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# Regioselective bromination of activated aromatic substrates with a $ZrBr_4$/diazene mixture

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## Abstract

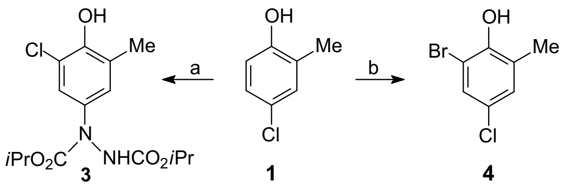
A regioselective method for the bromination of phenols, ethers and anilines using a $ZrBr_4$/diazene mixture is described. The reaction takes place under mild reaction conditions and the bromine atom adds first at the *para* unsubstituted position with respect to the OH, OR or $NR_2$ group of the activated aromatic substrate. Less reactive compounds such as toluene, phenyl acetate, benzonitrile and trifluoromethylbenzene remain intact under the same conditions.

*Keywords:* Regioselective bromination; Diazenes; Zirconium tetrabromide; Phenols; Ethers; Anilines

The bromination of aromatic substrates has received a great deal of interest in recent years owing to the commercial importance of brominated compounds in the synthesis of natural products, and in the manufacture of pharmaceuticals and agrochemicals. A variety of brominating reagents are available,[1] and recent reports describe the use of NBS-sulfonic-acid-functionalized silica,[2] NBS/$Al_2O_3$,[3] NBS/$BF_3$–$H_2O$,[4] NBS–$NH_4OAc$,[5] NBS–TEAB,[6] NBS–$Pd(OAc)_2$,[7] NBS–DMF (or THF),[8] KBr–benzyltriphenylphosphonium peroxymonosulfate[9] or peroxodisulfate,[10] 1-benzyl-4-aza-1-azoniabicyclo[2.2.2]octane tribromide,[11] $Br_2$ (for lithiated haloarenes),[12] a 2:1 bromide/bromate reagent as a source of HOBr,[13] *N*-methylpyrrolidin-2-one hydrotribromide–$H_2O_2$,[14] [Bmim]$Br_3$,[15] hexamethylenetetramine–$Br_2$,[16] $Br_2/SO_2Cl_2$/zeolite,[17] 1,2-dipyridiniumditribromide-ethane,[18] alkylpyridinium tribromide,[19] IBX amide resin-TEAB,[20] poly(4-vinylpyridine)-supported bromate,[21] tribromoisocyanuric acid,[22] bromodichloroisocyanuric acid,[23] polymer-supported organotin reagents,[24] $NH_4VO_3$–$H_2O_2$–HBr,[25] $CuBr_2$,[26] etc.

In connection with our continuing interest in hydrazides[27] and other N–N-containing compounds,[28] we recently described the $ZrCl_4$-mediated electrophilic amination of aromatic substrates.[29] In the course of this Letter, we also found that migration of the halogen took place during amination of the 4-halophenols.[30] An example of chlorine migration is also illustrated by the reaction of 4-chloro-2-methylphenol (**1**) with diisopropyl diazenedicarboxylate (**2**) in the presence of $ZrCl_4$ (Scheme 1).

Thus, product **3**[31] was obviously formed by the amination of phenol **1**, which was accompanied by migration of the chlorine atom from the *para* to the *ortho* position with



Scheme 1. Reagents and conditions: (a) $iPrO_2CN{=}NCO_2iPr$ (**2**, 1 equiv), $ZrCl_4$ (1.1 equiv), $CH_2Cl_2$, argon, −62 °C, 5 h, radial chromatography, 67% yield of **3**; (b) $iPrO_2CN{=}NCO_2iPr$ (**2**, 1 equiv), $ZrBr_4$ (1 equiv), $CH_2Cl_2$, argon, 0 °C, 1 h, then rt, 30 min, radial chromatography, 74% yield of **4**.

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Table 1
The bromination of phenol **1** with $ZrBr_4$ in the presence of various diazenes

$$\mathbf{1} \xrightarrow[ZrBr_4,\ CH_2Cl_2]{R^1O_2CN{=}NCOR^2} \mathbf{4}$$

| Entry | Diazene | $R^1$ | $R^2$ | Time (h) | Temp (°C) | Product **4** yield[a,b] (%) |
|---|---|---|---|---|---|---|
| 1 | **2** | *i*Pr | O*i*Pr | 1 + 0.5 | 0; rt | 74 |
| 2 | **5** | Et | OEt | 1.5 | 0 | 78 |
| 3 | **6** | $Cl_3CH_2$ | $OCH_2Cl_3$ | 1 + 1 | 0; rt | 62 |
| 4 | **7** | *t*Bu | O*t*Bu | 1.5 + 48 | 0; rt | — |
| 5 | **8** | Me | $NHCH_2CH_2Cl$ | 1 + 0.5 | 0; rt | 75 |

[a] Isolated yields (after radial chromatography) are given.

[b] Mp 51–52 °C (petroleum ether); $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 2.27 (3H, s), 5.49 (1H, s), 7.06 (1H, d, $J$ 2.1 Hz), 7.29 (1H, d, $J$ 2.1 Hz); mp (lit.)[33] 43 °C.

respect to the phenolic OH. In order to modify the conditions of the latter transformation, we decided to apply $ZrF_4$ and $ZrBr_4$ as the Lewis acids in place of $ZrCl_4$. $ZrF_4$ was completely ineffective: phenol **1** remained unchanged after being treated with diazene **2** in the presence of $ZrF_4$ (2 days, room temperature). To our great surprise, however, the experiment with $ZrBr_4$ as the Lewis acid gave 2-bromo-4-chloro-6-methylphenol (**4**) together with the reduced derivative of **2**, that is, diisopropyl 1,2-hydrazinedicarboxylate. The two compounds were easily separated by radial chromatography. Thus, electrophilic bromination of the substrate took place rather than electrophilic amination accompanied by halogen migration. This result indicated that the diazene/$ZrBr_4$ mixture could serve as a reagent for the bromination of aromatic compounds. The application of some other diazenes was also taken into account. Indeed, the brominated phenol **4** was prepared under similar reaction conditions when diazenedicarboxylates **5** and **6** or aminocarbonyldiazenecarboxylate **8** were employed as the diazene partners (Table 1). It should be noted that diazene **7** did not react (Table 1, entry 4), probably due to steric hindrance. To the best of our knowledge, there are no reports in the literature concerning the application of $ZrBr_4$ in bromination procedures. Only $ZrCl_4$ has been described as a catalyst in the bromination of aromatic compounds with NBS.[32]

The above-mentioned outcome encouraged us to study the bromination of several aromatic substrates with the diazene/$ZrBr_4$ mixture to provide insight into the scope and limitation of the process. Diazenes **2** and **5** are commercially available and were selected as the partners of choice in further experiments. An attempt to brominate nitrobenzene

Table 2
The bromination of phenols, ethers and anilines

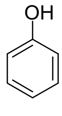
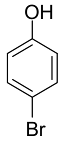
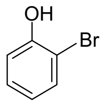
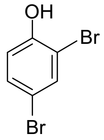
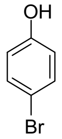
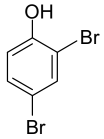
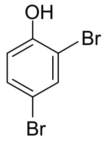
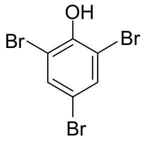
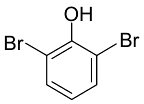
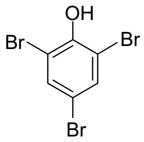
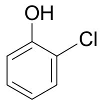
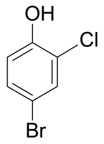
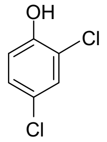
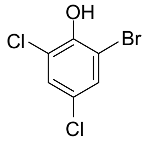
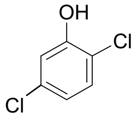
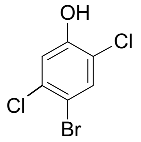
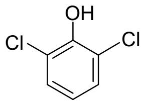
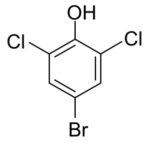
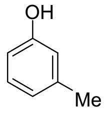
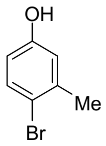
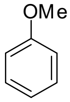
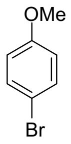
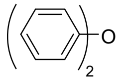
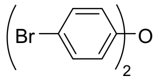
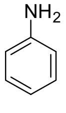
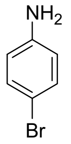
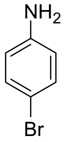
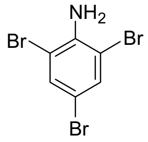
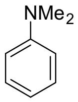
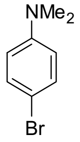
| Entry | Diazene | Substrate | Time (h) | Temp (°C) | Product | Mp (°C) | Mp$^{lit.}$ (°C) | Yield[a] (%) |
|---|---|---|---|---|---|---|---|---|
| 1 | **5** |  | 0.67 | rt |  | 63 | 64[35] | 82 |
| 2 | **2** |  | 1.5 | rt |  | 40 | 38[36] | 90 |
| 3 | **2** |  | 1 | rt |  | 40 | 38[36] | 90 |
| 4 | **2** |  | 4 | rt |  | 85–86 | 92[37] | 75 |
| 5 | **2** |  | 2 | rt |  | 85–86 | 92[37] | 79 |
| 6 | **2** |  | 8 | rt |  | 55 | 49–50[38] | 76 |

Table 2 (*continued*)

| Entry | Diazene | Substrate | Time (h) | Temp (°C) | Product | Mp (°C) | Mp$^{lit.}$ (°C) | Yield[a] (%) |
|---|---|---|---|---|---|---|---|---|
| 7 | **2** |  | 6 | rt |  | 62 | 68–69[39] | 79 |
| 8 | **2** |  | 8 | rt |  | 68 | 71–72[39] | 87 |
| 9 | **2** |  | 6 | rt |  | 66 | 54–58[40] | 78 |
| 10 | **5** |  | 0.67 | rt |  | 54 | 59[41] | 70 |
| 11 | **5** |  | 1.5 | rt |  | 15 | 13[42] | 76 |
| 12 | **5**[b] |  | 26 | rt |  | 55–57 | 60.5[43] | 70 |
| 13 | **2** |  | 6 + 21 | −70; rt |  | 57–58 | 59–61[44] | 66 |
| 14 | **5**[b] |  | 1.5 | rt |  | 112[c] | 121–123[45] | 83 |
| 15 | **2** |  | 4 + 20 | −70; rt |  | 48–49 | 52–53[16] | 89 |

[a] Isolated yields (after radial chromatography) are given.

[b] 2 mol of **5** and 2 mol of $ZrBr_4$ per 1 mol of the substrate were used.

[c] $^1H$ NMR ($CDCl_3$, 300 MHz): $\delta$ 4.57 (2H, br), 7.51 (2H, s).

with $ZrBr_4$/**2** did not lead to the desired product (rt, 102 h) and the starting material was completely recovered. Compounds such as toluene, phenyl acetate, benzonitrile and trifluoromethylbenzene also remained unchanged under similar reaction conditions. These experiments indicated that the diazene/$ZrBr_4$ mixture could be applied successfully on substrates that are sufficiently activated for electrophilic aromatic substitutions. This turned out to be the case, as demonstrated by the examples in Table 2.[34] Only one regioisomer was always formed, as supported by the $^1H$ NMR spectra of the crude reaction mixtures.

The bromination of various phenols took place exclusively at the *para* position with respect to the phenolic OH (Table 2, entries 1, 2, 5, 6 and 8–10). The substrate was brominated *ortho* to the phenolic OH only when the *para* position was occupied (entries 3, 4 and 7). Similar results were observed for ethers (entries 11 and 12) or anilines (entries 13–15) with the $ZrBr_4$/diazene mixture under similar reaction conditions. Two equivalents of this mixture were required for the introduction of two bromine atoms into the molecule (entries 12 and 14). This indicates that the position of the electrophilic attack as well as the number of entering bromine atoms can be regulated by controlling the ratio of substrate: $ZrBr_4$/diazene.

In conclusion, this Letter describes the first example of the use of a $ZrBr_4$/diazene mixture for the selective bromination of various phenols, aromatic ethers and anilines. The method is completely regioselective thus offering numerous synthetic applications. Mild reaction conditions, a relatively rapid conversion, good-to-excellent yields, and the selectivity profile are notable characteristics of the described protocol. Studies concerning the reaction pathway are now in progress.

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31. Aminated phenol **3**: mp 117–118 °C (hexane/diethyl ether); IR (KBr) 3428, 2976, 1738, 1675, 1489, 1412, 1326, 1244, 1111 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 300 MHz) $\delta$ 1.27 (6H, d, *J* 6.2 Hz), 1.28 (6H, d, *J* 6.2 Hz), 2.26 (3H, s), 5.00 (1H, h, *J* 6.2 Hz), 5.01 (1H, h, *J* 6.2 Hz), 5.57 (1H, s), 6.80 (1H, s), 7.12 (1H, br), 7.28 (1H, br); $^{13}C$ NMR ($CDCl_3$, 75 MHz) $\delta$ 16.4, 21.90, 21.93, 70.2, 71.0, 118.9, 122.9, 125.7, 126.3, 134.3, 148.2, 154.5, 156.0; MS (EI) *m*/*z* 344 ($M^+$, 13), 258 (38), 216 (100), 171 (78). Anal. Calcd for $C_{15}H_{21}ClN_2O_5$ (344.79): C, 52.25; H, 6.14; N, 8.12. Found: C, 52.57; H, 6.20; N, 7.99.
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34. *Typical procedure*: A mixture of the substrate (1 mmol) and the diazene (1 mmol) in anhydrous dichloromethane (5 mL) was added over 30 min to a stirred suspension of $ZrBr_4$ (419 mg, 1 mmol) in anhydrous dichloromethane (7 mL) at room temperature. The reaction was monitored by TLC until the substrate was consumed (Table 2). Then, water was added (5 mL), followed by a saturated solution of $NaHCO_3$ until pH 7 was reached. The two phases were separated and the aqueous phase was extracted with dichloromethane (2 × 5 mL). The combined organic phases were dried over anhydrous $Na_2SO_4$, filtered, evaporated to dryness and purified by radial chromatography using petroleum ether/ethyl acetate (7:1) to separate dialkyl 1,2-hydrazinedicarboxylate from the desired brominated product.

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