

One-Pot Synthesis of 1-Iodoalkynes and Trisubstituted Alkenes from Benzylic and Allylic Bromides

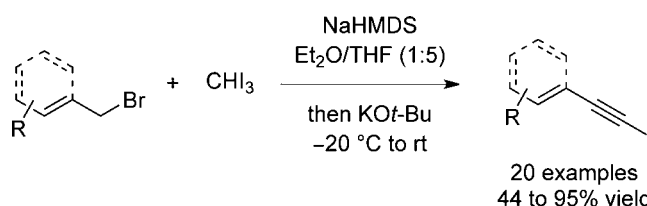
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ABSTRACT



1-Iodoalkynes are formed in moderate to high yields from readily accessible benzylic and allylic alkyl bromides by a one-pot homologation/double elimination procedure with iodoform (CHI_3). The developed conditions include facile purification and avoid the use of an excess of triphenylphosphine (PPh_3), as described in classical Corey–Fuchs iodoalkynylation conditions. Replacing CHI_3 with CHI_2Cl allows the isolation of the corresponding *gem*-(*Z*)-chloro-(*E*)-iodoalkene in good yield and stereoselectivity. Moreover, the use of benzhydryl bromides as nucleophiles enables the synthesis of trisubstituted alkenes under similar reaction conditions.

The importance of 1-iodoalkynes as versatile building blocks has been demonstrated in several synthetic

methodologies,¹ total syntheses,² pharmaceutical applications,³ and material/polymer sciences.⁴ Such compounds are operative in copper-catalyzed azide–alkyne cycloadditions, exhibiting exceptional regioselectivities and reactivities.^{1c–4a} Moreover, these haloalkynes are increasingly involved in cross-coupling processes, particularly in the synthesis of 1,3-diynes (Cadiot–Chodkiewicz reaction),^{1h,2b–2d,5} and in Nozaki–Hiyama–Kishi–Takai couplings.^{1a,2a,6} However, there are few commercially available 1-iodoalkynes, and new methods enabling their synthesis remain desired.

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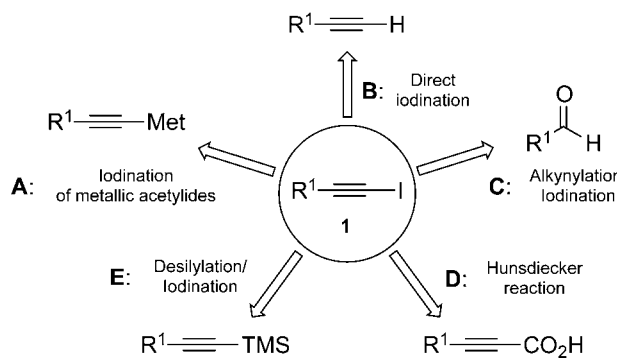


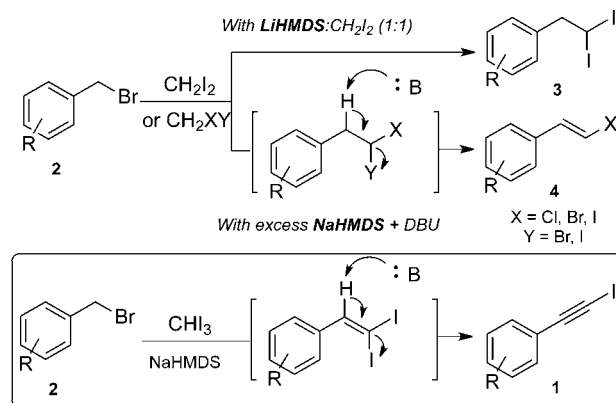
Figure 1. Classic methodologies employed for the synthesis of 1-iodoalkynes (**1**).

1-Iodoalkynes (**1**) are traditionally synthesized from iodination of preformed metal acetylides,⁷ direct iodination of the corresponding terminal alkyne,⁸ or by a two-step homologation/iodination sequence from an aldehyde (Corey–Fuchs reaction) (Figure 1, **A–C**).⁹ Alternatively, these alkynes can be prepared via an Et₃N-catalyzed Hunsdiecker reaction with NIS,¹⁰ or AgNO₃-mediated direct iodination of trimethylsilylacetylenes (**D** and **E**).¹¹ While these methods are routinely employed, the majority rely on acetylene precursors or intermediates that are often not readily available. In order to provide another means of manipulating terminal alkynes and an alternative to the Corey–Fuchs reaction, we report herein the direct synthesis of 1-iodoalkynes through a one-pot homologation/double elimination from commercially available benzylic and allylic bromides.

We envisioned the synthesis of 1-iodoalkynes (**1**) following our experience developing methods for the preparation of *gem*-diiodoalkanes (**3**) and (*E*)-vinyl halides (**4**) (Scheme 1).¹² We demonstrated that dihalomethanes can be readily deprotonated and subjected to nucleophilic substitution with benzylic bromides (**2**), efficiently providing differently homologated halide species (**3** and **4**). The nature of the products obtained, as well as the *anti*-elimination process, can be effectively controlled by both the basicity

of the medium and the reactants' stoichiometry. Our next target was to replace CH₂I₂ by iodoform (CHI₃) in order to trigger a base-mediated double *anti*-elimination to form **1**.

Scheme 1. Synthesis of *gem*-Diiodoalkanes, (*E*)-Vinyl Halides, and 1-Iodoalkynes from Benzylic Bromides



We treated iodoform (CHI₃) with NaHMDS at –78 °C in the dark for 40 min, followed by the addition of 2-chlorobenzyl bromide (2-ClBnBr, **2a**) as a test substrate (Table 1, entry 1). Analysis of the crude mixture indicated incomplete conversion to the 1-iodoalkyne (**1a**) with a small amount of the desired *gem*-diiodoalkene.¹³ In order to achieve complete elimination to **1a**, KO*t*-Bu was added as an external base resulting in a 52% yield of the desired target after 16 h at rt.¹⁴ A temperature screening determined that –20 °C was optimal (63%, entry 8). Heating the reaction above –20 °C during the deprotonation step is detrimental (< 10%, entry 10). A possible decomposition pathway of CHI₃ results from the formation of a carbene (or carbenoid).¹⁵ Base screening determined that NaHMDS and KO*t*-Bu were optimal for yield and reproducibility (entries 2–7). Performing the reaction for longer periods of time for both the deprotonation step (1 h) and the nucleophilic substitution with **2a** (5 h) proved beneficial (67%, entry 9). The use of KO*t*-Bu as an external base is essential while an excess of NaHMDS (4.0 equiv) does not improve the conversion to **1a** and the reaction was comparatively more sluggish (41%, entry 11).

With the optimal conditions in hand, a variety of 1-iodoalkynes (**1**) were synthesized starting from benzylic and allylic bromides (**2**) as summarized in Scheme 2. Overall, the reactions performed with benzylic bromides

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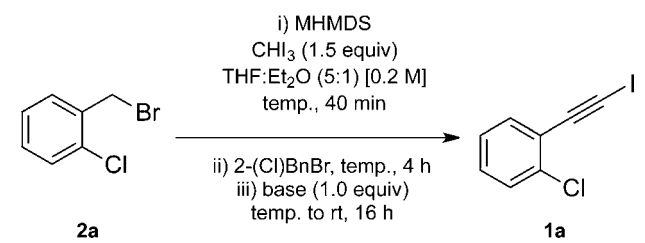
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Table 1. Optimization of the Reaction Parameters for the One-Pot Homologation/Double Elimination with 2-ClBnBr (**1a**)



entry	MHMDS (equiv) ^a	temp (°C)	base	yield 1a (%) ^b
1	NaHMDS (3.0)	-78	KO <i>t</i> -Bu	52
2	NaHMDS (3.0)	-40	KO <i>t</i> -Bu	61
3	NaHMDS (3.0)	-40	NaOAc	52
4	NaHMDS (3.0)	-40	NaOMe	58
5	NaHMDS (3.0)	-40	Barton's base ^c	59
6	LiHMDS (3.0)	-40	KO <i>t</i> -Bu	48
7	KHMDS (3.0)	-40	KO <i>t</i> -Bu	37
8	NaHMDS (3.0)	-20	KO <i>t</i> -Bu	63 (60%) ^d
9	NaHMDS (3.0)	-20	KO <i>t</i> -Bu	67 (69%) ^{d,e}
10	NaHMDS (3.0)	rt	KO <i>t</i> -Bu	<10%
11	NaHMDS (4.0)	-20	None	41

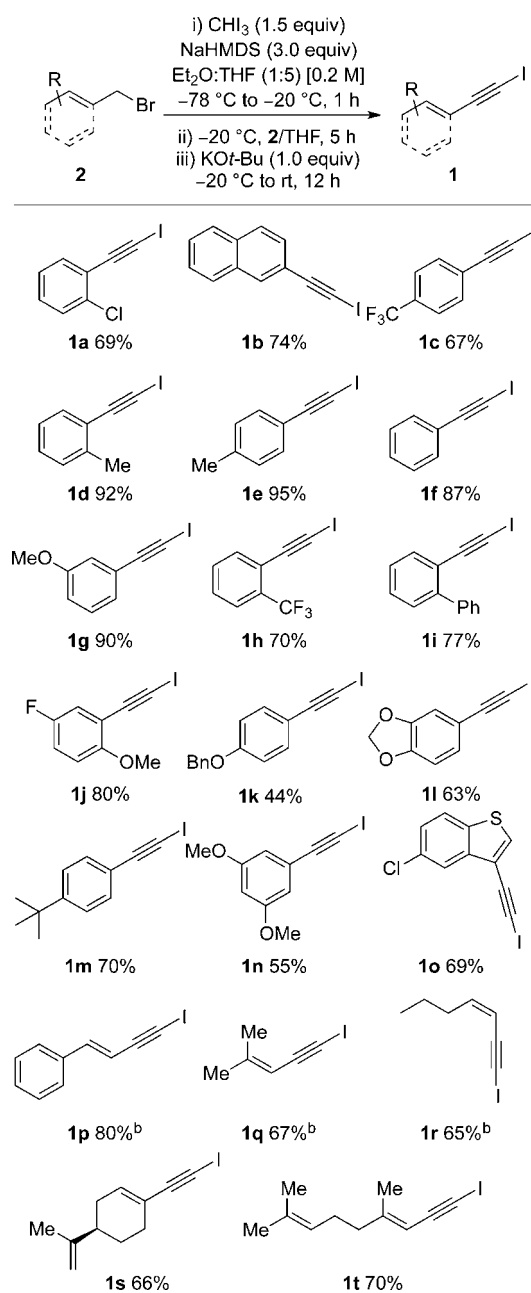
^a Neat MHMDS was used. ^b Yield determined on the crude reaction mixture by HPLC using pure **2a** as an external standard analyte. ^c Barton's base: 2-*tert*-butyl-1,1,3,3-tetramethylguanidine. ^d Isolated yields in parentheses. ^e Reaction between NaHMDS and CHI₃ was stirred at -20 °C for 1 h and then 2-ClBnBr was added at -20 °C and reaction was stirred for 5 h before KO*t*-Bu was added.

containing electron-donating groups furnished higher yields than those performed with electron-withdrawing substituents (Scheme 2; compare yields of **1d**, **1e**, **1g** to **1a**, **1c**, **1h**). This behavior can be explained by the higher electrophilicity of the former electron-rich benzylic bromides. Unfortunately, using the optimal conditions with unactivated bromo- or iodoalkanes did not lead to a significant conversion to their corresponding 1-iodoalkynes. It is important to note that, for most of the substrates investigated, complete consumption of the starting material was required as the starting bromides coeluted with the desired alkynes by purification with silica gel. The reactions were also easily worked up by a simple filtration on a Celite pad with a glass filter adapter and a mixture of Et₂O/hexanes in order to separate the product from the residual CHI₃ and insoluble sodium/potassium salts. For allylic bromides **1p**–**1r**, small quantities of the corresponding *gem*-diiodoalkenes were also isolated.¹³

In an attempt to extend our conditions to the synthesis of other alkyne and alkene derivatives,¹⁶ we explored the possibility of forming mixed *gem*-dihaloalkenes by replacing CHI₃ with different trihalomethane derivatives (Scheme 3). By submitting *p*-tolyl bromide (**2e**) to modified conditions with CHI₂Cl, and by avoiding the inclusion of

(16) The replacement of CHI₃ by CHCl₃ or CHBr₃ in the optimized conditions did not lead to a significant conversion to the corresponding 1-haloalkyne.

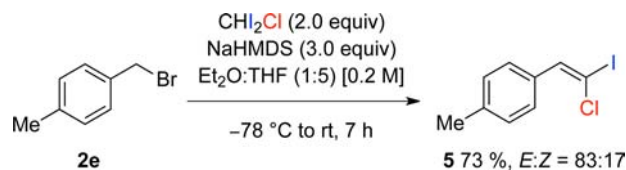
Scheme 2. Synthesis of 1-Iodoalkynes from Their Corresponding Benzylic or Allylic Bromides^a



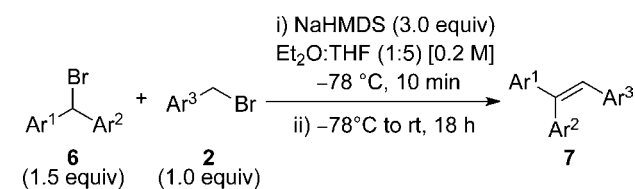
^a Reactions performed on a 1.0 mmol scale. Isolated yield. ^b The corresponding *gem*-diiodoalkene was also isolated as a minor product.

additional base, (*E*)-iodo-(*Z*)-chloroalkene **5** could be isolated with good yields and stereoselectivity. Currently, there are very few available methods for the stereoselective synthesis of such alkenes.¹⁷ The stereochemistry observed was confirmed by derivatization via a chemoselective Stille cross-coupling.^{13,17} However, with CHI₃ and CHI₂Br, the second elimination step from the corresponding alkene

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Scheme 3. Synthesis of *gem*-(*E*)-Iodo-(*Z*)-chloroalkene^a

^a Reaction performed on a 1.0 mmol scale. Isolated yield.

Table 2. Synthesis of Trisubstituted Alkenes from Benzhydryl Bromides^a

entry	benzhydryl bromide (6)	benzyl bromide (2)	yield 7 (%)
1			72 (7a)
2			80 (7b)
3			77 (7c)
4			50 ^b (7d)

^a Reaction performed on a 1.0 mmol scale. Isolated yield. ^b The dimerization product from the benzhydryl bromide was also isolated.

could not be avoided, and a significant amount of 1-iodoalkyne (**1e**) was observed by crude ¹H NMR.

In the context of forming *gem*-diiodoalkenes from benzylic bromides, we also submitted secondary benzhydryl bromides (**6**) to our optimized conditions and did not observe any formation of the corresponding homologated *gem*-diiodoalkene. Conversely, 1,1,2,2-tetraphenylethylene arising from deprotonation and dimerization of benzhydryl bromide was isolated in low yield.¹³ Following optimization of the benzhydryl bromide deprotonation,¹³ we were successful in the synthesis of trisubstituted alkenes by reacting the stabilized anion with benzyl bromides at -78°C (Table 2). By premixing benzhydryl bromide and benzyl bromide and adding the mixture to a solution of NaHMDS in THF/ Et_2O , various trisubstituted alkenes could be isolated after warming the reaction to rt.

In conclusion, we developed a method for the facile synthesis of 1-iodoalkynes by using a direct homologation/double elimination strategy with CHI_3 and benzyl bromides. The 1-iodoalkynes were isolated after an easy filtration workup, and the reaction showed good chemoselectivity for different functionalities. Furthermore, trisubstituted alkenes could be isolated by replacing iodoform with mixed trihalomethane derivatives or benzhydryl bromides.

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Supporting Information Available. Experimental procedures, NMR spectra, and compound characterization data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

The authors declare no competing financial interest.