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Regioselective Fluorination of 1-(2,2-Dibromovinyl)benzene Derivatives with Wet Tetra-*n*-butylammonium Fluoride: One-Pot Synthesis of (*Z*)-1-(2-Bromo-1-fluorovinyl)benzenes

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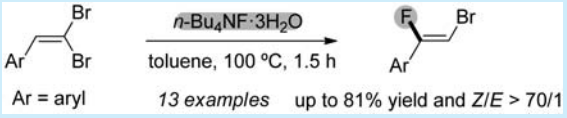
Supporting Information

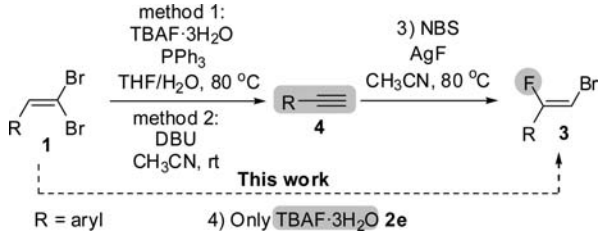
ABSTRACT: A direct fluorination of 1-(2,2-dibromovinyl)benzene derivatives using wet tetra-*n*-butylammonium fluoride (TBAF·3H$_2$O) as either a base or a fluorine source in toluene was accomplished, which provided (*Z*)-1-(2-bromo-1-fluorovinyl)benzene compounds in up to 81% yields with high regioselectivities. This reaction results strongly depend upon the reaction conditions. The mechanism of this reaction was investigated as well.



Fluorovinyl compounds are of great importance in the pharmaceutical and material chemistry.[1] The introduction of a fluorine atom into a vinyl fragment may lead to significant changes in biological activities owing to the unique properties of fluorine.[2] The synthetic method for fluorovinyl compounds has received greatly increasing attention during the recent decade. These compounds can be prepared by elimination,[3] electrophilic fluorination,[4] Julia–Kocienski olefination,[5] Peterson olefination,[6] and transition-metal-catalyzed fluorination of alkynes with triethylamine hydrogen fluoride[7] (Et$_3$N·3HF) or silver fluoride[8] (AgF). However, these methods show poor tolerance for functional groups, low stereoselectivity, and moderate to low yields and use transition metals. Nevertheless, the Horner–Wadsworth–Emmons reaction[9] has been viewed as the most practical protocol for the preparation of vinyl fluorides, as the halofluorocarbons as the starting material for the preparation of fluoromethyl phosphorane ylides have been limited in utilization by the law owing to their ozone depletion and greenhouse effects.[10] Therefore, the development of a practical method for the synthesis of vinyl fluorides is highly desirable.

1,1-Dibromovinnyl derivatives **1** generally produce the terminal alkynes under the following reaction conditions: (1) *n*-butyl lithium (*n*-BuLi) and water at −78 °C;[11] (2) excess wet tetra-*n*-butylammonium fluoride (TBAF·3H$_2$O) as a base, triphenylphosphine (PPh$_3$) as a reductant in THF/H$_2$O at 40–80 °C (method 1 in Scheme 1);[12] and (3) 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as either base or reductant, in acetonitrile (CH$_3$CN) at room temperature (method 2 in Scheme 1).[13] Interestingly, the terminal alkynes **4** could be transformed into vinyl fluoride compounds **3** through a fluorination with the use of *N*-bromosuccinimide (NBS) and excess AgF (condition 3 in Scheme 1).[8,14] Inspired by these works, we envision that transition-metal-free reaction of 1,1-dibromovinnyl derivatives **1** with TBAF[15] may occur to give 2-bromo-1-fluorovinyl compounds **3** (condition 4 in Scheme 1). Noticeably, this fluorination poses a significant challenge, since the formation of alkynes[12] and acetones[16] should be inhibited. To the best of our knowledge, such a fluorination reaction has not yet been reported until now. In this paper, we report a direct fluorination of 1-(2,2-dibromovinyl)benzene derivatives **1** with TBAF·3H$_2$O to produce 2-bromo-1-fluorovinyl compounds, which are particularly valuable synthetic building blocks for the incorporation of a fluorine atom into organic molecules.

Scheme 1. Reactions of 1,1-Dibromovinylbenzene Derivatives and Alkynes



Initial exploration of our hypothesis was aimed at a direct fluorination of 1-chloro-4-(2,2-dibromovinyl)benzene **1a** in the absence of transition metal catalyst. Thus, the reaction of **1a** with a fluorinating reagent including cesium fluoride (CsF, **2a**), potassium fluoride[17] (KF, **2b**), and silver fluoride[18] (AgF, **2c**) in DMF was conducted at 100 °C; only the formation of 1-(bromoethynyl)-4-chlorobenzene **5a** was observed after 12 h (Table 1, entries 1–3). Et$_3$N·3HF[7] **2d** showed no reactivity (entry 4). To our excitement, commercially available TBAF·3H$_2$O **2e** was employed and the formation of (*Z*)-1-(2-bromo-1-fluorovinyl)-4-chlorobenzene[8] **3a** (62%) and 1-chloro-4-ethynylbenzene[12] **4a** (37%) was observed after the completion of this reaction; a ratio of (*Z*)-**3a** to (*E*)-**3a**′,[8] an isomer of (*Z*)-**3a**, in 80/1 was detected by the analysis of GC-MS as well

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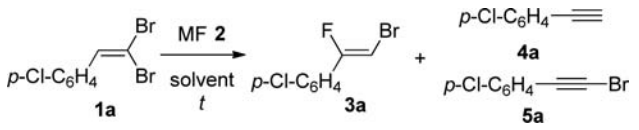
Table 1. Optimizing Reaction Conditions for a Fluorination of 1-Chloro-4-(2,2-dibromovinyl)benzene 1a[a]



entry	MF	solvent	temp (°C)	3a[b]	4a[b]	5a[b]
1	CsF	DMF	100	0	0	97
2	KF	DMF	100	0	0	41
3	AgF	DMF	100	0	0	18
4	$Et_3N{\cdot}3HF$	DMF	100	–	–	–
5	$TBAF{\cdot}3H_2O$	DMF	100	62	37	0
6	$TBAF{\cdot}3H_2O$	DMF	60	3	12	84
7	$TBAF{\cdot}3H_2O$	DMF	80	57	38	4
8	$TBAF{\cdot}3H_2O$	DMF	120	31	68	0
9	$TBAF{\cdot}3H_2O$	MeCN	100	0	99	0
10	$TBAF{\cdot}3H_2O$	DCE	100	0	0	90
11	$TBAF{\cdot}3H_2O$	*t*-BuOH	100	6	0	93
12	$TBAF{\cdot}3H_2O$	dioxane	100	61	38	0
13[c]	$TBAF{\cdot}3H_2O$	toluene	100	75	21	0
14[d]	$TBAF{\cdot}3H_2O$	toluene	100	65	30	4
15	TBAF·4(*t*-BuOH)	toluene	100	73	25	0
16	TMAF	toluene	100	–	–	2

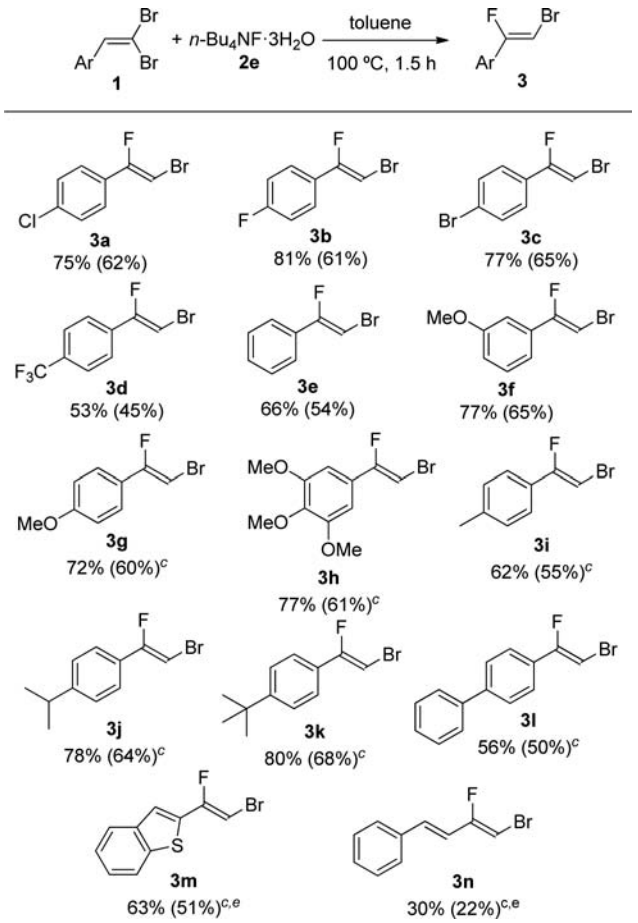
[a]Reaction conditions: **1a** (0.20 mmol, 1.0 equiv), MF **2** (2.0 mmol, 10.0 equiv) in solvent (2.0 mL) at appropriate temperature in a sealed tube. [b]Yields were determined by GC-MS and are expressed as area percent, uncorrected. [c]The *Z*/*E* ratio was determined by GC-MS, unless otherwise noted; *Z*/*E* ratio >70/1. [d]**1a**/**2e** ratio was 1/5.

(entry 5). Further investigation revealed that the reaction results tremendously depend upon the reaction temperature in the range of 60 to 120 °C. For example, the reaction at 60 °C afforded similar outcomes to the known work,[12] except for which a 3% yield of **3a** was unexpectedly observed (entry 6). The reaction at 80 °C gave a 57% yield of **3a** and a 38% yield of **4a**, respectively; a trace amount of **5a** was obtained (entry 7). However, the reaction at 120 °C provided **4a** as a major product and **3a** as a minor one; no **5a** was achieved (entry 8). The nature of solvents has a crucial influence on the reaction of (1,1-dibromovinyl)benzene derivatives.[12,13] Consequently, a variety of solvents such as acetonitrile (MeCN), 1,2-dichloroethane (DCE), *t*-BuOH, dioxane, and toluene were screened (entries 5, 9–13). Unexpectedly and interestingly, MeCN led to the formation of the nearly quantitative **4a** (entry 9); on the other hand, either DCE or *t*-BuOH resulted in **5a**[19] in high yield, which is consistent with the reported work[19] (entries 10–11). Toluene is the optimum solvent for the fluorination, whereas other solvents such as DMF and dioxane gave rise to similar results (entries 5 and 12–13). In contrast, both TBAF·4(*t*-BuOH)[20] and tetramethylammonium fluoride (TMAF) were utilized and TBAF·4(*t*-BuOH) led to **5a** in a slightly lower yield than that of $TBAF{\cdot}3H_2O$ **2e** (entry 15). TMAF only resulted in a trace amount of **5a**, and both **3a** and **4a** were not observed (entry 16). The presence of water,[16] in which the ionization of TBAF releases a fluoride anion, was beneficial to the formation of **3a**. The variation of **1a**/**2e** ratio had a considerable influence on the efficiency of this reaction. For example, the 1/10 ratio of **1a**/**2e** led to the highest yield (entries 5, 13–14). In all cases without a transition-metal catalyst, the fluorination of **1a** with $TBAF{\cdot}3H_2O$ **2e** proceeded to completion within a short reaction time (1.5 h) (entries 5–15).

Subsequently, we evaluated the scope of a series of 1-(2,2-dibromovinyl)benzene substrates **1** with $TBAF{\cdot}3H_2O$ **2e** under the optimized conditions presented in entry 13 of Table 1.

General observations were as follows: (1) phenyl- and aryl-substituted 1-(2,2-dibromovinyl) compounds **1a–e** with electron-withdrawing groups (e.g., *p*-Cl, *p*-F, *p*-Br, and *p*-CF_3) on the phenyl ring produced the corresponding (*Z*)-1-(2-bromo-1-fluorovinyl)benzene compounds **3a–e** in 53–81% yields (Scheme 2). (2) When aryl-substituted 1-(2,2-dibromovinyl) compounds **3f–g**, and **i–l** bearing electron-donating groups (e.g., *p*-MeO, *m*-MeO, *p*-Me, *p*-(*i*-Pr), *p*-(*t*-Bu), and *p*-Ph) on the phenyl ring, were employed, the fluorination reactions occurred at 120 °C; the corresponding (*Z*)-1-(2-bromo-1-fluorovinyl)benzene compounds **3f–g** and **i–l** were obtained in 56–80% yields (Scheme 2). Trisubstituted phenyl such as **1h** can undergo this reaction at 120 °C, and it provided **3h** in a 77% yield. These results obviously revealed that the presence of the electron-donating substituent on the phenyl ring could decrease the activity of the substrates in the fluorination reaction. (3) In a particularly interesting case, heteoaryl-substituted substrate **1m** afforded **3m** with a 63%

Scheme 2. Scope of the 1-(2,2-Dibromovinyl)benzene Compounds 1[a–e]



[a]Reaction conditions: **1a** (0.20 mmol, 1.0 equiv), $TBAF{\cdot}3H_2O$ **2e** (2.0 mmol, 10.0 equiv) in toluene (2.0 mL) at 100 °C in a sealed tube. [b]Yield determined by GC-MS and expressed as area percent, uncorrected; isolated yields are in brackets. [c]At 120 °C. [d]The *Z*/*E* ratio was determined by GC-MS, unless otherwise noted, *Z*/*E* ratio >70/1. [e]*Z*/*E* > 40/1.

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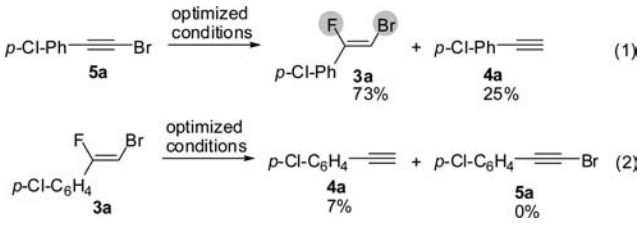
yield. (4) 1-(2,2-Dibromovinyl)benzene compound **1** with a substituent at the *ortho* position on the phenyl ring (e.g., *o*-Me and *o*-Cl) gave a trace amount of the corresponding product, respectively. We reasoned that the *ortho*-substituent may block the nucleophilic attack of the fluoride anion to the intermediate **6** in these cases (see Scheme 4). (5) (*E*)-(4,4-Dibromobuta-1,3-dienyl)benzene **1n** was also tested, and the corresponding **3n** was obtained in a 30% yield (Scheme 2). (6) We found that the *Z*/*E* ratio of **3a**−**n**/**3a**′−**n**′ is in the range of 40/1−70/1, which was determined by GC-MS. It is important to note that the fluorinated styrene compounds are highly volatile for isolation. As a result, we evaluated the efficiency of this reaction based on both GC yield and isolated yield.

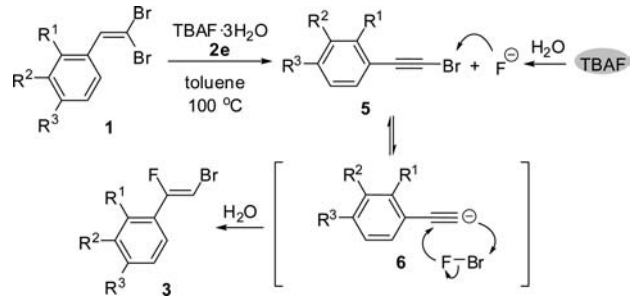
Two control experiments were performed under the optimized conditions: (i) (bromoethynyl)benzene **5a** produced **3a** (73%) along with **4a** (25%) (eq 1), and (ii) (*Z*)-1-(2-bromo-1-fluorovinyl)-4-chlorobenzene **3a** was treated with TBAF·3H_2O **2e** only giving 7% of **4a**; **5a** was not detected by GC-MS analysis (eq 2, Scheme 3).

Scheme 3. Two Control Experiments



On the basis of these control experiments and the previous reports,[8,12,14,19] a possible mechanism is proposed in Scheme 4.

Scheme 4. Possible Mechanism of the Present Reaction



In one pot, the debromination reaction of 1-(2,2-dibromovinyl)benzene compound **1** with TBAF·3H_2O **2e** in toluene at 100 °C occurs to produce the (bromoethynyl)-benzene[19] **5**. The ionization of TBAF in H_2O gives a fluoride anion,[12] which attacks the bromine atom on **5** to form an ethynyl anion[12] **6** and BrF[21] by a reversible process. Finally, an addition reaction of **6** with BrF[21] in the presence of H_2O would afford (*Z*)-1-(2-bromo-1-fluorovinyl)benzene product **3**;[22] meanwhile minor product **4**[12,14] is released in the course of the reaction.

In conclusion, we have developed a direct fluorination of 1-(2,2-dibromovinyl)benzene compounds **1** with TBAF·3H_2O **2e**, which afforded (*Z*)-1-(2-bromo-1-fluorovinyl)benzene compounds in good to high yields with excellent regioselectivities. This method allows the use of wet tetra-*n*-butylammonium fluoride as the fluorine source in the absence of a transition metal. This is the first example of the synthesis of (*Z*)-1-(2-bromo-1-fluorovinyl)benzene compounds derived from TBAF·3H_2O.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03448.

Details for experiments conditions, characterization data, copies of ^{1}H and ^{13}NMR spectra for all isolated compounds (PDF)

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†M.Z. and L.M. contributed equally.

Notes

The authors declare no competing financial interest.

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