5,6-DIHYDRO-[1,2,4]TRIAZOLO[1,5-c]QUINAZOLINES.
MESSAGE 3. SYNTHESIS OF 2-ARYL-5-TRICHLOROMETHYL-
5,6-DIHYDRO[1,2,4]TRIAZOLO[1,5-c]QUINAZOLINES AND THEIR
REACTIVITY TOWARDS N-NUCLEOPHILES

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Features of 5-trichloromethyl-2-aryl-5,6-dihydro-[1,2,4]triazolo[1,5-c]quinazolines formation as result of [5+1]-cyclocondensation of the corresponding [2-(3-aryl-1H-1,2,4-triazole-5-yl)phenyl]amines with chloral hydrate are described in the article. It has been shown that this transformation is regioselective, occurs by refluxing of the initial compounds in acetic acid with formation of 2-aryl-5-trichloromethyl-5,6-dihydro-[1,2,4]triazolo[1,5-c]quinazolines. The possible mechanism of 5,6-dihydro-[1,2,4]triazolo[1,5-c]quinazolines has been proposed and substantiated. It has been shown that the reaction proceeds as step-by-step transformation that includes A\(\_\)E and A\(\_\)A processes. The 2-phenyl-5-trichloromethyl-5,6-dihydro-[1,2,4]triazolo[1,5-c]quinazoline obtained was studied in reactions with N-nucleophiles. It has been found that regardless of the nature of nucleophile the reaction mentioned above leads to formation of 2-phenyl-5-(dichloromethyl)-[1,2,4]triazolo[1,5-c]quinazoline. The mechanism of the transformation mentioned above is given; it is β-elimination on the E\(\_\)A-mechanism followed by isomerisation. The structure of the compounds synthesized has been confirmed by the complex of physicochemical methods, including \(^1\)H-, \(^13\)C-NMR-spectrometry, chromatography-mass spectrometry and X-ray structural study. A detailed analysis of \(^1\)H and \(^13\)C-NMR spectral data of the compounds synthesized has been conducted. It has been found that the signals of the carbon atom in position 5 at 79.25-77.95 ppm were characteristic for 2-aryl-5-trichloromethyl-5,6-dihydro-[1,2,4]triazolo[1,5-c]quinazolines, whereas aromatization of the molecule leads to significant deshielding of this carbon atom (163.41 ppm). The prospects of further chemical modification of 2-aryl-5-(dichloromethyl)-[1,2,4]triazolo[1,5-c]quinazolines has been discussed.
N-, O-substituted heterocyclic fragments [1-3]. In connection with trichloromethyl substituent at sp³-hybridized carbon atom, it would be interesting to study the interaction of non-aromatic heterocyclic compounds obtained with N-, О-nucleophiles by SNAr mechanism and transformations of the corresponding N-, O-substituted heterocyclic fragments [1-3]. In order to expand the synthetic potential of the reaction mentioned above it would be interesting to study the interaction of non-aromatic heterocyclic compounds with trichloromethyl substituent at sp³-hybridized carbon atom.

The aim of the work is to study the features of the interaction between 2-[3-(aryl-1H-1,2,4-triazol-5-yl)phenyl]amines with chloral hydride and transformations of the non-aromatic heterocyclic compounds obtained with the trichloromethyl moiety at sp²-hybridized carbon atom under the action of N-nucleophiles.

The reactions were carried out by refluxing equimolar amounts of diamines 1a-g and chloral hydrate in acetic acid or methanol with an acidic catalyst (Scheme 1). It is worth noting that 1a-g normally exist in two tautomeric forms, which may invoke parallel formation of isomeric 1,2,4-triazolo[1,5-c] and -[4,3-c]quinazolines. Nevertheless, our experiments have demonstrated that the reaction proceeds regioselectively through an azomethine intermediate A with the subsequent intramolecular nucleophilic cyclization into tricycles 2a-g (Scheme 1). We attribute such selectivity to an +M-effect (a-effect) of the neighbouring nitrogen atom.

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\text{Scheme 1. The synthesis of 5-trichloromethyl-2-aryl-5,6-dihydro[1,2,4]triazolo[1,5-c]quinazolines.}
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Purity of the compounds synthesized was confirmed by LC-MS (APCI) analysis; the structure was determined using 1H and 13C NMR, IR spectroscopic and MS (EI) spectrometric methods. In 1H NMR-spectra, 6-NH and H5 protons were observed as broad singlets or doublets at 8.41-8.26 ppm (J = 3.3-4.0 Hz) and 6.96-6.69 ppm (J = 3.7-4.1 Hz), respectively. Other protons of the heterocyclic fragment were registered as sequentially located doublets of H10 (7.96-7.78 ppm) and H7 (7.06-7.04 ppm), as well as triplets of H8 (7.33-7.27 ppm) and H-9 (6.88-6.86 ppm). The 13C NMR-spectral data for compounds 2a, 2e and 2g additionally substantiated our structural conclusions. The low field signals of Csp² atoms were observed at 163.6-157.7 ppm (C2), 150.8-150.7 ppm (C6a) and 145.2-141.1 ppm (C10b). Characteristic Csp² signals were located at 117.6-102.6 ppm (CCl₃) and 79.25-77.95 ppm (CH₃).

The crystals of compound 2a were also studied by X-ray diffraction (Fig. 1). The compound crystallized in a non-centrosymmetric space group, which indicated the presence of only one enantiomer in the crystal phase. Configuration of the chiral C8 atom was unambiguously determined using the Flack parameter (-0.04(8)). The dihydropirimidine ring was in an intermediate conforma- tion between a twist-boat and sofa (puckering parameters [4] were: S = 0.41, θ = 53.1°, Ψ = 28.3°). Deviations of N3 and C8 from the mean plane of other atoms were 0.20 Å and 0.49 Å, respectively. The N2 atom had a pyramidal configuration with a small degree of pyramidality (the sum of centred...
bond angles was 357°). The trichloromethyl substituent was located in the axial position and turned in such a way that the C16-Cl2 bond was antiperiplanar to the N3-C8 bond (the C1-N3-C8-C16 and N3-C8-C16-Cl2 torsion angles were 100.6(3)° and 179.6(2)°, respectively). We also observed shortened intramolecular Cl3…N4 and H(N2)…Cl2 bonds (3.18 Å and 2.77 Å vs. the sums of van der Waals radii as 3.40 Å and 3.06 Å [5], respectively). Despite the presence of H11…N4 and H15…N1 attractive interactions (the H…N distance for both was 2.62 Å) the phenyl substituent was slightly out of the triazole ring plane (the N4-C9-C10-C11 torsion angle was -15.6(5)°). In the crystal phase the intermolecular hydrogen bonds between the molecules of 2a were observed: N-H(N2)…C3' (p) (1-x, -0.5+y, 0.5-z) H…C 2.78 Å N-H…C 135° and (C6)H…N-1' (1-x, -0.5+y, 0.5-z) H…N 2.64 Å C-H…N 143°.

The experiments have shown that the reaction of 2a with different N-nucleophiles ((2,2-dimethoxyethyl) amine, benzylamine, morpholine, piperidine and triethylamine) results in the same product, namely dichloromethylated aromatic heterocycle 3a (Scheme 2). Most likely the reaction proceeds via the step-by-step mechanism with \( E_{1cb} \) b-elimination followed by isomerization of the resulting enamine (intermediate B). It starts with elimination of the acidic hydrogen in position 5 in the presence of a base giving a carbanion (intermediate A). Next the negative charge is displaced towards the electron withdrawing trichloromethyl group causing elimination of a chloride anion. At the final stage isomerization into a heterocyclic aromatic system takes place (Scheme 2).

The structure of 3a was confirmed using NMR-spectroscopy. In \( ^1\text{H} \) NMR-spectrum the NH-proton signal in position 5 vanished; instead a new one appeared at 7.80 ppm indicating the presence of the CHCl2 group. Most importantly, we observed a significant paramagnetic shift of protons in the annelated benzene fragment (H-7 (8.60 ppm), H-10 (8.17 ppm), H-9 (7.98 ppm) and H-8 (7.89 ppm)), which demonstrated formation of the aromatic triazinoquinazoline system (Fig. 2).

Additionally, characteristic Csp\(^2\) signals in the \( ^{12}\text{C} \) NMR-spectrum: 163.41 ppm (C-5), 152.01 ppm (C-2), 143.43 ppm (C-6a), 141.55 ppm (C-7) were observed. The resonance of Csp\(^3\) in CHCl\(_2\) was noted at 65.24 ppm (Fig. 3).

**Experimental Part**

Melting points were determined in open capillary tubes in a Thiele apparatus and were given uncorrected. The elemental analysis (C, H, N, S) was performed using an ELEMENTAR vario EL cube analyzer (Elementar Analysensysteme GmbH, Hanau, Germany). IR-spectra (4000–600 cm\(^{-1}\)) were recorded on a Bruker ALPHA FT-IR spectrometer (Bruker Bioscience, Germany) using an ATR eco ZnSe module. \( ^1\text{H} \) NMR-spectra (400 MHz) were recorded on a Varian–Mercury 400 spectrometer (Varian, Palo Alto, CA) in DMSO-d\(_6\) with SiMe\(_4\) as an internal standard. LC-MS were recorded using the chromatography/mass spectrometric system consisting of an “Agilent 1100 Series” (Agilent, Palo Alto, CA) HPLC chromatograph equipped with an “Agilent LC/MSD SL” diode-matrix and mass-selective detector (atmospheric pressure chemical ionization – APCI). Electron impact mass spectra (EI-MS) were measured on a Varian 1200 L instrument (Varian, USA) at 70 eV.

Compounds 1a-g were obtained according to the protocols described [6, 7]. All other reactants and sol-
vents were purchased commercially and used without additional purification.

The general method for the synthesis of 2-aryl-5-(trichloromethyl)-5,6-dihydro[1,2,4]triazolo[1,5-c]quinazolines (2a-g). Reflux the mixture of 10 mmol of the corresponding {2-[3-aryl-1H-1,2,4-triazol-5-yl]phenyl}amine (1a-g) and 1.65 g (10 mmol) of chloral hydrate in 10 ml of acetic acid (or isopropanol with 2 drops of sulphuric acid) for 6 h. Upon completion pour the mixture into 10 ml of 1% sodium acetate solution. Filter the precipitate, dry and recrystallize from methanol.

2-Phenyl-5-(trichloromethyl)-5,6-dihydro[1,2,4]triazolo[1,5-c]quinazoline (2a). Yield – 93.4%; white crystals. M. p. – 166-168°C; IR, ν, cm⁻¹: 3414, 1625, 1596, 1553, 1520, 1503, 1475, 1463, 1443, 1414, 1346, 1315, 1280, 1258, 1239, 1175, 1160, 1124, 1112, 1086, 1073, 1022, 963, 947, 928, 861, 830, 814, 790, 750, 723, 693, 641, 619, 608; ¹H NMR, δ, ppm (J, Hz): 8.26 (d, J = 3.3, 1H, NH), 8.13 (d, J = 7.1, 2H, H-2,6 Ph), 7.82 (d, J = 7.5, 1H, H-10), 7.51-7.36 (m, 3H, H-3,4,5 Ph), 7.27 (t, J = 7.5, 1H, H-8), 7.04 (d, J = 8.1, 1H, H-7), 6.86 (t, J = 7.4, 1H, H-9), 6.69 (d, J = 3.7, 1H, H-5); ¹³C NMR, δ, ppm: 163.62 (C-2), 150.85 (C-6a), 142.48 (C-10b), 139.11, 132.38, 130.78, 129.86, 129.16, 128.62, 127.11, 123.52, 123.44 (C-10a), 117.64 (CCl₃), 79.25 (C-5); MS (EI): m/z = 369 (1.2), 367 (3.8), 365 (4.9, M⁺), 330 (5.3), 329 (8.2), 296 (7.4), 295 (6.8), 294 (14.9), 293 (50.0), 237 (9.4), 236 (44.7), 172 (5.5), 171 (34.3), 145 (6.2), 144 (51.0), 143 (28.0), 119 (50.8), 118 (38.8), 117 (100.0), 116 (37.8), 115 (16.9), 114 (18.8), 103 (23.3), 102 (8.6), 90 (24.3), 89 (12.7), 88 (9.2), 87 (9.4), 86 (20.3), 85 (15.0), 84 (56.0), 83 (18.8), 82 (33.3), 77 (67.8), 76 (34.3), 75 (12.8), 52 (19.6), 51 (65.0), 50 (27.0); LC-MS, m/z = 366 [M+1], 368 [M+3], 371 [M+6]; Found: %: C, 52.58; H, 3.06; N, 15.35; Calculated for C₁₆H₁₁Cl₃N₄, %: C, 52.56; H, 3.03; N, 15.32.

2-(3-Methylphenyl)-5-(trichloromethyl)-5,6-dihydro[1,2,4]triazolo[1,5-c]quinazoline (2b). Yield – 53.9%; white crystals. M. p. – 175-176°C; IR,
5-(Trichloromethyl)-2-(3-trifluoromethyl)quinazoline (2c) Yield – 99.9%; white crystals. M. p. – 201-202°C; IR, ν, cm⁻¹: 3256, 3236, 3123, 3111, 3040, 2962, 2933, 2829, 1624, 1606, 1590, 1517, 1482, 1463, 1437, 1409, 1349, 1317, 1284, 1273, 1236, 1193, 1154, 1112, 1078, 1026, 990, 953, 862, 848, 829, 808, 792, 771, 757, 741, 710, 688, 639, 613; ¹H NMR, δ, ppm (J, Hz): 8.39 (d, J = 4.0 Hz, 1H, NH), 7.96 (d, J = 8.0 Hz, 2H, H-2, Ar), 7.78 (d, J = 7.7 Hz, 1H, H-10), 7.38-7.27 (m, 3H, H-4, Ar, H-8), 7.06 (d, J = 8.2 Hz, 1H, 7), 6.93 (d, J = 4.0 Hz, 1H, H-5), 6.87 (t, J = 7.5 Hz, 1H, H-9), 2.34 (s, 3H, CH₃); Found: %: C, 53.75; H, 3.40; N, 14.75; Calculated for C₁₇H₁₀Cl₃N₄: %: C, 53.78; H, 3.45; N, 14.76.

2-(3-Methoxyphenyl)-5-trichloromethyl)-5,6-dihydro-[1,2,4]triazolo[1,5-c]quinazolin (2f) Yield – 72.6%; white crystals. M. p. – 72-74°C; IR, ν, cm⁻¹: 3202, 3193, 3121, 3057, 2925, 2854, 1611, 1611, 1594, 1553, 1503, 1474, 1456, 1423, 1339, 1305, 1289, 1279, 1252, 1181, 1170, 1156, 1123, 1109, 1084, 1034, 1018, 956, 945, 842, 813, 751, 707, 679, 648, 630, 613, 604; ¹H NMR, δ, ppm (J, Hz): 8.38 (d, J = 4.0 Hz, 1H, NH), 8.01 (d, J = 8.8 Hz, 2H, H-2, Ar), 7.76 (d, J = 7.7 Hz, 1H, H-10), 7.31 (t, J = 7.8 Hz, 1H, H-8), 7.08-7.02 (m, 1H, H-3, Ar), 6.91 (d, J = 4.0 Hz, 1H, H-5), 6.87 (t, J = 7.7 Hz, 1H, H-9), 3.79 (s, 3H, CH,O); ¹³C NMR, δ, ppm: 161.32 (C-2), 160.42 (C-4a), 150.75 (C-6a), 141.11 (C-10b), 132.34, 127.67, 123.84, 123.02, 118.92, 114.58, 112.42, 109.22, 102.61 (Cl), 77.95 (C-5), 55.41 (CH₂O); Found: %: C, 51.60; H, 3.29; N, 14.13; Calculated for C₁₇H₁₀Cl₃N₄O: %: C, 51.60; H, 3.31; N, 14.16.

The reaction of 2-phenyl-5-(trichloromethyl)-5,6-dihydro-1,2,4]triazolo[1,5-c]quinazoline (2a) with N-nucleophiles. To a solution of 3.65 g (10 mmol) of 2-phenyl-5-(trichloromethyl)-5,6-dihydro-[1,2,4]triazolo[1,5-c]quinazoline (2a) in 10 ml of isopropanol add 11 mmol of the corresponding nucleophile ([2,2-dimethoxymethyl]amine, benzylamine, morpholine, pipiridine, triethylamine). Then reflux the mixture for 1-1.5 h. While cooling to room temperature filter the precipitate and dry in the air.

2-Phenyl-5-(dichloromethyl)-1,2,4]triazolo[1,5-c]quinazoline (3a) Yield – 95%; white crystals. M. p. – 240-242°C; IR, ν, cm⁻¹: 3072, 3010, 2958, 2920, 2825, 1624, 1608, 1556, 1521, 1476, 1443, 1397, 1348, 1319, 1298, 1279, 1265, 1215, 1176, 1134, 1113, 1072, 1024, 964, 928, 894, 874, 806, 791, 780, 745, 722, 690, 669, 660, 629; ¹H NMR, δ, ppm (J, Hz): 8.60 (d, J = 7.6 Hz, H-7), 8.35 (d, J = 7.0 Hz, H-2, Ph), 8.17 (d, J = 8.0 Hz, H-10), 7.98 (t, J = 7.6 Hz, H-9), 7.89 (t, J = 7.3 Hz, H-8), 7.80 (s, 1H, -CH(Cl)), 7.54 (m, 3H, H-3,4,5 Ph); ¹³C NMR, δ, ppm: 163.41 (C-5), 152.01 (C-2), 143.43 (C-6a), 141.55 (C-7), 133.05, 113.15,
X-ray study

The colourless crystals of 2a \((C_{16}H_{11}N_{4}Cl_3)\) were rhombic. At 293 K, \(a = 6.1949(4)\), \(b = 10.9669(5)\), \(c = 23.4532(2)\) Å, \(V = 1593.41(2)\) Å\(^3\), \(M_r = 365.64\), \(Z = 4\), space group \(P2_12_12_1\), \(d_{calc} = 1.524 \text{ g/cm}^3\), \(\mu(\text{MoK} \alpha) = 0.578\) mm\(^{-1}\), \(F(000) = 744\). Intensities of 8685 reflections (4625 independent, \(R_\text{int} = 0.072\)) were measured on a "Xcalibur-3" diffractometer (graphite-monochromated MoK\( \alpha \) radiation, a CCD detector, \(\omega\)-scanning, \(2\Theta_{\text{max}} = 60^\circ\)). The structure was solved using a SHELXTL package [8]. Positions of the hydrogen atoms were located on electron density difference maps and refined by "riding" the model with \(U_{iso} = 1.2U_{eq}\) of the carrier atom. A hydrogen atom of the amino group was refined using isotropic approximation. Full-matrix least-squares refinement against \(F^2\) in anisotropic approximation for non-hydrogen atoms using 4582 reflections was converged to \(wR_2 = 0.124\) (\(R_1 = 0.060\) for 2645 reflections with \(F>4\sigma(F)\), \(S = 0.940\)). The final atomic coordinates and crystallographic data for molecule 2a were deposited to the Cambridge Crystallographic Data Centre, 12 Union Road, CB2 1EZ, UK (fax: +44-1223-336033; E-mail: deposit@ccdc.cam.ac.uk). They are available on request quoting the deposition number CCDC 1408958.

Conclusions

It has been shown that \([5+1]\) cyclocondensation of [2-(3-aryl-1H-1,2,4-triazole-5-yl)phenyl]amines with chloral hydrate leads to 5-trichloromethyl-2-aryl-5,6-dihydro-[1,2,4]triazolo[1,5-c]quinazolines, and it has allowed to expand their combinatorial library. When treating with \(N\)-nucleophiles the products eliminate hydrogen chloride to yield 2-phenyl-5-(dichloromethyl)-[1,2,4]triazolo[1,5-c]quinazolines. This happens irrespective of the nature of \(N\)-nucleophile used. The mechanism of this reaction has been discussed.

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