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SYNTHESIS OF A NEW HETROCYCLIC SYSTEM 7,8-DIHYDROIMIDAZO[1,2-*c*][1,3]OXAZOLO[4,5-*e*]PYRIMIDINE

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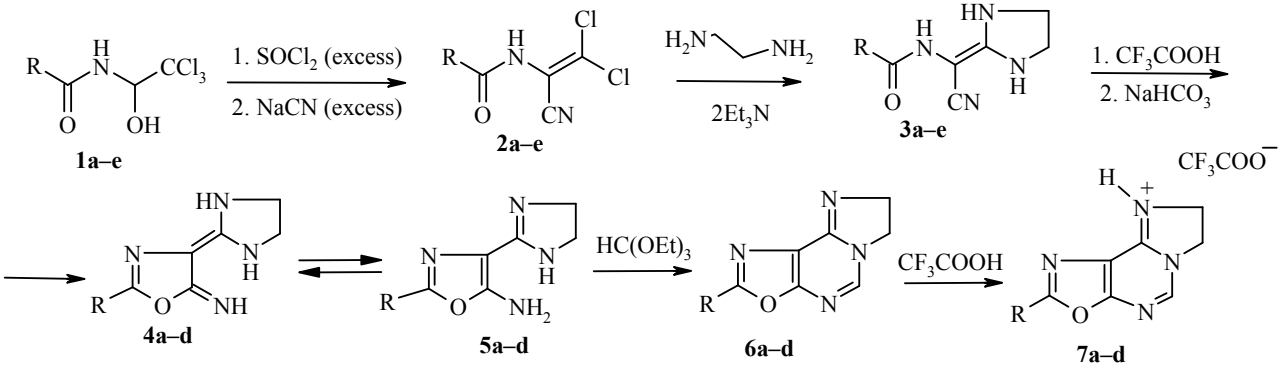
2-(Acylaminocyanomethylene)imidazolidines are formed on interacting 2-acylamino-3,3-dichloroacrylonitriles with ethylenediamine. The former are converted into new derivatives of oxazolo-[4,5-e]pyrimidine on treatment with trifluoroacetic acid, and then with triethyl orthoformate.

Keywords: 5-aminooxazoles, 2-acylamino-3,3-dichloroacrylonitriles, trifluoroacetic acid, triethyl orthoformate, ethylenediamine, heterocyclization.

While continuing investigations on the chemistry of 2-acylamino-3,3-dichloroacrylonitriles **2** we have developed a simple and convenient method of synthesis of a new heterocyclic system, in which the oxazole ring is annelated to a 2,3-dihydroimidazo[1,2-*c*]pyrimidine fragment.

Dichloroacrylonitriles **2**, represented in the Scheme, are readily obtained from available adducts of chloral with carboxylic acid amides **1** [1-4]. On interacting them with N-nucleophiles (primary aliphatic and aromatic amines), as a rule, derivatives of 5-amino-4-cyanooxazole are formed [3, 5, 6]. Totatally differently, interaction of the indicated reagents with 1,4-[N,N]-dinucleophiles occurs, for example with ethylenediamine. Derivatives of 5-aminooxazole are not formed, but substitution occurs of the two chlorine atoms in reagents **2** by the ethylenediamine fragment, which leads to the formation of an imidazolidine ring and the preparation of products **3** (Table 1).



1a–e **2a–e** **3a–e** **4a–d** **5a–d** **6a–d** **7a–d**

1–7 a R = Ph, **b** R = 2-MeC_6H_4, **c** R = 4-MeC_6H_4, **d** R = 4-ClC_6H_4; **1–3 e** R = Me

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In the IR spectra of compounds **3** there were absorption bands for the stretching vibrations of the carbonyl group in the 1652-1673 cm^{-1} region, and also absorption bands for the CN bond in the 2149-2177 cm^{-1} region (Table 2). In the ^1H NMR spectra of these compounds signals were recorded for the NH group (6.55-6.85 ppm) and also signals for the aromatic and aliphatic protons with appropriate ratios of integral intensities. In addition, one of these compounds **3e** was obtained previously by Japanese investigators [5], which raises no doubt as to the structure of products **3**.

As a result of the favorable disposition of the nitrile group and the acylamino residue in compounds **3** the possibility arises of an intramolecular cyclization under the action of trifluoroacetic acid (see [7-9]) into new derivatives of oxazole **4**, which exist preferentially in the tautomeric form **5**. Attempts to introduce compound **3e** into this cyclization with an acetylamine residue were unsuccessful, a mixture of unidentified substances was formed. A characteristic special feature of the IR spectra of compounds **5a-d** was the presence in them of three intense absorption bands in the 1592-1690 cm^{-1} region. One of them belongs to the C=N bond of the imidazolidine ring, and two to a 5-aminooxazole fragment which is natural for a derivative of 5-aminooxazole [10]. In addition, there were no singlet signals in the 2100-2200 cm^{-1} region, which indicates the involvement of the nitrile group in the heterocyclization of **3** → **5**.

TABLE 1. Characteristics of the Synthesized Compounds

Compound	Empirical formula	Found, % / Calculated, %			mp, °C*	Yield, %
		C	H	N		
3a	$C_{12}H_{12}N_4O$	63.08 / 63.15	5.22 / 5.30	24.47 / 24.55	213-215	52
3b	$C_{13}H_{14}N_4O$	64.54 / 64.45	5.91 / 5.82	23.17 / 23.12	258-260	58
3c	$C_{13}H_{14}N_4O$	64.53 / 64.45	5.75 / 5.82	23.03 / 23.12	245-247	60
3d	$C_{12}H_{11}ClN_4O$	54.94 / 54.87	4.29 / 4.22	21.38 / 21.33	224-226	62
3e	$C_7H_{10}N_4O$	50.50 / 50.59	6.13 / 6.07	33.78 / 33.71	203-205*[2]	51
5a	$C_{12}H_{12}N_4O$	63.08 / 63.15	5.22 / 5.30	24.48 / 24.55	193-195	68
5b	$C_{13}H_{14}N_4O$	64.38 / 64.45	5.75 / 5.82	23.07 / 23.12	215-217	72
5c	$C_{13}H_{14}N_4O$	64.37 / 64.45	5.74 / 5.82	23.07 / 23.12	235-237	74
5d	$C_{12}H_{11}ClN_4O$	54.80 / 54.87	4.31 / 4.22	21.41 / 21.33	219-221	75
6a	$C_{13}H_{10}N_4O$	65.62 / 65.54	4.16 / 4.23	23.60 / 23.52	269-271	84
6b	$C_{14}H_{12}N_4O$	66.59 / 66.66	4.85 / 4.79	22.29 / 22.21	239-241	87
6c	$C_{14}H_{12}N_4O$	66.57 / 66.66	4.70 / 4.79	22.28 / 22.21	267-269	90
6d	$C_{13}H_9ClN_4O$	57.32 / 57.26	3.41 / 3.33	20.62 / 20.55	292-294	92
7a	$C_{15}H_{11}F_3N_4O_3$	51.21 / 51.14	3.22 / 3.15	15.98 / 15.90	231-233 (dec.)	68
7b	$C_{16}H_{13}F_3N_4O_3$	52.54 / 52.46	3.63 / 3.58	15.36 / 15.30	207-209 (dec.)	71
7c	$C_{16}H_{13}F_3N_4O_3$	52.53 / 52.46	3.64 / 3.58	15.35 / 15.30	225-227 (dec.)	73
7d	$C_{15}H_{10}ClF_3N_4O_3$	46.65 / 46.59	2.68 / 2.61	14.55 / 14.49	230-232 (dec.)	76

*Solvents for recrystallization: 2-propanol (compounds **3a-e**), ethanol–water, 1:1 (compounds **5a-d**), ethanol (compounds **6a-d**, **7a-d**).

*[2]Agrees with the data of [5].

TABLE 2. IR and Mass Spectra of the Synthesized Compounds

Compound	IR spectrum, ν, cm^{-1}	*m/z* $[M]^+$
3a	1652* (C=O), 2177 (CN), 3100–3300 (NH ass.)	228
3b	1673* (C=O), 2149 (CN), 3150–3450 (NH ass.)	242
3c	1655* (C=O), 2171 (CN), 3200–3450 (NH ass.)	242
3d	1657* (C=O), 2155 (CN), 3130–3540 (NH ass.)	262
5a	1605, 1630, 1681, 2940–3550 (NH ass.)	228
5b	1603, 1633, 1690, 2910–3470 (NH ass.)	242
5c	1592, 1638, 1678, 2740–3410 (NH ass.)	242
5d	1596, 1644, 1676, 2750–3300 (NH ass.)	262
6a	1691* (C=N)	238
6b	1694* (C=N)	252
6c	1688* (C=N)	252
6d	1688* (C=N)	272
7a	1672* (C=N), 1705 (C=O)	238
7b	1674* (C=N), 1703 (C=O)	252
7c	1677* (C=N), 1706 (C=O)	252
7d	1670* (C=N), 1710 (C=O)	272

* Band with shoulder.

TABLE 3. ^{1}H NMR Spectra of the Synthesized Compounds

Com-pound	Chemical shifts, δ, ppm*
3a	3.42 (4H, m, $2CH_2$); 6.56 (1H, s, NH); 6.65 (1H, s, NH); 7.39-7.92 (5H, m, H arom); 8.74 (1H, s, NH)
3b	2.36 (3H, s, CH_3); 3.43 (4H, m, $2CH_2$); 6.48 (1H, s, NH); 6.55 (1H, s, NH); 7.18-7.50 (4H, m, H arom); 8.40 (1H, s, NH)
3c	2.37 (3H, s, CH_3); 3.41 (4H, m, $2CH_2$); 6.56 (1H, s, NH); 6.61 (1H, s, NH); 7.20-7.80 (4H, m, H arom); 8.66 (1H, s, NH)
3d	3.36 (4H, m, $2CH_2$); 6.66 (1H, s, NH); 6.85 (1H, s, NH); 7.52-7.93 (4H, m, H arom); 8.92 (1H, s, NH)
5a	4.12 (4H, s, $2CH_2$); 7.64-8.00 (5H, m, H arom)*[2]
5b	2.37 (3H, s, CH_3); 4.16 (4H, s, $2CH_2$); 7.35-7.88 (4H, m, H arom)*[2]
5c	2.40 (3H, s, CH_3); 4.15 (4H, s, $2CH_2$); 7.36-7.92 (4H, m, H arom); 8.92 (1H, s, NH)*[2]
5d	4.11 (4H, s, $2CH_2$); 7.65-8.05 (4H, m, H arom)*[2]
6a	3.98-4.12 (4H, m, $2CH_2$); 7.56-8.02 (5H, m, H arom); 8.14 (1H, s, H-2 pyrimidine)
6b	2.66 (3H, s, CH_3); 3.97-4.15 (4H, m, $2CH_2$); 7.41-7.97 (4H, m, H arom); 8.14 (1H, s, H-2 pyrimidine)
6c	2.38 (3H, s, CH_3); 3.97-4.13 (4H, m, $2CH_2$); 7.38-7.89 (4H, m, H arom);
6d	3.98-4.14 (4H, m, $2CH_2$); 7.62-8.02 (4H, m, H arom); 8.15 (1H, s, H-2 pyrimidine)
7a	4.19 (2H, t, *J* = 9.7, CH_2); 4.79 (2H, t, *J* = 9.7, CH_2); 7.67-8.15 (5H, m, H arom); 8.99 (1H, s, H-2 pyrimidine); 11.65 (1H, br. s, N^+–H)
7b	2.75 (3H, s, CH_3); 4.19 (2H, t, *J* = 9.6, CH_2); 4.79 (2H, t, *J* = 9.6, CH_2); 7.42-8.10 (4H, m, H arom); 8.91 (1H, s, H-2 pyrimidine); 11.67 (1H, br. s, N^+–H)
7c	2.44 (3H, s, CH_3); 4.18 (2H, t, *J* = 9.8, CH_2); 4.78 (2H, t, *J* = 9.8, CH_2); 7.49-8.04 (4H, m, H arom); 8.97 (1H, s, H-2 pyrimidine); 11.58 (1H, br. s, N^+–H)
7d	4.19 (2H, t, *J* = 9.3, CH_2); 4.79 (2H, t, *J* = 9.3, CH_2); 7.73-8.17 (4H, m, H arom); 8.99 (1H, s, H-2 pyrimidine); 11.70 (1H, br. s, N^+–H)

*^{1}H NMR spectra of compounds **3a-d, 6a-d, 7a-d** were recorded in DMSO-d_6, and compounds **5a-d** in CF_3COOD.
*[2] NH and NH_2 exchanged.

The presence of two nucleophilic centers (NH_2 and NH) in compounds **5** was used by us to form a pyrimidine ring. On heating derivatives of 5-aminooxazole **5a-d** with triethyl orthoformate closure of the pyrimidine fragment occurs fairly readily (cf. [11]) and derivatives of the new heterocyclic system **6** are formed in high yield. In the IR spectra of compounds **6a-d** the broad absorption bands of NH_2 and NH groups in the 2700-3600 cm^{-1} region, characteristic of compounds **5a-d**, have disappeared. At the same time the elemental analysis and mass spectra show the involvement of the orthoformate fragment in the molecular composition of the reaction products. In addition, in the ^1H NMR spectra a singlet signal is present in the 8.14-8.15 ppm region, which may be assigned with a high degree of probability to the H-2 proton of the pyrimidine ring. But all these data may not indicate unequivocally the formation of the new heterocyclic system. Attempts to grow crystals of compounds **6** for X-ray structural analysis were unsuccessful, consequently they were converted into trifluoroacetates **7a-d** and X-ray structural analysis was carried out on one of them. The general shape of the **7b** molecule and its main bond lengths and valence angles are given in Fig. 1 and in Table 4. The central tricyclic system O(1)N(1-4)C(1-7) is approximately planar, the deviation of atoms from the mean square plane did not exceed 0.047 Å. Furthermore, even the exocyclic benzene ring C(8-13), in spite of the obvious steric hindrance, was practically coplanar with this system (the appropriate dihedral angle was only 3.2°), which is caused by efficient π-π conjugation. The N(3) and N(4) atoms have a plane-trigonal bond configuration, the corresponding sum of valence angles at these atoms amounts to 359.3 and 359.9°. A special feature of the crystal structure of compound **7b** is the formation of an extremely stable cationic–anionic hydrogen bond N(4)–H(4)··O(3) with geometric parameters N···O 2.672(4), H···O 1.92(3) Å, NHO 148(3)° (mean statistical interatomic N···O distance for hydrogen bonds of the N–H···O type is 2.89 Å [12]).

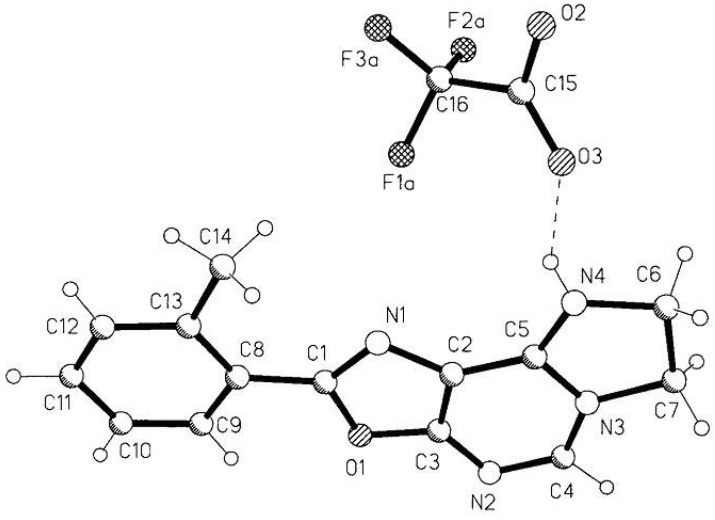

Fig. 1. General view of the compound 7b molecule.

TABLE 4. Main Bond Lengths (*l*) and Valence Angles (ω)

Bond	*l*, Å	Valence angles	ω, deg
N(1)–C(1)	1.297(5)	C(1)N(1)C(2)	103.7(3)
N(1)–C(2)	1.385(4)	C(3)N(2)C(4)	111.9(3)
N(2)–C(3)	1.339(5)	C(5)N(3)C(7)	109.6(3)
N(2)–C(4)	1.311(5)	C(4)N(3)C(5)	123.8(3)
N(3)–C(4)	1.351(5)	C(5)N(4)C(6)	111.9(3)
N(3)–C(5)	1.381(4)		
N(3)–C(7)	1.489(4)		
N(4)–C(5)	1.308(5)		
N(4)–C(6)	1.467(5)		

EXPERIMENTAL

The IR spectra of substances were recorded on a Vertex 70 spectrometer in KBr disks, the ^{1}H NMR spectra on a Varian 300 (300 MHz) instrument, internal standard was TMS, and mass spectra of compounds on an Agilent 1100/DAD/MSD VL G1965 instrument. Melting points were measured on a Fisher-Johns instrument.

2-(Aroylaminocyanomethylene)imidazolidines 3a-d. Ethylenediamine (15 g, 0.25 mol) was added with stirring to a suspension of one of compounds **2a-e** (0.05 mol) in 2-propanol (100 ml), the solid dissolved, after 3-5 min imidazolidines **3a-d** were precipitated, were filtered off, washed with water, and purified by recrystallization.

5-Amino-2-aryl-4-(4,5-dihydro-1H-imidazol-2-yl)-1,3-oxazoles 5a-d. A solution of one of compounds **3a-d** (0.005 mol) in trifluoroacetic acid (10 ml) was stirred for 10 min, the excess of acid was removed in vacuum, the residue was treated with 5% aqueous $NaHCO_3$ solution, the solid was filtered off, washed with water, and purified by recrystallization.

2-Aryl-7,8-dihydroimidazo[1,2-*c*][1,3]oxazolo[4,5-*e*]pyrimidines 6a-d. A solution of the appropriate aminooxazole **5a-d** in triethyl orthoformate (20 ml) was boiled for 20 min, the precipitated solid was filtered off, washed with diethyl ether, and purified by recrystallization.

Trifluoroacetates of 2-Aryl-7,8-dihydroimidazo[1,2-*c*][1,3]oxazolo[4,5-*e*]pyrimidines 7a-d. One of compounds **6a-d** (0.002 mol) was dissolved in ethyl alcohol (20 ml), trifluoroacetic acid (1 ml) was added, the solution stirred for 10 min, evaporated to dryness, and compounds **7a-d** were purified by recrystallization.

X-Ray Structural Investigation of a monocrystal of compound **7b** of dimensions 0.04×0.28×0.38 mm was carried out at room temperature on a Bruker Apex II automatic CCD diffractometer (MoKα radiation, $\lambda = 0.71069$ Å, $\theta_{max} = 26.5^o$, $-12 \le h \le 13$, $-24 \le k \le 24$, $-8 \le l \le 9$). In all 12423 reflections (3226 independent reflections, $R_{int} = 0.01$) were collected. Crystals of compound **7b** were monoclinic, $a = 11.1903(4)$, $b = 19.5679(8)$, $c = 7.3233(3)$ Å, $\beta = 95.598(2)^o$, $V = 1595.9(1)$ Å^3, $M = 366.3$, $Z = 4$, $d_{calc} = 1.52$ g/cm^3, $\mu = 1.31$ cm^{-1}, $F(000) = 752$, space group $P_1/2n$ (No. 14). The structure was solved by the direct method and refined by the method of least squares in a full matrix anisotropic approximation using the CRYSTALS set of programs [13]. In the refinement 1473 reflections with $I > 3\sigma(I)$ were used (239 parameters were refined, reflections per parameter 6.2). All hydrogen atoms were made apparent from an electron density difference synthesis and were included in the refinement with fixed positions and thermal parameters (with the exception of atom H(4), participating in the intermolecular hydrogen bond, which was refined isotropically). The Chebyshev weighting factor was used in the refinement [14] with five parameters, 0.65, 0.38, 0.55, 0.14, and 0.19. The final values of the divergence factors were $R = 0.047$ and $R_w = 0.047$, *GOOF* 1.178. Residual electron density from the Fourier difference series was -0.26 and 0.46 e/Å^3. A complete set of X-ray structural data for compound **7b** has been deposited in the Cambridge structural data bank (deposit CCDC 785919).

REFERENCES

1. K. Matsumura, T. Saraie, and N. Hashimoto, *J. Chem. Soc.,Chem. Commun.*, 705 (1972).
2. B. S. Drach, E. P. Sviridov, A. A. Kisilenko, and A. V. Kirsanov, *Zh. Org. Khim.*, **9**, 1818 (1973).
3. B. S. Drach, E. P. Sviridov, and T. Ya. Lavrenyuk, *Zh. Org. Khim.*, **10**, 1271 (1974).
4. K. Matsumura, T. Saraie, and N. Hashimoto, *Chem. Pharm. Bull.*, **24**, 912 (1976).
5. K. Matsumura, T. Saraie, and N. Hashimoto, *Chem. Pharm. Bull.*, **24**, 924 (1976).
6. B. S. Drach and G. N. Mis'kevich, *Zh. Org. Khim.*, **13**, 1398 (1977).
7. D. Clerin and J.-P. Fleury, *Bull. Soc. Chim. Fr.,* 3127 (1973).
8. D. Clerin and J.-P. Fleury, *Bull. Soc. Chim. Fr.,* 3134 (1973).

9. D. Clerin, B. Meyer, and J.-P. Fleury, *Bull. Soc. Chim. Fr.,* 2053 (1976).
10. H. Nayer, R. Gindicelli, and J. Menin, *Bull. Soc. Chim. Fr.,* 2052 (1960).
11. A.-R. Farghaly and H. El-Kashef, *Monatsh. Chem.*, **137**, 1195 (2006).
12. L. N. Kuleshova and P. M. Zorkii, *Acta Crystallogr.*, **B37**, 1363 (1981).
13. D. L. Watkin, C. K. Prout, J. R. Carruthers, and P. W. Betteridge, *CRYSTALS, Issue 10.* Chemical Crystallography Laboratory, Univ. Oxford (1996).
14. J. R. Carruthers and D. J. Watkin, *Acta Crystallogr.*, **A35**, 698 (1979).