Preparation of Several Active *N*-Chloro Compounds from Trichloroisocyanuric Acid

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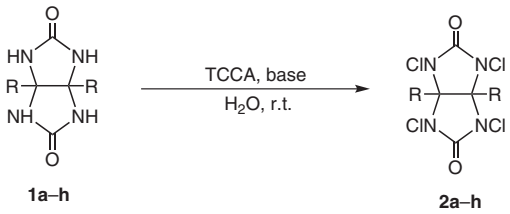
Abstract: A very simple method for the preparation of several active *N*-chloro compounds that have extensive applications in organic synthesis, industry, and medicine has been developed. Tetrachloroglycolurils, chloramine-T, *N*-chlorosaccharin, *N*-chlorosuccinimide, *N*-chlorophthalimide, *N*,*N*′-dichlorophenobarbital, and *N*,*N*′-dichlorobarbital were synthesized by chlorination with trichloroisocyanuric acid under mild reaction conditions at room temperature. This method is clean, fast, and efficient; the yields are 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.[1,2]

Following the synthesis of *N*-chloroamides in methanol and *N*,*N*′-dichloroamines in dichloromethane at 15 °C with TCCA,[3,4] we decided to prepare a series of valuable active *N*-chloro compounds from this relatively safe reagent in water as a green solvent at room temperature. These compounds, which comprise tetrachloroglycolurils, chloramine-T, *N*-chlorosaccharin, *N*-chlorosuccinimide, *N*-chlorophthalimide, *N*,*N*′-dichlorophenobarbital, and *N*,*N*′-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,[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 proposed as a source of chlorine for controlling algae in industrial water and sewage treatment.[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 radioiodination of proteins and cell membranes and continues to be used widely for this purpose.[11–15] This reagent is as effective as enzymatic methods for iodination of externally exposed residues and as effective as chloramine-T for general protein iodination, in addition to being more mild, resulting in limited oxidative damage and retained cell viability.[11,16–19] Chlorination of iodogen (**2d**) has been effected by chlorine in the presence of surfactants at high temperature in 12 hours. However, chlorine is a toxic gas and irritates the respiratory system; it is also heavier than air and tends to accumulate at the bottom of poorly ventilated spaces. Instead, we have prepared these compounds using a safe and easily handled reagent, TCCA, at room temperature without using any surfactant (Scheme 1 and Table 1).



Scheme 1 Preparation of tetrachloroglycolurils

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

Entry	Product	R	Time (h)	Yield (%)	Mp (°C) (found)	Mp (°C) (Lit.)
1	**2a**	H	3	97	>275 (dec)	>280 (dec)[8]
2	**2b**	Me	1.5	93	220–223	218–219[6]
3	**2c**	Et	12	91	194–198	–
4	**2d**	Ph	8	96	249–252	247–247.5[6]
5	**2e**	3-BrC_6H_4	5	93	220–224	–
6	**2f**	4-BrC_6H_4	3	95	210–214	–
7	**2g**	3-ClC_6H_4	7	92	231–235	–
8	**2h**	4-ClC_6H_4	4	95	217–220	–

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-

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lecular transformations: aminohydroxylation, aminohalogenation of alkenes, allylic aminations, and aziridination.[20] According to the literature, chloramine-T was first prepared by Chattaway by the action of sodium hydroxide upon *N*,*N*′-dichloro-*p*-toluenesulfonamide.[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

Entry	Product	Time (h)	Yield (%)	Mp (°C) (found)	Mp (°C) (Lit.)
1	*N*-chlorosaccharin	24	60	146–148	148–151[23]
2	*N*,*N*′-dichlorophenobarbital	1	89	147–150	147–152[24a]
3	*N*,*N*′-dichlorobarbital	1	65	120–124	125–127[24c]
4	*N*-chlorophthalimide	1	98	180–182	181–183[26]
5[a]	*N*-chlorosuccinimide	1	95	151–152	150–151[26]
6[b]	*N*-chlorosuccinimide	1	87		
7	chloramine-T	1	93	178–180	167–169[21]

[a] In the presence of AcOH.
[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 chlorine is highly electrophilic and it is commonly used in diverse organic transformations, such as halogenation, cohalogenation, addition, oxidation, and allylic and benzylic halogenation.[22] *N*-Chlorosaccharin has been prepared from sodium saccharinate in many different ways; the latest method has used potassium chloride in the presence of Oxone®, resulting in moderate yields.[23] Taking into account that Oxone® is an expensive reagent with low atom efficiency, we synthesized *N*-chlorosaccharin directly 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® in methanol and studied as a potential antimalarial.[24a] The synthesis of *N*,*N*′-dichlorobarbital (entry 3) has been reported to be by reaction of barbital either with *tert*-butyl hypochlorite (TBH) in dichloromethane at low temperatures or with chlorine gas.[24b,c] We have succeeded in preparing these compounds under green reaction conditions (entries 2 and 3). Experiments showed that for the *N*-chlorination of barbital, the reaction did not proceed in the absence of a base.

N-Chlorophthalimide (Table 2, entry 4) is a useful reagent for chlorination,[25] and has been prepared by several methods: by the reaction of phthalimide and *tert*-butyl hypochlorite in *tert*-butyl alcohol (74.6% yield),[26] by the action of chlorine gas on either a metal salt of phthalimide in chlorinated solvents, or from phthalimide in dichloromethane in the presence of 4-vinylpyridine–divinylbenzene copolymer and quinoline (at –10 to 50 °C).[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 °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.[28] However, when phthalimide was used directly, the reaction proceeded in excellent yield without any change in color (Table 2, entry 4).

N-Chlorosuccinimide (NCS) (Table 2, entries 5 and 6) is a versatile reagent, the significance of which is not limited to chlorination and oxidation. It mediates or catalyzes many chemical reactions, including halocyclizations, the formation of heterocyclic systems and new carbon–carbon bonds, rearrangements, and functional-group transformations.[29] *N*-Chlorosuccinimide has previously been synthesized from *tert*-butyl hypochlorite (35.2% yield)[26] and chlorine gas.[27] In our laboratory, several experiments were attempted to optimize the preparation of this compound. 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_2CO_3, or K_2CO_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 applications of active *N*-chloro compounds in organic reactions and to overcome the experimental difficulties when sodium hypochlorite, *tert*-butyl hypochlorite, and toxic chlorine 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 conditions with the aid of the nontoxic, easily handled, and inexpensive 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 glycolurils were prepared in our laboratory by conventional methods. The well-known *N*-chloro compounds chloramine-T, *N*-chlorosaccharin, *N*-chlorosuccinimide, *N*-chlorophthalimide, *N*,*N*′-dichlorobarbital, and *N*,*N*′-dichlorophenobarbital, as well as benzils, were identified by comparing their IR and ^1H NMR spectra or melting points with those of the authentic samples. *N*-Chloroglycolurils were characterized by their spectral data (IR and NMR) and elemental 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 apparatus 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[30]

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): 3053, 1670, 1586, 1302, 1189, 889, 722 cm^{-1}.

^1H NMR (90 MHz, $CDCl_3$): δ = 7.31–8.00 (m).

4-Bromobenzil
Yellow solid.

IR (Nujol): 3090, 1665, 1586, 1312, 1173, 833, 724 cm^{-1}.

^1H NMR (90 MHz, $CDCl_3$): δ = 7.58–7.85.

3-Chlorobenzil
Yellow solid.

IR (KBr): 3076, 1673, 1582, 1260, 897, 749 cm^{-1}.

^1H NMR (90 MHz, $CDCl_3$): δ = 7.37–8.12 (m).

4-Chlorobenzil
Yellow solid.

IR (KBr): 3093, 1661, 1586, 1210, 834, 765 cm^{-1}.

^1H NMR (90 MHz, $CDCl_3$): δ = 7.40–7.90 (dd).

Glycolurils

Note that for the synthesis of aryl-bearing glycolurils, we have replaced TFA by trichloroacetic acid (TCA), which is cheaper, more available, and more easily handled.[31]

Glycoluril (1a)[8]
White solid; slightly soluble in H_2O.

IR (Nujol): 3184, 1698, 1510, 1337, 1112, 721 cm^{-1}.

^1H NMR (300 MHz, D_2O): δ = 5.51 (s, CH).

Dimethylglycoluril (1b)[5]
Off-white solid; slightly soluble in DMSO.

IR (Nujol): 3237, 1727, 1667, 1510, 1163, 723 cm^{-1}.

^1H NMR (90 MHz, DMSO-d_6): δ = 1.32 (s, 6 H, CH_3) 7.07 (s, 4 H, NH)

Diethylglycoluril (1c)
Urea (0.6 g, 10 mmol) was dissolved in H_2O (20 mL), and then 36% HCl (0.5 mL) was added. The soln was stirred at r.t. and hexane-3,4-dione (0.51 g, 5 mmol) was added dropwise. The soln was stirred at r.t. for 12 h. The precipitate was filtered, washed with H_2O (3×) and acetone (2 × 10 mL), and then dried in air.

Yield: 222 mg (20%); brownish powder (slightly soluble in DMSO).

IR (Nujol): 3226, 1716, 1670, 1504, 1158, 722, 692 cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 0.940 (t, J = 7.3 Hz, 6 H, CH_3), 1.60 (q, J = 7.3 Hz, 4 H, CH_2), 7.20 (s, 4 H, NH).

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-d_6): δ = 7.06 (s, 10 H, H_{arom}) 7.74 (s, 4 H, NH).

^{13}C NMR (23 MHz, DMSO-d_6): δ = 81.7, 127.0, 127.2, 127.7, 138.2, 160.6.

Bis(3-bromophenyl)glycoluril (1e)
White solid.

IR (Nujol): 3228, 1717, 1691, 1671, 1494, 1147, 719 cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 7.07–7.31 (m, 8 H, H_{arom}), 7.98 (s, 4 H, NH).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 81.7, 121.5, 130.1, 130.4, 131.3, 141.2, 160.8.

Bis(4-bromophenyl)glycoluril (1f)
White solid.

IR (Nujol): 3230, 1722, 1682, 1584, 1136, 725 cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 6.95–7.38 (2 d, J = 8.5 Hz, 8 H, H_{arom}), 7.90 (s, 4 H, NH).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 81.7, 121.8, 129.7, 130.9, 138.2, 160.9.

Bis(3-chlorophenyl)glycoluril (1g)
White solid.

IR (Nujol): 3233, 1691, 1671, 1496, 1143, 740 cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 7.03–7.40 (m, 8 H, H_{arom}), 7.98 (s, 4 H, NH).

^{13}C NMR (23 MHz, DMSO-d_6): δ = 81.3, 125.6, 127.0, 127.9, 132.5, 140.6, 160.4.

Bis(*p*-chlorophenyl)glycoluril (1h)
White solid.

IR (Nujol): 3228, 1683, 1599, 1098, 724 cm^{-1}.

^1H NMR (90 MHz, DMSO-d_6): δ = 7.01–7.26 (2 d, J = 8.8 Hz, 8 H, H_{arom}), 7.88 (s, 4 H, NH).

^{13}C NMR (23 MHz, DMSO-d_6): 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 H_2O (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 H_2O (2×), and dried to give the product; yield: 97%. In the case of glycoluril and dimethylglycoluril, $NaHCO_3$ (0.1 g) and 1 N NaOH were used, respectively, as base to adjust the pH to 7–8. The products were used without further purification.

Tetrachloroglycoluril (2a)
Yield: 272 mg (97%); white solid.

IR (Nujol): 1774, 1759, 1224, 1171, 715 cm^{-1}.

^1H NMR (90 MHz, acetone-d_6): δ = 5.80 (s, CH).

Anal. Calcd for $C_4H_2Cl_4N_4O_2$: C, 17.1; H, 0.71; N, 20.0. Found: C, 17.7; H, 0.71; N, 20.2.

Tetrachlorodimethylglycoluril (2b)
Yield: 286 mg (93%); white solid.

IR (Nujol): 1767, 1747, 1344, 1160, 730 cm^{-1}.

^1H NMR (90 MHz, $CDCl_3$): δ = 1.86 (s, CH_3).

Anal. Calcd for $C_6H_6Cl_4N_4O_2$: C, 23.4; H, 2.0; N, 18.2. Found: C, 24.2; H, 2.2; N, 18.3.

Tetrachlorodiethylglycoluril (2c)
Yield: 300 mg (91%); white solid.

IR (Nujol): 1781, 1769, 1330, 1142, 794, 727 cm^{-1}.

^1H NMR (90 MHz, $CDCl_3$): δ = 1.07 (t, *J* = 7.5 Hz, 3 H, CH_3), 2.40 (q, *J* = 7.5 Hz, 2 H, CH_2).

^{13}C NMR (23 MHz, $CDCl_3$): δ = 7.11, 22.60, 86.42, 154.40.

Anal. Calcd for $C_8H_{10}Cl_4N_4O_2$: C, 28.6; H, 3.0; N, 16.6. Found: C, 29.0; H, 3.0; N, 16.0.

Tetrachlorodiphenylglycoluril (Iodogen, 2d)
Yield: 393 mg (96%); white solid.

IR (Nujol): 3054, 1782, 1770, 1331, 1143, 707 cm^{-1}.

^1H NMR (90 MHz, acetone-d_6): δ = 6.97–7.30 (m, H_{arom}).

Anal. Calcd for $C_{16}H_{10}Cl_4N_4O_2$: C, 44.4; H, 2.3; N, 12.9. Found: C, 44.9; H, 2.3; N, 12.7.

Bis(3-bromophenyl)tetrachloroglycoluril (2e)
Yield: 547 mg (93%); white solid.

IR (Nujol): 3095, 1790, 1769, 1571, 1241, 1153, 708 cm^{-1}.

^1H NMR (90 MHz, $CDCl_3$): δ = 6.84–7.46 (m, H_{arom}).

Anal. Calcd for $C_{16}H_8Br_2Cl_4N_4O_2$: C, 32.5; H, 1.3; N, 9.5. Found: C, 33.6; H, 1.5; N, 9.6.

Bis(4-bromophenyl)tetrachloroglycoluril (2f)
Yield: 560 mg (95%); white solid.

IR (Nujol): 3093, 1784, 1589, 1253, 1148, 711 cm^{-1}.

^1H NMR (90 MHz, $CDCl_3$): δ = 6.73–7.39 (2 d, *J* = 8.7 Hz, 4 H, H_{arom}).

Anal. Calcd for $C_{16}H_8Br_2Cl_4N_4O_2$: C, 32.5; H, 1.3; N, 9.5. Found: C, 33.2; H, 1.3; N, 10.1.

Tetrachlorobis(3-chlorophenyl)glycoluril (2g)
Yield: 460 mg (92%); white solid.

IR (Nujol): 1791, 1767, 1596, 1577, 1324, 1142, 726 cm^{-1}.

^1H NMR (90 MHz, acetone-d_6): δ = 7.17–7.43 (m, H_{arom}).

Anal. Calcd for $C_{16}H_8Cl_6N_4O_2$: C, 38.3; H, 1.6; N, 11.1. Found: C, 38.5; H, 1.6; N, 11.1.

Tetrachlorobis(4-chlorophenyl)glycoluril (2h)
Yield: 475 mg (95%); white solid.

IR (Nujol): 1776,1596, 1492, 1325, 1253, 1149, 1096, 852, 812, 722 cm^{-1}.

^1H NMR (90 MHz, $CDCl_3$): δ = 6.81–7.22 (2 d, *J* = 8.3 Hz, 4 H, H_{arom}).

Anal. Calcd for $C_{16}H_8Cl_6N_4O_2$: C, 38.3; H, 1.6; N, 11.1. Found: C, 38.7; H, 1.7; N, 11.0.

***N*-Chlorophthalimide**
A suspension of phthalimide (0.185 g, 1 mmol) in H_2O (10 mL) was treated with TCCA (0.078 g, 0.33 mmol), and the mixture was stirred at r.t. for 1 h. Then the solid was collected by filtration, washed with H_2O, and dried.

Yield: 177 mg (98%); white solid; mp 180–182 °C.

IR (Nujol): 3093, 1787, 1741, 1714, 1302, 1270, 1172, 1076, 701 cm^{-1}.

^1H NMR (90 MHz, $CDCl_3$): δ = 7.73–7.97 (m, H_{arom}).

***N*-Chlorosuccinimide**
A suspension of succinimide (0.59 g, 6 mmol) in H_2O (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 $CHCl_3$ (3 × 10 mL), and the soln was dried ($MgSO_4$), filtered, and evaporated.

Yield: 126 mg (95%); colorless crystalline solid; mp 151–152 °C.

IR (Nujol): 1713, 1328, 1296, 1159, 961, 651 cm^{-1}.

^1H NMR (90 MHz, $CDCl_3$): δ = 2.88 (s, CH_2).

***N*,*N*′-Dichlorophenobarbital**
A suspension of phenobarbital (0.232 g, 1mmol) in H_2O (10 mL) was treated with TCCA (0.176 g, 0.76 mmol) for 1 h at r.t. Then the solid was filtered, washed with H_2O, dried, and recrystallized from $CHCl_3$ 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, $CDCl_3$): δ = 0.96 (t, *J* = 7.1 Hz, 3 H, CH_3), 2.54 (q, *J* = 7.1 Hz, 2 H, CH_2), 7.13–7.45 (m, 5 H, H_{arom}).

***N*,*N*′-Dichlorobarbital**
Barbital (0.184 g, 1 mmol) and $NaHCO_3$ (0.6 g, 0.0083 mmol) were mixed in H_2O (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 H_2O (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, $CDCl_3$): δ = 0.82 (t, *J* = 7.3 Hz, 3 H, CH_3), 2.11 (q, *J* = 7.3 Hz, 2 H, CH_2).

***N*-Chlorosaccharin**
Saccharin (0.183 g, 1 mmol) and $NaHCO_3$ (0.6 g, 0.0083 mmol) were mixed in H_2O (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 H_2O (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, $CDCl_3$): δ = 7.85–8.18 (m, H_{arom}).

Chloramine-T
TCCA (0.176 g, 0.76 mmol) was added to a soln of *p*-toluenesulfonamide (0.171 g, 1 mmol) in 2 N NaOH (1 mL), and the mixture was stirred for 1 h at r.t. The soln was then cooled at 0 °C 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, D_2O): δ = 2.23 (s, 3 H, CH_3), 7.21–7.57 (2 d, *J* = 8.1 Hz, 4 H, H_{arom}).

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References

(1) Weinmann, H.; Tilstam, U. *Org. Process Res. Dev.* **2002**, *6*, 384.
(2) Kolvari, E.; Ghorbani-Choghamarani, A.; Salehi, P.; Shirini, F.; Zolfigol, M. A. *J. Iran. Chem. Soc.* **2007**, *4*, 126.
(3) Hiegel, G. A.; Hogenauer, T. J.; Lewis, J. C. *Synth. Commun.* **2005**, *35*, 2099.
(4) Luca, L. D.; Giacomelli, G. *Synlett* **2004**, 2180.
(5) Biltz, H.; Behrens, O. *Chem. Ber.* **1910**, *43*, 1984.
(6) Williams, J. W. US Patent 2649389, **1953**; *Chem. Abstr.* **1953**, *48*, 8267.
(7) Adkins, H. B. US Patent 2654763, **1953**; *Chem. Abstr.* **1953**, *48*, 10778.
(8) Slezak, F. B.; Hirsch, A.; Rosen, I. *J. Org. Chem.* **1960**, *25*, 660.
(9) Slezak, F. B.; Bluestone, H.; Magee, T. A.; Wotiz, J. H. *J. Org. Chem.* **1962**, *27*, 2181.
(10) (a) Zettler, T. T. US Patent 3252901, **1966**; *Chem. Abstr.* **1966**, *65*, 6922. (b) Horvath, R. J.; Parsons, C. G.; Zettler, T. T. US Patent 3445383, **1969**; *Chem. Abstr.* **1969**, *70*, 109008.
(11) Fraker, P. J.; Speck, J. C. *Biochem. Biophys. Res. Commun.* **1978**, *80*, 849.
(12) Unak, T.; Akgun, Z.; Yildirim, Y.; Dumanb, Y.; Erenel, G. *Appl. Radiat. Isot.* **2001**, *54*, 749.
(13) Yuan, H.; Luo, J.; Field, S.; Weissleder, R.; Cantley, L.; Josephson, L. *Bioconjugate Chem.* **2005**, *16*, 669.
(14) Safavy, A.; Georg, G. I.; Velde, D. V.; Raisch, K. P.; Safavy, K.; Carpenter, M.; Wang, W.; Bonner, J. A.; Khazaeli, M. B.; Buchsbaum, D. J. *Bioconjugate Chem.* **2004**, *15*, 1264.
(15) Cook, J. H.; Pratt, R. S.; Lilien, J. *Biochemistry* **1984**, *23*, 899.
(16) Markwell, M. A. K.; Fox, C. F. *Biochemistry* **1978**, *17*, 4807.
(17) Luqman, W. A.; Matej, L. A.; Smith, M. L. *J. Endocrinol.* **1979**, *81*, 131.
(18) Salacinski, P. R. P.; McLean, C.; Sykes, J. E. C.; Clement-Jones, V. V.; Lowry, P. J. *Anal. Biochem.* **1981**, *117*, 136.
(19) Goding, J. W. *Monoclonal Antibodies: Principles and Practice*; Academic Press: London, **1986**, 142.
(20) Agnihotri, G. *Synlett* **2005**, 2857.
(21) Chattaway, F. D. *J. Chem. Soc. Trans.* **1905**, 145.
(22) Gama, P. E. *Synlett* **2005**, 1742; and references cited therein.
(23) de Souza, S. P. L.; da Silva, J. F. M.; de Mattos, M. C. S. *Synth. Commun.* **2003**, *33*, 935.
(24) (a) Craig, J. C.; Pearson, D. E. *J. Med. Chem.* **1971**, *14*, 1221. (b) Barer, S. J. US Patent 3919232, **1975**; *Chem. Abstr.* **1975**, *84*, 59549. (c) Otsuji, Y.; Kuroda, T.; Imoto, E. *Bull. Chem. Soc. Jpn.* **1968**, *41*, 2124.
(25) Mosher, M. W.; Estes, G. W. *J. Am. Chem. Soc.* **1977**, *99*, 6928.
(26) Zimmer, H.; Audrieth, L. F. *J. Am. Chem. Soc.* **1954**, *76*, 3856.
(27) Chou, T. S. US Patent 4212977, **1980**; and references cited therein (*Chem. Abstr.* reference not found).
(28) Chou, T.-S.; Burgtorf, J. R. US Patent 4082766, **1978**; *Chem. Abstr.* **1978**, *89*, 42843.
(29) Golebiewski, W. M.; Gucma, M. *Synthesis* **2007**, 3599.
(30) Vogel, A. A. *Textbook of Practical Organic Chemistry including Qualitative Organic Analysis*; Longman: London, **1978**, 805.
(31) These compounds have been extensively investigated since their discovery by Schiff in 1877. Glycoluril (IUPAC name: perhydroimidazo[4,5-*d*]imidazole-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,[32] Nolte,[33] and Isaacs[34] have extensively studied the synthesis and behavior of a wide variety of glycoluril derivatives.
(32) (a) Rebek, J. Jr. *Chem. Soc. Rev.* **1996**, *25*, 255. (b) Conn, M. M.; Rebek, J. Jr. *Chem. Rev.* **1997**, *97*, 1647. (c) Rebek, J. Jr. *Acc. Chem. Res.* **1999**, *32*, 278; and references cited therein.
(33) (a) Sijbesma, R. P.; Nolte, R. J. M. *Top. Curr. Chem.* **1995**, *175*, 25. (b) Rowan, A. E.; Elemans, J. A. A. W.; Nolte, R. J. M. *Acc. Chem. Res.* **1999**, 995. (c) Elemans, J. A. A. W.; Rowan, A. E.; Nolte, R. J. M. *Ind. Eng. Chem. Res.* **2000**, *39*, 3419; and references cited therein.
(34) (a) Wang, Z.-G.; Zhou, B.-H.; Chen, Y.-F.; Yin, G.-D.; Li, Y.-T.; Wu, A.-X.; Isaacs, L. *J. Org. Chem.* **2006**, *71*, 4502. (b) Chen, Y.; She, N.; Meng, X.; Yin, G.; Wu, A.; Isaacs, L. *Org. Lett.* **2007**, *9*, 1899.