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Improved Halogenation of Methyl Aromatics and Methyl Heteroaromatics: Unexpected Reactivity of Tetrahalogeno-diphenylglycolurils

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ABSTRACT: *1,3,4,6-Tetrachloro (TCDGU) and 1,3,4,6-tetrabromo-3α,6α-diphenylglycolurils smooth halogen oxidizers have been exploited in a new direction as reagents for free radical substitution toward some N-halosuccinimide nonreactive bis-heterocycles. An unexpected selectivity and reactivity were observed with methyl benzenes, methyl heterocycles, and methyl-bis-heterocycles of interest. A chemometric study has been performed to optimize five independent factors of the chlorination reaction with TCDGU. The predictive model was established either for the halogenation conversion and the ratio of monochlorination.* © 2016 Wiley Periodicals, Inc. Heteroatom Chem. 27:173–183, 2016; View this article online at wileyonlinelibrary.com. DOI 10.1002/hc.21314

INTRODUCTION

It is obvious that efforts to discover efficient and selective methods to functionalize organic compounds remain of high priority. In this sense, free radical reactions represent an important field of valuable methods [1a–1d]. One of the most employed methodology in the field of radical substitution reactions of alkyl aromatics or heteroaromatics is the halogenation under UV–visible irradiation, using the *N*-halosuccinimides (NBS, NCS, or NIS) as reagents and 2,2′-azo-*bis*-isobutyronitrile (AIBN) as an initiator [2,3a,3b,4–6]. Nevertheless, in recent years we already observed a dramatic failure of bromination of some essential nitrogen heterocycles and *bis*-heterocycles building blocks often involved in the synthesis of metallo-supramolecular structures, under such conditions, e.g., 6,6′-dimethyl-bipyrazine [7], methyl-1,2,4-triazines, or bistriazines [8]. Otherwise, it is known that the free radical reaction with *N*-halosuccinimides authorizes a strongly limited choice of compatible but hazardous solvents (i.e., CCl_4 or benzene) whereas alkyl-benzenes are of course totally excluded.

RESULTS AND DISCUSSION

We report here results about selective efficient free radical chlorination and bromination methods of especially *N*-halosuccinimide nonreactive heterocycles, also compatible with toluene as solvent medium, too. This concerns first the tetrachloro-diphenylglycoluril (Iodogen®) marketed reagent **1,** which was early and is still used as an in situ smooth oxidizer generating I^+ electrophile from iodine for SEAr radiolabeling of phenol nuclei [9a-c]. Before preliminary results of our group [7], **1** was not used as a chlorine radical source for free radical substitution reactions. Initially, we prepared tetrachloro-diphenylglycoluril (TCDGU) in bulk (30 g) by chlorination of diphenylglycoluril [8]. A successful first substitution was obtained on

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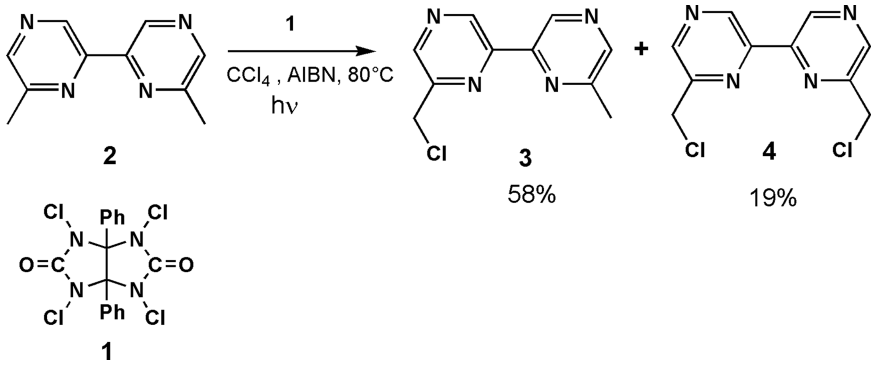


SCHEME 1 Synthesis of chloromethyl bipyrazines with TCDGU. Caution! : CCl_4 hazardous solvent should be worked up in a well-ventilated hood.

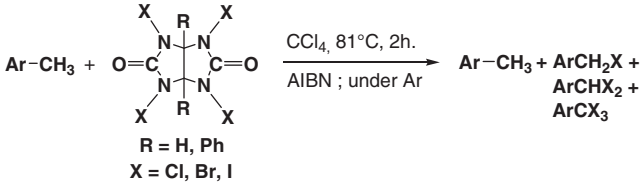
6,6′-dimethyl-2,2′-bipyrazine **2,** knowing that the bromination with NBS failed to afford the corresponding bromomethyl derivatives in the same solvent (CCl_4) [10]. Under such conditions, TCDGU afforded a mixture of the monochloromethylated derivative **3** (58%) and the dichloromethylated derivative **4** (19%) (see Scheme 1) [7]. It appeared recently that other aza-heterocyles were only poorly reactive if not reactive at all, toward radical substitution using *N*-halosuccinimide/AIBN systems. 1,2,4-Triazinyl and 1,2,4-bis-triazinyl heterocycles are the most significant examples [8].

As reported in Scheme 2, one can notice that the triazinyl methyl group of the 3,3′-dimethyl-5,5′-*bis*-1,2,4-triazine **5** was only poorly brominated in 5% yield whereas those of the 3-methyl-5-(6-methylpyridine-2-yl)-1,2,4-triazine **6** and its cyclopentyl derivative **7** remain totally unaffected in that conditions. Finally, another interesting application of the reaction was found in the case of the nonsymmetrical *bis*-heterocycle 3-methyl-5-(6-methylpyridine-2-yl)-1,2,4-triazine **6**. As depicted in Scheme 3., it becomes then possible, combining the TCDGU chlorination method with classical NBS bromination, to functionalize independently, even in low yields, the two methyls of the *bis*-heterocycle **6** with a complete regioselectivity. To our delight, we noted that the methyl of the triazinyl nucleus reacts only with the TCDGU but not with NBS, whereas the methyl of the pyridyl nucleus displays the opposite reactivity (no traces of benzyl chloride byproduct, coming from toluene have been detected using TCDGU).

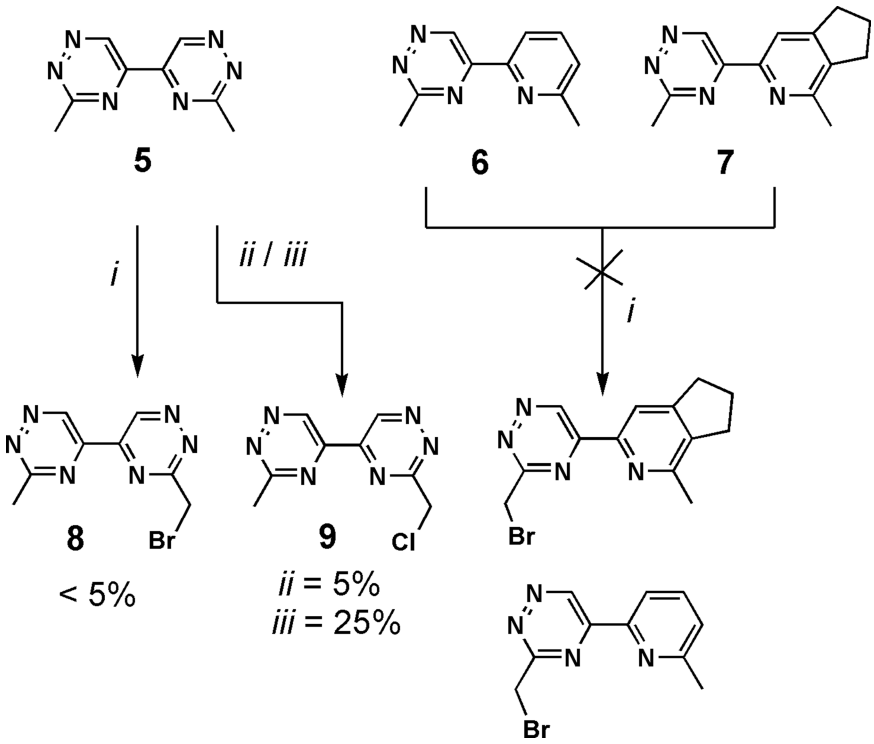
The latter example enlightens the different reactivities of the 2-methyl pyridyl nuclei in **6** from those of 2-picoline under the same conditions (see Table 1). Trying to enhance the monochloromethylated derivative yield of **5**, we replaced CCl_4 by toluene as the solvent of reaction. In these conditions, the monochloromethylated derivative **9** was isolated in 25% yield compared to 5% in CCl_4. At this occasion, an unexpected event was observed: Toluene remains totally unreactive toward TCDGU (as checked by GCMS analysis of the reaction mixture). This property has never been observed before and suggests that TCDGU should possess a peculiar reactivity.

Chlorination of Methyl Benzenes and Methyl Heterocycles with TCDGU

All the experiments were performed in standardized conditions (see general equation (1)), using equimolecular amounts of the aromatic substrate and tetrahalogeno-glycoluril reagent (see Table 1).



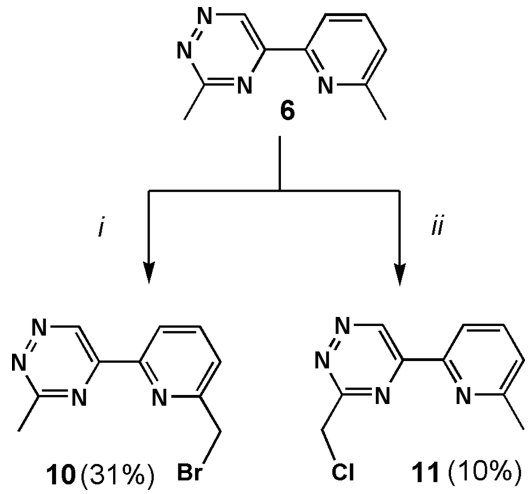
Above reaction conditions (temperature and time) have been selected to ensure optimal halogenation yields by a set of 10 experiments. We have interestingly observed that reaction advancement was strongly dependent on the temperature (with $T < 80$°C, only 7% of a monochlorinated compound was formed and no reaction occurred at 60°C), whereas irradiation initially used (via a 100-W tungsten lamp) at room temperature has no effect, indicating that the reaction was strictly under thermal control. Experiments were also carried out in two conditions of dilution; (i) in a limited volume of solvent (5 mL) which placed the reaction in heterogeneous conditions (TCDGU plays the role of solid phase) and (ii) in a 25 mL of solvent which placed the reaction in homogeneous conditions. To our surprise, optimal yields



SCHEME 2 (i) CCl_4/NBS/100 W; (ii) CCL_4/TCDGU/AIBN/100 W; (iii) toluene/TCDGU/AIBN/100 W.

were only obtained in heterogeneous conditions whereas very surprisingly no reaction occurred in homogeneous ones [11].

Otherwise, it is interesting to note that, under the same conditions, unsubstituted and monosubstituted tetrahalogenoglycolurils [12] did not allow halogenation of the substrates, whereas fairly good chlorination yields (up to 70%) were achieved with TCDGU. Examining the results obtained on methyl benzenes reported in Table 1, one can see little differences in reactivity and selectivity among them. Except the toluene which remained nonreactive toward TCDGU, it was observed that *o,m,p*-xylenes and trimethyl benzenes were chlorinated giving mixtures of monochloromethylated derivatives as the major products. *Gem*-dichloromethylated species were also detected but as minor by-products (≤10%), and trichloromethyl species were not detected except only as traces (≤ 1%) in the case of 1,2,4-trimethylbenzene as the substrate. The different isomeric position of the methyl groups on the benzene nuclei seems to have a minor incidence on the final regioselectivity. Concerning, monoheterocycles (Table 1), differences could be observed between 4-methyl pyrimidine, 2-methyl pyrazine, 2-methyl pyridine, and 2, 4-dimethyl-pyrimidine. In this series, monochlorinated species were the major products, but an increasing reactivity was observed



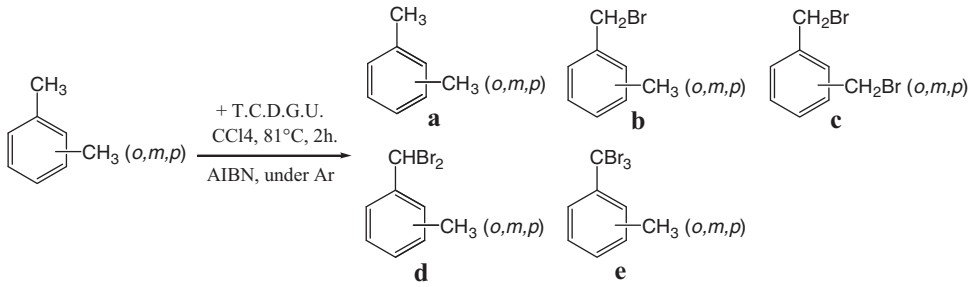
SCHEME 3 (i) NBS/CCl4/AIBN/100 W/ 75 min; (ii) TCDGU /toluene/AIBN/100 W/24 h.

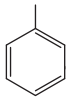
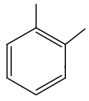
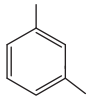
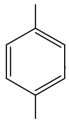
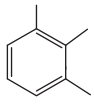
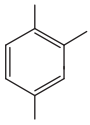
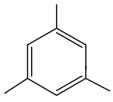
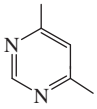
between 4-methyl-pyrimidine (which remains unchanged in 87%) and the three other four heterocycles.

Bromination of Methyl Benzenes and Methyl-bis-heterocycles with TBDGU

As previously depicted, methyl benzenes and methyl-*bis*-heterocycles bromination were investigated

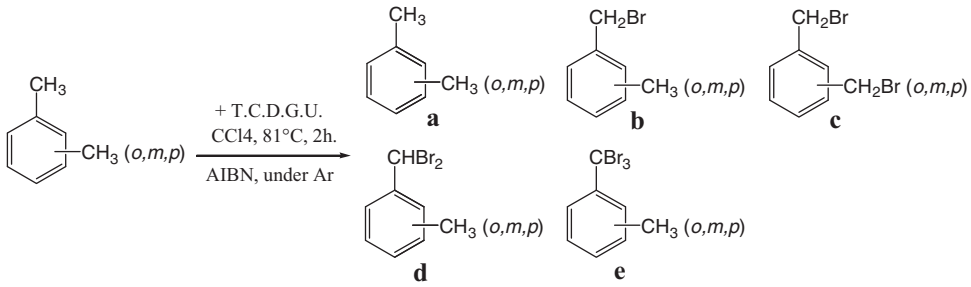
TABLE 1 Chlorination of Methyl Benzenes and Methyl Heterocycles by TCDGU

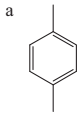
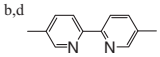
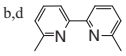
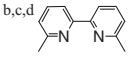
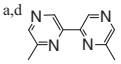
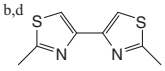


Entry	*Substrate*	*a (%)*	*b (%)*	*c (%)*	*d (%)*	*e (%)*
1		100	0	0	0	0
2		30	41	26	3	0
3		29	52	16	3	0
4		24	51	20	5	0
5		21	36	41	2	0
6		14	59	23	3	1
7		32	20	40	8	0
8		0	60	-	40	0
9		87	13	-	0	0
10		33	60	-	7	0
11		5	44	25.5	25.5	0

Reaction conditions: TCDGU 1 equiv; solvent CCl_4 (5 mL); methyl benzenes 1 equiv; AIBN 0.1 equiv; $T = 81°C$; percentages were determined by GC-MS and ^1H NMR analysis.

TABLE 2 Bromination of Methyl Benzenes and Methyl-*bis*-heterocycles by TBDGU



Entry	*Substrate*	*a (%)*	*b (%)*	*c (%)*	*d (%)*	*e (%)*
1		0	99	1	0	0
2		0	20	61	0	19
3		3	8	38	50	1
4		0	1	61	30	9
5		0	0	0	43	57
6		0	15	61	11	13
7		16	4	0	6	74
8		59	41	0	0	0
9		2	45	34	13	5

Reaction conditions: TBDGU 1 equiv, solvent CCl_4 (5 mL), substrate 1 equiv, AIBN 0.1 equiv, $T = 81°C$.
[a]Determined by CG-MS and NMR analysis.
[b]Isolated products, purified by column chromatography.
[c]Solvent toluene (5 mL).
[d]Reaction time = 1 h, solvent (10 mL).

using tetrabromodiphenylglycoluril (TBDGU) under the same standardized conditions. TBDGU was synthesized by a known method of literature [13a–b] and was used in the conditions of Eq. (1). Focusing on methyl benzenes (Table 2), significant differences appeared in reactivity compared to the chlorination reaction. Notably, the toluene, previously found unreactive toward TCDGU, was almost entirely and selectively converted into benzyl bromide by TBDGU (99% yield). In comparison to the chlorination reaction, results of Table 2 revealed overall best conversion yields of methyl benzenes into their brominated derivatives (unchanged substrate ≤3%). Bromination of *o,m,p,*-xylenes selectively gave *sym*-dibromomethyl and *gem*-dibromethyl derivatives as major products whereas bromomethyl or tribromomethyl derivatives remained only minor by-products. A limited number of useful synthetic routes to α-methyl functionalization of electron-poor heterocycles of interest have been reported in the literature [14a and14b]. This concern notably, *bis*-heterocyclic building blocks is often present as metal coordinating subunits (e.g., 2,2′-bipyridine) into numerous metallo-supramolecular architectures. Looking at our results, TBDGU appeared to be a good candidate to play this role. The case

of the 6,6′-dimethyl-2,2′-bipyrazine **2** affording selectively, for the first time in the literature, the 6-bromomethyl-6′-methyl-2,2′-bipyrazine derivative **2b** in 41% yield was one of the best examples. Other *bis*-heterocyclic systems were almost fully converted into mixtures of mono-, *sym*-dibromomethyl, *gem*-dibromomethyl, or *unsym*-tribromomethyl derivatives by TBDGU. Interesting features were observed with the 5,5′-dimethyl- and the 6,6′-dimethyl-2,2′-bipyridine isomers (Table 2.); (i) in the same conditions of solvent (CCl_4), the 5,5′ isomer only gave *gem*-dibromomethyl and *unsym*-tribromomethyl species in a medium yield (50%), whereas the 6,6′ isomer afforded the *sym*-dibromomethyl derivative as the major product in a good yield (61%). In comparison, Rodriguez-Ubis et al. [15] reported the formation of *unsym*-monobromomethyl derivative with the NBS method in 33% yield; (ii) in toluene as a solvent, the 6-tribromomethyl-6′-methyl-2,2′-bipyridine was almost exclusively obtained in fair yield (74%). The latter was another unexpected result that showed a total compatibility of toluene in the presence of the tetrahalogeno-diphenylglycoluril (see above in the case of *bis*-triazine chlorination). Finally, the 2,2′-dimethyl-4,4′-bithiazole gave the *unsym*-monobromomethyl and *sym*-dibromomethyl derivatives (in 45% and 34% yield, respectively) as the major products, which are the most interesting with regard to their potent inclusion as subunits in several supramolecular architectures. In comparison with the NBS method, Pellet-Rostaing et al. [16] reported the formation of *unsym*-2-monobromomethyl-4,4′-bithiazole in 35% yield from 2,2′-dimethyl-4,4′-bithiazole. Examining these results, some general features are, e.g., unusual nonreactivity of toluene and/or unexpected selectivities of halogenations, enlightening the fundamental role played by the glycoluril structure. This is a peculiar point that should retain our attention. Regarding glycoluril structures, one can see that only the diphenylglycolurils had undergone the selective halogenations, whereas unsubstituted and monosubstituted glycolurils totally failed. So that a hypothesized assisted reactivity by the formation of complexes in solution between the U-shaped cavity of tetrahalogeno-diphenylglycolurils and aromatic nuclei could be at least suggested. This idea is well supported by the diphenylglycoluril structure reported in seminal works of Rebek [17a and17b], Nolte [18], and Isaacs [19a–19c], who described this compound as a "molecular clip" and as a subunit for the construction of supramolecular architectures. In the same sense, a recent work [20] has established diphenylglycoluril was a good receptor for the 1,3-dihydroxybenzene guest molecule in chloroform as a solvent.

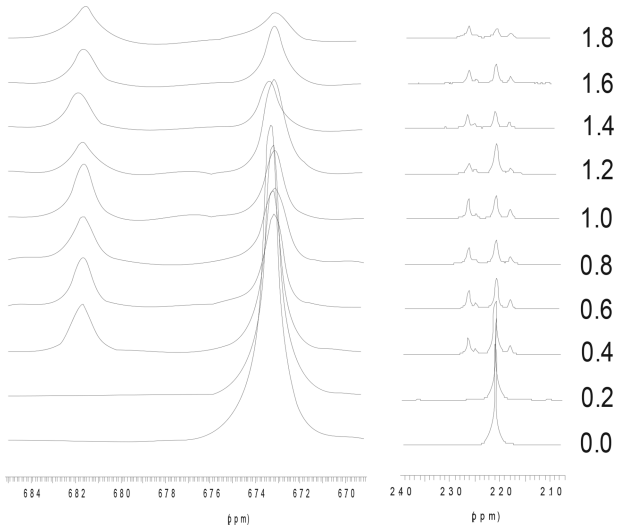


FIGURE 1 ^{1}H NMR titration of mesitylene by TCDGU in CH_2Cl_2 as the solvent.

To verify formation of such a complex, titration experiments of mesitylene by TCDGU were performed either by ^{1}H NMR and UV–vis spectrometry. Addition of TCDGU aliquots (7.5 μL) into a solution of mesitylene in CH_2Cl_2 readily induces a strong decreasing intensity of the benzene nucleus aromatic protons peak at 6.73 ppm, which splits into two signals at 6.82 and 6.73 ppm. In the same way, the methyl protons signal (single peak at 2.21 ppm; Fig. 1) split into an AB system. These features indicate that an association occurs between these two molecules. In this complex, the aromatic and methyl protons were located as they now appeared nonequivalent magnetically. Similarly, UV–vis titration in the same conditions of solvent (Fig. 2.) shows a strong hypochromic effect and a λ_{max} red-shift corresponding to the benzene nucleus (π,π*) absorption band from 265 to 278 nm. A total disappearance of the signal obtained after addition of 1 equiv of TCDGU suggests formation of a [1:1] donor–acceptor charge-transfer complex between TCDGU and mesitylene. In the light of these results and as mentioned above, the maximum of halogenation only occurs with a TCDGU only partly soluble with a solid phase persistency in the reaction medium. Thus, one cannot conclude to the sole charge transfer complex involvement as a possible mechanism. Consequently, critical points that concern the real working mode and reaction mechanism of tetrahalogeno-diphenylglycoluril reagents should be precise in a near future by relevant investigations.

Chemometry

To optimize the reaction, the effects of five different parameters on (Conv. = the substrate conversion, MCl = monochlorination, and DCl = dichlorination yields) of *O*-xylene and mesitylene was investigated by means of experimental design treatment The factors considered were : (Sub. = nature of the reactant, Sto. = stoichiometry of the reagent, T = temperature, V = volume of the solvent, *ti* = time). Using TCDGU as the chlorination reagent, a chemometric study has been performed to optimize the above cited five independent factors. (for details, see the Supporting Information). A graphical representation of the different factors' effect is given in Fig. 3. It was observed that the conversion yield strongly depends on three factors: (i) the nature of the substrate, (ii) the stoichiometry, and (iii) the volume of the solvent.

In particular, one can note that substrate conversion and chlorination yields dramatically decrease as the solvent volume increases. This result is correlated to the TCDGU halogenation mode that works well only in heterogeneous media as previously observed by others [11] and by us in the present work. Also interesting is the ratio of MCl/DCl yields, which were relatively independent with regard to the same factors. This could indicate the selectivity of chlorination is also independent from these factors. Finally, it was possible to establish predictive models either for the halogenation conversion (Conv) and the ratio of monochlorination (MCl).

$$\begin{aligned}\text{Conv.} = {} & 58.18 + 5.43 \times \text{Sub.} + 6.51 \times \text{Sto.} - 6.08 \\ & \times V - 3.869 \times \text{Sub.} \times \text{Sto.} + 4.294 \times \text{Sto.} \\ & \times V\text{MCl} = 41.4 - 3.37 \times T \times \text{ti}\end{aligned}$$

Application of above equations provides parameter values for which the maximum yields of conversion and monochlorination can be predicted.

CONCLUSION

In summary, first results about the use of tetrahalogenodiphenylglycolurils as original halogenation agents were presented. Unexpected features were observed notably, the compatibility of toluene with TCDGU in chlorination reactions or with TBDGU in bromination of the corresponding 6,6′-dimethyl-2,2′-bipyridine isomer. Interestingly, an overall equivalent or superior radical halogenation efficiency of either nonreactive and reactive *bis*-heterocyclic systems has been observed. In selected conditions, the substitutions with the tetrahalogeno-diphenylglycolurils became highly selective toward some aromatic substrates providing an attractive new method to functionalize nonreactive or *N*-halosuccinimide-sensitive *bis*-heterocycles. This could be considered of primary interest especially for the α-methyl functionalization of *bis*-heterocycles. One can note that the by-product DGU (diphenylglycoluril) was fully recyclable after a new chlorination step. Furthermore, formation of a donor–acceptor complex between the tetrahalogeno-diphenylglycoluril and the methyl aromatic guests in solution was suggested in relation with the surprising reactivities and selectivities observed with tetrahalogeno-diphenylglycolurils. Albeit we are unable up to now to explain the exact mechanism (s) in details, it is obvious that additional work is now necessary to elucidate it. An extended study is needed giving an access to scope and limitation of the reaction with tetrahalogeno-diphenylglycolurils reagents.

EXPERIMENTAL

General Considerations

Unless otherwise noted, all reagents were purchased from commercial suppliers and used without purification. All reactions were performed under argon. All the new compounds gave satisfactory spectroscopic IR, UV–vis, ESIMS, elemental analyses, ^{1}H and ^{13}C NMR data. FTIR spectra were recorded in KBr pellets. Relative percentage and identity of each compound were determined coupling ^{1}H NMR and CG-MS analyses of the reaction mixtures. CG-MS spectra were obtained on a mass selective detector instrument operating at an ionizing voltage of 70 eV connected to a GC with an AT-1 capillary column type (25 m × 0.32 mm × 0.30 μm) film thickness.

Procedure for the Synthesis of 1,3,4,6-Tetrachloro-3α,6α-diphenylglycoluril ***1***. A mixture of 3,6-diphenyl glycoluril (15 g, 0.05 mol), sodium acetate (18.8 g, 0.23 mol), H_2O (250 mL), and sodium di-*n*-octyl sulfosuccinate (AOT) is stirred at 55°C. A stream of Cl_2 was bubbled through the solution until the mass of the mixture increased to 15.3 g. The solution was stirred at the same temperature 12 h more. The resulting suspension was filtered, and the solid phase extracted with dichloromethane. The organic phases were dried over anhydrous $MgSO_4$, and the solvent was evaporated to dryness. The pure product, a white solid **1**: 17.49 g (81%) was kept between 0 and 4°C. ^{1}H NMR ($CDCl_3$; 25°C) δ 7.27 (d, J = 7.8 Hz, 2H), 7.21 (d, J = 7.8, 4H), 6.98 (d, J = 7.8Hz, 4H).

*Procedure for the Synthesis of 1,3,4,6-Tetrabromo-3α,6α-diphenylglycoluril **1a**.* **1a** was synthesized by a modified procedure of literature [13a]. A mixture of diphenylglycoluril (2.98 g, 10.0 mmol) and bromine (16.0 g, 100 mmol) in water (400 mL) was stirred at room temperature and pH 9–10 over 3 h. The resulting solid was filtered, washed with water (2 × 200 mL) then dried under vacuum over 48 h. Orange solid **1a** 5.0 g (83%) was kept between 0 and 4°C. ^{1}H NMR (DMSO-6*d*; 25°C) δ: 7.75 (m, 2H), 7.06 (m, 8H); MS (EI): *m/z* 601.5 $[M]^+$; Anal Calcd. for $C_{16}H_{10}Br_4N_4O_2$: C, 31.50; H, 1.65; N, 9.21. Found: C, 31.85; H, 1.86; N, 9.63.

6,6'-dimethyl-bipyrazine **2** was synthesized by a known procedure of literature [21].

6-Bromomethyl-6′-methyl-2,2′-bipyrazine **2b** [23]. To a solution of 6,6′-dimethyl-2,2′- bipyrazine (0.1 g, 0.538 mmol) in CCl_4 (10 mL) under Ar, tetrabromodiphenyl glycoluril (0.325 g, 0.538 mmol) and AIBN (0.088 g, 0.054 mmol) were added. The

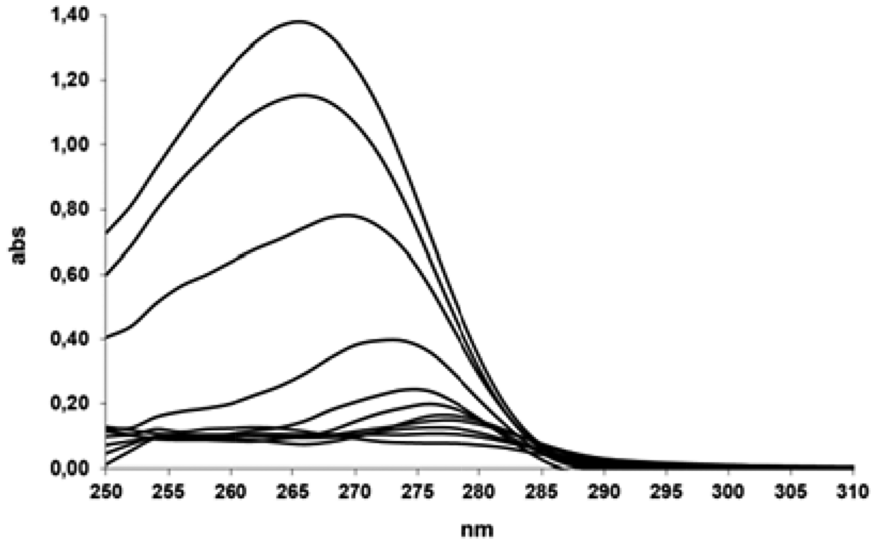


FIGURE 2 Spectrophotometric titration of mesitylene ($C = 6.98 \times 10^{-3}$ mol L^{-1}) by TCDGU (6.97×10^{-2} mol.L^{-1}) in CH_2Cl_2 as the solvent.

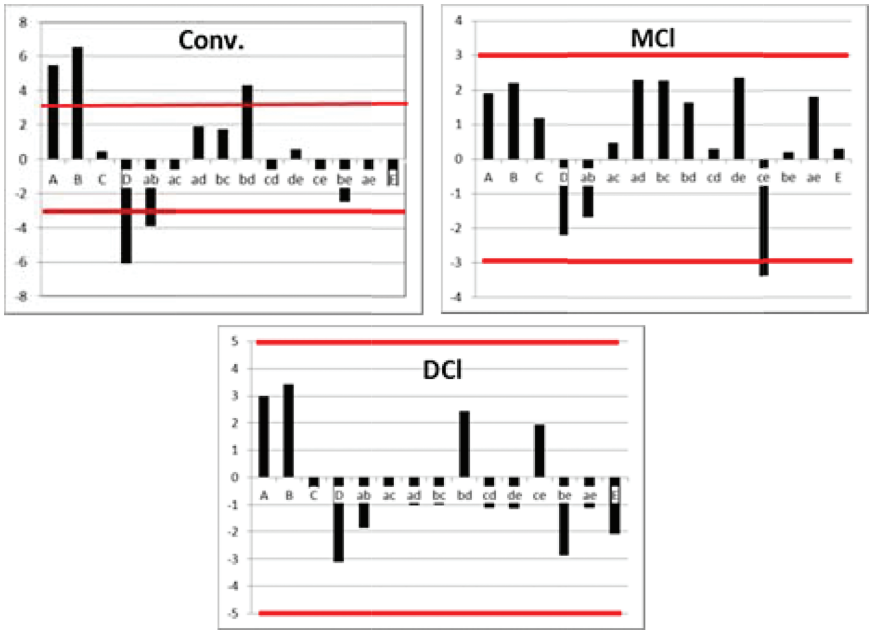


FIGURE 3 Graphical representation of the effects function of the factors (A–E) and of their interactions (ab to ae) calculated for the substrate conversion and chlorination yields from the fractional factorial design. The red continuous lines represent the level of 2σ.

mixture was then refluxed 1 h. After reaction, the mixture was filtered and the solid phase was washed three times with CCl_4. After evaporation of the solvent, the residue was chromatographed on a silicagel 60 Merck (0.04–0.063 mm) column; with CH_2Cl_2/Et_2O: 9/1 as the eluent. The pure product **2b** was obtained as a yellow solid 0.026 g (10%). ^{1}H NMR ($CDCl_3$; 25°C) δ: 9.44 (s, 1H), 9.34 (s, 1H), 8.71 (s, 1H), 8.48 (s, 1H), 4.57 (s, 2H), 2.60 (s 3H); ^{13}C NMR ($CDCl_3$; 25°C) δ: 154.3, 153.1, 151.8, 145.5, 145.1, 141.5, 139.5, 59.4, 21.2. MS (EI) *m/z* (%): 264 (45) [M]+, 185 (100) [M-Br]$^+$; Anal. Calcd. for $C_{10}H_9BrN_4$: C, 45.30; H, 3.42; N, 21.13. Found: C,45.05; H, 3.41; N, 21.01.

6-Chloromethyl-6′-methyl-2, 2′-bipyrazine **3** [22]. To a solution of 6,6′-dimethyl-2,2′-bipyrazine (1 g, 5.38 mmol) in CCl_4 (100 mL) under argon, tetrachloro-diphenyl glycouril (1 g, 2.32 mmol) and AIBN were added. The mixture was refluxed and irradiated by a tungsten lamp (100 W) for 24 h. The resulting precipitate was filtered, washed with CH_2Cl_2, and the solvent was removed in vacuo. The crude product was purified by chromatography on silica gel (eluent: CH_2Cl_2/Et_2O, 95/5), gave 6-chloromethyl-6′-methyl-2,2′-bipyrazine **3**: white solid; 0.595 g, (50.5%). ^{1}H NMR ($CDCl_3$; 25°C) δ: 9.54 (s, 1H), 9.38 (s, 1H), 8.81 (s, 1H), 8.53 (s, 1H), 4.78 (s, 2H), 2.66 (s, 3H). ^{13}C NMR ($CDCl_3$; 25°C) δ: 153.1, 151.0, 148.5, 147.7, 145.2, 144.4, 143.1, 142.4, 43.9, 21.6. *6,6′-Chloromethyl-2, 2′-bipyrazine* 4: [20] white solid 0.257 g, (19%). ^{1}H NMR ($CDCl_3$; 25°C) 9.57 (2H, s), 8.84 (2H, s), 4.80 (4H, s). ^{13}C NMR ($CDCl_3$; 25°C) 151.1, 147.8, 144.8, 142.6, 43.8.

3,3′-Dimethyl-5,5′-bis-(1,2,4-triazine) **5** [8]. To a solution of acetamidrazone (5.0 g, 45.6 mmol) in water (30 mL), KOH (2.3 g, 41.04 mmol) and glyoxal (5.5 mL, 47.8 mmol) were added. The mixture turned into bright yellow after 15 min. K_2CO_3 (0.457 g, 4.56 mmol) was added. The reaction mixture was stirred for 3 h more and warmed up to 40°C. Then solid KCN (2.0 g, 30.8 mmol) was added, the color turn into red, and some precipitates appeared. The temperature was maintained for 1 h more. After opening the stopper, the reaction turns to black color. After evaporation of water, the black residue was extracted by continuous stirring with ether (3.0 L). The organic phase was dried over anhydrous $MgSO_4$, filtered, and evaporated to afford **5** as an orange crude solid, which was crystallized in $CHCl_3$/hexane affording pure bright yellow crystals; 2.34 g (55%). FTIR (ν_{max}/cm^{-1}): 3036, 2926, 1537, and 1500; UV–vis λ_{max} (MeOH), nm 360 ($\varepsilon/dm^3\ mol^{-1}\ cm^{-1}$ 9000), 290 (25,000); ^{1}H NMR ($CDCl_3$; 25°C) δ: 10.08 (s, 2H), 2.97 (s, 3H). ^{13}C NMR ($CDCl_3$; 25°C) δ: 167.8, 151.1, 144.7, 24.2. MS (EI) *m/z* (%): 188.2 [M]$^+$, 160 [M – N_2]+, 91 [C_4HN_3]$^+$; Anal Calcd. for $C_8H_8N_6$: C, 51.10; H, 4.25; N, 44.68. Found: C, 51.10; H, 4.15; N, 44.29.

3-Methyl-5-(6-methyl pyridine-2-yl)-1,2,4-triazine **6** [8]. The 3,3′-dimethyl-5,5′-bis-(1,2,4-triazine) **5** (2 g, 5.32 mmol) was added into a solution of vinylpyrrolidine (2.06 g; 10.63 mmol) into toluene (10.5 mL). The solution was stirred at 60°C during 18 h. After evaporation of the solvent, the residue was chromatographed on a silicagel 60 Merck (0.04–0.063 mm) column; with hexane/AcOEt : 4/6 as the eluent. The pure product **6** was obtained as a yellow powder: 1.65 g, (79.4%). ^{1}H NMR ($CDCl_3$; 25°C) δ: 10.05 (s, 1H), 8.27 (d, J = 7.8Hz, 1H), 7.71 (t, J = 7.8 Hz, 1H), 7.26 (d, J = 7.8 Hz, 1H), 2.87 (s, 3H), 2.60 (s, 3H). ^{13}C NMR ($CDCl_3$; 25°C) δ: 167.1, 159.4, 154.3, 151.7, 144.9, 137.7, 126.4, 120.2, 24.9, 24.3; MS (EI): *m/z* 186 [M]$^+$; 158 [M – N_2]$^+$; Anal. Calcd. for $C_{10}H_{10}N_4$: C, 64.50; H, 5.41, N, 30.10. Found: C, 64.80; H, 5.20; N, 30.21.

6,7-Dihydro-1-methyl-3-(3-methyl-1,2,4-triazine-5-yl)-5H-cyclopenta[c]pyridine **7** [8]. 1-Pyrrolidino-1-cyclopentene (0.073 g, 0.53 mmol, 78 μL) was added to a solution of **5** (0.1 g, 0.53 mmol) into toluene (5 mL). The mixture was stirred 18 h at 60°C. After evaporation of the solvent, the resulting residue was chromatographed on a silicagel 60 Merck (0.04-0-.063 mm) column; with CH_2Cl_2/Et_2O : 8/2 as the eluent. The pure product **7** was obtained as a yellow powder: 0.099 g, (82%). ^{1}H NMR ($CDCl_3$; 25°C) δ 10.05 (1H, s), 8.20 (1H, s), 2.99 (t, J = 7.6 Hz, 2H), 2.92 (t, J = 7.6 Hz, 2H), 2.89 (s, 3H), 2.53 (s, 3H), 2.15 (m, 2H); ^{13}C NMR ($CDCl_3$; 25°C) δ: 166.9, 155.1, 154.9, 154.7, 149.7, 145.2, 142.3, 117.2, 33.3, 31.2, 24.6, 24.3, 22.6; MS (EI): *m/z* 227 [M + H]$^+$; Anal. Calcd. for $C_{13}H_{14}N_4$: C, 69.00; H, 6.21; N, 24.70. Found: C, 68.80; H, 6.32; N 24.80.

3-Chloromethyl-3′-methyl-5,5′-bis-1,2,4-triazine **9** [8]. A mixture of **5** (0.2 g, 1.06 mmol), TCDGU (0.46 g, 1.06 mmol) and AIBN (0.009 g, 0.05 mmol), was stirred 18 h at 78°C into degased toluene (5 mL) under argon and irradiation with a (100-W) tungsten lamp. The resulting suspension was filtered, and the solid phase washed with toluene (3 × 5 mL). After evaporation of the solvent, the residue was chromatographed on a silica gel 60 Merck (0.04–0.063 mm) column; with CH_2Cl_2/Et_2O : 9/1 as the eluent. The pure product **9** was obtained as yellow oil, which crystallizes at 4°C. The product should be kept at 4°C, without light 0.054 g (25%). ^{1}H NMR ($CDCl_3$; 25°C) δ: 10.20 (1H, s), 10.13 (1H, s), 4.99 (2H, s), 2.99 (3H, s); ^{13}C NMR ($CDCl_3$; 25°C) δ: 167.9, 165.9, 152.2, 150.4, 145.2, 144.7, 44.9, 24.2; MS (EI): *m/z* 222 [M]$^+$; Anal. Calcd. for $C_8H_7ClN_6$: C, 43.16; H, 3.14; N 37.75. Found: C, 43.50; H, 3.39; N, 36.45.

5-(6-(Bromomethyl)-pyridin-2-yl)-3-methyl-1,2,4-triazine **10** [8]. *N*-Bromosuccinimide (0.870 g, 4.89 mmol) and AIBN (0.081 g, 0.49 mmol) were added to a solution of **6** (1 g, 5.37 mmol) into CCl_4 (50 mL) under argon. The reaction mixture was stirred 75 min. under reflux and irradiation with a (100-W) tungsten lamp. After reaction, the mixture was filtered, and the solid phase was washed three times with CCl_4. After evaporation of the solvent, the residue was chromatographed on a silica gel 60 Merck (0.04–0.063 mm) column; with CH_2Cl_2/Et_2O : 9/1 as the eluent. The pure product **10** was obtained as a yellow solid: 0.436 g (31%). ^{1}H NMR ($CDCl_3$; 25°C) δ: 10.05 (s, 1H), 8.39 (d, $J = 7.8$ Hz, 1H), 7.84 (t, $J = 7.8$Hz), 7.57 (d, $J = 7.8$Hz,1H), 4.57 (s, 2H), 2.88 (s, 3H); ^{13}C NMR ($CDCl_3$; 25°C) δ 167.2, 157.8, 153.6, 152.2, 144.9, 138.8, 122.2, 33.6, 24.3; MS (CI): *m/z* 265 $[M]^+$, 185 $[M - Br]^+$, 116 $[M - Br - N_2]^+$; Anal. Calcd. for $C_{10}H_9BrN_4$: C, 45.30; H, 3.41; N, 21.10. Found: C, 45.05; H, 3.72; N, 20.98.

3-(Chloromethyl)-5-(6-methylpyridin-2-yl)-1,2,4-triazine **11** [8]. A mixture of **6** (0.020 g, 0.11 mmol), TCDGU (0.046 g, 0.11 mmol) and AIBN (0.001 g, 0.005 mmol) was stirred 24 h at 78°C into degased toluene (2 mL) under argon and irradiation with a (100-W) tungsten lamp. The resulting suspension was filtered, and the solid phase was washed with toluene (3 × 5 mL). After evaporation of the solvent, the residue was chromatographed on a silicagel 60 Merck (0.04–0.063-mm) column; with CH_2Cl_2 as the eluent. The pure product **11** was obtained as a yellow solid: 0.025 g, (10%). ^{1}H NMR ($CDCl_3$; 25°C) δ: 10.16 (s, 1H), 8.33 (d, $J = 7.8$ Hz, 1H), 7.73 (t, $J = 7.8$, 1H), 7.28 (d, $J = 7.8$ Hz, 1H), 4.90 (s, 2H), 2.60 (s, 3H); ^{13}C NMR ($CDCl_3$; 25°C) δ 165.3, 159.6, 155.2, 151.1, 146.2, 137.9, 126.9, 120.7, 45.5, 24.9; MS (EI): *m/z* 221 $[M]^+$; Anal. Calcd. for $C_{10}H_9ClN_4$: C, 54.42; H, 4.11; N, 25.30. Found: C, 54.31; H, 4.05; N 25.31.

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