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Concise and regioselective synthesis of *5H*-imidazo[1,2-*e*][1,3,5]triazepines

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Dedicated to Prof. Girolamo Cirrincione in recognition of his outstanding contributions to the fields of organic and medicinal chemistry on the occasion of his retirement

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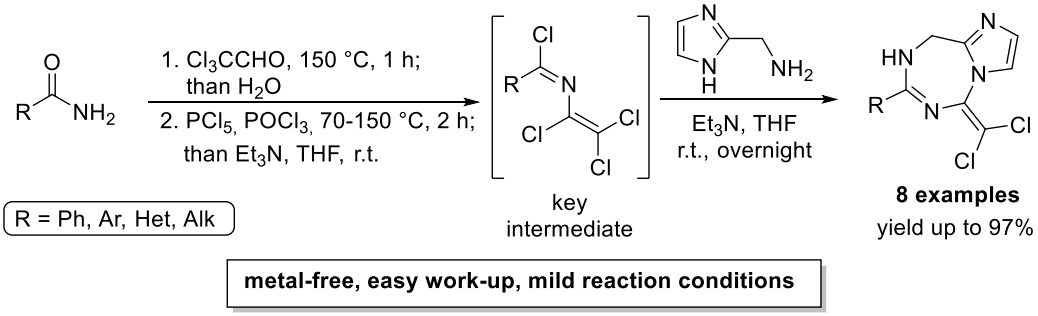
Abstract

In this communication, we report a regioselective synthesis of novel 5*H*-imidazo[1,2-*e*][1,3,5]triazepines *via* the interaction of tetrachloro-2-aza-1,3-butadienes with (1*H*-imidazol-2-yl)methanamine. The advantages of the presented method are mild reaction conditions, a simple work-up procedure, available reagents, and high yields. A possible mechanism is proposed for the synthesis of key products. The structure of one of the obtained products was proven with asingle crystal X-ray diffraction-based structure.



Keywords: Tetrachloro-2-aza-1,3-butadienes, (1*H*-imidazol-2-yl)methanamine, 1,3,5-triazepine, imidazotriazepine, regioselective annulation

Introduction

Aza-heterocycles are common structural motifs found in naturally occurring systems and bioactive molecules.[1,2] Among them, imidazotriazepines are privileged structural scaffolds that show a broad spectrum of potent biological activity and have been widely applied in medicinal chemistry as inhibitors of adenosine deaminase (like example **1**, Figure 1),[3] inhibitors of NTPases/helicases of Flaviviridae - including the West Nile virus (WNV), hepatitis C virus (HCV), and Japanese encephalitis virus (JEV)[4] -, selective inhibitors of hepatitis B virus (HBV)[5] (for example, compound **2**), inhibitors of the growth of carcinoma nasopharynx, breast cancer and cervical cancer cell lines (see compound **3**)[6] and potential drug candidates for treating the central nervous system diseases (see compounds **4** and **5**).[7,8]

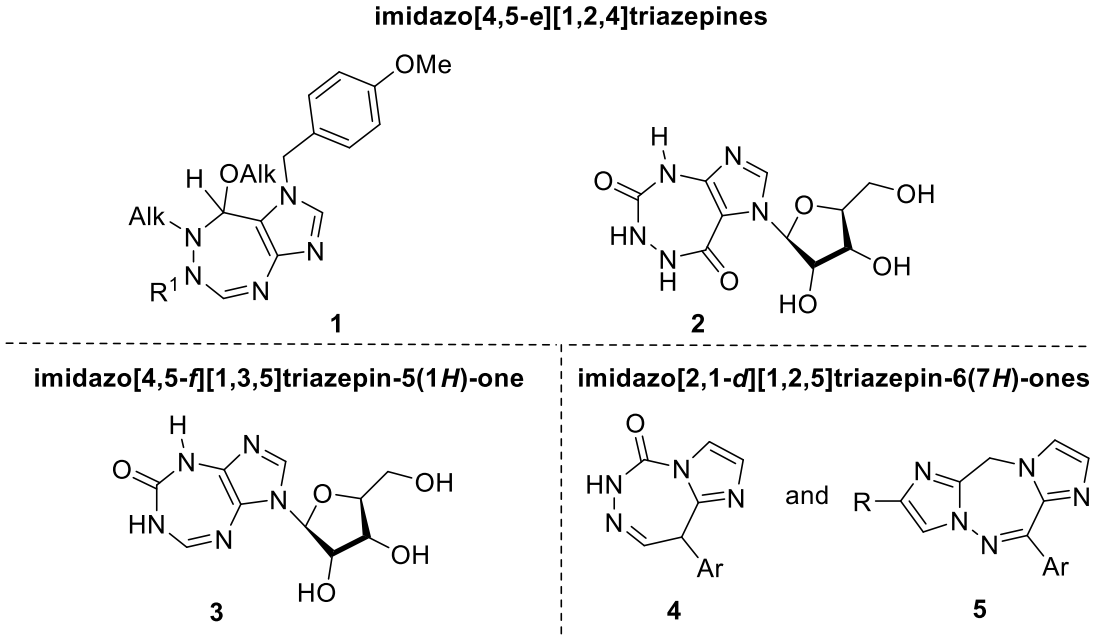


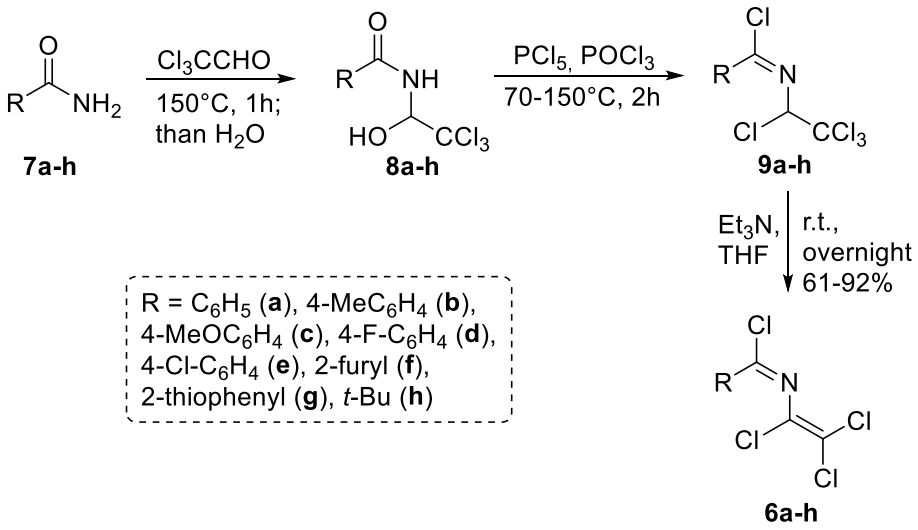
Figure 1. Examples of biologically active imidazotriazepine frameworks.

Different approaches for the synthesis of imidazo-fused triazepines have been developed because of their profound biological importance, and fairly recent reviews have summarized the synthetic approaches to fused 1,2,5-triazepines[9] and 1,3,5-triazepines.[10] Of note is that the first representatives of imidazo[1,2-*e*][1,3,5]triazepines were obtained by Kaupp and Sailer using a synthetic strategy based on the interaction of 2-chloromethylbenzimidazole with 2 equivalents of methylamine or ethylamine in dichloromethane.[11]

The chemistry of tetrachloro-2-aza-1,3-diene derivatives has been our research group's ongoing interest. Previously, we have reported our studies on the successful synthesis of [1,3,5]triazepino[1,7-*a*]benzimidazoles, [1,3,5]triazocino[1,8-*a*]benzimidazoles and [1,3,5]triazonino[1,9-*a*]benzimidazoles,[12] 1,3,5-benzotriazocines[13] and bicyclic 1,3,5-triazepines.[14] In the current study, we investigated a synthetic approach to target 5*H*-imidazo[1,2-*e*][1,3,5]triazepines starting with the corresponding tetrachloro-2-aza-1,3-butadienes.

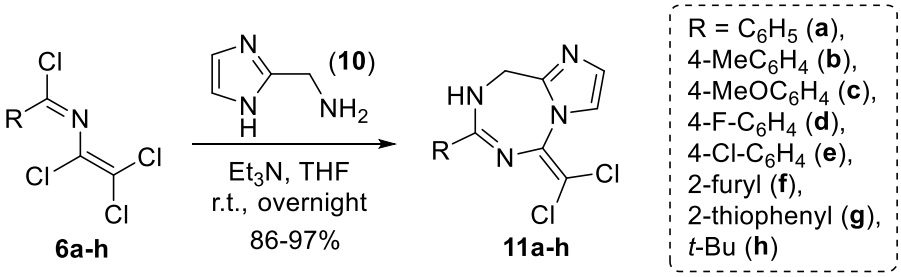
Results and Discussion

After carefully optimizing reaction conditions, *N*-(1,2,2-trichlorovinyl)-benzimidoylchlorides **6a-h** were obtained in 3 steps with good yields (Scheme 1). The first stage of the synthetic sequence was the interaction of amides **7a-h** with chloral while heating, resulting in the corresponding chloralamides **8a-h**. Further reaction of products **8a-h** with PCl_5 in $POCl_3$ while heating, gave imidoyl chlorides **9a-h**, which were then treated with triethylamine in THF to obtain the target *N*-(1,2,2-trichlorovinyl)benzimidoylchlorides **6a-h** in yields of up to 92% (Scheme 1). The purity of **8a-h** and **9a-h** was 98% or higher (based on ^{1}H NMR spectra data of reaction mixtures), and the products were successfully used in subsequent stages without additional purification and characterization (spectral data are given only for product **8g**, **9f**, **9g**, and **9h**).



Scheme 1. Synthesis of target *N*-(1,2,2-trichlorovinyl)benzimidoylchlorides **6a-h.**

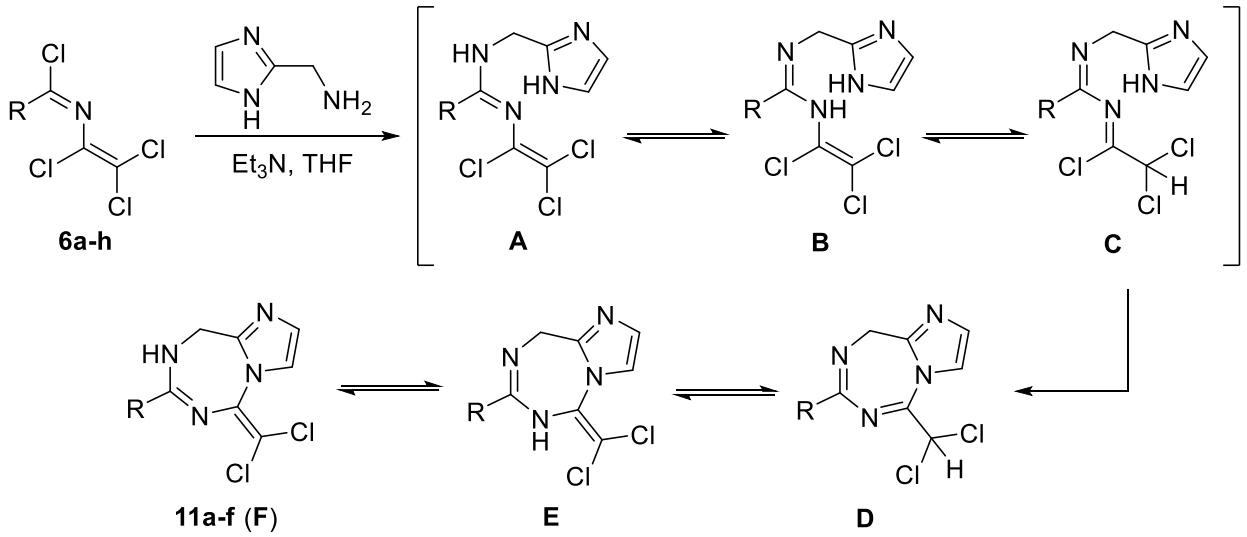
The key step of the process was based on the intramolecular nucleophilic substitution of 2-(aminomethyl)imidazole (**10**) in the presence of Et_3N, resulting in the regioselective formation of 5*H*-imidazo[1,2-*e*][1,3,5]triazepines **11a-h** (Scheme 2).



Scheme 2. Synthesis of target 5*H*-imidazo[1,2-*e*][1,3,5]triazepines **11a-h.**

A plausible mechanism of the reaction is presented on Scheme 3. Presumably, products **6** interact first with the amino group of 2-(aminomethyl)imidazole, first resulting in the intermediary **A**, for which prototropic forms **B** and **C** are possible. The direction of the imidazotriazepine system-forming process (**6** to product **11**) is determined by the high nucleophilicity of the side chain amino group compared to the N^1 and N^3 centers of

the imidazole ring (Scheme 3). Additionally, chlorine atom mobility near C^1 and C^3 of **6** and prototropy of intermediaries **A-C** play an important role. The combination of these factors results in the formation of product **D** or its prototropic isomers **E** and **F**, which contain a 7-membered triazepine ring (Scheme 3). Among the three prototropic forms **D**, **E**, or **F**, the form **F** (products **11a-h**) is more probable, as evidenced by the lack of $CHCl_2$ group characteristic signal and the presence of the characteristic NH triplet at 7.86-8.89 ppm in the DMSO-d_6 ^{1}H NMR spectra.



Scheme 3. A possible mechanism for the formation of the 5*H*-imidazo[1,2-*e*][1,3,5]triazepines **11a-h**.

NMR spectra obtained at a higher temperature (40°C) demonstrated the presence of all three prototropic forms **D**, **E**, and **F**, where a proton moved from one part of the molecule to another accompanied by the migration of the double bond.

In addition, single crystal X-ray crystallography of **11a** showed that the single most energetically favorable prototropic form **11** existed in the crystal state (Figure 2).

The five-membered N3N4C3C12C13 cycle in structure **11a** is planar (the rms deviation of fitted atoms is 0.0021) and bond distances and angles are typical for the pyrazole cycle. The seven-membered N1N2N3C1C2C3C4 cycle has a butterfly-like conformation with a dihedral angle between C2N3C3C4 and C2N2C1N1C4 planes of 126.4°; in addition, the bond distances indicate conjugation in the N1C1N2C2C11 fragment. In the crystal form, two molecules are connected in a centrosymmetric dimer N1H1n···N4a by a hydrogen bond with the following parameters: N1-H1n 0.88(3), N1···N4a 2.952(4)Å, N1-H1n-N4a 154(2)° (nitrogen atom labeled 'a' is connected to original atoms by symmetry operation *-x, -y,-z*).

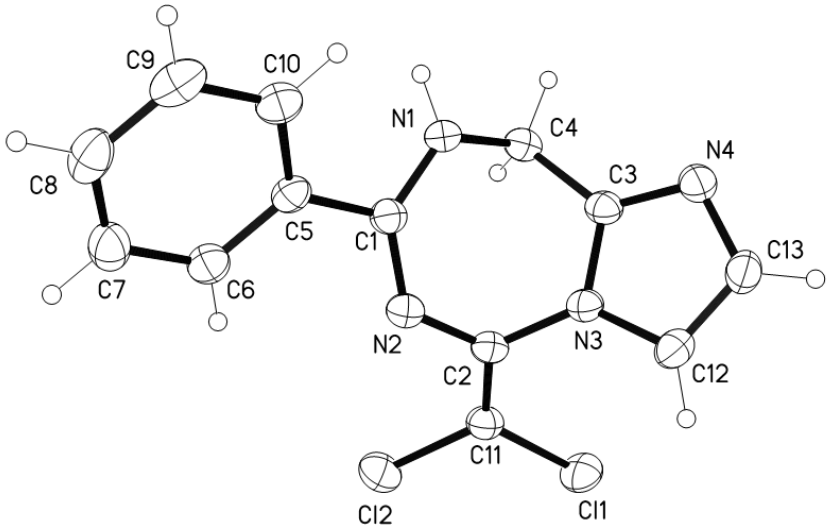
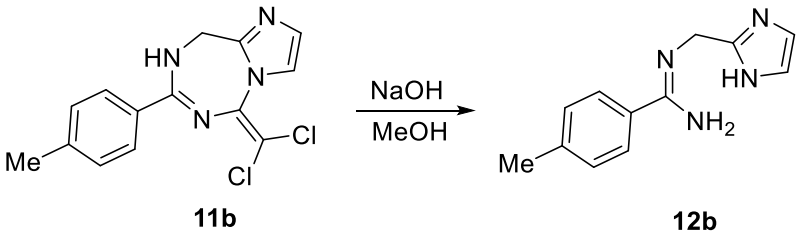


Figure 2. Molecular structure of **11a** (the ellipsoids are drawn at 50% probability level) and selected bond lengths and angles: N1 C1 1.346(2), N1 C4 1.457(2), N2 C1 1.303(2), N2 C2 1.376(2), N3 C3 1.364(2), N3 C12 1.384(2), N3 C2 1.436(2), N4 C3 1.315(2), N4 C13 1.387(2), C12 C13 1.354(3), C2 C11 1.342(2)Å; C1 N1 C4 123.04(14) N2 C1 N1 128.06(16) C1 N2 C2 126.47(15), N2 C2 N3 119.46(14)°.

The scope of application of this heterocyclization allowed the introduction of substituted aliphatic, aromatic, and heterocyclic substituents onto the C-7 position of the imidazotriazepine system. However, the introduction of a CH_3 group *via* this approach turned out to be impossible due to the high reactivity of methyl-2-azatetrachloro-1,3-butadiene **6** (R = CH_3), which appeared to spontaneously polymerize. An attempt to perform the cyclization of this compound with **9** did not result in the desired end product **11** with a methyl group as R. Additionally, this method did not allow the introduction of hydrogen into the C-7 position of the imidazotriazepine due to isocyanate formation from the corresponding chloralamide and phosphorus pentachloride.

It should be noted that the prototropy of the obtained imidazotriazepines makes them susceptible to polymerization. Thus, heating solutions of these compounds above 60°C, or melting them, results in resinification, complicating the purification of these compounds *via* recrystallization from solvents with a high boiling point.

We also demonstrated that imidazotriazepines decompose in an aqueous base medium. Thus, treating product **11b** in methanol with an aqueous solution of NaOH resulted in a stable amidine **12b** (Scheme 4).



11b **12b**

Scheme 4. Synthesis of amidine **12b.**

Conclusions

We have developed an efficient synthetic strategy for obtaining imidazo[1,2-*e*][1,3,5]triazepines in high yields, starting with commercially available amides as precursors of tetrachloro-2-aza-1,3-butadienes. The proposed approach leads to an efficient regioselective synthesis of 7-(het)aryl-5*H*-imidazo[1,2-*e*][1,3,5]triazepines, which are essential frameworks in the synthesis of bioactive molecules and naturally occurring systems.

Experimental Section

General. The solvents were purified according to the standard procedures.[15] All other starting materials were purchased from commercial sources. Analytical TLC was performed using Polychrom SI F254 plates. Elemental analyses were performed at the Analytical Laboratory of the V.P. Kukhar Institute of Bioorganic Chemistry and Petrochemistry NAS of Ukraine. Melting points were measured on MPA100 OptiMelt automated melting point system. InfraRed (IR) spectra were recorded on a VERTEX 70v FT-IR spectrometer in KBr plates. NMR spectra were recorded on a Varian Unityplus 400 spectrometer (400 and 100 MHz respectively) in DMSO-d_6 and $CDCl_3$ solutions; chemical shifts are reported in ppm with solvent residual signal used as an internal standard (^{1}H, ^{13}C). Mass spectra were recorded on an Agilent 1100 LCMSD SL instrument (chemical ionization (APCI)).

***N*-(2,2,2-Trichloro-1-hydroxyethyl)thiophene-2-carboxamide (8g)** (general procedure). To a thiophene-2-carboxamide (**7g**, 76 g, 0.60 mol), chloral hydrate (115.7 g, 0.6995 mol) was added. The reaction mixture was heated to 150°C, and kept at this temperature for 1 h. After cooling, water (500 mL) was added, the residue was filtered, washed with water and dried. Yield 155 g (94%). mp 171-172 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ_H δ 5.99 (dd, 1H, *J* 6 and 8 Hz,), 7.16 (t, 1H, *J* 4.8 Hz), 7.81 (d, 1H, *J* 4.8 Hz), 7.89 (d, 1H, *J* 5.6 Hz), 8.10 (d, 1H, *J* 4.0 Hz), 9.15 (d, 1H, *J* 8.4 Hz). ^{13}C NMR (100 MHz, DMSO-d_6): δ_C 81.7, 102.9, 128.5, 130.3, 132.5, 138.9, 161.6. Anal. calcd for $C_7H_6Cl_3NO_2S$ (274.55): C, 30.62; H, 2.2; Cl, 38.74; N, 5.10; O, 11.66; S, 11.68. Found: C, 30.50; H, 2.12; Cl, 38.81; N, 5.00; S, 11.71. MS (ESI$^+$) *m/z*: 272 [M-2]$^-$, 275.9 [M+H]$^-$.

***N*-(1,2,2,2-Tetrachloroethyl)furan-2-carbimidoylchloride (9f).** To **8f** (90 g, 0.348 mol), phosphoryl chloride (100 mL) and phosphorus pentachloride (181 g, 0.861 mol) were added. The reaction mixture was then heated at 70°C for 2 h. After cooling, acetic acid (10 mL, 0.17 mol) was added and phosphoryl chloride removed *in vacuo*. The residue was distilled *in vacuo* and the yellow product crystallized. Yield 76.1 g (75%). mp 70-72 °C. bp 120-122 °C /1mm Hg/. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 6.12 (s, 1H), 6.57 (dd, 1H, *J* 1.6 and 3.6 Hz), 7.30 (d, 1H, *J* 3.6 Hz), 7.68 (d, 1H, *J* 1.6 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 83.3, 99.6, 112.8, 120.4, 141.7, 147.6, 148.1. Anal. calcd. for $C_7H_4Cl_5NO$ (295.38): C, 28.47; H, 1.37; Cl, 60.01; N, 4.74; O, 5.42. Found: C, 28.53; H, 1.22; Cl, 59.84; N, 4.63. MS (ESI$^+$) *m/z*: 296.6 [M+H]$^-$.

***N*-(1,2,2,2-Tetrachloroethyl)thiophene-2-carbimidoylchloride (9g)** (*general procedure*)**.** To **8g** (60 g, 0.22 mol), phosphoryl chloride (100 mL) and phosphorus pentachloride (113.7 g, 0.546 mol) were added. After a rapid discharge of HCl, the reaction mixture was heated at 140°C for 2 h, until the complete release of hydrogen chloride was achieved. After cooling, phosphoryl chloride was removed *in vacuo*. Hexane (200 mL) was then added, the excess of phosphorus pentachloride was removd by filtration, and the product was obtained by distillation *in vacuo*. Yield 62 g (91%). bp 92-93 °C /1mm Hg/. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 6.11 (s, 1H), 7.14 (dd, 1H, *J* 3.6 and 5.2 Hz), 7.65 (dd, 1H, *J* 1.2 and 5.2 Hz), 7.87 (dd, 1H, *J* 1.2 and 4 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 83.3, 99.7, 128.0, 134.2, 134.5, 139.0, 146.1. Anal. calcd. for $C_7H_4Cl_5NS$ (311.43): C, 27.00; H, 1.29; Cl, 56.92; N, 4.50; S, 10.29. Found: C, 27.03; H, 1.27; Cl, 56.94; N, 4.43; S, 10.27. MS (ESI$^+$) *m/z*: 312.5 [M+H]$^-$.

***N*-(1,2,2,2-Tetrachloroethyl)pivalimidoylchloride (9h).** To **8h** (10 g, 0.04 mol), 10 mL of phosphoryl chloride and phosphorus pentachloride (17.5 g, 0.0840 mol) were added. After a rapid discharge of HCl, the reaction mixture was heated at 140°C for 8 h until the complete release of hydrogen chloride. After cooling, phosphoryl chloride was removed *in vacuo*. The product was then obtaind by distillation *in vacuo*. Yield 10.2 g (89%). bp 54-56 °C /0.5 mm Hg/. ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.29 (s, 9H), 5.86 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 28.0, 44.7, 82.6, 99.7, 165.3. Anal. calcd. for $C_7H_{10}Cl_5N$ (285.43): C, 29.46; H, 3.53; Cl, 62.10; N, 4.91. Found: C, 29.34; H, 3.61; Cl, 62.11; N, 4.83. MS (ESI$^+$) *m/z*: 286.8 $[M+H]^-$.

General procedure for the preparation of *N*-(1,2,2-trichlorovinyl)(het)arylchlorides (6a-h). To a solution of 0.0535 mol of one of compounds **(9a-g)** in THF (100 mL) was added triethylamine (7.5 mL, 0.054 mol). The reaction mixture was then stirred for 24 h. The precipitate was filtered, washed with THF (20 mL), and the filtrate was evaporated *in vacuo*. The resulting imodyl chloride was subsequently obtained by distillation *in vacuo*.

***N*-(1,2,2-Trichlorovinyl)benzimidoylchloride (6a).** Yield 12.9 g (90%). bp 135-138 °C /0.5 mm Hg/. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.51 (t, 2H, *J* 7.6 Hz), 7.64 (t, 1H, *J* 7.6 Hz), 8.19 (d, 2H, *J* 7.6 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 110.0, 128.3, 129.4, 129.5, 133.2, 133.7, 151.9. Anal. calcd. for $C_9H_5Cl_4N$ (268.95): C, 40.19; H, 1.87; Cl, 52.73; N, 5.21. Found: C, 40.20; H, 1.73; Cl, 52.39; N, 4.98. MS (ESI$^+$) *m/z*: 269.4 $[M+H]^-$.

4-Methyl-*N*-(1,2,2-trichlorovinyl)benzimidoylchloride (6b). Yield 11.8 g (78%). bp 95-102 °C /0.4 mm Hg/. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 2.48 (s, 3H), 7.30 (d, 2H, *J* 8 Hz), 8.07 (d, 2H, *J* 8.4 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 21.7, 110.0, 129.4, 129.9, 130.1, 131.4, 144.7, 152.4. Anal. calcd. for $C_{10}H_7Cl_4N$ (282.99): C, 42.44; H, 2.49; Cl, 50.11; N, 4.95. Found: C, 42.48; H, 2.50; Cl, 50.18; N, 4.78. MS (ESI$^+$) *m/z*: 283.9 $[M+H]^-$.

4-Methoxy-*N*-(1,2,2-trichlorovinyl)benzimidoylchloride (6c). Yield 11.9 g (74%). mp 29-30 °C, bp 110-112 °C /0.03 mm Hg/. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 3.89 (s, 3H), 6.95 (d, 2H, *J* 8.8 Hz), 8.10 (d, 2H, *J* 9.2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 55.2, 109.2, 113.5, 125.9, 129.8, 131.5, 151.4, 163.7. Anal. calcd. for $C_{10}H_7Cl_4NO$ (298.99): C, 40.17; H, 2.36; Cl, 47.43; N, 4.68; O, 5.35. Found: C, 40.21; H, 2.41; Cl, 47.48; N, 4.59. MS (ESI$^+$) *m/z*: 299.9 $[M+H]^-$.

4-Fluoro-*N*-(1,2,2-trichlorovinyl)benzimidoylchloride (6d). Yield 9.4 g (61%). bp 90-91 °C /0.5 mm Hg/. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.17 (t, 2H, *J* 8.8 Hz), 8.16-8.19 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 110.7, 115.8, 129.7, 130.3, 132.2, 150.8, 165.09, 167.1. ^{19}F NMR (100 MHz, $CDCl_3$): δ_F -72.4, -72.2. Anal. calcd. for $C_9H_4Cl_4FN$ (286.95): C, 37.67; H, 1.41; Cl, 49.42; F, 6.62; N, 4.88. Found: C, 37.52; H, 1.43; Cl, 49.48; F, 6.54; N, 4.69. MS (ESI$^+$) *m/z*: 287.7 $[M+H]^-$.

4-Chloro-*N*-(1,2,2-trichlorovinyl)benzimidoylchloride (6e). Yield 13.1 g (81%). mp 36-37 °C, bp 103-105 °C /0.5 mm Hg/. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.45 (d, 2H, *J* 8.8 Hz), 8.07 (d, 2H, *J* 8.8 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 111.1, 128.9, 129.1, 129.5, 131.0, 132.6, 140.2, 150.8. Anal. calcd. for $C_9H_4Cl_5N$ (303.40): C, 35.63; H, 1.33; Cl, 58.43; N, 4.62. Found: C, 35.57; H, 1.23; Cl, 58.48; N, 4.60. MS (ESI$^+$) *m/z*: 304.6 $[M+H]^-$.

***N*-(1,2,2-Trichlorovinyl)furan-2-carbimidoylchloride (6f).** Yield 10.9 g (79%). bp 94-95 °C (destr.) /0.5 mm Hg/. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 6.59 (dd, 1H, *J* 1.6 and 3.6 Hz), 7.31 (d, 1H, *J* 3.6 Hz) 7.69 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 111.2, 113.0, 120.8, 129.3, 145.1, 147.8, 148.2. Anal. calcd. for $C_7H_3Cl_4NO$ (258.92): C, 32.47; H, 1.17; Cl, 54.77; N, 5.41; O, 6.18. Found: C, 32.51; H, 1.13; Cl, 54.82; N, 5.36. MS (ESI$^+$) *m/z*: 256.8 $[M+H]^-$.

***N*-(1,2,2,-Trichlorovinyl)thiophene-2-carbimidoylchloride (6g).** Yield 12.6g (86%). bp 119-120 °C /1 mm Hg/. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.15 (t, 1H, *J* 4.0 Hz), 7.65 (d, 1H, *J* 5.2 Hz) 7.87 (d, 1H, *J* 4.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 83.3, 99.7, 128.0, 134.2, 134.5, 139.0, 146.1. Anal. calcd. for $C_7H_3Cl_4NS$ (274.98): C, 30.58; H, 1.10; Cl, 51.57; N, 5.09; S, 11.66. Found: C, 30.52; H, 1.09; Cl, 51.46; N, 5.01; S, 11.61. MS (ESI$^+$) *m/z*: 275.9 $[M+H]^-$.

***N*-(1,2,2-Trichlorovinyl)pivalimidoylchloride (6h).** The compound **9h** (15.3 g, 0.0535 mol) was dissolved in THF (100 mL) and triethylamine (7.5 mL, 0.054 mol) was added. The reaction mixture was then heated for 24 h. After cooling, the precipitate was filtered, washed with THF (20 mL), and the filtrate was evaporated *in vacuo*. The resulting imodyl chloride was obtained by distillation in vacuo. Yield 12.2 g (92%), bp 40-42 °C /0.5 mm Hg/. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 1.29 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 28.0, 44.7, 77.1, 99.7, 165.3. Anal. Calcd. for $C_7H_9Cl_4N$ (248.97): C, 33.77; H, 3.64; Cl, 56.96; N, 5.63. Found: C, 33.68; H, 3.54; Cl, 57.08; N, 5.46. MS (ESI$^+$) *m/z*: 249.9 $[M+H]^-$.

General procedure for the preparation of 5-(Dichloromethylene)-7-(het)aryl-8,9-dihydro-5*H*-imidazo[1,2-*e*][1,3,5]triazepine (11a-h). To a suspension of 2-aminomethylimidazole dihydrochloride (**10**) (0.56 g, 3.3 mmol) in THF (50 mL) was added triethylamine (2.77 mL, 19.8 mmol) and the mixture was stirred for 5 min. Then 3.3 mmol of a corresponding imidoylchloride **6a-h** THF (10 mL) was added and the mixture stirred at 20 °C for 5-7 days. The triethylamine hydrochloride was filtered off and the filtrate was evaporated *in vacuo*. Water (50 mL) was then added to the residue and the crystalline product was filtered off and dried *in vacuo*.

5-(Dichloromethylene)-7-phenyl-8,9-dihydro-5*H*-imidazo[1,2-*e*][1,3,5]triazepine (**11a**). Yield 0.84 g (87%). mp 160 – 165 °C (decomp.). IR (solid, KBr, νmax, cm^{-1}): 3209, 3061, 2998, 2847, 1615, 1564, 1541, 1485, 1444, 1426, 1350, 1310, 1232, 1123, 946, 873, 786, 747, 688. ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 4.50 (2H, broad s., CH_2), 6.92 (1H, d, *J* 1.2, $CH_{imidazole}$), 7.42-7.52 (4H, m, ArH), 7.82 (2H, d, *J* 7.2, PhH), 8.82 (1H, t, *J* 4.0 NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ_C 39.2, 103.9, 121.5, 127.0, 127.7, 128.8, 131.5, 135.9, 136.3, 145.2, 154.9. Anal. Calcd. for $C_{13}H_{10}Cl_2N_4$ (293.15): C, 53.26; H, 3.44; N, 19.11; Cl, 24.19. Found: C, 54.11; H, 3.51; N, 18.7; Cl, 24.19. LC-MS, *m/z*: 293 $[M]^+$, 311 $[M+H_2O]^+$, 309 $[M-2+H_2O]^-$.

Crystal data for **11a**: $C_{13}H_{10}Cl_2N_4$, M= 293.15, monoclinic, space group $P2_1/n$, a = 11.0251(3), b = 8.6552(2), c = 13.8370(4)Å, β = 102.793(1)°, V 1287.61(6)Å^3, Z = 4, d_c = 1. 512, μ 0.494 mm^{-1}, F(000) 600, crystal size ca. 0.26 x 0.34 x 0.43mm. All crystallographic measurements were performed at 173K on a Bruker Smart Apex II diffractometer operating in the ω scans mode. The intensity data were collected within the $\theta_{max} \leq 26.4°$ using Mo-K_α radiation (λ = 0.71078 Å). The intensities of 12848 reflections were collected (2645 unique reflections, R_{merg} = 0.0288). The structure were solved by direct methods and refined by the full-matrix least-squares technique in the anisotropic approximation for main non-hydrogen atoms using the Bruker SHELXTL program package.[16] Solvate THF molecule is disordered over two position A and B with occupancies 0.64 and 0.36 and refined in isotropic approximation. All CH hydrogen atoms were placed at calculated positions and refined as 'riding' model, and hydrogen atoms supported N atom were located from DF synthesis and refined isotropically. Convergence for **11a** was obtained at R1 = 0.0333 and wR2 = 0.0788 for 2258 observed reflections with $I \geq 2\sigma(I)$; R1 = 0.0408 and wR2 = 0.0836, GOF = 1.032 for 2645 independent reflections, 176 parameters, the largest and minimal peaks in the final difference map 0.26 and –0.23 e/Å^3.

Crystallographic data for the structures in this paper have been deposited at Cambridge Crystallographic Data Centre as supplementary publication number CCDC 2121519. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK, (fax: +44-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).

5-(Dichloromethylene)-7-(p-tolyl)-8,9-dihydro-5*H*-imidazo[1,2-*e*][1,3,5]triazepine (**11b**). Yield 0.97 g (97%). mp 200 – 205 °C (decomp.). IR (solid, KBr, νmax, cm^{-1}): 3215, 3037, 1609, 1584, 1558, 1498, 1428, 1347, 1307, 1233, 1123, 873, 745. ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 2.33 (3H, s, CH_3), 4.48 (2H, broad s, CH_2), 6.90 (1H, s, $CH_{imidazole}$), 7.24 (2H, d, *J* 6.0, ArH), 7.48 (1H, s, $CH_{imidazole}$), 7.71 (2H, d, *J* 5.6, ArH), 8.72 (1H, t, *J* 3.2, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ_C 21.40, 39.11, 103.54, 121.50, 126.98, 127.61, 129.33, 133.03, 136.33, 141.42, 145.27, 154.72. Anal. Calcd. for $C_{14}H_{12}Cl_2N_4$ (307.18): C, 54.74; H, 3.94; N, 18.24; Cl, 23.08. Found: C, 54.79; H, 3.86; N, 17.52; Cl, 23.24. LC-MS, *m/z*: 307 $[M]^+$, 325 $[M+H_2O]^+$.

5-(Dichloromethylene)-7-(4-methoxyphenyl)-8,9-dihydro-5*H*-imidazo[1,2-*e*][1,3,5]triazepine (**11c**). Yield 0.99 g (94%). mp 180 – 185 °C (decomp.). IR (solid, KBr, νmax, cm^{-1}): 3200, 2993, 2912, 2837, 1604, 1557, 1501, 1422, 1353, 1302, 1253, 1235, 1182, 1121, 1030, 870, 836, 796, 737. ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 3.79 (3H, s, OCH_3), 4.46 (2H, broad s., CH_2), 6.90 (1H, s, $CH_{imidazole}$), 6.98 (2H, d, *J* 8,8, ArH), 7.48 (1H, s, $CH_{imidazole}$), 7.79 (2H, d, *J* 8,8, ArH), 8.70 (1H, s, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ_C 39.08, 55.85, 103.22, 114.05, 121.46, 126.95, 127.93, 129.37, 136.38, 145.36, 154.35, 161.98. Anal. Calcd. for $C_{14}H_{12}Cl_2N_4O$ (323.18): C, 52.03; H, 3.74; N, 17.34; Cl, 21.94; O, 4.95. Found: C, 52.11; H, 3.79; N, 16.9; Cl, 22.09. LC-MS, *m/z*: 323 $[M]^+$, 341 $[M+H_2O]^+$.

5-(Dichloromethylene)-7-(4-fluorophenyl)-8,9-dihydro-5*H*-imidazo[1,2-*e*][1,3,5]triazepine (**11d**). Yield 0.93 g (92%). mp 173 °C (decomp.). IR (solid, KBr, νmax, cm^{-1}): 3204, 3080, 3013, 1621, 1550, 1499, 1426, 1353, 1316, 1233, 1165, 1124, 872, 846, 737, 639, 478. ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 4.49 (2H, broad s, CH_2), 6.90 (1H, d, *J* 0.8, $CH_{imidazole}$), 7.27 (2H, d, *J* 8.8, ArH), 7.49 (1H, d, *J* 0.8, $CH_{imidazole}$), 7.87 (2H, dd, J_1=8.8, J_2=5.6 ArH), 8.83 (1H, t, *J* 2.4, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ_C 39.1, 104.0, 115.7, 121.5, 127.0, 130.2, 132.3, 136.1, 145.2, 153.8, 163.2, 165.2. Anal. Calcd. for $C_{13}H_9Cl_2FN_4$ (311.14): C, 50.18; H, 2.92; N, 18.01; Cl, 22.79; F, 6.11. Found: C, C, 50.22; H, 2.86; N, 17.65; Cl, 22.35. LC-MS, *m/z*: 311 $[M]^+$, 329 $[M+H_2O]^+$.

7-(4-Chlorophenyl)-5-(dichloromethylene)-8,9-dihydro-5*H*-imidazo[1,2-*e*][1,3,5]triazepine (**11e**). Yield 1.01 g (94%). mp 185 – 190 °C (decomp.). IR (solid, KBr, νmax, cm^{-1}): 3160, 2979, 1613, 1592, 1557, 1542, 1485, 1428, 1354, 1321, 1235, 1086, 875, 837, 742, 680, 440. ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 4.48 (2H, broad s, CH_2), 6.89 (1H, s, $CH_{imidazole}$), 7.47 (1H, d, $CH_{imidazole}$), 7.49 (2H, d, *J* 8.0, ArH), 7.81 (2H, d, *J* 8.0, ArH), 8.87 (1H, t, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ_C 39.9, 104.2, 121.5, 126.9, 128.7, 129.4, 134.5, 136.0, 136.2, 145.0, 153.6. Anal. Calcd. for $C_{13}H_9Cl_3N_4$ (325.99): C, 47.66; H, 2.77; N, 17.10; Cl, 32.47. Found: C, 47.70; H, 2.71; N, 16.66; Cl, 32.47. LC-MS, *m/z*: 329 $[M+1]^+$, 325 $[M-3]^-$, 347 $[M+1+H_2O]^+$, 344.8 $[M+1+H_2O]^-$.

5-(Dichloromethylene)-7-(furan-2-yl)-8,9-dihydro-5*H*-imidazo[1,2-*e*][1,3,5]triazepine (**11f**). Yield 0.79 g (86%). mp 155-160°C (decomp.). IR (solid, KBr, νmax, cm^{-1}): 3145, 3123, 1617, 1586, 1539, 1512, 1470, 1426, 1297, 1238, 987, 867, 747, 608. ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 4.46 (2H, broad s, CH_2), 6.62 (1H, d, *J* 3.2, $CH_{imidazole}$), 6.89 (1H, s, CH_{furan}), 7.01 (1H, d, *J* 3.2, $CH_{imidazole}$), 7.47 (1H, s, CH_{furan}), 7.85 (1H, s, CH_{furan}), 8.77 (1H, s, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ_C 38.7, 103.9, 112.6, 113.2, 121.5, 126.8, 135.9, 145.1, 145.6, 146.3, 148.7. Anal. Calcd. for $C_{11}H_8Cl_2N_4O$ (283.11): C, 46.67; H, 2.85; N, 19.79; Cl, 25,04. Found: C, 46.71; H, 2.81; N, 19.61; Cl, 25.12. LC-MS, *m/z*: 283, 285 $[M+1]^+$, 281, 283 $[M-1]^-$.

5-(Dichloromethylene)-7-(thiophen-2-yl)-8,9-dihydro-5*H*-imidazo[1,2-*e*][1,3,5]triazepine (**11g**). Yield 0.89 g (91%). mp 170-173°C (decomp.). IR (solid, KBr, νmax, cm^{-1}): 3167, 1605, 1581, 2837, 1604, 1580, 1547, 1424, 1357, 1322, 1247, 927, 735, 710, 487. ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 4.48 (2H, broad s, CH_2), 6.69 (1H, s, $CH_{imidazole}$), 7.10 (1H, t, *J* 4.4, $CH_{thiophen}$), 7.50 (1H, s, $CH_{imidazole}$), 7.64 (1H, d, *J* 3.2, $CH_{thiophen}$), 7.68 (1H, d, *J* 4.8, $CH_{thiophen}$), 8,89 (1H, broad t., *J* 4.8, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ_C 38.9, 104.2, 121.5, 126.9, 127.9, 128.3, 131.5, 135.6, 140.9, 145.0, 150.0. Anal. Calcd. for $C_{11}H_8Cl_2N_4S$ (299.17): C, 44.16; H, 2.70; N, 18.73; Cl, 23.70; S, 10.72. Found: C, 44.23; H, 2.63; N, 18.61; Cl, 23.20; S, 10.58. LC-MS, *m/z*: 299 $[M]^+$, 317 $[M+H_2O]^+$, 297 $[M-2]^-$, 315$[M+H_2O]^-$.

7-(*tert*-Butyl)-5-(dichloromethylene)-8,9-dihydro-5*H*-imidazo[1,2-*e*][1,3,5]triazepine (**11h**). Yield 0.77 g (86%). mp 155-162°C (decomp). IR (solid, KBr, νmax, cm^{-1}): 3225, 1610, 1585, 1532, 1513, 1487, 1421, 1307, 1238, 879, 735. ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 1.11 (9H, s, $C(CH_3)_3$), 4.30 (2H, broad s, CH_2), 6.86 (1H, s, $CH_{imidazole}$), 7.43 (1H, s, $CH_{imidazole}$), 7.86 (1H, broad s, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ_C 28.35, 38.79, 39.58, 101.74, 120.76, 126.36, 135.91, 144.8, 165.06. Anal. Calcd. for $C_{11}H_{14}Cl_2N_4$ (273.16): C, 48.37; H, 5.17; N, 20.51; Cl, 25.96. Found: C, 48.43; H, 5.09; N, 20.6; Cl, 26.12. LC-MS, *m/z*: 273 $[M]^+$, 291$[M+H_2O]^+$.

(*Z,E*)-*N*'-((1*H*-imidazol-2-yl)methyl)-4-methylbenzimidamide (**12b**). To a suspension of triazepine **11b** (1.0 g, 3.3 mmol) in MeOH (25 mL), an excess of saturated aqueous sodium hydroxide was added dropwise. The mixture was stirred for 2 h after which water (25 mL) was added. The resultant precipitate was filtered, washed with a small amount of water and then dried. Yield 0.68 g (97%). mp 172-173°C. ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 2.39 (3H, s, CH_3), 4.63 (2H, s, CH_2), 6.35 (3H, broad s, NH), 6.92 (2H, s, $CH_{imidazole}$), 7.20 (2H, d, *J* 8.0, ArH), 7.45 (2H, d, *J* 8.0, ArH). Anal. Calcd. for $C_{12}H_{14}N_4$ (248.97): C, 67.27; H, 6.59; N, 26.17. Found: C, 67.36; H, 6.51; N, 25.75. LC-MS, *m/z*: 215 $[M]^+$, 213 $[M]^-$.

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Supplementary Material

Copies of ^{1}H NMR and ^{13}C NMR spectra of compounds are given in the Supplementary Material file associated with the manuscript.

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