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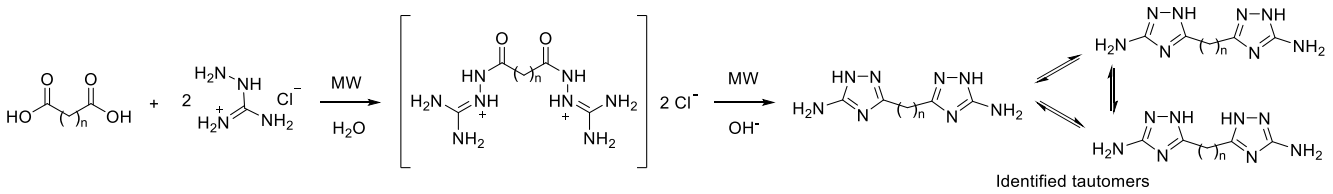

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One-pot, microwave-assisted synthesis of polymethylene-bridged bis(1*H*-1,2,4-triazol-5(3)-amines) and their tautomerism

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ABSTRACT

A highly selective and efficient method for the synthesis of 3,3'(5,5')-polymethylene-bis(1*H*-1,2,4-triazol-5(3)-amines) was developed using the reaction of dicarboxylic acids and aminoguanidine in an aqueous medium. This one-pot, microwave-promoted method was proved to be scalable affording the desired products in good yields and purity. The scope of the method was successfully explored by the preparation of a small library of polymethylene-bis(1*H*-1,2,4-triazol-5(3)-amines) with different alkyl chain linkers. The annular prototropic tautomerism in the prepared compounds was studied using NMR spectroscopy and X-ray crystallography.

The twin-drugs strategy involves linking two identical pharmacophores in one molecule by a chemically and pharmacologically inert bridge. It is one of the efficient approaches to significantly improve effectiveness of bioactive agents. A polymethylene chain is often used as a link between pharmacophores in twin-drugs and the length of this chain is adjusted to achieve optimal therapeutic properties.

Many symmetrical polymethylene-bridged diamines, their derivatives and analogues, including bis(*N*-heterocycles), have been found to possess antiparasitic,[1] antibacterial,[2] and anticancer[3] properties. Some notable recent examples of these bioactive compounds include highly potent antimalarial diamine **1**;[1d] bis-thiourea **2** inhibiting soluble epoxide hydrolase at a low nanomolar concentration range;[4] bis-imidazoles **3** and **4** possessing strong anti-biofilm activity against *Staphylococcus aureus* and *Pseudomonas aeruginosa*, respectively;[2c] compound **5** effectively bis-intercalating into the tatelomeric DNA/RNA duplex;[3e] and bis(1*H*-1,2,4-triazol-5-amine) **6** possessing anticancer properties[3f] (Fig. 1).

Bis-triazole **6** was synthesized using the reaction of the corresponding bis-urea **8** or bis-thiourea **9**, which were prepared from sebacoyl chloride (**7**), with hydrazine (Scheme 1).[3f] This two-step process produced **6** in 59-61% overall yield. However, using a relatively unstable acid chloride and extended reaction times (4-8 h for each step) makes this process less practical. Moreover, the selectivity of all steps is questionable as confirmed by the low purity of products (by reported elemental analysis data for **6**, **8**, and **9**).[3f]

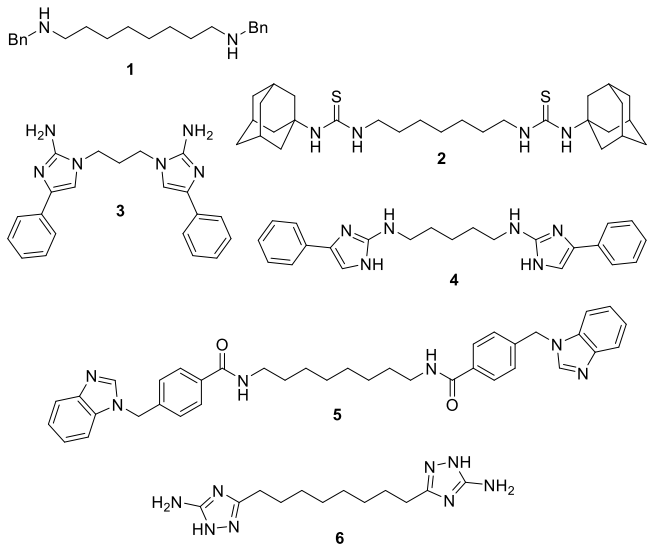

Figure 1. Selected bioactive symmetrical polymethylene-bridged compounds.

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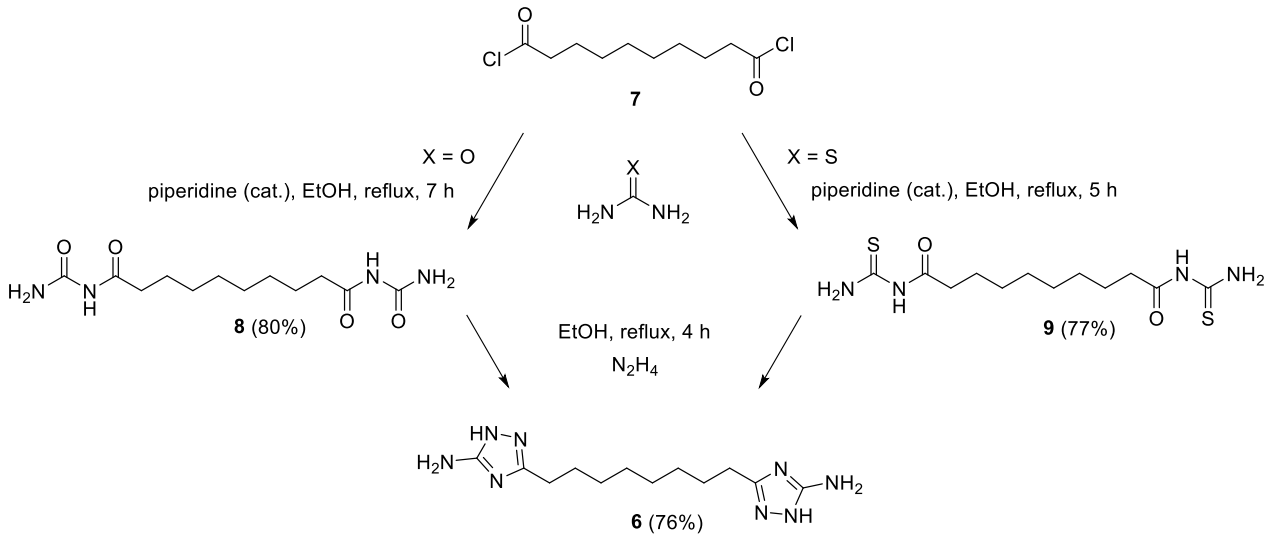
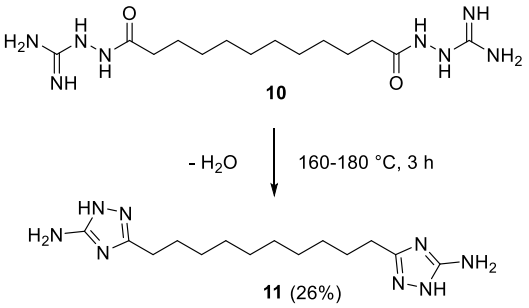


Scheme 1. Synthesis of octamethylene-bis(1*H*-1,2,4-triazol-5-amine) (**6**).[3f]



Scheme 2. Synthesis of decamethylene-bis(1*H*-1,2,4-triazol-5-amine) (**11**).[5]

A homologue of compound **6**, decamethylene-bis(1*H*-1,2,4-triazol-5-amine) (**11**) was prepared *via* the intramolecular cyclization of bis-amidoguanidine **10** (Scheme 2).[5] This reaction required heating at high temperature (160-180 °C) for 3 h but afforded **11** in rather modest yield (26%). Previously, we developed an effective method for the cyclization of amidoguanidines in water under microwave irradiation affording the corresponding aminotriazoles in excellent yields.[6] This approach was further elaborated for the synthesis of more complex compounds in a one-pot manner.[7] Therefore, we decided to adopt a similar microwave-assisted methodology to prepare 3,3'(5,5')-polymethylene-bis(1*H*-1,2,4-triazol-5(3)-amines). Furthermore, we attempted to carry out the synthesis in one-pot starting from readily available dicarboxylic acids.

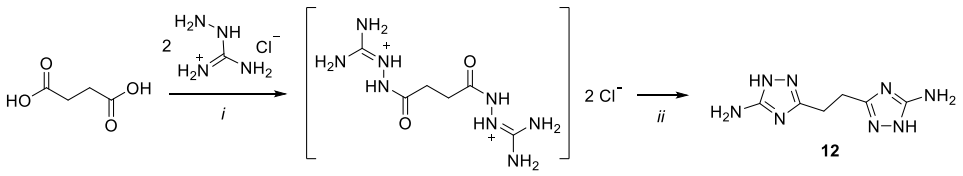
As the model reaction, we decided to use condensation of succcinic acid with aminoguanidine. This reaction under conventional heating was reported to suffer from a lack of selectivity resulting in the formation of a mixture of products, from which pure ethylene-bis(1*H*-1,2,4-triazol-5-amine) **12** was isolated in 8-11% yield only.[8] To overcome this problem, we optimized the reaction conditions under microwave irradiation.

Initially, using the Discover SP (CEM) microwave synthesizer, succinic acid was heated with aminoguanidine hydrochloride in water at 200 °C for 15 min. After cooling, an aqueous solution of potassium carbonate was added to the reaction mixture and heating was continued at 200 °C for 5 min. To our satisfaction, we observed the formation of ethylene-bis(1*H*-1,2,4-triazol-5-amine) **12**, which was isolated in pure form *via* filtration (Entry 1). To further improve the reaction yield, we continued the optimization process and found that increasing the amount of potassium carbonate led to a slight increase in product yield (Entry 2). However, a further optimization of the reaction conditions, particularly increase of the temperature, was limited due to exessive pressure generated in the reaction vessel. Screening other bases for the reaction (Entries 3-4), we identified that under similar conditions sodium hydroxide was equally efficient as a base in terms of yield. Hence, the optimization was continued using sodium hydroxide as a base. Further variations in the reaction parameters revealed that **12** could be obtained in good yield by heating succinic acid and aminoguanidine hydrochloride in water at 220 °C for 15 min followed by the addition of an aqueous solution of sodium hydroxide and further microwave irradiation at 200 °C for 5 min (Entry 16). It should be noted that the exclusive presence of ethylene-bis(1*H*-1,2,4-triazol-5-amine) **12** was observed in the crude product isolated from the reactions.

To explore the scope of the method, various dicarboxylic acids were used as substrates in the reaction with aminoguanidine hydrochloride to produce polymethylene-bis(1*H*-1,2,4-triazol-5(3)-amines). The optimized conditions[9] were found to be sufficiently general and suitable for the synthesis of compounds **6, 11-17** in good yields (Table 2). In all cases, the reaction was selective and only polymethylene-bis(1*H*-1,2,4-triazol-5(3)-amines) were isolated in high purity *via* filtration. The reaction was also effectively performed on 3.4 mmol and 17 mmol scales with similar outcomes.

It should also be noted that the developed method was successfully tested using another microwave reactor Monowave 450 (Anton Paar) microwave synthesizer for the synthesis of **12** under the conditions optimized using the Discover SP (CEM). The outcome was satisfactory affording **12** in 91% yield, therefore confirming the reproducibility of the method in different microwave reactors.

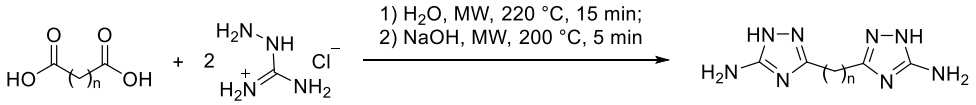
Table 1. Optimization of the reaction conditions for the synthesis of ethylene-bis(1*H*-1,2,4-triazol-5(3)-amine) **12**[a]

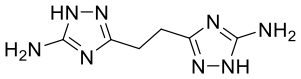
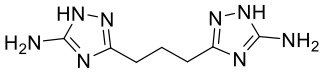
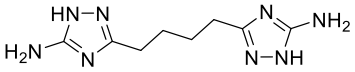
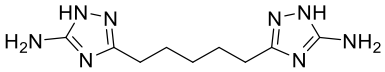
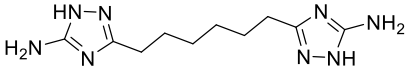
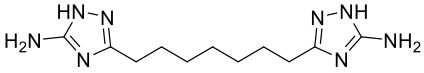
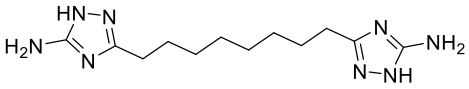
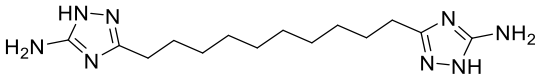


Entry	Molar ratio of succinic acid: aminoguanidine	Conditions	Isolated yield of **12** (%)
1	1: 2	*i*: water, 200 °C, 15 min; *ii*: K_2CO_3 (0.5 equiv.), water, 200 °C, 5 min	33
2	1: 2	*i*: water, 200 °C, 15 min; *ii*: K_2CO_3 (1.0 equiv.), water, 200 °C, 5 min	37
3	1: 2	*i*: water, 200 °C, 15 min; *ii*: $NaHCO_3$ (1.0 equiv.), water, 200 °C, 5 min	27
4	1: 2	*i*: water, 200 °C, 15 min; *ii*: NaOH (1.0 equiv.), water, 200 °C, 5 min	36
5	1: 3	*i*: water, 200 °C, 15 min; *ii*: NaOH (1.0 equiv.), water, 200 °C, 5 min	58
6	1: 4	*i*: water, 200 °C, 15 min; *ii*: NaOH (1.0 equiv.), water, 200 °C, 5 min,	66
7	1: 5	*i*: water, 200 °C, 15 min; *ii*: NaOH (1.0 equiv.), water, 200 °C, 5 min	79
8	1: 6	*i*: water, 200 °C, 15 min; *ii*: NaOH (1.0 equiv.), water, 200 °C, 5 min	74
9	1: 7	*i*: water, 200 °C, 15 min; *ii*: NaOH (1.0 equiv.), water, 200 °C, 5 min	71
10	1: 5	*i*: water, 200 °C, 10 min; *ii*: NaOH (1.0 equiv.), water, 200 °C, 5 min	58
11	1: 5	*i*: water, 180 °C, 30 min; *ii*: NaOH (1.0 equiv.), 200 °C, 5 min	58
12	1: 5	*i*: water, 200 °C, 15 min; *ii*: NaOH (1.0 equiv.), 180 °C, 5 min	68
13	1: 5	*i*: water, 180 °C, 15 min; *ii*: NaOH (1.0 equiv.), 200 °C, 5 min	46
14	1: 5	*i*: water, 190 °C, 15 min; *ii*: NaOH (1.0 equiv.), 200 °C, 5 min	54
15	1: 5	*i*: water, 210 °C, 15 min; *ii*: NaOH (1.0 equiv.), 200 °C, 5 min	79
16	1: 5	*i*: water, 220 °C, 15 min; *ii*: NaOH (1.0 equiv.), 200 °C, 5 min	**85**
17	1: 5	*i*: water, 230 °C, 15 min; *ii*: NaOH (1.0 equiv.), 200 °C, 5 min	77

[a] The reaction was performed using the Discover SP (CEM) microwave synthesizer on a 3.4 mmol scale (succinic acid) using 2 mL of water in the first step, followed by the addition of 1 mL of the specified aqueous base in the second step.

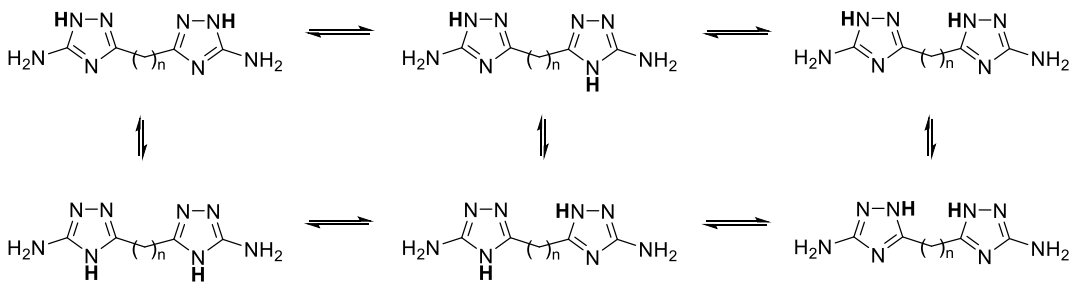
Table 2. One-pot synthesis of polymethylene-bis(1*H*-1,2,4-triazol-5(3)-amines)[a]



Compound	Structure	Scale (mmol)	Yield (%)
12		3.4	85
		17	88
13		3.4	58
		17	63
14		3.4	77
		17	66
15		3.4	52
		17	56
16		3.4	72
		17	65
17		3.4	57
		17	54
6		3.4	63
		17	63
11		3.4	72
		17	67

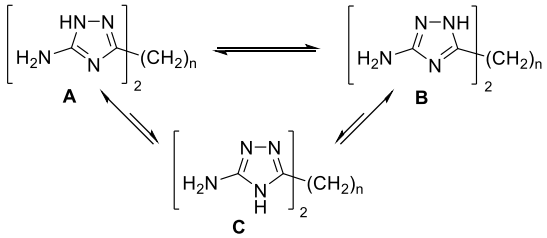
[a] The reaction was performed using a Discover SP CEM microwave synthesizer at 220 °C for 15 min in water followed by addition of aq. NaOH and heating at 200 °C for 5 min.

The annular prototropic tautomerism, possible in both triazole rings of the prepared compounds, might result in six different tautomers representing different combinations of the 5-amino-1*H*-1,2,4-triazole, 3-amino-1*H*-1,2,4-triazole, and 5-amino-4*H*-1,2,4-triazole rings (Scheme 3). These three principal forms of the 1,2,4-triazole ring can be distinguished on the basis of NMR spectroscopy data (though without allowing assigning the presence of individual tautomers). The ^{1}H NMR spectra of the products in DMSO-d_6 gave two sets of signals for the protons for the primary amino group and the triazole ring. These signals together with two sets of signals for the triazole ring carbon atoms in the ^{13}C NMR spectra served for the assignments of two main forms (**A** and **B**) of the triazole ring (three potential tautomers). The assignments were confirmed with the literature data,[6-8,10] and the equilibrium constant (K_T) and corresponding Gibbs free energy (ΔG_{300}) values were estimated (Table 3).



Scheme 3. Theoretically possible tautomers of polymethylene-bis(1*H*-1,2,4-triazol-5(3)-amines).

Table 3. Tautomeric composition polymethylene-bis(1,2,4-triazol-5(3)-amines) in DMSO-d_6 solution[a]



Compounds	n	Composition (%)		K_T	$-\Delta G_{300}$ (kJmol^{-1})
		A	**B**		
12	2	72	28	2.57	2.35
13	3	68	32	2.13	1.89
14	4	67	33	2.03	1.77
15	5	66	34	1.94	1.65
16	6	66	34	1.94	1.65
17	7	65	35	1.86	1.55
6	8	65	35	1.86	1.55
11	10	65	35	1.86	1.55

[a] Assigned by the NMR spectroscopy performed at 27 °C.

In DMSO-d_6 solution, the tautomeric equilibria was shifted mainly towards the 5-amino-1*H*-form (**A**) of the triazole ring with the 3-amino-1*H*-form (**B**) being less prominent and the 4*H*-form (**C**) undetectable. The expansion of the polymethylene link between the triazole rings led to some increase in the 3-amino-1*H*-form (**B**) presence in the equilibrium. This trend can be explained by the diminishing distance electron-withdrawing effect of one triazole ring on another. However, for compounds possessing seven or more methylenic groups in the linking chain, the equilibrium constant remained the same. It should be noted that the tautomer signals were indistinguishable when the NMR spectra of the compounds were recorded in $CDCl_3$.

In crystals, the tautomerizable 5(3)-amino-1,2,4-triazoles usually appear in the 5-amino-1*H*-tautomer form.[11] An example of 5-amino-1*H*- and 3-amino-1*H*-tautomers crystallising together has also been reported.[12] With the objective to investigate the tautomeric preference in crystals of the prepared compounds, we performed single crystal X-ray crystallography for representative compound **14**.[13] The molecular structure of **14**, shown in Fig. 2(a), revealed that this compound crystallised with the 3-amino-1*H*-1,2,4-triazole rings on both sides of the molecule. This tautomeric form is not typical for crystals of tautomerizable 5(3)-amino-1,2,4-triazoles and represents a rather unique case of finding 3-amino-1*H*-1,2,4-triazoles in crystals.

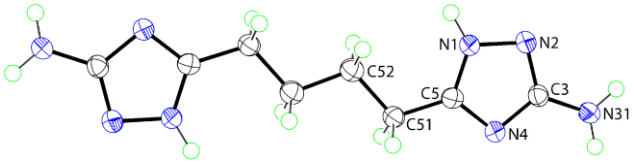


Figure 2. Molecular structure of **14** showing atom labelling and 70% probability displacement ellipsoids; unlabelled atoms are related by the symmetry operation -x, 2-y, -z.

In conclusion, we have developed an efficient and practical one-pot microwave-promoted synthesis of polymethylene-bis(1*H*-1,2,4-triazol-5(3)-amines) from readily available dicarboxylic acids. The method was found to be scalable and transferable to another microwave reactor. The tautomeric preferences in the products were determined in solution (by NMR spectroscopy) and solid state (X-ray crystallography). The tautomeric equilibrium in the solution depended on the length of the chain connecting the triazole rings. A unique crystallisation of the 5-substituted 3-amino-1*H*-1,2,4-triazole tautomeric form was also observed.

Acknowledgments

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References and notes

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9. *General method for the microwave-assisted synthesis of bis(5(3)-amino-1,2,4-triazol-3(5)-yl)polymethylenes (**6**, **11-17**).* A mixture of the corresponding dicarboxylic acids (3.4 mmol) and aminoguanidine hydrochloride (1.88 g, 17 mmol) in water (2 mL) was irradiated in a 10 mL seamless pressure vial using the microwave system operating at maximum microwave power (up to 300 W) at 220 °C for 15 min. After cooling to ambient temperature, 17 M aq. NaOH (1 mL) was added to the vial and the reaction mixture was irradiated again at 200 °C for 10 min. After cooling to ambient temperature, the precipitated solid was filtered, washed with cold water and recrystalised from water to give desired product. The reaction was also replicated on an increased scale of the dicarboxylic acids (17 mmol) and aminoguanidine hydrochloride (9.40 g, 85 mmol) in water (10 mL).
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13. Crystal data for $C_8H_{14}N_8$ (**14**): M = 222.27, monoclinic, $P2_1/n$, a = 5.00860(10), b = 5.1190(2), c = 19.5646(6) Å, β= 93.306(3)˚, V = 500.78(3) Å^3, Z = 2, D_x = 1.474 g cm^{-3}, F(000) = 236, μ = 0.844 mm^{-1}. CCDC 1851291.

Supplementary Material

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2018.XX.XXX. These data include experimental details, copies of ^{1}H and ^{13}C NMR spectra of the prepared compounds, and X-ray crystallography data for compound **14**.