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Stereoselective Synthesis of Trisubstituted Vinyl Bromides by Addition of Alkynes to Oxocarbenium Ions

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Abstract

We have developed an efficient method for the synthesis of (E)-trisubstituted vinyl bromides via a Friedel–Crafts-type addition of alkynes to oxocarbenium ions formed in situ from acetals. The success of this reaction relies on identification of $\text{MgBr}_2 \cdot \text{OEt}_2$ as both a Lewis acid promoter and bromide source. This reaction employs simple, inexpensive starting materials and proceeds under mild conditions to allow the preparation of a range of vinyl bromide products in high yields and E:Z selectivities. Furthermore, the vinyl bromide products also contain an allylic ether functional group. Both the vinyl bromide and allylic ether are effective handles for the elaboration of these useful synthetic intermediates.

Graphical abstract

Keywords

trisubstituted vinyl bromide; stereoselective; oxocarbenium ion; Friedel–Crafts; alkyne; vinylation

Vinyl bromides are versatile synthetic intermediates, allowing access to a wide range of organic molecules. In particular, highly substituted vinyl bromides undergo stereospecific coupling reactions, providing tri- and tetrasubstituted olefins with excellent control over olefin stereochemistry.¹ Popular methods for the preparation of trisubstituted vinyl halides include carbometallation,² cross couplings of dihaloalkenes,³ dehydrobromination of dibromides,⁴ and bromination of α,β -unsaturated carbonyl compounds.^{5,6} In the course of

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Primary Data

YES (this text will be updated with links prior to publication)

Supporting Information

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our research program investigating the metal-catalyzed addition of alkynes to oxocarbenium ion intermediates,⁷ we discovered a three-component coupling of benzylic acetals, terminal alkynes and MgBr_2 to deliver trisubstituted vinyl bromides (Scheme 1B).⁸ In addition to a vinyl bromide group, this 1-bromo-3-methoxy propene product also contains an allylic ether functionality to enable elaboration. Enticed by the simplicity of the starting materials, the incorporation of multiple functional group handles, and the possibility for control of the olefin stereochemistry, we pursued the development of this reaction.

The Friedel–Crafts-type addition of alkynes to cationic intermediates has been previously described. In particular, the stereoselective preparation of trisubstituted vinyl bromides has been accomplished via three-component couplings of terminal alkynes, metal bromides, and several classes of carbocationic intermediates.^{9,10,11} However, to our knowledge, previous Lewis acid-catalyzed additions to benzylic oxocarbenium ions have resulted in the addition of two equivalents of alkyne, delivering a 1,4-diene scaffold (Scheme 1A).¹² To maintain an oxygen functional group at the allylic position, vinylations of acid chlorides have been accomplished.¹³ In addition, via gold catalysis, the adducts of alkyne additions to aldehydes or oxocarbenium ions can be trapped with oxygen nucleophiles, ultimately delivering ketone or enol products.¹⁴ Herein, we report the formation of 3-methoxy-1-bromopropenes via the addition of a single equivalent of alkyne to a benzylic oxocarbenium ion intermediate (Scheme 1B). This reaction proceeds under mild conditions, tolerates a broad range of functional groups, and delivers products with multiple functional group handles for further elaboration.

We selected the reaction of dimethyl benzaldehyde acetal (**1A**) and phenyl acetylene (**2a**) for optimization studies. Based on previous reports,⁸ we expected that use of a halogenated solvent would stabilize the carbocation intermediates. Indeed, when CH_2Cl_2 was used as solvent, the reaction yielded 30% of desired product **3Aa** in a 1:1 *E:Z* ratio (Table 1, entry 1).¹⁵ The use of CHCl_3 as solvent resulted in an increased yield and *E:Z* ratio (entry 2). In contrast, nonpolar solvents gave only trace product (entry 3), and ethereal solvents (Et_2O or THF) gave no product (not shown). Increasing the equivalents of alkyne further increased the yield (entry 4). The addition of K_2CO_3 led to an even higher yield of 95%, suggesting that adventitious acid or water may cause slight decomposition of acetal **1A** (entry 5). The yield and *E:Z* selectivity were sensitive to reaction temperature. Increasing the reaction temperature to 70 °C resulted in a loss in *E:Z* selectivity (entry 6), whereas reducing the temperature to 50 °C led to only 12% yield (entry 7). Notably, MgBr_2 must be used as its etherate; MgBr_2 provides only trace product, likely due to low solubility (not shown).

A range of benzylic acetals successfully underwent vinylation under our optimized conditions (Scheme 2).¹⁶ Substituents were tolerated at the *ortho* (**3Fa**, **3Ga**), *meta* (**3Ea**), and *para* (**3Ba**, **3Ca**, **3Da**) positions of the phenyl group. A variety of functional groups can be utilized, including bromide (**3Ba**), fluoride (**3Ca**), trifluoromethyl (**3Da**), and silyl-protected phenol (**3Ea**). Larger aryl groups can also be used (**3Fa**). In addition, isochroman acetal **1G** smoothly underwent the vinylation, providing isochroman **3Ga** in 87% yield and a 16:1 ratio of olefin isomers. A limitation of this method is that electron-donating substituents on the acetal result in over-vinylation to give symmetric diene products (see Scheme 1A above). In addition, strongly Lewis basic substituents inhibit the reaction;

complete recovery of starting material was observed with pyridyl or amino-substituted acetals.

With respect to the alkyne component, various aryl acetylenes can be employed (Scheme 3). *O*-, *m*-, and *p*-tolyl acetylene all resulted in high yields of the vinyl bromide products (**3Aa**, **3Ab**, **3Ac**). Both electron-donating (**3Ae**) and electron-withdrawing (**3Af**) aryl substituents are tolerated. In addition, larger aryl groups, such as 2-naphthyl, can be used (**3Ag**). Notably, the reaction scale can be increased without detriment to yield or *E*:*Z* selectivity; using 10 g of benzaldehyde dimethyl acetal **1A**, 89% yield of vinyl bromide **3Aa** was obtained with 10:1 *E*:*Z* selectivity.

Investigation of non-aryl acetylenes suggests that this Lewis-acid mediated process may also enable entry to other useful motifs. For example, the addition of cyclohexenyl acetylene **2h** to acetal **1A** results in triene **4** in 85% yield (Scheme 4). This reaction likely proceeds via elimination of the expected product **3Ah**. Similarly, addition of cyclopropyl acetylene resulted in ring-opening to give dibromide **5** (Scheme 5).

Consistent with the proposed Friedel–Crafts-type mechanism, as well as previous examples of divinylolation of oxocarbenium ion intermediates,^{9, 12} the alkyne substituent must be able to stabilize the putative vinyl cation intermediate. Thus, other alkyl-substituted alkynes do not participate in this reaction. In addition, similar to the acetal scope, Lewis basic groups (pyridyl and amino) are not tolerated on the alkyne. Finally, only trace product (<5%) was observed with internal alkynes.

Assignment of the olefin configuration of the major isomer of the vinyl bromide products was made via the following analysis. First, the *E* configuration of the major isomer of vinyl bromide **3Ba** was determined by X-ray crystallography (Figure 1).¹⁷ Secondly, in product **3Ad**, an nOe correlation is observed between the *ortho* methyl and the benzylic proton, consistent with an *E* olefin geometry. Finally, for bromides **3Ba**, **3Ad**, and all other products, we observed a consistent upfield chemical shift of the benzylic proton of the major isomer. We thus assign the configuration of the major isomer of the other products as *E*. Formation of the *E* isomer may be favored due to minimization of steric hindrance in the approach of the bromide anion to the vinyl cation or due to antiperiplanar addition of halide simultaneously with attack of the alkyne on the carbocation.^{9b, 9c, 10, 18}

Both the vinyl bromide and the allylic ether can be harnessed for further elaboration. For example, Suzuki–Miyaura cross coupling of vinyl bromide **3Aa** produced trisubstituted olefin **6** (Scheme 6).¹⁹ The isomers of **6** could be separated, allowing isolation of (*E*)-**6** as a single isomer in 76% yield. An nOe correlation was observed between H_b and H_c, consistent with the assignment of the major isomer at **3Aa** as *E*. Via Lewis acid catalysis, allylic ether **6** was then cyclized to provide indene **7** in 96% yield.²⁰ This method provides an efficient route to highly substituted indenenes, many of which possess biological activity.²¹

In summary, we have developed an efficient method for the synthesis of (*E*)-trisubstituted vinyl bromides via a Friedel–Crafts-type addition of terminal alkynes to oxocarbenium ions formed in situ from benzylic acetals. The success of this reaction relied identification of

MgBr₂·OEt₂ as both a Lewis acid promoter and bromide source. The mild reaction conditions allow the preparation of a range of vinyl bromide products in high yields and *E:Z* selectivities. Furthermore, the 1-bromo-3-methoxy propene products contain useful functional group handles for downstream elaboration.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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15. Reactions were conducted in 1-dram vials, capped with Teflon-lined caps, and heated using aluminum heating blocks deep enough to completely enclose the glass of the vial.
16. Typical procedure for the formation of vinyl bromides, described for vinyl bromide **3Ba**: In a N₂-atmosphere glovebox, MgBr₂·OEt₂ (30.9 mg, 0.12 mmol, 1.2 equiv) was weighed into a 1-dram vial equipped with a magnetic stirbar. Na₂CO₃ (13.3 mg, 0.10 mmol, 1.0 equiv), acetal **1B** (23.1 mg, 0.10 mmol, 1.0 equiv), alkyne **2a** (15.3 mg, 0.30 mmol, 1.5 equiv), and then CHCl₃ (0.5 mL) were added. The vial was capped with a Teflon-lined cap and heated in an aluminum heating block at 60 °C with vigorous stirring (700 rpm) for 24 h. The vial was removed from the glovebox, and the reaction mixture was filtered through a plug of silica gel, which was then rinsed with Et₂O, to remove insoluble salts. A minimal amount of silica gel was added to the filtrate. The mixture was concentrated and then loaded directly onto a silica gel column and purified via chromatography (5% Et₂O/hexanes) to give **3Ba** (run 1: 34.8 mg, 91%; run 2: 34.2 mg, 90%) as a yellow solid (mp 73–82 °C). ¹H NMR analysis showed **3Ba** was isolated as a 13:1 ratio of olefin isomers: ¹H NMR (400 MHz, CDCl₃, major isomer) δ 7.54–7.49 (m, 2H), 7.46–7.34 (m, 5H), 7.18 (d, *J* = 8.3 Hz, 2H), 6.33 (d, *J* = 9.6 Hz, 1H), 4.58 (d, *J* = 9.6 Hz, 1H), 3.26 (s, 3H); ¹³C NMR (101 MHz, CDCl₃, major isomer) δ 139.1, 138.1, 133.8, 131.8, 129.1, 128.7, 128.5, 128.4, 125.0, 121.9, 80.0, 56.0; FTIR (thin film) 1010, 1071, 1443, 1485, 2820, 2902, 2925 cm⁻¹; HRMS (EI+) [M]⁺ calculated for C₁₆H₁₄Br₂: 365.9554, found: 365.9550. (*E*)-(1-Bromo-3-methoxyprop-1-ene-1,3-diyl)dibenzene (**3Aa**): ¹H NMR (400 MHz, CDCl₃, major isomer) δ 7.47–7.26 (m, 10H), 6.42 (d, *J* = 9.6 Hz, 1H), 4.63 (d, *J* = 9.6 Hz, 1H), 3.27 (s, 3H); ¹³C NMR (101 MHz, CDCl₃, major isomer) δ 140.0, 138.3, 134.3, 129.0, 128.8, 128.7, 128.4, 128.1, 126.7, 124.5, 80.6, 56.0; FTIR (thin film) 700, 768, 1088, 1099, 1444, 2819, 2889, 3029, 3060 cm⁻¹; HRMS (EI+) [M]⁺ calculated for C₁₆H₁₅O: 223.1119, found: 223.1123. (*E*)-(3-(3-Bromo-1-methoxy-3-phenylallyl)phenoxy)(tert-butyl)dimethylsilane (**3Ea**): ¹H NMR (400 MHz, CDCl₃, major isomer) δ 7.39 (d, *J* = 3.2 Hz, 5H), 7.21 (t, *J* = 7.7 Hz, 1H), 6.86 (d, *J* = 7.6 Hz, 1H), 6.77 (m, 2H), 6.35 (d, *J* = 9.6 Hz, 1H), 4.51 (d, *J* = 9.6 Hz, 1H), 3.22 (s, 3H), 0.98 (s, 9H), 0.21 (s, 6H); ¹³C NMR (101 MHz, CDCl₃, major isomer) δ 155.9, 141.5, 138.2, 134.3, 129.7, 129.0, 128.8, 128.3, 128.2, 124.4, 119.7, 118.4, 80.5, 56.1, 25.7, 18.2, -4.3; FTIR (thin film) 699, 782, 1257, 1277, 1444, 1600, 2857, 2895, 2929, 3060 cm⁻¹; HRMS (EI+) [M]⁺ calculated for C₁₅H₂₆O₃Si: 282.1651, found: 282.1655.

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Figure 1. Molecular diagram of 3Ba with ellipsoids at 30% probability. Vinyl H-atom depicted with arbitrary radius. All other H-atoms and a second symmetry-unique compound molecule are omitted for clarity.

Scheme 1.

Formation of trisubstituted vinyl halides from benzylic oxocarbenium ions

Scheme 2. Scope of Acetals

Conditions: acetal **1** (0.1 mmol), alkyne **2a** (1.5 equiv), $\text{MgBr}_2 \cdot \text{OEt}_2$ (1.2 equiv), K_2CO_3 (1.0 equiv), solvent (0.5 mL), 60°C , 24 h. Average isolated yields from duplicate experiments ($\pm 2\%$). *E:Z* ratios of isolated product mixtures determined by ^1H NMR spectroscopy. ^a 0.2 mmol scale.

Scheme 3. Scope of Alkynes

Conditions: acetal **1A** (0.1 mmol), alkyne **2** (1.5 equiv), $\text{MgBr}_2 \cdot \text{OEt}_2$ (1.2 equiv), K_2CO_3 (1.0 equiv), CHCl_3 (0.5 mL, 0.2 M), 60 °C, 24 h. Average isolated yields from duplicate experiments ($\pm 4\%$). *E:Z* ratios of isolated product mixtures determined by ^1H NMR spectroscopy. ^a 0.2 mmol scale. ^b 3.0 equiv **2e**, CHCl_3 (0.1 M). Result of a single experiment.

Scheme 4.
Triene Synthesis via Addition of 1-Cyclohexenylacetylene.

Scheme 5.
Dibromide Synthesis via Addition of Cyclopropylacetylene.

Scheme 6.
Scale up and Functionalization of Vinyl Bromide

Table 1

Reaction Optimization^a

Entry	Solvent	Equiv 2a	Base	Temp (°C)	Yield (%) ^b	E:Z ^c
1	CH ₂ Cl ₂	1.0	None	60	30	1:1
2	CHCl ₃	1.0	None	60	83	10:1
3	PhMe	1.0	None	60	<1	N.D. ^d
4	CHCl ₃	1.5	None	60	87	10:1
5	CHCl ₃	1.5	K ₂ CO ₃	60	95	10:1
6	CHCl ₃	1.5	K ₂ CO ₃	70	90	4:1
7	CHCl ₃	1.5	K ₂ CO ₃	50	12	16:1

^a Conditions: Substrate 1A (0.1 mmol, 1.0 equiv), alkyne 2a, MgBr₂·OEt₂ (0.12 mmol, 1.2 equiv), base (1.0 equiv), solvent (0.5 mL, 0.2M), 24 h.

^b Determined by ¹H NMR spectroscopy using 1,3,5-trimethoxybenzene as internal standard.

^c E:Z ratio was determined by ¹H NMR spectroscopy of the crude reaction mixture.

^d N.D. = not determined.