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Regioselective synthesis of bicyclic 1,3,5-triazepine system starting from tetrachloro-2-aza-1,3-butadienes

Bohdan A. Demydchuk[a*], Eduard B. Rusanov[b], Julia A. Rusanova[c] and Volodymyr S. Brovarets[a]

[a]*Institute of Bioorganic Chemistry and Petrochemistry, National Academy of Sciences of Ukraine, Murmanska str. 1, 02094 Kyiv, Ukraine*
[b]*Institute of Organic Chemistry, National Academy of Sciences of Ukraine, Murmanska str. 5, 02094 Kyiv, Ukraine*
[c]*Department of Chemistry, Taras Shevchenko National University, Volodymyrska Str. 64/13, Kyiv, 01601, Ukraine*

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Readily available tetrachloro-2-aza-1,3-butadienes enter into directed cyclocondensation reaction with N-phenyl-1,2-cyclopentanediamine which leads to regioselective cyclopentane annulation by the 1,3,5-triazepine. The formation of the 1,3,5-triazepine derivatives was confirmed proved by ^{1}H- and ^{13}C-NMR spectral study, elemental analysis and, in one case, single-crystal x-ray crystallographic study.

1. Introduction

1,3,5-Triazepines and their derivatives are found to be associated with various biological activities: antibacterial, antiviral, psychotropic activity,[1,2] CCK_2 receptor antagonists,[3] phospholipase A2 inhibitors,[4] HIV capsid assembly inhibitors.[5] However, information about hydrogenated 1,3,5-triazepine derivatives is very limited. Thus, due to the difficulty of such structures obtaining, 6,7-dihydro-1*H*-1,3,5-triazepines are presented by only two compounds.[6-8]

The efficient and selective method for synthesis of 7-membered heterocycles are [4+3]-cycloaddition processes.[9,10] Unfortunately, this approach is not adequate for preparation of 1,3,5-triazepines. Previously we proposed to use readily available 1-aryl-1,3,4,4-tetrachloro-2-aza-1,3-butadienes **1** for synthesis [1,3,5]triazepino[1,7-*a*]benzimidazole derivatives.[11] In the present work we use **1** for preparation of novel 1-substituted 6,7-dihydro-1*H*-1,3,5-triazepines which are annulated with cyclopentane fragment by *f*-edge.

* Corresponding author. Fax: +380(44) 5732561
E-mail address: bogdem@ukr.net (B. A. Demydchuk)

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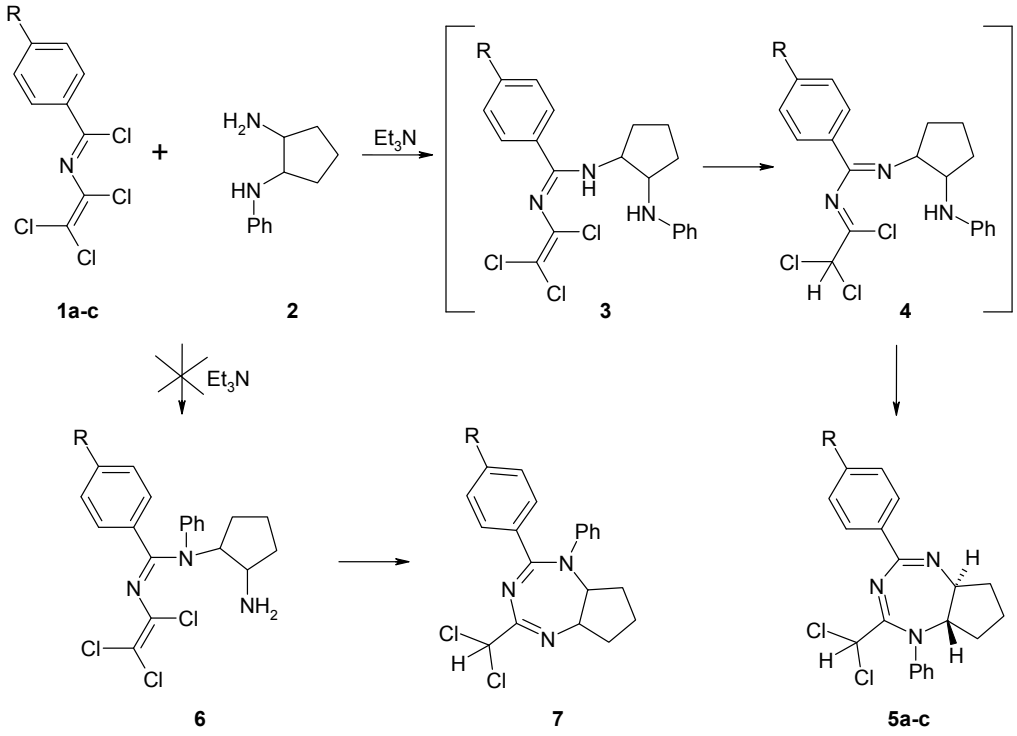
2. Results and discussion

Synthesis of cyclopenta[*f*][1,3,5]triazepines **5** was performed via interaction of reagents **1** with N-phenyl-1,2-cyclopentadiamine **2**. This reaction proceeds in THF at room temperature quite regioselectively and involves electrophilic centre C^1 and primary aminogroup giving intermediates **3** (see **Scheme 1**).



Scheme 1. Synthesis of cyclopenta[*f*][1,3,5]triazepine from tetrachloro-2-aza-1,3-butadienes.

The last ones are ready to undergo a [1,5]-sigmatropic shift **3** → **4** to form imidoyl chloride fragments which leads to further intramolecular heterocyclization with formation of a 1,3,5-triazepine cycle. In such way 4-aryl-2-(dichloromethyl)-1-phenyl-1*H*,5a*H*,6*H*,7*H*,8*H*,8a*H*-cyclopenta[*f*][1,3,5]triazepines were prepared and isolated with 92-96% yields. The probability of alternatively interaction of imidoyl chlorides **1** with diamine **2** resulting in formation of **6** and **7** is very small as far nucleophilicity of NH_2-group is much higher then nucleophilicity of NH-phenyl-group.

Such selectivity of tetrachloro-2-aza-1,3-butadienes **1** to N,N-bisnucleophiles was shown earlier.[12]

The structure of the reaction products was completely proved by combined spectral and crystallographic study of **5c**. The molecular structure of compound **5c** is shown on F**ig. 1** and characterised with selected bond lengths and angles: N1 C1 1.355(5), N1 C4 1.476(5), N2 C1 1.290(5), N2 C2 1.394(5), N3 C2 1.276(5), N3 C3 1.451(5), C3 C4 1.533(5), Cl1 C14 1.758(5), Cl2 C14 1.750(4)Å; C1 N1 C4 118.3(3), N1 C4 C3 111.6(3), N3 C3 C4 112.6(4), C2 N3 C3 115.5(4), N3 C2 N2 130.7(4), C1 N2 C2 129.9(4), N2 C1 N1 130.7(4)°**.**

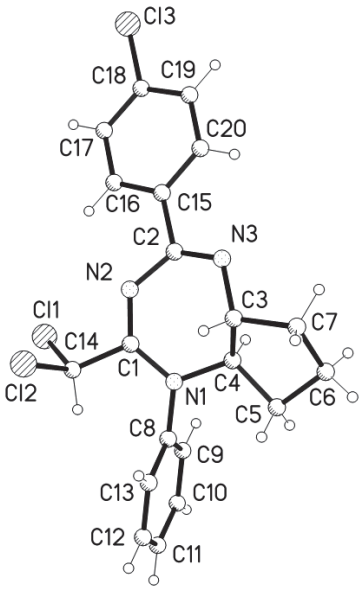


Fig. 1. Molecular structure of **5c**

In structure **5c** central bicyclic system is non planar. Atoms N3C3C2N2 of seven membered C_4N_3 cycle lies in the plane with rms deviations of fitted atoms 0.0184Å and atoms C1, N1 and C4 vary from that plane for 0.390(7), 0.994(9) and 1.239(7)Å respectivelly. In seven membered cycle the hydrogen atoms which is attached to C3 and C4 atoms has trans arrangement. The cyclopentane ring has envelope conformation. In seven membered ring bond lengths N2C1 and C2N3 corresponds to double C=N bonds (standard value is 1.28Å), whereas N3-C3 and N1C4 close to standard single C-N bond lengths which is 1.45Å. Both C1N1 and C2N2 bond lengths are corresponds to an intermediate value between single and double bond due to conjugation in N1C1N2C2N3 fragment.

3. Conclusion

An interaction between 1-aryl-1,3,4,4-tetrachloro-2-aza-1,3-butadienes **1** and 1,2-cyclopentanediamine **2** is regioselective by the primary aminogroup with further intramolecular heterocyclization with formation of unknown earlier 1-aryl-2-(dichloromethyl)-4-phenyl-1*H*,5a*H*,6*H*,7*H*,8*H*,8a*H*-cyclopenta[*f*][1,3,5]triazepines with high yields.

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4. Experimental

^{1}H (500 MHz) and ^{13}C (125 MHz) NMR spectra were recorded on Bruker Avance DRX 500 spectrometer in DMSO-d_6 solution with TMS as an internal standard. The IR spectra were recorded on a Vertex 70 spectrometer from KBr pellets. Melting points were measured with a Büchi melting point apparatus and are uncorrected. Elemental analysis was carried out by the Analytical Laboratory of Institute of Bioorganic Chemistry and Petrochemistry, National Academy of Sciences of Ukraine. The chromatomass spectra were recorded on an Agilent 1100 Series high performance liquid chromatograph equipped with a diode matrix with an Agilent LC\MS mass selective detector allowing a fast switching the ionization modes positive/negative. The reaction progress was monitored by the TLC method on Silica gel 60 F_{254} Merck.

1-Aryl-1,3,4,4-tetrachloro-2-aza-1,3-butadienes **1a-c** were prepared according to the data available in the literature.[13] N-Phenyl-1,2-cyclopentanediamine **2** were purchased from Enamine Ltd.

General procedure for the preparation of 4-aryl-2-(dichloromethyl)-1-phenyl-1*H*,5a*H*,6*H*,7*H*,8*H*,8a*H*-cyclopenta[*f*][1,3,5]triazepines **5a-c**.

To a suspension of N-phenyl-1,2-cyclopentanediamine dihidrochloride (0.87 g; 3.5 mmol) in dry THF (80 mL) compound **1** (3.5 mmol) and triethylamine (1.96 mL; 14 mmol) were added. The reaction mixture was stirred at room temperature for 6 days then the precipitated triethylammonium hydrochloride was filtered off and the solvent was removed under reduced pressure. The crude product was washed with deionized water and recrystallized from 2-propanol.

2-(Dichloromethyl)-1,4-diphenyl-1H,5aH,6H,7H,8H,8aH-cyclopenta[f][1,3,5]triazepine **5a**.
Compound **5a** was prepared following the general procedure from **1a** (0.94 g). Yield 1.23 g (94%), yelow crystals, mp 114-115 ^{0}C.
IR (KBr): 647; 704; 788; 1169; 1215; 1252; 1280; 1308; 1381; 1445; 1487; 1578; 1605 (cm^{-1}). ^{1}H NMR, δ: 1.40 (2H, m, CH_2), 1.57 (2H, m, CH_2), 1.99 (1H, m, CH_2), 2.40 (1H, m, CH_2), 3.92 (1H, m, CH), 4.22 (1H, m, CH), 6.12 (1H, s, $CHCl_2$), 7.40-7.50 (8H, m, ArH), 8.21 (2H, d, *J* 5.5 Hz, ArH). ^{13}C NMR, δ: 21.8, 32.9, 33.6, 67.9, 69.2, 72.8, 128.1, 128.2, 129.0, 129.7, 130.0, 130.3, 139.1, 140.3, 154.6, 158.0. MS: 372 $[M]^+$. Anal. calcd for $C_{20}H_{19}Cl_2N_3$: C, 64.52; H, 5.14; Cl, 19.05; N, 11.29. Found: C, 64.62; H, 5.08; Cl, 19.02; N, 11.2.

2-(Dichloromethyl)-4-(4-methylphenyl)-1-phenyl-1H,5aH,6H,7H,8H,8aH-cyclopenta[f][1,3,5]-triazepine **5b**.
Compound **5b** was prepared following the general procedure from **1b** (0.99 g). Yield 1.24 g (92%), yelow crystals, mp 121-126 ^{0}C.
IR (KBr): 698; 736; 781; 1172; 1248; 1284; 1488; 1576; 1608 (cm^{-1}). ^{1}H NMR, δ: 1.40 (2H, m, CH_2), 1.58 (2H, m, CH_2), 1.99 (1H, m, CH_2), 2.34 (3H, s, CH_3), 2.39 (1H, m, CH_2), 3.91 (1H, m, CH), 4.20 (1H, m, CH), 6.11 (1H, s, $CHCl_2$), 7.19 (2H, d, *J* 7.5 Hz, ArH), 7.37 (2H, d, *J* 6.5 Hz, ArH), 7.49 (3H, m, ArH), 8.10 (2H, d, *J* 8 Hz, ArH). ^{13}C NMR, δ: 21.4, 21.8, 32.9, 33.6, 67.7, 69.2, 72.8, 128.2, 128.87, 129.0, 129.7, 130.3, 136.4, 139.5, 140.4, 154.6, 158.1. MS: 386 $[M]^+$. Anal. calcd for $C_{21}H_{21}Cl_2N_3$: C, 65.29; H, 5.48; Cl, 18.35; N, 10.88. Found: C, 65.3; H, 5.52; Cl, 18.31; N, 10.76.

4-(4-Chlorophenyl)-2-(dichloromethyl)-1-phenyl-1H,5aH,6H,7H,8H,8aH-cyclopenta[f][1,3,5]triazepine **5c**.
Compound **5c** was prepared following the general procedure from **1c** (1.06 g). Yield 1.36 g (96%), yelow crystals, mp 139-140 ^{0}C.
IR (KBr): 687; 702; 771; 840; 1013; 1087; 1164; 1258; 1277; 1489; 1582; 1612 (cm^{-1}). ^{1}H NMR, δ: 1.43 (2H, m, CH_2), 1.60 (2H, m, CH_2), 1.99 (1H, m, CH_2), 2.41 (1H, m, CH_2), 3.93 (1H, s, CH), 4.22 (1H, s, CH), 6.10 (1H, s, $CHCl_2$), 7.38 (2H, d, *J* 5.5 Hz, ArH), 7.44 (2H, d, *J* 8 Hz, ArH), 7.50 (3H, s, ArH), 8.20 (2H, d, *J* 7 Hz, ArH). ^{13}C NMR, δ: 21.9, 32.8, 33.6, 68.1, 69.2, 72.6, 128.3, 129.0, 129.8, 129.9, 130.3, 134.9, 138.1, 140.2, 154.9, 157.1. MS: 408 $[M+1]^+$. Anal. calcd for $C_{20}H_{18}Cl_3N_3$: C, 59.06; H, 4.46; Cl, 26.15; N, 10.33. Found: C, 59.23; H, 4.54; Cl, 26.11; N, 10.25.

X-ray Structure determination for 5c.

Crystal data: $C_{20}H_{18}Cl_3N_3$, M 406.72, monoclinic, space group C2/c, a = 34.894(12), b = 6.3457(16), c = 17.416(4)Å, β = 94.58(1) V = 3844.0(18)Å^3, Z = 8, d_c = 1.406 g·cm^{-3}, μ = 0.486 mm^{-1}, F(000) = 1680, crystal size ca. 0.18 × 0.28 × 0.29 mm. All crystallographic measurements were performed at room temperature on a Bruker Smart Apex II diffractometer operating in the ω scans mode. The intensity data were collected within the range of $1.17 \le \theta \le 26.42°$ using Mo-K_α radiation (λ = 0.71078Å). The intensities of 13386 reflections were collected (3928 unique reflections, R_{merg} =

0.0776). The structure was solved by direct methods and refined by the full-matrix least-squares technique in the anisotropic approximation for non-hydrogen atoms using the Bruker SHELXTL program package.[14] The atom C6 of five membered cycle C3-C7 is disordered over two position A and B with occupancy 80 and 20% respectively. All CH hydrogen atoms were refined as 'riding' model. Convergence was obtained at R1 = 0.0715 and wR2 = 0.1087, GOF = 1.00 for 1772 observed reflections with $I \geq 2\sigma(I)$, 239 parameters; the largest and minimal peaks in the final difference map 0.56 and –0.44 e/Å^3. Full crystallographic details have been deposited at Cambridge Crystallographic Data Centre (CCDC). Any request to the CCDC for these materials should quote the full literature citation and reference number CCDC 1506735.

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