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CYCLOCONDENSATION OF α-ACYLACETAMIDINES WITH ESTERS OF 2-FLUORO-5-NITROBENZOIC AND 4-CHLORO-2-METHYL-5-PYRIMIDINE-CARBOXYLIC ACIDS

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The cyclocondensation of α-acylacetamidines with esters of 2-fluoro-5-nitrobenzoic and 4-chloro-2-methyl-5-pyrimidinecarboxylic acids leads to condensed azines. The reaction proceeds chemoselectively such that the α-carbon atom of the amidine replaces the halogen atom in the aromatic ring, while the amino group reacts with the ester group.

Keywords: α-acylacetamidines, C,N-dinucleophiles, aromatic dielectrophiles, enediamines, 1-isoquinolinones, pyrido[4,3-*d*]pyrimidines, aromatic nucleophilic substitution, cyclocondensation.

In a continuation of our study of the reactivity of α-acylacetamidines with aromatic dielectrophiles [1, 2], we investigated the reactions of amidines **1a-c** with esters **2** and **4**. α-Acylacetamidines **1a-c** exist in DMSO-d_6 solution in the enediamine tautomeric form, which accounts for their C,N-dinucleophilic properties upon reaction with dielectrophiles.

α-Acylacetamidines **1a-c** act as C,N-dinucleophiles in their reactions with ester **2** and selectively give the corresponding isoquinolines **3** in good yield. The reactions with amidines **1a** and **1b** were carried out at room temperature. The reaction with benzoylacetamidine **1c** proceeds more slowly and required heating to 50°C.

We should note that our proposed method for the synthesis of isoquinolines **3** complements a recently reported method for the synthesis of analogous 3-aminoisoquinolines from amides of 2-chloro-5-nitrobenzoic acid and aryl and hetaryl acetonitriles [3, 4].

The reaction of amidines **1a** and **1b** with ester **4** proceeds smoothly at room temperature over 60-100 h and pyrido[4,3-*d*]pyrimidines **5a** and **5b** are formed in high yield. The reaction with amidine **1c** proved rather slow as in the case of ester **2** but significant tar formation occurred upon attempting to carry out this reaction with heating. On the other hand, carrying out this reaction at room temperature required 60 days. The major product was also pyrido[4,3-*d*]pyrimidine **6c**, which was isolated chromatographically as a mixture of *E*- and *Z*-isomers as indicated by the double set of signals in the ^{1}H and ^{13}C NMR spectra.

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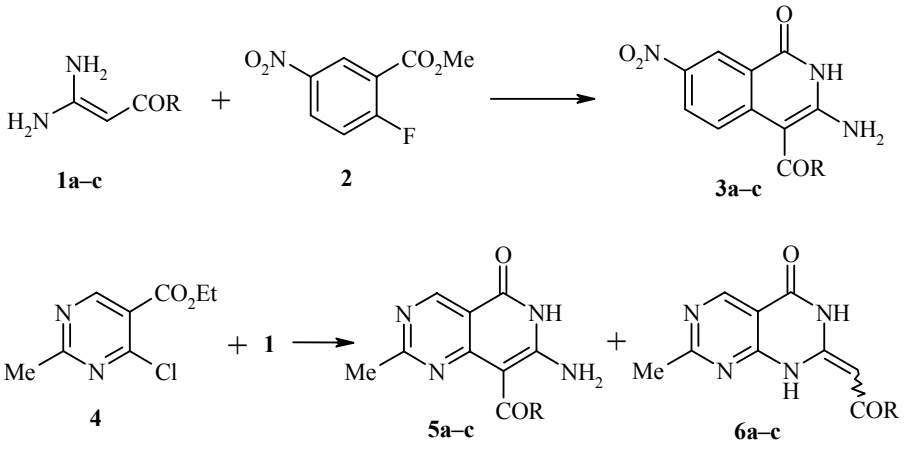


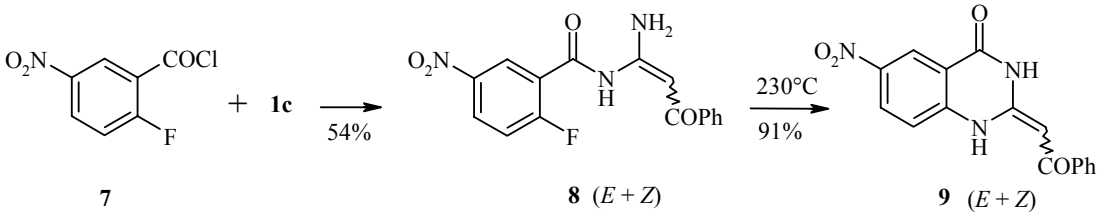
1, **3**, **5 a** R = $N(CH_2)_4$, **b** R = OEt; **1**, **3**, **5**, **6 c** R = Ph

Yield, %: **3 a** 80, **b** 83, **c** 57; **5 a** 85, **b** 81, **c** 64; **6 c** 5

The structures of all isoquinolines **3** and pyrido[4,3-*d*]pyrimidines **5a** and **5b** were proven by ^{1}H and ^{13}C NMR spectroscopy as well as by their NOESY correlational spectra, in which cross peaks were observed between the signals of the protons of the substituent R and signals of the protons H-5 for the isoquinolines and the methyl group at C-2 for the pyrido[4,3-*d*]pyrimidines, indicating an NOE between these protons. The structure of pyrido[4,3-*d*]pyrimidine **5c**, for which the corresponding NOE in the NOESY spectrum was not observed, was confirmed by the chemical shift of the ring carbonyl group carbon atom (C-5, 161.1 ppm), which depends strongly on the arrangement of the nitrogen atom and carbonyl group in the ring (chemical shifts for C-2 and C-4 in 2- and 4-pyridones are 162.3 and 175.7 ppm, respectively [5]), and corresponds within 1 ppm to the chemical shifts of the analogous carbon atoms in isoquinolines **3** and pyrido[4,3-*d*]pyrimidines **5a** and **5b**.

The reactivities of amidines **1a-c** toward ester **4** differ strongly and correlate qualitatively with the electronic properties of the substituents at the carbonyl group. Amidine **1a**, which has a strong electron-donor pyrrolidinyl substituent, reacts over 60 h, while amidine **1b** (OEt) requires 100 h and amidine **1c** requires 1500 h. We may assume that the reaction commences as nucleophilic replacement of the chlorine atom by the carbon nucleophilic site and, then, rapid cyclization occurs with participation of the amino group. Thus, the rate of the reaction is a function of the nucleophilicity of the α-carbon atom of the amidine, which depends on the electronic properties of the substituent at the amidine carbonyl group.

The carbonyl carbon atom in acid chloride **7** is much more electrophilic than aromatic atoms C-2. Thus, we might expect the formation of other products in the reaction of compound **7** with α-acylacetamidines. The reaction of compound **7** with amidine **1b** led to a complex mixture of many components, which could not be separated or analyzed. On the other hand, a synthetic result was achieved with the less reactive amidine **1c**. This reaction was carried out with a two-fold excess of amidine.



The initially formed N-benzoylation product **8** was isolated as a mixture of *E*- and *Z*- isomers. Upon heating above the melting point, these isomers cyclize to give quinazoline **9** in high yield.

The use of triethylamine leads to more tar formation and significantly reduces the yield of N-benzoylation product **8**, while less basic pyridine does not hinder the formation and precipitation of the starting amidine.

EXPERIMENTAL

The ^{1}H and ^{13}C NMR spectra were taken on a Bruker DPX 300 spectrometer at 300 and 75 MHz, respectively, in DMSO-d_6 as the solvent. The signals of the solvent at δ 2.50 ppm (for the ^{1}H NMR spectra) and δ 39.7 ppm (for the ^{13}C NMR spectra) were used as the internal standard. The coupling constants in the ^{1}H NMR spectra were measured to the first-order approximation. The elemental analysis was carried out on a Hewlett-Packard HP-185B CHN-analyzer. The purity of the compounds and reaction course were followed by thin-layer chromatography on Silufol UV-254 plates.

3-Amino-7-nitro-4-pyrrolidinocarbonylisoquinolin-1(2H)-one (3a). A mixture of ester **2** [6] (0.3 g, 1.5 mmol), amidine **1a** [2] (0.31 g, 2 mmol), and DMF (2 ml) was stirred at room temperature for 72 h and then added to water (35 ml). The crystals formed were filtered off and dried at 130°C to give isoquinolinone **3a** (0.36 g, 80%). An analytically pure sample was obtained by recrystallization from ethanol, mp 335-344°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.83 (4H, m, N(CH$_2$C$\underline{\text{H}}_2$)$_2$); 3.15 (1H, m, N(C$\underline{\text{H}}_2$CH$_2$)$_2$); 3.26 (1H, m, N(C$\underline{\text{H}}_2$CH$_2$)$_2$); 3.53 (2H, m, N(C$\underline{\text{H}}_2$CH$_2$)$_2$); 6.47 (2H, s, NH$_2$); 7.24 (1H, d, *J* = 9.0, H-5); 8.20 (1H, dd, *J* = 2.3 and *J* = 9.0, H-6); 8.72 (1H, d, *J* = 2.3, H-8); 11.24 (1H, s, NH). ^{13}C NMR spectrum, δ, ppm: 25.0, 26.3 (N(CH$_2$$\underline{\text{C}}H_2$)$_2$); 46.3, 47.7 (N($\underline{\text{C}}H_2CH_2$)$_2$); 92.8 (C-4); 118.0 (C-4a); 123.3 (C-5); 124.7 (C-6); 127.5 (C-8); 141.2, 143.2 (C-7, C-8a); 148.4 (C-3); 161.6 (C-1); 165.0 ($\underline{\text{C}}$ON(CH$_2$CH$_2$)$_2$). Found, %: C 55.64; H 4.75; N 18.34. $C_{14}H_{14}N_4O_4$. Calculated, %: C 55.63; H 4.67; N 18.53.

Ethyl Ester of 3-Amino-7-nitro-1-oxo-1,2-dihydro-4-isoquinolinecarboxylic Acid (3b). A solution of ester **2** (0.33 g, 1.65 mmol) and amidine **1b** [2] (0.22 g, 1.7 mmol) in DMF (3 ml) was maintained for 80 h at room temperature and then poured into water (30 ml). The crystalline precipitate was filtered off and dried at 130°C to give compound **3b** (0.38 g, 83%); mp 336-339°C (decomp.). An analytical sample was prepared by recrystallization from acetonitrile. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.36 (3H, t, *J* = 7.3, CH$_3$); 4.32 (2H, q, *J* = 7.3, CH$_2$); 7.68 (2H, s, NH$_2$); 8.26 (1H, dd, *J* = 2.2 and *J* = 9.2, H-6); 8.55 (1H, d, *J* = 9.2, H-5); 8.72 (1H, d, *J* = 2.2, H-8); 11.37 (1H, s, NH). ^{13}C NMR spectrum, δ, ppm: 14.6 (CH$_3$); 60.5 (CH$_2$); 83.4 (C-4); 119.2 (C-4a); 123.3 (C-5); 125.5 (C-6); 126.9 (C-8); 141.5, 143.5 (C-7, C-8a); 155.1 (C-3); 160.6 (C-1); 167.1 ($\underline{\text{C}}$O$_2$Et). Found, %: C 51.66; H 4.02; N 15.20. $C_{12}H_{11}N_3O_5$. Calculated, %: C 51.99; H 4.00; N 15.16.

3-Amino-4-benzoyl-7-nitro-1(2H)-isoquinolinone (3c). A solution of ester **2** (0.33 g, 1.65 mmol) and amidine **1c** [7] (0.28 g, 1.7 mmol) in DMF (3 ml) was maintained for 20 h at room temperature and then heated at 55°C for an additional 20 h. The mixture was poured into water (25 ml). The solution was decanted off the oil formed, which was heated at reflux in acetonitrile (15 ml) and cooled. The crystalline precipitate was filtered off and dried to give isoquinolinone **3c** (0.26 g). A crystalline precipitate formed from the aqueous mother liquor, which was heated at reflux in acetonitrile (5 ml) and cooled. An additional compound **3c** (30 mg) was filtered off. The total yield of **3c** was 0.29 g (57%); mp 328-330°C (decomp.). An analytical sample was obtained by recrystallization from acetonitrile. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 6.84 (1H, d, *J* = 8.7, H-5); 7.39-7.62 (5H, m, C$_6$H$_5$); 7.70 (2H, s, NH$_2$); 7.89 (1H, d, *J* = 8.7, H-6); 8.70 (1H, s, H-8); 11.54 (1H, s, NH). ^{13}C NMR spectrum, δ, ppm: 93.6 (C-4); 119.1 (C-4a); 123.4 (C-5); 125.5, 125.9 (C-6, C-8); 128.9 (*m*-C$_6$H$_5$); 129.1 (*o*-C$_6$H$_5$); 132.1 (*p*-C$_6$H$_5$); 141.2, 141.5 (*ipso*-C$_6$H$_5$, C-7); 144.2 (C-8a); 154.0 (C-3); 161.0 (C-1); 193.5 ($\underline{\text{C}}$OC$_6$H$_5$). Found, %: C 62.15; H 3.65; N 13.60. $C_{16}H_{11}N_3O_4$. Calculated, %: C 62.14; H 3.58; N 13.59.

7-Amino-2-methyl-8-pyrrolidinocarbonylpyrido[4,3-*d*]pyrimidin-5(6H)-one (5a). A solution of ester **4** [8] (0.34 g, 1.7 mmol) and amidine **1a** (0.71 g, 4.6 mmol) in DMF (3 ml) was maintained for 60 h at room temperature. The solvent was distilled off at reduced pressure. The residue was purified by chromatography on a column packed with 60 g silica gel. Chloroform methanol served as the eluent. The methanol fraction was gradually increased from 1 to 10%. The yield of **5a** was 0.39 g (85%); mp 340-345°C (decomp.). An analytical sample was prepared by recrystallization from 1:1 acetonitrile–methanol. ^{1}H NMR spectrum, δ, ppm: 1.70-2.00 (4H, m, N($CH_2C\underline{H}_2)_2$); 2.51 (3H, s, CH_3); 3.10-3.60 (4H, m, N($C\underline{H}_2CH_2)_2$); 6.55 (2H, s, NH_2); 8.89 (1H, s, H-4); 11.10 (1H, s, NH). ^{13}C NMR spectrum, δ, ppm: 24.4, 25.8 (N($CH_2\underline{C}H_2)_2$); 26.7 (CH_3); 45.9, 47.4 (N($\underline{C}H_2CH_2)_2$); 91.3 (C-8); 108.9 (C-4a); 152.4 (C-7); 156.8 (C-4); 157.1 (C-8a); 161.1 (C-5); 164.5 ($\underline{C}ON(CH_2CH_2)_2$); 169.9 (C-2). Found, %: C 57.26; H 5.60; N 25.64. $C_{13}H_{15}N_5O_2$. Calculated, %: C 57.13; H 5.53; N 25.63.

Ethyl Ester of 7-Amino-2-methyl-5-oxo-5,6-dihydropyrido[4,3-*d*]pyrimidine-8-carboxylic Acid (5b). A solution of ester **4** (0.34 g, 1.7 mmol) and amidine **1b** (0.6 g, 4.6 mmol) in DMF (3 ml) was maintained for 100 h at room temperature and then cooled to -10°C. The crystalline precipitate was filtered off, thoroughly washed with water and hot acetonitrile, and dried to give compound **5b** (0.34 g, 81%); mp 300-302°C (decomp.). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.31 (3H, t, *J* = 7.3, CH_3); 2.56 (3H, s, CH_3); 4.24 (2H, q, *J* = 7.3, CH_2); 7.65 (2H, s, NH_2); 8.93 (1H, s, H-4); 11.27 (1H, s, NH). ^{13}C NMR spectrum, δ, ppm: 14.5 ($OCH_2\underline{C}H_3$); 26.9 (CH_3); 59.9 ($O\underline{C}H_2CH_3$); 84.5 (C-8); 109.7 (C-4a); 156.7 (C-7); 156.8 (C-4); 159.2 (C-8a); 161.0 (C-5); 167.4 ($\underline{C}O_2CH_2CH_3$); 169.9 (C-2). Found, %: C 53.11; H 4.84; N 22.26. Calculated: % $C_{11}H_{12}N_4O_3$: C 53.22; H 4.87; N, 22.57.

7-Amino-8-benzoyl-2-methylpyrido[4,3-*d*]pyrimidin-5(6H)-one (5c) and 2-(Benzoylmethylene)-7-methyl-2,3-dihydropyrimido[4,5-*d*]pyrimidin-4(1H)-one (6c). A solution of ester **4** (0.3 g, 1.5 mmol) and amidine **1c** (0.6 g, 3.7 mmol) in DMF (3 ml) was maintained for 60 days at room temperature. The solvent was distilled off at reduced pressure and the residue was subjected to chromatography on a column packed with 60 g silica gel using chloroform–methanol as the eluent. The methanol fraction was gradually raised from 0 to 7%. The first fraction was composed of highly impure pyrimido[4,5-*d*]pyrimidine **6c** as a 1:1 mixture of *E*- and *Z*- isomers. The yield after recrystallization from methanol was 20 mg (5%); mp 318-322°C. ^{1}H NMR spectrum, δ, ppm: 2.61, 2.64 (3H, s, CH_3); 6.95 (1H, s, =CH); 7.4-7.9 (5H, m, C_6H_5); 8.95, 8.97 (1H, s, H-5); 11.3-12.8 (1H, s, NH); 13.65 (0.5H, s, NH); 14.7 (0.5H, s, NH). Found, %: C 63.89; H 4.72; N 18.24. $C_{15}H_{12}N_4O_2$. Calculated, %: C 64.28; H 4.32; N 18.99.

The next chromatographic fraction gave 0.27 g (64%) compound **5c**; mp 306-308°C. An analytical sample was prepared by recrystallization from methanol. ^{1}H NMR spectrum, δ, ppm: 2.04 (3H, s, CH_3); 7.29-7.49 (5H, m, C_6H_5); 7.98 (2H, s, NH_2); 8.92 (1H, s, H-4); 11.37 (1H, s, NH). ^{13}C NMR spectrum, δ, ppm: 26.7 (CH_3); 93.9 (C-8); 110.2 (C-4a); 128.2 (*m*-C_6H_5); 128.5 (*o*-C_6H_5); 130.9 (*p*-C_6H_5); 143.7 (*ipso*-C_6H_5); 157.2 (C-7); 157.3 (C-4); 159.97 (C-8a); 161.6 (C-5); 169.1 (C-2); 195.1 ($\underline{C}OC_6H_5$). Found, %: C 64.45; H 4.35; N 19.93 $C_{15}H_{12}N_4O_2$. Calculated, %: C 64.28; H 4.32; N 19.99.

2-(Benzoylmethylene)-6-nitro-2,3-dihydroquinazolin-4(1H)-one (9). A solution of 2-fluoro-5-nitrobenzoyl chloride **7** [9] (0.305 g, 1.5 mmol) in methylene chloride (10 ml) was added dropwise with stirring over 1 h to a solution of benzoylacetamidine **1c** (0.42 g, 3 mmol) in acetonitrile (30 ml). Stirring was continued for an additional 3 h and the mixture was left overnight at room temperature. The crystalline precipitate was filtered off, heated at reflux in acetonitrile (30 ml), and cooled to room temperature. Benzoylacetamidine hydrochloride was filtered off. The combined mother liquors were evaporated in vacuum and the residue was recrystallized twice from acetonitrile to give N-(1-amino-3-oxo-3-phenylpropenyl)-2-fluoro-5-nitrobenzamide (**8**) (0.27 g, 54%) as a 1:1 mixture of the *E*- and *Z*- isomers; mp 196-198°C (with cyclization). ^{1}H NMR spectrum, δ, ppm: 5.72, 5.82 (0.5H, 0.5H, s, =CH); 7.48-7.53 (3H, m, *m*-C_6H_5, *p*-C_6H_5); 7.67-7.84 (3H, m, *o*-C_6H_5, H-3); 8.25-8.73 (3.5H, m, NH, H-4, H-6); 10.45 (0.5H, s, NH); 11.12 (0.5H, s, NH); 15.29 (0.5H, s, NH). Found, %: C 58.31; H 3.77; N 12.81. $C_{16}H_{12}FN_3O_4$. Calculated, %: C 58.36; H 3.67; N 12.76.

Amide **8** (0.1 g, 0.3 mmol) was heated for 20 min at 220°C and an additional 10 min at 240°C. The product was recrystallized from DMF, heated at reflux in ethanol, filtered off, washed with ether, and dried to give compound **9** (85 mg, 91%) as a 3:2 mixture of the *E*- and *Z*- isomers; mp 296-303°C (decomp.). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 5.86, 5.99 (0.4H, 0.6H, s, =C<u>H</u>-COC$_6$H$_5$); 7.38 (0.4H, d, *J* = 8.8, H-8); 7.45-7.60, 7.70-7.90 (5.6H, C$_6$H$_5$ and m, H-8); 8.45 (1H, m, H-7); 8.61 (1H, s, H-5); 12.19 (1H, s, NH); 13.93 (0.4H, s, NH); 14.57 (0.6H, s, NH). Found, %: C 61.90; H 3.55; N 13.49. $C_{16}H_{11}N_3O_4$. Calculated, %: C 62.14; H 3.58; N 13.59.

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