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Terminal alkynes from aldehydes via dehydrohalogenation of (*Z*)-1-iodo-1-alkenes with TBAF

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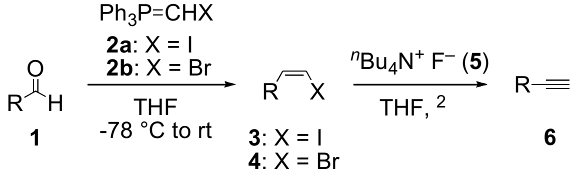
ABSTRACT

Terminal alkynes were prepared in near quantitative yields via dehydrohalogenation of (*Z*)-1-iodo-1-alkenes with tetrabutylammonium fluoride (TBAF) under mild conditions. The methodology was expanded to include a one-pot, direct synthesis of terminal alkynes from aldehydes without the necessity of isolating and purifying the intermediate iodoalkene.

The carbon–carbon triple bond is an important and versatile functional group in organic chemistry. Alkynes are present in numerous important products that have application in biological, medicinal, and materials chemistry.[1] Consequently, a variety of protocols have been developed to synthesize alkynes,[2] including the widely used Corey–Fuchs reaction[3,4] and the Seyferth–Gilbert homologation.[5]

During the course of an alkaloid synthesis program, we encountered an unanticipated side reaction during a routine deprotection of a silyl ether using tetrabutylammonium fluoride (TBAF, **5**). In addition to the removal of the silyl protecting group, we observed a facile dehydrohalogenation of an appended (*Z*)-1-iodo-1-alkene that resulted in the formation of the corresponding terminal alkyne (Scheme 1). The dehydrohalogenation of 1-halo-1-alkenes has been employed as a deliberate strategy in several natural product syntheses albeit with strong/harsh bases,[6–8] and is thus ripe for further improvement.



Scheme 1. Formation of (*Z*)-1-halo-1-alkenes (**3**,**4**) and subsequent TBAF (**5**)-mediated dehydrohalogenation to form terminal alkynes (**6**).

A search in the literature revealed that Naso and Ronzini had previously disclosed the dehydrohalogenation of a (*Z*)-1-bromo-1-alkene (Scheme 1, **4**: R = *p*-$NO_2C_6H_4$) using tetraethylammonium fluoride.[9] Recently, Okutani and Mori have also reported the dehydrobromination of 2-bromo-1-alkenes using TBAF.[10] Inspired by both these precedents, we aimed to explore in more detail the dehydrohalogenation of (*Z*)-1-iodo-1-alkenes (**3**) with particular emphasis on expanding the substrate scope and developing an alternate direct, one-pot route to terminal alkynes from aldehydes via **3** (Scheme 1).

We initially investigated the parameters of the methodology using **3a** as the test substrate (Table 1, vide infra). First, the (*Z*)-1-iodo-1-alkenes (**3**) were selected as test substrates because the corresponding (*Z*)-1-bromo-1-alkenes (**4**) could not be reliably synthesized with high diastereoselectivities using phosphorane **2b** (Scheme 1).[11,12] In contrast, **3** could be readily synthesized in good yields (90–72%, see Supplementary data) and high diastereoselectivities [dr = ⩾93:7 (*Z*:*E*)] using Stork's procedure with phosphorane **2a**.[13] The high (*Z*)-selectivity is essential because the subsequent dehydrohalogenation reaction with TBAF (**5**) requires the *anti*-relationship of the hydrogen and halogen atoms (i.e., (*E*)-1-halo-1-alkene are unreactive in the presence of TBAF).[9,12]

With **3a** in hand, we initiated optimization studies as shown in Table 1. The reaction parameters that were varied included the solvent, stoichiometry, and temperature, full details of which are included in Supplementary data. Prior reports on the dehydrohalogenation of 1-halo-1-alkenes utilized much stronger and potentially harsher bases such as ^{n}BuLi, LDA, and KO^{t}Bu.[7,8] We,

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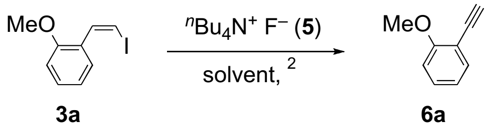
Table 1

Optimization studies for the formation of terminal alkyne **6a** from (*Z*)-1-iodo-1-alkene **3a**



Entry	Solvent	Temperature (°C)[a]	TBAF (equiv)	Yield[b] (%)
1	THF	20	1.5	22
2	THF	60	1.5	96
3	THF	80	1.5	96
4	THF	60	1.0	82
5	THF	60	2.0	97
6	DME	60	1.5	94
7	DMF	60	1.5	85
8	$PhCH_3$	60	1.5	19

[a] Reactions were conducted in a sealed tube.

[b] Isolated yield (average of two runs).

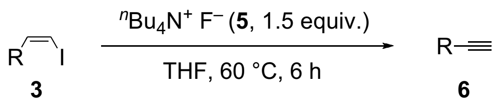
however, settled on tetrabutylammonium fluoride (TBAF, **5**) as the base of choice for the dehydrohalogenation reaction due to two factors: (i) it is a much milder base with greater functional group tolerance; and (ii) its tolerance to moisture and oxygen.[9,10]

The results in Table 1 show that the elimination reaction is promoted at slightly elevated temperatures (entries 1–3), in polar, aprotic solvents (entries 2, 6–8), and that TBAF (**5**) is required in excess (entries 2, 4, and 5). The reaction conditions that were subsequently employed for all subsequent reactions were as follows: **3** (1 equiv), $^nBu_4N^+$ F^- (1.5 equiv), THF, 60 °C, 6 h.[14] The scope of the reaction is then evaluated by examining other (*Z*)-1-iodo-1-alkenes (**3**) under the reaction conditions listed above, as listed in Table 2. It should be noted that the dehydrohalogenation reactions were carried out under ambient atmospheric conditions without undue regard to oxygen or moisture, which is a direct benefit of using a mild and tolerant base such as TBAF (**5**).

The results in Table 2 indicate that a variety of aromatic (entries 1–8) and heteroaromatic (entries 9, 10) (*Z*)-1-iodo-1-alkenes (**3**) successfully underwent the dehydrohalogenation reaction with $^nBu_4N^+$ F^- to afford the corresponding terminal alkynes (**6**) in uniformly high isolated yields ranging from 98% to 81% (average of two runs). The reaction methodology was tolerant of several functional groups such as the nitro (entry 2), carbonyl (entry 3), aromatic halogens (entry 4), and trifluoromethyl groups (entry 6). In addition, heteroaromatic groups such as pyridine (entries 9 and 10) did not pose a problem under the standard reaction conditions. We could not, however, generate enynes in high yields from the corresponding (*Z*)-1-iodo-1,2-diene due to decomposition of the starting materials under the standard reaction conditions.

Table 2

Dehydrohalogenation of (*Z*)-1-iodo-1-alkenes (**3**) with TBAF (**5**)



Entry	R	Yield[a,b] (%)
1	2-$MeOC_6H_4$ (**3a**)	96 (**6a**)
2	2-$NO_2C_6H_4$ (**3b**)	95 (**6b**)
3	4-$CH_3C(O)C_6H_4$ (**3c**)	94 (**6c**)
4	4-BrC_6H_4 (**3d**)	92 (**6d**)
5	4-$Me_2NC_6H_4$ (**3e**)	98 (**6e**)
6	3,5-$(CF_3)_2C_6H_3$ (**3f**)	93 (**6f**)
7	1-Naphthyl (**3g**)	92 (**6g**)
8	2-Naphthyl (**3h**)	92 (**6h**)
9	2-Pyridyl (**3i**)	88 (**6i**)
10	3-Pyridyl (**3j**)	91 (**6j**)
11	Cyclohexyl (**3k**)	87 (**6k**)[c]
12	C_7H_{15} (**3l**)	81 (**6l**)[c]

[a] Isolated yield (average of two runs).

[b] Reactions were conducted in a sealed tube.

[c] Reaction conducted at 80 °C for 12 h.

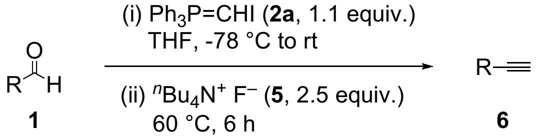
Aliphatic variants of **3** (Table 2, entries 11 and 12) did react with TBAF (**5**), albeit in a sluggish manner. Consequently, the reaction temperature had to be elevated to 80 °C, and the reaction time had to be lengthened to 12 h in order to obtain satisfactory isolated yields of the resulting alkynes (entries 11 and 12).[15]

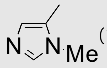
After establishing the validity of synthesizing terminal alkynes via TBAF-mediated dehydrohalogenation of (*Z*)-1-iodo-1-alkenes (**3**), we next sought to investigate the possibility of developing a one-pot variant of preparing terminal alkynes directly from aldehydes without the necessity of isolating **3**.[12] The outcome of these studies is summarized in Table 3 (vide infra). The results show that it is indeed not necessary to isolate the intermediate (*Z*)-1-iodo-1-alkenes (**3**). After the initial Wittig olefination of aldehyde **1** with phosphorane **2a**, $^nBu_4N^+$ F^- (TBAF, **5**, 2.5 equiv) was directly added to the crude reaction mixture.[16] The entire reaction mixture was then heated at 60 °C for 6 h (80 °C for 12 h for aliphatic aldehydes **1s** and **1t**). A variety of terminal alkynes (**6**) were thus synthesized in isolated yields ranging from 86% to 73% (Table 3, average of two runs).[17]

The overall yield of this two-step, one-pot reaction is limited by initial lower yielding Wittig olefination with phosphorane **2a** rather than the subsequent near quantitative yielding dehydrohalogenation step. A comparison of this newly developed one-pot methodology to the earlier developed procedure shows that the overall isolated yields, from the corresponding aldehyde, are comparable (e.g., for **6a** the overall isolated yields was 81% and 79% for the one-pot and two-pot protocols, respectively).[18] We did not observe any difference in the two procedures in terms of substrate scope or functional group tolerance. The advantages of the one-pot methodology, however, are the omission of a work-up step, and subsequent chromatographic purification with attended savings in time and materials.

Table 3

One-pot direct synthesis of terminal alkynes from aldehydes



Entry	R	Yield[a] (%)
1	2-$MeOC_6H_4$ (**1a**)	81 (**6a**)
2	2-$NO_2C_6H_4$ (**1b**)	80 (**6b**)
3	4-$CH_3C(O)C_6H_4$ (**1c**)	83 (**6c**)
4	3,5-$(CF_3)_2C_6H_3$ (**1f**)	77 (**6f**)
5	1-Naphthyl (**1g**)	80 (**6g**)
6	3-Pyridyl (**1j**)	74 (**6j**)
7	4-CNC_6H_4 (**1m**)	80 (**6m**)
8	2,4-$F_2C_6H_3$ (**1n**)	81 (**6n**)
9	4-MeO-2-MeC_6H_3 (**1o**)	77 (**6o**)
10	4-PhC_6H_4 (**1p**)	86 (**6p**)
11	 (**1q**)	78 (**6q**)
12	3-Thienyl (**1r**)	75 (**6r**)
13	$PhCH_2CH_2$ (**1s**)	73 (**6s**)[b]
14	$CH_3CH_2CH_2CH_2CH(OTBS)$ (**1t**)	78 (**6t**)[b,c]

[a] Isolated yield (average of two runs).

[b] Reaction conducted at 80 °C for 12 h.

[c] 3.5 equiv of $^nBu_4N^+$ F^- was used.

In conclusion, we have demonstrated that a variety of terminal alkynes can be readily synthesized in high yields via dehydrohalogenation of the corresponding 1-iodo-1-alkenes using a mild and tolerant base, tetrabutylammonium fluoride. In addition, the one-pot direct synthesis of terminal alkynes from aldehydes, without the necessity of isolating the intermediate iodoalkene, was also presented. The broad substrate scope and functional group tolerance of this reaction methodology make it an attractive addition to the current repertoire of routes to synthesize terminal alkynes from aldehydes.

Acknowledgments

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Supplementary data

Supplementary data (complete experimental details, characterization data, and copies of NMR spectra (^{1}H and ^{13}C) of **3** and **6**) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.09.060.

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11. For example, in our hands, the reaction of aldehyde **1a** with phosphorane **2b** afforded a 75:25 (*Z*:*E*) mixture of the corresponding 1-bromo-1-alkene under otherwise identical conditions.
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14. *General procedure for the dehydrohalogenation of (Z)-1-iodo-1-alkenes* (**3**) *with TBAF* (Table 2): To a solution of the (*Z*)-1-iodo-1-alkene (**3**) (0.500 mmol) in anhydrous THF (0.75 mL) in a Swagelock® 50 mL stainless steel cylinder or an Ace® pressure tube was added a solution of TBAF (1.0 M in THF, 0.75 mL, 0.75 mmol) dropwise. The cylinder (or tube) was sealed and heated in an oil bath at 60 °C or 80 °C (for **3k** and **3l**) for 6 h or 12 h (for **3k** and **3l**), respectively. The cylinder (or tube) was then removed and allowed to cool to rt. The Swagelock® cylinder (or pressure tube) was opened, and the contents were transferred to a small round bottom flask. All the volatiles were removed in vacuo and the crude product was purified by silica gel chromatography (gradient, hexanes/EtOAc, 100:0/80:20). Note: The dehydro-halogenation reaction of aliphatic (*Z*)-1-iodo-1-alkene **3k** and **3l** was carried on a 5 mmol scale. The resulting aliphatic alkynes (**6k** and **6l**) were isolated by fractional distillation from the crude reaction mixture. See Supplementary data for full details including complete characterization data.
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16. We found it necessary to increase the equivalence of ^{n}Bu$_4$N$^+$ F$^-$ (TBAF) from 1.5 to 2.5 in order to obtain satisfactory isolated yields of the terminal alkynes (**6**). Also note that we observed the addition of HMPA as cosolvent during the formation of the (*Z*)-1-iodo-1-alkene caused a decrease in the isolated yield of the terminal alkyne (**6**), and was thus omitted in the one-pot protocol.
17. *General procedure for the one-pot direct synthesis of terminal alkynes from aldehydes* (Table 3): To a suspension of iodomethyltriphenylphosphonium iodide (584 mg, 1.10 mmol) in THF (1.5 mL) was added NaHMDS (1M in THF, 1.10 mL, 1.10 mmol) dropwise. The mixture was allowed to stir at rt for 10 min. The resulting red solution that formed was cooled to −78 °C, and a solution of the aldehyde (1.00 mmol) in THF (1.0 mL) was slowly added dropwise. The reaction mixture was allowed to stir for 2.5 h while warming to rt. TBAF (1.0 M in THF, 2.50 mL, 2.50 mmol) was then added dropwise. The reaction mixture was subsequently heated to 60 °C or 80 °C for 6 h or 12 h, respectively. After cooling to rt, all volatiles were removed in vacuo. Hexanes (3 × 10 mL) was then added, and the mixture was filtered through Celite®. The filtrate was concentrated in vacuo and the residue was purified by silica gel chromatography (gradient, hexanes/EtOAc from 100:0 to 80:20) to afford terminal alkyne **6**. Note: The reaction of aldehyde **1r** was carried out on a 5 mmol scale. Alkyne **6r** was isolated by Kugelrohr distillation from the crude reaction mixture after removal of the solvent under atmospheric pressure. See Supplementary data for full details including complete characterization data.
18. (*Z*)-1-iodo-1-alkene **3a** was prepared in 82% isolated yield (see Supplementary data).