Efficient Electrophilic Cobromination of Alkenes and Bromination of Activated Arenes with Bromodichloroisocyanuric Acid under Mild Conditions

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Abstract: Efficient methodologies for the preparation of bromodichloroisocyanuric acid were developed (70–75%). This new reagent is very efficient for regioselective electrophilic bromination of activated arenes (86–93%) and cobromination of alkenes with oxygenated nucleophiles (31–98%). The reaction of bromodichloroisocyanuric acid with anisole, acetanilide, *N*-methylacetanilide leads to 4-substituted monobromoarene and with 2-methoxynaphthalene leads to 1-bromo-2-methoxynaphthalene. Alkenes were cobrominated in the presence of oxygenated nucleophilic solvents (water, alcohols, and acetic acid), leading to the corresponding bromohydrins, β-bromoethers and β-bromoacetates.

Key words: alkenes, arenes, electrophilic addition, electrophilic aromatic substitution, halogenation

Organic halides are a very important class of compounds with applications in many fields of chemistry, specially as synthetic intermediates.[1] Many techniques for halogenation of organic compounds employing alternative reagents are found in the literature,[2] once direct halogenation with X_2 (X = Cl, Br, I) generates HX which are polluting and corrosive strong acids.[3] The use of *N*-haloimides is a good alternative for halogenation of organic molecules, due to their lower toxicity compared to X_2 and furnish the corresponding imides as byproduct after workup. In this class of compounds, the halogen has a stronger electrophilic character because it is directly bonded to the nitrogen of the imide.[4]

Trichloroisocyanuric acid (TCCA, Scheme 1), a white solid sold at 99% of purity at supermarkets and used as pool disinfectant and bleaching agent, has shown to be a very good reagent in organic synthesis, finding application in oxidative[5] and chlorinating reactions.[6] It was formerly prepared by Chattaway and Wadmore in 1902 by the reaction of cyanuric acid with Cl_2/NaOH.[7] Similarly, the disubstituted analogue, dichloroisocyanuric acid (DCCA, Figure 1) can be prepared by the stoichiometric control. Its monosodic salt, sodium dichloroisocyanurate, is also sold for pool disinfection in 65% purity. Other interesting analogues of TCCA are the tribromoisocyanuric acid (TBCA, Figure 1) and dibromoisocyanuric acid (DBCA, Figure 1), formerly prepared by Gottardi[8] using a difficult and tedious methodology employing expensive silver salts and elementary bromine. This generates a mixture of AgBr and TBCA or DBCA, which are insoluble in most solvents making their separation difficult. A green alternative methodology developed by us for the preparation of TBCA in 87%, consists of the reaction of cyanuric acid with KBr and Oxone® in the presence of NaOH for 24 hours at room temperature.[9] This methodology is quite simple and the product is obtained by vacuum filtration needing no further purification. A previous work showed that TBCA is a very good regioselective brominating agent for alkenes[9] and activated aromatic rings.[2a]

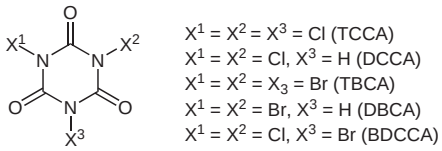

Figure 1 Haloisocyanuric acids

In this paper we introduce the preparation of bromodichloroisocyanuric acid (BDCCA, Figure 1) and its application on regioselective bromination of alkenes and activated aromatic rings.

The first step of this work was the preparation of BDCCA from the commercially available sodium dichloroisocyanurate (65% pure). The two methodologies employed to prepare BDCCA are shown in Scheme 1. In the former, a solution of 100 mmol of sodium dichloroisocyanurate in 1 L of water reacted with 107 mmol of Br_2. The formation of BDCCA can easily be observed by the rapid precipitation of a white solid with simultaneous discoloration of the solution. After a vacuum filtration and drying over P_2O_5, the pure product is obtained in 75% yield. The second alternative route used KBr and Oxone® to generate Br_2 in situ and led to BDCCA in 70% yield.

Both methodologies lead to the same product in good yields. The reaction with Br_2 is faster, but worst to manipulate. On the other hand, the reagents used on the second methodology (KBr and Oxone®) are solids, much less toxic and easier to handle. The reactivity of BDCCA towards arene brominations and alkenes cobrominations was investigated.

Alkenes are rapidly converted into the corresponding bromohydrins in excellent yields (Table 1), when 2 mmol of substrate react with 2 mmol of BDCCA in 15 mL of aqueous acetone (1:5) at room temperature. The substrates

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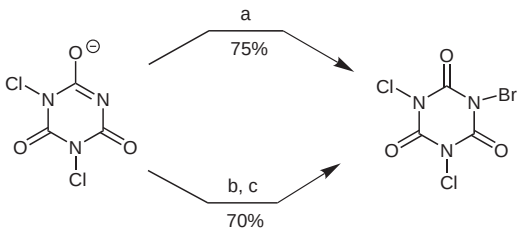
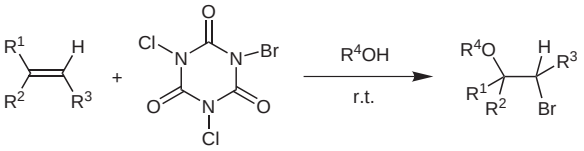


Scheme 1 Preparation of BDCCA. *Reagents and conditions*: a) Br_2, H_2O, r.t.; b) Na_2CO_3, KBr, H_2O, r.t.; c) Oxone®, r.t., 24 h.

used in these reactions were α-methylstyrene, styrene, 1-methylcyclohexene, and cyclohexene. The cobromination of styrene and cyclohexene with BDCCA in methanol, isopropanol, and acetic acid has led to the corresponding β-bromoethers and β-bromoacetates in moderate to good yields. The reactions are regioselective, forming products in Markownikoff's fashion, and featuring *trans*-configuration, which were analyzed by analytical procedures (GCMS and ^{1}H NMR and ^{13}C NMR spectroscopy). The results (Table 1) show that reactions in water–acetone system are faster than in alcohol or acid media. No chlorinated products were detected by analytical techniques.

Table 1 Cobromination of Alkenes with BDCCA



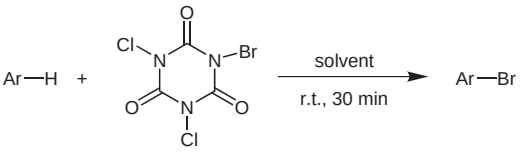
R^1	R^2	R^3	R^4	T (min)	Yield (%)[a]
Me	Ph	H	H[b]	5	98
H	Ph	H	Me	120	71
H	Ph	H	*i*-Pr	120	77
H	Ph	H	Ac	30	97
H	Ph	H	H[b]	5	97
Me	$-(CH_2)_4-$		H[b]	5	95[c]
H	$-(CH_2)_4-$		Me	15	79[c]
H	$-(CH_2)_4-$		*i*-Pr	1200	31[c]
H	$-(CH_2)_4-$		Ac	5	69[c]
H	$-(CH_2)_4-$		H[b]	5	97[c]

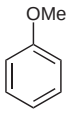
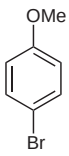
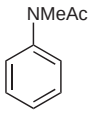
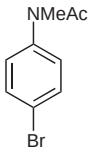
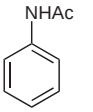
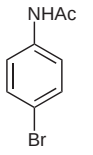
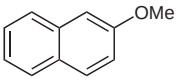
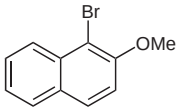
[a] Isolated yield based on the alkene.
[b] H_2O–acetone (1:5) used as nucleophile.
[c] *trans*-Product.

Brominations of activated arenes were performed at room temperature using 2 mmol substrate (anisole, acetanilide, *N*-methylacetanilide, and 2-methoxynaphthalene) in 10 mL of methanol or 20 mL of water (just for *N*-methylacetanilide). After workup, the corresponding monobromoarenes were obtained in excellent yields (Table 2). The regioselectivity was very high, leading to 4-substituted monobromoarene and 1-bromo-2-methoxynaphthalene. No regioisomers or chlorinated products could be detected by analytical procedures (GCMS and ^{1}H NMR and ^{13}C NMR spectroscopy).

In a previous work, the brominations of the same substrates using TBCA or TCCA/KBr system were performed in longer reaction times[2a] (0.5–72 h), whilst in the present work all the reactions with the arenes were carried out in just 30 minutes (Table 2). This higher reactivity of BDCCA compared to TBCA seems to be associated to the dipole of the BDCCA molecule. The chlorine atoms increase the dipole toward the carbonyl between them, and consequently the electrophilicity of the bromine atom increases, too.

Table 2 Bromination of Arenes with BDCCA



Arene	Product	Solvent	Yield (%)[a]
		MeOH	93
		H_2O	94
		MeOH	86
		MeOH	95

[a] Isolated yield based on the arene.

In conclusion, the present work describes two preparations of the bromodicloroisocyanuric acid. Both methods are efficient, but the alternative one, with KBr/Oxone®, is more ecofriendly, because these reagents are not polluting and not corrosive. The reactions of BDCCA with arenes and alkenes present high regioselectivity, forming monobromo arenes and bromohydrins, β-bromoethers and β-bromoacetates in moderate to excellent yields.

Preparation of Bromodichloroisocyanuric Acid (BDCCA)
Procedure 1 (Using Br_2)
To a well-stirred solution of sodium dichloroisocyanurate (100 mmol) in H_2O (1 L) was added dropwise Br_2 (107 mmol). A white solid precipitates forming a dense suspension. Then, the product was isolated by filtration, washed with cold H_2O and dried over P_2O_5, needing no further purification.[10] Yield 75%; mp not determined because it decomposes on heating.

Procedure 2 (Using KBr/oxone®)
To a well-stirred solution of sodium dichloroisocyanurate (10 mmol), Na_2CO_3 (10 mmol) and KBr (10 mmol) in H_2O (150 mL) cooled in an ice bath a solution of Oxone® (10 mmol) in H_2O (40 mL) was added dropwise. A white solid precipitates during the addition of the oxidant solution forming a dense suspension, which was stirred for 24 h. The product was isolated by filtration, washed with cold H_2O and dried over P_2O_5. No further purification is necessary.[10] Yield 70%; mp not determined because it decomposes on heating.

Typical Procedure for Cobromination of Alkenes
To a stirred solution of the alkene (2 mmol) in the appropriated solvent (12.5 mL of acetone and 2.5 mL of H_2O for bromohydrins, or 5 mL of alcohols or AcOH for β-bromoethers or β-bromoacetates, respectively), was added BDCCA (2 mmol) at r.t. in small portions. After the elapsed time in Table 1 (the termination of the reaction was determined by gas chromatography), CH_2Cl_2 (10 mL) and H_2O (10 mL) were added, dichlorocyanuric acid was filtered off, and the resulting solution was treated with 10% aq Na_2SO_3 (30 mL). The aqueous phase was washed with CH_2Cl_2 (2 × 10 mL) and the combined organic layer was dried over anhyd Na_2SO_4. After the evaporation of the solvent on a rotatory evaporator, the product was collected.[11]

Typical Procedure for Bromination of Arenes
To a stirred solution of the arene (2 mmol) in MeOH (10 mL) or H_2O (20 mL, for *N*-methylacetanilide) was added BDCCA (2 mmol). The reaction was monitored by GC. After 30 min, CH_2Cl_2 (30 mL) and H_2O (20 mL) were added, dichlorocyanuric acid was filtered off, and the resulting solution was treated with 10% aq Na_2SO_3 (30 mL). The aqueous phase was washed with CH_2Cl_2 (2 × 10 mL) and the combined organic layer was dried over anhyd Na_2SO_4. After evaporation of the solvent on a rotatory evaporator, the product was collected.[12]

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(10) CP-MAS ^{13}C NMR: δ = 159.5 (br, C=O) ppm. IR: 1697, 1654, 1620, 1484, 1450, 1421, 1409, 1349, 1319, 1203, 1149, 1110, 1074, 1047, 796, 755, 725, 602, 555 cm^{-1}.
(11) **Selected Analytical Data**
1-Bromo-2-phenylpropan-2-ol
^1H NMR ($CDCl_3$): δ = 1.68 (s, 3 H), 2.63 (s, 1 H), 3.73 (dd, 2 H, J_1 = 12.45 Hz, J_2 = 10.20 Hz), 7.25–7.49 (m, 5 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 28.0, 46.2, 73.1, 124.8, 127.5, 128.4, 144.2 ppm. MS (70 eV): *m*/*z* = 216 [M^+ + 2], 214 [M^+], 199, 201, 121 (100), 77, 43.
(2-Bromo-1-methoxyethyl)benzene
^1H NMR ($CDCl_3$): δ = 3.31 (s, 3 H), 3.42–3.59 (m, 2 H), 4.39 (dd, 1 H, J_1 = 7.86 Hz, J_2 = 4.44 Hz), 7.34–7.43 (m, 5 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 36.2, 57.2, 83.4, 126.7, 128.6, 139.0 ppm. MS (70 eV): *m*/*z* = 216 [M^+ + 2], 214 [M^+], 121 (100), 91, 77, 51.
(2-Bromo-1-isopropoxyethyl)benzene
^1H NMR ($CDCl_3$): δ = 1.12 (d, 3 H, *J* = 6.15 Hz), 1.23 (d, 3 H, *J* = 6.14 Hz), 3.38–3.48 (m, 2 H), 3.57 (hept, 1 H, *J* = 6.14 Hz), 4.58 (dd, 1 H, J_1 = 7.86 Hz, J_2 = 4.78 Hz) 7.35 (s, 5 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 21.2, 23.1, 37.0, 70.4, 79.3, 126.7, 128.2, 128.5, 140.6 ppm. MS (70 eV): *m*/*z* = 185, 183, 149, 107 (100), 79, 43.
2-Bromo-1-phenylethyl Acetate
^1H NMR ($CDCl_3$): δ = 2.13 (s, 3 H), 3.54 (m, 2 H), 5.98 (dd, 1 H, J_1 = 7.41 Hz, J_2 = 5.12 Hz), 7.36 (s, 5 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 20.9, 34.2, 74.8, 126.5, 128.6, 137.6, 169.8 ppm. MS (70 eV): *m*/*z* = 244 [M^+ + 2], 242 [M^+], 162, 121, 120, 103, 77, 43 (100).
2-Bromo-1-phenylethanol
^1H NMR ($CDCl_3$): δ = 2.81 (d, 1 H, *J* = 2.73 Hz) 3.48–3.64 (m, 2 H), 4.89–4.94 (m, 1 H), 7.37 (s, 5 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 40.1, 73.7, 125.9, 128.4, 128.6, 140.3 ppm. MS (70 eV): *m*/*z* = 202 [M^+ + 2], 200 [M^+], 107 (100), 79, 77, 51.
***trans*-2-Bromo-1-methylcyclohexanol**
^1H NMR ($CDCl_3$): δ = 1.25–1.48 (m, 5 H), 1.68–2.05 (m, 4 H), 2.15 (br s, 1 H), 2.21–2.27 (m, 1 H), 4.15 (dd, 1 H, J_1 = 11.52 Hz, J_2 = 4.10 Hz) ppm. ^{13}C NMR ($CDCl_3$): δ = 22.8, 23.2, 26.3, 34.7, 38.2, 66.0, 72.5. MS (70 eV): *m*/*z* = 194 [M^+ + 2], 192 [M^+], 177, 179, 113, 95, 71 (100), 43 ppm.
***trans*-1-Bromo-2-methoxycyclohexane**
^1H NMR ($CDCl_3$): δ = 1.20–1.40 (m, 3 H), 1.64–1.88 (m, 3 H), 2.15–2.34 (m, 2 H), 3.17–3.28 (m, 1 H), 3.42 (ddd, 1 H, J_1 = 9.56 Hz, J_2 = 8.53 Hz, J_3 = 4.44 Hz) ppm. ^{13}C NMR ($CDCl_3$): δ = 23.1, 25.3, 29.9, 35.4, 55.2, 57.1, 83.1 ppm. MS (70 eV): *m*/*z* = 194 [M^+ + 2], 192 [M^+], 113, 81, 71 (100), 41.
***trans*-1-Bromo-2-isopropoxycyclohexane**
^1H NMR ($CDCl_3$): δ = 1.13–1.43 (m, 9 H), 1.62–1.90 (m, 3 H), 2.02–2.11 (m, 1 H), 2.30–2.37 (m, 1 H), 3.33–3.40 (m,

1 H), 3.78 (hept, 1 H, J = 6.15 Hz), 3.90 (ddd, 1 H, J_1 = 9.76 Hz, J_2 = 8.93 Hz, J_3 = 4.43 Hz) ppm. ^{13}C NMR ($CDCl_3$): δ = 27.5, 23.0, 23.5, 25.5, 32.5, 35.8, 56.6, 71.2, 79.7 ppm. MS (70 eV): m/z = 222 [M^+ + 2], 220 [M^+], 178, 180, 99, 81 (100), 57, 43.

***trans*-2-Bromocyclohexyl acetate**

^{1}H NMR ($CDCl_3$): δ = 1.27–1.47 (m, 3 H), 1.74–1.96 (m, 3 H), 2.08 (s, 3 H), 2.13 (m, 1 H), 2.32–2.39 (m, 1 H), 3.96 (ddd, 1 H, J_1 = 10.45 Hz, J_2 = 9.29 Hz, J_3 = 4.26 Hz), 4.84–4.93 (m, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 21.0, 23.3, 25.6, 35.7, 52.8, 75.8, 170.0 ppm. MS (70 eV): m/z = 222 [M^+ + 2], 220 [M^+], 160, 162, 81, 43 (100).

***trans*-2-Bromocyclohexanol**

^{1}H NMR ($CDCl_3$): δ = 1.24–1.37 (m, 3 H), 1.67–1.86 (m, 3 H), 2.10–2.20 (m, 1 H), 2.25–2.60 (m, 2 H), 3.50–3.70 (m, 1 H), 3.90 (ddd, 1 H, J_1 = 11.68 Hz, J_2 = 9.57 Hz, J_3 = 4.35 Hz) ppm. ^{13}C NMR ($CDCl_3$): δ = 24.1, 26.6, 33.5, 36.2, 61.8, 75.3 ppm. MS (70 eV): m/z = 180 [M^+ + 2], 178 [M^+], 99, 81 (100), 57, 41.

(12) **Selected Analytical Data**

4-Bromoanisole

^{1}H NMR ($CDCl_3$): δ = 3.77 (s, 3 H), 6.78 (d, J = 8.90 Hz, 2 H), 7.37 (d, J = 8.90 Hz, 2 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 55.4, 112.8, 115.7, 139.2, 158.7 ppm. MS (70 eV): m/z = 188 (100) [M^+ + 2], 186 (100) [M^+], 173, 171, 145, 143, 119, 117, 84, 63, 49 ppm.

4-Bromo-*N*-methylacetanilide

Mp 91 °C (lit.[13] 95 °C). ^{1}H NMR ($CDCl_3$): δ = 1.83 (s, 3 H), 3.20 (s, 3 H), 7.04, (d, J = 8.30 Hz, 2 H), 7.50 (d, J = 8.30 Hz, 2 H). ^{13}C NMR ($CDCl_3$): δ = 22.4, 37.0, 121.4, 128.7, 132.9, 143.5, 205.6. MS (70 eV): m/z = 229 [M^+ + 2], 227 [M^+], 187 (100), 185 (100), 186, 184, 157, 155, 104, 77, 56, 43.

4-Bromoacetanilide

Mp 166 °C (lit.[14] 167 °C). ^{1}H NMR (DMSO-d_6): δ = 2.03 (s, 3 H), 7.43, (d, J = 8.92 Hz, 2 H), 7.54 (d, J = 8.92 Hz, 2 H) ppm. ^{13}C NMR (DMSO-d_6): δ = 24.0, 114.5, 120.8, 131.5, 138.7, 168.5 ppm. MS (70 eV): m/z = 215 [M^+ + 2], 213 [M^+], 173 (100), 171 (100), 157, 155, 92, 43.

1-Bromo-2-methoxynaphthalene

Mp 82 °C (lit.[15] 85 °C). ^{1}H NMR ($CDCl_3$): δ = 4.03 (s, 3 H), 7.26 (d, J = 9.67 Hz, 1 H), 7.41 (t, J = 7.90 Hz, 1 H), 7.59 (t, J = 7.90 Hz, 1 H), 7.80 (d, J = 7.9 Hz, 1 H), 7.81 (d, J = 9.67 Hz, 1 H), 8.26 (d, J = 7.90 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 56.9, 108.6, 113.6, 124.2, 126.0, 127.7, 128.0, 128.9, 129.8, 133.0, 153.7 ppm. MS (70 eV): m/z = 238 [M^+ + 2], 236 [M^+], 223, 221, 195 (100), 193 (100), 127, 114.

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