2,4,6-Tris[(4-dichloroiodo)phenoxy)]-1,3,5-triazine as a New Recyclable Hypervalent Iodine(III) Reagent for Chlorination and Oxidation Reactions

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Abstract: The synthesis of 2,4,6-tris[(4-dichloroiodo)phenoxy)]-1,3,5-triazine, as a new recyclable nonpolymeric analogue of (dichloroiodo)benzene, is achieved in two steps using 2,4,6-trichloro-1,3,5-triazine and 4-iodophenol. The application of 2,4,6-tris[(4-dichloroiodo)phenoxy)]-1,3,5-triazine for the chlorination reaction of various activated arenes, olefin, and 1,3-diketone is demonstrated. The reagent 2,4,6-tris[(4-dichloroiodo)phenoxy)]-1,3,5-triazine can be applied also for the oxidative synthesis of 1,3,4-oxadiazoles and 1,2,4-thiadiazoles under mild conditions in excellent yields. The recyclability of the 2,4,6-tris[(4-dichloroiodo)phenoxy)]-1,3,5-triazine was possible owing to the facile recovery and reuse of the coproduced 2,4,6-tris(4-iodophenoxy)-1,3,5-triazine from the reaction mixture due to its practical insolubility in methanol.

Key words: oxidation, hypervalent iodine reagent, (dichloroiodo)benzene, 1,3,5-triazine, chlorination

The hypervalent iodine reagents are commercially available, mild, highly selective, and are similar in reactivity to heavy-metal oxidants such as mercury(II), thallium(III), and lead(IV) with fewer toxicity issues.[1] Currently, both iodine(III) and iodine(V) reagents are widely employed in a plethora of oxidative transformations.[2] Dichloroiodoarenes are one of the oldest hypervalent iodine(III) reagents which have been employed as reagents for chlorination and oxidation of various organic substrates, including industrial applications.[3] Dichloroiodoarenes have practical advantage over gaseous elemental chlorine, due to their safe handling and operational simplicity. However, such hypervalent iodine reagents do not have good 'green' credentials because they are commonly used as stoichiometric oxidants and iodoarenes are produced as byproducts.[4] This demands extensive chromatographic purifications to recover and reuse the relatively expensive iodoarenes from the reaction mixture and a quantitative recovery of the iodoarene is seldom achieved. To circumvent this particular problem of atom economy, two strategies have emerged in the last decade of hypervalent iodine chemistry studies: (a) the utilization of several types of recyclable hypervalent iodine reagents including dichloroiodoarenes to facilitate the separation of the iodine coproduct from the reaction mixture as well as the reuse of the reagents (Figure 1)[5–8] and (b) in situ generation of hypervalent iodine using a catalytic quantity of iodoarene in combination with a terminal oxidant (MCPBA, Oxone, or peracetic acid).[9] Regarding dichloroiodoarenes, attempts have been made to recycle the coproduced iodoarene using a polymer-supported reagents strategy[10] as well as fluorous techniques[11] (Figure 1, reagents **1** and **2**). 4,4′-Bis(dichloroiodo)biphenyl (**3**) has been also reported as a recyclable reagent for the halomethoxylation reaction due to the insolubility of 4,4′-diiodobiphenyl in hexane.[12] 3-(Dichloroiodo) benzoic acid (**4**) is the most noteworthy recyclable reagent due to the facile recovery of 3-iodobenzoic acid from the reaction mixture using aqueous $NaHCO_3$ followed by its precipitation using HNO_3.[12] Kita and co-workers have developed the recyclable hypervalent iodine(III) reagents **6** and **7** with a close proximity to the concept of supramolecular chemistry.[9] Inspired by these reports and the chemistry of dendrimers derived from 1,3,5-triazine,[13] we wish to report herein the synthesis of 2,4,6-tris[(4-dichloroiodo)phenoxy)]-1,3,5-triazine (**8**) as a new recyclable nonpolymeric analogue of (dichloroiodo)benzene and its application in the chlorination of various organic substrates. The synthetic utility of **8** as a recyclable oxidizing agent has been also demonstrated in the oxidative synthesis of 1,2,4-thiadiazole and 1,3,4-oxadiazoles from the corresponding thioamides and aldehyde *N*-acylhydrazones, respectively. The recyclability of the reagent **8** is possible owing to the facile recovery and reuse of the coproduced triiodide **11** from the reaction mixture due to its near total insolubility in methanol.

Our initial studies started with a two-step preparation of the recyclable hypervalent iodine(III) reagent **8** (Scheme 1). The reaction of 2,4,6-trichloro-1,3,5-triazine (**9**, 1 equiv) with a mixture of 4-iodophenol (**10**, 4 equiv) and KOH in acetone, under stirring at room temperature for 48 hours, furnished 2,4,6-tris(4-iodophenoxy)-1,3,5-triazine (**11**) in 93% yield.[14,15] The subsequent oxidation of **11** with gaseous chlorine at 0 °C in chloroform resulted in the formation of the reagent **8** in 94% yield[16] as a yellow, stable, and nonexplosive microcrystalline solid that could be stored for several weeks in a refrigerator in the dark. The reagent **8** was analyzed by iodometric titration as analysis by NMR spectroscopy was impossible due to its insolubility in $CHCl_3$.

We then investigated the application of **8** in the chlorination of various substrates such as activated arenes, 1,3-diketone, and olefins.[17] The results are summarized in Table 1. The activated arenes (entries 1–7) underwent clean nuclear chlorination to form monochlorination products exclusively in good to excellent yields. Cyclooctene, *trans*-stilbene, and indene (Table 1, entries 8–10) also un-

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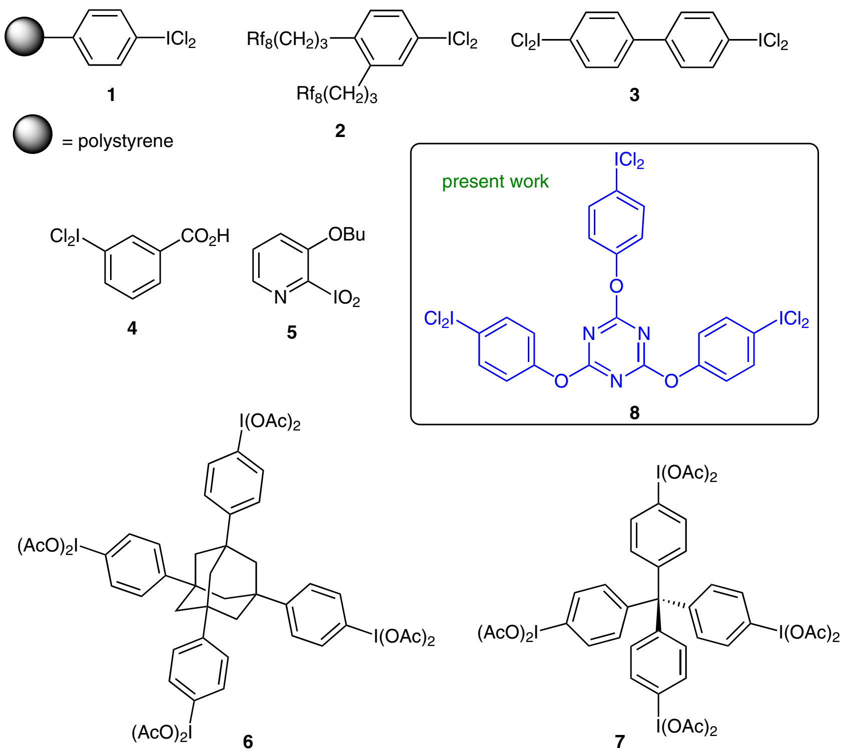
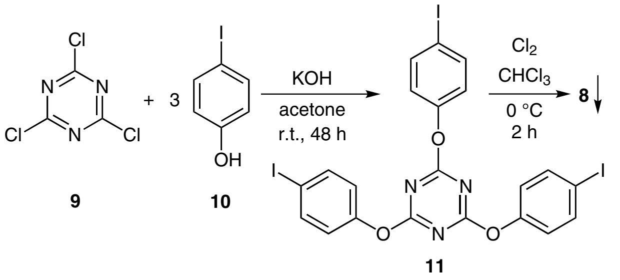


Figure 1 Recyclable hypervalent iodine reagents including dichloroiodoarenes

derwent addition reaction with **8** to form the respective dichlorination products. *trans*-Stilbene, 1,1-diphenylethylene, indene, and α-methyl styrene (Table 1, entries 11–14) on reaction with **8** in methanol resulted in the formation of their respective chloromethoxylation products. Dibenzoylmethane (Table 1, entry 15) on reaction with **8** yielded the α-monochlorinated product. The outcome and the yields of all the products of chlorination reactions in Table 1 are comparable with $PhICl_2$.[3]



Scheme 1 Preparation of 2,4,6-tris[(4-iodo)phenoxy)]-1,3,5-triazine (**11**) and 2,4,6-tris[(4-dichloroiodo)phenoxy)]-1,3,5-triazine (**8**)

Table 1 Chlorination of Various Substrates Using **8**

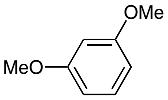
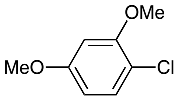
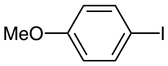
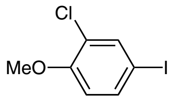
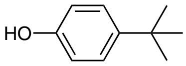
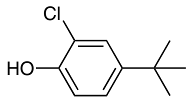
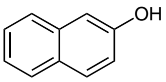
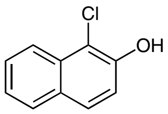
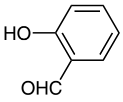
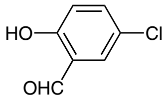
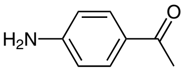
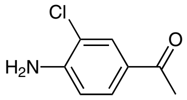
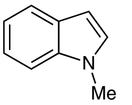
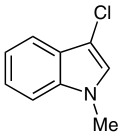
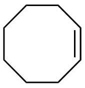
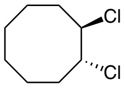
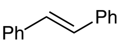
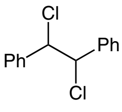
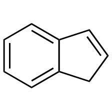
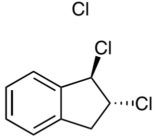
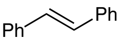
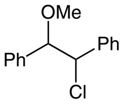
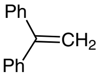
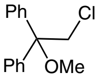
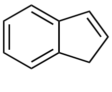
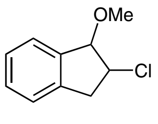
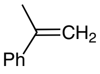
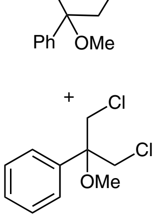
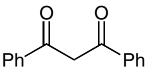
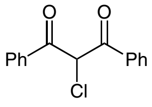
Entry	Substrate **12**	Product **13**	Solvent	Time (h)	Yield (%)[a,b]
1			CH_2Cl_2	4	85
2			CH_2Cl_2	4	89
3			MeCN	2	88
4			CH_2Cl_2	4	81

Table 1 Chlorination of Various Substrates Using **8** (continued)

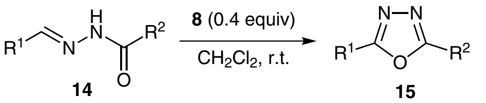
Entry	Substrate **12**	Product **13**	Solvent	Time (h)	Yield (%)[a,b]
5			CH_2Cl_2	7	90
6			CH_2Cl_2	6	85
7			CH_2Cl_2	4	89
8			MeCN	3	67
9			MeCN	3	90
10			MeCN	3	85
11			MeOH	3	62
12			MeOH	3	65
13			MeOH	3	67
14			MeOH	3	69
15			CH_2Cl_2	7	93

[a] Isolated yields after column chromatography.

[b] Stirring at r.t. for 2–7 h.

Symmetrical and unsymmetrical 2,5-disubstituted 1,3,4-oxadiazoles are biologically important scaffolds and have found applications in the field of material science.[18] The most common synthetic approach to 2,5-disubstituted 1,3,4-oxadiazoles involves the oxidation of aldehyde *N*-acylhydrazones using different transition-metal-based oxidizing agents such as ceric ammonium nitrate,[19a] $FeCl_3$,[19b] PbO_2,[19c] $KMnO_4$,[19d] $Cu(OTf)_2/O_2/Cs_2CO_3$,[19e] and HgO/I_2.[19f] To overcome certain issues of toxicity associated with the transition-metal oxidants, hypervalent iodine reagents such as (diacetoxyiodo)benzene,[20a–d] bis(trifluoroacetoxyiodo)benzene,[20e,f] IBX, and Dess–Martin periodinane[20g] have been also reported for similar transformations. In all the cases, a stoichiometric quantity of hypervalent iodine reagent has been employed and no attempt has been made to address the recyclability of the iodobenzene byproduct. Therefore, we investigated the application of **8** as a recyclable hypervalent iodine(III) reagent for the oxidative conversion of aldehyde *N*-acylhydrazones **14** into 2,5-disubstituted 1,3,4-oxadiazoles **15** (Table 2). The optimized reaction conditions showed that the highest yields of the product **15** were obtained using 0.4 equivalents of **8** with respect to the substrate **14** in dichloromethane. Using these optimized conditions, the reactions of various aldehyde *N*-acylhydrazones were carried out, and the results are shown in Table 2.[21] In all cases, the reaction proceeded smoothly to give the corresponding 2,5-disubstituted 1,3,4-oxadiazoles in good yields.

Table 2 Oxidative Synthesis of 1,3,4-Oxadiazoles from Aldehyde *N*-Acylhydrazones in CH_2Cl_2 Using **8**

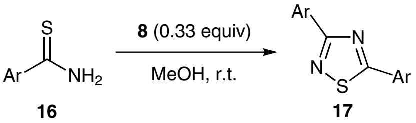


Entry	Substrate **14**		Product **15**	Yield (%)[a,b]
	R^1	R^2		
1	Ph	Ph	**15a**	81
2	4-MeC_6H_4	Ph	**15b**	79
3	2-$MeOC_6H_4$	Ph	**15c**	78
4	3-$MeOC_6H_4$	Ph	**15d**	76
5	4-$MeOC_6H_4$	Ph	**15e**	78
6	3,4-$(MeO)_2C_6H_3$	Ph	**15f**	69
7	4-HOC_6H_4	Ph	**15g**	81
8	2-ClC_6H_4	Ph	**15h**	71
9	4-ClC_6H_4	Ph	**15i**	84
10	3-BrC_6H_4	Ph	**15j**	78
11	4-$O_2NC_6H_4$	Ph	**15k**	82
12	4-MeC_6H_4	Me	**15l**	80
13	*i*-Pr	Ph	**15m**	74
14	*i*-Bu	Ph	**15n**	68

[a] Isolated yields after column chromatography.
[b] Stirring at r.t. for 2–6 h.

The oxidative dimerization of thioamides to form 3,5-disubstituted 1,2,4-thiadiazole has been reported using stoichiometric IBX/TEAB and polymer-supported (diacetoxyiodo)benzene.[22] The utilization of (diacetoxyiodo)benzene on polymeric support leads to concerns about the steric accessibility and the insolubility of the reagent in most organic solvents. In fact, the repeated use of the resin was found to result in the sequential degradation of the polymeric backbone which affected overall efficiency of the process. Hence, we decided to explore the reagent **8** for the oxidative dimerization of thioamides **16** to form 1,2,4-thiadiazoles **17**, and the results are summarized in Table 3. All the reactions were carried by treating three equivalents of thioamide with one equivalent of **8** (0.948 gm) in methanol.[23] In all the cases, the yields obtained were usually good to excellent with a short reaction time (1 h).[24]

Table 3 Synthesis of 3,5-Diaryl-1,2,4-thiadiazole through Oxidative Dimerization of Thioamides Using **8**



Entry	Substrate **16**	Product **17**	Yield (%)[a]
1	Ph	**17a**	84
2	4-MeC_6H_4	**17b**	81
3	3-MeC_6H_4	**17c**	77
4	2-MeC_6H_4	**17d**	76
5	4-$MeOC_6H_4$	**17e**	81
6	3-$O_2NC_6H_4$	**17f**	79

[a] Isolated yields after column chromatography.

Being a triazine-based reagent **8**, we were prompted to separate the coproduced triiodo derivative **11** by an acid–base extraction protocol analogous to the earlier reported pyridine-based pentavalent iodine reagent **5** using dilute HCl or H_2SO_4.[7b] However, we were unable to separate the coproduced triiodo derivative **11** efficiently from the reaction mixture by treatment with diluted HCl or H_2SO_4 followed by neutralization with NaOH. Our failure to separate the coproduced triiodo derivative **11** in this manner led us to consider solubility criteria previously reported for hypervalent iodine(III) reagents based on 4,4′-diiodobiphenyl **3**,[12] adamantane **6**, and tetraphenylmethane **7** structures.[9] Thus, after the completion of chlorination as well as the oxidative synthesis of 1,3,4-oxadiazoles, the reaction solvent (CH_2Cl_2 or MeCN) was evaporated under reduced pressure followed by addition of methanol (Figure 2). The coproduced triiodide **11** was found to be insoluble in methanol.[25] The resulting heterogeneous solution was then filtered, and the residue was washed several times with small amounts of methanol to recover **11** in nearly quantitative yield (93–97%). This was subsequently subjected to chlorination in $CHCl_3$ at 0 °C to form **8**. In the case of the oxidative synthesis of 1,2,4-thiadiazoles, the triiodide byproduct **11** was simply filtered from the reaction mixture followed by washing with methanol. The crude chlorinated or oxidation product present in the filtrate was then purified by column chromatography.

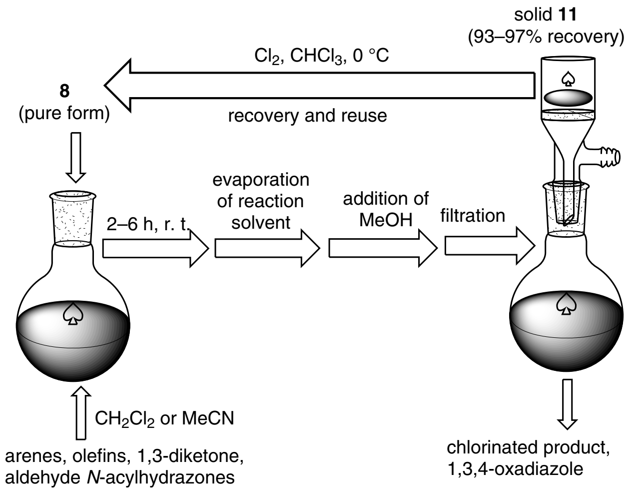


Figure 2 Strategy of recovery and reuse of 2,4,6-tris(4-iodophenoxy)-1,3,5-triazine

In summary, we have synthesized 2,4,6-tris[(4-dichloroiodo)phenoxy)]-1,3,5-triazine as a nonpolymeric recyclable analogue of (dichloroiodo)benzene from the relatively inexpensive starting materials like 4-iodophenol and 2,4,6-trichloro-1,3,5-triazine. Its application has been demonstrated for the chlorination of various organic substrates and for the oxidative synthesis of biologically important heterocyclic scaffolds such as 1,3,4-oxadiazoles and 1,2,4-thiadiazoles. The final products of chlorination and oxidation reactions are conveniently separated from the coproduced 2,4,6-tris(4-iodophenoxy)-1,3,5-triazine (**11**) by simple filtration from methanol which permits recycling without degradation or loss of the reagent **8**. The advantages of this procedure over previous processes include the transition-metal-free conditions for the oxidative synthesis of heterocycles, recyclability of the oxidizing agents, mild conditions, short reaction period, simple workup, and good yields of the products.

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Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(15) **Preparation of 2,4,6-Tris(4-iodophenoxy)-1,3,5-triazine (11)**
KOH (20 mmol, 1.12 g) was added to acetone (150 mL) and stirred for 45 min. 4-Iodophenol (20 mmol, 4.4 g) was then added to this solution and again stirred for 30 min. The resulting mixture was cooled to 0 °C, cyanuric chloride (5 mmol, 0.92 g) was added, and the mixture stirred for a further 1 h at 0 °C. The reaction mixture was allowed to stir for 48 h at r.t., poured into crushed ice, the resulting white precipitate was filtered with suction and then washed with MeOH to furnish **11** in 93% yield. White solid, mp 236–238 °C. ^{1}H NMR 400 MHz ($CDCl_3$): $\delta = 6.88$ (2 H, d, $J = 8.6$ Hz, ArH), 7.66 (2 H, d, $J = 8.6$ Hz, ArH) ppm. ^{13}C NMR 100 MHz ($CDCl_3$): $\delta = 90.54$, 123.56, 138.65, 151.26, 173.40 ppm. IR (neat): $\nu = 1589$, 1562, 1480, 1378, 1358, 1204, 1172, 1055, 1008, 820, 803, 704 cm^{-1}. ESI-MS: *m/z* $[M + H]^+$ calcd for $C_{21}H_{12}I_3N_3O_3$: 735.05; found: 735.75.

(16) **Synthesis of 2,4,6-Tris(4-dichloroiodophenoxy)-1,3,5-triazine (8)**
2,4,6-Tris(4-iodophenoxy)-1,3,5-triazine was dissolved in $CHCl_3$, and chlorine gas was passed through this solution at 0 °C with stirring for 2 h. 2,4,6-Tris(4-dichloroiodophenoxy)-1,3,5-triazine precipitated out as yellow, stable, microcrystalline solid. The reaction mixture was kept under refrigeration for 24 h, then filtered and washed with $CHCl_3$ to produce **8** in 94% yield. Yellow solid, mp 232–234 °C. IR (neat): $\nu = 1586$, 1561, 1479, 1380, 1360, 1212, 1176, 1002, 838, 807, 749 cm^{-1}.

(17) **General Procedure for Nuclear Chlorination of Arenes**
Reagent **8** (0.5 mmol) was added to a stirred solution of the appropiate activated arene (1 mmol) in CH_2Cl_2 (3 mL). The reaction mixture was stirred at r.t. for the period of time given in Table 1, and progress of reaction was monitored by TLC. When the substrate was consumed, the CH_2Cl_2 was evaporated under reduced pressure. MeOH was added to the reaction mass, and the white precipitate was isolated by filtration. The residue was washed several times with small aliquote of MeOH and air-dried to recover 2,4,6-tris(4-iodophenoxy)-1,3,5-triazine in 93% yield. The filtrate was concentrated in vacuo to afford the crude product which was purified by column chromatography on silica gel using PE–EtOAc (9:1) as eluent to give the chlorinated product in excellent purity.

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(21) **General Experimental Procedure for the Synthesis of 2,5-Disubstituted 1,3,4-Oxadiazoles 15 from Aldehyde *N*-Acylhydrazones 14**
2,4,6-Tris(4-dichloroiodophenoxy)-1,3,5-triazine (**8**, 0.4 mmol) was added to a stirred solution of the appropriate aldehyde *N*-acylhydrazone (1 mmol) in CH_2Cl_2 at r.t. The progress of the reaction was monitored by TLC, and the reaction was complete within 2–6 h. After completion, the solvent was removed in vacuo followed by addition of MeOH to precipitate out triiodide **11**. The resulting heterogeneous solution was filtered to recover **11** which was subsequently subjected to chlorination at 0 °C in $CHCl_3$ to form **8**. The filtrate, meanwhile, was concentrated in vacuo to afford the crude product which was purified by column chromatography on silica gel using PE–EtOAc (9:1) as eluent to give 2,5-disubstituted 1,3,4-oxadiazoles in excellent purity.

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(23) The same reaction in CH_2Cl_2 resulted in the formation of few other side products as revealed by TLC.

(24) **General Procedure for 1,2,4-Thiazoles 17**
2,4,6-Tris(4-dichloroiodophenoxy)-1,3,5-triazine (**8**, 0.947 g, 1 mmol) was added to a stirred solution of appropriate thiobenzamide (3 mmol) in MeOH at r.t. The progress of the reaction was monitored by TLC, and the reaction was complete within 2 h. After completion of reaction, the mixture was filtered, and the resulting white precipitate was washed several times with MeOH to recover **11** which was subsequently subjected to chlorination at 0 °C in $CHCl_3$ to form **8**. The original filtrate was concentrated in vacuo to afford the crude product which was purified by column chromatography on silica gel using PE–EtOAc (9:1) as eluent to give the substituted 1,2,4-thiazole in excellent purity.

(25) The measured solubilities of the coproduced triiodide **11**, a reduced form of the 2,4,6-tris[(4-dichloroiodo)phenoxy]-1,3,5-triazine (**8**) reagent, in several (mixed) solvents at 25 °C are as follows: 0.02 $mg\cdot mL^{-1}$ (MeOH); 0.02 $mg\cdot mL^{-1}$ (*i*-PrOH); 0.2 $mg\cdot mL^{-1}$ (MeCN); 4.1 $mg\cdot mL^{-1}$ (EtOAc); 4.3 $mg\cdot mL^{-1}$ (acetone); 0.04 $mg\cdot mL^{-1}$ (MeOH–EtOAc = 10:1); 0.06 $mg\cdot mL^{-1}$ (MeOH–EtOAc = 5:1); 0.6 $mg\cdot mL^{-1}$ (MeOH–EtOAc = 1:1).