JOC*Note*

Structure-Dependent Oxidative Bromination of Unsaturated C−C Bonds Mediated by Selectfluor

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Abstract: A number of olefins were subjected to oxidative bromination using Selectfluor/KBr. For different types of substrates, addition, monobromine-substituted, or Hunsdiecker−Borodin reaction products can be readily afforded.

Since its discovery in 1980, 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) (Selectfluor, F-TEDA-BF_4) (**1**) has been the subject of considerable interest as a powerful and user-friendly (nongaseous, nonexplosive, less-toxic) site-selective, electrophilic fluorinating agent.[1] In the presence of Selectfluor, some additional halogenation reactions were also performed;[2] e.g., iodine was introduced at the most electron-rich and the least sterically hindered position on the substituted benzene ring[2a,b] and reactions of aryl alkyl ketones in methanol solutions of iodine resulted in the formation of the corresponding α-iodoketones in good yields.[2c−e] Recently, **1** also was used to generate useful electrophiles, such as Cl^+, Br^+, SCN^+, and NO_2^+, from their respective sodium and potassium salts in acetonitrile (Scheme 1), which were reacted subsequently in situ with a variety of aromatic substrates.[3]

At the present time, oxidative halogenation continues to be of great interest because it precludes the use of gaseous or volatile halogens. A number of protocols are available to achieve bromination of alkenes and alkynes using Br^- instead of Br_2. The most commonly used oxidant is 30% H_2O_2[4] with concomitantly poor stereoselectivity and unwanted side products. Other widely used oxidants for this purpose include cerium(IV) ammonium nitrate (CAN),[5] HNO_3,[6] and oxone,[7]etc. Some other systems such as DMP/TBAB[8] and $NaIO_4$/NaX[9] also give interesting results.

SCHEME 1. Proposed Mechanism for Selectfluor with Bromide

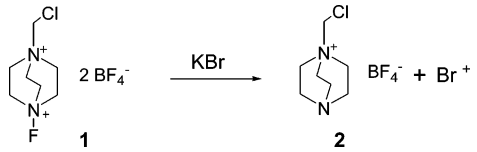
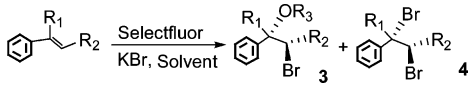


TABLE 1. Oxidative Halogenation of Olefins[a]



			yield (%)	
no.	substrate	sol	**3**	**4**
1	styrene	A	98 (**3a**)	
2	α-Me-styrene	A	99 (**3b**)	
3	*trans*-stilbene	A	93 (**3c**)	
4	styrene	B	66 (**3d**)	30 (**4d**)[b]
5	α-Me-styrene	B	79 (**3e**)	13 (**4e**)[b,c]
6	*trans*-stilbene	B	89 (**3f**)	8 (**4f**)

[a] Conditions: olefin (1 mmol), KBr (2.5 mmol), and Selectfluor (2 mmol), solvent: CH_3CN (25 mL), and methanol (A) or water (B) (1 mL); for solvent A, $R_3 = CH_3$, for B, $R_3 = H$; reaction time 30 min. [b] GC−MS result. [c] Plus 8% addition−elimination product.

In this paper, we describe mild and structure-dependent brominations of olefins using Selectfluor/KBr. More than a decade ago, Lal reported that, in the presence of the weak nucleophiles H_2O, AcOH, or MeOH in CH_3CN, Selectfluor reacts with styrene derivatives or *trans*-stilbene to introduce a fluorine atom and the nucleophile component on the adjacent carbon atom.[10] Similarly, in our work, when styrene derivatives were treated with Selectfluor/KBr, the bromomethoxylation addition products (entries 1−3, Table 1) were readily obtained in high yields when methanol was used as the counter nucleophile.[11] When water was used as the counter nucleophile under the same conditions, more complex, dibrominated compounds were detected in addition to the expected bromohydrins. For α-methyl styrene, a small quantity of addition−elimination products were also formed which may have resulted from the corresponding dibromide (**4e**) by elimination in the presence of base (**2**) which is the reduction product of Selectfluor (Scheme 1).[9] The formation of the *trans* product of *trans*-stilbene indicates it undergoes a bromonium intermediate (Table 1). However, chloride is less reactive than bromide, i.e., when NaCl was used with α-methyl styrene, a mixture of fluorinated and chlorinated products was obtained in a ratio of 3:1.

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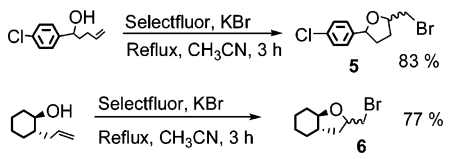
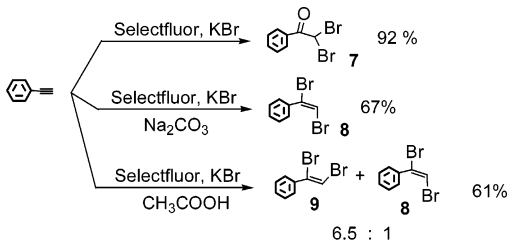
SCHEME 2. Selectfluor-Mediated Brominating Ring-Closure Reactions



SCHEME 3. Oxidative Bromination of Phenylacetylene[a,b]



[a] Conditions: olefin (1 mmol), KBr (2.5 mmol), and Selectfluor (2 mmol), solvent CH_3CN/H_2O = 25:1 (v/v); reaction time 30 min. [b]Isolated yields.

TABLE 2. Oxidative Bromination of Conjugated Olefins[a]

No	Substrate	Product	Yield (%) [b]
1		 **10**	81
2		 **11**	84
3		 **12**	87
4		 **13**	91

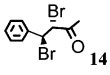
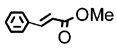
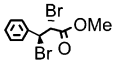
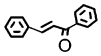
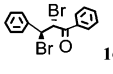
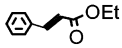
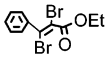
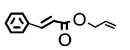
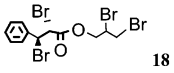
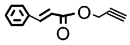
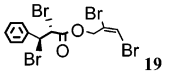
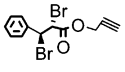
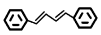
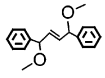
[a] Conditions: olefin (1 mmol), KBr (2.5 mmol), and Selectfluor (2 mmol), solvent CH_3CN/H_2O = 25:1 (v/v); reaction time 2 h. [b] Isolated yields.

Intramolecular ring-closure reactions also proceeded smoothly with heating but lacked diastereoselectivity (Scheme 2).

Interestingly, treatment of phenylacetylene with Selectfluor/KBr/H_2O gave α,α-dibromoacetophenone not α-bromoacetophenone, similar to the difluorinated product obtained with Selectfluor in CH_3CN/H_2O.[10] Moreover, when a small amount of acid or base was added, the products were entirely different. When Na_2CO_3 was added to the reaction system followed by Selectfluor, the sole product was *trans*-1, 2-dibromostyrene, while using acetic acid led to the formation of c*is*-1,2-dibromostyrene as the major product (Scheme 3).

For a system having a double bond conjugated with a carbonyl group, α-bromo-conjugated products were obtained in good yields (Table 2). Such compounds are normally synthesized by a two-step procedure, i.e., dibromination followed by elimination in the presence of base.[12] Few one-pot syntheses have been reported directly involving oxidative bromination of corresponding conjugated carbonyl compounds except DMP/TBAB.[8,9] It is likely that the byproduct of Selectfluor, compound **2**, plays an important role as base to trigger the elimination reaction in our case. Also, noteworthy for 2-cyclopentenone, when CH_3CN/methanol was used as solvent, an unidentified volatile product was formed. Because of its low boiling point, it was difficult to separate from acetonitrile, and only when CH_3CN/H_2O was used as solvent was it possible to obtain 2-bromo-2-cyclopenten-1-one.

TABLE 3. Oxidative Bromination of Conjugated Olefins with a Phenyl Group at β-Position[a]

No	Substrate	Product	Yield (%)[b]
1		 **14**	87
2		 **15**	89
3		 **16**	83
4		 **17**	87
5		 **18**	84
6		 **19**	67
		 **20**	21
7		 **21**	37

[a] Conditions: olefin (1 mmol), KBr (2.5 mmol), and Selectfluor (2 mmol), solvent CH_3CN/H_2O = 25:1 (v/v); reaction time 2 h except entry 6 needed 20 h. [b] Isolated yields.

However, the current method described here is very sensitive to the structure of the substrate. When a conjugated carbonyl with a phenyl group at the β-position was subjected to oxidative bromination under the same conditions, only *erythro*-dibromination products were obtained when either CH_3CN/methanol or CH_3CN/H_2O was used as solvent. For the conjugated alkyne (entry 4, Table 3) only the dibrominated alkene, and not the α,α-dibromo carbonyl compound, was found. For the substrate containing both a conjugated double bond and an allyl or propargyl group, tetrabrominated products were observed, and no ring-closure product was detected. Interestingly, for *trans,trans*-1,4-diphenyl-1,3-butadiene (Table 3, entry 7), a nonbrominated rearrangement product was observed along with other unidentified species.

It is supposed that owing to the electronic and bulky effects of the phenyl group on the dibrominated inter-

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SCHEME 4. Oxidative Bromination of Chalcone

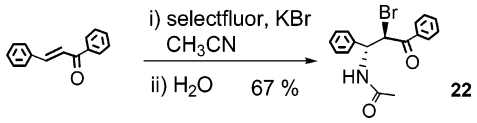
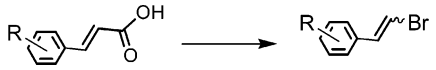


TABLE 4. Oxidative Decarboxylic Bromination Reaction[a]



no.	R	product	*E*/*Z*	yield[b] (%)
1	H	**23**	95:5	84
2	3-Cl	**24**	97:3	86
3	4-OH	**25**	>99:1	82

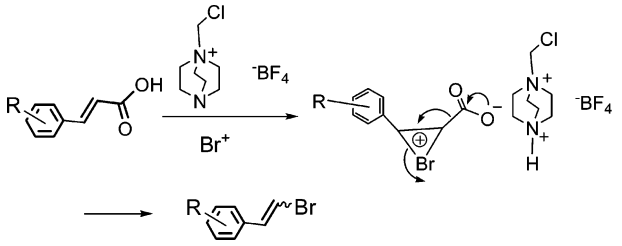
[a] Conditions: olefin (1 mmol), KBr (2.5 mmol), and Selectfluor (2 mmol), solvent CH_3CN/H_2O = 25:1 (v/v); reaction time 5 h. [b] Isolated yields for (*E*) isomer.

mediate, a stronger base like Et_3N or K_2CO_3 was needed to initiate the elimination reaction[13] since **2** is not strong enough to trigger the reaction. This may explain why the olefins described in Tables 2 and 3 behave differently.

Additionally, we found that, when chalcone was treated with Selectfluor in dry acetonitrile without use of methanol or water as a counter nucleophile, a bromoamidation product was isolated in 67% yield (Scheme 4). Direct fluoroamidation of active double bonds is not surprising;[14] however, there are only rare reports of the direct bromoamidation of olefins.[15] Unfortunately, efforts to extend this reaction mode to other substrates were unsuccessful. In such cases, bromoamidation products do form, but in low yields and concomitantly with other very complex products.

The products obtained with conjugated carboxylic acids were totally different from the above systems; a Hunsdiecker−Borodin reaction−decarboxylic bromination reaction took place accompanied by the formation of a small amount of the *cis* isomers (Table 4). The ratio of *trans*/*cis* isomers was greatly affected by the solvent used. For *trans*-cinnamic acid, when the solvent was changed from CH_3CN/methanol (25:1) to CH_3CN/H_2O (25:1), the corresponding ratio increased from 4.5:1 to 95:5. Classical Hunsdiecker−Borodin reactions usually involve use of elemental bromine and salts of Hg(II), Tl(I), Pb(IV), Ag(I). Although some improved procedures are available using Br^+, stemming from NBS or KBr/H_2O_2, a specific catalyst is required, such as lithium acetate, tetrabutylammonium trifluoroacetate, or triethylamine.[16] This paper is the first report of a Hunsdiecker−Borodin reaction using Br^+ without a catalyst; compound **2** is considered to be an effective catalyst for this kind of reaction (Scheme 5).

SCHEME 5. Proposed Hunsdiecker Mechanism Involved with Selectfluor



In conclusion, because of involvement of the reduced product of Selectfluor (compound **2**), the protocol of Selectfluor/KBr behaves very differently from other oxidative brominating systems causing it to be a substrate structure-dependent brominating system.

Experimental Section

General Methods. All of the reagents used were analytical reagents purchased from commercial sources and used as received. ^1H, ^{19}F, and ^{13}C NMR spectra were recorded on a spectrometer operating at 300, 282, and 75 MHz, respectively, in $CDCl_3$ unless otherwise stated. Chemical shifts are reported in ppm relative to the appropriate standard, $CFCl_3$ for ^{19}F, and TMS for ^1H and ^{13}C NMR spectra.

General Procedure. To a stirred mixture of olefin (1.0 mmol) and KBr (2.5 mmol), CH_3CN (25 mL), methanol or water (1 mL), and Selectfluor (2.0 mmol) were added. The reaction was monitored by TLC. After completion of the reaction, the mixture was diluted with water and extracted with CH_2Cl_2 (25 mL × 3). The organic layers were combined and washed with dilute solutions of $NaHCO_3$, Na_2SO_3, and brine. It was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give crude products, which were purified by column chromatography packed with silica gel to afford the pure products.

2′,3′-Dibromopropyl *trans*-2,3-dibromo-3-phenylpropanoate (18): mp 53 °C, two isomers; ^1H NMR δ 3.83 (dd, 1H, J = 10.8, 8.6 Hz), 3.90 (dd, 1H, J = 10.8, 4.9 Hz), 4.41−4.47 (m, 1H), 4.71 (dd, 1H, J = 12.0, 3.4 Hz), 4.79 (dd, 1H, J = 12.0, 5.3 Hz), 4.93 (d, 1H, J = 11.8 Hz), 5.37 (d, 1H, J = 11.8 Hz), 7.40−7.46 (m, 5H); ^{13}C NMR δ 32.9, 46.8, 47.32 (47.35), 51.2 (51.3), 67.55 (67.60), 128.9, 129.8, 130.4, 138.1, 168.1. Anal. Calcd for $C_{12}H_{12}Br_4O_2$: C, 28.38; H, 2.38. Found: C, 28.68; H, 2.60.

(*E*)-2′,3′-Dibromoallyl *trans*-2,3-dibromo-3-phenylpropanoate (19): ^1H NMR δ 4.94 (d, 1H, J = 11.8 Hz), 5.18 (s, 2H), 5.38 (d, 1H, J = 11.8 Hz), 6.79 (s, 1H), 7.38−7.45 (m, 5H); ^{13}C NMR δ 47.3, 51.2, 67.0, 109.5, 119.0, 129.0, 128.8, 130.4, 138.3, 168.0. Anal. Calcd for $C_{12}H_{10}Br_4O_2$: C, 28.49; H, 1.99. Found: C, 28.16; H, 1.99.

Prop-2′-ynyl *trans*-2,3-dibromo-3-phenylpropanoate (20): ^1H NMR δ 2.60 (t, 1H, J = 2.4 Hz), 4.90 (d, 1H, J = 11.8 Hz), 4.91 (d, 2H), 5.37 (d, 1H, J = 11.8 Hz), 7.38−7.46 (m, 5H); ^{13}C NMR δ 47.2, 51.2, 54.8, 77.0, 128.9, 129.8, 130.4, 138.3, 167.9. Anal. Calcd for $C_{12}H_{10}Br_2O_2$: C, 41.65; H, 2.91. Found: C, 41.55; H, 2.92.

***N*-((*trans*-2-bromo)-3-oxo-1,3-diphenylpropyl)acetamide (22):** mp 94−95 °C; ^1H NMR δ 1.85 (s, 3H), 5.54 (d, 1H, J = 8.9 Hz), 6.67 (d, 1H, J = 8.9 Hz), 7.73−7.95 (m, 10 H); ^{13}C NMR δ 23.7, 55.7, 76.4, 127.9, 128.7, 129.4, 129.6, 129.7, 129.8, 129.9, 134.4, 135.2, 140.6, 170.6, 200.3. Anal. Calcd for $C_{17}H_{16}BrNO_2$: C, 58.97; H, 4.66; N, 4.05. Found: C, 58.70; H, 4.74; N, 4.30.

Acknowledgment. We acknowledge the support of the National Science Foundation (Grant No. CHE-0315275) and AFOSR (Grant No. F49620-03-1-0209).

Supporting Information Available: Experimental procedure and characterization data for known compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JO048383X

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