Regiospecific aromatic chlorination of alkyl phenyl ethers using sodium chlorite catalysed by manganese(III) acetylacetonate and moist alumina in dichloromethane

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A solid–liquid biphasic system (dichloromethane and chromatographic neutral alumina) has been tested for the aromatic chlorination of various alkyl aryl ethers using a reagent combination of sodium chlorite and manganese(III) acetylacetonate catalyst. Efficient incorporation of a chlorine atom into the benzene ring with high *para*-selectivity results. This catalytic system is also applicable to the regiocontrolled chlorination of polyether substrates.

Electrophilic aromatic halogenation is one of the most important basic reactions in organic chemistry[1] since halogenoarenes are useful not only as bulk materials, but as fine chemicals for both industrial and laboratory use.[2] From a literature search, however, it was apparent that there are relatively few systems which give chlorinations in high yield (>90%) and with high regiospecificity. Numerous reagent systems and/or technical improvements have been recommended to enable chlorinations to be carried out efficiently and, more recently, in keeping with the concept of Clean Synthesis.[3] The use of supported reagent systems[4] is a particularly promising strategy due to the simplified set-up and work-up procedures, mild conditions, and enhanced reaction rate as well as reduced waste.[5] It is encouraging to note that both the yields of halogenoarenes and the regiospecificities of the reactions resulting from the reactions with solid/solution biphasic systems are, in general, superior to those from their simple solution phase counterparts.[3,6,7]

In a recent study on the oxidation of sulfides with sodium chlorite (NaClO$_2$, **1**),[8] we have shown that a reagent combination of **1**, manganese(III) acetylacetonate catalyst [Mn(acac)$_3$, **2**], and chromatographic neutral alumina pre-loaded with water (moist alumina **3**, *vide infra*) brings about aromatic chlorination of anisole **4a**, giving predominantly *p*-chloroanisole **5a** (**5a**/**6a** ratio, 95:5, total yield 94%: Scheme 1). This method compares
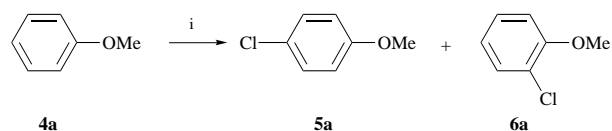
Scheme 1 *Reagents and conditions*: i, NaClO$_2$, Mn(acac)$_3$, moist Al$_2$O$_3$, CH$_2$Cl$_2$, 20 °C

favourably with the chlorination of alkyl phenyl ethers with alumina-supported CuCl$_2$ reagent (100 °C, 3 h, [CuCl$_2$]/[**4a**] = 5):[9] thus, the new reaction uses a smaller amount of chlorinating agent, proceeds smoothly under much milder conditions, and is complete within a shorter reaction period (20 °C, 40 min, [**1**]/[**4a**] = 2). As a part of our current research interest in the utilization of solid catalysts for new cleaner synthetic procedures,[8,10] we now report an extension of the preliminary observation to a series of alkyl phenyl ethers. As might be expected, the NaClO$_2$/Mn(acac)$_3$/moist alumina system furnishes a mild, selective, and inexpensive electrophilic chlorine source for activated arenes.

The efficiency of supported reagent systems is known to be highly dependent on the choice of support material, the solvents, and the presence of water.[4b] Consequently, these factors were first studied so as to optimise the reaction conditions. Thus, when anisole **4a** was treated with NaClO$_2$ **1** alone (Entry 1 in Table 1) or with a combination of **1** and a catalytic amount of Mn(acac)$_3$ **2** (1 mol% with respect to **4a**) in dichloromethane (abbreviated as a **1**/**2** system; Entry 5) at 25 °C no reaction occurred, **4a** being recovered without substantial loss (**4a** recovery 98% by GLC on every experiment). Similarly, in the absence of catalyst **2**, no reaction occurred even when differently activated aluminas were added (Entries 2–4). Remarkably, a combination of **1**, **2**, and alumina pre-loaded with an optimum amount of water (moist alumina **3**; water content 17% by weight) (a **1**/**2**/**3** system) was found to show excellent activity in the model reaction. Thus, treatment of **4a** with a mixture of **1**, **2**, and **3** in dichloromethane for 40 min led to complete consumption of **4a**, giving rise to a mixture of monochloroanisoles, **5a** and **6a**, in quasi-quantitative yield (total 95%) with high selectivity in respect of **5a** (Entry 10); *viz*. **5a**/**6a** ratio 38.0:1 after statistical correction. Repeat runs with the **1**/**2** combination in the presence of untreated alumina (Entry 6) or pre-carcinated alumina (500 °C/6 h; dry alumina, Entry 7) gave no reaction. It is clear that in addition to the catalyst **2** the presence of a small amount of water on the alumina surface is essential for chlorination to occur under mild conditions. Use of an alumina with a smaller (Entries 8 and 9) or a larger water content (Entry 11) resulted in a decrease in the conversion of anisole, the yield of the products and/or the *para*-selectivity. Since sodium chlorite is insoluble in dichloromethane, the effect of particle size on the yield and regioselectivity of chloroanisoles was also investigated by studying untreated sodium chlorite (commercial reagent; Entry 10) and differently sized reagents (32, 65, and 100 mesh; Entries 12, 13 and 14, respectively). No marked effect was observed. Consequently, the commercial sodium chlorite was used as received from the supplier for subsequent investigations.

The effect of the solvent on the reactivity of **4a** and on the product selectivity was examined in the presence of moist alumina in various common organic solvents which were distilled and stored over molecular sieves for a few days prior to use. Table 2 clearly shows that the choice of solvent is another

Table 1 Effects of catalyst and alumina on the chlorination of anisole **4a**[a]

Entry No.	Alumina	Distribution (%)[b]			5a/6a Ratio
		4a	**5a**	**6a**	
1*	†	98	0	0	
2*	Commercial[c]	96	0	0	
3*	Dry[d]	96	0	0	
4*	Moist (17%)[e]	94	0	0	
5	†	98	0	0	
6	Commercial[c]	95	0	0	
7	Dry[d]	96	0	0	
8	Moist (9%)[e]	98	0	0	
9	Moist (13%)[e]	5.6	80	8.7	90:10
10	Moist (17%)[e]	0	90	4.7	95:5
11	Moist (20%)[e]	4.7	83	5.2	94:6
12[f]	Moist (17%)[e]	0	91	4.9	95:5
13[g]	Moist (17%)[e]	0	90	4.9	95:5
14[h]	Moist (17%)[e]	0	91	4.8	95:5

[a] At 25 °C, for 40 min; anisole 1 mmol, $NaClO_2$ 2.0 mmol, $Mn(acac)_3$ 0.01 mol (1 mol% with respect to anisole), alumina 1 g, dichloromethane 10 ml. Commercial $NaClO_2$ was used as received from the supplier. [b] Determined by GLC using biphenyl as an internal standard. [c] Commercial alumina (ICN BIOMEDICAL, Alumina N, Super I) was used as received. [d] Oven-dried (500 °C, 6 h) alumina was used. [e] Moist alumina prepared from the oven-dried alumina[d] and deionized water was used; numbers in parentheses are water contents by wt%; for details of moist aluminas, see Starting Materials in the Experimental section. [f] $NaClO_2$ 32 mesh. [g] $NaClO_2$ 65 mesh. [h] $NaClO_2$ 100 mesh. * No $Mn(acac)_3$ was added. † No alumina was used.

Table 2 Aromatic chlorination of anisole in various solvents[a]

Entry No.	Solvent	Distribution (%)[b]			5a/6a Ratio
		4a	**5a**	**6a**	
10[c]	Dichloromethane	0	90	4.7	95:5
15[c,d]		96	0	0	
16[c,e]		99	0	0	
17[c]	Chloroform	98	0	0	
18		98	0	0	
19[c,f]		32	59	7.6	89:11
20[c,g]		17	53	7.5	88:12
21[c]	Tetrachloromethane	97	0	0	
22		99	0	0	
23	1,2-Dichloroethane	97	0	0	
24	Hexane	97	0	0	
25	Ethyl acetate	96	0	0	
26	Diethyl ether	97	0	0	
27	Tetrahydrofuran	96	0	0	
28	Acetonitrile	95	0	0	
29	Acetone	97	0	0	
30	Ethanol	98	0	0	
31	1,4-Dioxane	95	0	0	

[a] At 25 °C, for 2 h; anisole 1 mmol, $Mn(acac)_3$ 0.01 mmol (1 mol% with respect to anisole), $NaClO_2$ 2.0 mmol, the moist alumina 1 g, solvent 10 ml. [b] Determined by GLC using biphenyl as an internal standard. [c] For 40 min. [d] In dichloromethane (10 ml) admixed with ethanol (0.05 ml). [e] In dichloromethane (10 ml) admixed with ethanol (0.1 ml). [f] Chloroform, which was washed repeatedly with water and dried over calcium chloride and then molecular sieves, was used. [g] Chloroform stored over molecular sieves for over two weeks was used.

important factor; of the commercial solvents used, only dichloromethane favoured chlorination (Entry 10). Attempted reactions in the other solvents afforded no indication of chlorination during the same (40 min; Entries 15–17, and 21) and/or prolonged periods of time (2 h), giving **4a** essentially unchanged (**4a** recovery 95–99% by GLC). However, since commercial chloroform is stabilised with ethanol and its removal is assumed to be difficult by ordinary distillation due to the small difference in their boiling points (bps 61 and 78 °C, respectively), additional experiments were also carried out in dichloromethane–ethanol mixed solvents. Surprisingly, the reactions were inhibited by the addition of a small amount of ethanol to dichloromethane (Entries 15 and 16; ethanol contents, 0.5 and 1%, respectively). Another reaction in chloroform (Entry 19), which had been washed repeatedly with water in order to remove completely the ethanol and dried over calcium chloride and then molecular sieves, further demonstrated the inhibition by ethanol, although the conversion of **4a** and yield of monochloroanisoles were much inferior to those observed in Entry 10. Additional experiments showed that reactions in chloroform, which had been stored over molecular sieves for a longer period (over 2 weeks; Entry 20), gave monochloroanisoles but in lower yield. Consequently, dichloromethane appears to be the best solvent for these reactions.

Another comparative study was carried out using a number of typical solid support materials (Table 3). There are significant differences in the efficiencies of the chlorinations using the various supports: aluminas, silica gels, and clays were moderately to highly active as solid catalysts, but aluminium silicate and zeolites exhibited little activity. Among the supports tested, neutral alumina is probably the best in terms of ease of use, product yield and selectivity of reaction to p-chloroanisole.

It is also worth noting that in the reactions in Tables 1–3 there is no evidence for the formation of 2,4-dichloroanisole or polychlorinated compounds in any appreciable amounts or for any other side reaction such as chlorination of the methyl moiety, demethylation or rearrangement to a phenolic compound etc.

Although it is known that some heterogeneous reactions have been affected by the presence of water,[11,12] the remarkable sensitivity of the current reaction towards the water content of the

alumina and towards the solvent are unexpected and unusual. Previous investigations showed that oxidation of sulfides with the **1/2/3** system can be carried out in a number of solvents especially in acetone and the importance of water was considerably less.[8] Atomic absorption analyses of the reaction solvents showed no detectable amount of manganese indicating that the chlorination presumably occurs on the alumina surface. These observations suggest that the solvent/alumina surface interface plays a decisive role in the present reaction. There might be a fine balance between keeping the right amount of water on the alumina surface to help break up the sodium chlorite lattice[13] and moderate solvent polarity to enable the chlorination to occur under mild conditions.

The reactions of a series of alkyl phenyl ethers **4a–n** clearly illustrates the synthetic value of the **1/2/3** system as a mild and highly efficient electrophilic chlorine source (Scheme 2, Table 4).
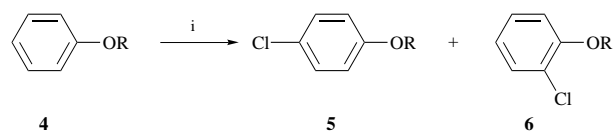
R: **a** = Me; **b** = Et; **c** = Pr; **d** = Pr[i]; **e** = Bu; **f** = Bu[s]; **g** = Bu[i]; **h** = Bu[t]; **i** = C_5H_{11}; **j** = C_6H_{13}; **k** = C_8H_{17}; **l** = c -C_5H_9; **m** = c -C_6H_{11}; **n** = CH$_2$CH=CH$_2$

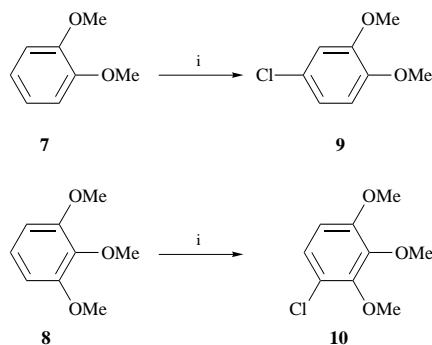**Scheme 2** *Reagents and conditions*: i, $NaClO_2$, $Mn(acac)_3$, moist Al_2O_3, CH_2Cl_2, 25 °C

The ethers afforded nuclear chlorination products in good to essentially quantitative yields, irrespective of carbon-chain length or steric bulk of alkyl groups. Of special note is the observation that with alkyl groups in the ethers larger than methyl, 100% regiospecificity is achieved, giving rise to the single product **5** in excellent yield in almost all cases. It seems likely that the high regioselectivity is a result of geometric constraints on the alumina surface, enabling the ethers to be substituted only at the para-positions and thus precluding the formation of the ortho-isomers. Comparative studies using ethers with C_3 (Entries 47 and 48) and C_4 alkyl groups (Entries 49–52), and cycloalkyl groups (Entries 56 and 57) clearly suggest that the

Table 3 Aromatic chlorination of anisole using various inorganic support materials[a]

| Entry No. | Support materials | Time (min) | Distribution (%)[b] | | | 5a/6a Ratio |
			4a	5a	6a	
10	Neutral alumina	40	0	90	4.7	95:5
32	Acidic alumina	35	0	85	8.0	91:9
33	Basic alumina	60	0	85	7.9	91:9
34	Silica gel 60	40	16	65	14	82:18
35	Silica gel BW-127ZH	55	20	62	13	83:17
36	Silica gel BW-300	50	0	77	17	82:18
37	Kaolin	40	0	87	4.7	95:5
38	Montmorillonite K10	40	0	73	11	87:13
39	Bentonite	110	33	61	5.5	92:8
40	Japanese acid clay	30	0	83	6.5	93:7
41	Florisil	50	50	40	5.2	88:12
42	Celite	45	7.9	83	5.6	94:6
43	Aluminium silicate	180	97	0	0	
44	Zeolite A-3	420	98	0	0	
45	Zeolite F-9	80	91	8.0	0	100:0

[a] At 25 °C; anisole 1 mmol, Mn(acac)$_3$ 0.01 mmol (1 mol% with respect to anisole), NaClO$_2$ 2.0 mmol, moist support material 1 g (water content 17% by weight), dichloromethane 10 ml. [b] Determined by GLC using biphenyl as an internal standard.

Table 4 Aromatic mono-chlorination of alkyl phenyl ethers[a]

| Entry No. | Ether | NaClO$_2$ (mmol) | Time (min) | Chlorination products | |
					Yield (%)[b]
10	**4a**	2.0	40	**5a**[c] + **6a**[d]	94 [95:5][e]
46	**4b**	2.0	40	**5b**[f]	90
47	**4c**	2.0	45	**5c**[f]	93
48	**4d**	2.0	60	**5d**[f]	94
49	**4e**	2.0	40	**5e**[f]	96
50	**4f**	1.9	45	**5f**[g]	95
51	**4g**	2.0	40	**5g**[f]	95
52	**4h**	2.0	40	**5h**[h]	92
53	**4i**	2.0	40	**5i**[i]	97
54	**4j**	2.0	45	**5j**[i]	91
55	**4k**	2.0	35	**5k**[j]	99
56	**4l**	1.9	35	**5l**[k]	91
57	**4m**	1.9	40	**5m**[l]	97
58	**4n**	2.1	120	**5n**[i]	56[m]
59[n]	**7**	3.0	35	**9**[o]	87
60[n]	**8**	2.4	40	**10**[p]	92

[a] At 25 °C; ether 1.0 mmol, Mn(acac)$_3$ 0.01 mmol (1 mol% with respect to the ether), moist alumina 1 g, dichloromethane 10 ml. [b] Isolated yield of chromatographically purified **5** [**5a** plus **6a** in the case of Entry 10] based on the starting ether **4**. [c] Beilstein, **6**, 186. [d] Beilstein, **6**, 184. [e] Regioselectivity of monochloroanisoles, **5a** vs. **6a**, determined by GLC. [f] Beilstein, **6**, II, 176. [g] L. E. Cook and R. C. Spangelo, Anal. Chem., 1974, **46**, 122, but no physical datum is available (vide Experimental section). [h] F. Camps, J. Coll and J. M. Moretó, Synthesis, 1982, 186. [i] Beilstein, **6**, III, 689. [j] R. M. Ismail, Z. Naturforsch., 1964, **19b**, 964 (Chem. Abstr., 1965, **62**, 2790d). [k] M. Saha, J. Bangladesh Acad. Sci., 1990, **14**, 241 (Chem. Abstr., 1991, **114**, 206664a), reported bp 116–121 °C/5 mmHg. [l] D. T. Dalgleish, D. C. Nonhebel and P. L. Pauson, J. Chem. Soc. C, 1971, 1174. [m] GLC yield. [n] Ether 1.5 mmol, Mn(acac)$_3$ 0.015 mmol. [o] Beilstein, **6**, IV, 5614. [p] Beilstein, **6**, IV, 7334.

steric environment around the ether linkage exercises no serious influence on the reactivity of the ether, the product selectivity, or the yield. Interestingly the unsaturated ether **4n**, for which side-chain halogenation might be expected, again gives the p-chlorinated product **5n** in good yield (Entry 58; 60% based on consumed **4n**). In addition, the di- **7** and tri-ether substrates **8** also gave highly regiocontrolled monochlorinations (Scheme 3; Entries 59 and 60 in Table 4).

Scheme 3 Reagents and conditions: i, NaClO$_2$, Mn(acac)$_3$, moist Al$_2$O$_3$, CH$_2$Cl$_2$, 25 °C

The chlorinations can be run smoothly to 100% conversion of aromatic ether in every case and no deactivation of the reagents was apparent. It has not yet proven possible however, to recycle the alumina. Indeed, re-use of alumina resulted in incomplete conversion of **4a**, or reduction in the rate of reaction or in product selectivity depending on different methods of treatment of the recovered alumina, viz. air drying on the filter funnel, thermal drying followed by addition of water, washing with water to remove residual Na salt plus thermal drying and water addition, further addition of Mn(acac)$_3$ catalyst, and so on. We are not able to offer a detailed explanation for the loss of activity of the alumina although we do observe an acidic gas evolved during the reaction and acidic conditions can damage alumina.[14] Furthermore, we have observed some skeleton destruction of a (salen)manganese(III) complex catalyst in other reactions,[15] implying that the organic ligands, Schiff bases for example, are sensitive to the experimental conditions.[16] Thermal drying of alumina is also thought to have a negative effect and freshly prepared moist alumina should, therefore, be used for successful and reproducible chlorination.

Finally, it should be noted that while the chlorinations described here have worked safely, we have experienced ignition of the reaction mixture immediately on addition of a large excess of sodium chlorite in other experiments with a (salen)-manganese(III) complex as a catalyst[15] in place of Mn(acac)$_3$ and, in another case, ignition occurred during the work-up stage of an experiment employing a large amount of the reagent even with a nonflammable solvent, dichloromethane. In order to check safety on scale-up a chlorination has been carried out on a 1 g scale. Chlorination of anisole **4a** was again chosen as the test reaction. Although the reaction is exothermic the chlorination proceeded safely by following the method described in the Experimental section. It is interesting to note that the chlorination proceeds smoothly with the use of the same quantity of Mn(acac)$_3$ catalyst (0.01 mmol; 0.1 mol% with respect to **4a**) as that in Entry 10 (1 mol% in that case). Moreover, the synthesis of **10** using 10 mmol (1.68 g) of pyrogallol trimethyl ether **8** has also been successfully carried out.

In summary, the solid–solution biphasic system made up of an inexpensive and easy to use reagent NaClO$_2$, small quantities of Mn(acac)$_3$ catalyst, and moist alumina serves as a mild and efficient electrophilic chlorine source for alkyl phenyl ethers, providing an operationally simple, fast, and practical procedure for regioselective and high-yielding aromatic chlorination. Regrettably, however, the fact that the **1/2/3** system shows little tendency to chlorinate benzene, toluene, aniline, benzaldehyde, nitroanisoles (o- and p-), and xylenes (o-, m-, and p-) under comparable conditions to those indicated in Table 4 places restriction on its use for less reactive arenes. In order to elucidate the synthetic utility of sodium chlorite, further studies into this interesting heterogeneous catalytic system are now under way in our laboratory.

Experimental

General

^{1}H NMR spectra were measured with a JEOL JNM-FX200 or JNM-FX500 spectrometer for solutions in deuteriochloroform

using SiMe$_4$ as an internal standard. Analytical GLC was carried out on a Shimazdu GC-4BM or GC-14B instrument, equipped with a flame ionization detector through a 2 m × 6 mm diameter glass column packed with 5% PEG-20M on Chromosorb WAW-DMCS and interfaced with a Shimadzu Chromatopac C-R6A integrator, with temperature programming. Mass spectra were determined on a JEOL SX-102A model mass spectrometer which was coupled with a Hewlett Packard GC5890 Series II model GLC apparatus *via* a heated capillary column. Atomic absorption analyses were carried out on a Hitachi 170-30 model instrument.

Starting materials

Dichloromethane was rigorously dried, distilled, and stored over molecular sieves. Sodium chlorite (purity 82.3% by iodometry) and manganese(III) acetylacetonate were purchased from Kanto Chemical Co., Inc. and Tokyo Chemical Industry Co., Ltd., respectively, and were used as received. Anisole **4a**, phenetole **4b**, butyl phenyl ether **4e**, allyl phenyl ether **4n**, 1,2-dimethoxybenzene **7** and 1,2,3-trimethoxybenzene **8** are commercial chemicals and the reagents can be used without further purification. Cycloalkyl phenyl ethers, **4l** and **4m**, were prepared by heating a mixture of phenol, potassium hydroxide, and cycloalkyl chlorides in DMSO.[17] Other alkyl phenyl ethers **4c**, **4d** and **4f–k** were synthesized from sodium phenoxide and alkyl bromides in ethanol according to a standard method.[18] The purities of all substrates were checked by GLC prior to use. *p*-**5a** And *o*-chloroanisole **6a** as reference compounds were commercially available. Addition of deionized water (0.1, 0.15, 0.2 and 0.25 g) in portions to chromatographic neutral alumina (ICN BIOMEDICAL, Alumina N, Super I; 1.0 g), which had been pre-dried in an oven at 500 °C for 6 h (dry alumina), followed by vigorous shaking of the mixtures after every addition until free-flowing powder was obtained (it should be readily done within a few minutes), afforded aluminas with 9, 13, 17 (moist alumina, **3**), and 20 wt% loading of water, respectively, 1.0 g of which were immediately employed for the chlorination. Acidic and basic aluminas (ICN BIOMEDICAL, Alumina A and B, respectively, Super I), silica gel 60 (Merck), silica gel BW-127ZH and BW-300 (Fuji-Davison), kaolin (Wako), Montmorillonite K10 (Aldrich), Bentonite (Wako), Japanese acid clay (Wako), Florisil (Kishida Chemical), Celite (Kokusan Chemical), aluminium silicate (Wako), and zeolite A-3 and F-9 (Wako) were treated with deionized water as described above. Solvents were purified according to methods described in the literature.[19]

Chlorination procedures

Common procedures are exemplified by the chlorination of anisole **4a**. A 30-ml round-bottom, two-necked flask, equipped with a 1.5-cm long Teflon-coated stirrer bar, a 25-cm long condenser, and a glass gas-inlet tubing connected to an argon-filled balloon, was arranged in order to perform the reaction under dry conditions by linking the top of the condenser to a liquid paraffin trap *via* flexible silicone rubber tubing. The flask was charged with **4a** (1.0 mmol), moist alumina **3** (1 g), manganese(III) acetylacetonate catalyst **2** (1 mol% with respect to **4a**), and dichloromethane (10 ml) in that order, and the resultant dark mixture was stirred for a few minutes. Sodium chlorite **1** (2.0 mmol) was added in one portion with magnetic stirring to the flask which was then deaerated by gently passing a stream of dry argon throughout the system. The reaction was carried out by vigorously stirring the heterogeneous mixture at 25 °C; care should be taken in continuing the efficient stirring during the chlorination to ensure smooth reaction and to attain reproducible results. After 40 min (agitation periods after complete addition of **1** are indicated in Tables 1–4), the whole mixture was transferred onto a sintered glass funnel, and the insoluble residues were thoroughly washed with dry ether (required *ca.* 100 ml). The combined clear filtrate was condensed on a rotary

evaporator under reduced pressure to leave an oil, which was immediately chromatographed on a silica gel column (Merck, silica gel 60; hexane–AcOEt, 9:1) to afford a mixture of monochloroanisoles, **5a** and **6a**, in 95% yield based on starting **4a** (Entry 10).

The recovery of anisole and the yield of *p*- and *o*-chloroanisole in Tables 1–3 were determined by GLC analyses of the crude reaction mixtures after adding biphenyl as an internal standard. The other mono-, di-, and tri-alkoxybenzenes were similarly subjected to the chlorination with the **1/2/3** system in dichloromethane at 25 °C, followed by common work-up and chromatographic separation, to yield the indicated products, which were characterised by MS and NMR spectroscopy.

5b: *m/z* 158 (M + 2, 32.2% of M$^+$) and 156 (M$^+$); δ_H(CDCl$_3$) 1.40 (t, 3H), 4.95 (q, 2H), 6.70 (d, 2H) and 7.15 (d, 2H).

5c: *m/z* 172 (M + 2, 34.2% of M$^+$) and 170 (M$^+$); δ_H(CDCl$_3$) 1.03 (t, 3H), 1.74–1.85 (m, 2H), 3.88 (t, 2H), 6.81 (d, 2H) and 7.21 (d, 2H).

5d: *m/z* 172 (M + 2, 32.2% of M$^+$) and 170 (M$^+$); δ_H(CDCl$_3$) 1.31 (d, 6H), 4.89–5.03 (m, 1H), 6.80 (d, 2H) and 7.21 (d, 2H).

5e: *m/z* 186 (M + 2, 34.0% of M$^+$) and 184 (M$^+$); δ_H(CDCl$_3$) 0.97 (t, 3H), 1.39–1.56 (m, 2H), 1.71–1.83 (m, 2H), 3.92 (t, 2H), 6.81 (d, 2H) and 7.21 (d, 2H).

5f: *m/z* 186 (M + 2, 33.0% of M$^+$) and 184 (M$^+$); δ_H(CDCl$_3$) 0.96 (t, 3H), 1.27 (d, 3H), 1.59–1.77 (m, 2H), 4.19–4.28 (m, 1H), 6.81 (d, 2H) and 7.21 (d, 2H).

5g: *m/z* 186 (M + 2, 31.3% of M$^+$) and 184 (M$^+$); δ_H(CDCl$_3$) 1.01 (d, 6H), 2.00–2.13 (m, 1H), 3.67 (d, 2H), 6.81 (d, 2H) and 7.20 (d, 2H).

5h: *m/z* 186 (M + 2, 29.7% of M$^+$) and 184 (M$^+$); δ_H(CDCl$_3$) 1.33 (s, 9H), 6.92 (d, 2H) and 7.22 (d, 2H).

5i: *m/z* 200 (M + 2, 33.2% of M$^+$) and 198 (M$^+$); δ_H(CDCl$_3$) 0.92 (t, 3H), 1.32–1.47 (m, 4H), 1.70–1.84 (m, 2H), 3.90 (t, 2H), 6.80 (d, 2H) and 7.21 (d, 2H).

5j: *m/z* 214 (M + 2, 32.6% of M$^+$) and 212 (M$^+$); δ_H(CDCl$_3$) 0.90 (t, 3H), 1.28–1.69 (m, 6H), 1.70–1.83 (m, 2H), 3.91 (t, 2H), 6.81 (d, 2H) and 7.21 (d, 2H).

5k: *m/z* 242 (M + 2, 33.0% of M$^+$) and 240 (M$^+$); δ_H(CDCl$_3$) 0.89 (t, 3H), 1.29–1.52 (m, 10H), 1.67–1.85 (m, 2H), 3.90 (t, 2H), 6.81 (d, 2H) and 7.20 (d, 2H).

5l: *m/z* 198 (M + 2, 32.3% of M$^+$) and 196 (M$^+$); δ_H(CDCl$_3$) 1.58–1.84 (m, 8H), 4.65–4.77 (m, 1H), 6.79 (d, 2H) and 7.20 (d, 2H).

5m: *m/z* 212 (M + 2, 33.0% of M$^+$) and 210 (M$^+$); δ_H(CDCl$_3$) 1.17–2.17 (m, 10H), 4.12–4.24 (m, 1H), 6.81 (d, 2H) and 7.21 (d, 2H).

5n: *m/z* 170 (M + 2, 34.8% of M$^+$) and 168 (M$^+$); δ_H(CDCl$_3$) 4.50 (d, 2H), 5.25–5.45 (q, 2H), 5.93–6.12 (m, 1H), 6.83 (d, 2H) and 7.21 (d, 2H); δ_C 69.1, 116.0, 117.8, 125.7, 129.3, 132.9 and 157.2.

9: *m/z* 174 (M + 2, 32.4% of M$^+$) and 172 (M$^+$); δ_H(CDCl$_3$) 3.86 (s, 3H), 3.88 (s, 3H) and 6.75–6.91 (m, 3H); δ_C 56.0, 56.1, 112.0, 112.1, 120.3, 125.7 and 149.6.

10: *m/z* 204 (M + 2, 34.1% of M$^+$) and 202 (M$^+$); δ_H(CDCl$_3$) 3.84 (s, 3H), 3.89 (s, 3H), 3.91 (s, 3H), 6.62 (d, 1H) and 7.05 (d, 1H); δ_C 56.2, 61.1, 107.8, 107.9, 123.9, 143.6, 150.0 and 152.7.

All monochlorinated aromatic ethers obtained here, **5a–n**, **6a**, **9** and **10**, are known compounds and their physical data, *e.g.* bps, are available from literature sources (see Table 4) except for *sec*-butyl *p*-chlorophenyl ether **5f**. A reference sample of **5f** independently prepared from a reagent combination of *sec*-butyl bromide, metallic sodium, and *p*-chlorophenol in ethanol according to the literature procedure[18] had bp 98–98.5 °C/8 mmHg and ^{1}H NMR (CDCl$_3$) and mass spectra well in accord with those shown above.

A 1-g scale chlorination was carried out with anisole **4a** (1.08 g, 10 mmol), moist alumina **3** (3 g), Mn(acac)$_3$ (0.01 mmol, *viz.* 0.1 mol% with respect to **4a**), NaClO$_2$ (20 mmol) and dichloromethane (30 ml) in a 100-ml round-bottom three-necked flask, fitted with the same equipment as those employed in the small-

scale experiments summarised in Table 4. After the brownish heterogeneous mixture had been efficiently stirred at 25 °C for *ca.* 20 min, an exothermic reaction occurred, with gentle refluxing of the solvent and gas evolution. After the gas evolution ceased, the stirring was continued for an additional 20 min, during which the colour of the reaction mixture turned pale yellow. Filtration, washing with ether, and removal of the combined solvent gave monochloroanisoles with no serious decrease in yield (91%) and a *p*- to *o*- ratio of 93:7 (*vs.* 94% and 95:5, respectively, in Entry 10). This procedure also allowed the successful monochlorination of 1,2,3-trimethoxybenzene **8** (1.68 g, 10 mmol) to be performed with 16 mmol of $NaClO_2$ under otherwise the same conditions as above, producing **10** in 90% yield.

Acknowledgements

References

1 Reviews are available: H. Heavy, in *Comprehensive Organic Chemistry*, ed. D. H. R. Barton and W. D. Ollis, Pergamon Press, Oxford, 1979, vol. 1, p. 291; P. B. D. de la Mare, *Acc. Chem. Res.*, 1974, **7**, 361; J. March, *Advanced Organic Chemistry. Reactions, Mechanisms, and Structure*, 4th edn., John Wiley & Sons, New York, 1992, p. 531–534; E. B. Merkushev, *Synthesis*, 1988, 923; D. E. Pearson and C. A. Buehler, *Synthesis*, 1971, 455; R. Taylar, *Electrophilic Aromatic Substitution*, John Wiley & Sons, Chichester, 1990, ch. 9.

2 *Speciality Chemicals*, ed. B. Pearson, Elsevier Applied Science, London, 1991, p. 15–93.

3 For recent aromatic chlorinations, see: H. A. Muathen, *Tetrahedron*, 1996, **52**, 8863; R. Breslow, *Acc. Chem. Res.*, 1995, **28**, 146; S. M. Hubig, W. Jung and J. K. Kochi, *J. Am. Chem. Soc.*, 1994, **116**, 6233; R. Rathore, S. H. Loyd and J. K. Kochi, *J. Am. Chem. Soc.*, 1994, **116**, 8414; Y. Goldberg and H. Alper, *J. Org. Chem.*, 1993, **58**, 3072; F. Bellesia, F. Ghelfi, U. M. Pagnoni and A. Pinetti, *J. Chem. Res.*, 1991, (*S*), 284; J. G. Lee, H. T. Cha, U. C. Yon, Y. S. Suh, K. C. Kim and I. S. Park, *Bull. Korean Chem. Soc.*, 1991, **12**, 4; L. Delaude and P. Laszlo, *Catal. Lett.*, 1990, **5**, 35; K. H. Chung, H. J. Kim, H. R. Kim and E. K. Ryu, *Synth. Commun.*, 1990, **20**, 2991; K. Smith, M. Butters and B. Nay, *Synthesis*, 1985, 1157; K. Smith, M. Butters, W. E. Paget and B. Nay, *Synthesis*, 1985, 1155; N. Kamigata, T. Satoh, M. Yoshida, H. Matsuyama and M. Kameyama, *Bull. Chem. Soc. Jpn.*, 1989, **61**, 2226; F. Minisci, E. Vismara and F. Fontana, *J. Chem. Soc., Perkin Trans. 2*, 1989, 123; K. Shibata, Y. Itoh, N. Tokitoh, R. Okazaki and N. Inamoto, *Bull. Chem. Soc. Jpn.*, 1991, **64**, 3749; K. Smith, M. Butters and B. Nay, *Tetrahedron Lett.*, 1988, **29**, 1319; J. R. Lindsay Smith, L. C. McKeer and J. M. Taylor, *J. Chem. Soc., Perkin Trans. 2*, 1987, 1533; 1988, 385; 1989, 1529; 1989, 1537; S. Kajigaeshi, Y. Shinmasu, S. Fujisaki and T. Kakinami, *Chem. Lett.*, 1989, 415; G. A. Olah, L. Ohannesian and M. Arvanaghi, *Synthesis*, 1986, 868; W. D. Watson, *J. Org. Chem.*, 1985, **50**, 2145; T. E. Nickson and C. A. Roche-Dolson, *Synthesis*, 1985, 669; H. Konishi, K. Yokota, Y. Ichihashi, T. Okano and J. Kiji, *Chem. Lett.*, 1980, 1423; ref. 11*b*.

4 For comprehensive reviews on supported reagent chemistry, see: (*a*) J. H. Clark, *Catalysis of Organic Reactions by Supported Inorganic Reagents*, VCH, New York, 1994; (*b*) J. H. Clark, A. P. Kybett and D. J. Macquarrie, *Supported Reagents. Preparation, Analysis and Applications*, VCH, New York, 1992; (*c*) J. H. Clark and T. W. Bastock, in ref. 2, p. 383; (*d*) *Preparative Chemistry Using Supported Reagents*, ed. P. Laszlo, Academic Press, San Diego, 1987; (*e*) *Solid Supports and Catalysis in Organic Synthesis*, ed. K. Smith, Ellis Horwood, Chichester, 1992; (*f*) *Organic Chemistry Using Clays*, ed. M. Balogh and P. Laszlo, Springer-Verlag, Berlin, 1993.

5 J. H. Clark and D. J. Macquarrie, *Chem. Soc. Rev.*, 1996, 303; *Chemistry of Waste Minimization*, ed. J. H. Clark, Chapman and Hall, London, 1995; T. W. Bastock and J. H. Clark, in ref. 2, p. 383–396.

6 L. Delaude, P. Laszlo and K. Smith, *Acc. Chem. Res.*, 1993, **26**, 607.

7 M. E. Davis, *Acc. Chem. Res.*, 1993, **26**, 111.

8 M. Hirano, S. Yakabe, J. H. Clark and T. Morimoto, *J. Chem. Soc., Perkin Trans. 1*, 1996, 2693.

9 M. Kodomari, S. Takahashi and S. Yoshitomi, *Chem. Lett.*, 1987, 1901.

10 M. Hirano, S. Yakabe, J. H. Clark, H. Kudo and T. Morimoto, *Synth. Commun.*, 1996, **26**, 1875.

11 (*a*) T. Nishiguchi and F. Asano, *J. Org. Chem.*, 1989, **54**, 1531; (*b*) M. Kodomari, H. Satoh and S. Yoshitomi, *Bull. Chem. Soc. Jpn.*, 1988, **61**, 4149; (*c*) S. Yasui, M. Fujii, K. Nakamura and A. Ohno, *Bull. Chem. Soc. Jpn.*, 1987, **60**, 963; (*d*) M. O. Brimeyer, A. Mehrota, S. Quici, A. Nigam and S. L. Regen, *J. Org. Chem.*, 1980, **45**, 4254; (*e*) F. M. Menger and C. Lee, *J. Org. Chem.*, 1979, **44**, 3446; (*f*) E. Keinan and Y. Mazur, *J. Org. Chem.*, 1978, **43**, 1020; M. Hojo and R. Masuda; (*g*) *Synth. Commun.*, 1975, **5**, 169; (*h*) *Tetrahedron Lett.*, 1976, 613; (*i*) B. B. Jarvis and M. M. Evans, *J. Org. Chem.*, 1974, **39**, 643; refs. 7 and 9.

12 M. Onaka, K. Sugita and Y. Izumi, *J. Org. Chem.*, 1989, **54**, 1116; T. Ando, T. Kawate, J. Yamawaki and T. Hanafusa, *Chem. Lett.*, 1982, 935.

13 Similar explanation was given for the acceleration of reactions with the use of solid reagents by a small amount of water: L. A. Carpino and A. C. Sau, *J. Chem. Soc., Chem. Commun.*, 1979, 514; M. Tanaka and M. Koyanagi, *Synthesis*, 1981, 973; ref. 12.

14 L. Delaude and P. Laszlo, *J. Org. Chem.*, 1990, **55**, 5260; D. Antenucci, L. Delaude, A. M. Fransolet and P. Laszlo, *J. Catal.*, 1992, **135**, 92; and references cited therein.

15 (Salen)manganese(III) complex can be used as a catalytic activator of sodium chlorite in the sulfoxidation of sulfides[10] and nuclear chlorination of aromatic ethers (unpublished data) in dichloromethane in the presence of moist alumina.

16 A large amount of (salen)manganese(III) complex catalysts (≤13 mol%) were frequently required because of, in part, destruction of them during the reactions: T. Nagata, K. Imagawa, T. Yamada and T. Mukaiyama, *Bull. Chem. Soc. Jpn.*, 1995, **68**, 1455; *Chem. Lett.*, 1994, 1259; T. Mukaiyama, T. Yamada, T. Nagata and K. Imagawa, *Chem. Lett.*, 1993, 327; R. Irie, K. Noda, Y. Ito, N. Matsumoto and T. Katsuki, *Tetrahedron Lett.*, 1990, **31**, 7345; P. Pietikäinen, *Tetrahedron Lett.*, 1994, **35**, 941.

17 M. Siskin, G. Brons, A. R. Katritzky and R. Murugan, *Energy Fuels*, 1990, **4**, 482.

18 R. A. Smith, *J. Am. Chem. Soc.*, 1933, **55**, 3718.

19 *Technique of Organic Chemistry, Vol. II, Organic Solvents*, ed. J. A. Ridick and W. B. Bunger, Wiley Interscience, New York, 3rd edn., 1970.