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Kaolin-assisted Aromatic Chlorination and Bromination†

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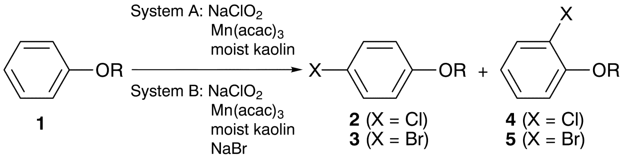
Moist kaolin catalyses the regioselective and high-yielding chlorination and bromination of C_6H_5OR (R = C_1–C_8 alkyl, Bu^t, allyl, cyclohexyl, benzyl) to 4-XC_6H_4OR (X = Cl and Br, respectively) with $NaClO_2$ and $Mn(acac)_3$ in CH_2Cl_2 in the absence and presence of NaBr, respectively, under mild and neutral conditions.

Use of supported reagents and catalysts for organic synthesis has gained general acceptance as a new, environmentally benign protocol.[1] Aluminosilicate clays are well characterised by their surface acidities, which render them efficient, versatile supports or catalysts.[1c,2] Somewhat surprisingly, while montmorillonites (bentonites) have achieved very wide use, kaolin-based reagents or kaolin-assisted reactions appear to be extremely limited.[2] We felt from our own experiments on the oxidation of sulfides to sulfones[3a] and to sulfoxides[3b] that kaolin is slightly inferior as a catalyst to bentonite. However, a marked catalysis of natural kaolins has recently been observed upon the protection reaction of carbonyl compounds[4a] and the alkylation of benzene.[4b] It might therefore be of considerable interest to find further use of kaolin as a solid catalyst in a variety of organic reactions.



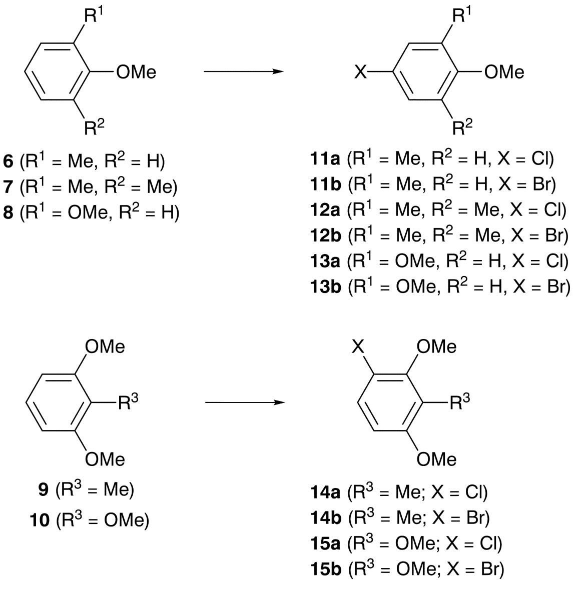
1 **2** (X = Cl) **3** (X = Br) **4** (X = Cl) **5** (X = Br)

R: **a** = Me; **b** = Et; **c** = Pr; **d** = Bu; **e** = Bu^t; **f** = C_5H_{11}; **g** = C_6H_{13}; **h** = C_8H_{17}; **i** = c-C_6H_{11}; **j** = $PhCH_2$; **k** = $CH_2CH{=}CH_2$

Scheme 1

We chose the electrophilic halogenation[5] of aromatic ethers as a target, since certain alkyl 4-halogenophenyl ethers exhibit bioactivity and are useful intermediates *en route* to many fine chemicals; for example, 4-chlorophenyl octyl ether **2h** is a very active plant growth regulator.[6] Thus, treatment of anisole **1a** with a combination of sodium chlorite ($NaClO_2$) and a catalytic amount of $Mn(acac)_3$ (1 mole % with respect to **1a**)[7] in CH_2Cl_2 at 25 °C in the presence of kaolin preloaded with a small amount of water (moist kaolin)‡ afforded monochloroanisoles with high selectivity to *p*-isomer **2a** (System A in Scheme 1). System A can successfully be used for the selective chlorination of a series of alkyl phenyl ethers **1b**–**1k**, irrespective of chain length or steric bulk of the alkyl groups. During this study, we have fortunately found that nuclear bromination is readily achieved by simple addition of NaBr to System A (System B), giving good to quantitative yield of alkyl *p*-bromophenyl ethers **3a**–**3k**, along with minor amounts of *p*-chloro derivatives **2** (< 4%). GLC analyses of reaction mixtures showed that Systems A, B achieved 100% regiospecificity, except for halogenations of **1a** where *o*-chloroanisole **4a** (4.9%) and *o*-bromoanisole **5a** (1.0%) were formed. Moreover, Systems A, B have proved to be applicable to gram scale halogenation of **1a** with the use of the same quantity of $Mn(acac)_3$ (0.1 mole % in this case) as that in the small scale experiment (see Table 1).

An independent experiment with compound **1a** carried out in the absence of moist kaolin brought about no halogenation even after a prolonged period (**1a** recovery 99% by GLC), clearly indicating that the clay efficiently catalyses the halogenation. Comparative halogenations of **1a** using a common acidic clay, Montmorillonite K10, and a mildly acidic support, silica gel, in place of kaolin, revealed that kaolin is superior to the others in its catalytic activity, selectivity or yield of the product (see Table 1). Another set of experiments showed that neither $NaClO_2$/NaBr/moist kaolin nor $Mn(acac)_3$/NaBr/moist kaolin can halogenate **1a**, and also that **2a** does not change to **3a** under bromination conditions. Consequently, it could be likely that a positive chlorine species responsible for the chlorination oxidises bromide ion quickly to generate an electrophilic Br^+ species.



6 (R^1 = Me, R^2 = H)
7 (R^1 = Me, R^2 = Me)
8 (R^1 = OMe, R^2 = H)

11a (R^1 = Me, R^2 = H, X = Cl)
11b (R^1 = Me, R^2 = H, X = Br)
12a (R^1 = Me, R^2 = Me, X = Cl)
12b (R^1 = Me, R^2 = Me, X = Br)
13a (R^1 = OMe, R^2 = H, X = Cl)
13b (R^1 = OMe, R^2 = H, X = Br)

9 (R^3 = Me)
10 (R^3 = OMe)

14a (R^3 = Me; X = Cl)
14b (R^3 = Me; X = Br)
15a (R^3 = OMe; X = Cl)
15b (R^3 = OMe; X = Br)

Scheme 2

The kaolin-based biphasic systems favorably aided the regiospecific halogenation of multisubstituted benzenes **6**–**10** (Scheme 2). Although highly activated arenes such as veratrole **8** and pyrogallol trimethyl ether **10** are vulnerable to polyhalogenations,[8] the present procedures can be controlled to stop at the monohalogenation stage. Like halogenations of simple alkyl phenyl ethers, the tendency that hydrogens attached to the more nucleophilic carbon atoms on the benzene rings[5a] are preferentially displaced by chlorine and bromine is quite general.

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‡The effect of water on surface-mediated reactions has been described elsewhere.[7]

Table 1 Aromatic mono-chlorination and -bromination of aromatic ethers[a]

	Chlorination			Bromination			
Ether	$NaClO_2$ (mmol)	*t*/min	Product (%)[b]	$NaClO_2$ (mmol)	NaBr (mmol)	*t*/min	Product (%)[b]
1a	1.7	100	**2a** (94), **4a** (4.9)	1.2	3.0	110	**3a** (98), **5a** (1.0)
1a[c]	2.1	60	**2a** (67), **4a** (7.5)[d]	1.4	3.0	60	**3a** (99)
1a[e]	2.1	60	**2a** (72), **4a** (13)[f]	1.4	3.0	120	**3a** (90)[g]
1a	14[h]	50	**2a** (94)	12[h]	30	130	**3a** (95)
1b	1.5	60	**2b** (96)	1.2	3.0	100	**3b** (95)
1c	1.6	80	**2c** (98)	1.2	3.0	160	**3c** (97)
1d	1.7	100	**2d** (quant.)	1.2	3.0	100	**3d** (96)
1e	1.5	70	**2e** (93)	1.2	3.0	140	**3e** (92)
1f	1.6	80	**2f** (99)	1.2	3.0	130	**3f** (97)
1g	1.6	100	**2g** (quant.)	1.2	3.0	110	**3g** (97)
1h	1.5	70	**2h** (99)	1.2	3.0	90	**3h** (95)
1i	1.5	60	**2i** (96)	1.2	3.0	90	**3i** (98)
1j	1.9	60	**2j** (99)	1.2	4.0	80	**3j** (98)
1k	2.2	120	**2k** (60)[i]	1.5	4.5	150	**3k** (66)[j]
6	1.5	110	**11a** (93)	1.0	4.5	120	**11b** (95)
7	2.0	70	**12a** (96)	1.3	4.5	60	**12b** (quant.)
8	1.5	60	**13a** (94)	1.0	3.5	120	**13b** (quant.)
9	1.2	80	**14a** (95)	1.1	4.5	90	**14b** (92)
10	1.3	80	**15a** (98)	1.0	3.5	120	**15b** (97)

[a] At 25 °C; 1 mmol ether, 0.01 mmol $Mn(acac)_3$, 1 g moist kaolin, 10 ml CH_2Cl_2. [b] Yield of chromatographically purified product based on the starting ether. [c] Moist montmorillonite K10 used as support. [d] *ca.* 20% of **1a** remained. [e] Silica gel as support. [f] *ca.* 13% (GLC area ratio) of a unknown product was formed. [g] *ca.* 3% of **2a** was formed. [h] At 30 °C; 10 mmol **1a**, 0.01 mmol $Mn(acac)_3$, 3 g moist kaolin, 30 ml CH_2Cl_2. [i] GLC yield. [j] GLC yield; 2.4% of **1k** remained.

Surface-mediated reactions afford excellent product yield and selectivity often unattainable by solution phase counterparts.[9] For fascinating instances, $CuCl_2$/alumina (100 °C, 2–3 h),[9b] Bu^tOCl/zeolite (25 °C, 1 h–2 weeks),[9c] and Br_2/zeolite (ambient, 1–5 h)[9d] systems have elegantly achieved high-yielding, regio-controlled nuclear chlorination[9b,c] and bromination[9d] of a number of arenes. Simple, inexpensive procedures demonstrated here accomplish efficient halogenations under mild conditions and their regiospecificities are impressive. In addition, NaBr is more attractive as the bromine source than Br_2. They could therefore be added to a list of synthetically useful halogenation methodologies.[9] In view of the easy accessibility and excellent reaction performance of the new biphasic system, we are now looking for another synthetic target to make use of the remarkable catalysis by kaolin.

Experimental

Sodium chlorite (available chlorine *ca.* 82% by iodometry), $Mn(acac)_3$, and substrates **1a**, **b**, **d**, **j**, **k**, **6**–**10** were used as received from commercial sources. Ethers **1c**, **1e**–**1h**[10] and **1i**[11] were prepared by known methods. Moist kaolin (H_2O content, 13 wt. %) was prepared by adding deionised water (0.15 g) in portions to commercial kaolin (Kukita; 1.0 g), followed by vigorous shaking of the mixture after every addition for a few minutes until a free-flowing powder was obtained. Montmorillonite K10 (Aldrich) and predried silica gel (Merck silica gel 60) were treated with deionised water as above.

Chlorination Procedure.—A representative procedure was as follows. A 30 ml, two-necked, round bottom flask, equipped with a Teflon-coated stirrer bar and reflux condenser, was charged with anisole **1a** (1 mmol), freshly prepared moist kaolin (1 g), $Mn(acac)_3$ (0.01 mmol) and dried (molecular sieves) CH_2Cl_2 (10 ml), and the mixture stirred for a few minutes. Sodium chlorite (1.7 mmol as available chlorine) was then added in one portion with stirring. The cloudy suspension was kept at 25 °C while efficient stirring was continued in order to ensure smooth reaction and to attain reproducible results. After 100 min (agitation periods after complete addition of $NaClO_2$ are indicated in Table 1) the whole material was transferred to a sintered glass funnel and the filter cake washed thoroughly with portions of dry diethyl ether (*ca.* 100 ml). Rotary evaporation of the solvent, followed by chromatography on a silica gel column (Merck silica gel 60, hexane–AcOEt), gave *p*-chloroanisole **2a** in 94% yield.

Bromination Procedure.—The bromination was carried out by adding $NaClO_2$ and NaBr both in one portion to a stirred mixture of ether, $Mn(acac)_3$, and moist kaolin CH_2Cl_2. After a given time, work-up and chromatographic isolation as above gave the pure bromination product. Halogenoethers thus obtained were fully characterised by MS and NMR spectroscopies.

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