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Tetrabutylammonium fluoride-induced dehydrobromination of vinyl bromides to terminal acetylenes

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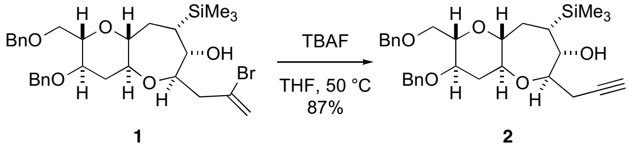
Abstract—Tetrabutylammonium fluoride (TBAF) was found to be a mild and efficient base for the dehydrobromination of vinyl bromides. Treatment of various 2-bromo-1-alkenes with TBAF·$3H_2O$ in DMF yielded terminal acetylenes in high yields without undue regard to the presence of water.

Terminal acetylenes are an important functional group and widely used in organic synthesis. Recent progress with transition metal-catalyzed carbon–carbon coupling reactions such as Sonogashira coupling reactions, Pauson–Khand reactions, and metatheses has also proven the importance of terminal acetylenes.[1] Dehydrobromination of vinyl bromides is a simple method for the preparation of terminal acetylenes, and many procedures have been reported: $NaNH_2$ in liquid NH_3,[2] KO*t*-Bu in THF,[3] NaOMe in DMSO,[4] NaH in DMSO or DMF,[5] LDA in THF,[6] KH in THF,[7] DBU in THF,[8] *n*-BuLi in Et_2O,[9] and *t*-BuLi in pentane–Et_2O.[10] The common disadvantages of these methods are the requirement of a strong base and anhydrous reaction conditions due to the low acidity of olefinic protons. It is therefore useful to find a new method that can tolerate moisture or water.

During the course of our synthetic studies of polycyclic ethers, we discovered an unexpected reaction of vinyl bromide **1** with tetrabutylammonium fluoride (TBAF) in THF. The reaction product obtained was the dehydrobromination product **2** instead of the desired desilylation compound.[11] Considering that the commercially available TBAF (1 M in THF) contains approximately 5% water,[12] the acetylene formation in the presence of water is quite interesting and stimulated us to investigate the dehydrobromination of vinyl bromides with TBAF.



Tetrabutylammonium fluoride is a versatile and popular reagent widely used in organic chemistry for many fluoride-assisted reactions such as deprotection of silyl ethers,[13] acetals,[14] esters,[15] carbamates,[16] and *N*-sulfonyl groups,[17] as well as desilylation[18] and fluorination.[19] Moreover, TBAF has been used as a mild base in a variety of base-catalyzed reactions such as aldol-type condensation reactions,[20] Michael-type reactions,[21] and the opening reaction of small rings,[22] and has also been employed as a promoter in homo- and cross-coupling reactions[23] and cyclization reactions for carbocycles[24] and heterocycles.[25] Recently, TBAF has been reported to be an efficient base for the dehydrohalogenation of alkyl halides to alkenes.[26] However, there has been no study on the reaction of 2-bromo-1-alkenes with TBAF. An analogue to this reaction found in the literature is the silicon-assisted dehydrohalogenation of bromo- or chlorovinyltrimethylsilanes.[8,27] We wish to report herein the TBAF-induced terminal alkyne-forming reaction of 2-bromo-1-alkenes.[28]

Initial experiments in dehydrobromination were carried out using vinyl bromide **3** in order to establish the optimal reaction conditions (Table 1). Treatment of **3** with 1.0 equiv of TBAF (1 M in THF) in THF at 60 °C resulted in reducing the reaction conversion to only a

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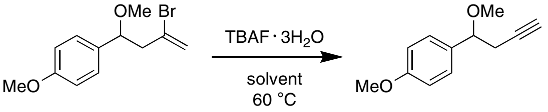
Table 1. Optimization of reaction conditions of dehydrobromination of **3** with TBAF at 60 °C



3 **4**

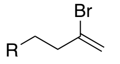
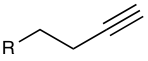
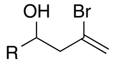
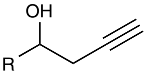
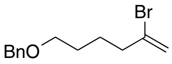
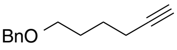
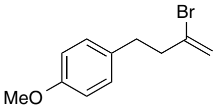
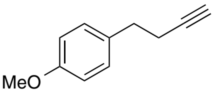
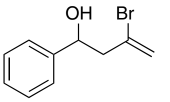
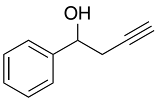
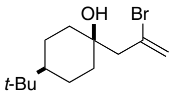
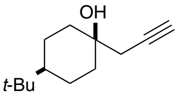
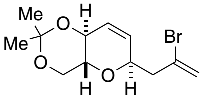
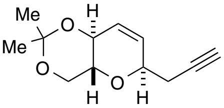
Entry	Solvent	TBAF (equiv)	Time (h)	Conversion[a] (%)	Isolated yield (%)
1	THF	1.0	25	44	40
2	THF	2.0	25	58	52
3	THF	3.0	25	82	74
4	THF	4.0	25	92	84
5	THF	5.0	25	97	85
6	DMF	1.0	25	55	50
7	DMF	2.0	25	72	65
8	DMF	3.0	25	92	83
9	DMF	5.0	1	90	—
10	DMF	5.0	2	97	—
11	DMF	5.0	3	99	91

[a] Conversions of entries 1–8 were determined based on the recovered **3**. The experiments of entries 9–11 were carried out in an NMR tube using DMF-d_7, and the conversions were determined by ^{1}H NMR.

44% value after 25 h (entry 1). Increasing the quantity of TBAF improved the conversion yield, and 5.0 equiv of TBAF was necessary for complete conversion (entry 5). We next examined the effects of solvent on shortening the reaction times. No reaction was observed with the halogenated solvent CH_2Cl_2 or a polar protic solvent such as MeOH. It has been recognized that the basic property of the fluoride ion increases in polar aprotic solvents such as DMF, MeCN, and DMSO.[27] In the present case, DMF was found to be an acceptable solvent, qualitatively as good and better than THF in terms of reaction times. Acetonitrile was found to be inferior when compared to THF. In the reaction with DMF, TBAF·3H$_2$O was selected as the reagent because it is readily available as a stable salt. The quantity of TBAF required to complete the reaction was then evaluated. It was found that 5.0 equiv of TBAF·3H$_2$O was needed to complete the reaction at 60 °C in a few hours (entries 9–11). Other fluoride salts such as CsF and KF were shown to be ineffective for this dehydrobromination.

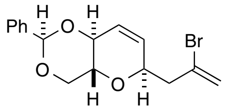
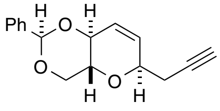
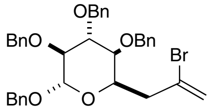
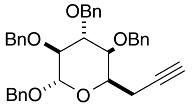
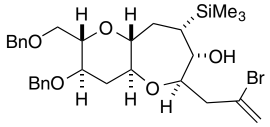
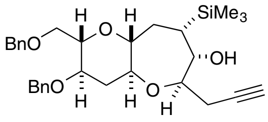
Next, we extended the optimized dehydrobromination conditions to various vinyl bromides: the results are represented in Table 2.[29] We were delighted to find that the reaction is quite general and that many substances tolerate the optimized reaction conditions, giving products in good to high yields. Vinyl bromides containing a hydroxy group were also found to give the corresponding acetylenes in good yields (entries 2, 5, and 6). It is notable that only trace amounts (<2%) of allenic products were detected in the experiments listed in entries 2, 5, and 6,

Table 2. Dehydrobromination of vinyl bromides with TBAF (5.0 equiv) in DMF at 60 °C

Entry	Substrate	Time (h)	Product	Isolated yield (%)
1	 R = C_9H_{19}	4		93
2	 R = C_9H_{19}	3		95
3		2		90
4		1.5		91
5		3		92
6		3		82
7		3		78 (+ allene 9%)

(*continued on next page*)

Table 2 (*continued*)

Entry	Substrate	Time (h)	Product	Isolated yield (%)
8		3		70 (+ allene 17%)
9		4.5		77 (+ allene 11%)
10		2		92

whereas large amounts (9–17%) of allene derivatives were formed in the dehydrobromination of the vinyl bromides derived from glucose (entries 7–9). The reason for this remarkable difference in the allene formation is not clear and under scrutiny. Vinyl bromides having a carbonyl group were not found to be suitable because of the concurrent aldol reaction,[20] giving a mixture of products.

In conclusion, TBAF was found to be an efficient and mild base in the dehydrobromination of vinyl bromides to terminal acetylenes. The reaction can be carried out by using TBAF$\cdot$3H$_2$O in DMF, and the water tolerance and the absence of metal salts make this method attractive. This procedure provides a reasonable alternative to other methods that require strong bases and anhydrous conditions. We are currently examining the scope and limitations of this method.

Acknowledgment

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29. *Typical procedure for* **3**: Vinyl bromide **3** (270 mg, 1.0 mmol) was dissolved in 5 mL of a 1 M solution of $TBAF\cdot 3H_2O$ in DMF, and the reaction mixture was heated at 60 °C for 4 h. The mixture was diluted with Et_2O and the organic phase was washed with water and brine. The organic layer was separated, dried over anhydrous $MgSO_4$, and filtered. The solvent was removed in vacuo and the residue was purified by flash chromatography (8% ethyl acetate in hexane) to give acetylene **4** (173 mg, 91%).