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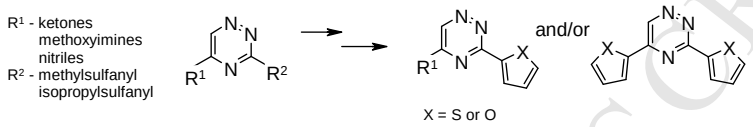

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ABSTRACT

The synthesis of novel mono- and di(substituted)-1,2,4-triazine derivatives containing thiophene and furan rings are described. Heteroaromatic rings were provided using palladium-catalyzed cross-coupling reaction between 3-alkylsulfanyl-5-acyl-1,2,4-triazines or 5-cyano-3-alkylsulfanyl-1,2,4-triazines and heteroaromatic tin compounds. New compounds bearing masked acyl groups were also obtained. These reactions were optimized to determine the scope and limitations of this methodology and were used for preparation of oligothiophenes bearing terminal heterocyclic ring.

1. Introduction

1,2,4-Triazines are important heterocyclic ring systems which are present in numerous biologically active compounds and are widely used in organic synthesis as azadiene equivalent in the inverse electron demand Diels-Alder reactions.[1] The oximes of an 5-acyl and 5-formyl-1,2,4-triazines, directly accessible via S_NH reaction between C-5 unsubstituted 1,2,4-triazines and nitronate ions, have shown considerable synthetic utility for a medicinal chemistry studies.[2] While the regioselective nucleophilic formylation or acylation of 3-R-1,2,4-triazines (R = alkyl, aryl, SR, OR, NR_2) by nitronates can be easily accomplished,[3,4] the same reactions of 1,2,4-triazines bearing heteroaromatic substituent at C-3 (R = furyl or thienyl) have been less successfully performed. Our studies have shown that the reactions of 3-(thiophen-2-yl)-1,2,4-triazine (**4b**) with nitroethane under basic conditions are relatively low yielding and complicated by uncharacterized side products. Considering the sluggish reactivity of these 3-heteroaromatic-1,2,4-triazines towards nitronate ions, we thought it would be interesting to utilize the Stille-type cross-coupling reaction between readily available 5-acyl-3-methylsulfanyl-1,2,4-triazines (**1a-c**) and 2-(tri-*n*-butylstannyl)thiophene or 2-(tri-*n*-butylstannyl)furan to provide rapid access to 5-acyl-3-heteroaryl-1,2,4-triazines **2a-f** (Scheme 1).[5] According to the literature many aryls and heteroarylstannanes were coupled in excellent yields with 3-methylsulfanyl-1,2,4-triazine (**1**) in the presence of CuBr•Me_2S and $Pd(PPh_3)_4$ in refluxing THF.[6] Surprisingly, to our knowledge such reactions have never been studied with the 5-substituted 3-methylsulfanyl-1,2,4-triazines. Herein we present a full account of this study[5] and of our recent findings on the synthesis of conducting thiophenes containing the 1,2,4-triazine ring. The latter or oligothiophenes bearing terminal heterocyclic ring are widely used to prepare conjugated polymers by chemical or electrochemical oxidative coupling reactions and have been found applications in optoelectrical devices.[7]

Our initial attempts to couple 5-acetyl-3-methylsulfanyl-1,2,4-triazine (**1a**) with commercially available 2-(tri-*n*-butylstannyl)thiophene using the conditions mentioned above provided two products: the desired 5-acetyl-3-(thiophen-2-yl)-1,2,4-triazine (**2a)** (12%) and rearranged product i.e. 3-(thiophen-2-yl)-5-(pyridin-3-yl)-1,2,4-triazine (**3a**) (42%) (Scheme 1).

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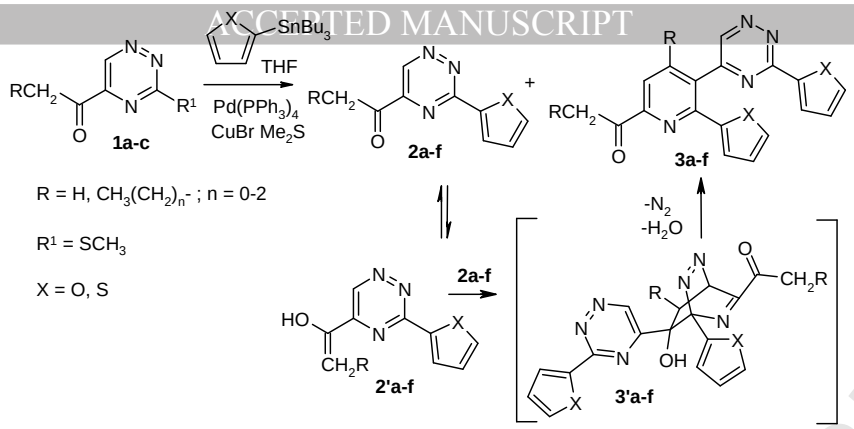


Scheme 1. The Stille cross-coupling reaction of 5-acyl-3-alkylsulfanyl-1,2,4-triazines **1a-c**.

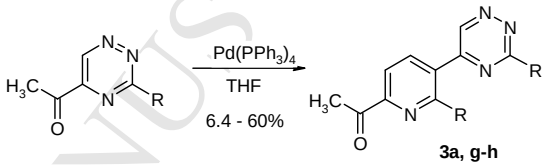
A similar reactivity pattern was observed in the reactions of 5-propanoyl- (**1b**) and 5-butanoyl-3-methylsulfanyl-1,2,4-triazine (**1c**) with 2-(tri-*n*-butylstannyl)thiophene and the results obtained are summarized in Table 1. Extending these studies by using 2-(tri-*n*-butylstannyl)furan in place of 2-(tri-*n*-butylstannyl)thiophene showed the generality of this process, however with increasing steric bulk of the alkyl chain both conversions decreased.

Table 1. Yields of Stille coupling reaction 1,2,4-triazine ketones **1**.

Comp.	**2** - X	**2** [%]	**3** [%]
1a (R = H)	**2a** - S	**2a** - 12	**3a** – 40
1a (R = H)	**2b** - O	**2b** - 21	**3b** – 26
1b (R = CH_3)	**2c** - S	**2c** - 17	**3c** – 27
1b (R = CH_3)	**2d** - O	**2d** - 42	**3d** – 13
1c (R = C_2H_5)	**2e** - S	**2e** - 16	**3e** – 5
1c (R = C_2H_5)	**2f** - O	**2f** - 11	**3f** – 2

The rearranged products **3a-f** were formed via a tandem Stille cross-coupling/Diels-Alder/*retro* Diels-Alder reaction. A plausible mechanism of this ring transformation including the keto-enol tautomerism of an acyl group in **2a-f** catalyzed by metal ions is outlined in Scheme 1. The existence of the enol form in **2'a-f** was supported by spectroscopic experiments, X-ray and in particular by extensive ab initio calculations.[5]
Consequently, in the primary step of the reaction not the carbonyl group itself but tautomeric enol forms **2'a-f** act as an electron-rich dienophiles and undergo Diels-Alder/*retro* Diels-Alder reaction with electron-poor unchanged 5-acyl-1,2,4-triazines **2a-f** giving the adducts **3'a-f**. After elimination of water and nitrogen from the adducts the corresponding pyridyltriazines **3a-f** were obtained. For a further proof of this mechanism, we determined the role of the palladium catalyst on the enolization and Diels-Alder reaction of 5-acetyl-3-R-1,2,4-triazines **2a** and **2g-h** bearing various substituents at C-3 (Scheme 2, Table 2).

In the absence of palladium catalyst ring-transformation products **3a**, **g-h** were not formed. However, the 5-acetyl-1,2,4-triazines **2a**, **g-h** refluxed in THF for 24 h in the presence of 5 mol % of $Pd(PPh_3)_4$ afforded the expected pyridyltriazines **3a**, **g-h**. From the data presented in Table 2 it is clear that reaction of 5-acetyl-3-(thiophen-2-yl)-1,2,4-triazine **2a** gives the corresponding pyridyltriazine **3a** in better yield than compound **2h** having less electron donating methylsulfanyl group.



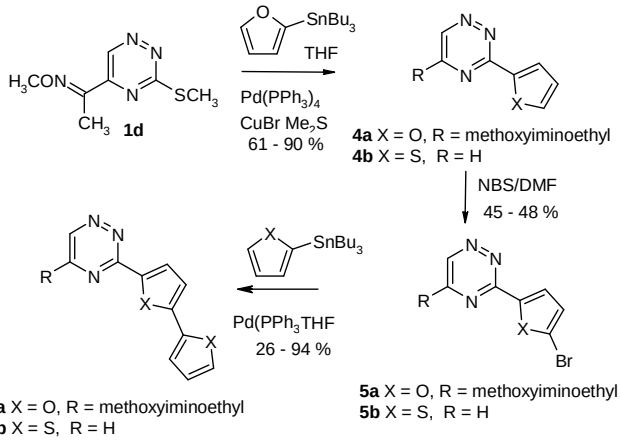
2a R = Th
2g R = Ph
2h R = SCH_3

Scheme 2. Palladium catalyzed Diels-Alder reaction of 5-acyl-3-substituted-1,2,4-triazines **2a, g-h**.

Table 2. Yields of the pyridyltriazine derivatives **3a, g-h** obtained in Diels-Alder reaction.

Comp.	Yield of **3** [%]	Yield of the recovered substrate **2** [%]
2a R = Th	60	36
2g R = Ph	24	33
2h R = SCH_3	6.4	38

Replacement of 5-acetyl-3-methylsulfanyl-1,2,4-triazine **1a** by **1d** containing methoxyimine group[8] at C-5, which is masked ketone function, should prevent the enolization and competitive Diels-Alder reaction of **1d** in the presence of palladium catalyst.

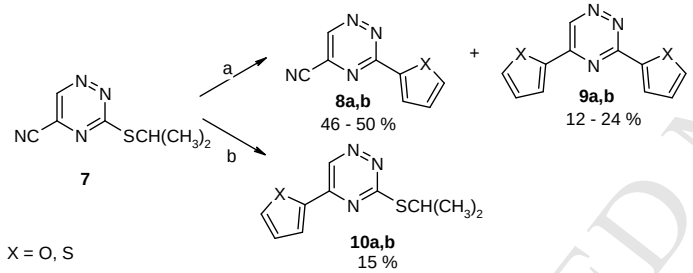


Scheme 3. Synthesis of 5-substituted and 5-unsubstituted 1,2,4-triazine oligomers **6a** and **6b**

When we allowed **1d** to react with 2-(tri-*n*-butylstannyl)furane in the presence of CuBr•Me_2S and $Pd(PPh_3)_4$ in refluxing THF, we found that the desired 3-(furan-2-yl)-5-methoxyimino-1,2,4-triazine **4a** was formed in 61% yield, as the only reaction product (Scheme 3). This result clearly shows that under the conditions mentioned above compound **1d**, with protected keto group, undergoes Stille reaction exclusively. Based on this last result, we examined the preparation of the oligomers **6a-b** bearing terminal 1,2,4-triazine ring (Scheme 3).

The synthesis of oligomer **6a** began with the preparation of the corresponding bromo compound **5a** by bromination of **4a** with NBS in DMF at room temperature. The product **5a** as yellow solid was obtained in satisfactory yield. Coupling **5a** with 2-(tri-*n*-butylstannyl)furan under mentioned above conditions without of CuBr•Me_2S yielded the required oligomer **6a**. Similarly, analogous sequence of reactions was applied to the synthesis of oligomer 3-(2,2'-bithiophen-5yl)-1,2,4-triazine (**6b**) starting from easily available 3-(thiophen-2-yl)-1,2,4-triazine (**4b**)[6]. The latter was obtained via this route in 94 % yield (Scheme 3).

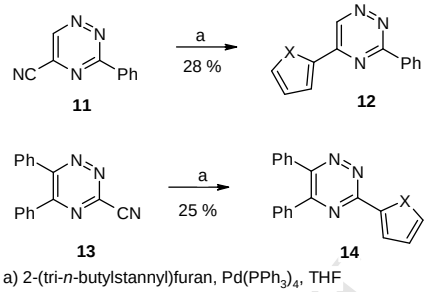
In searching an effective route to 3,5-di(heteroaryl)-1,2,4-triazines we have explored the Stille type reaction between 5-cyano-3-isopropylsulfanyl-1,2,4-triazine **7** and 2-(tri-*n*-butylstannyl)thiophene or 2-(tri-*n*-butylstannyl)furan (Scheme 4). It is well known that cyano substituent[9] at the 5-position of 1,2,4-triazine ring is an efficient leaving group[10] in reactions with nucleophiles.[3] To the best of our knowledge, the cyano substituent has never been used as a leaving group in the Stille coupling reaction.[11]



a) 2-(tri-*n*-butylstannyl)thiophene(furan), CuBr Me_2S, $Pd(PPh_3)_4$, THF
b) 2-(tri-*n*-butylstannyl)thiophene(furan), $Pd(PPh_3)_4$, THF

Scheme 4. The utilization of the cyano group in the Stille coupling reaction.

Initially, 3-(isopropylsulfanyl)-5-cyano-1,2,4-triazine (**7**) was heated with 2-(tri-*n*-butylstannyl)thiophene or 2-(tri-*n*-butylstannyl)furan in the presence of 2.2 equivalent of CuBr•Me_2S as a cofactor and 5 mol % of palladium catalyst. Under these conditions two kinds of products have been isolated from the reaction mixture. Compounds **8a** (X = S) and **8b** (X = O) were obtained in 50% and 46% yields respectively as a result of the replacement of alkylsulfanyl group in **7**. Disubstituted products **9a** (X = S, 24%) and **9b** (X = O, 12%) were formed by displacement both isopropylsulfanyl and cyano groups. In order to confirm the course of this reaction, the process was performed without cofactor CuBr•Me_2S (pathway b) which usually is used in the palladium-catalyzed cross-coupling reactions to polarize the Pd-S bond in the rate-determining transmetalation step.[12] In this case only cyano group was substituted afforded 3-isopropylsulfanyl-5-(thiophen-2-yl)-1,2,4-triazine (**10a**) in 15% yield. Similarly, coupling of 5-cyano-3-phenyl-1,2,4-triazine **11** and 3-cyano-5,6-diphenyl-1,2,4-triazine **13** with 2-(tri-*n*-butylstannyl)thiophene using $Pd(PPh_3)_4$ as the palladium source resulted in the formation of the desired products **12** and **14** in 28 and 25% yield. This means that both compounds were obtained via Stille coupling involving formation of the corresponding palladium complex which subsequently converts into substituted products **12** and **14**.



a) 2-(tri-*n*-butylstannyl)furan, $Pd(PPh_3)_4$, THF

Scheme 5. The reactivity of the cyano group of the 1,2,4-triazine derivatives **11, 13** in the Stille coupling procedure.

2. Conclusion

In conclusion, we have presented the direct introduction of five-membered heterocyclic rings into triazine nucleus by Stille coupling starting from 3-alkylsulfanyl-1,2,4-triazines bearing at C-5 the acyl, methoxyimine or cyano substituents. Utility of these compounds in the synthesis of oligthiophenes or oligofurans bearing heterocyclic ring are currently in progress.

3. Experimental section

3.1. General information

Melting points are uncorrected. ^1H and ^{13}C NMR spectra were determined at 400 and 100 MHz respectively on Varian Gemini spectrometer. Chemical shifts (δ) are given in parts per million and coupling constants are given as absolute values expressed in Hertz. Mass spectra were obtained using AMD 604 (AMD Intectra GmbH, Germany) and GC/MS QP 5050 Shimadzu (30 m × 0.25 mm ID-BPX 5 0.25 mm) spectrometers. Elemental analyses were recorded on Perkin-Elmer 2400-CHN analyzer and the results for indicated elements were within 0.3% of the calculated values. Thin layer chromatography (TLC) was carried out on aluminium sheets percolated with silica gel 60 F_{254}(Merck). Column chromatography separations were performed using Merck Kieselgel 60 (0.040-0.060 mm). Solvents were dried and distilled according to standard procedures. All reagents were purchased from Aldrich and used as received.

3-Thiophen-2-yl-1,2,4-triazine **4b**[6] was obtained according known procedure.

4.1. General procedure of Stille coupling reaction for 5-acetyl-3-methylsulfanyl-1,2,4-triazine (1a) with 2-(tri-*n*-butylstannyl)thiophene.

A solution of 5-acetyl-3-methylsulfanyl-1,2,4-triazine (**1a**) (0.25 g, 1.46 mmol) in THF (17 mL), CuBr•Me_2S (0.66 g, 3.2 mmol), corresponding stannyl derivatives (2.9 mmol) and $Pd(PPh_3)_4$ (5 mol%) was stirred at reflux under nitrogen until starting compound was consumed (TLC control). THF was then evaporated and residue was treated with hexane and filtered. The filtrate was dissolved in ethyl acetate and washed a few times with brine. After evaporation of the solvent from the combined extracts, the remaining residue was purified by column chromatography using CH_2Cl_2 as eluent.

*4.1.1. 5-Acetyl-3-thiophen-2-yl-1,2,4-triazine (**2a**):* 0.05 g (12 %), mp 107-108 ºC. R_f (99 % CH_2Cl_2/acetone) 0.68. IR (KBr) cm^{-1}: 1712 (C=O), 1076 (C-S-C). ^1H NMR (400 MHz, $CDCl_3$) δ: 9.52 (s, 1H, triazine), 8.25 (dd, J_1 = 1.2 Hz, J_2 = 4.0 Hz, 1H, Th), 7.66 (dd, J_1 = 1.2 Hz, J_2 = 5.2 Hz, 1H, Th), 6.25 (dd, J_1 = 1.2 Hz, J_2 = 5.2 Hz, 1H, Th), 2.01 (s, 3H, Me).^{13}C NMR (100 MHz, $CDCl_3$) δ: 199.5, 161.9, 148.4, 142.9, 139.1,132.6, 131.6, 129.2, 25.7. Anal. Calcd for $C_9H_7N_3OS$: C; 52.68, H; 3.41, N; 20.49. Found: C; 52.65, H; 3.26, N; 20.21.

*4.1.2. 5-[6-Acetyl-2-(thiophen-2-yl)pyridin-3-yl-3-thiophen-2-yl]-1,2,4-triazine-(**3a**)*: 0.15 g (40 %), mp 142-143 ºC. R_f (99 % CH_2Cl_2/acetone) 0.88. IR (KBr) cm^{-1}: 1700 (C=O), 1062 (C-S-C). ^1H NMR (400 MHz, $CDCl_3$) δ: 8.95 (s, 1H, triazine), 8.25 (dd, J_1 = 0.8 Hz, J_2 = 3.6 Hz, 1H, Th), 8.19 (d, J = 8.0 Hz, 1H, Py), 8.09 (d, J = 8.0 Hz, 1H, Py), 7.65 (dd, J_1 = 1.2 Hz, J_2 = 5.2 Hz, 1H, Th), 7.50 (dd, J_1 = 0.8 Hz, J_2 = 5.2 Hz, 1H, Th), 7.24 (dd, J_1 = 4.0 Hz, J_2 = 5.2 Hz, 1H, Th), 6.97 (dd, J_1 = 3.6 Hz, J_2 = 4.8 Hz, 1H, Th), 6.87 (dd, J_1 = 1.2 Hz, J_2 = 4.0 Hz, 1H, Th), 2.81 (s, 3H, Me). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 199.1, 161.4, 157.2, 153.8, 150.4, 146.6, 141.4, 140.5, 139.1, 132.0, 130.9, 130.8, 129.7, 129.4, 128.7, 128.1, 119.5, 25.7. Anal. Calcd for $C_{18}H_{12}N_4OS_2$: C; 59.30, H; 3.30, N; 15.40. Found: C; 59.30, H; 3.22, N; 15.32.

*4.1.3. 5-Acetyl-3-furan-2-yl-1,2,4-triazine (**2b**)*: 0.08 g (21 %), mp. 99-100 ºC. R_f (99 % CH_2Cl_2/acetone) 0.62. IR (KBr) cm^{-1}: 1702 (C=O), 1070 (C-O-C). ^1H NMR (400 MHz, $CDCl_3$) δ: 9.53 (s, 1H, triazine), 7.77 (dd, J_1 = 0.8 Hz, J_2 = 1.6, 1H, Fu), 7.61 (dd, J_1 = 0.4 Hz, J_2 = 3.2, 1H, Fu), 6.68 (dd, J_1 = 2.0 Hz, J_2 = 3.6, 1H, Fu), 2.01 (s, 3H, Me). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 199.1, 157.8, 148.1, 146.9, 146.9, 142.4, 116.5, 112.8, 25.3. Anal. Calcd for $C_9H_7N_3O_2$: C; 57.14, H; 3.70, N; 22.22. Found: C; 57.10, H; 3.80, N; 22.11.

*4.1.4. 5-[6-(Acetyl-2-furan-2-yl)pyridin-3-yl-3-furan-2-yl]-1,2,4-triazine (**3b**)*: 0.087 g (26 %), mp. 153-155 ºC. R_f (99 % CH_2Cl_2/acetone) 0.20, IR (KBr) cm^{-1}: 1710 (C=O). ^1H NMR (400 MHz, $CDCl_3$) δ: 9.53 (s, 1H, triazine), 8.17 (d, J = 8.0 Hz, 1H, Py), 8.07 (d, J = 8.0 Hz, 1H, Py), 7.75 (d, J = 0.8 Hz, 1H, Fu), 7.58 (d, J = 3.2 Hz, 1H, Fu), 7.31 (d, J = 0.8 Hz, 1H, Fu), 7.24 (d, J = 3.6 Hz, 1H, Fu), 6.66 (dd, J_1 = 1.6 Hz, J_2 = 3.2 Hz, 1H, Fu), 6.55 (dd, J_1 = 1.6 Hz, J_2 = 3.2 Hz, 1H, Fu), 2.81 (s, 3H, Me).^{13}C NMR (100 MHz, $CDCl_3$) δ: 199.1, 156.4, 154.1, 152.0, 146.5, 146.3, 145.1, 144.5, 142.4, 140.4, 132.0, 128.4, 119.5, 116.5, 113.0, 112.8, 112.4, 25.7. HRMS (ESI) m/z calcd for $C_{18}H_{14}N_4O_3$ $(M+H)^+$: 334.10157. Found 334.10143.

*4.1.5. 5-Propanoyl-3-thiophen-2-yl-1,2,4-triazine (**2c**):* 0.10 g (17 %), mp 112-113 ºC. R_f (99 % CH_2Cl_2/acetone) 0.65, IR (KBr) cm^{-1}: 1708 (C=O), 1062 (C-S-C). ^1H NMR (400 MHz, $CDCl_3$) δ: 9.51 (s, 1H, triazine), 8.23 (d, J_1 = *1.2* Hz, J_2 = 3.6 Hz, 1H, Th), 7.65 (d, J_1 = *1.2* Hz, J_2 = 4.8 Hz, 1H, Th), 7.24 (dd, J_1 = 4.0 Hz, J_2 = 5.6 Hz, 1H, Th), 3.30 (q, J = 7.2 Hz, 2H, $\underline{CH_2}CH_3$), 1.28 (t, J = 7.2Hz, 3H, $CH_2\underline{CH_3}$). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 201.7, 161.9, 147.9, 142.6, 138.8, 132.2, 131.1, 128.8, 31.2, 7.3. Anal. Calcd for $C_{10}H_9N_3O_2$: C; 59.11, H; 4.43, N; 20.69. Found: C; 59.05, H; 4.47, N; 20.53.

*4.1.6. 5-[4-(Methyl-6-propanoyl-2-thiophen-2-yl)pyridin-3-yl-3-thiophen-2-yl]-1,2,4-triazine (**3c**):* 0.16 g (27 %), 144-145 ºC. R_f (99 % CH_2Cl_2/acetone) 0.80. IR (KBr) cm^{-1}: 1697 (C=O), 1058 (C-S-C). ^1H NMR (400 MHz, $CDCl_3$) δ: 8.84 (s, 1H, triazine), 7.91 (s, 1H, Py), 8.22 (d, J_1 = *1.2* Hz, J_2 = 3.6 Hz, 1H, Th) 7.64 (d, J_1 = *1.2* Hz, J_2 = 4.8 Hz, 1H, Th), 7.37 (d, J_1 = *1.2* Hz, J_2 = 4.0 Hz, 1H, Th), 7.24 (d, J_1 = *4.0* Hz, J_2 = 5.2 Hz, 1H, Th), 6.86 (d, J_1 = 4.0 Hz, J_2 = *5.2* Hz 1H, Th), 6.52 (d, J_1 = *1.2* Hz, J_2 = 4.0 Hz, 1H, Th), 3.33 (q, J = 7.2 Hz, 2H, $\underline{CH_2}CH_3$), 1.27 (t, J = 7.2 Hz, 3H, $CH_2\underline{CH_3}$), 2.32 (s, 3H, Me). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 202.1, 161.2, 157.9, 153.1, 149.8, 148.8, 147.5, 142.5, 139.2, 132.2, 131.1, 129.9, 129.2, 128.9, 128.7, 127.9, 121.4, 31.3, 20.2, 7.9. Anal. Calcd for $C_{20}H_{16}N_4OS_2$: C; 61.22, H; 4.08, N; 14.28. Found: C; 60.98, H; 4.41 N; 14.28.

*4.1.7. 5-Propanoyl-3-furan-2-yl-1,2,4-triazine (**2d**):* 0.15 g (42 %), 107-108 ºC. R_f (99 % CH_2Cl_2/acetone) 0.40. IR (KBr) cm^{-1}: 1707 (C=O), 1099 (C-O-C). ^1H NMR (400 MHz, $CDCl_3$) δ: 9.53 (s, 1H, triazine), 7.76 (dd, J_1 = 0.8 Hz, J_2 = 1.6 Hz, 1H, Fu), 7.60 (dd, J_1 = 0.8 Hz, J_2 = 3.6 Hz, 1H, Fu), 6.68 (dd, J_1 = 1.6 Hz, J_2 = 3.6 Hz, 1H, Fu), 3.31 (q, J = 7.2 Hz, 2H, $\underline{CH_2}CH_3$), 1.27 (t, J = 7.2 Hz, 3H, $CH_2\underline{CH_3}$). ^{13}C NMR (100 MHz, $CDCl_3$) δ : 201.7, 157.7, 149.1, 148.1, 146.8, 142.6, 116.4, 112.8, 31.2, 7.2. Anal. Calcd for $C_{10}H_9N_3O_2$: C; 59.11, H; 4.43, N; 20.69. Found: C; 59.05, H; 4.47, N; 20.53.

*4.1.8. 5-[4-Methyl-(6-propanoyl-2-furan-2-yl)pyridin-3-yl-3-furan-2-yl]-1,2,4-triazine (**3d**):* 0.04 g (13 %), oil. R_f (99 % CH_2Cl_2/acetone) 0.78. IR (KBr) cm^{-1}: 1701 (C=O). ^1H NMR (400 MHz, $CDCl_3$) δ: 8.95 (s, 1H, triazine), 7.88 (s, 1H, Py), 7.74 (dd, J_1 = 0.8 Hz, J_2 = 1.6 Hz, 1H, Fu), 7.58 (dd, J_1 = 0.4 Hz, J_2 = 3.2 Hz, 1H, Fu), 7.16 (dd, J_1 = 0.4 Hz, J_2 = 1.6 Hz, 1H, Fu), 7.10 (dd, J_1 = 0.8 Hz, J_2 = 3.2 Hz, 1H, Fu), 6.66 (dd, J_1 = 2.0 Hz, J_2 = 3.6 Hz, 1H, Fu), 6.43 (dd, J_1 = 2.0 Hz, J_2 = 3.6 Hz, 1H, Fu), 3.33 (q, J = 7.2 Hz, 2H, $\underline{CH_2}CH_3$), 2.28 (s, 3H, Me), 0.92 (t, J = 7.2 Hz, 3H, $CH_2\underline{CH_3}$). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 202.2, 158.1, 157.2, 153.3, 152.4, 149.5, 148.5, 147.6, 146.5, 146.0, 144.2, 128.8, 121.2, 115.8, 112.7, 112.7, 111.9, 31.5, 20.1, 7.9. HRMS (EI) m/z calcd. for $C_{20}H_{16}N_4O_3$, 360.12224 (M^+). Found 360.12166.

*4.1.9. 5-Butanoyl-3-thiophen-2-yl-1,2,4-triazine (**2e**):* 0.06 g (16 %), mp. 89-90 ºC. R_f (99 % CH_2Cl_2/acetone) 0.62, IR (KBr) cm^{-1}: 1705 (C=O), 1070 (C-S-C). ^1H NMR (400 MHz, $CDCl_3$) δ: 9.53 (s, 1H, triazine), 8.24 (dd, J_1 = 1.2 Hz, J_2 = 3.6 Hz, 1H, Th), 7.65 (dd, J_1 = 1.2 Hz, J_2 = 4.8 Hz, 1H, Th), 7.24 (dd, J_1 = 1.6 Hz, J_2 = 5.2 Hz, 1H, Th), 3.24 (t, J = 7.2 Hz, 2H, $\underline{CH_2}CH_2CH_3$), 1.82 (sek, J = 7.2 Hz, 2H, $CH_2\underline{CH_2}CH_3$), 1.05 (t, J = 7.2 Hz, 3H, $CH_2CH_2\underline{CH_3}$). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 201.3, 149.1, 148.1, 142.6, 138.8, 132.3, 131.2, 128.9, 39.5, 16.9, 13.7. Anal. Calcd for $C_{11}H_{11}N_3OS$: C; 56.65, H; 4.72, N; 18.02. Found: C; 56.67, H; 4.80, N;17.87.

*4.1.10. 5-[4-Ethyl-6-butanoyl-2-thiophen-2-yl)pyridin-3-yl-3-thiophen-2-yl]-1,2,4-triazine (**3e**):* 0.015 g (4 %), 154-155 ºC, R_f (99 % CH_2Cl_2/acetone) 0.88, IR (KBr) cm^{-1}: 1697 (C=O), 1055 (C-S-C). ^1H NMR (400 MHz, $CDCl_3$) δ: 8.84 (s, 1H, triazine), 7.96 (s, 1H, Py), 8.24 (dd, J_1 = 1.2 Hz, J_2 = 3.6 Hz, 1H, Th), 7.65 (dd, J_1 = 1.2 Hz, J_2 = 4.8 Hz, 1H, Th), 7.38 (dd, J_1 = 1.2 Hz, J_2 = 5.2 Hz, 1H, Th), 7.25 (dd, J_1 = 1.2 Hz, J_2 = 5.2 Hz, 1H, Th), 6.86 (dd, J_1 = 4.0 Hz, J_2 = 5.2 Hz, 1H, Th), 6.49 (dd, J_1 = 1.2 Hz, J_2 = 4.0 Hz, 1H, Th), 3.26 (t, J = 2.8 Hz, 2H, $\underline{CH_2}CH_2CH_3$), 2.57 (q, J = 7.6 Hz, 2H, $\underline{CH_2}CH_3$), 1.84 (qui, J = 7.6 Hz, 2H, $CH_2\underline{CH_2}CH_3$), 1.23 (t, J = 7.6 Hz, 3H, $CH_2CH_2\underline{CH_3}$), 1.06 (t, J = 7.2 Hz, 3H, $CH_2\underline{CH_3}$).^{13}C NMR (100 MHz, $CDCl_3$) δ: 201.7, 161.1, 157.8, 154.5, 153.5, 149.9, 147.7, 142.7, 139.3, 132.1, 131.1, 129.5, 129.2, 128.9, 128.8, 127.9, 119.7, 39.8, 26.5, 17.7, 14.6, 13.9. Anal. Calcd for $C_{22}H_{20}N_4OS_2$: C; 62.86, H; 4.76, N; 13.33. Found: C; 62.72, H; 4.52, N;13.30.

*4.1.11. 5-Butanoyl-3-furan-2-yl-1,2,4-triazine (**2f**):* 0.036 g (11 %). R_f (99 % CH_2Cl_2/acetone) 0.42. IR (KBr) cm^{-1}: 1697 (C=O), 1074 (C-O-C). ^1H NMR (400 MHz, $CDCl_3$) δ 9.50 (s, 1H, triazine), 7.79 (dd, J_1 = 0.8 Hz, J_2 = 1.6 Hz, 1H, Fu), 7.61 (d, J_1 = 0.8 Hz, J_2 = 3.6 Hz, 1H, Fu), 6.68 (d, J_1 = 1.6 Hz, J_2 = 3.6 Hz, 1H, Fu), 3.24 (t, J = 7.2 Hz, 2H, $\underline{CH_2}CH_2CH_3$), 1.81 (qui, J = 7.2 Hz, 2H, $CH_2\underline{CH_2}CH_3$), 1.04 (t, J = 7.2 Hz, 3H, $CH_2CH_2\underline{CH_3}$). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 201.1, 149.1, 148.0, 146.8, 142.5, 116.3, 112.7, 112.7, 39.4, 16.8, 13.6. HRMS (ESI) m/z calcd for $C_{11}H_{13}N_3O_2$ $(M+H)^+$: 219.09576. Found 219.09564.

*4.1.12. 5-[4-Ethyl-(6-butanoyl-2-furan-2-yl)pyridin-3-yl-3-furan-2-yl]-1,2,4-triazine (**3f**):* 0.006 g (2 %), oil, R_f (99 % CH_2Cl_2/acetone) 0.64. IR (KBr) cm^{-1}: 1699 (C=C). ^1H NMR (400 MHz, $CDCl_3$) δ: 8.96 (s, 1H, triazine), 7.93 (s, 1H, Py), 7.73 (dd, J_1 = 0.8 Hz, J_2 = 1.2 Hz, 1H, Fu), 7.55 (dd, J_1 = 0.8 Hz, J_2 = 2.8 Hz, 1H, Fu), 7.14 (dd, J_1 = 0.8 Hz, J_2 = 1.2 Hz, 1H, Fu), 7.09 (dd, J_1 = 0.8 Hz, J_2 = 2.8 Hz, 1H, Fu) 6.65 (dd, J_1 = 1.6 Hz, J_2 = 2.0 Hz, 1H, Fu), 6.42 (dd, J_1 = 1.6 Hz, J_2 = 2.0 Hz, 1H, Fu), 3.26 (t, J = 7.2 Hz, 2H, $\underline{CH_2}CH_2CH_3$), 1.83 (q, J = 7.2 Hz, 2H, $\underline{CH_2}CH_3$), 1.62 (qui, J = 7.6 Hz, 2H, $CH_2\underline{CH_2}CH_3$), 1.21 (t, J =7.6 Hz, 3H, $CH_2CH_2\underline{CH_3}$), 1.17 (t, J = 7.2 Hz, 3H, $\underline{CH_2}CH_3$). HR-EI m/z: Calcd for $C_{22}H_{20}N_4O_3$: 388.15352. Found 388.15294.

*4.1.13. 5-[(6-Acetyl-2-phenyl-2-yl)pyridin-3-yl-3-phenyl-2-yl]-1,2,4-triazine (**3g**)*: 0.007 g (24 %). R_f (99 % CH_2Cl_2/acetone) 0.74. IR (KBr) cm^{-1}: 1712 (C=O). ^1H NMR (400 MHz, $CDCl_3$) δ: 8.70 (s, 1H, triazine), 8.60 (dd, J_1 = 6.4 Hz, J_2 = 12.8 Hz, 2H, Ph), 8.44 (d, J = 7.6 Hz, 1H, Py), 8.21 (d, J = 8.0 Hz, 1H, Py), 7.60-7.55 (m, 3H, Ph), 7.49-7.40 (m, 5H, Ph), 2.86 (s, 3H, Me). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 199.6, 163.9, 157.4, 154.2, 147.4, 143.1, 140.4, 138.2, 134.5, 132.4, 132.1, 129.9, 129.8, 129.1, 129.0, 128.9, 128.5, 128.4, 120.1, 29.7, 25.9, 25.4. HRMS (EI) m/z calcd. for $C_{22}H_{17}N_4O$ $(M+H)^+$: 353.13935. Found: 353.13969.

*4.1.14. 5-[(6-Acetyl-2-metylsulfanyl)pyridin-3-yl-3-metylsulfanyl-2-yl]-1,2,4-triazine (**3h**)*: 0.003 g (6.4 %), mp. 136-137 ºC. R_f (99 % CH_2Cl_2/acetone) 0.28, IR (KBr) cm^{-1}: 1693 (C=O). ^1H NMR (400 MHz, $CDCl_3$) δ: 9.41 (s, 1H, triazine), 8.06 (d, J = 8.0 Hz, 1H, Py), 7.87(d, J = 7.6 Hz, 1H, Py), 2.77 (s, 3H, Me), 2.75 (s, 3H, SMe), 2.67 (s, 3H, SMe). MR (100 MHz, $CDCl_3$) δ: 199.0, 173.9, 159.6, 154.0, 153.6, 143.7, 138.4, 130.9, 116.6, 25.9, 14.2, 13.9. HRMS (MSI) m/z for $C_{12}H_{13}N_4OS_2$ $(M+H)^+$: 293.05183. Found 293.05253.

*4.1.15. 3-Furan-2-yl-5-(1-methoxyiminoethyl)-1,2,4-triazine (**4a**)*: 0.12 g (61 %), mp 132-133 ºC. R_f (99 % CH_2Cl_2/acetone) 0.21, IR (KBr) cm^{-1}: 1585 (C=C), 1035 (C-O-C), 1016 (N-O-CH_3). ^1H NMR (400 MHz, $CDCl_3$) δ: 9.56 (s, 1H, triazine), 7.71 (dd, J_1 = 1.0 Hz, J_2 = 1.8 Hz, 1H, Fu), 7.49 (dd, J_1 = 1.0 Hz, J_2 = 3.5 Hz, 1H, Fu), 6.62 (dd, J_1 = 1.8 Hz, J_2 = 3.5 Hz, 1H, Fu), 4.14 (s, 3H , OMe), 2.32 (s, 3H, Me). HR (ESI) m/z calcd. for $C_{10}H_{11}N_4O_2$ $(M+H)^+$: 219.08765. Found: 219.08748.

*4.1.16. 5-Cyano-3-thiophen-2-yl-1,2,4-triazine (**8a**)*: 0.19 g (50 %), mp 155 ºC. R_f (99 % CH_2Cl_2/acetone) 0.81. IR (KBr) cm^{-1}: 2135 (C≡N), 1606 (C=C), 1120 (C-S-C). ^1H NMR (400 MHz, $CDCl_3$) δ: 8.75 (s, 1H, triazine), 7.68 (dd, J_1 = 0.8 Hz, J_2 = 1.6 Hz, 1H, Th), 7.41 (dd, J_1 = 0.8 Hz, J_2 = 3.6 Hz, 1H, Th), 6.60 (dd, J_1 = 1.6 Hz, J_2 = 3.6 Hz, 1H, Th), ^{13}C NMR (100 MHz, $CDCl_3$) δ: 157.5, 148.0, 147.9, 146.4, 135.0, 118.4, 113.5, 113.3. HRMS (ESI) m/z calcd. for $C_8H_5N_4S$ $(M+H)^+$: 189.02294. Found: 189.02272.

*4.1.17. 5-Cyano-3-furan-2-yl-1,2,4-triazine (**8b**)*: 0.19 g (46 %), mp 152-153 ºC. R_f (99 % CH_2Cl_2/acetone) 0.78. IR (KBr) cm^{-1}: 2142 (C≡N), 1587 (C=C), 1055 (C-O-C). ^1H NMR (400 MHz, $CDCl_3$) δ: 9.28 (s, 1H, triazine), 7.79 (dd, J_1 = 0.8 Hz, J_2 = 1.6 Hz, 1H, Fu), 7.66 (dd, J_1 = 0.8 Hz, J_2 = 3.6 Hz, 1H, Fu), 6.70 (dd, J_1 = 1.6 Hz, J_2 = 3.6 Hz, 1H, Fu). ^{13}C NMR (100 MHz, $CDCl_3$) δ:157.5, 148.0, 147.9, 146.4, 135.0, 118.4, 113.5, 113.3. Anal. Calcd for $C_{10}H_4N_4O$: C; 55.80, H; 2.32, N; 32.56. Found: C; 55.70, H; 2.34, N; 32.60.

*4.1.18. 3,5-Bi-thiophen-2-yl-1,2,4-triazine (**9a**)*: 0.15 g (24 %), mp 122-123 ºC. R_f (99 % CH_2Cl_2/acetone) 0.23. IR (KBr) cm^{-1}: 1577 (C=C), 1010 (C-S-C). ^1H NMR (400 MHz, $CDCl_3$) δ: 9.28 (s, 1H, triazine), 7.66 (dd, J_1 = 0.8 Hz, J_2 = 1.6 Hz, 1H, Th), 7.65 (dd, J_1 = 0.8 Hz, J_2 = 1.6 Hz, 1H, Th), 7.48 (dd, J_1 = 0.8 Hz, J_2 = 3.6 Hz, 1H, Th), 7.45 (dd, J_1 = 0.8 Hz, J_2 = 3.6 Hz, 1H, Th), 6.59 (dd, J_1 = 1.6 Hz, J_2 = 3.6 Hz, 1H, Th), 6.56 (dd, J_1 = 1.6 Hz, J_2 = 3.6 Hz, 1H, Th). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 150.0, 149.3, 147.4, 147.2, 146.6, 146.5, 142.3, 116.8, 115.7, 113.6, 112.8. ESI $(M+H)^+$ calcd. for $C_{11}H_8N_3S_2$: 246.01542. Found: 246.01543.

*4.1.19. 3,5-Bi-furan-2-yl-1,2,4-triazine (**9b**):* 0.04 g (12 %), mp 164ºC. R_f (99 % CH_2Cl_2/acetone) 0.20. IR (KBr) cm^{-1}: 1595 (C=C), 1015 (C-S-C). ^1H NMR (400 MHz, $CDCl_3$) δ: 9.35 (s, 1H, triazine), 7.73 (dd, J_1 = 0.8 Hz, J_2 = 1.6 Hz, 1H, Fu), 7.71 (dd, J_1 = 0.8 Hz, J_2 = 1.6 Hz, 1H, Fu), 7.55 (dd, J_1 = 0.8 Hz, J_2 = 3.6 Hz, 1H, Fu), 7.53 (dd, J_1 = 0.8 Hz, J_2 = 3.6 Hz, 1H, Fu), 6.67 (dd, J_1 = 2.0 Hz, J_2 = 3.6 Hz, 1H, Fu), 6.62 (dd, J_1 = 2.0 Hz, J_2 = 3.6 Hz, 1H, Fu). ^{13}C NMR (100 MHz, $CDCl_3$) δ:157.1, 149.7, 148.9, 147.1, 146.8, 146.1, 141.9, 116.5, 115.3, 113.2, 112.4. HRMS (ESI) m/z calcd for $C_{11}H_9N_3O_2$ $(M+H)^+$: 215.06446. Found 215.06444.

4.2. General procedure for bromination of 5a and 5b.

To a round bottom flask 1.0 mmol of **4a** or **4b** respectively in 5 ml DMF was added and 1.1 mmol NBS was added in few portions. The reaction was stirred at room temperature to disappear starting compound. The mixture was poured into ice-water. The precipitate was filtered and dried. The crude product was purified on chromatography column on silica gel using dichloromethane as eluent. Compound was obtained as light yellow solid.

*4.2.1. 3-[(5-Bromo-furan-2-yl)-5-(1-methoxyiminoethyl)]-1,2,4-triazine (**5a**):* 0.03 g (45 %), mp 160-161 ºC. R_f (99 % CH_2Cl_2/acetone) 0.74, IR (KBr) cm^{-1}: 1591 (C=C), 1049 (C-O-C), 1020 (N-O-CH_3), 694 (C-Br). ^1H NMR (400 MHz, $CDCl_3$) δ: 9.58 (s, 1H, triazine), 7.44 (d, J = 3.6 Hz, 1H, Fu), 7.57 (d, J = 3.6 Hz, 1H, Fu), 3.99 (s, 3H, OMe), 2.31 (s, 3H , Me). Anal. Calcd for $C_{10}H_9BrN_4O_2$: C; 40.40, H; 3.00, N; 18.80. Found: C; 40.62, H; 2.91, N; 18.70.

*4.2.2. 3-(5-Bromo-thiophen-2-yl)-1,2,4-triazine (**5b**)* 0.68 g (48 %), mp 162.5 ºC. R_f (99 % CH_2Cl_2/acetone) 0.46. IR (KBr) cm^{-1}: 1535 (C=C), 1047 (C-S-C), 659 (C-Br). ^1H NMR (400 MHz, $CDCl_3$) δ: 9.05 (d, J = 2.0 Hz, 1H, triazine), 8.52 (d, J = 2.0 Hz, 1H, Th), 7.90 (d, J = 4.0 Hz, 1H, Th), 7.16 (d, J = 4.0 Hz, 1H, Th). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 148.8, 147.2, 131.6, 130.7, 119.5. HRMS (ESI) m/z calcd. for $C_7H_6BrN_3S$ $(M+H)^+$: 244.93952. Found 244.93949.

*4.3. Compounds **6a** and **6b** were obtained according from **5a** and **5b** following the general Stille coupling procedure without using of CuBr•Me_2S.*

*4.3.1. 3-[(5-(Furan-2-yl)-furan-2-yl)-5-(1-methoxyiminoethyl)]-1,2,4-triazine (**6a**)*: 0.02 g (26 %), mp 139-140 ºC. R_f (99 % CH_2Cl_2/acetone) 0.30. IR (KBr) cm^{-1}: 1575 (C=C), 1051 (N-O-CH_3), 1016, (C-O-C). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.55 (s, 1H, triazine), 7.55 (d, *J* = 3.2 Hz, 1H, Fu), 7.49 (d, *J* = 0.8 Hz, 1H, Fu), 6.88 (d, *J* = 3.2 Hz, 1H, Fu), 6.77 (d, *J* = 3.6 Hz, 1H, Fu), 6.52 (dd, J_1 = 1.6 Hz, J_2 = 3.2 Hz, 1H, Fu), 4.14 (s, 3H, OMe), 2.33 (s, 3H, Me). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 157.2, 153.3, 153.1, 150.2, 148.9, 146.0, 143.5, 117.8, 113.7, 112.2, 108.1, 107.9, 63.8, 9.9. HRMS (ESI) m/z calcd. for $C_{14}H_{13}N_4O_3$ $(M+H)^+$: 285.09793. Found: 285.09822.

*4.3.2. 3-(2,2'-Bi-thiophen-5-yl)-1,2,4-triazine (**6b**):* 0.119 g (94 %), mp 141-143 ºC. R_f (99 % CH_2Cl_2/acetone) 0.42. IR (KBr) cm^{-1}: 1516 (C=C), 1047 (C-S-C). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.03 (d, *J* = 2.0 Hz, 1H, triazine), 8.55 (d, *J* = 2.0 Hz, 1H, Th), 8.07 (d, *J* = 4.0 Hz, 1H, Th), 7.33 (d, *J* = 3.6 Hz, 1H, Th), 7.31 (d, *J* = 4.8 Hz, 1H, Th), 7.27 (d, *J* = 5.2 Hz, 1H, Th). 7.07 (t, *J* = 4.4 Hz, 1H, Th). ^{13}C NMR (100 MHz, $CDCl_3$) δ:161.49, 148.59, 146.70, 143.46, 137.32, 136.70, 131.44, 128.11, 125.79, 124.99, 124.85. Anal. Calcd for $C_{11}H_7N_3S_2$: C; 53.87, H; 2.86, N; 17.14. Found: C; 53.71, H; 2.84, N; 16.90.

*4.3.3. 3-Isopropyl-5-thiophen-2-yl-1,2,4-triazine (**10a**):* (15 %). R_f (99 % CH_2Cl_2/acetone) 0.64, IR (KBr) cm^{-1}: 1587 (C=C), 1015 (C-S-C). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.08 (s, 1H, triazine), 7.75 (d, = 3.6 Hz, 1H, Th), 7.61 (d, *J* = 0.8 Hz, 1H, Th), 6.68 (d, *J* = 1.6, 1H, Th), 4.06 (sep, *J* = 6.8 Hz, 1H, $\underline{CH}(CH_3)_2$), 1.49 (d, *J* = 6.8 Hz, 6H, $CH(\underline{CH_3})_2$). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 164.0, 146.2, 142.7, 116.8, 36.8, 23.0. HRMS (ESI) m/z calcd. for $C_{10}H_{12}N_3S_2$ $(M+H)^+$: 238.04672. Found 238.04647.

*4.3.4. 3-Phenyl-5-furan-2-yl-1,2,4-triazine (**12**)*: 0.06 g (28 %), mp 110 ºC. R_f (99 % CH_2Cl_2/acetone) 0.68. IR (KBr) cm^{-1}: 1592 (C=C). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.45 (s, 1H, triazine), 8.60 - 8.57 (m, 2H, Ph), 7.75 (dd, J_1=0.4 Hz, J_2=1.6 Hz, 1H, Fu), 7.60 (dd, J_1 = 0.4 Hz, J_2= 3.6 Hz, 1H, Fu), 7.57-7.53 (m, 3H, Ph), 6.69 (dd, J_1 =2.0 Hz, J_2 = 3.6 Hz, 1H, Fu). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 163.6, 149.8, 147.3, 147.2, 142.8, 135.3, 132.0, 129.1, 128.7, 116.4, 113.6. HRMS (ESI) m/z calcd. for $C_{13}H_{10}N_3O$ $(M+H)^+$: 224.02890. Found: 224.02897.

*4.3.5. 5,6-Di-phenyl-3-furan-2-yl-1,2,4-triazine (**14**)*: 0.06 g (25 %), mp 187 ºC. R_f (99 % CH_2Cl_2/acetone) 0.65. IR (KBr) cm^{-1}: 1585 (C=C), 1027 (C-O-C). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.74 (br s, 1H, triazine), 7.62- 7.57 (m, 5H, Ph), 7.45-7.35 (m, 6H, Ph), 6.65 (br s, 1H, Fu), 6.69 (dd, J_1 = 2.0 Hz, J_2 = 3.6 Hz, 1H, Fu). ^{13}C NMR (100 MHz, $CDCl_3$) δ:155.8, 155.3, 155.0, 149.8, 146.1, 135.5, 135.41, 130.6, 129.7, 129.5, 129.4, 128.5, 115.1, 112.4. HRMS (ESI) m/z calcd. for $C_{19}H_{15}N_3O$ $(M+H)^+$: 301.11649. Found 301.11646.

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