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RECYCLIZATION REACTIONS OF 2-(1-BENZOYLPYRROLIDIN-2-YLIDENE)MALONONITRILE

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Acylation of pyrrolidin-2-ylidenemalononitrile with benzoyl chloride leads to the formation of 2-(1-benzoylpyrrolidin-2-ylidene)malononitrile. The obtained product was used as starting material in the synthesis of γ-aminopropylpyrazoles and pyrimidines.

Keywords: ω-aminoalkylheterocycles, binucleophiles, cyclic enamines, recyclization.

For some time a large number of studies have been devoted to heterocycles containing an ω-aminoalkyl fragment [1]. These compounds are used as intermediates for the synthesis of medicinal preparations, pesticides, and corrosion inhibitors, and may also be used as promising building-blocks [2-5].

One of the approaches to the making of compounds of a similar nature is the use of the reaction of recyclization of saturated lactam rings, lactim esters, cyclic amidines, and enamines by the reaction of nucleophilic reagents [1]. A significant limitation of this method is the fact that the opening of the ring in the initial compounds frequently occurs under the action of strong nucleophilic reagents and under the fairly rigid conditions. Thus, recyclization of pyrrolidin-2-ylidenemalononitrile (**1**) into γ-aminopropylpyrazole readily occurs on brief boiling of the starting material in a 60% excess of hydrazine hydrate [6]. At the same time the authors mention that under milder conditions, boiling compound **1** in alcoholic solution, the analogous opening of the saturated ring was not observed. There is no information in the literature on reactions of cyclic enamine **1** with other nucleophilic reagents.

It is known that the introduction of an electron-withdrawing group at the nitrogen atom in the heterocycle increases the electrophilicity of the adjacent oxygen atom, and subsequent nucleophilic attack at this position may lead to cleavage and/or recyclization of the initial compounds with the formation of linear structures or cyclic products [7-9]. We showed previously that acylation of 2-(nitromethylene)azepane with carboxylic acid chlorides in the presence of aqueous alkali is accompanied by opening of the saturated ring with the formation of derivatives of 7-amino-1-nitroheptan-2-one [10]. While continuing investigations in this area we attempted to use an analogous approach for the synthesis of γ-aminopropyl heterocycles from enamine **1**.

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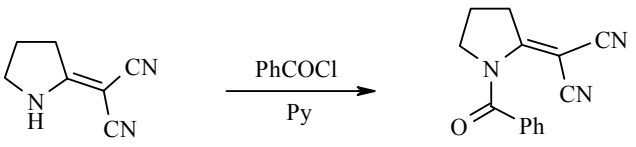
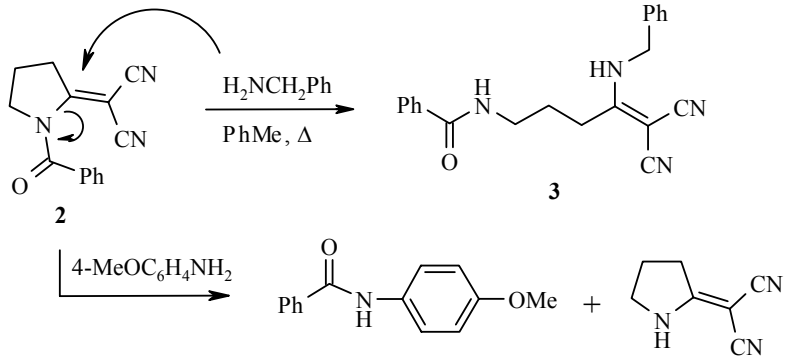
We obtained 2-(1-benzoylpyrrolidin-2-ylidene)malononitrile (**2**) by the action of benzoyl chloride on compound **1** in pyridine. This compound was chosen as a model and its interaction with a series of nucleopohilic and bisnucleophilc reagents has been investigated.

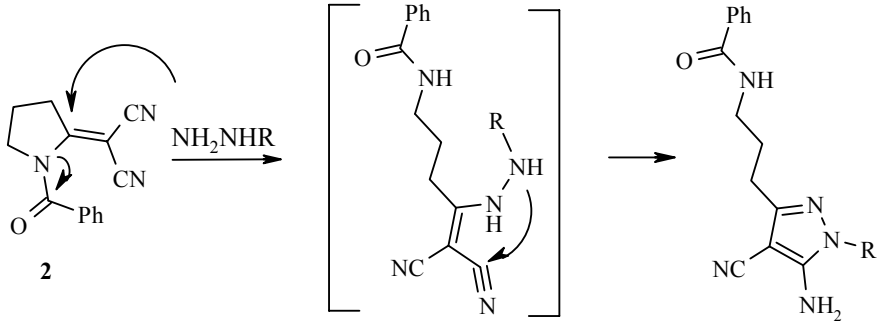


1 **2**

As might have been expected the electrophilic properties of benzoyl derivative **2** were expressed far more strongly than for enamine **1**. Thus compound **2** interacts smoothly with benzylamine in boiling toluene (1 h) forming N-(4-benzylamino-5,5-dicyanopent-4-enyl)benzamide **3**. Nucleophilic attrack in this case is effected at the α-carbon of the enamine and is accompanied by cleavage of the saturated ring. The reaction of benzoylenamine **2** with *p*-anisidine requires more prolonged boiling (5 h), and the nucleophilic attack is directed at the benzoylamino group. In this case, deacylation of compound **2** occurs with regeneration of the initial enamine **1** and the formation of 4-methoxybenzanilide. Compound **1** does not interact with amines under the indicated conditions.



The N-benzoyl derivative **2** was used as a 1,3-biselectrophile (C-2 and CN) in reactions with 1,2- and 1,3-bisnucleophilic reagents for obtaining γ-aminopropyl heterocycles, It was found that reaction of **2** with arylhydrazines leads to the formation of N-[3-(5-amino-1-aryl-4-cyano-1H-pyrazol-3-yl)propyl]benzamides **5** containing a benzoylaminopropyl fragment. Reaction was readily effected on heating the initial compounds in pyridine.

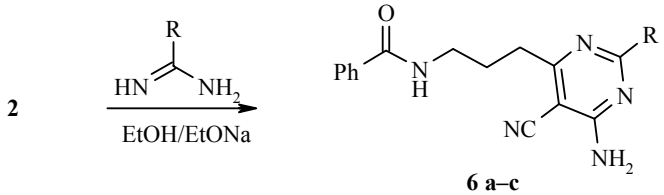


4 **5 a–c**

5 a R = Ph, **b** R = 4-FC_6H_4, **c** R = 4-MeC_6H_4

Evidently, as in the reaction of compound **1** with benzylamine, the first nucleophilic attack is directed at the α-position of the enamine, which leads to opening of the saturated ring and the formation of the linear intermediate **4**. Subsequent intramolecular nucleophilic attack by the nitrogen atom of the hydrazine fragment at the nitrile group leads to closing of the pyrazole ring and the formation of compounds **5**.

Reaction with 1,3-bisnucleophilic reagents, alkyl and arylamidines, was carried out under standard conditions, boiling in alcohol in the presence of sodium ethylate. As in the previous case the formation of a heterocyclic nucleus is accompanied by opening of a saturated ring of the initial compound. N-[3-(2-R-6-amino-5-cyanopyrimidin-4-yl)propyl]benzamides **6** were obtained in this way in moderate yield.



6 a–c

6 a R = Ph, **b** R = pyrid-3-yl, **c** R = Me

The structures of the obtained aminopropyl products **3**, **5**, and **6** were demonstrated by ^{1}H NMR spectra, and were confirmed by data of elemental analysis. It is necessary to note that in the ^{1}H NMR spectra of these compounds the signals of the protons of the methylene group next to the nitrogen atom of the amide group in the case of 7-amino-1-nitroheptan-2-ones [10], are displaced towards higher field compared with the initial cyclic compound. Thus in the initial benzoylenamine **2** the triplet at 3.99 ppm corresponds to the methylene group, and in the aminopropyl products this signal is displayed as a multiplet at 3.20-3.40 ppm. Additional confirmation of the presence of an aminoalkyl chain in compounds **3**, **5**, and **6** is the presence of a triplet at 8.5 ppm (J = 5.4 Hz), corresponding to the amide group proton, absent from the initial cyclic benzoylenamine **2**.

It has therefore been shown that 2-pyrrolidin-2-ylidenemalononitrile **1** is readily acylated by benzoyl chloride. The obtained benzoylenamine **2** may be used as a starting material in the synthesis of γ-benzoyl-aminopropylpyrazoles and pyrimidines.

EXPERIMENTAL

Melting points are not corrected. Commercially available reagents were used. Enaminonitrile **1** was obtained by the procedure of [6]. Pyridine, benzene, and ethanol were purified by standard methods [11]. The ^{1}H NMR spectra were recorded on a Varian 300 instrument (300 MHz) in DMSO-d_6, internal standard was TMS.

2-(1-Benzoylpyrrolidin-2-ylidene)malononitrile (2). Benzoyl chloride (0.45 ml, 3.8 mmol) was added dropwise to a stirred solution of enaminonitrile **1** (0.5 g, 3.8 mmol) in freshly distilled pyridine (7 ml) in an atmosphere of dry argon at 0^{o}C. The reaction mixture was left overnight, then boiled for 1 h, cooled, and water was added dropwise with stirring. The mixture was stirred for 1 h, the resulting brown solid was filtered off, and washed with 2-propanol. Yield of compound **2** was 0.54 g (61%); mp 126-128^{o}C (2-propanol). ^{1}H NMR spectrum, δ, ppm (J, Hz): 1.99-2.09 (2H, m, H-4); 3.19 (2H, t, J = 7.2, H-3); 3.99 (2H, t, J = 7.2, H-5); 7.52-7.58 (2H, m, Ar); 7.64-7.69 (1H, m, Ar); 7.76 (2H, d, J = 7.2, Ar). Found, %: C 70.97; N 17.93. $C_{14}H_{11}N_3O$. Calculated, %: C 70.87; N 17.71.

N-(Benzylamino-5,5-dicyanopent-4-enyl)benzamide (3). Benzylamine (0.23 ml, 2.1 mmol) was added to a suspension of benzoylenamine **2** (0.5 g, 2.1 mmol) in dry toluene (15 ml) and the reaction mixture was boiled for 1 h. The precipitated solid was filtered off. The yield of benzamide **3** was 0.47 g (65%); mp 170-172 ^{o}C (ethanol). ^{1}H NMR spectrum, δ, ppm (J, Hz): 1.68-1.92 (2H, m, 2-CH_2); 2.42-2.55 (2H, m, 3-CH_2);

3.28-3.36 (2H, m, 1-CH_2); 4.50 and 4.74 (2H, m, N–CH_2Ph); 7.18-7.52 (8H, m, Ar); 7.82 (2H, t, *J* = 6.9, Ar); 8.48-8.52 (1H, m, PhCONH); 9.17 and 9.29 (1H, m, NHBz). Found, %: C 73.39; N 16.33. $C_{21}H_{20}N_4O$. Calculated, %: C 73.23; N 16.27.

N-[3-(5-Amino-4-cyano-1-phenyl-1H-pyrazol-3-yl)propyl]benzamide (5a). Phenylhydrazine (0.17 ml, 1.6 mmol) was added to benzoylenamine **2** (0.39 g, 1.6 mmol) in freshly distilled pyridine (7 ml) and the reaction mixture was boiled for 2 h. The pyridine was evaporated, and the residue triturated with water. Yield of pyrazole **5a** was 0.34 g (61%); mp 160-162°C (2-propanol). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.87-1.97 (2H, m, 2-CH_2); 2.60 (2H, t, *J* = 7.8, 3-CH_2); 3.34 (2H, q, *J* = 7.8, 1-CH_2); 6.53 (2H, s, NH_2); 7.35-7.49 (8H, m, Ar); 7.82 (2H, d, *J* = 7.2, Ar); 8.45 (1H, t, *J* = 5.4. NH). Found, %: C 69.45; N 20.12. $C_{20}H_{19}N_5O$. Calculated, %: C 69.55; N 20.28.

N-[3-(5-Amino-4-cyano-1-(4-fluorophenyl)-1H-pyrazol-3-yl)propyl]benzamide (5b) was obtained analogously to compound **5a** from benzoylenamine **2** (0.4 g, 1.6 mmol) and 4-fluorophenylhydrazine hydrochloride (0.28 g, 1.6 mmol) in a yield of 0.41 g (67%); mp 185-187°C (2-propanol). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.87-1.97 (2H, m, 2-CH_2); 2.57 (2H, t, *J* = 7.8, 3-CH_2); 3.32 (2H, q, *J* = 7.8, 1-CH_2); 6.63 (2H, s, NH_2); 7.30-7.34 (2H, m, Ar); 7.42-7.51 (5H, m, Ar); 7.82 (2H, d, *J* = 7.5, Ar); 8.50 (1H, t, *J* = 5.4, NH). Found, %: C 66.31; N 19.42. $C_{20}H_{18}FN_5O$. Calculated, %: C 66.10; N 19.27.

N-[3-(5-Amino-4-cyano-1-(4-methylphenyl)-1H-pyrazol-3-yl)propyl]benzamide (5c) was obtained analogously to compound **5a** from benzoylenamine **2** (0.4 g, 1.6 mmol) and 4-methylphenylhydrazine hydrochloride (0.28 g, 1.6 mmol) in a yield of 0.35 g (58%); mp 175-177°C (2-propanol). ^{1}H NMR spectrum, δ, ppm (*J*,Hz): 1.87-1.97 (2H, m, 2-CH_2); 2.34 (3H, s, CH_3); 2.57 (2H, t, *J* = 7.8, 3-CH_2); 3.32 (2H, q, *J* = 7.8. 1-CH_2); 6.54 (2H, s, NH_2); 7.29 (2H, d, *J* = 8.0, Ar); 7.34 (2H, d, *J* = 8.0, Ar); 7.43 (2H, t, *J* = 7.0, Ar); 7.50 (1H, t, *J* = 7.0, Ar); 7.82 (2H, d, *J* = 7.0, Ar); 8.50 (1H, t, *J* = 5.4, NH). Found, %: C 70.31; N 19.62. $C_{21}H_{21}N_5O$. Calculated, %: C 70.18; N 19.48.

N-[3-(6-Amino-5-cyano-2-phenylpyrimidin-4-yl)propyl]benzamide (6a). Benzamidine hydrochloride (0.33 g, 2.1 mmol) and compound **2** (0.5 g, 2.1 mmol) were added to a solution of sodium ethylate (0.14 g, 2.0 mmol) in anhydrous ethanol (15 ml). The mixture was boiled for 3 h. The solvent was evaporated in vacuum, and the residue triturated with water. Yield of pyrimidine **6a** was 0.3 g (41%); mp 225-227°C (ethanol). ^{1}H NMR spectrum, δ, ppm: 1.91-2.15 (2H, m, 2-CH_2); 2.64-2.91 (2H, m, 3-CH_2); 3.24-3.42 (2H, m, 1-CH_2); 7.37-7.92 (10H, m, Ar + NH_2); 8.25-8.55 (3H, m, Ar + NH). Found, %: C 70.35; N 19.65. $C_{21}H_{19}N_5O$. Calculated, %: 70.57; N 19.59.

N-{3-[6-Amino--5-(cyanopyrimidin-4-yl)-2-(pyrid-3-yl)]propyl}benzamide (6b) was obtained analogously to compound **6a** from benzoylenamine **2** (0.4 g, 1.6 mmol) and pyridine-3-carboxamidine hydrochloride (0.26 g, 1.6 mmol) in a yield of 0.25 g (35%); mp 234-236°C (a mixture of ethanol–DMF). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.03-2.06 (2H, m, 2-CH_2); 2.87 (2H, t, *J* = 7.0, 3-CH_2); 3.37 (2H, m, 1-CH_2); 7.42 (2H, t, *J* = 7.5, Ar); 7.48-7.54 (2H, m, Ar); 7.81 (2H, d, *J* = 7.5, Ar); 7.60-8.20 (2H, br. s, NH_2), 8.51 (1H, t, *J* = 5.5, NH); 8.56 (1H, d, *J* = 7.5, H-4 Py); 8.70 (1H, d, *J* = 4.5, H-6 Py); 9.43 (1H, s, H-2 Py). Found, %: C 67.24; N 23.67. $C_{20}H_{18}N_6O$. Calculated, %: C 67.03; N 23.45.

N-[3-(6-Amino-5-cyano-2-methylpyrimidin-4-yl)propyl]benzamide (6c) was obtained analogously to **6a** from benzoylenamine **2** (0.7 g, 2.8 mmol) and acetamidine hydrochloride (0.27 g, 2.8 mmol) in a yield of 0.22 g (25%); mp 219-221°C (ethanol). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.88-1.91 (2H, m, 2-CH_2); 2.34 (3H, s, CH_3); 2.71 (2H, t, *J* = 7.0, 3-CH_2); 3.30 (2H, q, *J* = 7.0, 1-CH_2); 7.44 (2H, t, *J* = 7.0, Ar); 7.50 (1H, t, *J* = 7.0, Ar); 7.55-7.75 (2H, br. s, NH_2); 7.82 (2H, d, *J* = 7.0, Ar); 8.51 (1H, t, *J* = 5.5, NH). Found, %: C 65.24; N 23.69. $C_{16}H_{17}N_5O$. Calculated, %: C 65.07; N 23.71.

REFERENCES

1. M. Pätzel and J. Liebscher, *Synthesis*, 879 (1995).
2. A. Botta, Ger. Pat. 2110227; *Chem. Abstr.*, **78**, 43476 (1973).

3. H. W. Eckert and G. Koppensteiner, Ger. Pat. 2220016; *Chem. Abstr.*, **80**, 26779 (1974).
4. K. Schmitt, S. Brandt, and F. Gude, Ger. Pat. 1805411; *Chem. Abstr.*, **73**, 66009 (1970).
5. W. D. Emmons and J. F. Levy, Fr. Pat. 1507036; *Chem. Abstr.*, 70, 19556 (1969).
6. M. Pätzel and J. Liebscher, *J. Heterocycl. Chem.*, **28**, 1257 (1991).
7. F. T. Boyle and R. Hull, *J. Chem. Soc., Perkin Trans. 1*, 1541 (1974).
8. Y. Tamura, Y. Miki, T. Honda, and M. Ikeda, *J. Heterocycl. Chem.*, **9**, 865 (1972).
9. I. B. Dzvinchuk, A. V. Vypirailenko, M. O. Lozinskii, and A. Ya. Il'chenko, *Zh. Org. Farm. Khim.*, **1**, No. 1-2, 13 (2003).
10. K. G. Nazarenko, K. V. Shvidenko, A. M. Pinchuk, and A. A. Tolmachev, *Synth. Commun.*, **33**, 4241 (2003).
11. L. F. Tietze and T. Eicher, *Preparative Organic Chemistry* [Russian translation], Mir, Moscow (1999), 704 pp.