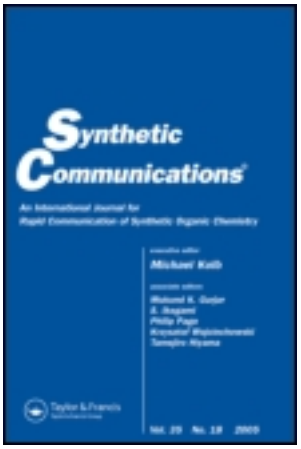

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EFFICIENT SYNTHESIS OF 1,3,5-BENZOTRIAZOCINES FROM TETRACHLORO-2-AZA-1,3-DIENES

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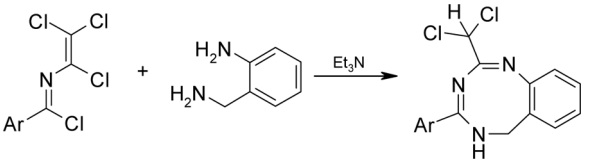
GRAPHICAL ABSTRACT



Abstract *Easily accessible 1-aryl-2-aza-1,3-butadienes undergo a regioselective cyclocondensation with 2-(aminomethyl)aniline, giving rise to 1,3,5-benzotriazocines in good yields. The structure of the title compounds was proved with the aid of* ^{1}H *and* ^{13}C *NMR spectra and, in one case, single-crystal x-ray analysis.*

[Supplementary materials are available for this article. Go to the publisher's online edition of Synthetic Communications® *for the following free supplemental resource(s): Full experimental and spectral details.]*

Keywords 2-(Aminomethyl)aniline; 1,3,5-benzotriazocine; heterocyclization; regioselective cyclocondensation; tetrachloro-2-aza-1,3-dienes

INTRODUCTON

1,3,5-Triazocines are a little explored class of heterocycles. To our knowledge there is only one report in the literature[1] on the synthesis of a 1,3,5-triazocine derivative that exhibited biological activity as a blood platelet aggregation inhibitor. Therefore, the development of novel synthetic approaches to the triazocine ring is of importance for medicinal chemistry and drug discovery.

In this context our attention was drawn by two reports showing that chlorinated 2-aza-1,3-dienes of type **A** (Scheme 1), in which two electrophilic units have remarkably different reactivity, undergo cyclocondensations with N-nucleophiles

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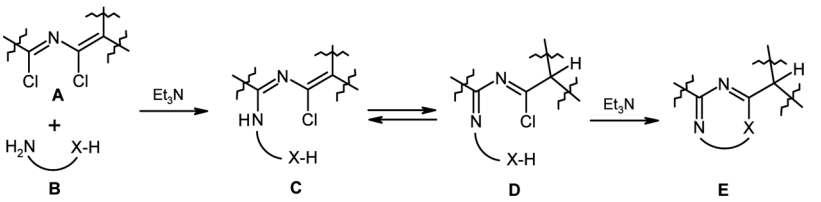
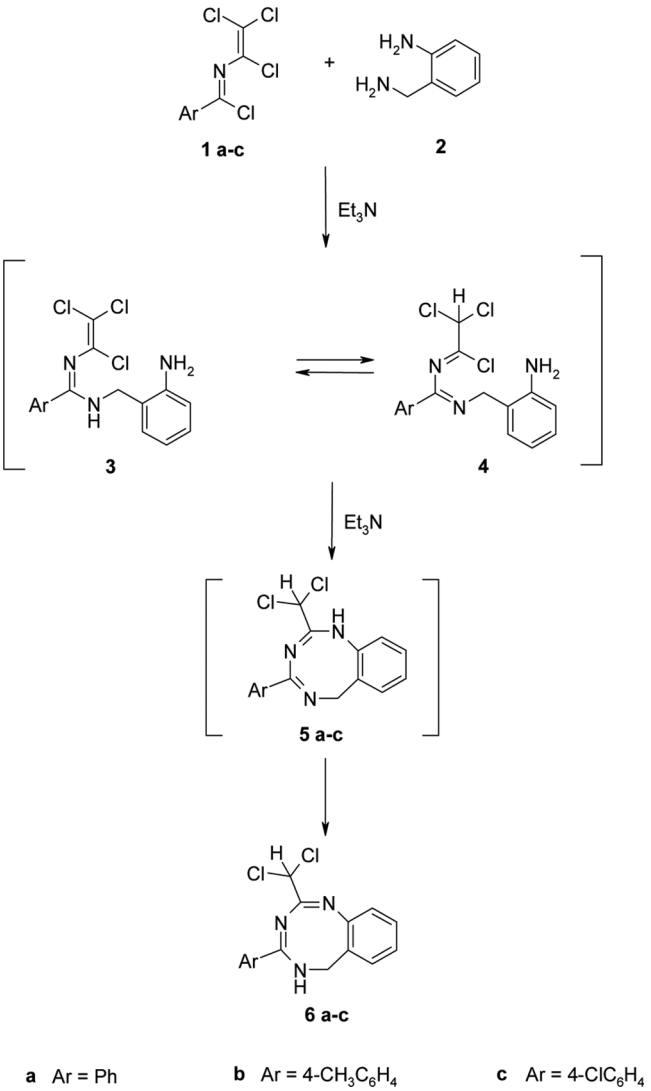


Scheme 1. Cyclocondensations of chlorinated 2-aza-1,3-dienes with N-nucleophiles.



Scheme 2. Synthesis of 1,3,5-benzotriazocines from tetrachloro-2-aza-1,3-dienes.

of type **B**.[2,3] As depicted in Scheme 1, the first step was the condensation at the more reactive electrophilic center of **A**, resulting in an intermediate **C**. The prototropic equilibrium between structures **C** and **D** activated the second electrophilic center to complete the cyclocondensation, yielding **E**.

1-Aryl-1,3,4,4-tetrachloro-4-aza-1,3-butadienes 1 (Scheme 2) were mainly used as structure **A**. These are easily prepared through an addition of aromatic amides to chloral.[4] Structure **B** was aromatic amines,[5] hydrazine derivatives and benzamidine,[6] and aminoazoles with an amidine unit.[7] However, in many cases the cyclocondensations proceeded in a nonregioselective manner, giving barely separable mixtures of products. At the same time, the regioselectivity was observed when two nucleophilic centers of structure **B** differed considerably in reactivity. The use of such ambivalent nucleophiles resulted in efficient syntheses of 7-, 8-, and 9-membered rings of type **E**.[8] In the present work we describe an efficient synthesis of several representatives of the 1,3,5-triazocine system through a regioselective cyclocondensation of 1-aryl-2-aza-1,3-butadienes **1** (Scheme 2) with 2-(aminomethyl)aniline.

The selectivity of the cyclization shown in Scheme 2 is seemingly due to the interplay of electrophilic and nucleophilic pairs. Thus, a noticeably greater nucleophilicity of methylamino group compared with aromatic amino group in compound **2** and different reactivity of the electrophilic centers in **1** and **4** contribute equally to the observed regioselectivity, resulting in 1,3,5-triazocines **6**. The analysis of ^{1}H and ^{13}C NMR spectra of compounds **6** as well as single-crystal x-ray study of compound **6a** (Fig. 1) leave no doubt about their correct structural assignment.

To sum up, hitherto unknown 1,3,5-benzotriazocines were synthesized on a preparative scale through the regioselective cyclocondensation of easily accessible tetrachloro-2-aza-1,3-dienes with 2-(aminomethyl)aniline. Further research of

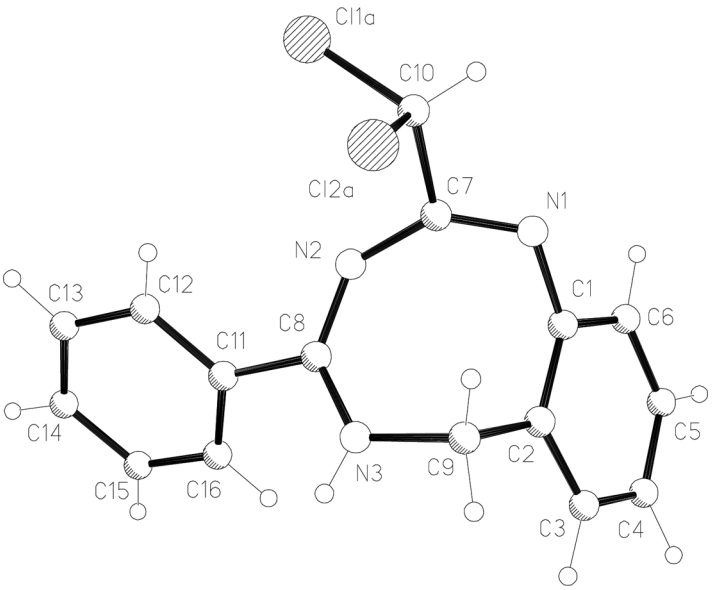


Figure 1. Molecular structure of compound **6a** was determined by single-crystal X-ray diffraction.

cyclocondensations of chlorinated azadienes with bis-nucleophiles is presently in progress in our laboratories.

EXPERIMENTAL

^{1}H (500 MHz) and ^{13}C (125 MHz) NMR spectra were recorded on Bruker Avance DRX 500 spectrometer in dimethylsulfoxide (DMSO-d_6) solution with tetramethylsilane (TMS) as an internal standard. 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\MSD SL mass selective detector, allowing fast switching of the ionization modes. The chromatomass spectral analysis parameters are as follows: column Zorbax SBC18 1.8 μm, 4.6.15 mm (PN 821975-932); solvents: A, acetonitrile–water mixture (95:5), 0.1% trifluoroacetic acid, B, 0.1% aqueous trifluoroacetic acid; eluent flow 3 ml min^{-1}, injection volume 1 μl, UV detectors 215, 254, 285 nm; the ionization method is atmospheric-pressure chemical ionization (APCI), scanning range m/z 80–1000. The reaction progress was monitored by thin-layer chromatography (TLC) on silica gel 60 F_{254} Merck.

Preparation and characterization details of compounds **1a**–**c**[2] are available from the literature; 2-(aminomethyl)aniline **2** was obtained from commercially available source (Aldrich) and used without further purification.

X-Ray Structure Determination for 6a

Crystal data: $C_{16}H_{13}Cl_2N_3$, M 318.19, monoclinic, space group $P2_1/c$, $a = 11.3880(5)$, $b = 10.8069(5)$, $c = 12.5643(6)$ Å, $\alpha = 94.161(3)^\circ$, $V = 1542.20(12)$Å^3, $Z = 4$, $d_c = 1.370\ g \cdot cm^{-3}$, $\mu = 0.417\ mm^{-1}$, $F(000) = 656$, crystal size ca. $0.08 \times 0.12 \times 0.46$ mm. All crystallographic measurements were performed at room temperature on a Bruker Smart Apex II diffractometer operating in the ω and φ scan mode. The intensity data were collected within the range of $1.79 \leq \theta \leq 28.32^\circ$ using Mo-K_α radiation ($\lambda = 0.71078$ Å). The intensities of 13575 reflections were collected (3825 unique reflections, $R_{merg} = 0.039$). The multiscan absorption correction (the minimum and maximum apparent transmissions are 0.8314 and 0.9674) was applied. The structure was solved by direct methods and refined by the full-matrix least-squares technique in the anisotropic approximation for nonhydrogen atoms using the Bruker SHELXTL program package.[9] Both chlorine atoms in the $CHCl_2$ group are disordered over two position with equal occupancies. All hydrogen atoms were refined isotropically. In the refinement 3825 reflections (2265 reflections with $I \geq 2\sigma(I)$) were used. Convergence was obtained at $R1 = 0.0889$ and $wR2 = 0.1282$ for all reflections, and $R1 = 0.0446$ and $wR2 = 0.1038$, $GOF = 0.996$ for observed (262 parameters; observed/variable ratio 8.6, The largest and minimal peaks in the final difference map 0.18 and $-0.26\ e/$Å^3. Weighting scheme is as follows: $\omega = 1/[\sigma^2(Fo^2) + (0.0495P)^2 + 0.4183P]$, where $P = (Fo^2 + 2Fc^2)/3$), 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 900508.

The eight-membered cycle is nonplanar. Atoms N2N3C7C8 lie in the plane with mean deviation from plane 0.0061 Å; atoms N1C1C2C9 situated in plane with mean deviation of 0.027 Å; dihedral angle between named planes is 82.2°.

Bond distances N1–C7 and N2–C8 have normal lengths (1.282 and 1.290 Å respectively) that are typical for standard C=N double bonds.

Bond distances N2–C7 1.360(2) and N3–C8 1.331(2) Å are short compared to standard single C-N bond because of conjugation in between π-systems of two C=N double bonds or π-system of the double bond with a lone pair of N3 atoms.

In the crystal, molecules are connected in chains by weak hydrogen N3-H3n . . . N1a bonds directed along crystallographic axes 0z. The parameters of H-bond is N3–H3n–N1a 173.98°, N3–H3n 0.81, N3 . . . N1a 3.054 Å. (By letter "a" the marked atom is connected to base atoms with symmetry operations x, $-y+3/2$, $z-1/2$).

General Procedure for the Preparation of 4-Aryl-2-dichloromethyl-5,6-dihydro-1,3,5-benzotriazocines (6a–c)

Compound **1** (3.5 mmol) and triethylamine (3.92 mL, 28 mmol) were added to a solution of 2-(aminomethyl)aniline (0.43 g, 3.5 mmol) in dry THF (20 mL). The reaction mixture was stirred at room temperature for 48 h and 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-4-phenyl-5,6-dihydro-1,3,5-benzotriazocin (6a). Compound **6a** was prepared following the general procedure from **1a** (0.94 g). Yield 0.95 g (85%), yellow crystals, mp 185–186 °C (destr.). ^{1}H NMR (500 MHz, DMSO-d_6): $\delta = 4.05$ (dd, 1H, CH_2), 4.69 (d, 1H, CH_2), 7.00 (s, 1H, $CHCl_2$), 7.04–7.81 (m, 9H, ArH), 8.49 (d, $^3J_{HH} = 0.5$ Hz, 1H, NH). ^{13}C NMR (125 MHz, DMSO-d_6): $\delta = 44.21$, 74.26, 123.56, 124.75, 127.98, 128.51, 128.77, 129.42, 130.63, 131.87, 135.06, 149.23, 157.66, 160.96. Anal. calcd. for $C_{16}H_{13}Cl_2N_3$: C, 60.39; H, 4.12; Cl, 22.28; N, 13.21. Found: C, 59.95; H, 4.24; Cl, 22.38; N, 13.17. LC\MS found m/z 318 $[M]^+$.

2-Dichloromethyl-4-(4-methylphenyl)-5,6-dihydro-1,3,5-benzotriazocin (6b). Compound **6b** was prepared following the general procedure from **1b** (1 g). Yield 0.91 g (89%), yellow crystals, mp 174–175 °C (destr.). ^{1}H NMR (500 MHz, DMSO-d_6): $\delta = 2.33$ (s, 3H, CH_3), 4.16 (dd, 1H, CH_2), 4.67 (dd, 1H, CH_2), 6.98 (s, 1H, $CHCl_2$), 7.01–7.70 (m 9H, ArH), 8.40 (s, 1H, NH). ^{13}C NMR (125 MHz, DMSO-d_6): $\delta = 21.39$, 44.18, 74.31, 123.57, 124.66, 127.94, 128.62, 129.26, 129.36, 130.59, 132.28, 141.80, 149.28, 157.53, 160.96. Anal. calcd. for $C_{17}H_{15}Cl_2N_3$: C, 61.46; H, 4.55; Cl, 21.34; N, 12.65. Found: C, 61.95; H, 4.38; Cl, 21.80; N, 12.07. LC\MS found m/z 334 $[M+2]^+$.

3-(4-Chlorophenyl)-2-dichloromethyl-5,6-dihydro-1,3,5-benzotriazocin (6c). Compound **6c** was prepared following the general procedure from **1c** (1.06 g).

Yield 1.18 g (96%), yellow crystals, mp 177–178 °C (destr.). Anal. calcd. for $C_{16}H_{12}Cl_3N_3$: C, 54.50; H, 3.43; Cl, 30.16; N, 11.92. Found: C, 54.91; H, 3.28; Cl, 30.27; N, 11.67. ^{1}H NMR (500 MHz, DMSO-d_6): $\delta = 4.05$ (dd, 1H, CH_2), 4.68 (dd, 1H, CH_2), 7.00 (s, 1H, $CHCl_2$), 7.03–7.82 (m, 8H, ArH), 8.57 (s, 1H, NH). ^{13}C NMR (125 MHz, DMSO-d_6): $\delta = 44.20$, 74.15, 123.56, 124.82, 128.27, 128.88, 129.46, 129.81, 130.65, 133.88, 136.71, 149.12, 156.64, 160.71. LC\MS found m/z 354 $[M + 1]^+$.

SUPPORTING INFORMATION

Full experimental detail, ^{1}H and ^{13}C NMR spectra, and HPLC traces can be found via the Supplementary Content section of this article's Web page.

REFERENCES

1. Kienzle, F.; Kaiser, A.; Chodnekar, M. S. 1,5-Dihydroimidazoquinazolinones as blood platelet aggregation inhibitors. *Eur. J. Med. Chem.* **1982**, *6*, 547–556.
2. (a) Drach, B. S.; Kovalev, V. A.; Kirsanov, A. V. Interaction of acyl chlorides N-1,2,2,2-thetrachloroethyl-, N-perchlorovinyl-, and N-perchloroethylimino carboxylic acids with amines. *Zh. Org. Khim.* **1975**, *11*, 122–127; (b) *Chem. Abstr.* **1975**, *83*, 9415 k.
3. (a) Drach, B. S.; Kovalev, V. A.; Lavreniyk, T. Ya. Halogenation of N-perchlorovinyliminoesters. *Zh. Org. Khim.* **1975**, *11*, 1913–1917; (b) *Chem. Abstr.* **1976**, *84*, 30571.
4. Jacobsen, O. Ueber einige Verbindungen des Chlorals mit Alkoholen und mit Amiden. *Just. Lieb. Ann. Chem.* **1871**, *157*, 243–248.
5. (a) Drach, B. S.; Kovalev, V. A.; Kirsanov, A. V. Cyclization reaction of acyl chlorides of N-perchlorovinyliminocarboxylic acids. *Zh. Org. Khim.* **1976**, *12*, 673–678; (b) *Chem. Abstr.* **1976**, *85*, 21300.
6. Drach, B. S.; Kovalev, V. A. Acyl chlorides of N-1-chloroalkyl-N-1-chloro-1-alkenyliminobenzoic acids. *Zh. Org. Khim.* **1976**, *12*, 2319–2325.
7. (a) Demydchuk, B. A.; Brovarets, V. S.; Chernega, A. N.; Hovard, J. A. K.; Vasilenko, A. N.; Turov, A. V.; Drach, B. S. Reaction of 1-aryl-1,3,4,4-tetrachloro-2-azabuta-1,3-dienes with aminoazoles. *Zh. Obsh. Khim.* **2007**, *77*, 510–517; (b) *Russian J. Gen. Chem.* **2007**, *77*, 474–481.
8. Demydchuk, B. A.; Gakh, A. A.; Brovarets, V. S.; Chernega, A. N.; Drach, B. S. Regioselective annulation of seven-, eight-, and nine-membered azaheterocycles to benzimidazole starting from chloro-substituted 2-aza-1,3-dienes. *Synthesis* **2006**, *14*, 2323–2326.
9. Sheldrick, G. M. A short history of SHELX. *Acta Cryst.* **2008**, *A64*, 112–122.