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Full Paper

Phenol as a Modulator in the Chemical Reactivity of 2,4,6-Trichloro-1,3,5-triazine: Rules of the Game II*

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2,4,6-Trichloro-1,3,5-triazine (TCT) is a privileged core that has the capacity to undergo sequential nucleophilic substitution reactions. Three nucleophiles, namely phenol, thiol and amine, were studied and the preferential order of incorporation on TCT was found to be first phenol, second thiol and third amine. The introduction of phenol was achieved at −20°C. The incorporation of this nucleophile in TCT helped to replace the third 'Cl' at 35°C, which is compatible with a biological context. The atomic charges on 'Cl' calculated by theoretical approaches were consistent with the experimental findings.

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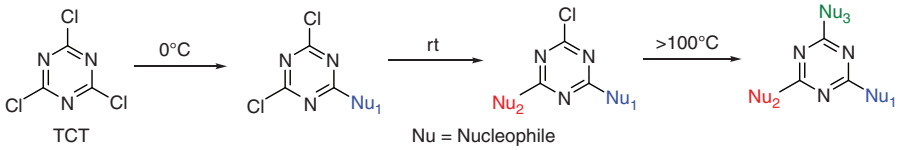
Introduction

The s-triazine, 2,4,6-trichloro-1,3,5-triazine (TCT), is one of the most privileged core units, finding applications ranging from industrial usage, such as melamine resins[1,2] and energetics,[3] to pharmaceutical molecules.[4,5] The major advantage associated with TCT is the reactivity of the 'Cl' atoms, which is easily controlled by temperature.[6,7] This feature thus allows the incorporation of nucleophiles to prepare mono-, di- and tri-substituted triazines (Scheme 1).[8–11]

Orthogonality and chemoselectivity are two common terminologies in the field of synthetic chemistry. Orthogonality was introduced in 1977 by Barany and Merrifield to explain the context of a protecting group,[12] while chemoselectivity was coined by Trost in 1983 to differentiate between reactive sites.[13] In 1985, Barany and Albericio introduced and demonstrated triorthogonality to explain the removal of different protecting groups in any sequential order.[14] We recently reported the concept of 'orthogonal chemoselectivity', which is defined as the discrimination between reactive sites in any order, and demonstrated the concept preserving TCT as the core unit.[15] Triorthogonality has been demonstrated using azide, thiol and phenol as nucleophiles. The concourse of alcohol (due



Scheme 1. Nucleophilic substitution reaction for TCT.

*This paper is dedicated to Paul Alewood for his inestimable contributions to solid-phase peptide synthesis and for his friendship as well.

to the poor reactivity and deactivation of the aromatic ring as a result of its electron-donating behaviour)[16] and amine (as once it is substituted, only one further amine can be incorporated) was not present in the previous study as these compounds restrict the triorthogonality principle.[17] However, TCT carrying amines as substituents is a key player in the biological arena.[11] Furthermore, phenol can mimic the side chain of Tyr and *a priori* should be electron withdrawing, a property that can enhance the reactivity. Given these considerations, here we examined the preferential order of incorporation of phenol, thiol and amine. We demonstrate the influence of phenol on the TCT core for undergoing further nucleophilic substitution and unveil the preferential order of incorporation of three distinct nucleophiles onto this core.

Results and Discussion

As a model, we used phenol, thiol and amine as nucleophiles (Fig. 1).

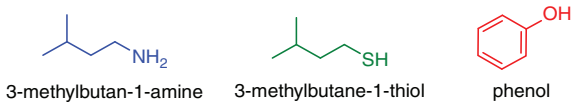
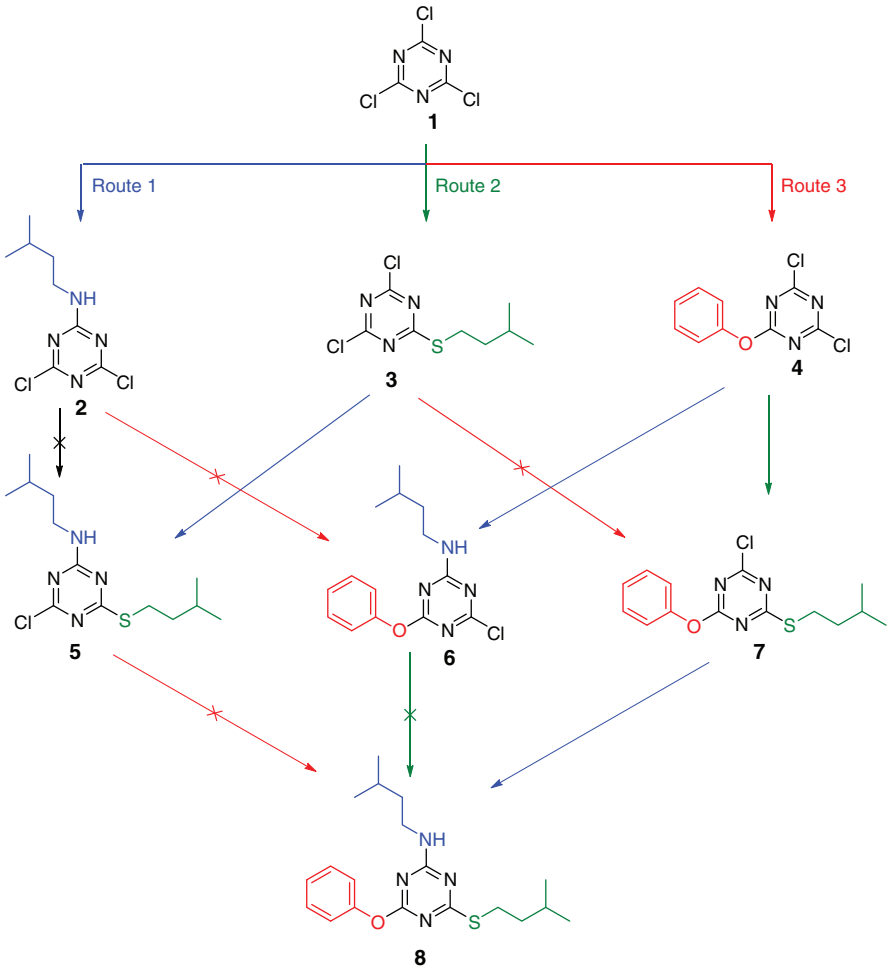


Fig. 1. Nucleophiles chosen for the study.

To study the order of nucleophile incorporation, several reactions were attempted using ethyl acetate as solvent and *N*, *N* diisopropylethyamine (DIEA) as base, as shown in Scheme 2. Three routes were tested for the synthesis of **8**, which contains phenol, thiol and amine as three substituents on the TCT core. In route 1, TCT was reacted with amine first to form an amine derivative (**2**). This was followed by thiol and then phenol, or phenol and finally thiol. In route 2, TCT was reacted with thiol first to form a thiol derivative (**3**), then followed by amine and then phenol, or phenol and then amine. In route 3, a phenol derivative (**4**) was formed first by reaction of TCT with phenol, followed by amine and thiol, or thiol and amine to form **8**. The routes are shown in Scheme 2.

Upon reaction with the above-mentioned nucleophiles at 0°C for 30 min, TCT formed di-chloro substituted triazine (DST). When amine and thiol were used, the reaction was completed in 30 min, as monitored by thin layer chromatography (TLC), affording an amine and thiol derivative (**2** and **3**) in high yields (see Figs S1–S6, Supplementary Material). However, in the case of the synthesis of a phenol derivative (**4**), two spots were formed on TLC. The reaction condition for **4** was further optimized by lowering the temperature to −20°C, which yielded **4** in high purity and good yield (as confirmed by HPLC) (see Figs S7–S9, Supplementary Material). This result was explained by the high nucleophilicity of phenol caused by the greater stability of the phenoxide ion compared with that of phenol



Scheme 2. A priori approaches to form compound **8**.

alone. This result was the first indication of support for the hypothesis regarding the suitability of phenol to enhance reactivity. After the synthesis of DST, we addressed the preparation of mono-chloro substituted triazine (MST). The reactions were performed at room temperature (rt) using the same conditions as explained previously. The next possibility for an amine derivative (**2**) was the reaction with thiol or phenol. Therefore, **2** was reacted with thiol and phenol at rt for 3 h using ethyl acetate as solvent. However, no product was observed. The reaction was then stirred at rt overnight, but still only the amine derivative (**2**) was present in the reaction mixture. This agrees well with our earlier findings where we reported once an amine is incorporated, it is not possible to incorporate any other nucleophile except another amine owing to its high nucleophilicity.[15] Thus, route 1 was ruled out for the synthesis of **8**. In parallel, the thiol derivative (**3**) was left to react with amine and phenol at rt for 3 h using the reaction conditions mentioned before. These conditions led to the formation of a thiol-amine derivative (**5**) (see Figs S10–S12, Supplementary Material) and a thiol-phenol derivative (**7**) (see Figs S16–S18, Supplementary Material). Compound **5** was obtained in good yield and high purity, while poorer results were obtained for **7**. TLC monitoring showed a spot corresponding to product **7**, in addition to several other spots including the starting material (**3**). It was concluded that these results arise from the high reactivity of phenol. Therefore, another attempt was made to conduct the reaction at 0°C for 3 h. Under these conditions, only thiol derivative (**3**) was observed by TLC. Thus, the thiol-phenol route is not a suitable approach for the synthesis of **8**.

The reaction of the thiol-amine derivative (**5**) with phenol was first carried out for the third position to form **8** at >60°C. Several attempts were made at a higher temperature, as TCT usually requires a more elevated temperature for the replacement of the third 'Cl'. However, no product was observed. These results are consistent with our earlier work, in that no nucleophile can be incorporated after the amine has been introduced. Therefore, this route was ruled out for the synthesis of **8**.

Following route 3, compound **4** was reacted with amine and thiol separately for its incorporation at position 2 to form the phenol-amine derivative (**6**) (see Figs S13–S15, Supplementary Material) and phenol-thiol derivative (**7**). The reaction was attempted at rt for 3 h using the same reaction condition as earlier. Compounds **6** and **7** were obtained in good yield and high purity. Replacement of the third 'Cl' in **6** was attempted with a thiol at 35°C. However, no product was observed. The reaction was also attempted at >60°C. As expected, no product formation was detected, since amine had already been incorporated onto the TCT core. However, in the case of **7**, the reaction was carried out at 35°C for 12 h with amine as nucleophile. TLC showed complete consumption of **7**, affording the formation of **8** (see Figs S19–S21, Supplementary Material).

Theoretical Calculations

To understand the electronic effect on TCT and several intermediates (as shown in Scheme 2) for the synthesis of **8**, including the charges carried by 'Cl' after each substituent, we performed a density functional theory (DFT) geometry optimization using the *Gaussian09* program package and employing the B3LYP (Becke three parameters Lee–Yang–Parr exchange correlation functional) and the 6–311G++(d,p) basis set in the gas phase.[18] Natural bond orbital (NBO) calculations were performed on the optimized geometries to determine the atomic charges.[19] The charges carried by 'Cl' in each case were compared (Table 1).

Table 1. Charges carried by 'Cl' in the molecules

Compound no.	Charges carried by 'Cl'		
	First 'Cl'	Second 'Cl'	Third 'Cl'
1	0.088	0.088	0.088
2	-	0.049	0.049
3	-	0.062	0.062
4	-	0.069	0.069
5	-	-	0.025
6	-	-	0.030
7	-	-	0.044

The atomic charges carried by 'Cl' in each molecule reveals important details about the chemical reactivity of each one upon reaction with nucleophiles.[15,17] In the case of **1**, the charge carried by 'Cl' was 0.088, which accounts for the high reactivity of TCT when treated with nucleophiles. Hence, the reaction was carried out at lower temperature (0°C or even lower). Upon the first substitution, the charges present on 'Cl' decreased, lowering the reactivity of DST. In the case of **2**, **3** and **4**, the charges decreased to 0.049, 0.062 and 0.069 respectively. Therefore, the conditions for further reactions required a longer time and higher temperature (rt in this case). Of **2**, **3** and **4**, the former carried the least charge, whereas **4** carried the highest, thereby indicating the high reactivity of this compound. Based on these results, the incorporation of phenol as the first substituent emerged as the best approach to maintain the reactivity of triazine core.

To further determine the preferential order of substitution, we compared the charges carried by last 'Cl' present on disubstituted TCT. The charge carried by 'Cl' in the case of **5**, **6** and **7** was 0.025, 0.030 and 0.044 respectively (Table 1). Of all the derivatives, **7** showed the highest charge, thus confirming it as the best choice to afford **8**. In contrast, **5** and **6** might require elevated temperature or harsh conditions to afford **8**. Our findings therefore show that the ideal order to incorporate the nucleophiles was first phenol, second thiol and third amine.

Conclusion

Here we report on the preferential incorporation of nucleophiles (phenol, amine and thiol) onto TCT. The order was found to be first phenol, second thiol and third amine. Taking advantage of the high chemical reactivity of phenol, the third replacement with amine was done at 35°C, a temperature compatible with biological systems. However, the presence of amine on TCT blocks the incorporation of phenol, despite its high reactivity. A comparison of these results with our previous findings[15] reveals that both alcohol and phenol show the same trend of incorporation. However, the presence of phenol facilitates the incorporation of the rest of the nucleophiles. This is significant in the case of amine incorporation in the third position, which was carried out at 35°C instead of 75°C when the alcohol was present. Theoretical calculations were performed and compared with the experimental findings. NBO calculations helped to determine the atomic charges of 'Cl' in each molecule. The charges found supported the experimental results, thus validating the findings. Replacement of the third 'Cl' at 35°C extends the use of TCT beyond a triorthogonal linker in the biological

context, thereby paving the way for nucleophilic reactions involving various peptides, antibodies and drugs.

Experimental

Materials and Methods

2,4,6-Trichloro-1,3,5-triazine (cyanuric chloride, TCT), 3-methylbutan-1-amine, 3-methylbutane-1-thiol, phenol and diisopropylethylamine were purchased from Sigma-Aldrich (Sigma-Aldrich, Germany). The solvents used were of analytical and HPLC reagent grade. Magnetic resonance spectra (^{1}H and ^{13}C) were recorded on a Bruker 400 MHz instrument. Chemical shift values were reported in δ units (ppm) using TMS as internal standard. Follow-up of the reactions and checks of the purity of the compound was done by TLC on silica-gel-protected aluminium sheets 60 F254 (Merck), and the spots were detected by exposure to UV light at $\lambda = 254$ nm. Analytical HPLC was performed on an Agilent 1100 system using a Phenomenex C_{18} column (3 µm, 4.6 × 50 mm). Data were processed using *Chemstation* software. Buffer A: 0.1 % TFA in H_2O; and buffer B: 0.1 % TFA in CH_3CN were used in HPLC. Liquid chromatography–mass spectrometry (LCMS) was performed on Shimadzu 2020 UFLC using a YMC-Triart C_{18} (5 µm, 4.6 × 150 mm) column and data processing was carried out using *Laboratory Solution* software. Buffer A: 0.1 % formic acid in H_2O; and buffer B: 0.1 % formic acid in CH_3CN were used.

Synthesis of 4,6-Dichloro 2-Substituted s-Triazine (DST)

TCT (50 mg, 0.27 mmol) was dissolved in EtOAc (1 mL) and cooled to 0°C for 5 min. The nucleophile (0.27 mmol) was then added to the above solution with stirring, followed by the addition of DIEA (47 µL, 0.27 mmol). The reaction was stirred at 0°C (−20°C in the case of phenol) for 30 min. The progress of the reaction was monitored by TLC (EtOAc/hexane as mobile phase) until no starting material was observed. The solution was then concentrated to dryness, and the residue was dissolved in EtOAc and washed several times with water to remove DIEA salts. The organic layer was collected, dried over $MgSO_4$, filtered and concentrated to afford pure product, which was used for the next step without further purification.

4,6-Dichloro-N-isopentyl-1,3,5-triazin-2-amine (**2**)

Off-white semi-solid; HPLC [30–95 % of CH_3CN (0.1 % TFA/H_2O (0.1 % TFA) over 15 min] $t_R = 7.6$ min; ^{1}H NMR (400 MHz, $CDCl_3$): 0.90 (d, 2H, $J = 6.8$ Hz, $2CH_3$), 1.40 (m, 2H, CH_2), 1.60 (m, 1H, CH), 3.4 (m, 2H, CH_2-N), 5.7 (s, -NH); ^{13}C NMR (100 MHz, $CDCl_3$): 22.5 ($2CH_3$), 25.7 (CH), 29.7 (CH_2), 39.1 (CH_2-N), 166.5 (N-C=N, triazine moiety), 166.8 (Cl^-C=N, triazine moiety).

2,4-Dichloro-6-(isopentylthio)-1,3,5-triazine (**3**)

Yellowish oil; HPLC [30–95 % of CH_3CN (0.1 % TFA/H_2O (0.1 % TFA) over 15 min] $t_R = 10.5$ min; ^{1}H NMR (400 MHz, $CDCl_3$): 0.90 (d, 6H, $J = 6.4$ Hz, $2CH_3$), 1.55 (m, 2H, CH_2), 1.65 (m, 1H, CH), 3.1 (m, 2H, CH_2-S); ^{13}C NMR (100 MHz, $CDCl_3$): 21.2 ($2CH_3$), 26.5 (CH), 28.3 (CH_2-S), 36.2 (CH_2), 169.0 (Cl^-C=N, triazine), 185.6 (S-C=N).

2,4-Dichloro-6-phenoxy-1,3,5-triazine (**4**)

Off-white solid; HPLC [30–95 % of CH_3CN (0.1 % TFA/H_2O (0.1 % TFA) over 15 min] $t_R = 6.7$ min; ^{1}H NMR (400 MHz, $CDCl_3$): 7.10 (d, 2H, $J = 1.6$ Hz, CH, Ar), 7.30 (t, 1H, $J = 1.6$ Hz, CH, Ar), 7.40 (t, 2H, $J = 2.0$ Hz, CH, Ar); ^{13}C NMR (100 MHz, $CDCl_3$): 114.2 (C_2,C_6), 120.0 (C_4), 125.9 (C_3,C_5), 128.9 (C-O), 170.0 (Cl^-C=N, triazine), 172.0 (O-C=N, triazine).

Synthesis of 2-Chloro-4,6-disubstituted s-triazine (MST)

Nucleophile (0.27 mmol) was added to DST (0.27 mmol) in EtOAc (1 mL), followed by addition of DIEA (47 µL, 0.27 mmol). The reaction was stirred at rt for 3 h. The progress of the reaction was monitored by TLC (ethyl acetate/hexane as mobile phase) until the complete consumption of the starting material. The solution was concentrated to dryness and the residue was dissolved in EtOAc and washed several times with water to remove DIEA salts. The organic layer was collected, dried over $MgSO_4$, filtered and concentrated to afford pure product, which was used for the next step without further purification.

4-Chloro-N-isopentyl-6-(isopentylthio)-1,3,5-triazin-2-amine (**5**)

Creamy oil; HPLC [30–95 % of CH_3CN (0.1 % TFA/H_2O (0.1 % TFA) over 15 min] $t_R = 10.7$ min; ^{1}H NMR (400 MHz, $CDCl_3$): 0.86 (m, 12H, $4CH_3$), 1.39 (m, 2H, 2CH), 1.51 (m, 4H, $2CH_2$), 3.00 (m, 2H, CH_2), 3.36 (m, 2H, CH_2), 5.28 (brs, -NH); ^{13}C NMR (100 MHz, $CDCl_3$): 21.3 (CH_3), 21.5 (CH_3), 26.5 (CH), 26.6 (CH), 27.0 (CH_2-S), 27.2 (CH_2), 37.4 (CH_2), 38.1 (CH_2-N), 161.7 (-N-C=N, triazine), 178.2 (Cl^-C=N, triazine), 179.2 (-S-C=N, triazine).

4-Chloro-N-isopentyl-6-phenoxy-1,3,5-triazin-2-amine (**6**)

Off-white solid; HPLC [30–95 % of CH_3CN (0.1 % TFA/H_2O (0.1 % TFA) over 15 min] $t_R = 9.1$ min; ^{1}H NMR (400 MHz, $CDCl_3$): 0.80 (d, 6H, $J = 6.6$ Hz, $2CH_3$), 1.45 (m, 2H, CH_2), 1.55 (m, 1H, CH), 3.27 (m, 2H, CH_2), 7.05–7.33 (m, 5H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): 22.5 (CH_3), 25.7 (CH), 38.6 (CH_2), 39.1 (CH_2-O), 122.1 (C_2,C_6), 124.9 (C_4), 129.1 (C_3,C_5), 152.5 (Ph-O, phenoxy), 167.4 (Cl^-C=N, triazine), 175.4 (-O-C=N, triazine), 179.7 (PhO-C=N, triazine).

2-Chloro-4-(isopentylthio)-6-phenoxy-1,3,5-triazine (**7**)

Yellowish semi-solid; HPLC [30–95 % of CH_3CN (0.1 % TFA/H_2O (0.1 % TFA) over 15 min] $t_R = 12.4$ min; ^{1}H NMR (400 MHz, $CDCl_3$): 0.90 (d, 6H, $2CH_3$), 1.50 (m, 2H, CH_2), 1.60 (m, 1H, CH), 3.0 (m, 2H, CH_2), 7.10–7.40 (m, 5H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): 21.1 (CH_3), 26.4 (CH), 27.7 (CH_2), 36.9 (CH_2-O), 120.5 (C_2,C_6), 124.9 (C_4), 128.4 (C_3,C_5), 150.7 (Ph-O, phenoxy), 170.0 (Cl^-C=N, triazine), 172.6 (PhO-C=N, triazine), 185.6 (-S-C=N, triazine).

Synthesis of N-isopentyl-4-(isopentylthio)-6-phenoxy-1,3,5-triazin-2-amine (**8**)

Isopentyl amine (0.27 mmol) was added to a stirred solution of MST (0.27 mmol) in EtOAc (1 mL), followed by addition of DIEA (0.27 mmol). The reaction mixture was heated to 35°C for 8 h. The progress of the reaction was monitored by TLC (ethyl acetate/hexane as mobile phase) until the complete consumption of the starting material. Solvent was removed under vacuum, and the residue was dissolved in EtOAc (5 mL). The organic layer was washed several times with water to remove DIEA salts. The organic layer was collected, dried over $MgSO_4$, filtered and concentrated to afford pure product.

Brownish semi-solid; HPLC [30–95 % of CH_3CN (0.1 % TFA/H_2O (0.1 % TFA) over 15 min] $t_R = 13.3$ min; ^{1}H NMR

(400 MHz, $CDCl_3$): 0.85 (m, 12H, $4CH_3$), 1.38 (m, 2H, CH), 1.45 (m, 4H, $2CH_2$), 2.88 (m, 2H, CH_2), 3.37 (m, 2H, CH_2), 5.82 (brs, NH), 7.05–7.30 (m, 5H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): 21.2 (CH_3), 21.4 (CH_3), 26.4 (CH), 26.6 (CH), 27.1 (CH_2-S), 27.3 (CH_2), 38.2 (CH_2), 38.4 (CH_2-N), 120.9 (C_2,C_6), 124.4 (C_4), 128.2 (C_3,C_5), 151.1 (Ph-O, phenoxy), 164.6 (-N-C=N, triazine), 168.6 (Ph-O-C=N, triazine, 182.6 (-S-C=N, triazine).

Theoretical Calculations

The models were drawn using *GaussView05*,[20] and all quantum chemical calculations were performed using *Gaussian09* with B3LYP functional and 6–311G++(d,p) basis set. No solvent corrections were made with these calculations. Vibration analysis showed that the optimized structure indeed represented a minimum on the potential energy surface (no negative eigenvalues). NBO calculations were performed on the optimized geometries to determine atomic charges.

Supplementary Material

HPLC, ^{1}H NMR, and ^{13}C NMR spectra and optimized geometry coordinates for NBO calculations for all compounds are available on Journal's website.

Conflicts of Interest

The authors declare no conflicts of interest.

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