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SYNTHESIS OF NOVEL TRICHLOROMETHYL SUBSTITUTED AZOLO[1,3,5]TRIAZINES[1]

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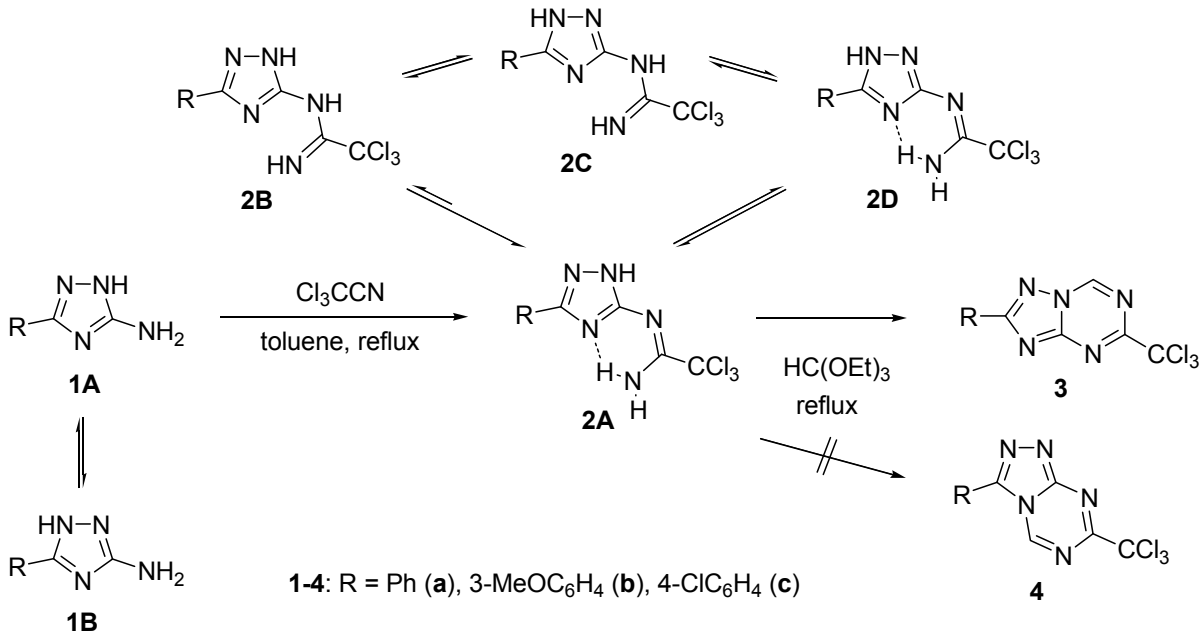
Abstract – The triazine ring bearing a trichloromethyl group was annelated to various aminoazoles using a new effective synthetic procedure. The method of preparation involved initial formation of trichloroacetamidines in the reaction of aminoazoles with trichloroacetonitrile followed by the triazine ring closure with triethyl orthoformate affording therefore the titled compounds.

Recently, chemistry and biological activity of azolo-fused 1,3,5-triazines have been extensively explored.[2] Particular attention was addressed to the heterocycles possessing ring systems isosteric to the purine scaffold, *e.g.* 1,2,4-triazolo[1,5-*a*][1,3,5]triazines (5-azapurines)[2b] and pyrazolo[1,5-*a*][1,3,5]triazines (5-aza-9-deazapurines).[2c]

Trichloromethyl substituted 1,3,5-triazines have been reported as potent polymerization photoinitiators[3] and pesticides.[4] 1,3,5-Triazines, bearing a trichloromethyl group, also have great potential for synthetic organic chemistry applications. Trichloromethyl group has been well recognized as versatile tool for various chemical transformations.[5] In heterocyclic compounds, this group usually is highly reactive making them valuable synthons for diverse range of interesting molecules. Recently, we reported[6] a method for preparation of 5-amino-2-phenyl-7-trichloromethyl-1,2,4-triazolo[1,5-*a*][1,3,5]triazine, which was the key intermediate in the convenient synthesis of 7-amino-substituted 1,2,4-triazolo[1,5-*a*][1,3,5]triazines.

The present study aims to develop a practical method for preparation of 5-trichloromethyl-1,2,4-triazolo[1,5-*a*][1,3,5]triazines and to assess applicability of this method for the synthesis of other structurally related azolo-fused 1,3,5-triazines.

The starting 5(3)-amino-1,3,5-triazoles (**1**) required for the preparation of targeted 5-trichloromethyl-1,2,4-triazolo[1,5-*a*][1,3,5]triazines (**3**) were prepared according to previously reported methods.[7] The trichloromethyl group was introduced into the structure *via* the reaction of **1** with trichloroacetonitrile, a versatile building block in heterocyclic chemistry.[8] Previously, we successfully applied this reagent for the construction of 1,3,5-triazines annelated to other heterocyclic rings.[6,9] In the present work, we established that upon heating in toluene, the reaction of **1** with trichloroacetonitrile proceeded smoothly and regioselectively at the primary amino group of **1**, affording therefore trichloroacetamidines (**2**) (Scheme 1). The trichloromethyl activation of the cyano group abolished necessity of any catalysis for this reaction.

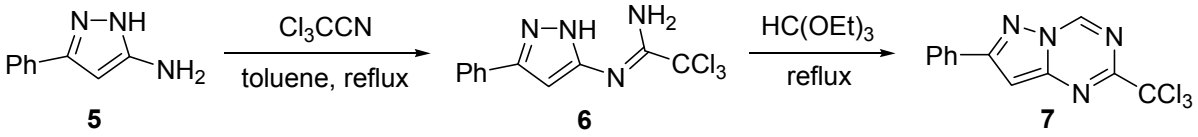


Scheme 1

It has been established that for aryl substituted **1**, 5-amino-tautomeric form (**1A**) is highly preferred over the 3-amino-form (**1B**).[7] The ΔG_{298} values of this equilibrium for **1a-c** in DMSO solution were 5.2 kJ/mol,[7] 4.9 kJ/mol,[10] and 7.5 kJ/mol,[7] correspondingly. Trichloroacetamidines (**2**) were involved in both, annular tautomersim (similarly to **1**) and tautomeric exchange at the amidino group. ^{1}H NMR spectroscopy data (two broad signals at 8.95-8.99 and 9.41-9.45 ppm attributed to the NH_2 protons) suggested that forms **2A** and **2D** were preferred in the equilibrium when compared with alternative amidine forms **2B** and **2C**. Tautomers **2A** and **2D** were stabilized by the intramolecular N-H···N hydrogen bonding with the N-4 triazole atom resulting in deshielding one of the NH_2 protons. It seems that proton tautomeric exchange in the triazole ring was too fast on the NMR time scale making forms **2A** and **2D** indistinguishable in the spectra.

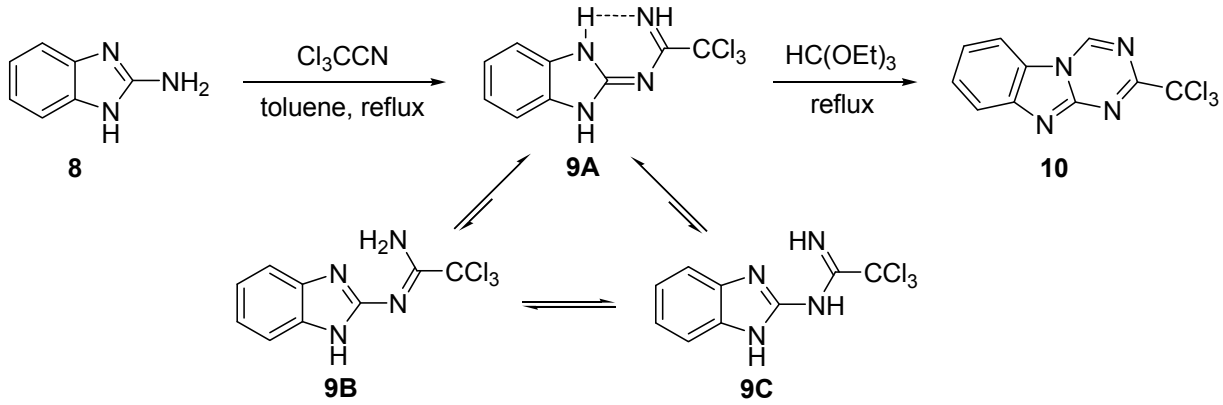
Heating trichloroacetamidines (**2**) in triethyl orthoformate resulted in the 1,3,5-triazine ring closure thus affording 2-aryl-5-trichloromethyl-1,2,4-triazolo[1,5-*a*][1,3,5]triazines (**3**). The reaction was found to proceed regioselectively to the N-1 triazole atom of **2**; no formation of isomer **4** was observed. The structure of **3** was confirmed by NMR spectroscopy. 2D NOESY experiments revealed no cross-peaks between the methine proton singlet of the triazine ring at 10.34-10.36 ppm and signals of aromatic substituent at the triazole ring, ruling out therefore alternative structure **4**. The diagnostic signal of trichloromethyl group appeared in ^{13}C NMR spectra at ~ 95 ppm.

To further explore scope of the developed method in the synthesis of other trichloromethyl substituted azolo-fused 1,3,5-triazines, the same sequence of the reactions with trichloroacetonitrile and triethyl orthoformate was performed using 5(3)-amino-3(5)-phenylpyrazole (**5**) and 2-aminobenzimidazole (**8**) (Schemes 2 and 3). It appears that product of the reaction between **5** and trichloroacetonitrile had a structure similar to its triazole based analogues **2**, but the absence of the nitrogen atom involved in the intramolecular hydrogen bonding resulted in only one signal for both protons of the amidine group of **6** in ^{1}H NMR spectrum. Treatment of **6** with triethyl orthoformate conveniently provided 7-phenyl-2-trichloromethylpyrazolo[1,5-*a*][1,3,5]triazine (**7**). ^{1}H NMR spectrum of this compound had a characteristic unusual long range coupling between protons H-4 and H-8 at the triazine and pyrazole rings (^5J = 0.9 Hz).



Scheme 2

The nucleophilic addition of 2-aminobenzimidazole (**8**) to the cyano group of trichloroacetonitrile successfully furnished trichloroacetamidine (**9**) (Scheme 3).



Scheme 3

Three tautomeric forms are theoretically possible for **9** due to proton exchange within the amidine group and between the amidine group and the benzimidazole ring. Interestingly, transfer of one proton of the amidino group to the ring nitrogen atom generating tautomer **9A** was observed in the DMSO solution. ^{1}H NMR spectrum of **9** had two downfield shifted signals at 10.40 and 12.40 ppm assignable to the benzimidazole ring NH protons of the tautomeric form **9A**. Substantially higher deshielding of one of these protons can be explained by intramolecular hydrogen bonding and anisotropic effect of the imine-like =NH moiety located in the plane of the heterocyclic ring. The cyclocondensation of **9** with triethyl orthoformate led to the formation of 2-trichloromethyl-1,3,5-triazino[1,2-*a*]benzimidazole (**10**).

In summary, novel trichloromethyl substituted 1,2,4-triazolo[1,5-*a*][1,3,5]triazines (**3**), pyrazolo[1,5-*a*][1,3,5]triazine (**7**) and 1,3,5-triazino[1,2-*a*]benzimidazole (**10**) were successfully prepared from corresponding aminoazoles. The developed method seemed to be practical and generally applicable to variety of substrates. Reactivity of the prepared compounds towards various nucleophiles is currently under extensive explorations.

EXPERIMENTAL

General Methods. Melting points (uncorrected) were determined on a Gallenkamp melting point apparatus. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance III spectrometer (400 MHz), using DMSO-d_6 as a solvent and TMS as an internal reference. 5(3)-Amino-3(5)-aryl-1,2,4-triazoles (**1**) were prepared according to previously reported method;[7] 5(3)-amino-3(5)-phenylpyrazole (**5**) was synthesized using known method.[11] Other reagents were purchased from Alfa Aesar.

N-[3(5)-Aryl-1,2,4-triazol-5(3)-yl]trichloroacetamidines (2)

A mixture of 5(3)-amino-3(5)-aryl-1,2,4-triazole (**1**, 10 mmol) with trichloroacetonitrile (3 mL, 30 mmol) in toluene (15 mL) was heated under reflux for 12 h. Preparation of **2c** required heating for 60 h with addition of two more portions of trichloroacetonitrile (3 mL, 30 mmol) after 18 h and 40 h. After cooling, the precipitate was filtered, washed with hexane and recrystallized from toluene.

N-[3(5)-Phenyl-1,2,4-triazol-5(3)-yl]trichloroacetamidine (2a)

Yield 59%; mp 164-166 °C (toluene). ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.43 (1H, t, J = 7.2 Hz, H-4'), 7.49 (2H, t, J = 7.2 Hz, C-3' and C-5'), 8.05 (2H, d, J = 6.9 Hz, C-2' and C-6'), 8.94 (1H, br. s, NH), 9.45 (1H, br. s, NH), 13.95 (1H, br. s, H-1). Anal. Calcd for $C_{10}H_8Cl_3N_5$: C, 39.44; H, 2.65; N, 22.99. Found: C, 39.38; H, 2.69; N, 22.78.

N-[3(5)-(3-Methoxyphenyl)-1,2,4-triazol-5(3)-yl]trichloroacetamidine (2b)

Yield 52%; mp 136-138 °C (toluene). ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.83 (3H, s, OMe), 7.01 (1H, dd, J = 8.2, 1.8 Hz, C-4'), 7.40 (1H, t, J = 7.9 Hz, C-5'), 7.57 (1H, dd, J = 2.4, 1.4 Hz, C-2'), 7.63 (1H, dt, J = 7.6, 1.1 Hz, C-6'), 8.94 (1H, br. s, NH), 9.44 (1H, br. s, NH), 13.97 (1H, br. s, H-1). Anal. Calcd for $C_{11}H_{10}Cl_3N_5O$: C, 39.49; H, 3.01; N, 20.93. Found: C, 39.40; H, 3.15; N, 20.82.

N-[3(5)-(4-Chlorophenyl)-1,2,4-triazol-5(3)-yl]trichloroacetamidine (2c)

Yield 59%; mp 193-195 °C (toluene). ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.55 (2H, t, J = 8.6 Hz, C-3' and C-5'), 8.06 (2H, d, J = 8.6 Hz, C-2' and C-6'), 8.99 (1H, br. s, NH), 9.41 (1H, br. s, NH), 14.01 (1H, br. s, H-1). Anal. Calcd for $C_{10}H_7Cl_4N_5$: C, 35.43; H, 2.08; N, 20.66. Found: C, 35.28; H, 2.00; N, 20.43.

2-Aryl-5-trichloromethyl-1,2,4-triazolo[1,5-a][1,3,5]triazines (3)

Trichloroacetamidine (**2**, 2 mmol) was heated in triethyl orthoformate (10 mL) under reflux for 8 h. After cooling, the precipitate was filtered, washed with hexane and recrystallized from toluene.

2-Phenyl-5-trichloromethyl-1,2,4-triazolo[1,5-a][1,3,5]triazine (3a)

Yield 72%; mp 231-233 °C (toluene). ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.60-7.66 (3H, m, H-3', H-4', and H-5'), 8.25-8.32 (2H, m, H-2' and H-6'), 10.34 (1H, s, H-7). ^{13}C NMR (100 MHz, DMSO-d_6): δ 95.1 (CCl_3), 127.4 (C-3' and C-5'), 129.0 (C-4'), 129.3 (C-2' and C-4'), 131.8 (C-1'), 150.7 (C-7), 155.9 (C-3a), 162.8 (C-5), 167.5 (C-2). Anal. Calcd for $C_{11}H_6Cl_3N_5$: C, 42.00; H, 1.92; N, 22.26. Found: C, 41.86; H, 2.00; N, 22.14.

2-(3-Methoxyphenyl)-5-trichloromethyl-1,2,4-triazolo[1,5-a][1,3,5]triazine (3b)

Yield 76%; mp 219-221 °C (toluene). ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.88 (3H, s, OMe) 7.20 (1H, ddd, J = 8.3, 2.7, 0.9 Hz, C-4'), 7.54 (1H, dd, J = 8.3, 7.7 Hz, C-5'), 7.78 (1H, dd, J = 2.6, 1.5 Hz, C-2'), 7.63 (1H, ddd, J = 7.6, 1.6, 0.8 Hz, C-6'), 10.34 (1H, s, H-7). ^{13}C NMR (100 MHz, DMSO-d_6): δ 55.2 (OMe), 95.0 (CCl_3), 112.0 (C-4'), 117.6 (C-2'), 119.6 (C-6'), 130.2 (C-1'), 130.4 (C-5'), 150.6 (C-7), 155.7 (C-3a), 159.6 (C-3'), 162.7 (C-5), 167.2 (C-2). Anal. Calcd for $C_{12}H_8Cl_3N_5O$: C, 41.83; H, 2.34; N, 20.32. Found: C, 41.77; H, 2.44; N, 20.18.

2-(4-Chlorophenyl)-5-trichloromethyl-1,2,4-triazolo[1,5-a][1,3,5]triazine (3c)

Yield 56%; mp 205-207 °C (toluene). ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.70 (2H, d, J = 8.7 Hz, C-3' and C-5'), 8.29 (2H, d, J = 8.7 Hz, C-2' and C-6'), 10.36 (1H, s, H-7). ^{13}C NMR (100 MHz, DMSO-d_6): δ 95.0 (CCl_3), 127.4 (C-1'), 129.1 (C-3' and C-5'), 129.5 (C-2' and C-6'), 136.6 (C-4'), 150.8 (C-7), 156.0 (C-3a),

163.0 (C-5), 166.5 (C-2). Anal. Calcd for $C_{11}H_5Cl_4N_5$: C, 37.86; H, 1.44; N, 20.07. Found: C, 37.73; H, 1.51; N, 19.90.

N-[3(5)-Phenylpyrazol-5(3)-yl]trichloroacetamidine (6)

A mixture of 5(3)-amino-3(5)-phenylpyrazole (**5**, 10 mmol) with trichloroacetonitrile (3.0 mL, 30 mmol) in toluene (10 mL) was heated under reflux for 2 h. After cooling, the precipitate was filtered, washed with hexane and recrystallized from toluene to give 1.52 g of orange crystalline powder.

Yield 50%; mp 186-188 °C (toluene). ^{1}H NMR (400 MHz, DMSO-d_6): δ 6.64 (1H, s, H-4), 7.36 (1H, t, J = 7.4 Hz, H-4'), 7.46 (2H, t, J = 7.6 Hz, C-3' and C-5'), 7.78 (2H, d, J = 7.7 Hz, C-2' and C-6'), 8.27 (2H, br. s, NH_2), 13.14 (1H, br. s, H-1). Anal. Calcd for $C_{11}H_9Cl_3N_4$: C, 43.52; H, 2.99; N, 18.46. Found: C, 43.58; H, 3.08; N, 18.24.

7-Phenyl-2-trichloromethylpyrazolo[1,5-a][1,3,5]triazine (7)

Trichloroacetamidine (**6**, 0.61 g, 2 mmol) was heated in triethyl orthoformate (8 mL) under reflux for 6 h. After cooling, the precipitate was filtered, washed with hexane and recrystallized from toluene to give 0.35 g of yellow powder.

Yield 56%; mp 234-236 °C (toluene). ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.51-7.60 (2H, m, H-3', H-4', and H-5'), 7.64 (1H, d, J = 0.9 Hz, H-8), 8.13 (2H, dd, J = 8.1, 1.5 Hz, H-2' and H-6'), 10.06 (1H, d, J = 0.9 Hz, H-4). ^{13}C NMR (100 MHz, DMSO-d_6): δ 95.4 (CCl_3), 95.7 (C-8), 126.7 (C-3' and C-5'), 129.0 (C-2' and C-6'), 130.3 (C-4'), 130.9 (C-1'), 147.9 (C-7), 149.5 (C-4), 157.3 (C-8a), 159.5 (C-2). Anal. Calcd for $C_{12}H_7Cl_3N_4$: C, 45.96; H, 2.25; N, 17.87. Found: C, 45.77; H, 2.36; N, 17.68.

N-(Benzimidazol-2-yl)trichloroacetamidine (9)

A mixture of 2-aminobenzimidazole (**8**, 1.34 g, 10 mmol) with trichloroacetonitrile (2.5 mL, 25 mmol) in toluene (15 mL) was heated under reflux for 3 h. After cooling, the precipitate was filtered, washed with hexane and recrystallized from toluene to give 1.58 g of pale cream crystalline powder.

Yield 57%; mp 196-198 °C decomp. (toluene). ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.10-7.20 (2H, m, H-5 and H-6), 7.34-7.56 (2H, m, H-4 and H-7), 9.02 (1H, s, NH), 10.40 (1H, br. s, NH), 12.40 (1H, br. s, NH). Anal. Calcd for $C_9H_7Cl_3N_4$: C, 38.95; H, 2.54; N, 20.19. Found: C, 39.01; H, 2.65; N, 20.03.

2-Trichloromethyl-1,3,5-triazino[1,2-a]benzimidazole (10).

N-(Benzimidazol-2-yl)trichloroacetamidine (**9**, 0.56 g, 2 mmol) was heated in triethyl orthoformate (8 mL) under reflux for 5 h. After cooling, the precipitate was filtered, washed with hexane and

recrystallized from toluene to give 0.43 g of yellow crystalline powder.

Yield 75%; mp 284-286 °C decomp. (toluene). ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.61 (1H, ddd, J = 8.2, 7.2, 1.0 Hz, H-7), 7.69 (1H, ddd, J = 8.2, 7.2, 1.1 Hz, H-8), 7.98 (1H, ddd, J = 8.2, 1.4, 0.8 Hz, H-9), 8.44 (1H, ddd, J = 8.2, 1.2, 0.8 Hz, H-6), 10.40 (1H, s, H-4). ^{13}C NMR (100 MHz, DMSO-d_6): δ 95.6 (CCl_3), 113.7 (C-6), 119.9 (C-9), 123.9 (C-7), 125.6 (C-5a), 127.9 (C-8), 144.3 (C-9a), 147.6 (C-10a), 151.5 (C-4), 162.1 (C-2). Anal. Calcd for $C_{10}H_5Cl_3N_4$: C, 41.77; H, 1.75; N, 19.49. Found: C, 41.82; H, 1.88; N, 19.43.

ACKNOWLEDGEMENTS

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10. *5(3)-Amino-3(5)-(3-methoxyphenyl)-1,2,4-triazole* (**1b**); mp 174-176 °C (water); ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.79 (3H, s, OMe), 5.38* and 6.14 (2H, two s, NH_2), 6.91 (1H, dd, J = 8.1, 2.3 Hz, C-4'), 7.32 (1H, t, J = 7.9 Hz, C-5'), 7.46 (1H, dd, J = 2.3, 1.2 Hz, C-2'), 7.51 (1H, d, J = 7.6 Hz, C-6'), 12.11 and 13.26* (two s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 54.9 (OMe), 55.1* (OMe), 110.3 (C-4'), 110.6* (C-4'), 113.9 (C-2'), 115.3* (C-2'), 117.6 (C-6'), 129.4 (C-5'), 130.0* (C-5'), 133.7 (C-1'), 152.1* (C-3/5), 157.2 (C-3/5), 158.2 (C-3/5), 159.2 (C-3'), 159.4* (C-3'), 164.3* (C-3/5).

* - signals of minor tautomeric form **1B**; $K_T = 0.14$. Anal. Calcd for $C_9H_{10}N_4O$: C, 56.83; H, 5.30; N, 29.46. Found: C, 56.83; H, 5.30; N, 29.46.

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