

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

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Received 12 December 2007; revised 10 January 2008; accepted 17 January 2008

Available online 20 January 2008

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.

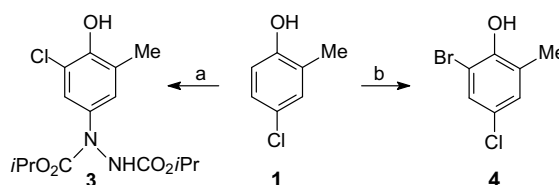
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Keywords: Regioselective bromination; Diazenes; Zirconium tetrabromide; Phenols; Ethers; Anilines

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/ $BF_3 \cdot H_2O$,⁴ NBS- NH_4OAc ,⁵ NBS-TEAB,⁶ NBS- $Pd(OAc)_2$,⁷ NBS-DMF (or THF),⁸ KBr-benzyltriphenylphosphonium peroxydisulfate⁹ or peroxydisulfate,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-dipyridiniumdibromide-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 $NH_4VO_3 \cdot H_2O_2 \cdot HBr$,²⁵ $CuBr_2$,²⁶ etc.

In connection with our continuing interest in hydrazides²⁷ 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 diazenedicarbonylate (**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, $-62^\circ C$, 5 h, radial chromatography, 67% yield of **3**; (b) $iPrO_2CN=NCO_2iPr$ (**2**, 1 equiv), $ZrBr_4$ (1 equiv), CH_2Cl_2 , argon, $0^\circ C$, 1 h, then rt, 30 min, radial chromatography, 74% yield of **4**.

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Table 1
The bromination of phenol **1** with ZrBr₄ in the presence of various diazenes

Entry	Diazene	R ¹ O ₂ CN=NCOR ²		Time (h)	Temp (°C)	Product 4 yield ^{a,b} (%)
		R ¹	R ²			
1	2	<i>i</i> Pr	O <i>i</i> Pr	1 + 0.5	0; rt	74
2	5	Et	OEt	1.5	0	78
3	6	Cl ₃ CH ₂	OCH ₂ Cl ₃	1 + 1	0; rt	62
4	7	<i>t</i> Bu	O <i>t</i> Bu	1.5 + 48	0; rt	—
5	8	Me	NHCH ₂ CH ₂ Cl	1 + 0.5	0; rt	75

^a Isolated yields (after radial chromatography) are given.

^b Mp 51–52 °C (petroleum ether); ¹H NMR (CDCl₃, 300 MHz) δ 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 ZrF₄ and ZrBr₄ as the Lewis acids in place of ZrCl₄. ZrF₄ was completely ineffective: phenol **1** remained unchanged after being treated with diazene **2** in the presence of ZrF₄ (2 days, room temperature). To our great surprise, however, the experiment with ZrBr₄ as the Lewis acid gave 2-

bromo-4-chloro-6-methylphenol (**4**) together with the reduced derivative of **2**, that is, diisopropyl 1,2-hydrazine-dicarboxylate. 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/ZrBr₄ 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 aminocarbonyldiazenedicarboxylate **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 ZrBr₄ in bromination procedures. Only ZrCl₄ 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/ZrBr₄ 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

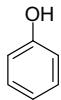
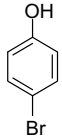
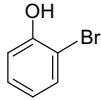
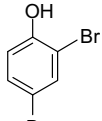
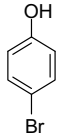
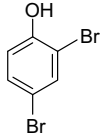
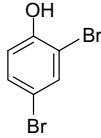
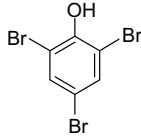
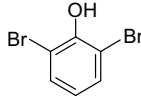
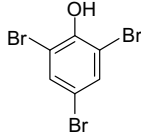
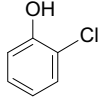
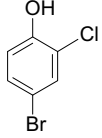
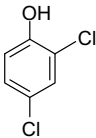
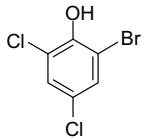
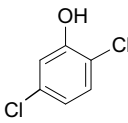
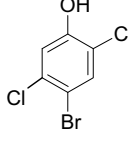
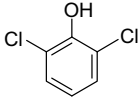
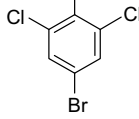
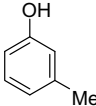
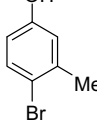
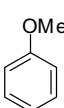
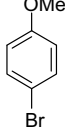
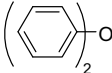
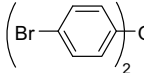

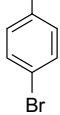
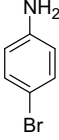
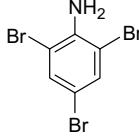

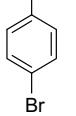
Entry	Diazene	Substrate	Time (h)	Temp (°C)	Product	Mp (°C)	Mp ^{lit.} (°C)	Yield ^a (%)
1	5		0.67	rt		63	64 ³⁵	82
2	2		1.5	rt		40	38 ³⁶	90
3	2		1	rt		40	38 ³⁶	90
4	2		4	rt		85–86	92 ³⁷	75
5	2		2	rt		85–86	92 ³⁷	79
6	2		8	rt		55	49–50 ³⁸	76

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 ZrBr₄ per 1 mol of the substrate were used.

^c ¹H NMR (CDCl₃, 300 MHz): δ 4.57 (2H, br), 7.51 (2H, s).

with ZrBr₄/2 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/ZrBr₄ mixture could be applied successfully on substrates that are sufficiently activated for electro-

philic 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 ZrBr₄/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: ZrBr₄/diazene.

In conclusion, this Letter describes the first example of the use of a ZrBr₄/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.

Acknowledgements

The Ministry of Higher Education, Science and Technology of Slovenia and the Slovenian Research Agency are gratefully acknowledged for their financial support (P1-0230-103). We would like to thank Dr. Bogdan Kralj and Dr. Dušan Žigon (Mass Spectrometry Center, Jožef Stefan Institute, Ljubljana, Slovenia) for recording the mass spectra.

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- 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 (CDCl₃, 300 MHz) δ 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); ¹³C NMR (CDCl₃, 75 MHz) δ 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 C₁₅H₂₁ClN₂O₅ (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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- 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 ZrBr₄ (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 NaHCO₃ 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 Na₂SO₄, 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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