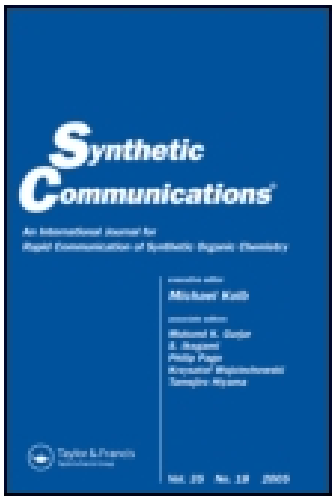

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SELECTIVE HALOGENATION OF AROMATICS BY DIMETHYL-DIOXIRANE AND HALOGEN IONS

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ABSTRACT

The oxidation of halogen anions by dimethyldioxirane (DMD) produced reactive species which led, in acidic media, to the halogenation of activated aromatic rings. The reaction can be efficiently controlled to obtain selective and mixed halogenated species.

During our experiments on the selective oxidation of natural substances by dimethyldioxirane to obtain compounds with potential biological activities, we observed that dimethyldioxirane (DMD) was able to insert oxygen into several substrates in a very selective manner.[1]

*Corresponding author.

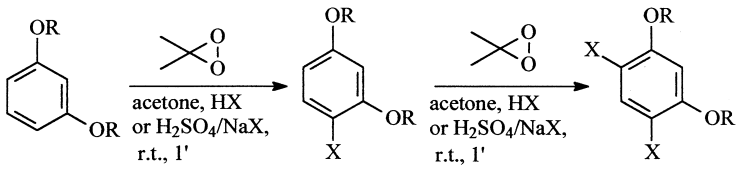
In the case of aromatic compounds activated towards aromatic electrophilic substitutions, the reaction with DMD gave the hydroxylation of the aromatic rings in moderate yields.[2]

Proceeding with our research in this field, and with the aim of making dimethyldioxirane more electrophilic, we performed some tests in acidic media, obtaining in some cases better yields.

We report now how a different behaviour was observed when hydrochloric acid was used as co-solvent: DMD oxidised chloride anions to reactive species which, in acidic medium introduced a halogen atom into activated sites of aromatic rings.

The importance of aryl halides as precursors of various functional group transformations makes these compounds valuable for organic synthesis, and their preparation of general interest. Therefore we were prompted to investigate the reaction to explore their advantages and limits.

In our first experiment resorcinol **1** was selectively transformed in 4-chloro-resorcinol **2**, in high yield, by a careful addition of DMD to a solution of the substrate in hydrochloric acid. The addition of an excess of DMD to the reaction mixture led, with the same efficiency, to 4,6-dichloro-resorcinol **5** (Scheme 1).



1 a:R=H **b:**CH_3

2a-b X=Cl, 90-95%
3a-b X=Br, 95%
4b X=I, R=CH_3, >95%

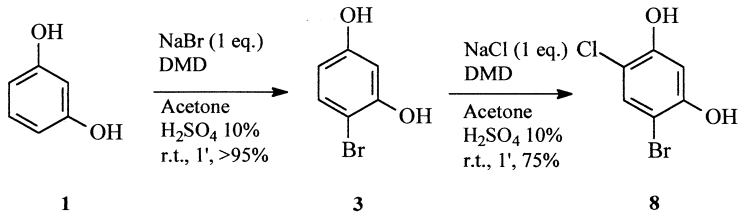
5a-b X=Cl, 85-90%
6a-b X=Br, 78-85%
7b X=I, R=CH_3, 90%

Scheme 1. Selective chlorination of resorcinol by DMD/HCl system.

The same reaction was then performed using a solution of resorcinol in hydrobromic or hydroiodic acid. In this case bromo- or iodo-derivatives were obtained. The selectivity of the process, which led to the insertion of halogen atoms in the less steric hindered positions, is worthy of note. When the reaction was carried out in other acidic media, and sodium chloride, sodium bromide or sodium iodide were used as generators of electrophilic halogens, the results were exactly the same.

The method was exploited to obtain products with two different halogens in a highly selective procedure.

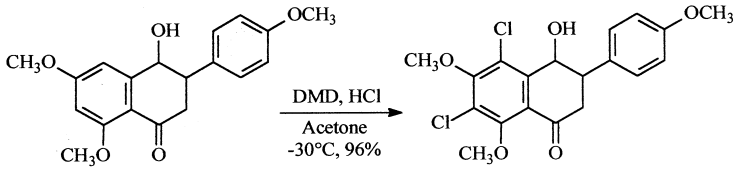
In a sulphuric acid diluted solution of resorcinol, an equivalent amount of sodium bromide and a little excess of dimethyldioxirane were added. After no more then 1′ all the substrate was transformed in 4-bromo-resorcinol **3**. At this step an equivalent amount of sodium chloride and other portions of dimethyldioxirane were added in succession. The final main product was 4-chloro-6-bromo-resorcinol **8**, which was obtained in very good yields (Scheme 2).



1 **3** **8**

Scheme 2. Mixed halogenation of resorcinol by DMD/H^+/NaX system.

The same reaction performed on flavonoid compounds gave the 6,8-dichloro derivatives in excellent yield, while in absence of halogen ions the 6-hydroxy derivative was obtained (Scheme 3).[2]



Scheme 3. Halogenation of flavanones by DMD/HCl system.

In the same way we obtained a highly selective functionalisation of flavones, compounds carrying a double bond in ring B (Scheme 4). In this case the reaction was chemo-selective. In fact, in neutral conditions or in the absence of halogen ions, DMD reacts rapidly with the double bond.

The advantage of this system for the preparation of aromatic halogenated compounds is mainly the use of easy manipulating reagents instead of elementary halogens or more complicated systems,[3] together with the easyness of their dosage to prepare mixed halogenated compounds.

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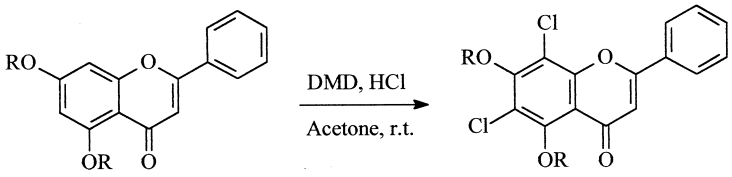


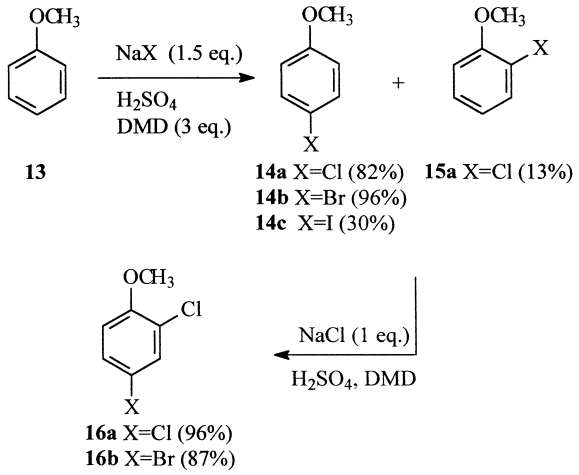
11a R=H
11b R=CH_3

12a R=H
12b R=CH_3

Scheme 4. Halogenation of flavones by DMD/HCl system.

In the case of mono substituted benzenes such as anisole, there is also the regioselective aspect to discuss. The chlorination of anisole led to a mixture of *para* and *ortho* chloro-anisole, **14a** and **15a** in a 5:1 ratio, and the double chlorination led to the 2,4-dichloro-anisole **16** in a quantitative yield. No 2,6-dichloro derivative was observed.

The bromination led instead, with an almost complete regiochemical control, to the *para* bromo-anisole **14b** and the iodination led to low yield of the corresponding *para* iodo-anisole **14c** (Scheme 5).



13

14a X=Cl (82%) **15a** X=Cl (13%)
14b X=Br (96%)
14c X=I (30%)

16a X=Cl (96%)
16b X=Br (87%)

Scheme 5. Halogenation of anisole by DMD/H^+/NaX system.

In nature, halogenated organic compounds are mainly found in marine organisms.[4] This area of natural product chemistry has received

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intense study over the past thirty years. Aromatic halogen compounds have been found to possess interesting biological activities in many cases. As for example the highly antimutagenic cymobarbatol,[5] some halogenated indoles[6] and carbazoles[7] which have a range of antiviral, antimicrobial and other biological activities including activity against the Polio virus and Herpes simplex virus.

Ortho halogen phenols are commonly present in nature[8] and some of them are believed to function as a chemical defence to deter potential predators of the organisms in which they are produced.[9] Moreover a large number of marine metabolites are derived from halogenated tyrosine.[10] In addition chloro-phenols are used industrially on a large scale, and polyhalogenated phenol derivatives are used in the synthesis of policyclic natural compounds.[11]

Given the chemical importance of aromatic halogenated compounds, principally as synthetic intermediates, our interest is to prosecute the studies to exploit the selective halogenation of phenols by DMD/HX system for the synthesis of more interesting compounds.

EXPERIMENTAL

General. ^{1}H- and ^{13}C-NMR spectra were recorded with VARIAN Gemini 2000 and VARIAN Mercure 300 apparatus in $CDCl_3$. Reactions were monitored either by TLC using Merck silica gel 60 F-254 plates with UV indicator or/and visualized with phosphomolybdic acid (10% solution in EtOH) and by gas chromatography. Flash column chromatography on silica gel was normally used for purification of the reaction mixtures, when necessary. Elemental analyses were performed by the Servizio Microanalisi of the Dip. Chimica of the Università of Roma "La Sapienza."

Dimethyldioxirane (DMD). A 0.08 M solution of DMD in acetone was typically prepared as follows. In a 2 l round bottom flask equipped with a magnetic stirrer, 240 g of Oxone® were added in portion to a mixture of 500 mL of water, 360 mL of acetone and 120 g of sodium hydrogen carbonate cooled at 0°C and vigorously stirred, during 20–30 min. The solution was then distilled under vacuum (500 mmHg) taking the collecting flask at −78°C.

General procedures for the halogenation reactions. *Method A*. To a solution of the substrate (0.5 mmol) in acetone (1 mL) and HX (X=Cl, Br; 10% sol. in water, 1 mL), a 0.08 M solution of DMD in acetone (12–20 mL) was added during 1 min. Acetone was distilled under vacuum and the mixture extracted with diethyl acetate. *Method B*. To a solution of the substrate (0.5 mmol), acetone (1 mL) and H_2SO_4 (10% sol. in water, 1 mL) and NaX

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(X=Cl, Br, 0.5 mmol), a 0.08 M solution of DMD in acetone (12–20 mL) was added during 1 min. The mixture was worked up as usual. *Dihalogenations*. Double halogenations were performed using method A or method B with an excess of halogen ions and DMD. More substituted compounds were never observed.

For all the methods, the double halogenation can require more equivalents of the oxidant. This is due to the less reactivity of the monohalogenated compounds and the competitive degradation of DMD in acidic medium. In that case, further portions of DMD solution were added until disappearance of the starting material (monitoring by GC).

4-Chloro-resorcinol 2a. Method A or B, yield 90%. ^{1}H-NMR, δ (ppm): 6.39 (dd, 1H, J = 8.8, 3.3), 6.54 (d, 1H, J = 3.3), 7.15 (d, 1H, J = 8.8). ^{13}C-NMR, δ (ppm): 108.8, 111.6, 129.3, 152.1, 155.8.

3-Methoxy-4-chloro-anisole 2b. Method A or B, yield 95%. ^{1}H-NMR, δ (ppm): 3.8 (s, 3H), 3.88 (s, 3H), 6.44 (dd, 1H, J = 8.8, 2.9), 6.49 (d, 1H, J = 2.9), 7.24 (d, 1H, J = 8.8). ^{13}C-NMR, δ (ppm): 55.4, 55.9, 99.9, 105, 113, 130, 155.5, 159.4.

4-Bromo-resorcinol 3a. Method A or B, yield 95%. ^{1}H-NMR, δ (ppm): 6.36 (dd, 1H, J = 8.2, 2.7), 6.56 (d, 1H, J = 2.7), 7.25 (d, 1H, J = 8.2). ^{13}C-NMR, δ (ppm): 98.1, 103.7, 108.1, 132.5, 154.5, 157.7.

3-Methoxy-4-bromo-anisole 3b. Method A or B, yield 95%. ^{1}H-NMR, δ (ppm): 3.82 (s, 3H), 3.89 (s, 3H), 6.42 (dd, 1H, J = 2.2, 8.8), 6.50 (d, 1H, J = 2.2), 7.44 (d, 1H, J = 8.8). ^{13}C-NMR, δ (ppm): 55.5, 56.1, 99.9, 102.4, 105.9, 133.1, 156.5, 160.2.

3-Methoxy-4-iodo-anisole 4b. Method B, yield 95%. ^{1}H-NMR, δ (ppm): 3.82 (s, 3H), 3.88 (s, 3H), 6.33 (dd, 1H, J = 2.2, 8.8), 6.45 (d, 1H, J = 2.2), 7.65 (d, 1H, J = 8.8). ^{13}C-NMR, δ (ppm): 55.5, 56.2, 74.7, 99.2, 106.9, 139.1, 158.8, 161.3.

4,6-Dichloro-resorcinol 5a. Method A or B, yield 85%. ^{1}H-NMR, δ (ppm): 6.72 (s, 1H), 7.28 (s, 1H). ^{13}C-NMR, δ (ppm): 103.9, 110, 126.2, 151.4.

3-Methoxy-4,6-dichloro-anisole 5b. Method A or B, yield 90%. ^{1}H-NMR, δ (ppm): 3.86 (s, 6H), 6.49 (s, 1H), 7.28 (s, 1H). ^{13}C-NMR, δ (ppm): 56.2, 97.5, 113.6, 130.1, 154.3.

4,6-Dibromo-resorcinol 6a. Method A or B, yield 78%. ^{1}H-NMR, δ (ppm): 5.48 (br, 2H), 6.74 (s, 1H), 7.53 (s, 1H). ^{13}C-NMR, δ (ppm): 98.7, 103.1, 134.5, 151.6.

3-Methoxy-4,6-dibromo-anisole 6b. Method A or B, yield 85%. ^{1}H-NMR, δ (ppm): 3.89 (s, 6H), 6.48 (s, 1H), 7.65 (s, 1H). ^{13}C-NMR, δ (ppm): 56.5, 97.46, 102.46, 135.9, 156.1.

3-Methoxy-4,6-diiodo-anisole 7b. Method B, yield 90%. ^{1}H-NMR, δ (ppm): 3.88 (s, 6H), 6.36 (s, 1H), 8.03 (s, 1H). ^{13}C-NMR, δ (ppm): 56.5, 75.5, 95.9, 146.8, 159.6.

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4-Bromo-6-chloro-resorcinol 8. Method B was used for the preparation of **3a**, then 1 eq. of NaCl and an other amount of DMD were added to the mixture. After additions were completed, the usual work up gave **8** which resulted pure from NMR analysis. ^{1}H-NMR, δ (ppm): 3.90 (s, 3H), 3.91 (s, 3H), 6.50 (s, 1H), 7.49 (s, 1H). ^{13}C-NMR, δ (ppm): 56.3, 56.5, 97.5, 101.8, 114.4, 113.1, 135.8, 155.1. Analysis: calc. for $C_6H_4BrClO_2$ C 32.25, H 1.80; found C 32.3, H 2.0.

5,7,4′-Trimethoxy-6,8-dichloro-flavanone 10. Method A, quant. yield. ^{1}H-NMR, δ (ppm): 2.88 (dd, 1H, J = 3, 16.4), 3.07 (dd, 1H, J = 13, 16.4), 3.81 (s, 3H), 3.89 (s, 3H), 3.96 (s, 3H), 5.48 (dd, 1H, J = 3, 13), 6.93 (d, 1H, J = 5.5), 7.39 (d, 1H, 5.5). 44.8, 55.3, 60.9, 61.8, 79.3, 113.4, 114.2, 127.5, 129.7, 156.0, 157.4, 158.5, 160.0, 188.6. Analysis: calc. for $C_{18}H_{16}Cl_2O_5$ C 56.41, H 4.21; found C 56.2, H 4.5.

5,7-Dihydroxy-6,8-dichloro-flavone 12a. Method A, yield 72%. ^{1}H-NMR (DMSO-d_6), δ (ppm): 7.16 (s, 1H), 7.52–7.68 (m, 3H), 8.08–8.18 (m, 2H). 99.4, 103.9, 104.5, 105.3, 126.4, 129.3, 130.2, 132.5, 155.1, 155.9, 161.6, 163.5, 170.9, 181.7. Analysis: calc. for $C_{15}H_8Cl_2O_4$ C 55.76, H 2.5; found C 55.9, H 2.8.

5,7-Dimethoxy-6,8-dichloro-flavone 12b. Method A, yield 87%. ^{1}H-NMR, δ (ppm): 3.99 (s, 3H), 4.04 (s, 3H), 6.77 (s, 1H), 7.48–7.60 (m, 3H), 7.90–8.20 (m, 2H). ^{13}C-NMR, δ (ppm): 61.2, 62.1, 108.3, 14.2, 16.5, 121.5, 126.1, 129.1, 130.6, 131.9, 152.2, 154.8, 156.9, 161.5, 175.9. Analysis: calc. for $C_{17}H_{12}Cl_2O_4$ C 58.14, H 3.44; found C 57.8, H 3.4.

4-Chloro-anisole 14a. Method B, yield 82%. ^{1}H-NMR, δ (ppm): 3.81 (s, 3H), 6.84 (bd, 2H, J = 9.5), 7.26 (bd, 2H, J = 9.5). ^{13}C-NMR, δ (ppm): 55.4, 115.1, 127.7, 129.3, 158.2.

4-Bromo-anisole 14b. Method B, yield 96%. By NMR analysis of the crude, 1.3% of 2-bromo-anisole was also detected. An excess of DMD did not give the dibromo derivative in any condition. ^{1}H-NMR, δ (ppm): 3.80 (s, 3H), 6.78 (bd, 2H, J = 9.2), 7.38 (bd, 2H, J = 9.2). ^{13}C-NMR, δ (ppm): 55.4, 112.8, 115.7, 132.2, 158.7.

4-Iodo-anisole 14c. Method B, yield 30%. Further additions of DMD resulted in decomposition of the mixture. ^{1}H-NMR, δ (ppm): 3.79 (s, 3H), 6.78 (bd, 2H, J = 9.4), 7.55 (bd, 2H, J = 9.4). ^{13}C-NMR, δ (ppm): 55.3, 82.7, 116.4, 138.2, 159.5.

2-Chloro-anisole 15a. Method B, yield 13%. ^{1}H-NMR, δ (ppm): 3.89 (s, 3H), 6.89 (m, 2H), 7.21 (m, 1H), 7.4 (dd, 1H, J = 2.2, 8.1). ^{1}H-NMR, δ (ppm): ^{13}C-NMR, δ (ppm): 56.0, 112.1, 121.2, 125.5, 127.5, 130.2, 155.0.

2,4-Dichloro-anisole 16a. Method B, yield 96%. ^{1}H-NMR, δ (ppm): 3.9 (s, 3H), 6.86 (d, 1H, J = 8.8), 7.22 (dd, 1H, J = 2.2, 8.8), 7.38 (d, 1H, J = 2.2). ^{13}C-NMR, δ (ppm): 56.3, 112.8, 123.3, 125.6, 127.6, 129.9, 153.9.

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2-Chloro-4-bromo-anisole 16b. Method B, yield 87%. ^{1}H-NMR, δ (ppm): 3.81 (s, 3H), 6.72 (d, 1H, J = 8.8), 7.26 (dd, 1H, J = 2.2, 8.8), 7.42 (d, 1H, J = 2.2). ^{13}C-NMR, δ (ppm): 56.2, 112.4, 113.3, 123.6, 130.4, 132.6, 154.3.

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