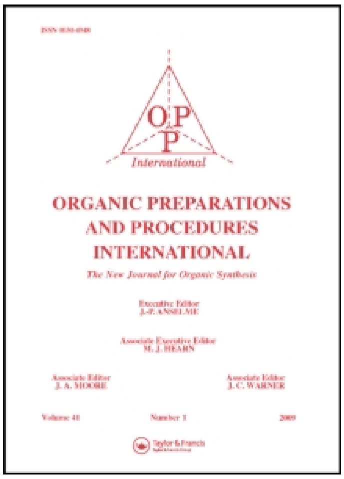

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A SIMPLE REGIOSELECTIVE NUCLEAR BROMINATION OF ALKYL PHENYL ETHERS

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A SIMPLE REGIOSELECTIVE NUCLEAR BROMINATION OF ALKYL PHENYL ETHERS

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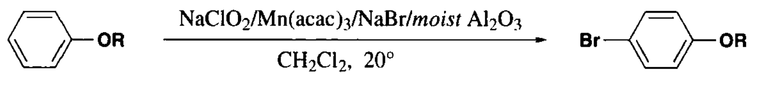
Oxohalogen acids and their organic and inorganic derivatives have been extensively employed as versatile, mild oxidizing and halogenating reagents in organic syntheses.[1] Sodium chlorite ($NaClO_2$, **1**) has enjoyed an important position in carbohydrate chemistry[2] and is also known as a specific reagent for the oxidation of aldehydes to carboxylic acids.[3] However, there has been no synthetically useful reactions other than the above oxidations. Indeed, reaction of aromatic hydrocarbons and of alcohols with aqueous $NaClO_2$ gave complex mixtures of products ascribed to the competing oxidation and chlorination.[4] Our recent investigation into *cleaner* syntheses using *in situ* generated supported reagents[5] in aprotic solvents showed that a combination of **1**, Mn(acac)$_3$ (**2**), and *moist* alumina (**3**) can be successfully used for the selective oxidation of sulfides.[5a] In view of the synthetic importance of halogenation reactions,[6] we now report a novel aromatic bromination[7] of a series of alkyl phenyl ethers with the (**1**:**2**:**3**) system in the presence of NaBr (Schemes 1 and 2).

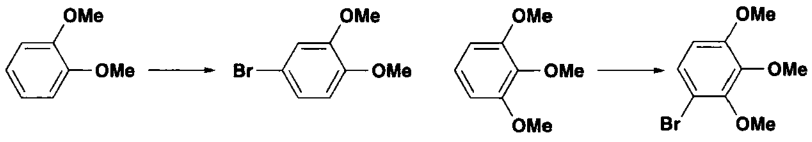
Bromination was readily accomplished by our *in situ* method[5] in a mild and selective fashion. For example, vigorous stirring of a heterogeneous mixture of **1**, anisole (**4a**), NaBr, **3** and a catalytic amount of **2** (1 mole % with respect to **4**) in dichloromethane at 20° under a dry atmosphere produced a mixture of bromoanisoles in 96% yield with a markedly high selectivity for the *p*-isomer (**5a**); *viz.*, *p*-:*o*- = 99:1 by GC, where *m*- or side-chain bromination was absent (Entry 1). Entries 2-13 demonstrate the applicability of the (**1**:**2**:**3**:NaBr) system to the nuclear bromination of a wide range of alkyl phenyl ethers, affording **5b-m** in good to nearly quantitative yields, irrespective of carbon-chain length or steric bulk of alkyl groups. Indeed, comparative studies using ethers with C$_3$ (Entries 4 and 5), C$_4$ (Entries 8-11), and C$_6$ alkyl or cycloalkyl groups (Entries 12 and 13) suggest that the steric environment around the ether linkage exercises no serious influence on the reactivity of **4**, and selectivity and yield of **5**. Although a mechanistic explanation for the high *p*-selectivity has not yet emerged from experiments performed so far, it seems likely that the high regioselectivity is a result of geometric constraints on the alumina surface, since the regiospecificities resulting from reactions with solid/solution biphasic systems are, in general, superior to those from simple solution phase counterparts.[7] It is noteworthy that the allylic double bond of the unsaturated ether (**4g**) survived bromination in large part, affording **5g** (Entry 7; 77% based on consumed **4g**. Moreover, di- and tri-ether substrates (**6** and **8**) also gave highly regiocontrolled monobrominations (Scheme 2; Entries 14 and 15).



4 **5**

a) R= Me
b) R= Et
c) R= $(CH_2)_2Cl$
d) R= *n* -Pr
e) R= *i* -Pr
f) R= $(CH_2)_3Cl$
g) R= $CH_2CH=CH_2$
h) R= *n* -Bu
i) R= *s* -Bu
j) R= *i* -Bu
k) R= *t* -Bu
l) R= *n* $-C_6H_{13}$
m) R= *c* $-C_6H_{11}$

Scheme 1



6 **7** **8** **9**

Scheme 2

In short, we have demonstrated here an extended utility of NaClO$_2$ in combination with Mn(acac)$_3$, NaBr and *moist* alumina as an efficient source of electrophilic bromine for aromatic ethers. Further work on the bromination of ketones and olefins, for example, using this inexpensive, operationally simple, and environmentally friendly system is now underway in our laboratory.

TABLE 1. Selective *p*-Bromination of Aromatic Ethers[a]

Entry No.	Ether	Time (min)	Product	Yield (%)[b]	mp. (°C) or bp (°C/torr) Found	Reported
1	**4a**	80	**5a**	95	86-87/8	89-90/10[e]
2	**4b**	90	**5b**	93	105-107/13	109.2-109.5/17[f]
3	**4c**	80	**5c**	93	1130-133/6	135/6.5[f]
4	**4d**	80	**5d**	97	116-118/13	117-120/13[g]
5	**4e**	110	**5e**	97	115-117/18	119-120/20[h]
6	**4f**	80	**5f**	93	150-151/10	153.5/10.3[g]
7[c]	**4g**	190	**5g**	67	109-110/7	110.5-111.5/7.5[i]
8	**4h**	90	**5h**	98	128-129/10	127-130/9[h]
9	**4i**	80	**5i**	97	94-95.5/3	95-97/3[h]
10	**4j**	100	**5j**[m]	96	86-86.3/2	—
11	**4k**	80	**5k**	97	64-65/0.3	63-65/0.3[j]
12	**4l**	80	**5l**	95	153-154/12	156-157/13[i]
13	**4m**	100	**5m**	96	43-44	44-45[i]
14	**6**	110	**7**	90	135-136/10	140/12[k]
15[d]	**8**	80	**9**	86	94-96/0.5	97/0.5[l]

a) At 20°, under argon; ether 1 mmol, $NaClO_2$ 1.25 mmol, NaBr 2 mmol, $Mn(acac)_3$ 0.01 mmol, *moist* alumina 1 g, hexane 10 mL. *b*) Yield of chromatographically purified product based on the starting ether. *c*) 13% of **4g** was recovered. *d*) $NaClO_2$ 1 mmol. *e*) *Beilstein*, **6**, II, 185. *f*) *Beilstein*, **6**, III, 742. *g*) *Beilstein*, **6**, IV, 1045. *h*) *Beilstein*, **6**, IV, 1046. *i*) *Beilstein*, **6**, IV, 1047. *j*) S. O. Laweson and C. Frisell, *Arkiv. Kemi*, **17**, 393 (1961) [*Chem. Abstr.*, **57**, 2058*c* (1962)]. *k*) *Beilstein*, **6**, III, 4254. *l*) *Beilstein*, **6**, IV, 7335. m) Calcd for $C_{10}H_{13}BrO$: C, 52.40; H, 5.68. Found: C, 52.28; H, 5.62.

EXPERIMENTAL SECTION

^1H NMR spectra were recorded with a JEOL PMX-60 (60 MHz) spectrometer for solutions in $CDCl_3$ using TMS as an internal standard. Analytical gas chromatography was performed on a Shimadzu GC-4BM or GC-4CM instrument equipped with a flame ionization detector through a 2 mx5 mm0 glass column packed with 5% PEG-20M on Chromosorb WAW-DMCS or 3% Silicone OV-17 on Uniport HP, respectively, and interfaced with a Shimazdu Chromatopac C-R6A integrator, with temparature programming. Mass spectra were determined on a JEOL SX-102A model mass spectrometer which was coupled with a Hewlett Packard GC5890 Series II model GC apparatus *via* a heated capillary column. $NaClO_2$ (available chlorine 82.3% by iodometry) and $Mn(acac)_3$ were purchased from Kanto Chemical and Tokyo Chemical Industry, respectively, and were used as received. Addition of deionized water (0.25 g) in portions to predried (500°, 6 h) chromatographic neutral alumina (ICN BIOMEDICAL, Alumina N, Super I; 1.0 g), followed by vigourous shaking of the mixtures after every addition until free-flowing powder was obtained (it should be readily done within a few minutes), afforded alumina with 20 wt-% loading of water [*moist* alumina (**3**)], 1.0 g of which was immediately employed for the bromination. Anisole (**4a**), phenetole (**4b**), chloroethyl phenyl ether (**4c**), allyl phenyl ether (**4g**), butyl phenyl ether (**4h**), 1,2-dimethoxybenzene (**6**), and 1,2,3-trimethoxybenzene (**8**) are commercial chemicals and the reagents can be used without further purification. Cyclohexyl phenyl ether (**4m**) was prepared by heating a mixture of phenol, KOH, and cyclohexyl chloride in DMSO.[8] Other alkyl phenyl ethers (**4d-f**) and (**4i-l**) were synthesized from sodium phenoxide and alkyl bromides in ethanol according to the standard method.[9] The purities of all substrates were checked by GC prior to use. *p*- (**5a**) and *o*-Bromoanisole as reference compounds were commercially available. Dichloromethane was rigorously dried, distilled, and stored over molecular sieves.

Bromination Procedure.- Bromination of anisole (**4a**) (Entry 1) is representative. A 30 mL two-necked round-bottom flask, equipped with a 1.5 cm Teflon-coated stirrer bar, a reflux condenser and a glass tubing connected to an argon-filled balloon *via* a flexible silicon-rubber tubing, was arranged for conducting the reaction under dry conditions by connecting the top of the condenser to a liquid paraffin trap. The flask was charged with (**4a**) (1 mmol, 0.108 g), dichloromethane (10 mL), $Mn(acac)_3$ (0.01 mmol, 3.5 mg), freshly prepared *moist* alumina (1 g), NaBr (2 mmol, 0.206 g), and $NaClO_2$ (1.25 mmol, 0.136 g), and then deaerated by gently passing dry argon stream throughout the system. After vigorously stirring at 20° for 80 min, the reaction mixture was filtered through a sintered glass funnel and the filter cake was washed thoroughly with portions of dry ether (*in toto* 50 mL). Removal of the solvent from the combined filtrate and washings on a rotary evaporator, followed by chromatography on a silica gel column (hexane/ethyl acetate) afforded *p*-bromoanisole (**5a**) [95%, 0.178 g].

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SYNTHESIS OF 3,6-DI-(*tert*-BUTYL)FLUORENE BY NICKEL(0) CATALYZED COUPLING OF ARYL HALIDES

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In the course of our investigations of fluorenyl substituted *m*-xylylenes, substantial amounts of 3,6-di-(*tert*-butyl)fluorenone were required. An obvious route is *via* the corresponding 3,6-di-(*tert*-butyl)fluorene. Unfortunately electrophilic substitution of fluorene occurs at 2- and 7-positions rather than the 3- and 6-positions. This led Kajigaeshi and coworkers[1] to synthesize the title compound from