–3.70 m [4H, N(CH_2CH_2)$_2$], 7.19 s (2H, NH_2), 9.00 s (1H, H^5). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 14.7 (SCH_3), 25.0, 26.4 [N(CH_2CH_2)$_2$], 46.5, 48.0 [N(CH_2CH_2)$_2$], 104.5 (C^8), 110.8 (C^{4a}), 152.2 (C^7), 152.9 (C^5), 160.3, 161.9 ($C^{4,8a}$), 165.6 [CON(CH_2CH_2)$_2$], 173.2 (C^2). Found, %: C 48.30; H 4.42; N 21.32. $C_{13}H_{14}ClN_5OS$. Calculated, %: C 48.22; H 4.36; N 21.63.

Ethyl 7-amino-2-methylsulfanyl-4-chloropyrido-[4,3-*d*]pyrimidine-8-carboxylate (IIIb. A solution of 0.3 g (1.3 mmol) of aldehyde **I** in 3 ml of anhydrous DMF at room temperature while stirring was added dropwise within 80 min to a mixture of 37 g (2.8 mmol) of amidine **IIb** and 1 g of molecular sieves 4 E. The reaction mixture was maintained for 20 min at room temperature and then 2 h at –15°C. The precipitated crystals and molecular sieves were filtered off, thoroughly washed with water, dried, mixed with 20 ml

of chloroform, the molecular sieves and insoluble impurities were filtered off, and the filtrate was evaporated at a reduced pressure. Yield 0.36 g (86%), mp 157–159°C (from acetonitrile). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.32 t (3H, CH_3), 2.56 s (3H, SCH_3), 4.34 q (2H, CH_2), 7.93 s (2H, NH_2), 9.05 s (1H, H^5). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 14.1 (OCH_2CH_3), 14.2 (SCH_3), 61.0 (OCH_2CH_3), 95.6 (C^8), 110.0 (C^{4a}), 154.6 (C^7), 154.8 (C^5), 160.9 (C^4), 162.3 (C^{8a}), 167.5 ($CO_2CH_2CH_3$), 173.3 (C^2). Found, %: C 44.07; H 3.80; N 18.72. $C_{11}H_{11}ClN_4O_2S$. Calculated, %: C 44.22; H 3.71; N 18.75.

7-Amino-8-benzoyl-2-methylsulfanyl-4-chloropyrido[4,3-*d*]pyrimidine (IIIc). A solution of 0.3 g (1.3 mmol) of aldehyde **I** in 3 ml of anhydrous DMF at room temperature while stirring was added dropwise within 80 min to a mixture of 0.45 g (2.8 mmol) of benzoylacetamidine (**IIc**) [10] and 1 g of molecular sieves 4 E. The mixture was maintained 20 min at room temperature and 2 h at –15°C. The precipitated crystals and molecular sieves were filtered off, thoroughly washed with water, dried, mixed with 20 ml of chloroform, the molecular sieves and insoluble impurities were filtered off, and the filtrate was evaporated at a reduced pressure. The residue was subjected to column chromatography (gradient elution with the mixture hexane–ether with ether content growing from 10 to 50%). Yield 0.255 g (57%), mp 213–215°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.67 s (3H, SCH_3), 7.41–7.66 m (5H, Ph), 7.84 s (2H, NH_2), 9.13 s (1H, H^5). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 13.5 (SCH_3), 103.2 (C^8), 109.8 (C^{4a}), 129.1 (Ph^m), 129.6 (Ph^o), 133.2 (Ph^p), 141.3 (Ph^i), 155.1 (C^7), 155.3 (C^5), 161.0, 161.9 ($C^{4, 8a}$), 171.6 (C^2), 196.6 (COPh). Found, %: C 54.20; H 3.48; N 16.97. $C_{15}H_{11}ClN_4OS$. Calculated, %: C 54.46; H 3.35; N 16.94.

The signals of 7-amino-6-benzoyl-2-methylsulfanyl-4-chloropyrido[2,3-*d*]pyrimidine (**IVc**) detected in the ^{1}H NMR spectrum of the reaction mixture before the chromatographic separation were as follows, δ, ppm: 2.58 s (3H, SCH_3), 8.22 s (1H, H^5).

REFERENCES

1. Kotsuki, H., Sakai, H., Morimoto, H., and Suenaga, H., *Synlett.,* 1999, p. 1993.
2. Sollhuber-Kretzer, M., and Troschutz, R., *Arch. Pharm*., 1982, vol. 315, p. 783.
3. Batt, D.G. and Hoghton, G.C., *J. Heterocycl. Chem*., 1995, vol. 32, p. 963.
4. Dar'in, D.V., Selivanov, S.I., Lobanov, P.S., and Potekhin, A.A., *Khim. Geterotsikl. Soedin*., 2002, p. 1155.
5. Dar'in, D.V., Selivanov, S.I., Lobanov, P.S., and Potekhin, A.A., *Khim. Geterotsikl. Soedin*., 2004, p. 1036.
6. Ryazanov, S.G., Selivanov, S.I., Dar'in, D.V., Lobanov, P.S., and Potekhin, A.A., *Vestn. SPbGU, Ser. 4*, 2005, no. 2, p. 138.
7. Katritzky, A.R., Ostercamp, D.L., and Yousaf, T.I., *Tetrahedron,* 1987, vol. 43, p. 5171.
8. McElvain, S.M. and Tate, B.E., *J. Am. Chem. Soc.,* 1951, vol. 73, p. 2760.
9. Santilli, A.A., Han, Kim, D., and Wanser, S.V., *J. Heterocycl. Chem.,* 1971, vol. 8, p. 445.
10. Roth, B. and Smith, J. M., *J. Am. Chem. Soc*., 1949, vol. 71, p. 616.