



Synthesis of internal alkynes via one-pot palladium-catalyzed and dehydrobromination reactions of 1,1-dibromo-1-alkenes

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ARTICLE INFO

Article history:

Received 2 May 2008

Received in revised form 24 July 2008

Accepted 7 August 2008

Available online 12 August 2008

Keywords:

Alkynes

Alkenes

1,1-Dibromoalkenes

Suzuki–Miyaura reaction

Palladium catalysts

ABSTRACT

Tandem palladium-catalyzed cross-coupling of alkyl, alkenyl, alkynyl, aryl, and heteroaryl 2-substituted 1,1-dibromo-1-alkenes with aryl or heteroaryl boronic acids or borate esters and dehydrobromination of the intermediate coupled products afforded internal alkynes in moderate to good yields (up to 89%). The synthesis has been carried out in a one-pot process and in a two-step sequence according to the nature of the starting 1,1-dibromoalkenes. The reported protocol is compatible with the presence in the 1,1-dibromo-1-alkene molecule of additional reactive halogen–carbon bonds, thus allowing to build up more complex alkyne derivatives.

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1. Introduction

Alkynes are among the most important compounds in organic chemistry, since they are useful and versatile intermediates en route to complex systems including natural products.¹ Among the several approaches described in the literature to obtain such compounds, some of them use 1,1-dibromoalkenes as starting points. Thus, the treatment of *gem*-dibromoalkenes with a strong base such as NaHMDS,² *t*-BuOK,³ DBU,⁴ or NaOH/phase-transfer agents⁵ yields 1-bromoalkynes, whereas the use of 2 equiv of *n*-BuLi (more rarely MeLi or *t*-BuLi) produces the related lithium-acetylides, that can be quenched with MeOH to give terminal alkynes or trapped with various electrophiles to furnish the corresponding internal alkynes.⁶ 1,1-Dibromoalkenes are precursors of intermediate alkyldiene carbenes that can generate, by a 1,2-migration process, terminal or internal alkynes according to whether the group bonded to the alkene of the alkyldiene carbene is a hydrogen or an alkyl, alkenyl, or aryl group, respectively.⁷ Finally, internal alkynes have been directly obtained by coupling of 2-alkyl and 2-aryl-1,1-dibromoalkenes with organostannanes under Stille coupling conditions (Pd₂dba₃, TFP, DIPEA, DMF, 80 °C).⁸ This method is very effective for the synthesis of internal alkynes, but organostannanes generally suffer from toxicity and environmental

concerns, as well as issues associated to the purification of the final products.

Organoboron compounds used in the Suzuki–Miyaura cross-coupling⁹ represent a valuable alternative to the use of organostannanes utilized in the Stille coupling.¹⁰ Moreover, a variety of organoboron compounds are now commercially available or readily prepared from a variety of starting points via transmetalation or hydroboration reactions.⁹

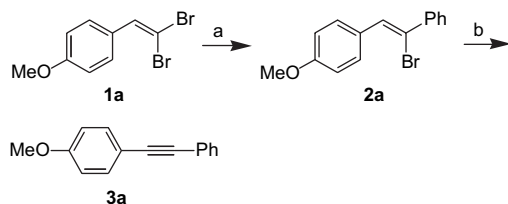
Since the Suzuki–Miyaura reaction of 1,1-dibromoalkenes with alkyl,¹¹ alkenyl,^{11,12} alkynyl,¹³ aryl,¹⁴ and heteroaryl^{14b} boronic acids and organotrifluoroborates¹¹ has proven to be successful for the synthesis of tri- and tetrasubstituted olefins and also the stereoselective formation of (*Z*)-1-aryl- or (*Z*)-alkenyl-1-bromo-1-alkenes,^{11–14} it was of interest to explore the feasibility to obtain internal alkynes from 1,1-dibromoalkenes exploiting this reaction.

Herein we report the one-pot conversion of 1,1-dibromoalkenes into internal alkynes by sequential Suzuki and dehydrobromination reactions.¹⁵

2. Results and discussion

As a model substrate for our studies we prepared (*Z*)-1-[1-bromo-2-(4-methoxyphenyl)vinyl]benzene **2a** (Scheme 1) starting from dibromide 1-(2,2-dibromovinyl)-4-methoxybenzene **1a** and phenylboronic acid under the optimized reaction conditions established by Shen for the Suzuki–Miyaura coupling of 1,1-dibromoalkenes with arylboronic acids [Pd₂dba₃, TFP, Na₂CO₃, 1,4-dioxane, H₂O, 65 °C, 4–6 h].^{14a}

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Scheme 1. (a) PhB(OH)_2 , Pd_2dba_3 (2.5%), TFP (15%), Na_2CO_3 (2.0 equiv), 1,4-dioxane, H_2O , 65 °C, 4 h; (b) Table 1.

With bromoalkene **2a** in hand, we devoted our attention to find a method for its dehydrobromination that should have been compatible with the aqueous conditions of the Suzuki–Miyaura reaction. When 10 equiv of NaOH was added to a mixture of **2a** in 1,4-dioxane and aqueous Na_2CO_3 , no reaction occurred at room temperature (Table 1, entry 1), whereas partial conversion of the starting material was obtained at 65 °C (entry 2). The addition of the phase-transfer catalyst $\text{Bu}_4\text{N(HSO}_4\text{)}$ greatly improved the reaction, but the yield was moderate (entry 3). Finally, nearly quantitative yield was obtained when $\text{Bu}_4\text{N(OH)} \cdot 3\text{H}_2\text{O}$ was added to the mixture and stirring was continued at 65 °C for 1 h (entry 4).

Based on these results, a sequential one-pot process was next examined. Thus, the Suzuki–Miyaura coupling of **1a** with phenylboronic acid (1.05 equiv) was accomplished using tri(2-furyl)phosphine (TFP, 15 mol%) and tris(dibenzylideneacetone)dipalladium (Pd_2dba_3 , 2.5 mol%) in 1,4-dioxane and aqueous cesium carbonate (2.0 equiv)¹⁶ at 65 °C and once all the dibromides have been converted (6 h, TLC monitoring), $\text{Bu}_4\text{N(OH)} \cdot 3\text{H}_2\text{O}$ was added. After stirring for further 1 h, the related terminal alkyne **3a** was obtained in 56% yield.

With a suitable protocol in hand, the scope of this methodology was examined by first using various 1,1-dibromoalkenes (Table 2) and phenylboronic acid as a prototype of boronic acids. Under the optimized reaction conditions, the corresponding alkynes were obtained in moderate to good yields with both electron rich (Table 2, entries 1 and 2) and electron deficient 1,1-dibromoalkenes (entries 3 and 4). These results did not change substantially when both π -excessive (entry 5) and π -deficient heteroaromatic substituents (entries 6 and 7) were used.

The scope of the method was next extended to functionalized boron reagents. Thus, a number of 1,1-dibromoalkenes were cross-reacted with the electron deficient boronate esters **4b** and **4c** and electron rich boronate ester **4d**. Also in this instance moderate to good results were obtained (Table 3) indicating that this procedure allows the synthesis of aryl–aryl, aryl–heteroaryl, and heteroaryl–heteroaryl substituted internal alkynes by a proper choice of the *gem*-dibromide or boron reagent.

Next, the conversion of some examples of alkyl, alkenyl, and alkynyl-1,1-dibromo-1-alkenes into internal alkynes was examined using phenylboronic acid as the coupling partner (Table 4). In this case, however, in order to determine the best conditions for both coupling and dehydrobromination reactions, a two-step protocol was initially followed. Coupling of alkyl 2-substituted 1,1-dibromo-

Table 1
Dehydrobromination of **2a**^a

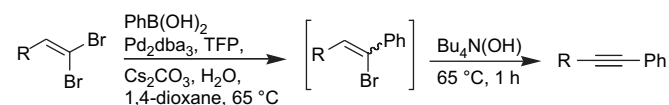
Entry	Base (equiv)	Time /temperature (°C/h)	Conversion ^b (%)	Yield ^c (%)
1	NaOH (10.0)	25/24	0	—
2	NaOH (10.0)	65/15	65	—
3	NaOH (10.0)/ $\text{Bu}_4\text{N(HSO}_4\text{)}$ (1.0)	65/4	100	72
4	$\text{Bu}_4\text{N(OH)} \cdot 3\text{H}_2\text{O}$ (5.0)	65/1	100	>95

^a The reaction was carried out at 1.0 mmol scale with Na_2CO_3 (2.0 equiv) in a mixture of 1,4-dioxane (5.0 ml) and H_2O (2.0 ml).

^b Determined by ¹H NMR spectroscopy.

^c Isolated yields after flash chromatography.

Table 2
Synthesis of alkynes from 1,1-dibromoalkenes^a



Entry	Dibromide	Coupling time (h)	Product	Yield ^b (%)
1	1a	6	3a	56
2	1b	14	3b	76
3	1c	14	3c	94
4	1d	6	3d	82
5	1e	17	3e	67
6	1f	17	3f	79
7	1g	4	3g	72

^a Reaction conditions: 1,1-dibromoalkene (1.0 mmol), boronic acid or ester (1.05 equiv), Pd_2dba_3 (2.5 mol%), TFP (15.0 mol%), Cs_2CO_3 (1.0 M in H_2O , 2.0 ml, 2.0 equiv), 1,4-dioxane (5.0 ml), 65 °C, 4–17 h; then $\text{Bu}_4\text{N(OH)} \cdot 3\text{H}_2\text{O}$ (4 g, 5.0 equiv), 65 °C, 1 h.

^b Isolated yields after flash chromatography.

1-alkenes **1h–j** afforded the related (*Z*)-1-bromo-1-phenyl-1-alkenes **2b–d** in moderate yields (50–56%). However, while the coupling of **1h** and **1i** was carried out at 65 °C, that of **1j** gave a better yield when the reaction was performed at room temperature, though a longer reaction time was required.

The coupling of alkenyl and alkynyl *gem*-dibromides **1k** and **1l** occurred smoothly to give the phenyl derivatives **1e** and **1f** in satisfactory yields (77 and 62%, respectively). These compounds were isolated as single stereoisomers, although the exact geometry of the double bond was not determined. When the dehydrobromination of bromoalkenes **2b–f** was carried out using $\text{Bu}_4\text{N(OH)} \cdot 3\text{H}_2\text{O}$ at 65 °C, no reaction occurred, so the reaction temperature was gradually increased. A right compromise between yield and reaction time was found carrying out the reaction at 100 °C. Under these conditions, the related alkynes were obtained in high yields (81–95%), except alkyne **3q** that was formed in 50% yield. Having determined the proper conditions for each starting point, the one-pot process was pursued. The data reported in Table 4 show that the alkyne products were isolated in yields that are very close to that obtained in the two-step protocol.

It was also of interest to determine the compatibility of this method by using 1,1-dibromo-1-alkene bearing additional reactive halogen–carbon bonds. The successful implementation of this process should allow for further elaboration of the remaining halogen in order to build up more complex derivatives. With the aim of demonstrating this opportunity 2-bromo-3-(2,2-

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