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CYCLOCONDENSATION OF ETHYL 3,3-DIAMINOACRYLATE WITH AROMATIC KETONES AND NITRILES CONTAINING A LABILE HALOGEN ATOM IN THE *ortho* POSITION

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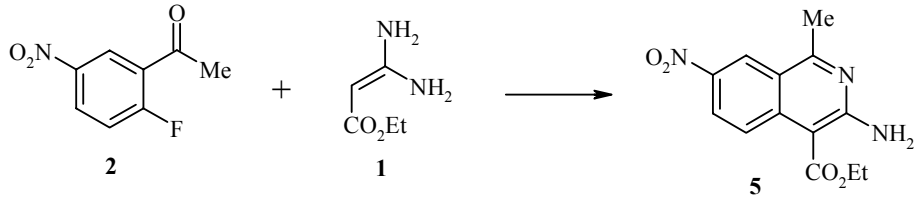
The cyclocondensation of aromatic o-halo ketones and o-halo nitriles with ethyl 3,3-diaminoacrylate proceeds as the replacement of the aromatic halogen by the α-carbon atom of the enediamine, while the amino group of the enediamine is bound by the α-carbon atom of the ketone or nitrile group.

Keywords: aromatic *o*-halo ketones and *o*-halo nitriles, 3,3-diaminoacrylate, cyclocondensation.

α-Acylacetamidines, which exist in enediamine form, react with aromatic aldehydes and esters containing a labile halogen atom in the *ortho* position to give predominantly or exclusively condensed aminopyridines [1-3]. In the present work, we studied the feasibility of using ketones and nitriles in this reaction and investigated the cyclocondensation of ethyl 3,3-diaminoacrylate (**1**) with 2-fluoro-5-nitroacetophenone (**2**) [4], three 5-acyl-4,6-dichloropyrimidines (**3a-c**) [5-7], and two pyrimidinecarbonitriles (**4a**,**b**) [8, 9].

Acetophenone **2** reacts with diaminoacrylate **1** to give only 3-aminoisoquinoline **5**. The structure of this product was confirmed by the ^{1}H NMR spectrum, which is extremely similar to the spectrum of ethyl 3-amino-7-nitroisoquinoline-4-carboxylate (obtained from 2-fluoro-5-nitrobenzaldehyde [1]). NOE cross peaks are found in the NOESY correlation spectrum between H-5 and the ethoxy group protons.

The nature of the acyl group has the predominant effect on the direction of the reaction for 5-acylpyrimidines **3** with diaminoacrylate **1**. Aldehyde **3a** (R = H) reacts similarly to its 2-methylsulfanyl analog [2] to give pyridopyrimidine **6**, albeit in low yield. The structure of **6** was confirmed by ^{1}H and ^{13}C NMR



2 **1** **5**

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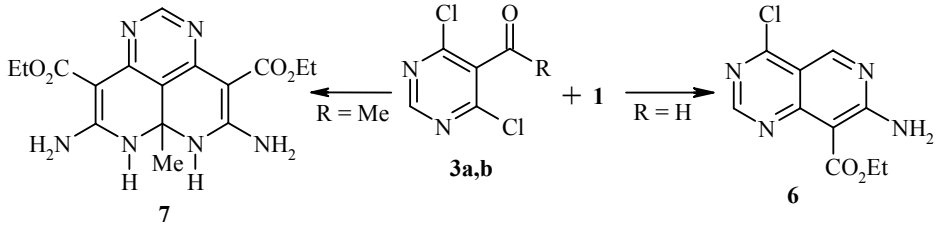
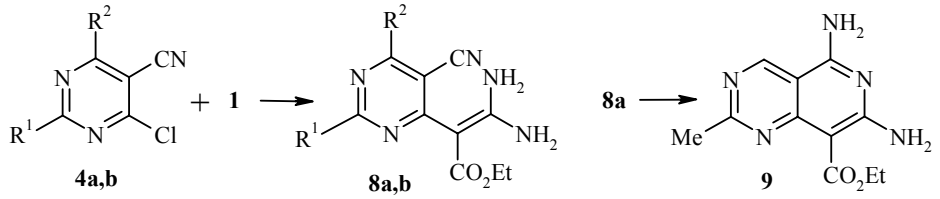
spectroscopy. These spectra are very similar to the spectrum of the 2-methylsulfanyl analog [2], while the $^1J_{C5\text{-}H}$ coupling constant (184 Hz) indicates that the C–H fragment is directly adjacent to the pyridine nitrogen atom ($^1J_{C1\text{-}H}$ = 178 Hz in isoquinoline, $^1J_{C4\text{-}H}$ = 162 Hz in quinoline [10]).

Methyl ketone **3b** reacts differently. The only product of this reaction is tricyclic diester **7**. The chemical shift of the nodal carbon atom bearing a methyl group is 65.9 ppm, indicating that two nitrogen atoms are adjacent to each other. The signals in the ^{13}C NMR spectrum were assigned by analyzing the spectrum without proton decoupling.



Phenyl ketone **3c** (R = Ph) reacts with diaminoacrylate **1** to give a complicated mixture of many products. We were unable to separate or analyze this mixture.

The reactions of nitriles **4a**,**b** with diaminoacrylate **1** under mild conditions proceed only with aromatic replacement of the chlorine atom by the acrylate α-carbon atom, while the nitrile group is not affected. Dichloronitrile **4b** reacts much more rapidly than monochloronitrile **4a**. This discrepancy may be related to the electron-withdrawing effect of the second chlorine atom. The reaction times were 80 min for **4b** and 120 h for **4a**. Ester **8a** cyclizes at 175°C to give pyridopyrimidine **9**, while ester **8b** is rapidly converted to a tar upon heating.



4, 8 a R^1 = Me, R^2 = H, **b** R^1 = H, R^2 = Cl

EXPERIMENTAL

The ^1H and ^{13}C NMR spectra were taken on a Bruker DPX 300 spectrometer at 300 and 75 MHz, respectively, in DMSO-d_6 (compounds **5, 7, 8a,b,** and **9**) or $CDCl_3$ (compound **6**). The residual signals of the solvents at δ 2.50 and 7.26 (for the ^1H NMR spectra in DMSO-d_6) and at δ 39.7 and 77.7 ppm (for the ^{13}C NMR spectra respectively) were used as the internal standards. The coupling constants in the ^1H NMR spectra were measured to a first-order approximation. The elemental analysis was carried out on a Hewlett-Packard HP-185B CHN-analyzer. The purity of the compounds and the reaction course were followed by thin-layer chromatography on Silufol UV-254 plates.

Ethyl Ester of 3-Amino-1-methyl-7-nitroisoquinoline-4-carboxylic Acid (5). A solution of 2-fluoro-5-nitroacetophenone (**2**) (366 mg, 2.0 mmol) and ethyl 3,3-diaminoacrylate (**1**) (390 mg, 3.0 mmol) in dry DMF (1.5 ml) was maintained for 20 h at room temperature. Then, an additional diaminoacrylate **1** (130 mg, 1.0 mmol) was added. After 8 h, the precipitate was filtered off and washed with ether to give

isoquinoline **5** (333 mg, 61%); mp 194-196°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.39 (3H, t, *J* = 7.3, CH_3); 2.86 (3H, s, 1-CH_3); 4.41 (2H, q, *J* = 7.3, CH_2); 7.83 (2H, s, NH_2); 8.29 (1H, dd, *J* = 10.0, *J* = 2.9, H-6); 8.56 (1H, d, *J* = 10.0, H-5); 8.81 (1H, d, *J* = 2.9, H-8). ^{13}C NMR spectrum, δ, ppm: 14.42 ($OCH_2\underline{C}H_3$); 22.82 (3H, 1-CH_3); 61.06 ($O\underline{C}H_2CH_3$); 93.21 (C-4); 119.72 (C-8a); 123.61 (C-8); 124.69 (C-5); 125.28 (C-6); 140.34 (C-4a); 141.06 (C-7); 159.06 (C-3);, 166.69 (C-1); 167.51 ($\underline{C}O_2CH_2CH_3$). Found, %: C 56.70; H 4.75; N 15.60. $C_{13}H_{13}N_3O_4$. Calculated, %: C 56.72; H 4.76; N 15.27.

Diethyl Ester of 5,8-Diamino-6a-methyl-6a,7-dihydro-(5H)pyrimido[4,5,6-*de*][1,8]naphthyridine-4,9-dicarboxylic Acid (7). A solution of methyl ketone **3b** (248 mg, 1.3 mmol) and diaminoacrylate **1** (370 mg, 2.8 mmol) in dry DMF (2 ml) was maintained for seven days at room temperature. The crystalline precipitate was filtered off, washed with cold water, and dried in the air. The mother liquor was evaporated at 1 mm Hg, not heating above 40°C. The residue was washed with cold water and the crystals were filtered off. The total yield of dihydrochloride **7** was 346 mg (62%); mp >300°C. The reaction takes 7 h at 52°C and gives the same result. A reduction in the amount of diaminoacrylate **1** to equimolar leads to the formation of the same product but with a lower yield. Found, %: C 44.35; H 5.52; N 19.06. $C_{16}H_{22}Cl_2N_6O_4$. Calculated, %: C 44.35; H 5.12; N 19.40.

Dihydrochloride (100 mg) was dissolved in methanol (5 ml) at reflux and 10 M methanolic ammonia (3 ml) was added dropwise. After 5 min, the precipitate formed was filtered off and dried in the air to give pyrimidonaphthyridine **7** (62 mg, 75%); mp >250°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.22 (6H, t, *J* = 7.3, $C\underline{H}_3CH_2$); 1.31 (3H, s, $C\underline{H}_3$-C); 4.10 (4H, m, $CH_3C\underline{H}_2$); 6.96-7.40 (2H, 2NH); 7.40-8.2 (4H, $2NH_2$); 8.36 (1H, s, H-2). ^{13}C NMR spectrum, δ, ppm: 14.9 ($C\underline{H}_3CH_2$); 26.1 (CH_3); 58.5 ($CH_3C\underline{H}_2$); 65.9 (C-6a); 78.6 (C-4, C-9); 106.9 (C-3b); 153.3 (C-3a, C-9a); 156.3 (C-2); 158.3 (C-5, C-8); 168.6 (CO_2Et). Found, %: C 53.34; H 5.32; N 23.20. $C_{16}H_{20}N_6O_4$. Calculated, %: C 53.33; H 5.59; N 23.32.

Ethyl Ester of 7-Amino-4-chloropyrido[4,3-*d*]pyridimidine-8-carboxylic Acid (6). 4,6-Dichloro-pyrimidine-5-carbaldehyde (**3a**) (230 mg, 1.3 mmol) was added with stirring to a solution of diaminoacrylate **1** (370 mg, 2.8 mmol) in dry DMF (1 ml) at 10°C. A precipitate formed 30 min after the mixing. The reaction mixture was cooled to -15°C. The precipitate was filtered off and washed with cold water to give pyridopyrimidine **6** (120 mg, 37%); mp 159-160°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.46 (3H, t, *J* = 7.5, CH_3); 4.52 (2H, q, *J* = 7.5, CH_2); 7.06 (2H, s, NH_2); 8.99 (1H, s, H-2); 9.30 (1H, s, H-5). ^{13}C NMR spectrum, δ, ppm (*J*, Hz): 14.7 ($OCH_2\underline{C}H_3$); 62.2 ($O\underline{C}H_2CH_3$); 97.6 (C-8); 113.5 (C-4a); 155.8 (C-7); 155.8 (C-5, $^1J_{C\text{-}H}$ = 184); 158.6 (C-2, $^1J_{C\text{-}H}$ = 210); 162.4, 163.0 (C-4, C-8a); 167.7 ($\underline{C}O_2CH_2CH_3$). Found, %: C 47.44; H 3.81; N 22.00. $C_{10}H_9ClN_4O_2$. Calculated, %: C 47.54; H 3.59; N 22.18.

Ethyl Ester of 3,3-Diamino-2-(5-cyano-2-methyl-4-pyrimidinyl)acrylic Acid (8a). A solution of nitrile of 4-chloro-2-methyl-5-pyrimidinecarboxylic acid (200 mg, 1.3 mmol) (**4a**) and diaminoacrylate **1** (370 mg, 2.8 mmol) in dry DMF (1.5 ml) was maintained at room temperature for five days. The solvent was evaporated at 1 mm Hg and 40°C. The residue was triturated with a small amount of diethyl ether. The crystals formed were filtered off, washed with diethyl ether and cold water, and dried in the air to give **8a** (220 mg, 69%); mp 134-136°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.15 (3H, t, *J* = 7.5, $C\underline{H}_3CH_2$); 2.57 (3H, s, CH_3), 4.05 (2H, q, *J* = 7.5, $CH_3C\underline{H}_2$); 7.00-8.20 (4H, s, $=C(N\underline{H}_2)_2$); 8.71 (1H, s, H-6). ^{13}C NMR spectrum, δ, ppm: 14.8 ($OCH_2\underline{C}H_3$); 27.0 (CH_3); 59.3 ($O\underline{C}H_2CH_3$); 79.0 ($=\underline{C}CO_2CH_2CH_3$); 105.0 (C-5); 118.0 (C≡N); 160.9 (C-6); 162.4 (C-4); 167.2 ($=C(NH_2)_2$); 168.4 ($\underline{C}O_2CH_2CH_3$); 169.0 (C-2). Found, %: C 53.49; H 5.42; N 28.49. $C_{11}H_{13}N_5O_2$. Calculated, %: C 53.43; H 5.30; N 28.32.

Ethyl Ester of 5,7-Diamino-2-methylpyrido[4,3-*d*]pyrimidine-8-carboxylic Acid (9). Ethyl ester of 3,3-diamino-2-(5-cyano-2-methyl-5-pyrimidinyl)acrylic acid (**8a**) (42 mg, 0.170 mmol) was maintained at 170-180°C for 10 min. During this time, the liquid crystallized to give pyridopyrimidine **9** (39 mg, 93%); mp 205-206°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.30 (3H, t, *J* = 7.5, $C\underline{H}_3CH_2$); 2.54 (3H, s, CH_3); 4.19 (2H, q, *J* = 7.5, $CH_3C\underline{H}_2$); 7.48 (2H, 5-NH_2); 7.71 (2H, 7-NH_2); 9.17 (1H, s, H-4). ^{13}C NMR spectrum, δ, ppm:

15.2 ($OCH_2\underline{C}H_2$); 27.3 (2-CH_3); 60.2 ($O\underline{C}H_2CH_3$); 88.1 (C-8); 104.2 (C-4a); 155.6 (C-5); 157.7 (C-7); 160.4, 163.8 (C-4, C-8a); 168.5 ($\underline{C}O_2CH_2CH_3$); 168.9 (C-2). Found, %: C 53.39; H 5.30; N 28.22. $C_{11}H_{13}N_5O_2$. Calculated, %: C 53.43; H 5.30; N 28.32.

Ethyl Ester of 3,3-Diamino-2-(6-chloro-5-cyano-4-pyrimidinyl)acrylic Acid (8b). A solution of a mixture of nitrile 4,6-dichloropyrimidine-5-carboxylic acid (**4b**) (226 mg, 1.3 mmol) and diaminoacrylate **1** (370 mg, 2.8 mmol) in dry DMF (5 ml) was maintained for 80 min at room temperature. Then, the solvent was evaporated at 1 mm Hg and 40°C. The residue was triturated with a small amount of diethyl ether, washed with cold water, filtered off, and dried to give pyridopyrimidine **8b** (280 mg, 81%); mp 165-170°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.17 (3H, t, *J* = 7.5, $C\underline{H}_3CH_2$); 4.08 (2H, q, *J* = 7.5, $CH_3C\underline{H}_2$); 6.50-8.50 (4H, $=C(NH_2)_2$); 8.74 (1H, s, H-2). ^{13}C NMR spectrum, δ, ppm: 14.8 ($OCH_2\underline{C}H_3$); 59.6 ($O\underline{C}H_2CH_3$); 80.7 ($=\underline{C}CO_2CH_2CH_3$); 105.6 (C-5); 115.8 (C≡N); 158.0 (C-2); 161.9 (C-4); 162.4 (C-6); 168.7 ($=C(NH_2)_2$); 168.9 ($\underline{C}O_2CH_2CH_3$). Found, %: C 45.03; H 4.02; N 26.01. $C_{10}H_{10}ClN_5O_2$. Calculated, %: C 44.87; H 3.77; N 26.16.

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