Preparation of Several Active \textit{N}-Chloro Compounds from Trichloroisocyanuric Acid

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Abstract: A very simple method for the preparation of several active \textit{N}-chloro compounds that have extensive applications in organic synthesis, industry, and medicine has been developed. Tetrachloroglycolurils, chloramine-T, \textit{N}-chlorosaccharin, \textit{N}-chlorosuccinimide, \textit{N}-chlorophthalimide, \(\textit{N},\textit{N}^{\prime}\)-dichlorophenobarbital, and \(\textit{N},\textit{N}^{\prime}\)-dichlorobarbital have generally great- er thermal stability than other known chloroamides, making them also good to excellent.

Key words: chlorinated compounds, imides, amides, halogenation, trichloroisocyanuric acid

Trichloroisocyanuric acid (TCCA) was first synthesized in 1902. The worldwide production of TCCA has increased considerably for its use in disinfecting swimming pools, cleaning and sterilizing bathrooms, and laundry. Recently, TCCA has also found many uses in organic synthesis, as shown by its treatment as the subject of reviews indicating the vast number of applications of TCCA in organic transformations.\textsuperscript{1,2}

Following the synthesis of \textit{N}-chloroamides in methanol and \(\textit{N},\textit{N}^{\prime}\)-dichloroamines in dichloromethane at 15 °C with TCCA,\textsuperscript{3,4} we decided to prepare a series of valuable active \textit{N}-chloro compounds from this relatively safe reagent in water as a green solvent at room temperature. These compounds, which comprise tetrachloroglycolurils, chloramine-T, \textit{N}-chlorosaccharin, \textit{N}-chlorosuccinimide, \textit{N}-chlorophthalimide, \(\textit{N},\textit{N}^{\prime}\)-dichlorophenobarbital, and \(\textit{N},\textit{N}^{\prime}\)-dichlorobarbital, have many uses in organic synthesis, industry, and medicine.

Di- and tetrachloroglycolurils were found to have good bactericidal activity against test organisms. Chloroglycolurils, prepared by chlorine gas,\textsuperscript{5–9} have generally greater thermal stability than other known chloroamides, making them very useful as impregnating agents for clothing; in addition, with a higher percentage of active chlorine, they are useful neutralizers or antivesicants for mustard gas and other vesicant vapors. Chlorinated glycolurils have been prepared as a source of chlorine for controlling algae in industrial water and sewage treatment.\textsuperscript{10} 1,3,4,6-Tetrachloro-3a,6a-diphenylglycoluril, known as iodogen (2d) (see Scheme 1 and Table 1), was first used by Fraker and Speck in 1978 for the radiiodi-

\[ \text{R} \quad \text{H} \quad \text{Me} \quad \text{Et} \quad \text{Ph} \quad \text{3-BrC}_6\text{H}_4 \quad \text{4-BrC}_6\text{H}_4 \quad \text{3-CIC}_6\text{H}_4 \quad \text{4-CIC}_6\text{H}_4 \]

\textbf{Scheme 1} Preparation of tetrachloroglycolurils

\begin{table}[h]
\begin{tabular}{|c|c|c|c|c|}
\hline
Entry & Product R & Time (h) & Yield (\%) & Mp (°C) \\
\hline
1 & 2a & H & 3 & 97 & >275 (dec) >280 (dec) \\
2 & 2b & Me & 1.5 & 95 & 220–223 218–219 \\
3 & 2c & Et & 12 & 91 & 194–198 – \\
4 & 2d & Ph & 8 & 96 & 249–252 247–247.5 \\
5 & 2e & 3-BrC\textsubscript{6}H\textsubscript{4} & 5 & 93 & 220–224 – \\
6 & 2f & 4-BrC\textsubscript{6}H\textsubscript{4} & 3 & 95 & 210–214 – \\
7 & 2g & 3-CIC\textsubscript{6}H\textsubscript{4} & 7 & 92 & 231–235 – \\
8 & 2h & 4-CIC\textsubscript{6}H\textsubscript{4} & 4 & 95 & 217–220 – \\
\hline
\end{tabular}
\end{table}

\textbf{Table 1} Chlorination of Glycolurils with TCCA in Water at Room Temperature To Give the Corresponding Tetrachloroglycolurils

\textit{N}-Chloro-p-toluenesulfonamide, commonly known as chloramine-T, has diverse chemical properties. Chloramine-T behaves as a source of both ‘halonium’ ion as well as a ‘nitrogen anion’; as a result, this reagent reacts with a vast range of functional groups, leading to an array of mo-
lecular transformations: aminohydroxylation, aminohalo-
genation of alkenes, allylic aminations, and aziridination.\textsuperscript{20} According to the literature, chloramine-T was first prepared by Chattaway by the action of sodium hydroxide upon \( N,N' \)-dichloro-\( p \)-toluenesulfonamide.\textsuperscript{21} However, we have synthesized it directly and simply from \( p \)-toluenesulfonamide and TCCA in the presence of sodium hydroxide (Table 2, entry 7).

Table 2 Preparation of Other Active \( N \)-Chloro Compounds by Use of TCCA in Water at Room Temperature

<table>
<thead>
<tr>
<th>Entry Product</th>
<th>Time (h)</th>
<th>Yield (%)</th>
<th>Mp (°C) (found)</th>
<th>Mp (°C) (Lit.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 ( N )-chlorosaccharin</td>
<td>24</td>
<td>60</td>
<td>146–148</td>
<td>148–151\textsuperscript{13}</td>
</tr>
<tr>
<td>2 ( N,N' )-dichlorophenobarbital</td>
<td>1</td>
<td>89</td>
<td>147–150</td>
<td>147–152\textsuperscript{24a}</td>
</tr>
<tr>
<td>3 ( N,N' )-dichlorobarbital</td>
<td>1</td>
<td>65</td>
<td>120–124</td>
<td>125–127\textsuperscript{24c}</td>
</tr>
<tr>
<td>4 ( N )-chlorophthalimide</td>
<td>1</td>
<td>98</td>
<td>180–182</td>
<td>181–183\textsuperscript{24d}</td>
</tr>
<tr>
<td>5\textsuperscript{a} ( N )-chlorosuccinimide</td>
<td>1</td>
<td>95 151–152 150–151\textsuperscript{24c}</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| 6\textsuperscript{b} \( N \)-chlorosuccinimide | 1 | 87  
| 7 \( p \)-dichlorophenobarbital       | 1        | 93        | 178–180        | 167–169\textsuperscript{21} |

\textsuperscript{a} In the presence of AcOH.

\textsuperscript{b} In the presence of NaHSO\(_4\) (2 equiv).

\( N \)-Chlorosaccharin (NCSac) (Table 2, entry 1) is of great importance in synthetic organic chemistry, since its chlo-
rine is highly electrophilic and it is commonly used in di-
verse organic transformations, such as halogenation, cohalogenation, addition, oxidation, and allylic and ben-
yllic halogenation.\textsuperscript{22} \( N \)-Chlorosaccharin has been pre-
pared from sodium saccharinate in many different ways; the latest method has used potassium chloride in the pres-
ence of Oxone\textsuperscript{20}, resulting in moderate yields.\textsuperscript{23} Taking int
to account that Oxone\textsuperscript{20} is an expensive reagent with low atom efficiency, we synthesized \( N \)-chlorosaccharin di-
rectly from saccharin and TCCA in a mildly alkaline aqueous solution (Table 2, entry 1).

According to a report, \( N,N' \)-dichlorophenobarbital (Table 2, entry 2) has been prepared by use of Clorox\textsuperscript{26} in methanol and studied as a potential antimalarial.\textsuperscript{24a} The synthesis of \( N,N' \)-dichlorobarbital (entry 3) has been re-
ported to be by reaction of barbital either with tert-butyl hypochlorite (TBH) in dichloromethane at low tem-
peratures or with chlorine gas.\textsuperscript{24b, c} We have succeeded in pre-
paring these compounds under green reaction conditions (entries 2 and 3). Experiments showed that for the \( N \)-chlo-
rination of barbital, the reaction did not proceed in the ab-
sence of a base.

\( N \)-Chlorophthalimide (Table 2, entry 4) is a useful reagent for chlorination,\textsuperscript{25} and has been prepared by several meth-
ods: by the reaction of phthalimide and tert-butyl hy-
pochlorite in tert-butyl alcohol (74.6% yield),\textsuperscript{26} by the action of chlorine gas on either a metal salt of phthalimide in chlorinated solvents, or from phthalimide in dichlo-
romethane in the presence of 4-vinylpyridine–divinylben-
zene copolymer and quinoline (at \(-10 \text{ to } 50 \, ^\circ \text{C})\textsuperscript{27}. Instead, we treated both phthalimide and its potassium salt with TCCA in water without adding any organic compound. It should be noted that for the chlorination of the potassium salt of phthalimide, it was necessary to add TCCA slowly to its water suspension at \( 0 \, ^\circ \text{C}; this led to the color of the white suspension changing to a brownish one, which might be interpreted as a sign of slight decomposition of phthalimide, as has been mentioned in a patent.\textsuperscript{28} However, when phthalimide was used directly, the reaction pro-
ceeded in excellent yield without any change in color (Table 2, entry 4).

\( N \)-Chlorosuccinimide (NCS) (Table 2, entries 5 and 6) is a versa
tile reagent, the significance of which is not limited to chlo-
ring and oxidation. It mediates or catalyzes many chemical reactions, including halocyclizations, the for-
mation of heterocyclic systems and new carbon–carbon bonds, rearrangements, and functional-group trans-
formations.\textsuperscript{29} \( N \)-Chlorosuccinimide has previously been syn-
thesized from tert-butyl hypochlorite (35.2% yield)\textsuperscript{26} and chlorine gas.\textsuperscript{27} In our laboratory, several experiments were attempted to optimize the preparation of this com-
pound. IR analysis showed that no reaction occurred when a water mixture of succinimide and TCCA stirred at room temperature for 24 hours. The reaction was not successful under mild alkaline conditions either (by addition of NaHCO\(_3\), Na\(_2\)CO\(_3\), or K\(_2\)CO\(_3\)). It was finally realized that the reaction proceeds in the presence of an acid: sodium hydrogen sulfate (entry 6) or acetic acid (entry 5).

In summary, taking into account the extensive applica-
tions of active \( N \)-chloro compounds in organic reactions and to overcome the experimental difficulties when sodium hypochlorite, tert-butyl hypochlorite, and toxic chlo-
rine gas are used, we have developed a benign procedure for the synthesis of such compounds. To achieve this goal, the room temperature chlorination of the corresponding starting materials was effected under mild reaction condi-
tions with the aid of the nontoxic, easily handled, and in-
expensive reagent TCCA. Furthermore, we have used the universal solvent water instead of organic solvents such as dichloromethane and methanol. We hope this work will stimulate further developments in organic synthesis and be of value to chemists both in academia and in industry.

In all cases, yields refer to isolated pure products. Benzils and gly-
colurils were prepared in our laboratory by conventional methods. The well-known \( N \)-chloro compounds chloramine-T, \( N \)-chlorosaccharin, \( N \)-chlorosuccinimide, \( N \)-chlorophthalimide, \( N,N' \)-dichlo-
rorobartial, and \( N,N' \)-dichlorophenobarbital, as well as benzils, were identified by comparing their IR and \(^1\)H NMR spectra or melting points with those of the authentic samples. \( N \)-Chloroglycolurils were characterized by their spectral data (IR and NMR) and ele-
mental analysis. If needed, solid starting materials were ground and the suspension stirred well for the chlorination to proceed.

Melting points were determined on a Stuart Scientific SMP3 appara
tus and are uncorrected. IR spectra were recorded on a Perkin-
Elmer FTIR spectrometer of samples prepared as Nujol mulls. NMR spectra were recorded of samples in CDCl\(_3\) (unless stated oth-
erwise) on Jeol FX90Q and Bruker 300 FT NMR spectrometers. Elemental analyses were carried out on a Heraeus CHNO-Rapid instrument by Research Institute of Petroleum Industry laboratory.

**Starting Materials**

**Aromatic Benzoins and Benzils**
The 3- and 4-chloro derivatives of the appropriate benzils were obtained directly upon condensation of the corresponding aldehydes in the presence of NaCN in EtOH.

**3-Bromobenzil**
Yellow solid.
IR (Nujol): 3090, 1665, 1586, 1312, 1173, 833, 724 cm⁻¹.
Yellow solid.

**4-Chlorobenzil**
White solid; slightly soluble in H₂O.
IR (Nujol): 3076, 1673, 1582, 1260, 897, 749 cm⁻¹.

**3-Chlorobenzil**
Yellow solid.
IR (KBr): 3093, 1661, 1586, 1210, 834, 765 cm⁻¹.
Yellow solid.

**Aromatic Glycolurils**

**Glycoluril (1a)**
White solid; slightly soluble in H₂O.
IR (Nujol): 3184, 1698, 1510, 1337, 1112, 721 cm⁻¹.

**Dimethylglycoluril (1b)**
Off-white solid; slightly soluble in DMSO.
IR (Nujol): 3237, 1727, 1667, 1510, 1163, 723 cm⁻¹.

**Diethylglycoluril (1c)**
Urea (0.6 g, 10 mmol) was dissolved in H₂O (20 mL), and then 36% HCl (0.5 mL) was added. The soln was stirred at r.t. and hexane-3,4-dione (0.5 g, 5 mmol) was added dropwise. The soln was stirred at r.t. for 12 h. The precipitate was filtered, washed with H₂O (3 × 10 mL), and then dried in air.
Yield: 222 mg (20%); brownish powder (slightly soluble in DMSO).

**Aromatic Glycolurils; Typical Procedure**
A mixture of urea (0.12 g, 2 mmol), benzil (0.21 g, 1 mmol), TCA (0.5 g), and toluene (20 mL) was refluxed for 12 h. The product was filtered and washed with an EtOH–MeOH mixture (9:1; 3×).

**Diphenylglycoluril (1d)**
White solid.
IR (Nujol): 3228, 3066, 1713, 1681, 1676, 1494, 1141, 773, 695 cm⁻¹.
¹H NMR (90 MHz, DMSO-d₆): δ = 7.06 (s, 10 H, H₋₋₋₋), 7.98 (s, 4 H, NH).
¹³C NMR (23 MHz, DMSO-d₆): δ = 81.7, 121.5, 130.1, 130.4, 131.3, 141.2, 160.8.

**Bis(3-bromophenyl)glycoluril (1e)**
White solid.
IR (Nujol): 3230, 1722, 1682, 1584, 1136, 725 cm⁻¹.
¹H NMR (300 MHz, DMSO-d₆): δ = 6.95–7.38 (2 d, J = 8.5 Hz, 8 H, H₋₋₋₋), 7.90 (s, 4 H, NH).
¹³C NMR (75 MHz, DMSO-d₆): δ = 81.7, 121.8, 129.7, 130.9, 138.2, 160.9.

**Bis(3-chlorophenyl)glycoluril (1f)**
White solid.
IR (Nujol): 3233, 1698, 1510, 1337, 1112, 721 cm⁻¹.
¹H NMR (90 MHz, DMSO-d₆): δ = 7.40–7.90 (dd).
¹³C NMR (23 MHz, DMSO-d₆): δ = 81.2, 127.4, 128.9, 132.6, 137.2, 160.3.

**Bis(p-chlorophenyl)glycoluril (1h)**
White solid.
IR (Nujol): 3228, 1683, 1599, 1098, 724 cm⁻¹.
¹H NMR (90 MHz, DMSO-d₆): δ = 7.01–7.26 (2 d, J = 5.8 Hz, 8 H, H₋₋₋₋), 7.74 (s, 4 H, NH).
¹³C NMR (23 MHz, DMSO-d₆): δ = 8.8 Hz, 8 H, H₋₋₋₋), 7.90 (s, 4 H, NH).
¹³C NMR (23 MHz, DMSO-d₆): δ = 81.2, 127.4, 128.9, 132.6, 137.2, 160.3.

**Active N-Chloro Compounds**

**Tetrachlorodiphenylglycoluril (2d); Typical Procedure**
A well-stirred suspension of a mixture of diphenylglycoluril (1d; 0.294 g, 1 mmol) and NaOAc (0.6 g) in H₂O (10–15 mL) was treated with TCCA (0.355 g, 1.5 mmol). After completion of the reaction (monitored by IR analysis), the resulting white solid was filtered, washed with H₂O (3×), and dried to give the product; yield: 272 mg (97%); white solid.
IR (Nujol): 3233, 1698, 1510, 1337, 1112, 721 cm⁻¹.
¹H NMR (300 MHz, DMSO-d₆): δ = 7.03–7.40 (m, 8 H, H₋₋₋₋), 7.98 (s, 4 H, NH).
¹³C NMR (75 MHz, DMSO-d₆): δ = 81.7, 121.8, 129.7, 130.9, 138.2, 160.9.

**Tetrachloroglycoluril (2a)**
Yield: 272 mg (97%); white solid.
IR (Nujol): 3230, 1722, 1682, 1584, 1136, 725 cm⁻¹.
¹H NMR (90 MHz, DMSO-d₆): δ = 7.01–7.26 (2 d, J = 5.8 Hz, 8 H, H₋₋₋₋), 7.74 (s, 4 H, NH).
¹³C NMR (23 MHz, DMSO-d₆): δ = 81.2, 127.4, 128.9, 132.6, 137.2, 160.3.
**Tetrachlorodimethylglycoluril (2b)**
Yield: 286 mg (93%); white solid.
IR (Nujol): 1767, 1747, 1344, 1160, 730 cm⁻¹.
¹H NMR (90 MHz, CDCl₃): δ = 1.86 (s, CH₃).
Anal. Calcd for C₈H₁₀Cl₄N₄O₂: C, 28.6; H, 3.0; N, 16.6. Found: C, 28.4; H, 2.9; N, 16.3.

**Tetrachlorodiethylyglycoluril (2c)**
Yield: 300 mg (91%); white solid.
IR (Nujol): 1781, 1769, 1330, 1142, 772 cm⁻¹.
¹H NMR (90 MHz, CDCl₃): δ = 2.07 (t, J = 7.5 Hz, 3 H, CH₂), 2.40 (q, J = 7.6 Hz, 2 H, CH₂).
¹³C NMR (23 MHz, CDCl₃): δ = 29.0; H, 2.3; N, 12.7.

**Anal. Calcd for C₆H₆Cl₄N₄O₂: C, 23.4; H, 2.0; N, 18.2. Found: C, 23.2; H, 2.0; N, 18.3.**

**N-Chlorosuccinimide**
A suspension of succinimide (0.59 g, 6 mmol) in H₂O (4 mL) and glacial AcOH (2 mL) was treated with TCCA (0.468 g, 2.0 mmol) and stirred at r.t. for 1 h. Then the product was extracted with CHCl₃ (3 × 10 mL), and the solid was dried (MgSO₄), filtered, and evaporated.
Yield: 126 mg (95%); colorless crystalline solid; mp 151–152 °C.
IR (Nujol): 3627, 3067, 1769, 1726, 1493, 1449, 1379, 1293, 1186, 1140, 818, 759 cm⁻¹.
¹H NMR (90 MHz, CDCl₃): δ = 2.88 (s, CH₂).

**N,N'-Dichlorophenobarbital**
Barbital (0.184 g, 1 mmol) and NaHCO₃ (0.6 g, 0.0083 mmol) were mixed in H₂O (5 mL); then TCCA (0.176 g, 0.76 mmol) was added and the mixture was allowed to stir for 1 h at r.t. Then the solid was filtered, washed with H₂O, dried, and recrystallized from HCl to give the pure product.
Yield: 267 mg (89%); white solid; mp 147–150 °C.
IR (Nujol): 3627, 3067, 1769, 1726, 1493, 1449, 1379, 1293, 1186, 1140, 818, 759 cm⁻¹.
¹H NMR (90 MHz, CDCl₃): δ = 0.96 (t, J = 7.1 Hz, 3 H, CH₂), 2.54 (q, J = 7.1 Hz, 2 H, CH₂), 7.13–7.45 (m, 5 H, Harom).

**N,N'-Dichlorobarbital**
Barbital (0.184 g, 1 mmol) and NaHCO₃ (0.6 g, 0.0083 mmol) were mixed in H₂O (5 mL); then TCCA (0.176 g, 0.76 mmol) was added and the mixture was allowed to stir for 1 h at r.t. The solid was filtered, washed with H₂O (2×), and dried.
Yield: 164 mg (65%); white solid; mp 120–124 °C.
IR (Nujol): 1777, 1718, 1580, 1352, 1145, 823, 708 cm⁻¹.
¹H NMR (90 MHz, CDCl₃): δ = 0.82 (t, J = 7.3 Hz, 3 H, CH₂), 2.11 (q, J = 7.3 Hz, 2 H, CH₂).

**N-Chlorosaccharin**
Saccharin (0.183 g, 1 mmol) and NaHCO₃ (0.6 g, 0.0083 mmol) were mixed in H₂O (5 mL); then TCCA (0.078 g, 0.33 mmol) was added and the mixture was allowed to stir for 24 h at r.t. The solid was filtered, washed with H₂O (2×), and dried.
Yield: 130 mg (60%); white solid; mp 146–148 °C.
IR (Nujol): 3094, 1748, 1740, 1464, 1374, 1194, 956, 748, 731, 587, 576 cm⁻¹.
¹H NMR (90 MHz, CDCl₃): δ = 7.85–8.18 (m, Harom).

**Chloramine-T**
TCCA (0.176 g, 0.76 mmol) was added to a soln of p-toluene-sulfonamide (0.171 g, 1 mmol) in 2 N NaOH (1 mL), and the mixture was stirred for 1 h at r.t. The solid was filtered, washed with H₂O (2×), and the resulting precipitate was collected by filtration and dried.
Yield: 261 mg (93%); white crystalline solid; mp 178–180 °C.
IR (Nujol): 3512, 3156, 1682, 1251, 1132, 1085, 927, 808, 700 cm⁻¹.
¹H NMR (300 MHz, D₂O): δ = 2.23 (s, 3 H, CH₃), 7.21–7.57 (2 d, J = 8.1 Hz, 4 H, Harom).
Acknowledgment

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References

(16) Gama, P. E. Synlett 2005, 15, 1742; and references cited therein.
(23) These compounds have been extensively investigated since their discovery by Schiff in 1877. Glycoluril (IUPAC name: perhydroimidazo[4,5-d]imidazol-2,5-dione) and its derivatives are heterocyclic compounds that have found a number of applications, including polymer cross-linking, explosives, stabilizers of organic compounds against photodegradation, and combinatorial chemistry. Glycoluril has also been used as a building block for various supramolecular objects. Among others, the groups of Rebek, Nolte, and Isaacs have extensively studied the synthesis and behavior of a wide variety of glycoluril derivatives.