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A CONVENIENT METHOD OF PREPARATION OF 3,3'-DICHLORO-5,5'-BI-1,2,4-TRIAZINE AND ITS SYTHETIC APPLICATIONS¹

Ewa Wolińska*

Department of Chemistry, Faculty of Sciences, University of Podlasie, 3 Maja 54,
08-110 Siedlce, Poland
e-mail: ewol@ap.siedlce.pl

Abstract – A convenient method for preparing of 3,3'-dichloro-5,5'-1,2,4-triazine (**4**) and its application to the synthesis of 3,3'-diamino-5,5'-bi-1,2,4-triazines **6a-i** by the nucleophilic aromatic substitution are described. An attempt to synthesis of cyclophanes containing 5,5'-bi-1,2,4-triazine subunit by ring-closing metathesis of the alkenyl ethers **7a,b** have been unsuccessful. A crossover experiment clearly shows that nitrogen atoms of the 1,2,4-triazine ring coordinate to the ruthenium catalyst and deactivate it.

Substituted 1,2,4-triazines are important class of compounds due to their biological activity and importance in organic synthesis.² The presence of three nitrogen atoms makes the 1,2,4-triazine ring one of the most π -deficient nitrogen-containing heterocycles. Every position of 3, 5 and 6 in 1,2,4-triazine is susceptible to nucleophilic attack, however their reactivity depends on the kind of substituents and nature of the leaving group in the ring.³ Furthermore, nucleophilic addition at 1,2,4-triazine ring carbon carrying hydrogen, S_NH reaction, produces stable σ -adducts, which can be converted into aromatic compounds on several ways.⁴

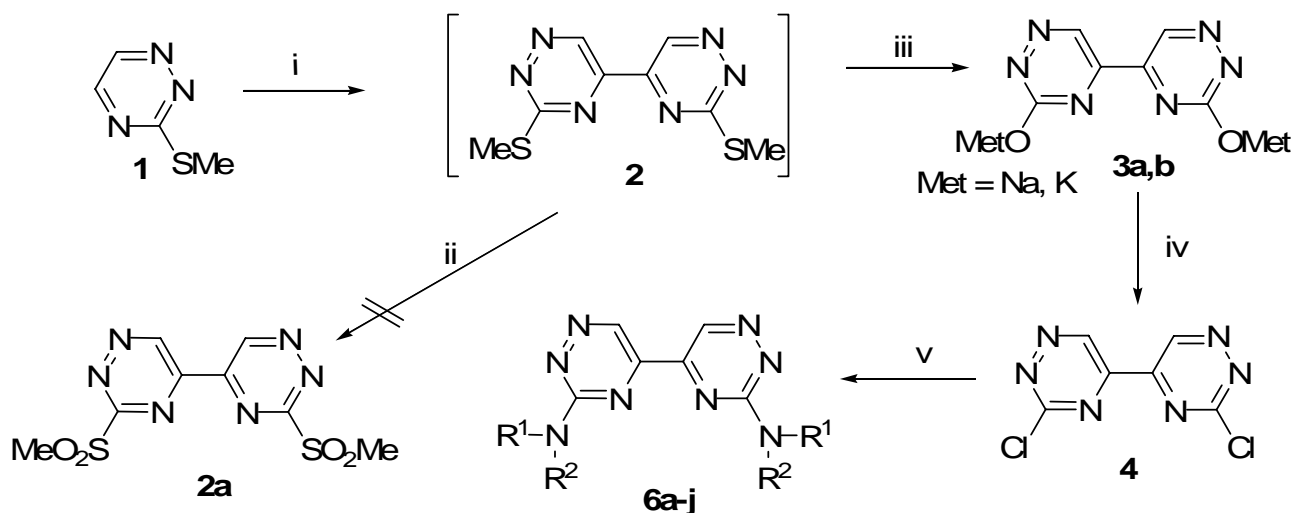
In contrast to well known 1,2,4-triazine chemistry only a limited number of reports have appeared regarding synthesis and chemical properties of its dimeric analogue, namely 5,5'-bi-1,2,4-triazine and its derivatives. These compounds have been easily prepared by homocoupling reactions of monocyclic 1,2,4-triazine derivatives unsubstituted at C-5 in the presence of cyanide.⁵ The direct functionalization of

such obtained 5,5'-bi-1,2,4-triazines by nucleophilic displacement of substituents present in the 1,2,4-triazine ring is still undeveloped area and have not been studied in details. According to literature there are only two reports concerning nucleophilic displacement of methylsulfinate from readily available 3,3'-bis(methylsulfanyl)-5,5'-bi-1,2,4-triazine (**2**) with aqueous dimethylamine⁶ and ethoxide.^{5a} However, in some cases a serious limitation for the above approach is rather difficult access to suitable substrates.^{7a} Also oxidation of methylsulfanyl group in **2** to methylsulfonyl one being more reactive toward nucleophilic displacements, cannot be completed due to the instability of 3,3'-bis(methylsulfonyl)-5,5'-bi-1,2,4-triazine (**2a**) (Scheme 1).^{7b}

In searching for more effective nucleophilic group for nucleophilic displacements we undertook study on the preparation of 3,3'-dichloro-5,5'-bi-1,2,4-triazine (**4**) and its application in organic synthesis. Since some amino and diamino derivatives of 1,2,4-triazine are biologically active and have medicinal value⁸ reaction of **4** with various amines leading to new diamino 5,5'-bi-1,2,4-triazines have been investigated.⁹ We also describe in this paper an attempt to synthesis of 5,5'-bi-1,2,4-triazine - based macrocycles by ring closing metathesis (RCM).

RESULTS AND DISCUSSION

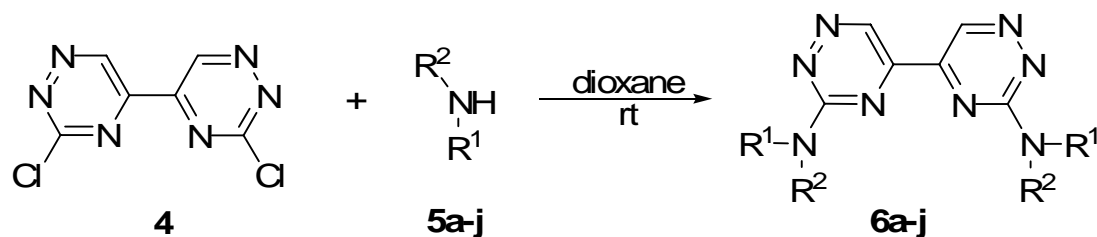
Synthetic approach to 3,3'-dichloro-5,5'-bi-1,2,4-triazine (**4**) starts with 3-(methylsulfanyl)-1,2,4-triazine (**1**) easily prepared using literature procedure¹⁰ (Scheme 1). Compound **1** was smoothly converted into disodium salt of 3,3'-dihydroxy-5,5'-bi-1,2,4-triazine (**3a**), *via* a two-step one-pot procedure which involved the homocoupling of **1** in the presence of 1.5 equivalents of potassium cyanide to give 3,3'-bis(methylsulfanyl)-5,5'-bi-1,2,4-triazine¹¹ (**2**), followed by nucleophilic displacement of methylsulfinate from the latter with sodium hydroxide. This route is practical for a large scale operation and avoids the use of time and solvent consuming isolation of bitriazine **2** from the reaction mixture. After 24 hours of stirring at rt disodium salt **3a** was isolated as precipitated solid in 86 % yield. When instead of sodium hydroxide, potassium hydroxide is applied under the identical reaction conditions a better soluble dipotassium salt **3b** is obtained in 80 % yield, after partial evaporation of solvent. Subsequent chlorination of salts **3a** or **3b** with an excess of phosphoryl chloride afforded 3,3'-dichloro-5,5'-bi-1,2,4-triazine (**4**) in 65 and 70 % yield respectively (Scheme 1). The resulted dichloro compound **4** exhibits good air and moisture stability. Evidence for its structure is obtained from ¹H, ¹³C NMR and elemental analysis (see EXPERIMENTAL).

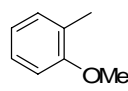






Scheme 1. Reagent and conditions: (i) KCN, H₂O, rt; (ii) KMnO₄, benzene/H₂O, Bu₄N⁺Br⁻, AcOH, rt; (iii) NaOH or KOH, H₂O/EtOH, rt; (iv) POCl₃, 105 °C; (v) **5a-j**, dioxane, rt.

With 3,3'-dichloro-5,5'-bi-1,2,4-triazine (**4**) in hand we next evaluated its reactivity toward nucleophilic substitution of chlorine atoms with a variety of amines **5a-j**. To optimize an amination conditions the reaction of **4** with *n*-butylamine **5a** was first investigated. Compound **4** was treated with *n*-butylamine **5a** in dioxane at ambient temperature. To avoid monosubstitution process five equivalents of amine were necessary to use. The same conditions were applied for reactions of **4** with other amines (Scheme 1). The reactions were completed within hours and appropriate diamino derivatives of 5,5'-bi-1,2,4-triazine **6a-f** were precipitated from the reaction mixture as yellow solids or oils in the case of **6g-i**. The latter, after evaporation of solvent were turned to solids by treatment with methanol. The yields of the prepared diamino compounds were good or excellent (Table 1). Only diisopropylamine **5j** did not undergo reaction with **4** due to steric effect of two diisopropyl groups.

Continuing our research on diamino bitriazines we decided to explore their derivatives **6h** and **6i** as potential intermediates for the synthesis of 5,5'-bi-1,2,4-triazine containing cyclophanes. The sulfur analogues of such systems and their application in Diels-Alder/*retro* Diels-Alder reactions were recently reported.¹² The approach presented in Scheme 2 is focused on the construction of the alkenyl ethers **7a,b** which may be converted into the target molecules by ring-closing metathesis.

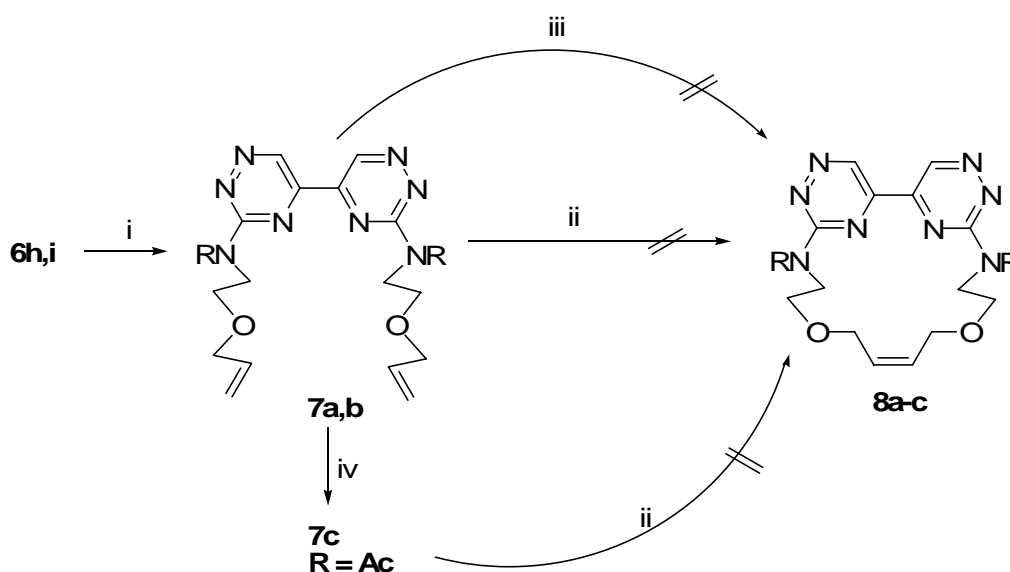
Table 1. Yields, reaction times and melting points of compounds **6a-j**.

Compound	R ¹	R ²	Reaction Time (h)	Yield (%)	Mp (°C)
6a	H	Bu	21	84	264-265
6b	H	<i>t</i> -Bu	7	52	310
6c	H	Bn	0.5	86	248-250
6d	H		3	84	219
6e		 ^a	1	80	255
6f	Et	Et	24	65	181
6g	H		0.25	80	221-222
6h	H		0.25	82	278
6i	Me		0.5	84	172-173
6j	<i>i</i> -Pr	<i>i</i> -Pr	24	0	-

^a pyrrolidine ring

Reactions of **6h** and **6i** with allyl bromide in the presence of sodium hydride afforded **7a,b** in good yield. However, treatment of the olefin substrates **7a,b** with rutenium benzylidene complex (Grubbs' catalyst I) (10 mol%) in 0.01 M solution of dichloromethane at reflux for 5 hours did not result in the formation of

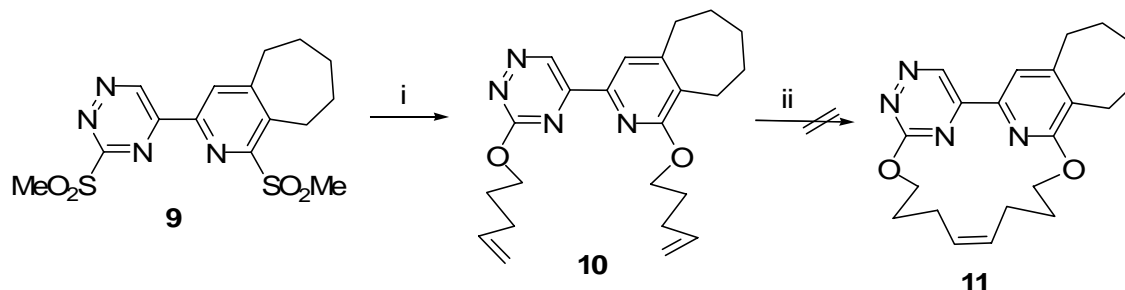
desired products; only starting **7a,b** were recovered unchanged. It is well documented that amino group being present in the olefin containing substrate can coordinate to ruthenium catalyst and deactivated it. To overcome these difficulties conversion of amine to the corresponding amide or the addition of Lewis acids into the reaction mixture is recommended.¹³ The latter, binding nitrogen prior to its reaction with ruthenium catalyst may improve olefin metathesis. Therefore, RCM of compounds **7a,b** were repeated in the presence of equivalent amounts of $\text{Ti}(\text{O}i\text{-Pr})_4$ and $\text{B}(\text{Et}_2\text{O})_4$, however, no expected products **8a,b** could be isolated (Scheme 2).



Scheme 2. Reagents and conditions: (i) allyl bromide, NaH, DMF, 50 °C; (ii) $\text{Cl}_2(\text{PCy}_3)_2\text{Ru}=\text{CHPh}$ (Grubbs' cat. I), 10 mol%, 0.01 M solution in CH_2Cl_2 , reflux; (iii) $\text{Ti}(\text{O}i\text{-Pr})_4$ or $\text{B}(\text{Et}_2\text{O})_3$, $\text{Cl}_2(\text{PCy}_3)_2\text{Ru}=\text{CHPh}$ (Grubbs' cat. I), 10 mol%, 0.01 M solution in CH_2Cl_2 , reflux; (iv) Ac_2O , rt.

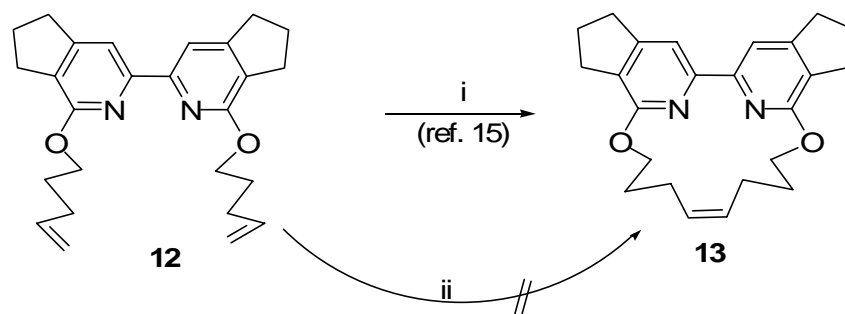
Also acetylation of the exocyclic amine group in **7a** into amide **7c** and RCM reaction of the latter did not result in the formation of **8c** (Scheme 2). On the other hand, 1,2,4-triazines are known to form stable complexes with transition metals including ruthenium.¹⁴ It seems likely that ring nitrogen atoms of compounds **7a,b** are able to coordinate to ruthenium catalyst and prevent its RCM reaction. The colour of the RCM reaction mixture is deeply green what indicates that Grubbs' catalyst can be destroyed under these reaction conditions. In order to explain which nitrogen atoms in **7a** and **7b** are responsible for coordination to the ruthenium catalyst, pyridotriazine derivative **10** without the exocyclic amino group was prepared (Scheme 3) and subjected to RCM reaction under conditions described above. When the compound **10** containing 1,2,4-triazine ring was treated with first generation Grubbs' catalyst, no reaction occurred (Scheme 3). This result clearly shows that nitrogen atoms of the 1,2,4-triazine part of **10** must

deactivate ruthenium benzylidene complex, since its 2,2'-bipyridine analogue **12** easily undergoes RCM to give cyclophane **13** in high yield¹⁵ (Scheme 4).



Scheme 3. Reagents and conditions: (i) 4-penten-1-ol, NaH, DMF, 0 °C to rt; (ii) $\text{Cl}_2(\text{PCy}_3)_2\text{Ru}=\text{CHPh}$ (Grubbs' cat. I), 10 mol%, 0.01 M solution in CH_2Cl_2 , reflux.

This conclusion is supported by a crossover experiment. When compound **12** was treated with Grubbs' catalyst in the presence of equivalent amount of **7a**, **7b** or **4** cyclophane **13** was not formed (Scheme 4). The deep green colour of the reactions mixtures again indicates that the catalyst is destroyed by the compounds **7a**, **7b** or **4**.



Scheme 4. Reagents and conditions: (i) $\text{Cl}_2(\text{PCy}_3)_2\text{Ru}=\text{CHPh}$ (Grubbs' cat. I), 10 mol%, 0.01 M solution in CH_2Cl_2 , reflux; (ii) **7a**, **7b** or **4**, $\text{Cl}_2(\text{PCy}_3)_2\text{Ru}=\text{CHPh}$ (Grubbs' cat. I), 10 mol%, 0.01 M solution in CH_2Cl_2 , reflux.

Thus, in marked contrast to the 2,2'-bipyridine containing alkenyl ethers, their bi-1,2,4-triazine **7a-c** or 5-(pyridyl-2-yl)-1,2,4-triazine **10** analogues do not undergo ring – closing metathesis by treatment with ruthenium benzylidene complex (Grubbs catalyst I). We suppose that the 1,2,4-triazine ring nitrogen atoms are responsible for deactivation of the catalyst. However, an influence of the nitrogen atoms of the exocyclic amine groups in compounds **7a,b** on the catalyst is also possible.

EXPERIMENTAL

All reagents were purchased from Sigma-Aldrich Company. Solvents were purchased from commercial sources or purified and dried according to standard procedures. Compounds 3-(methylsulfanyl)-1,2,4-triazine (**1**),^{5a} 1-methylsulfonyl-3-(3-methylsulfonyl-1,2,4-triazin-5-yl)-6,7,8,9-tetrahydro-5*H*-cyclohepta[*c*]pyridine (**9**)¹⁶ and 1,1'-bis-pent-4-enyloxy-6,7,6',7'-tetrahydro-5*H*,5'*H*-3,3'-bicyclopenta[*c*]pyridine (**12**)¹⁴ were synthesized according to procedures described in literature. Melting points are uncorrected. IR spectra were measured with a Magna IR-760 spectrophotometer in KBr pellets. The ¹H NMR spectra were recorded in varied deuterated solvents on a Varian-Gemini 200 MHz spectrometer. Mass spectra were measured with an AMD 604 (AMD Intectra GmbH, Germany) and GC/MS QP 5050 Shimadzu (30 m × 0.25 mm ID-BPX 5 0.25 mm). Column chromatography was performed on silica gel (230-400 mesh, 60 Merck). Analytical thin layer chromatography (TLC) was performed on 0.25 mm Merck silica gel 60 F₂₅₄ plates. The plates were inspected under UV light (254 nm). Elemental analyses were recorded on Perkin-Elmer 2400-CHN analyzer and the results for indicated elements were within 0.3 % of the calculated values.

Synthesis of 3,3'-dihydroxy-5,5'-bi-1,2,4-triazine disodium and dipotassium salts **3a** and **3b**.

3-Methylsulfanyl-1,2,4-triazine (**1**) (1 g, 7.9 mmol) was dissolved in water (50 mL). The excess of KCN (0.8 g, 12.3 mmol) was added as a solid. After 3 h of stirring at rt EtOH (80 mL) and a solution of NaOH or KOH (81.2 mmol) in water (30 mL) were added. The mixture was stirring at rt for 24 h. The precipitated product **3a** or **3b** was filtered, washed with EtOH/water (5:1) solvent system and dried at 105 °C in vacuum. The compounds were used to the next step without further purification.

Synthesis of 3,3'-dichloro-5,5'-bi-1,2,4-triazine (**4**).

Dissodium salt **3a** (0.6 g, 2.54 mmol) was placed in round bottom flask and phosphorus (V) oxychloride (10 mL) was added. The mixture was heated at 105 °C for 0.5 h. An excess of phosphorus oxychloride was evaporated under reduced pressure to dryness. The product was purified by column chromatography using CH₂Cl₂/acetone (50 : 1) and recrystallized from EtOH. Yield 65 % (0.44 g). Mp 185 °C. ¹H NMR (DMSO-*d*₆) δ: 10.23 (s, 1H). ¹³C NMR (DMSO-*d*₆) δ: 146.30, 152.95, 163.51. MS (EI *m/z*) 229 [M⁺]. Anal. Calcd for C₆H₂N₆Cl₂: C, 31.46; H, 0.88; N, 36.69. Found: C, 31.50; H, 1.00; N, 36.70.

General procedure for the nucleophilic substitution of **4** with amines **5a-j**.

To a mixture of **4** (0.229 g, 1 mmol) in dry dioxane (2 mL) a solution of **5a-j** (5 mmol) in dry dioxane (1 mL) was added. The mixture was stirred at rt until starting compound **4** was consumed (TLC) (Table 1). The precipitates of **6a-f** were filtered off and washed with dioxane. For **6g-i** the solvent was evaporated under reduced pressure. The oily residues were stirred with MeOH and the formed precipitate were

filtered off. The products were recrystallized from MeOH.

3,3'-bis(*n*-butylamino)-5,5'-bi-1,2,4-triazine (6a). IR (KBr) cm^{-1} : 3222 (NH). ^1H NMR (TFA - C_6D_6) δ : 0.95 (t, $J = 7$, 6H), 1.40–1.48 (m, 4H), 1.51–1.68 (m, 4H), 3.50–3.65 (m, 4H), 8.25 (s, 2H). ^{13}C NMR (TFA- C_6D_6) δ : 12.60, 19.92, 30.75, 43.00, 134.80, 157.86. MS (EI m/z) 302 [M^+]. Anal. Cald for $\text{C}_{14}\text{H}_{22}\text{N}_8$: C, 55.61; H, 7.33; N, 37.06. Found: C, 55.52; H, 7.29; N, 36.86.

3,3'-bis(*t*-butylamino)-5,5'-bi-1,2,4-triazine (6b). IR (KBr) cm^{-1} : 3247 (NH). ^1H NMR (CDCl_3) δ : 1.55 (s, 18H), 5.71 (br.s, 2H), 9.41 (s, 2H). MS (EI m/z) 302 [M^+]. Anal. Cald for $\text{C}_{14}\text{H}_{22}\text{N}_8$: C, 55.61; H, 7.33; N, 37.06. Found: C, 55.58; H, 7.20; N, 37.06.

3,3'-bis(benzylamino)-5,5'-bi-1,2,4-triazine (6c). IR (KBr) cm^{-1} : 3224 (NH). ^1H NMR (TFA- C_6H_6) δ : 4.59 (s, 4H), 7.19–7.30 (m, 10H), 8.50 (s, 2H). Anal. Cald for $\text{C}_{20}\text{H}_{18}\text{N}_8 \times \frac{1}{2}\text{H}_2\text{O}$: C, 63.31; H, 5.04; N, 29.53. Found: C, 63.57; H, 4.99; N, 29.03.

3,3'-bis(2-methoxybenzylamino)-5,5'-bi-1,2,4-triazine (6d). IR (KBr) cm^{-1} : 3233 (NH). ^1H NMR (CDCl_3) δ : 3.91 (s, 6H), 4.77 (s, 4H), 6.35 (br.s, 4H), 6.81–6.96 (m, 4H), 7.26–7.40 (m, 4H), 9.45 (s, 2H). Anal. Cald for $\text{C}_{22}\text{H}_{22}\text{N}_8\text{O}_2$: C, 61.38; H, 5.15; N, 26.03. Found: C, 61.26; H, 5.13; N, 25.98.

3,3'-bis(1-pyrrolidino)-5,5'-bi-1,2,4-triazine (6e). ^1H NMR (CDCl_3) δ : 2.05–2.11 (m, 8H), 3.69–3.79 (m, 4H), 9.42 (s, 2H). Anal. Cald for $\text{C}_{14}\text{H}_{18}\text{N}_8$: C, 56.36; H, 6.08; N, 37.56. Found: C, 56.37; H, 6.07; N, 37.60.

3,3'-bis(*N,N*-diethylamino)-5,5'-bi-1,2,4-triazine (6f). ^1H NMR (CDCl_3) δ : 1.28 (t, $J = 7.2$ 12H), 3.77 (m, 8H), 9.39 (s, 2H). Anal. Cald for $\text{C}_{14}\text{H}_{22}\text{N}_8$: C, 55.61; H, 7.33; N, 37.06. Found: C, 55.60; H, 7.32; N, 37.09.

3,3'-bis[(2-aminoethyl)amino]-5,5'-bi-1,2,4-triazine (6g). ^1H NMR (TFA- CD_2Cl_2) δ : 3.80–3.84 (m, 4H), 4.46–4.49 (m, 4H), 9.63 (s, 2H). HR–EI: calcd for $\text{C}_{10}\text{H}_{16}\text{N}_{10}$ 276.15594. Found 276.15518.

3,3'-bis[(2-hydroxyethyl)amino]-5,5'-bi-1,2,4-triazine (6h). IR (KBr) cm^{-1} : 3251 (NH), 3383 (OH). ^1H NMR (TFA- C_6D_6) δ : 3.62–3.85 (m, 8H), 8.98 (s, 2H). HR–EI: calcd for $\text{C}_{10}\text{H}_{14}\text{N}_8\text{O}_2$ 278.12397. Found 278.12511.

3,3'-bis[*N*-(2-hydroxyethyl)-*N*-methylamino]-5,5'-bi-1,2,4-triazine (6i). IR (KBr) cm^{-1} : 3293 (OH). ^1H NMR ($\text{DMSO}-d_6$) δ : 3.27 (s, 6H), 3.60–3.85 (m, 8H), 4.81 (t, $J = 5.2$, 2H), 9.38 (s, 2H). ^{13}C NMR ($\text{DMSO}-d_6$) δ : 37.01, 52.19, 59.08, 136.59, 151.95 161.43. Anal. Cald for $\text{C}_{12}\text{H}_{18}\text{N}_8\text{O}_2$: C, 47.05; H, 5.92; N, 36.60. Found: C, 47.11; H, 5.90; N, 36.47.

General procedure for synthesis of compounds 7a,b. To a mixture of NaH (10 mmol, 60 % in oil) and the substrate **6h,i** (1 mmol) in dry DMF (7 mL) a solution of allyl bromide (10 mmol) in dry DMF (2 mL) was added. The mixture was stirred at 50 °C for 4 h. The solvent was evaporated under reduced pressure. The residue was poured into ice/water and acidified with HCl (10 % solution). The products **7a,b** were

isolated from the water layer by extraction with EtOAc and purified by column chromatography using CH₂Cl₂/MeOH as eluent.

3,3'-bis[(2-allyloxyethyl)amino]-5,5'-bi-1,2,4-triazine (7a). Yield 45 %. Mp 150 °C. IR (KBr) cm⁻¹: 3359 (NH). ¹H NMR (DMSO-*d*₆) δ: 3.64-3.69 (m, 8H), 4.39-4.42 (m, 4H), 4.84 (t, *J* = 5.2, 2H), 5.12-5.24 (m, 4H), 5.81-6.01 (m, 2H), 9.39 (s, 2H). MS (EI *m/z*) 358 [M⁺]. HR-EI: calcd for C₁₆H₂₂N₈O₂ 358.18657. Found 358.18781.

3,3'-bis[*N*-(2-allyloxyethyl)-*N*-methylamino]-5,5'-bi-1,2,4-triazine (7b). Yield 77 %. Mp 58-59 °C. ¹H NMR (CDCl₃) δ: 3.41 (s, 6H), 3.74 (t, *J* = 5.3, 4H), 3.98-4.01 (m, 8H), 5.12-5.29 (m, 4H), 5.78-5.97 (m, 2H), 9.41 (s, 2H). MS (EI *m/z*) 386 [M⁺]. HR-EI: calcd for C₁₈H₂₆N₈O₂ 386.21787. Found 386.21878.

Acetylation of compound 7a.

To a mixture of **7a** (0.36 g, 1 mmol) and acetic anhydride (8 mL), sodium acetate (0.33 g, 4 mmol) was added and the mixture was stirred at rt for 2 hours. The remained acetic anhydride was hydrolyzed by heating with water at 45 °C. The mixture was neutralized with NaHCO₃ and extracted with EtOAc. Product was purified by column chromatography CH₂Cl₂/MeOH (50:1) as eluent.

3,3'-bis[*N*-acetyl-*N*-(2-allyloxyethyl)amino]-5,5'-bi-1,2,4-triazine (7c): oil, yield 89 %. IR (KBr) cm⁻¹: 1741 (C=O). ¹H NMR (CDCl₃) δ: 2.04 (s, 6H), 3.95-4.03 (m, 4H), 4.36-4.41 (m, 8H), 5.19-5.29 (m, 4H), 5.89-6.01 (m, 2H), 9.46 (s, 2H). MS (EI *m/z*) 442 [M⁺]. HR-EI: calcd for C₂₀H₂₆N₈O₄ 442.20770. Found 442.20863.

Synthesis of 1-(pent-4-enyloxy)-3-[3-(pent-4-enyloxy)-1,2,4-triazin-5-yl]-6,7,8,9-tetrahydro-5H-cyclohepta[*c*]pyridine (10).

To a mixture of sodium hydride (0.038 g, 0.95 mmol, 60 % in oil), and 4-penten-1-ol (0.086 g, 1 mmol), in dry DMF (4 mL) a solution of the substrate **9** (0.38 g, 1 mmol) in dry DMF (10 mL) was added. After stirring at 0 °C for 2.5 h the mixture was transferred to a flask containing a solution of sodium hydride (0.26 g, 6.55 mmol) and 4-penten-1-ol (0.48g, 5.62 mmol) in dry DMF (15 mL). The reaction mixture was stirred for additional 2.5 h at ambient temperature and than poured into ice/water and acidified with acetic acid. The precipitate was filtered off and washed with water. The product was purified by column chromatography using CH₂Cl₂/acetone mixture. Yield 14 % ¹H NMR (CDCl₃) δ: 1.60-1.75 (m, 2H), 1.86-2.06 (m, 8H), 2.21-2.32 (m, 4H), 2.82-2.94 (m, 4H), 4.44 (t, *J* = 6.4, 2H), 4.63 (t, *J* = 6.4, 2H), 4.99-5.13 (m, 4H), 5.79-6.00 (m, 2H). MS (EI *m/z*) 394 [M⁺]. HR-EI: calcd for C₂₃H₃₀N₄O₂ 394.23688. Found 394.23518.

General procedure of ring closing metathesis reaction. To a solution (0.01 M) of substrate in dry and

degassed CH_2Cl_2 Grubbs' catalyst I (10 % mol) was added and the mixture was refluxed for 5 h.

ACKNOWLEDGEMENTS

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8. For monoamino 1,2,4-triazine drugs: 3-amino-1,2,4-benzotriazine 1,4-dioxide (*Tirapazamine*), 3-amino-6-[(5-nitro-2-furyl)viny]-1,2,4-triazine (*Panfuran*), and diamino 1,2,4-triazine drug 3,5-diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine (*Lomatrigine*) see ref. 1b.
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