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Synthesis of 3-(Alkylamino)-, 3-(Alkoxy)-, 3-(Aryloxy)-, 3-(Alkylthio)-, and 3-(Arylthio)-1,2,4-triazines by Using a Unified Route with 3-(Methylsulfonyl)-1,2,4-triazine

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Synthesis of 3-(alkylamino)-, 3-(alkoxy)-, 3-(aryloxy)-, 3-(alkylthio)- and 3-(arylthio)-1,2,4-triazines *via* a unified route using 3-(methylsulfonyl)-1,2,4-triazine

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Abstract: In our attempts to develop methods for the synthesis of 3-(alkylthio)- and 3-(alkoxy)-1,2,4-triazines without substitution at the 5 or 6 positions, the synthesis of their anticipated precursor, 3-(methylsulfonyl)-1,2,4 triazine was optimized. The reactivity of 3-(methylsulfonyl)-1,2,4-triazine towards alkyl and aryl thiols, primary and secondary alkyl amines, phenols and alcohols were explored and optimised to maximise the recovery of the corresponding 3-substituted 1,2,4-triazines. Good yields were obtained for the products of these reactions with all the aforementioned nucleophiles except alcohols, using alkali metal carbonates. Higher yields of 3-(alkoxy)-1,2,4-triazines were obtained when sodium alkoxides were replaced by magnesium alkoxides.

Introduction

3-Substituted 1,2,4-triazines **1** (Figure 1) have been used as precursors in the synthesis of furo-, dihydrofuro-, thieno-, thiopyrano-, pyrrolo-, and dihydropyrano-[2,3,b]pyridines *via* intramolecular Diels Alder reactions.[1-3] A number of these cores are encountered in antibiotics and herbicides that are associated with pharmacological activity. [1-3] In the context of medicinal chemistry, 3-substituted 1,2,4-triazines **1** have enticed attention as mGluR5 antagonists as, a target for the development of pharmacotherapies to treat drug and alcohol addictions.[4-6] Some 3-substituted-1,2,4-triazines have been found to inhibit SCD-1, an enzyme linked to obesity and hepatocarcenogenesis,[7] while others have been identified as selective serotonin 5-HT$_7$ ligands.[8] A very recent report describes their potential as compounds that are capable of modulating skeletal muscle contractility.[9] Our group identified some 3,3'-disubstituted-5,5'-bis(1,2,4-triazines), which can be conveniently derived from 3-substituted-1,2,4-triazines *via* a cyanide-induced oxidative coupling (Scheme 1), having low nanomolar levels of activity against *P. falciparum* and low cytotoxicity.[10]

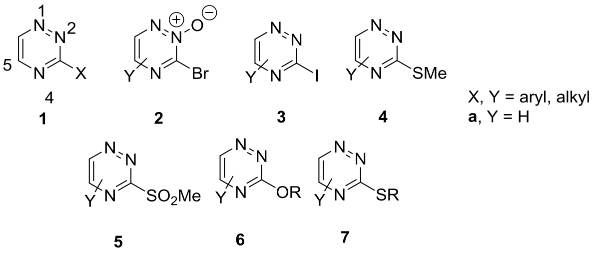
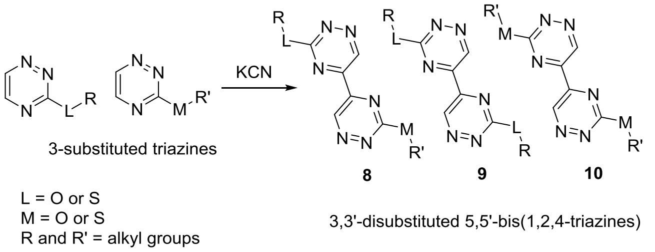


Figure 1. Some 3-substituted 1,2,4-triazines 1 with reported biological activity, and potential synthetic precursors 2-5 to related compounds.



Scheme 1. The synthesis of 3,3'-disubstituted 5,5'-bis(1,2,4-triazines) via cyanide ion mediated dimerization[10]

A literature survey on the synthesis of 3-substituted 1,2,4-triazines indicates that 3-halo-, 3-methylthio- and 3-methylsulfonyl 1,2,4-triazines (**2**-**5**) are most frequently used precursors to their synthesis (Figure 1). The substitution of a bromo group at the 3-position in 1,2,4 triazines with other nucleophiles is known *via* the precursor (**2**) with *N*-oxide at position 2, as described in a recent report.[9] The substitution of an iodo group at 3-position is also known, but is less appealing since synthetic procedures leading to the synthesis of 3-iodo-1,2,4 triazines **3** are poor yielding and are only known for triazines with substituents in either the 5 or 6 position.[4] The 3-methylthio (-SMe) substituted 1,2,4 triazine **4** has been used as a pecursor of choice for Cu(I)/Pd(0) or Pd(II) mediated Suzuki,[11,12] Stille,[12,13] and Buchwald-type[14] coupling reactions, leading to C-C bond formation that involves position 3 of 1,2,4 triazines. The 3-(methylsulfonyl)-1,2,4 triazines (**5**) are reported as preferred precursors for the synthesis of 3-(alkoxy)- and 3-(alkylthio)-1,2,4-triazines **6** and **7**.[3,10] We were specifically interested in exploring synthetic routes that would enable us to access 3-(alkoxy)- and 3-(alkylthio)-1,2,4-triazines (**6a** and **7a**) without substituents at positions 5 and 6. Our interest here was related to their use as precursors in the synthesis of corresponding 3,3'-disubstituted-5,5'-bis(1,2,4-triazines) **8**, **9** and **10**, for the purposes of antimalarial SAR exploration. Our

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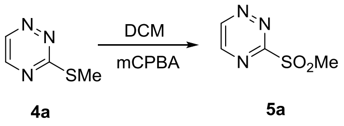
Supporting information for this article is given *via* a link at the end of the document preliminary SAR studies suggested that compounds such as **8**, **9** and **10** lost activity against *P. falciparum* when a 6-substituent was present.[10]

We noticed that although the reactivity of compounds that have the core structure represented as **5** has been explored with mercaptans, alcohols and amines, the reports describing their reactions use a variety of conditions that differ significantly with regards to the reaction conditions and the strength of the base used. For example, while some reports describe the use of milder bases such as lutidine or triethyl amine for the reaction of **5** with mercaptans[8,15] others use much harsher conditions preferring NaH as a base for the reaction.[16] Similarly, the reaction of alcohols with **5** has been carried with a stronger base such as BuLi in some reports[17,18] however NaH appears to be the most common base used for these reactions.[1] Likewise, some reports suggest **5** to be very reactive towards amines and use high temperature without any catalyst,[7] while others have preferred using phosphazides to synthesise 1,2,4-triazin-3-amines.[1,19] Furthermore, reported experimental protocols to obtain **5a** itself vary considerably.[1-4,7,20]

This paper describes our optimization of the synthesis of **5a** and study its application in the synthesis of 3-substituted 1,2,4-triazines using a variety of *S*-, *N*- and *O*-nucleophiles. Our studies were aimed at developing general and reliable procedures that are high yielding, preferably use mild reagents and conditions and offer convenient workup and separation procedure.

Results and Discussion

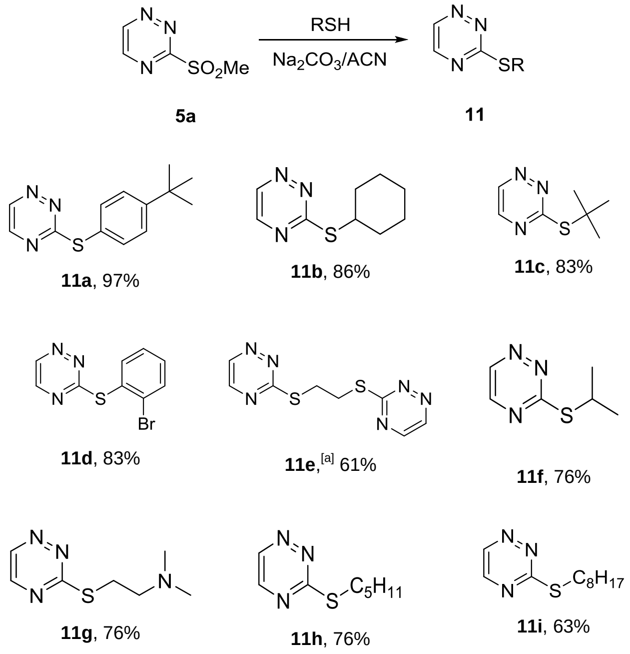
A number of literature reports describe that the synthesis of 3-(methylsulfonyl)-1,2,4 triazines, **5**, requires oxidation of the corresponding methylthio compounds **4** with *m*CPBA (Scheme 2).[1-4,7,20] In general, for reasons that are not apparent, the yields of 3-(methylsulfonyl)-1,2,4 triazines **5** obtained by this oxidation method are significantly higher for triazines which have substituents at the 5 or 6 positions. While a number of reports describe the synthesis of 3-(methylsulfonyl)-1,2,4 triazine **5a** (Scheme 2) using *m*CPBA, the synthetic procedures, workups and isolated yields (18 to 90%) vary considerably.[1-4,7,20] Some of these reports describe the use of anhydrous reaction conditions, workups and chromatography, whereas others do not.[1,7,20] We sought to clarify the literature by investigating this reaction and developing optimized approaches for the synthesis and separation procedure (Scheme 2) to allow the isolation of multigram quantities of **5a**. The triazine **4a** was synthesised following the procedure outlined in the experimental section.

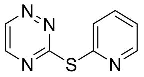


Scheme 2. Synthesis of 3-(methylsulfonyl)-1,2,4-triazine **5a** using *m*CPBA as an oxidant.

After substantial experimentation, we concluded that the best method for oxidising the thioether **4a** was indeed to use water-free conditions and solvent during the reaction and workup, in an optimized and reliable procedure as now described. Commercially obtained wet *m*CPBA was dissolved in DCM and dried over anhydrous $MgSO_4$. After filtration, this solution was gradually added to **4a** at -10 ^oC. After the reaction was completed, we noted that it was easy to remove by-product *m*CBA by filtration because of its poor solubility in DCM. Our repeated attempts to isolate **5a** by using column chromatography as suggested in the procedure documented in literature did not meet with any fruition.[1,7,20] We observed that when the DCM solution of the crude oxidised product was treated with Bu_4NI, a brown colour was released in the solution, suggesting the presence of I_3^- presumably from the reaction of unreacted *m*CPBA or other oxidiser(s) in the solution with I^- ions. We believe that Bu_4NI is necessary as it offers a non-aqueous alternative to remove the oxidisers, enabling efficient recovery of **5a**. We observed that an improved method was direct treatment of the crude reaction mixture with Bu_4NI, followed by concentration and loading on silica gel for chromatography. This had a profound, positive effect on the chromatographic recovery of **5a** and apart from improving the yields over the reported procedure, this modification also made the synthetic procedure reliable with reproducible yields. For separation, commercial silica gel and solvents were used as received. We were also able to obtain X-ray quality crystals of **5a** that were used to ascertain its structure (ORPET plot can be found in the Supporting Information file, pages131-133).[21]

Table 1. Synthesis of 3-(alkylthio)-1,2,4-triazines **11**.



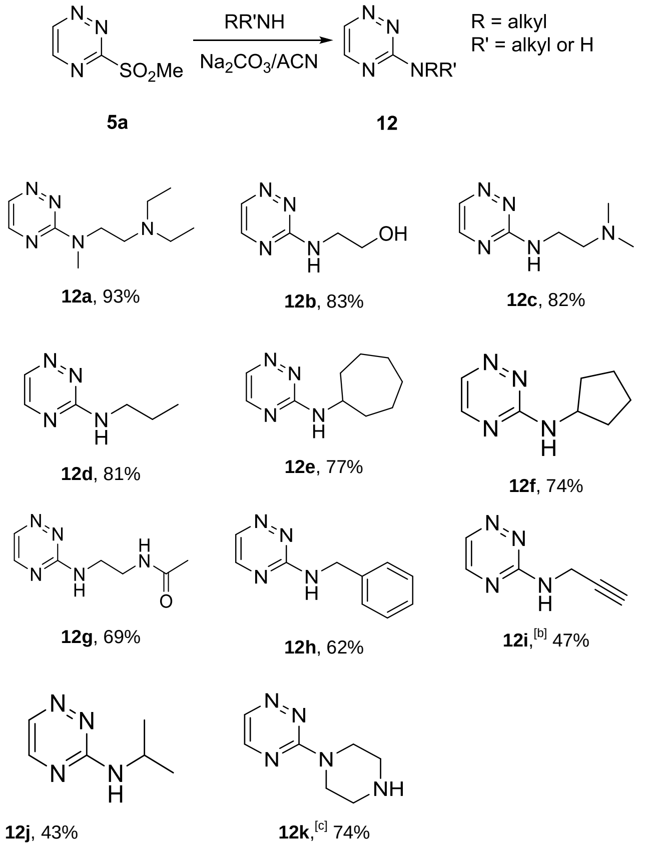


11j, 50%

[a] The ratio of the thiol : **5a** : Na_2CO_3 was 1 : 2 : 2

We then investigated the utility of **5a** in the synthesis of 3-substituted 1,2,4 triazines. While we were specifically interested in investigating the use of **5a** in the synthesis of 3-(alkylthio)-1,2,4-triazines **11** and 3-(alkoxy)-1,2,4-triazines **13** derived from it, we decided to broaden our study to include the reactivity of *S*, *O* and *N* nucleophiles towards **5a**.

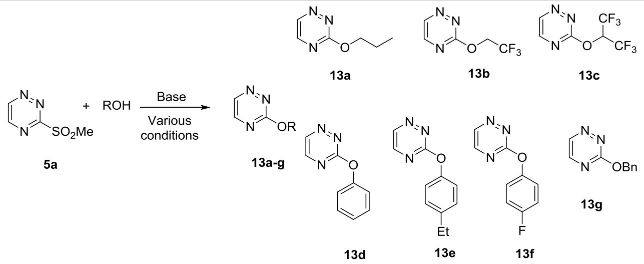
Table 2. Synthesis of *N*,*N*-dialkyl-1,2,4-triazin-3-amine **12**.



[b] Hydrochloride salt of the amine used during the reaction. [c] 300 mol% piperazine without Na_2CO_3.

When **5a** was reacted with a slight excess of an alkylthiols or thiophenols in acetonitrile in the presence of Na_2CO_3, (which serves as a base to quench methane sulfinic acid, the by-product formed during the reaction), we obtained high yields of the corresponding 3-(alkylthio)-1,2,4-triazines **11** (Table 1). High yields of the substitution product was also obtained when sterically hindered tertiary thiol was used (**11c**, Table 1). We found that the reaction conditions used for thiols can be easily extended to the primary and secondary amines as nucleophile (Table 2). The yields of 1,2,4-triazin-3-amines, **12** obtained from these reactions were good in most cases; however, for some amines the reactions gave relatively low yields of the product (**12i**-**j**, Table 2). In both these cases (**12i** and **12j**), by-product formation was clearly apparent by TLC, which helped to account for poor yields of the desired product. However, our attempts to identify the by-products did not meet fruition. Na_2CO_3 was used in the reactions of **5a** with amines to ascertain that the 1,2,4-triazin-3-amines **12** were isolated as free base after the chromatographic separation. The reaction indicated negligible conversions by TLC and LC MS when aniline was used as the participating amine in the presence of Na_2CO_3. To compare this method with that reported in the literature, a reaction of sulfone **5a** with 3 equivalents of piperazine in acetonitrile at room temperature was attempted. This reaction produced 74% yield of the product **12k**, which is slightly better than the published method that uses the less activated thioether **4a** and 3 equivalents of piperazine in butanol under harsh conditions that involve heating the mixture at 120 °C for 24 h.[7]

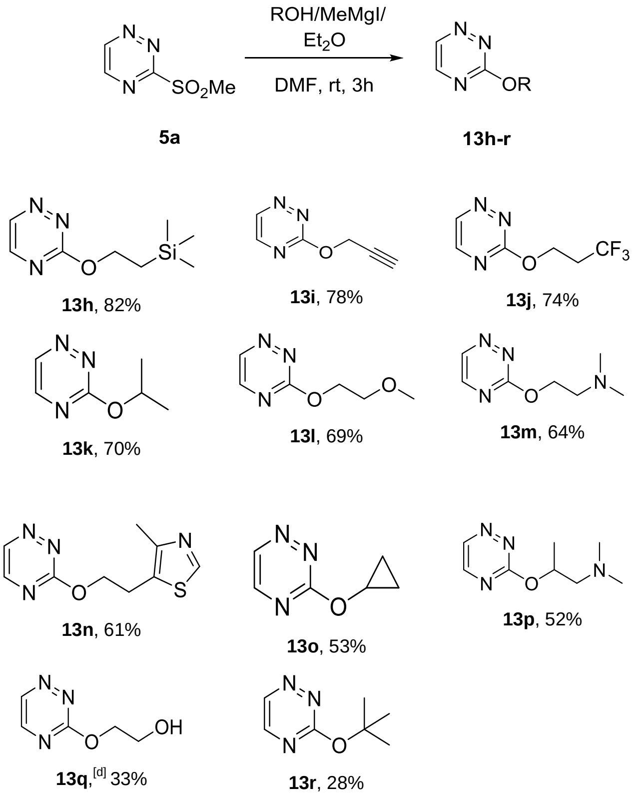
Table 3. Reaction of alcohols and phenols.



Entry	Conditions	ROH/ArOH	Product	Yield
1	Na_2CO_3, ACN, rt, 16 h	PrOH	**13a**	NR
2	Cs_2CO_3, ACN, rt, 16 h	PrOH	**13a**	29%
3	Cs_2CO_3, ACN, rt, 16 h	CF_3CH_2OH	**13b**	62%
4	Cs_2CO_3, ACN, rt, 16 h	$(CF_3)_2CHOH$	**13c**	55%
5	Cs_2CO_3, ACN, rt, 16 h	PhOH	**13d**	62%
6	Cs_2CO_3, ACN, rt, 16 h	4-EtC_6H_4OH	**13e**	81%
7	Cs_2CO_3, ACN, rt, 16 h	4-FC_6H_4OH	**13f**	78%
8	NaH, THF, -40 °C, then rt, 16 h	PrOH	**13a**	37%
9	NaH, THF, -40 °C, then rt, 16 h	BnOH	**13g**	55%
10	NaH, DMF, -40 °C, then rt, 16 h	PrOH	**13a**	20%
11	NaH, DMF, -40 °C, then rt, 16 h	BnOH	**13g**	42%
12	MeMgI, DMF, -40 °C, then rt, 16 h	PrOH	**13a**	72%
13	MeMgI, DMF, -40 °C, then rt, 16 h	BnOH	**13g**	80%

We were particularly interested in exploring alcohols as nucleophiles in these substitution reactions. The use of NaH to completely ionize alcohols for nucleophilic substitution on **5a** has been documented in the literature.[3] However, we were interested in investigating the reactivity of sulfone **5a** towards alcohol under more benign and convenient conditions where a relatively weaker base such as Cs_2CO_3 was used in this reaction. As shown in Table 3, we found that Cs_2CO_3 mediated the reaction of **5a** with alcohols. While the yield of 29% was modest when *n*-propanol was used to synthesize 3-(*n*-propoxy)-1,2,4-triazine **13a** (entry 2, Table 3), the yields were considerably improved when more acidic alcohols (entries 3 and 4, Table 3) or phenols (entries 5-7, Table 3) were used as nucleophilies.[22,23] It is worth pointing out that our observation that Cs_2CO_3 can be used as a milder and efficient base for the reaction of phenols with **5a**, presents a more desirable alternative to the literature procedure that prefers stronger, moisture sensitive base such as NaH.[16,24] In contrast, when weaker base such as Na_2CO_3 was used for the reaction of **5a** with *n*-propanol, we did not observe any formation of **13a** (entry 1, Table 3). In order to investigate the effect of switching to NaH as a base, we used *n*-propanol and benzyl alcohol to synthesize **13a** and **13g** respectively, and these were isolated in respective modest yields of 37% and 55% (entries 8 and 9, Table 3), suggesting some improvement in the yields of the recovered product.

Table 4**.** Synthesis of 3-(alkoxy)-1,2,4-triazines **13** using 3-(methylsulfonyl)-1,2,4-triazine **5a**, alcohols and MeMgI



5a

13h-r

13h, 82%

13i, 78%

13j, 74%

13k, 70%

13l, 69%

13m, 64%

13n, 61%

13o, 53%

13p, 52%

13q,[d] 33%

13r, 28%

[d] significant disubstituted product observed.

In order to obtain more acceptable yields for reactions with less acidic alcohols, we broadened our use of bases. Specifically, we used MeMgI to titrate *n*-propanol, to obtain its Mg-alkoxide salt that was dissolved in dry DMF and treated with 3-(methylsulfonyl)-1,2,4-triazine, **5a** under cold conditions. It is worth mentioning that magnesium salts have poorer solubility then the corresponding sodium counterparts and the more polar solvent, DMF was preferred to obtain their solution. Gratifyingly, we recovered 72% yield of the corresponding substitution product **13a**. An equally good yield (80%) was recovered for benzyl alcohol **13g**, for a reaction tried under the same conditions. To eliminate the solvent as a variable, the reaction of *n*-propanol and benzyl alcohol with **5a** and NaH in DMF was also attempted. We recovered 20% and 42% yields of the products **13a** and **13g** respectively from these reactions, indicating that good yields of the product were recovered when magnesium alkoxides were used in these reactions were not because of the change of solvent from THF to DMF.

A variety of alcohols were trialed to assess the scope of magnesium alkoxides as a nucleophiles in these substitution reaction (Table 4). Good yields were obtained in most of the reactions except for hindered secondary and tertiary alcohols (**13o**, **13p** and **13r**).

Conclusions

In conclusion, the substitution of methylsulfonyl group in 3-(methylsulfonyl)-1,2,4-triazine was investigated with *S*-, *N*- and *O*-nucleophiles. Facile methods that allowed for the substitution of the $-SO_2Me$ group by aliphatic and aromatic thiols, aliphatic amines, phenols and alcohols were developed and assessed for their scope and generalisability. In each method, we observed good tolerance to structural variation and generally good isolated yields of the products. Considering the applicability of 3-substituted 1,2,4-triazines, we believe that these methods will allow for easy access to the synthesis of a variety of 3-(alkoxy)-, 3-(aryloxy)-, 3-(alkylthio)-1,2,4-triazines and 1,2,4-triazin-3-alkylamines. We are currently utilizing these facile procedures to elaborate a variety of 3,3'-disubstituted 5,5'-bis(1,2,4-triazines) and study the impact of structural variation with respect to activity against *P. falciparum*.

Experimental Section

General Information: Commercially available reagents were used without further purification. Column chromatography was performed using silica gel 60 (40–60 µm). The solvents for chromatography were used without purification. The reactions were monitored by TLC on Silica Gel 60F-254 plates with detection by UV light and/or $KMnO_4$ stain (1.50 g $KMnO_4$, 10.0 g K_2CO_3, and 1.25 mL 10% NaOH in 200mL water). Melting points were determined using Mettler Toledo MP50 melting point system. The Attenuated Total Reflection-Fourier Transform Infrared Spectroscopy (ATR-FTIR) measurements were performed using a Shimazu IRTracer-100 Fourier transform spectrometer by averaging 128 scans with a resolution of 4 cm^{-1}. For the small molecules, ^{1}H and ^{13}C NMR spectra were recorded at 400.13 and 100.62 MHz respectively, on a Bruker Avance III Nanobay spectrometer with a BACS 60 sample changer. Proton resonances are annotated as: chemical shift (*δ*), multiplicity (s, singlet; d, doublet; m, multiplet), coupling constant (*J*, Hz), and the number of protons. High resolution MS was performed with an Agilent 6224 TOF LC/MS coupled to an Agilent 1290 Infinity LC.

Synthesis of *S*-methythiosemicarbazide iodohydrate: Iodo methane (17.04 g, 7.47 mL, 0.12 mol) was added to the mixture of thiosemicarbazide (10.01 g, 0.11 mol) and EtOH (200 mL). The resultant mixture was stirred and heated to reflux for 18 h. During this quaterization reaction, thiosemicarbazide slowly disappeared into the solution, after which a white solid (presumably the quaternary salt) starts to precipitate from the solution within a few hours. The reaction mixture was allowed to cool to room temperature. The solvent was evaporated under reduced pressure leaving a white residual solid. Diethyl ether (200 mL) was added to the residual solid and the mixture was stirred a few minutes at room temperature. The suspended quaternary salt was filtered, washed with ether (100 mL) and dried under reduced pressure to yield practically pure quaternary salt (25.24 g, 98% yield). Mp: 137–139 ^{o}C ; IR (neat) *v* 961, 1161, 1300, 1381, 1447, 1605, 1640, 3136, 3194, 3291, 3333 cm^{-1}; ^{1}H NMR (400 MHz, DMSO) *δ* 10.48 (s, 1H), 8.98 (s, 2H), 5.19 (s, 2H), 2.56 (s, 3H); ^{13}C NMR (101 MHz, DMSO) *δ* 167.9, 13.1; HRMS (EI) calculated for $C_2H_7N_3S$ [M + H]$^+$ 106.0433, found 106.0433.

Synthesis of 3-(methylthio)-1,2,4-triazine 4a: Water (150 mL) and glyoxal (40 w% aq. solution, 12.48 mL, 4.99 g, 86 mmol) were added to *S*-methythiosemicarbazide iodohydrate (10.00 g, 43 mmol) to obtain their aqueous solution. This solution was cooled to 0 ^{o}C over ice. $NaHCO_3$ (7.22 g, 86 mmol) was added in small portions to this solution, while it was being stirred, so that the evolution of CO_2 is kept under control. The stirring was continued at 0 ^{o}C for 6 h, by which time the gas evolution subside completely. The reaction mixture was maintained at 0 ^{o}C for 12 h. DCM (3 × 100 mL) was used for extraction of the product from the aqueous reaction mixture. Combined DCM layers were dried over anhydrous $MgSO_4$ and evaporated under reduced pressure to yield practically pure product **4a**, that was used in the next step for synthesis of **5a** without purification. Low melting solid (5.08 g, 93% yield): IR (neat) *v* 868, 961, 991, 1034, 1084, 1123, 1153, 1200, 1223, 1312, 1331, 1370, 1420, 1516, 1535, 2928, 3021, 3086 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 8.92 (d, *J* = 2.4 Hz, 1H), 8.36 (d, *J* = 2.4 Hz, 1H), 2.65 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) *δ* 174.7, 148.2, 145.4, 13.9; HRMS (EI) calculated for $C_4H_5N_3S$ [M + H]$^+$: m/z 128.0277, found: m/z 128.0278.

Synthesis of 3-(methylsulfonyl)-1,2,4-triazine 5a: DCM (200 mL) was added into moist technical grade *m*CPBA (24.77 g, 75 w%, 108 mmol). The mixture was stirred to obtain a turbid solution of *m*CPBA in DCM. Anhydrous $MgSO_4$ (20 g) was added to this solution, while stirring was continued for 10 min to ensure that the water suspended in DCM was removed. This solution was filtered under suction to remove $MgSO_4$ from the solution of *m*CPBA. DCM (3×20 mL) which was used for washing $MgSO_4$. These washings and filtrate were combined together and used for the oxidation of 3-(methylthio)-1,2,4-triazine **4a** as follows.

The solution of *m*CPBA in DCM (obtained as above) was added slowly (dropwise) over an hour to the cold solution of **4a** (4.95 g, 39 mmol) in DCM (20 mL) while being stirred and maintained at -10 ^{o}C. After the addition was completed, the solution was allowed to slowly warm to room temperature and the stirring continued for an additional 3 h. The solution was filtered under suction and the insoluble residue was washed with DCM (50 mL). The filtrate and washings were combined together, treated with Bu_4NI (0.500 g, 1.36 mmol) and stirred at room temperature for 5 min. The resultant solution was evaporated under reduced pressure to obtain a concentrated solution, to which silica gel (20 g) was added. The mixture was further dried under reduced pressure to impregnate the crude product on silica gel. Analytically pure **5a** was separated by column chromatography using 75% ethyl acetate in hexanes as a white solid (2.20 g, 36% yield). Mp 84–85 ^{o}C; ^{1}H NMR (400 MHz, DMSO) *δ* 9.74 (d, *J* = 2.5 Hz, 1H), 9.18 (d, *J* = 2.5 Hz, 1H), 3.55 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) *δ* 167.4, 151.8, 150.8, 39.8; IR (neat) *v* 841, 1038, 1099, 1146, 1254, 1327, 1427, 1458, 1524, 1562, 1647, 2114, 2782, 2824, 2947, 2978, 3260 cm^{-1}; HRMS (EI) calculated for $C_4H_5N_3O_2S$ [M + H]$^+$ 160.0175, found 160.0175.

General procedure for the synthesis of 3-(alkylthio)-1,2,4-triazines 11 from 3-(methylsulfonyl)-1,2,4-triazine 5a: Na_2CO_3 (0.367g, 3.46 mmol) was added to the solution of **5a** (0.500 g, 3.14 mmol) in acetonitrile (5 mL). Mercaptan (3.46 mmol) was added to this solution and the reaction mixture was stirred at room temperature for 16 h at which point the starting material appeared to be consumed as indicated by TLC. The reaction mixture was filtered under suction, and the filtrate was evaporated under reduced pressure to obtain a crude product. Analytically pure 3-(alkylthio)-1,2,4-triazine **11** was separated from the crude product using column chromatography.

General procedure for the synthesis of *N*,*N*-dialkyl- or *N*-alkyl-1,2,4-triazin-3-amines 12 from 3-(methylsulfonyl)-1,2,4-triazine 5a: Na_2CO_3 (0.367g, 3.46 mmol) was added to the solution of **5a** (0.500 g, 3.14 mmol) in acetonitrile (5 mL). Amine (3.46 mmol) was added to this solution and the reaction mixture was stirred at room temperature for 16 h at which point the starting material appeared to be consumed as indicated by TLC. The reaction mixture was filtered under suction, and the filtrate was evaporated under reduced pressure to obtain a crude product. Analytically pure **12** was separated from the crude product using column chromatography.

For the synthesis of 3-(alkoxy)-1,2,4-triazines **13b**-**f** the procedure used for the synthesis of 3-(alkylthio)-1,2,4-triazines **11a**-**j** was used, except mercaptans were replaced by phenol/alcohol and Cs_2CO_3 was used as a base for these reactions.

General procedure for the synthesis of 3-(alkoxy)-1,2,4-triazine 13h-r from 3-(methylsulfonyl)-1,2,4-triazine 5a: Alcohol (4.1 mmol) was added dropwise to the cold ethereal solution of methylmagnesium iodide (2.81 mL, 1.34 mol/L, 3.77 mmol) while being stirred and maintained at -10 ^{o}C under a nitrogen atmosphere. Provisions were made to compensate for the build-up of excess pressure, due to gas evolution, while maintaining an inert atmosphere. The solution was slowly warmed to room temperature and stirred for 30 min. Ether was evaporated under reduced pressure to obtain nearly ether free magnesium alkoxide that was dissolved in DMF (3 mL). This solution was cooled to -40 ^{o}C and **5a** (0.500 g, 3.14 mmol) was added in small portions, while the reaction was being stirred. The reaction mixture was then allowed to slowly warm while stirring was continued at room temperature for 3 h. The completion of the reaction was verified by TLC. DMF was evaporated under reduced pressure. The resulting viscous material was treated with water (5 mL) and extracted with EtOAc (3 × 15 mL). The organic extracts were combined, dried over anhydrous $MgSO_4$ and evaporated under reduced pressure to yield the crude product. Analytically pure 3-(alkoxy)-1,2,4-triazine **13** was separated from the crude product using column chromatography.

3-((4-(*tert*-Butyl)phenyl)thio)-1,2,4-triazine (11a): 20% Ethyl acetate in hexanes. Yellow solid (0.749 g, 97% yield): mp 67–69 ^{o}C; IR (neat) *v* 826, 860, 968, 1011, 1034, 1088, 1115, 1153, 1196, 1265, 1331, 1373, 1462, 1485, 1516, 1535, 1593, 1659, 2866, 2901, 2959, 3017, 3075 cm^{-1}; ^{1}H

NMR (400 MHz, DMSO) δ 9.18 (d, J = 2.4 Hz, 1H), 8.63 (d, J = 2.4 Hz, 1H), 7.63–7.55 (m, 2H), 7.55–7.47 (m, 2H), 1.31 (s, 9H); ^{13}C NMR (101 MHz, DMSO) δ 173.4, 152.6, 150.1, 147.0, 135.0, 126.6, 123.8, 34.6, 31.0; HRMS (EI) calculated for $C_{13}H_{15}N_3S$ $[M + H]^+$ 246.1059, found 246.1070.

3-(Cyclohexylthio)-1,2,4-triazine (11b): 20% Ethyl acetate in hexanes. Yellow solid (0.525 g, 86% yield): mp 50–52 ^{o}C; IR (neat) v 818, 872, 891, 918, 964, 999, 1030, 1150, 1192, 1258, 1319, 1362, 1439, 1508, 1535, 2851, 2928 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.88 (d, J = 2.4 Hz, 1H), 8.34 (d, J = 2.3 Hz, 1H), 3.95–3.89 (m, 1H), 2.14–2.11 (m, 2H), 1.79–1.75 (m, 2H), 1.65–1.41 (m, 5H), 1.36–1.30 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.7, 148.3, 145.2, 53.6, 43.6, 32.8, 26.0, 25.7; HRMS (EI) calculated for $C_9H_{13}N_3S$ $[M + H]^+$ 196.0903, found 196.0903.

3-(*tert*-Butylthio)-1,2,4-triazine (11c): 50% Ethyl acetate in hexanes. Yellow liquid (0.440 g, 83% yield): IR (neat) v 856, 930, 968, 991, 1030, 1080, 1111, 1150, 1204, 1312, 1362, 1454, 1474, 1508, 1535, 2862, 2920, 2963, 3078 cm^{-1}; ^{1}H NMR (400 MHz, DMSO) δ 9.14–9.13 (d, J = 2.4 Hz, 1H), 8.65–8.64 (d, J = 2.4 Hz, 1H), 1.61 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.3, 147.9, 145.2, 48.5, 29.9; HRMS (EI) calculated for $C_7H_{11}N_3S$ $[M + H]^+$ 170.0746, found 170.0744.

3-((2-Bromophenyl)thio)-1,2,4-triazine (11d): 15% Ethyl acetate in hexanes. Yellow liquid (0.695 g, 83% yield): IR (neat) v 853, 949, 988, 1018, 1115, 1150, 1204, 1227, 1250, 1319, 1381, 1427, 1447, 1508 cm^{-1}; ^{1}H NMR (400 MHz, DMSO) δ 9.22–9.21 (d, J = 2.4 Hz, 1H), 8.67–8.66 (d, J = 2.4 Hz, 1H), 7.87–7.85 (m, 2H), 7.54–7.45 (m, 2H); ^{13}C NMR (101 MHz, DMSO) δ 172.0, 150.2, 147.2, 137.9, 133.7, 132.2, 130.0, 128.8, 128.5; HRMS (EI) calculated for $C_9H_6BrN_3S$ $[M + H]^+$ 267.9539, found 267.9547.

1,2-Bis((1,2,4-triazin-3-yl)thio)ethane (11e): 50% Ethyl acetate in hexanes. Yellow solid (0.218 g, 61% yield): mp 118–120 ^{o}C; IR (neat) v 856, 876, 991, 1030, 1115, 1150, 1192, 1231, 1323, 1385, 1512, 1535, 3001, 3075 cm^{-1}; ^{1}H NMR (400 MHz, DMSO) δ 9.19 (d, J = 2.4 Hz, 2H), 8.67 (d, J = 2.4 Hz, 2H), 3.63 (s, 4H); ^{13}C NMR (101 MHz, DMSO) δ 172.2, 149.8, 146.8, 29.4; HRMS (EI) calculated for $C_8H_8N_6S_2$ $[M + H]^+$ 253.0325, found 253.0332.

3-(Isopropylthio)-1,2,4-triazine (11f): 50% Ethyl acetate in hexanes. Yellow solid (0.372 g, 76% yield): mp 49–51 ^{o}C; IR (neat) v 853, 930, 972, 1030, 1057, 1119, 1153, 1204, 1246, 1319, 1370, 1458, 1512, 1562, 2866, 2928, 2967, 3078, 3256 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.46 (d, J = 1.8 Hz, 1H), 8.06 (d, J = 1.8 Hz, 1H), 4.17 (s, 1H), 1.25–1.24 (d, J = 6.5 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.6, 149.3, 140.4, 42.9, 22.6; HRMS (EI) calculated for $C_6H_9N_3S$ $[M + H]^+$ 156.0590, found 156.0590.

2-((1,2,4-Triazin-3-yl)thio)-*N*,*N*-dimethylethan-1-amine (11g): 10% Methanol in dichloromethane. Yellow liquid (0.441 g, 76% yield): IR v 853, 1034, 1119, 1153, 1200, 1323, 1373, 1458, 1512, 1535, 1670, 2770, 2820, 2859, 2943, 2970 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.91 (d, J = 2.4 Hz, 1H), 8.35 (d, J = 2.4 Hz, 1H), 3.39–3.36 (t, J = 7.2 Hz, 2H), 2.70–2.66 (t, J = 7.2 Hz, 2H), 2.30 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.5, 148.3, 145. 5, 58.0, 45.4, 28.8; HRMS (EI) calculated for $C_7H_{12}N_4S$ $[M + H]^+$ 185.0855, found 185.0852.

3-(Pentylthio)-1,2,4-triazine (11h): 20% Ethyl acetate in hexanes. Yellow liquid (0.435 g, 76% yield): IR (neat) v 856, 972, 991, 1030, 1115, 1153, 1200, 1319, 1373, 1462, 1512, 1535, 2855, 2928, 2955 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.88 (d, J = 2.3 Hz, 1H), 8.33 (d, J = 2.3 Hz, 1H), 3.21–3.18 (t, J = 7.2 Hz, 2H), 1.76– 1.69 (m, 2H), 1.44–1.29 (m, 4H), 0.88–0.84 (t, J = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.6, 148.2, 145.3, 31.0, 30.7, 28.6, 22.2, 14.0; HRMS (EI) calculated for $C_8H_{13}N_3S$ $[M + H]^+$ 184.0903, found 184.0903.

3-(Octylthio)-1,2,4-triazine (11i): 10% Ethyl acetate in hexanes. Yellow liquid (0.445 g, 63% yield): IR (neat) v 853, 972, 991, 1030, 1115, 1153, 1200, 1323, 1373, 1408, 1458, 1512, 1535, 2851, 2920, 2951 cm^{-1}; ^{1}H NMR (400 MHz, DMSO) δ 9.14 (d, J = 2.4 Hz, 1H), 8.64 (d, J = 2.4 Hz, 1H), 3.21–3.17 (t, J = 7.4 Hz, 2H), 1.72–1.64 (m, 2H), 1.43–1.36 (m, 2H) 1.27–1.23 (m, 8H), 0.85–0.82 (t, J = 6.6 Hz, 3H); ^{13}C NMR (101 MHz, DMSO) δ 172.9, 149.6, 146.4, 31.2, 29.8, 28.6, 28.5, 28.2, 22.1, 13.9; HRMS (EI) calculated for $C_{11}H_{19}N_3S$ $[M + H]^+$ 226.1372, found 226.1381.

3-(Pyridin-2-ylthio)-1,2,4-triazine (11j): Ethyl acetate. Yellow solid (0.301 g, 50% yield): mp 61–63 ^{o}C; IR (neat) v 876, 969, 988, 1034, 1084, 1107, 1150, 1200, 1231, 1323, 1377, 1420, 1454, 1516, 1570, 3005, 3071 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.97–8.96 (d, J = 2.3 Hz, 1H), 8.65–8.64 (m, 1H), 8.37–8.38 (d, J = 2.3 Hz, 1H), 7.78–7.73(m, 2H), 7.34–7.31 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.1, 151. 6, 150.9, 148.7, 146.3, 137.7, 130.2, 123.9; HRMS (EI) calculated for $C_8H_6N_4S$ $[M + H]^+$ 191.0386, found 191.0386.

N^1,N^1-Diethyl-N^2-methyl-N^2-(1,2,4-triazin-3-yl)ethane-1,2-diamine (12a): 4% Methanol in dichloromethane. Yellow liquid (0.609 g, 93% yield): IR (neat) v 837, 964, 1011, 1042, 1099, 1200, 1238, 1289, 1339, 1408, 1435, 1528, 1555, 2801, 2870, 2932, 2967 cm^{-1}; ^{1}H NMR (400 MHz, DMSO) δ 8.55 (d, J = 2.2 Hz, 1H), 8.27 (d, J = 2.3 Hz, 1H), 3.69 (bs, 2H), 3.16 (bs, 3H), 2.58–2.54 (t, J = 6.7 Hz, 2H), 2.49–2.43 (q, J = 7.1 Hz, 4H), 0.91–0.88 (t, J = 7.1 Hz, 6H); ^{13}C NMR (101 MHz, DMSO) δ 160.8, 149.1, 139.5, 54.9, 49.4, 46. 8, 35.3, 12.0; HRMS (EI) calculated for $C_{10}H_{19}N_5$ $[M + H]^+$ 210.1713, found 210.1712.

2-((1,2,4-Triazin-3-yl)amino)ethan-1-ol (12b): 10% Methanol in dichloromethane. Yellow solid (0.365 g, 83% yield): mp 65–67 ^{o}C; IR (neat) v 833, 853, 868, 918, 926, 1011, 1042, 1099, 1126, 1157, 1231, 1319, 1339, 1427, 1512, 1524, 1582, 1601, 2870, 2928, 2947, 3113, 3248, 3372 cm^{-1}; ^{1}H NMR (400 MHz, DMSO) δ 8.54 (d, J = 2.0 Hz, 1H), 8.23 (d, J = 2.1 Hz, 1H), 7.63 (bs, 1H), 4.75–4.72 (t, J = 5.4 Hz, 1H), 3.55–3.53 (m, 2H), 3.39 (bs, 2H); ^{13}C NMR (101 MHz, DMSO) δ 162.0, 149.8, 140.5, 59.3, 43.2; HRMS (EI) calculated for $C_5H_8N_4O$ $[M + H]^+$ 141.0771, found 141.0770.

N^1,N^1-Dimethyl-N^2-(1,2,4-triazin-3-yl)ethane-1,2-diamine (12c): 10% Methanol in dichloromethane. Yellow liquid (0.396 g, 75% yield): IR (neat) v 841, 1038, 1099, 1146, 1254, 1327, 1427, 1458, 1524, 1562, 1647, 2114, 2781, 2824, 2947, 2978, 3260 cm^{-1}; ^{1}H NMR (400 MHz, DMSO) δ 8.55–8.54 (d, J = 2.2 Hz, 1H), 8.24–8.23 (d, J = 2.2 Hz, 1H), 7.51 (bs, 1H), 3.42 (bs, 2H), 2.46–2.43 (t, J = 6.7 Hz, 2H), 2.19 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.1, 149.4, 140.9, 57.8, 45.3, 38.7; HRMS (EI) calculated for $C_7H_{13}N_5$ $[M + H]^+$ 168.1244, found 168.1241.

***N*-Propyl-1,2,4-triazin-3-amine (12d)**: 5% Methanol in dichloromethane. Yellow liquid (0.351 g, 81% yield): IR (neat) v 837, 991, 1038, 1107, 1126, 1169, 1250, 1323, 1362, 1427, 1458, 1524, 1562, 2874, 2963, 3094, 3260 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.46 (d, J = 2.0 Hz, 1H), 8.06 (d, J = 1.8 Hz, 1H), 3.40 (s, 2H), 1.68–1.58 (m, 2H), 0.95–0.91 (t, J = 7.4 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.2, 149.3, 140.4, 43.0, 22.6, 11.4; HRMS (EI) calculated for $C_6H_{10}N_4$ $[M + H]^+$ 139.0978, found 139.0976.

***N*-Cycloheptyl-1,2,4-triazin-3-amine (12e)**: 50% Ethyl acetate in hexanes. Yellow solid (0.465 g, 77% yield): mp 102–104 ^{o}C; IR (neat) v 829, 1034, 1061, 1088, 1153, 1196, 1277, 1327, 1350, 1377, 1454, 1520, 1589, 2855, 2924, 3024, 3086, 3140, 3225 cm^{-1}; ^{1}H NMR (400 MHz, DMSO) δ 8.50 (s, 1H), 8.21 (s, 1H), 7.64 (s, 1H), 3.94 (bs, 1H), 1.88 (bs, 2H), 1.63–1.40 (m, 10H); ^{13}C NMR (101 MHz, DMSO) δ 160.8, 149.7, 140.1, 51.2, 33.9, 27.9, 23.7; HRMS (EI) calculated for $C_{10}H_{16}N_4$ $[M + H]^+$ 193.1448, found 193.1444.

***N*-Cyclopentyl-1,2,4-triazin-3-amine (12f)**: 50% Ethyl acetate in hexanes. Yellow solid (0.381 g, 74% yield): mp 89–91 °C; IR (neat) *v* 849, 876, 941, 1022, 1042, 1099, 1150, 1192, 1319, 1346, 1366, 1454, 1520, 1578, 2866, 2943, 3013, 3082, 3136, 3225 cm^{-1}; ^{1}H NMR (400 MHz, DMSO) δ 8.53 (d, *J* = 2.3 Hz, 1H), 8.22 (d, *J* = 2.3 Hz, 1H), 7.73 (bs, 1H), 4.18 (bs, 1H), 1.92–1.88 (m, 2H), 1.71–1.65 (m, 2H), 1.58–1.47 (m, 4H); ^{13}C NMR (101 MHz, DMSO) δ 161.4, 149.5, 140.2, 52.0, 32.0, 23.4; HRMS (EI) calculated for $C_8H_{12}N_4$ $[M + H]^+$ 165.1135, found 165.1136.

***N*-(2-((1,2,4-Triazin-3-yl)amino)ethyl)acetamide (12g)**: 5% Methanol in dichloromethane. Yellow solid **(**0.395 g, 69% yield): mp 128–130 °C; IR (neat) *v* 856, 1034, 1111, 1169, 1231, 1281, 1327, 1370, 1431, 1451, 1524, 1559, 1601, 1647, 2882, 2936, 3021, 3098, 3233, 3302 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.50 (d, *J* = 2.0 Hz, 1H), 8.18 (d, *J* = 1.8 Hz, 1H), 7.09 (bs, 1H), 3.63 (bs, 2H), 3.56–3.52 (m, 2H), 1.95 (s, 3H); ^{13}C NMR (101 MHz, DMSO) δ 169.5, 161.6, 149.8, 140.6, 40.3, 37.9, 22.7; HRMS (EI) calculated for $C_7H_{11}N_5O$ $[M + H]^+$ 182.1036, found 182.1040.

***N*-Benzyl-1,2,4-triazin-3-amine (12h)**: 75% Ethyl acetate in hexanes. Yellow solid (0.361 g, 62% yield): mp 87–89 °C; IR (neat) *v* 841, 1038, 1084, 1103, 1161, 1196, 1269, 1304, 1331, 1346, 1362, 1416, 1451, 1493, 1528, 1597, 2859, 2924, 3024, 3090, 3148, 3237 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.57 (s, 1H), 8.09 (s, 1H), 7.38–7.27 (m, 5H), 5.92 (bs, 1H), 4.72–4.71 (d, *J* = 5.0 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.1, 149.4, 141.1, 138.3, 128.7, 127.8, 127.6, 45.3; HRMS (EI) calculated for $C_{10}H_{10}N_4$ $[M + H]^+$ 187.0978, found 187.0979.

***N*-(Prop-2-yn-1-yl)-1,2,4-triazin-3-amine (12i)**: 80% Ethyl acetate in hexanes. Yellow liquid (0.198 g, 47% yield): IR (neat) *v* 829, 841, 914, 972, 1034, 1092, 1115, 1161, 1262, 1343, 1412, 1454, 1528, 1597, 2114, 2917, 3229 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.63–8.62 (d, *J* = 2.2 Hz, 1H), 8.20–8.19 (d, *J* = 2.1 Hz, 1H), 6.16 (bs, 1H), 4.31 (s, 2H), 2.26–2.25 (t, *J* = 2.4 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.4, 149.5, 141.7, 79.9, 71.6, 31.2; HRMS (EI) calculated for $C_6H_6N_4$ $[M + H]^+$ 135.0665, found 135.0664.

***N*-Isopropyl-1,2,4-triazin-3-amine (12j)**: 5% Methanol in dichloromethane. Yellow solid **(**0.186 g, 43% yield): mp 53–55 °C; IR (neat) *v* 845, 976, 1018, 1057, 1092, 1126, 1188, 1292, 1323, 1362, 1454, 1520, 1582, 2870, 2905, 2963, 3017, 3090, 3140, 3217 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.49 (d, *J* = 2.3 Hz, 1H), 8.09 (d, *J* = 2.2 Hz, 1H), 5.74 (bs,1H), 4.20–4.18 (m, 1H), 1.28–1.26 (d, *J* = 6.5 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.6, 149.4, 140.5, 43.0, 22.7; HRMS (EI) calculated for $C_6H_{10}N_4$ $[M + H]^+$ 139.0978, found 139.0978.

3-(Piperazin-1-yl)-1,2,4-triazine (12k): 15% Methanol in ethyl acetate. Yellow liquid (0.383 g, 74% yield): IR (neat) *v* 837, 918, 1003, 1034, 1057, 1119, 1169, 1262, 1335, 1443, 1512, 1555, 1655, 2851, 2913, 3291, 3387 cm^{-1}; ^{1}H NMR (400 MHz, DMSO) δ 8.59–8.58 (d, *J* = 2.2 Hz, 1H), 8.30–8.29 (d, *J* = 2.2 Hz, 1H), 3.73–3.70 (m, 4H), 3.07 (bs, 2H), 2.78–2.75 (m, 4H); ^{13}C NMR (101 MHz, DMSO) δ 160.8, 149.4, 140.2, 45.1, 44.0; HRMS (EI) calculated for $C_7H_{11}N_5$$[M + H]^+$ 166.1087, found 166.1087.

3-*n*-Propoxy-1,2,4-triazine (13a)*:* 50% Ethyl acetate in hexanes. Yellow liquid (0.313 g, 72% yield): IR *v* 860, 964, 988, 1022, 1045, 1065, 1100, 1153, 1300, 1335, 1354, 1427, 1470, 1520, 1551, 2878, 2936, 2967 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.88–8.87 (d, *J* = 1.9 Hz, 1H), 8.37–8.36 (d, *J* = 2.0 Hz, 1H), 4.42–4.38 (t, *J* = 6.7 Hz, 2H), 1.83–1.77 (m, 2H), 0.98–0.95 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.4, 150.8, 144.6, 70.2, 21.9, 10.2; HRMS (EI) calculated for $C_6H_9N_3O$ $[M + H]^+$ 140.0818, found 140.0813.

3-(2,2,2-Trifluoroethoxy)-1,2,4-triazine (13b): 50% Ethyl acetate in hexanes. Yellow liquid (0.348 g, 62% yield): IR (neat) *v* 841, 880, 957, 999, 1045, 1072, 1103, 1153, 1262, 1331, 1381, 1404, 1435, 1539 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.07 (d, *J* = 2.2 Hz, 1H), 8.51 (d, *J* = 2.2 Hz, 1H), 4.98–4.92 (qd, *J* = 8.1, 0.9 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.4, 151.4, 146.2, 122.9, 64.2; ^{19}F NMR (376 MHz, $CDCl_3$) δ -73.7 (s); HRMS (EI) calculated for $C_5H_4F_3N_3O$ $[M + H]^+$ 180.0379, found 180.038.

3-((1,1,1,3,3,3-Hexafluoropropan-2-yl)oxy)-1,2,4-triazine (13c): 50% Ethyl acetate in hexanes. Yellow liquid (0.423 g, 55% yield): IR (neat) *v* 872, 891, 1007, 1045, 1099, 1200, 1273, 1319, 1377, 1412, 1539, 1555, 1736, 2963 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.18 (d, *J* = 2.3 Hz, 1H), 8.58 (d, *J* = 2.3 Hz, 1H), 6.56–6.48 (hept, *J* = 5.9 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.8, 151.6, 147.3, 117.8, 70.0; ^{19}F NMR (376 MHz, $CDCl_3$) δ -73.4 (s); HRMS (EI) calculated for $C_6H_3F_6N_3O$ $[M + H]^+$ 248.0253, found 248.0249.

3-Phenoxy-1,2,4-triazine (13d): 50% Ethyl acetate in hexanes. Yellow solid (0.336 g, 62% yield): mp 52–54 °C; IR (neat) *v* 814, 872, 910, 1045, 1072, 1157, 1200, 1304, 1358, 1404, 1485, 1520, 1551, 1589 cm^{-1}; ^{1}H NMR (400 MHz, DMSO) δ 9.26 (d, *J* = 2.3 Hz, 1H), 8.73 (d, *J* = 2.3 Hz, 1H), 7.50–7.46 (m, 2H), 7.33–7.29 (m, 3H); ^{13}C NMR (101 MHz, DMSO) δ 165.8, 152.3, 152.3, 146.7, 129.9, 125.8, 121.4; HRMS (EI) calculated for $C_9H_7N_3O$ $[M + H]^+$ 174.0662, found 174.0654.

3-(4-Ethylphenoxy)-1,2,4-triazine (13e): 50% Ethyl acetate in hexanes. Yellow liquid (0.511 g, 81% yield): IR (neat) *v* 810, 845, 891, 1015, 1045, 1107, 1165, 1196, 1312, 1358, 1400, 1458, 1505, 1551, 2870, 2928, 2963 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.05 (d, *J* = 2.3 Hz, 1H), 8.45 (d, *J* = 2.3 Hz, 1H), 7.29–7.26 (m, 2H), 7.16–7.13 (m, 2H), 2.73–2.66 (q, *J* = 7.6 Hz, 2H), 1.28–1.25 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.6, 150.9, 150.3, 145.7, 142.2, 129.3, 121.2, 28.4, 15.6; HRMS (EI) calculated for $C_{11}H_{11}N_3O$ $[M + H]^+$ 202.0975, found 202.0969.

3-(4-Fluorophenoxy)-1,2,4-triazine (13f): 50% Ethyl acetate in hexanes. Yellow solid (0.467 g, 78% yield): mp 59–61 °C; IR (neat) *v* 823, 841, 868, 899, 1007, 1053, 1092, 1180, 1323, 1370, 1404, 1501, 1535, 1555, 3078 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.08–9.07 (d, *J* = 2.3 Hz, 1H), 8.47–8.46 (d, *J* = 2.3 Hz, 1H), 7.23–7.18 (m, 2H), 7.16–7.10 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 116.7, 123.0, 146.0, 148.2, 151.0, 160.5, 166.4; ^{19}F NMR (376 MHz, $CDCl_3$) δ -116.4 (s); HRMS (EI) calculated for $C_9H_6FN_3O$ $[M + H]^+$ 192.0568, found 192.0563.

3-(Benzyloxy)-1,2,4-triazine (13g): 50% Ethyl acetate in hexanes. Yellow solid (0.470 g, 80% yield): mp 67–69 °C; IR (neat) *v* 880, 988, 1026, 1103, 1165, 1231, 1323, 1359, 1381, 1416, 1454, 1493, 1543, 2886, 2955, 3024, 3086 cm^{-1}; ^{1}H NMR (400 MHz, DMSO) δ 9.17 (d, *J* = 2.3 Hz, 1H), 8.71 (d, *J* = 2.3 Hz, 1H), 7.52–7.50 (m, 2H), 7.43–7.34 (m, 3H), 5.54 (s, 2H); ^{13}C NMR (101 MHz, DMSO) δ 165.0, 152.2, 145.8, 135.9, 128.5, 128.3, 128.3, 69.3; HRMS (EI) calculated for $C_{10}H_9N_3O$ $[M + H]^+$ 188.0818, found 188.0816.

3-(2-(Trimethylsilyl)ethoxy)-1,2,4-triazine (13h): 50% Ethyl acetate in hexanes. Yellow liquid (0.507 g, 82% yield): IR (neat) *v* 833, 937, 961, 1015, 1038, 1099, 1153, 1177, 1246, 1319, 1343, 1378, 1431, 1470, 1520, 1551, 1697, 2897, 2951 cm^{-1}; ^{1}H NMR (400 MHz, DMSO) δ 9.11 (d, *J* = 2.3 Hz, 1H), 8.65 (d, *J* = 2.3 Hz, 1H), 4.57–4.53 (m, 2H), 1.19–1.15 (m, 2H), 0.06 (s, 9H); ^{13}C NMR (101 MHz, DMSO) δ 165.0, 151.9, 145.4, 66.0, 16.8, 2.0, -1.5; HRMS (EI) calculated for $C_8H_{15}N_3OSi$ [M + H]$^+$ 198.1057, found: m/z 198.1062.

3-(Prop-2-yn-1-yloxy)-1,2,4-triazine (13i): 50% Ethyl acetate in hexanes. Yellow solid (0.332 g, 78% yield): mp 51–53 ^{o}C; IR (neat) *v* 876, 964, 988, 1018, 1053, 1103, 1157, 1316, 1346, 1366, 1424, 1474, 1539, 1555, 2129, 2943, 2963, 3051, 3094, 3240 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.03–9.02 (d, *J* = 2.3 Hz, 1H), 8.49–8.48 (d, *J* = 2.3 Hz, 1H), 5.20–5.19 (d, *J* = 2.4 Hz, 2H), 2.54–2.53 (t, *J* = 2.4 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.8, 151.1, 145.6, 77.4, 75.9, 56.2; HRMS (EI) calculated for $C_6H_5N_3O$ [M + H]$^+$ 136.0505, found 136.0502.

3-(3,3,3-Trifluoropropoxy)-1,2,4-triazine (13j): 50% Ethyl acetate in hexanes. Yellow liquid (0.451g, 74% yield): IR (neat) *v* 826, 864, 910, 991, 1030, 1045, 1072, 1130, 1150, 1250, 1296, 1323, 1362, 1389, 1431, 1470, 1524, 1535, 1555, 2920, 2974 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.01 (d, *J* = 2.2 Hz, 1H), 8.46 (d, *J* = 2.2 Hz, 1H), 4.79–4.76 (t, *J* = 6.5 Hz, 2H), 2.79–2.68 (qt, *J* = 10.4, 6.5 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.0, 151.3, 145.5, 124.8, 61.6, 33.6; ^{19}F NMR (376 MHz, $CDCl_3$) δ -64.8; HRMS (EI) calculated for $C_6H_6F_3N_3O$ [M + H]$^+$ 194.0536, found 194.0531

3-Isopropoxy-1,2,4-triazine (13k): 50% Ethyl acetate in hexanes. Yellow liquid (0.307g, 70% yield): IR (neat) *v* 864, 949, 1015, 1049, 1103, 1153, 1180, 1316, 1335, 1373, 1420, 1466, 1520, 1551, 2874, 2940, 2982 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.90–8.89 (d, *J* = 2.2 Hz, 1H), 8.40–8.39 (d, *J* = 2.2 Hz, 1H), 5.49–5.42 (hept, *J* = 6.2 Hz, 1H), 1.44–1.43 (d, *J* = 6.2 Hz, 7H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.2, 151.0, 144.5, 72.1, 21.8; HRMS (EI) calculated for $C_6H_9N_3O$ [M + H]$^+$ 140.0818, found 140.0818.

3-(2-Methoxyethoxy)-1,2,4-triazine (13l): Ethyl acetate. Yellow solid (0.337 g, 69% yield): mp 68–70 ^{o}C; IR (neat) *v* 853, 880, 930, 1007, 1042, 1057, 1099, 1126, 1157, 1192, 1238, 1281, 1327, 1346, 1373, 1400, 1431, 1454, 1539, 1555, 2816, 2839, 2905, 2936, 2997, 3051, 3094 cm^{-1}; ^{1}H NMR (400 MHz, DMSO) δ 9.15 (d, *J* = 2.3 Hz, 1H), 8.68 (d, *J* = 2.3 Hz, 1H), 4.59–4.56 (m, 2H), 3.74–3.71 (m, 2H), 3.31 (s, 3H); ^{13}C NMR (101 MHz, DMSO) δ 165.1, 152.1, 145.7, 69.7, 67.0, 58.1; HRMS (EI) calculated for $C_6H_9N_3O_2$ [M + H]$^+$ 156.0768, found 156.0760.

2-((1,2,4-Triazin-3-yl)oxy)-*N*,*N*-dimethylethan-1-amine (13m): 5% Methanol in dichloromethane. Yellow liquid (0.337 g, 64% yield): IR (neat) *v* 833, 864, 918, 953, 991, 1026, 1099, 1153, 1192, 1319, 1339, 1373, 1424, 1458, 1520, 1551, 1670, 2770, 2820, 2947, 3414 cm^{-1}; ^{1}H NMR (400 MHz, DMSO) δ 9.13–9.12 (d, *J* = 2.3 Hz, 1H), 8.67–8.66 (d, *J* = 2.3 Hz, 1H), 4.53–4.51 (t, *J* = 5.8 Hz, 2H), 2.68–2.65 (t, *J* = 5.8 Hz, 2H), 2.20 (s, 6H). ^{13}C NMR (101 MHz, DMSO) δ 165.1, 152.0, 145.5, 65.7, 57.2, 45.4; HRMS (EI) calculated for $C_7H_{12}N_4O$ [M + H]$^+$ 169.1084, found 169.1086.

5-(2-((1,2,4-Triazin-3-yl)oxy)ethyl)-4-methylthiazole (13n): Ethyl acetate. Yellow solid (0.428 g, 61% yield): mp 103-105 ^{o}C; IR (neat) *v* 837, 876, 918, 988, 1011, 1042, 1107, 1161, 1188, 1297, 1316, 1350, 1408, 1435, 1458, 1532, 1555, 3040 cm^{-1}; ^{1}H NMR (400 MHz, DMSO) δ 9.15–9.14 (d, *J* = 2.3 Hz, 1H), 8.84 (s, 1H), 8.68–8.67 (d, *J* = 2.3 Hz, 1H), 4.64–4.61 (t, *J* = 6.4 Hz, 2H), 3.33–3.30 (t, *J* = 6.4 Hz, 2H), 2.34 (s, 3H); ^{13}C NMR (101 MHz, DMSO) δ 164.9, 152.2, 150.9, 149.6, 145.8, 127.0, 67.8, 25.2, 14.7; HRMS (EI) calculated for $C_9H_{10}N_4OS$ [M + H]$^+$ 223.0648, found 223.0653.

3-Cyclopropoxy-1,2,4-triazine (13o): 50% Ethyl acetate in hexanes. Yellow liquid (0.227 g, 53% yield): IR (neat) *v* 826, 860, 964, 1026, 1045, 1096, 1146, 1165, 1211, 1335, 1373, 1412, 1451, 1532, 1551, 1593, 3017, 3098 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.98 (d, *J* = 2.2 Hz, 1H), 8.42 (d, *J* = 2.2 Hz, 1H), 4.51–4.46 (m, 1H), 0.89–0.86 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.6, 150.8, 145.2, 52.8, 6.0; HRMS (EI) calculated for $C_6H_7N_3O$ [M + H]$^+$ 138.0662, found 138.0659.

2-((1,2,4-Triazin-3-yl)oxy)-*N*,*N*-dimethylpropan-1-amine (13p): 5% Methanol in dichloromethane. Yellow liquid (0.296 g, 52% yield): IR (neat) *v* 837, 856, 945, 1038, 1099, 1134, 1153, 1207, 1265, 1319, 1331, 1373, 1420, 1520, 1551, 1670, 2770, 2820, 2940, 2978 cm^{-1}; ^{1}H NMR (400 MHz, DMSO) δ 9.10 (d, *J* = 2.3 Hz, 1H), 8.65 (d, *J* = 2.3 Hz, 1H), 5.45–5.40 (m, 1H), 2.64–2.59 (dd, *J* = 12.9, 7.3 Hz, 1H), 2.43–2.38 (dd, *J* = 12.9, 4.9 Hz, 1H), 2.18 (s, 6H), 1.34–1.32 (d, *J* = 6.2 Hz, 3H); ^{13}C NMR (101 MHz, DMSO) δ 164.9, 151.9, 145.3, 72.0, 63.6, 45.8, 18.0; HRMS (EI) calculated for $C_8H_{14}N_4O$ [M + H]$^+$ 183.1240, found: m/z 183.1237.

2-((1,2,4-Triazin-3-yl)oxy)ethan-1-ol (13q): 2% Methanol in dichloromethane. Yellow liquid (0.144 g, 33% yield): IR (neat) *v* 823, 868, 922, 1030, 1157, 1319, 1339, 1377, 1424, 1462, 1524, 1555, 1690, 2947, 3333 cm^{-1}; ^{1}H NMR (400 MHz, DMSO) δ 9.14–9.13 (d, *J* = 2.3 Hz, 1H), 8.68–8.67 (d, *J* = 2.3 Hz, 1H), 4.93 (bs, 1H), 4.48–4.46 (m, 2H), 3.79–3.76 (m, 2H); ^{13}C NMR (101 MHz, DMSO) δ 165.2, 152.0, 145.5, 69.7, 59.0; HRMS (EI) calculated for $C_5H_7N_3O_2$ [M + H]$^+$ 142.0611, found 142.0607.

3-(*tert*-Butoxy)-1,2,4-triazine (13r): 50% Ethyl acetate in hexanes. Yellow liquid (0.133 g, 28% yield): IR (neat) *v* 826, 860, 910, 934, 1018, 1045, 1096, 1165, 1250, 1362, 1408, 1478, 1520, 1551, 2870, 2932, 2978 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.85–8.84 (d, *J* = 2.2 Hz, 1H), 8.35–8.34 (d, *J* = 2.2 Hz, 1H), 1.64 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.4, 150.5, 144.1, 83.6, 28.1; HRMS (EI) calculated for $C_7H_{11}N_3O$ [M + H]$^+$ 154.0975, found 154.0979.

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Keywords: 3-(methylsulfonyl)-1,2,4 triazine • SNAr reactions • alkali metal carbonates • magnesium alkoxides • 3-substituted 1,2,4-triazines

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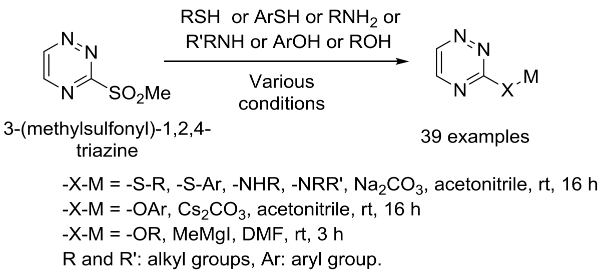

Studies focussed on our efforts to clarify the synthesis of 3-(methylsulfonyl)-1,2,4-triazine and also to optimise the reaction conditions that use it in the SNAr reactions with a variety of *S*-, *O*- and *N*-nucleophiles.
Antimalarial precursors

SNAr Reactions*

Da-Hua Shi,[a] Jitendra R. Harjani,[a] Robert W. Gable[b] and Jonathan B. Baell[a]**

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Synthesis of 3-(alkylamino)-, 3-(alkoxy)-, 3-(aryloxy)-, 3-(alkylthio)- and 3-(arylthio)-1,2,4-triazines *via* a unified route using 3-(methylsulfonyl)-1,2,4-triazine