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Straightforward Three-Component Synthesis of N′,N′′-Disubstituted *N*-Alkyl-1,3,5-Triazinanes

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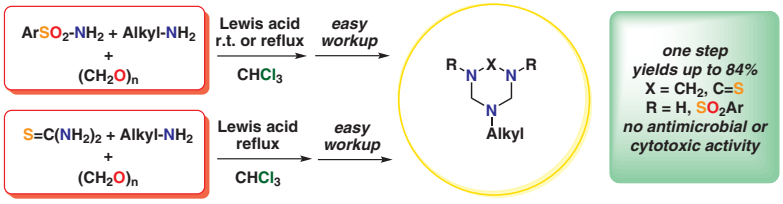

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Abstract Efficient approaches towards the synthesis of various N-substituted 1,3,5-triazinanes based on a transformation of *N*-alkyl-1,5,3-dioxazepanes or on a domino reaction involving condensation of various amines, amides, and paraformaldehyde are described for the first time. $Mg(ClO_4)_2$ was shown to be one of the most potent additives for the condensation. The proposed approaches permit the synthesis of a broad spectrum of substituted *sym*-triazinanes in good yields with relatively easy workup. In the case of the multicomponent reaction, the approach allows the preparation of the target substances from simple and easily accessible reagents. The representatives of the resulting compounds were found to possess no antimicrobial or cytotoxic activity in *in vitro* bioassays.

Key words triazinanes, domino reaction, sulfonamides, amides, amines, thiourea

Symmetrical N-substituted 1,3,5-triazinanes have been shown to be useful intermediates in organic synthesis, serving as synthons for the corresponding aldimines, which can be generated in situ for further chemical transformations.[1–4] 1,3,5-Triazinanes have found practical use as elements of synergistic antimicrobial compositions.[5] However, little information is available on straightforward approaches to the synthesis of unsymmetrically N-substituted 1,3,5-triazinanes. The reported methods have various disadvantages; some give mixtures of products, others require water-soluble starting materials, and some involve relatively harsh conditions that are not tolerated by some functional groups.[6–8] For instance, three *N*-*tert*-butyl-*N*′,*N*″-sulfonyltriazinanes have been synthesized from *N*-*tert*-butylmethanimine and various sulfonamides in refluxing benzene in the presence of an equimolar quantity of acetic anhydride (Figure 1).[8] Moreover, possible applications of such triazinanes in both organic synthesis and as bioactive substances remain underexplored.

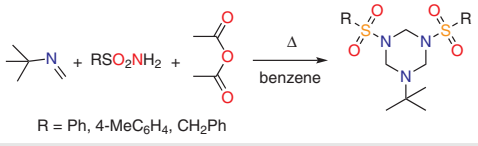

Figure 1 Synthesis of *N*-*tert*-butyl-*N*′,*N*′′-sulfonyltriazinanes

A key problem in the synthesis of polysubstituted molecules is the need for sufficiently complex reagents, which usually are not readily available. Therefore, the development of efficient methods for obtaining complex molecules from simple and widely available starting materials through multicomponent reactions remains a primary goal of modern synthetic organic chemistry. Here we report a straight-

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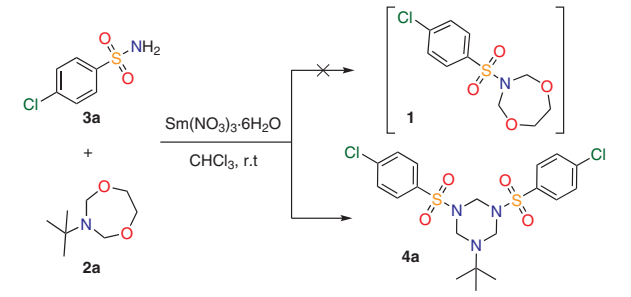
forward approach to the synthesis of various N-substituted triazinanes by a one-pot multicomponent reaction of paraformaldehyde, alkylamines, and sulfonamides or thiourea. There is good reason to believe that the high yields of the target products combined with the easy workup procedure of the method, the revealed lack of toxicity of the products, and the sufficiently broad scope of their possible applications will render *N*-alkyltriazinanes eye-catching products for a broad range of researchers.

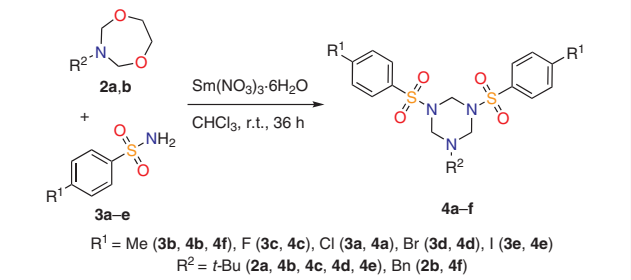
During our attempt to synthesize 3-[(4-chlorophenyl)sulfonyl]-1,5,3-dioxazepane (**1**) by the reaction of 3-*tert*-butyl-1,5,3-dioxazepane (**2a**) with 4-chlorobenzenesulfonamide (**3a**) under conditions previously described for the transamination of 3-*tert*-butyl-1,5,3-dioxazepane with (het)arylamines, we found that the reaction instead gave of 1-(*tert*-butyl)-3,5-bis[(4-chlorophenyl)sulfonyl]-1,3,5-triazinane (**4a**) exclusively (Scheme 1).[9]



Scheme 1 Unexpected formation of the 1,3,5-triazinane **4a**

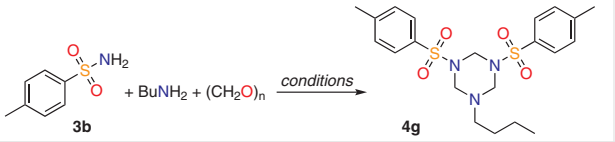
Presumably, the formation of the 1,3,5-triazine ring proceeds through double alkylation of two molecules of the sulfonamide with 3-*tert*-butyl-1,5,3-dioxazepane (**2a**) under catalysis by samarium trinitrate hexahydrate and a further interaction of the resulting intermediate with formaldehyde formed as a result of catalytic decomposition of 3-*tert*-butyl-1,5,3-dioxazepane (**2a**). To demonstrate the suitability of the method for the preparation of the 1,3,5-triazinanes, we expanded this approach to the synthesis of triazinane derivatives **4b–f** (Scheme 2).

We then decided to investigate the possibility of synthesizing the N-substituted-1,3,5-triazinanes under milder



Scheme 2 Two-component synthesis of triazinanes **4a–f** by the reaction of sulfonamides **3** with dioxazepanes **2**

conditions from simpler more-accessible reagents and various additives, including some rare-earth metal salts through a one-pot domino process. We established that corresponding triazinanes could be obtained by reaction of *tert*-butylamine, paraformaldehyde, and various sulfonamides in the presence of an acidic catalyst (samarium nitrate) in chloroform at r.t. Our subsequent efforts focused on the optimization of the reaction conditions. Condensation of 4-toluensulfonamide (**3b**) with butylamine and paraformaldehyde to give triazinane **4g** (Scheme 3) was chosen as a model reaction for the optimization of the synthesis conditions.



Scheme 3 Example chosen for the optimization of conditions for the three-component reaction

We established that practically any acid (Lewis or Brønsted type) promoted this reaction (Table 1). Moreover, the three-component condensation proceeded with a satisfactory yield even in the absence of a catalyst (Table 1, entries 4 and 5). The presence of water in crystalline hydrate catalysts did not have a noticeable effect on their activity (entries 13 and 15). Eventually, acetic acid (entry 20) and magnesium perchlorate (entries 21 and 22) were found to display the highest catalytic activity.

Interestingly, the addition of copper(II) chloride inhibited the formation of the desired product **4g** (Table1, entry 2). This might be explained by partial hydrolysis of copper(II) chloride under the reaction conditions with the formation of copper(II) hydroxide, which, in turn, decomposes the triazinane, thereby shifting the equilibrium of the reaction toward the starting materials. This fact might be used in future research on the activation of the corresponding *sym*-triazinane systems toward further chemical transformations.

It should be mentioned here that according to the stoichiometry of the reaction (Scheme 3), the ratio of its components should be primary amine/sulfonamide/formaldehyde = 1:2:3; however, it was established experimentally that the highest yield of the target triazine **4g** was achieved when the ratio of the reagents was 1.05:2.00:3.75, respectively. We also established that an increase in the reaction time to three hours moderately increased the yield of compound **4g** to 76%. Consequently, this reaction time was used in subsequent syntheses.

The assumed mechanism for the multicomponent reaction of sulfonamides, primary amines, and formaldehyde is presented in Scheme 4. The key steps of the transformation are (i) condensation of an amine with formaldehyde to give

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Table 1 Optimization of Conditions for the Synthesis of Triazinane **4g**

Entry	Additive[a]	Solvent	Temp	Time (h)	Yield[b] (%)
1	KOH	H_2O	r.t	36	–
2	$CuCl_2$	$CHCl_3$	reflux	2	11
3	KOH	EtOH	r.t	36	38
4	–	$CHCl_3$	reflux	2	41
5	–	$CHCl_3$	reflux	4	54
6	$NiClO_4·6H_2O$	$CHCl_3$	reflux	2	45
7	$LiClO_4$	$CHCl_3$	reflux	2	48
8	ZnO	$CHCl_3$	reflux	2	48
9	SmF_3	$CHCl_3$	r.t	36	55
10	$NdCl_3$	$CHCl_3$	reflux	2	57
11	$MnCl_2$	$CHCl_3$	reflux	2.5	57
12	$Sm(NO_3)_3·6H_2O$	$CHCl_3$	r.t	36	59
13	$NiCl_2$	$CHCl_3$	reflux	2	59
14	$SmCl_3·6H_2O$	$CHCl_3$	r.t	36	60
15	$NiCl_2·6H_2O$	$CHCl_3$	reflux	2	60
16	$Sm(NO_3)_3·6H_2O$	$CHCl_3$	reflux	2	63
17	$CoCl_2·6H_2O$	$CHCl_3$	reflux	2	65
18	$Pr(NO_3)_3·6H_2O$	$CHCl_3$	reflux	2	65
19	$Ni(OAc)_2$	$CHCl_3$	reflux	2	66
20	AcOH	$CHCl_3$	reflux	2	70
21	**$Mg(ClO_4)_2$**	**$CHCl_3$**	**reflux**	**2**	**71**
22	**$Mg(ClO_4)_2$**	**$CHCl_3$**	**reflux**	**3**	**76**

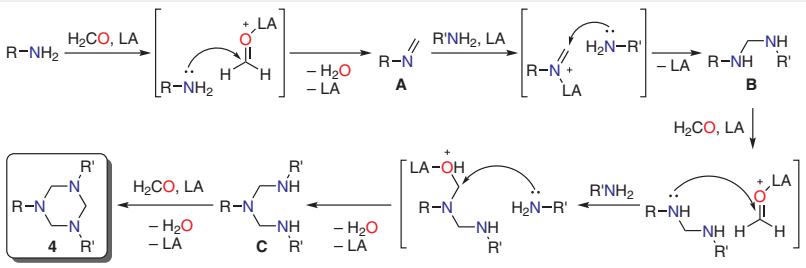
[a] 10 mol%.
[b] Isolated yield.

imine **A**; (ii) nucleophilic addition of a molecule of the sulfonamide to the C=N double bond to give diamine **B**. (iii) addition of a second molecule of formaldehyde to the diamine **B**, followed by Lewis acid catalyzed nucleophilic substitution of an OH group by a second molecule of the sulfonamide to give triamine **C**; and (iv) cyclization of the intermediate **C** by the action of a third molecule of formaldehyde.

The workup involves simple filtration of the reaction mixture through a thin layer of silica gel, partial evaporation of chloroform, and further precipitation of the product with diethyl ether when magnesium perchlorate or another salt is used as the catalyst. The workup in the case of acetic acid appears to be slightly more complicated, and involves an additional step for the neutralization of the acid.

Some of the products shown in Scheme 5 were synthesized by both the multicomponent reaction (Method a) and from dioxazepanes **2** (Method b; see Scheme 2). Although Method b for the synthesis of 1,3,5-triazinanes **4** from 3-alkyl-1,5,3-dioxazepanes **2** generally gave slightly higher yields, we believe that the multicomponent reaction approach is preferable because it does not require the synthesis of the corresponding 3-alkyl-1,5,3-dioxazepane **2**. The proposed conditions for the multicomponent reaction tolerate chiral amines as initial substrates; thus, chiral triazinanes **4j**, **4k**, **4n** and **4o** were obtained from the corresponding optically active phenethylamines. The conditions also permitted the preparation of derivatives containing alkenyl, alkynyl, or hydroxy groups (**4l**, **4p**, and **4w**, respectively) from on corresponding amines. The use of an argon atmosphere did not generally affect the yield of the product, although it reduced the slight coloration of the reaction mixtures and crude products. A study of this reaction of various substituted anilines is currently ongoing in our group.

As our preliminary experiments showed, the method for the preparation of triazinanes **4** from sulfonamides **3** could be extended to other amides, particularly thiourea (Scheme 6). Replacement of sulfonamide **3** with thiourea permitted easy access to 1,3,5-triazinane-2-thiones **5** in comparatively high yields (Scheme 6). Representative examples of these products have been shown to possess antioxidant activity.[10] We deliberately chose the previously known triazinane-2-thiones **5** to demonstrate the capabilities of the method and to permit comparison of the yields.[10–14] Compounds **5a–d** were previously synthesized by a two-step procedure using different conditions to those reported here. Generally, the lower yields of the previous syntheses (given in square brackets) can be explained either by the use of different solvent systems and catalysts, or by the absence of a catalyst in the case of compound **5d**. Compound **5e** was synthesized for the first time. It is also worth mentioning that thiourea is prone to react with acid anhydrides;[15,16] consequently, the corresponding derivatives are



Scheme 4 Possible mechanism for the multicomponent synthesis of substituted triazinanes by a domino reaction of formaldehyde, amines, and sulfonamides (R = alkyl; R' = SO_2Ar); LA = Lewis acid.

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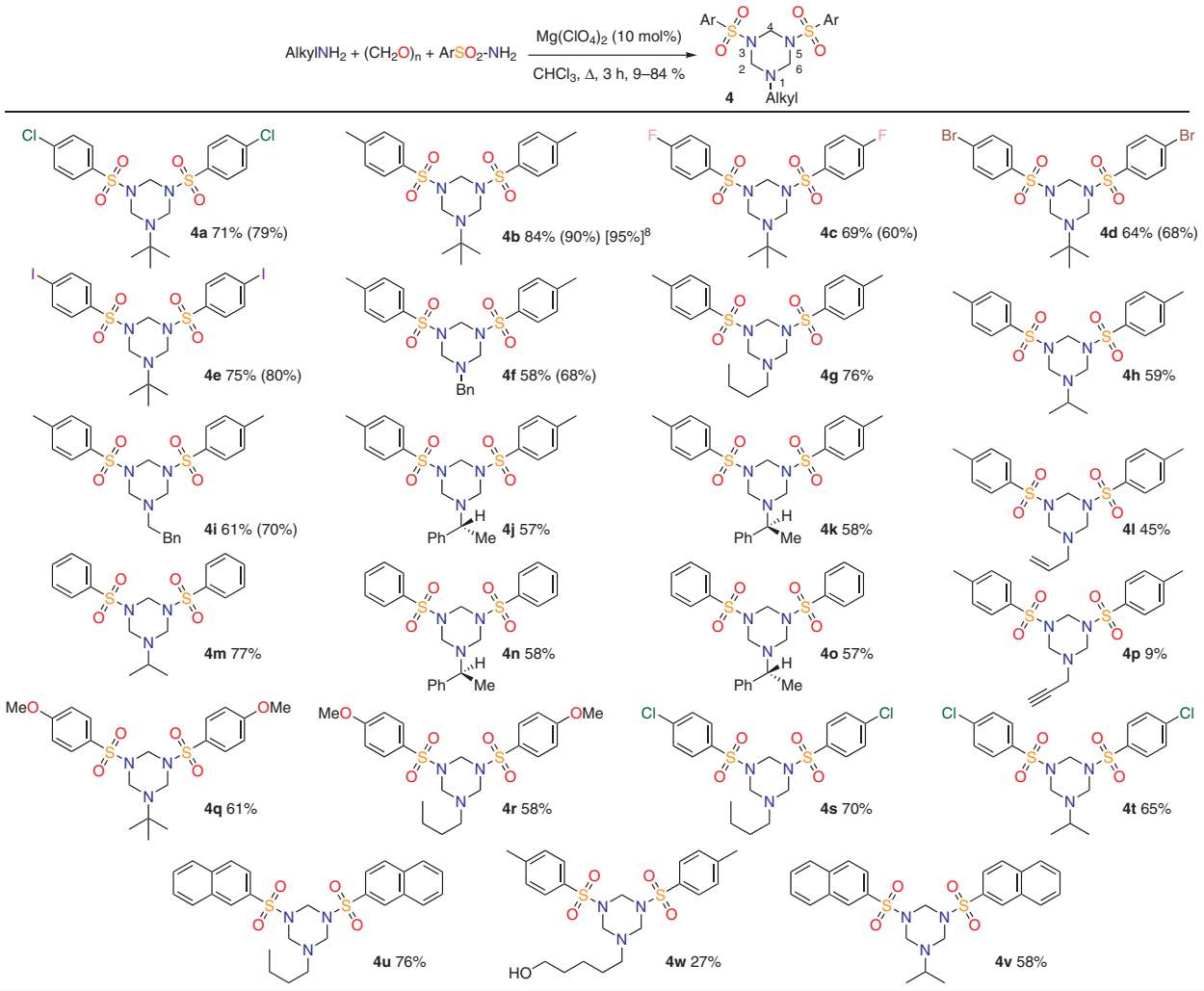

Scheme 5 Synthesized *N*,*N*′-disulfonamidotriazinanes **4**. Yields from dioxazepanes **2** (Method b) are shown in parentheses. Yields of previous preparations are shown in square brackets with references to the original work.

unlikely to be easily obtained if acetic anhydride is used as a reagent.[8] Our multicomponent approach therefore has greater synthetic versatility. We are currently studying the possibility of applying this approach in the synthesis of various *N*,*N*′,*N*″-trisubstituted 1,3,5-triazinane-2-thiones.

Formamide also reacted successfully under the conditions described above (Scheme 7). In this case, however, one amide and two amine fragments entered the resulting product **6**. The reasons for the difference in these results from the outcomes shown in Scheme 5 are unclear at present, and will be clarified in subsequent publications.

An X-ray crystallographic study confirmed that molecules **4i** and **4r** contain a 1,3,5-triazinane system with three substituents on the nitrogen atoms (Figure 2).[17] The general geometrical features of these systems are similar. The six-membered rings of both molecules have the usual slightly distorted chair conformation in which the *N*-alkyl substituent (CH_2Bn or Bu) occupies the axial position and the two *N*-sulfonamide fragments adopt the sterically favored pseudoequatorial orientation.

The N-1 nitrogen atoms bound with the alkyl substituents have to be sp^3-hybridized and have a pyramidal configuration, whereas the other two N-3 and N-5 nitrogen atoms belonging to the sulfonamide groups have to be sp^2-hybridized and, therefore, have a flat configuration in the triazinane ring. For these reasons, triazinanes **4i** and **4r** should both have a plane of symmetry passing through the N-1 nitrogen atom and the C-4 carbon atom. However, the X-ray crystal structure analysis revealed that in the solid state, the configurations of the N-3 and N-5 sulfonamide nitrogens are different; one of these atoms has an sp^3-hybridization and is pyramidal [the sum of the valence angles around N-3 is 344.1(2)° for **4i** and 352.9(8)° for **4r**], whereas the other is sp^2-hybridized and nearly flat [the sum of valence angles around N-5 is 359.9(6)° for **4i** and 357.9(4)° for **4r**].

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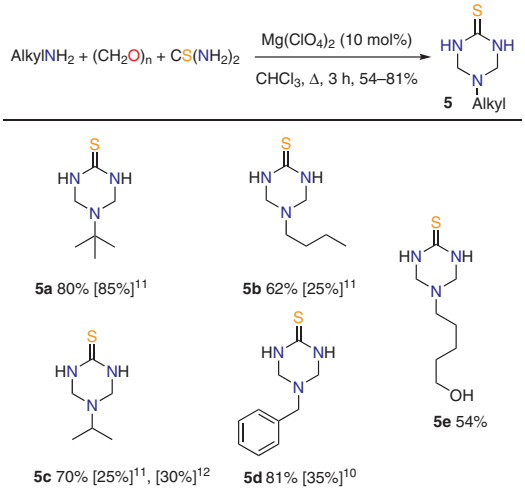

Scheme 6 Synthesis of 5-alkyl-1,3,5-triazinane-2-thiones **5**. The ratio of the amine, paraformaldehyde, and thiourea reactants was 1.05:2.00:1.00. Yields from previous syntheses are shown in square brackets.

These structural peculiarities lead to a violation of the symmetry of the molecules in the crystal, and might be studied in detail in further publications. Complete crystallographic data for the molecules **4i** and **4r** are given in the Supporting Information (SI; Tables 3S–9S).

Representative examples of the synthesized compounds were evaluated for their *in vitro* antimicrobial activity against Gram-positive and Gram-negative bacteria and their cytotoxicity against selected human cancer lines. They generally showed neither antimicrobial activity nor significant cytotoxic activity, apparently due to their stability towards hydrolysis under the biotesting conditions. Only compound **4f** exhibited a moderate cytotoxic activity against the HT 1080 cell line. Details of the biotesting are provided in the SI (Tables 1S and 2S).

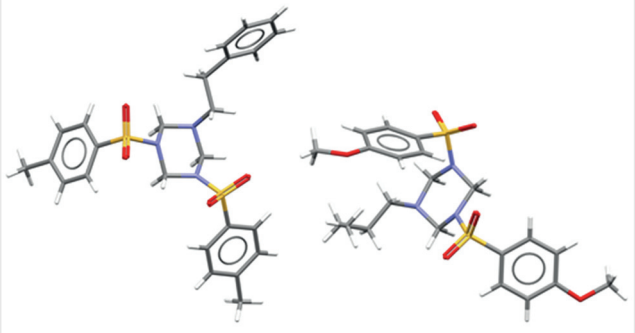

Figure 2 X-ray crystal structures of 1,3,5-trizinanes **4i** (left) and **4r** (right)

Scheme 7 An extension of the three-component reaction to formamide. The ratio of the amine, formamide, and formaldehyde was 2.05:1.00:3.10. The yield from a previous synthesis is shown in square brackets.

In conclusion, various N-substituted triazinanes were obtained by a multicomponent reaction of paraformaldehyde, alkylamines, and sulfonamides or thiourea in the presence of various additives, among which $Mg(ClO_4)_2$ was shown to be the most potent.[18] Formamide also reacted successfully under the conditions described. Representatives of the synthesized compound did not show any noticeable antimicrobial or cytostatic activity. However, they represent interesting targets for further screening for antifungal, herbicidal, or possibly antiviral activities. Triazinanes are known to decompose to give formaldehyde as well as reactive Schiff base intermediates; this limits their widespread application as disinfectants due to associated mutagenicity in some cases.[19] The fact that the tested representative examples of N-substituted 1,3,5-triazinanes did not show noticeable antimicrobial or cytotoxic activity indicates their stability towards decomposition in aqueous media under biotesting conditions, which makes them attractive targets for further careful evaluation of their bioactivities. This will include *in silico* studies, due to the practice of sorting out the 1,3,5-triazinane core as a potential source of formaldehyde or reactive Schiff bases in the initial stages of screening of molecular libraries.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0039-1690900.

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(17) CCDC 1984058 and 1984059 contain the supplementary crystallographic data for compounds **4a** and **4r**, respectively. The data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/getstructures.
(18) **1,3,5-Triazinanes 4–6; Typical Procedure Method a (Multicomponent Approach)**
Paraformaldehyde (90 mg, 3.00 mmol; 94.3 mg, 3.14 mmol in the case of thiourea derivatives) (based of formaldehyde) and $Mg(ClO_4)_2$ (36 mg, 0.157 mmol) were added to a solution the appropriate amide (1.57 mmol) in $CHCl_3$ (5 mL). The appropriate amine (0.8 mmol; 1.60 mmol in the case of thiourea) was then added, and the mixture stirred under reflux for 3 h in air or under argon. (A sealed vessel at 66 °C in oil bath was used in the case of *t*-$BuNH_2$ or *i*-$PrNH_2$. Refluxing for 4.5 h was required for derivative **6**). The mixture was then cooled to r.t. and filtered through a thin layer of silica gel. In the case of compounds **4u** and **4v**, the reaction was quenched with hot acetone (25 mL), due to the low solubility of corresponding compounds in $CHCl_3$, and filtered through a fritted glass filter with minimal porosity. The filtrate was concentrated to approximately 0.5–0.7 mL under reduced pressure, and Et_2O (5 mL) was added. The resulting solution was cooled to –20 °C and the precipitate was collected by filtration, washed with a small amount of cold EtOH and dried, initially in air and then in a vacuum desiccator over P_2O_5. Workup for products **4l**, **4p**, and **4w** after concentration of the filtrate included extraction of the crude viscous product with boiling hexane–Et_2O (1:2), followed by slow evaporation of the resulting extract, initially at r.t. and then at 0 °C, resulting in slow precipitation of the products as white solids. The resulting solids were collected by filtration and dried in air and then in a vacuum desiccator over P_2O_5. Compound **5e** precipitated from $CHCl_3$. The crude product was collected by filtration, washed with acetone, and dissolved in EtOH. The solution was filtered through a fritted glass filter with minimal porosity, evaporated, and treated with $CHCl_3$ (5 mL). The precipitate was collected by filtration and dried in air and then in a vacuum desiccator over P_2O_5. In the case of 3,5-di-*tert*-butyl-1,3,5-triazinane-1-carbaldehyde (**6**), 2.05 equivalents of the amine were used under the optimal conditions, as the use of equimolar combinations of formamide and *tert*-butylamine gave **6** in a lower yield. Pure compound **6** was obtained immediately after evaporation of the filtrate under reduced pressure. The use of an argon atmosphere did not generally affect the yields of the products, but did reduce the slight coloration of the reaction mixtures and the crude products.
Typical Procedure Method b (from 1,5,3-Dioxazepanes)
The appropriate 3-alkyl-1,5,3-dioxazepane (1.57 mmol) was added to the amide (1.57 mmol) and $Sm(NO_3)_3{\cdot}6H_2O$ (71 mg, 0.16 mmol) in $CHCl_3$ (5 mL), and the mixture was stirred for 36 h at r.t. $CHCl_3$ (35 mL) was added and the mixture was washed twice with H_2O in a separatory funnel. The organic layer was separated, dried (Na_2SO_4), and filtered through a thin layer of silica gel. Further workup of the filtrate was similar to that described in Method A.
1-(*tert*-Butyl)-3,5-bis[(4-chlorophenyl)sulfonyl]-1,3,5-triazinane (4a)
White powder; yield: 274 mg (71%; Method a); 304 mg (79%; Method b); mp 185–186 °C. IR (KBr): 3089, 3067 (CH_{arom}), 2974 (alkyl), 1347, 1161 (SO_2N) cm^{-1}. ^1H NMR (600.2 MHz, $CDCl_3$): δ = 7.73 (app. d, *J* ≈ 8.6 Hz, 4 H_{arom}), 7.49 (app. d, *J* ≈ 8.6 Hz, 4 H_{arom}), 4.64 (s, 2 H, CH_2), 4.16 (s, 4 H, $2CH_2$), 1.05 (s, 9 H, $3CH_3$). ^{13}C NMR (150.9 MHz, $CDCl_3$): δ = 139.87 (2 C_{quat}), 137.07 (2 C_{quat}), 129.57 (4 CH_{arom}), 129.09 (4 CH_{arom}), 62.56 (2 CH_2), 60.89 (CH_2), 54.23 (C_{quat}), 27.35 (3 CH_3). MS (ESI): *m/z* = 494.0 [M + H, ^{37}Cl, $^{37}Cl]^+$, 493.1, [M + H, ^{35}Cl, $^{37}Cl]^+$, 492.1 [M + H, ^{35}Cl, $^{35}Cl]^+$. Anal. Calcd for $C_{19}H_{23}Cl_2N_3O_4S_2$: C, 46.34; H, 4.71; N, 8.53; S, 13.02. Found: C, 46.33; H, 4.59; N, 8.58; S, 12.94.
(19) Kleber, M.; Blaszkewicz, M.; Lucas, S.; Bolt, H. M.; Föllmann, W. *Toxicol. Ind. Health* **2002**, *18*, 425.

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