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One-pot conversion of 1,1-dibromoalkenes into internal alkynes by sequential Suzuki–Miyaura and dehydrobromination reactions

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Abstract—A protocol for the one-pot synthesis of internal alkynes from 1,1-dibromoalkenes is reported. The method is hinged upon the Suzuki–Miyaura cross-coupling of 2-aryl- or 2-heteroaryl-1,1-dibromoalkenes with aryl or heteroaryl boronic acids or borate esters followed by dehydrobromination of the intermediate coupled products. Yields up to 89% were obtained.

Alkynes are useful and versatile intermediates in organic synthesis.[1] Amongst 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 agents[5] 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 precursor of intermediate alkylidene 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 alkylidene 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 (Pd_2dba_3, TFP, DIPEA, DMF and 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-coupling[9] represent a valuable alternative to the use of organostananes 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 transmetallation or hydroboration reactions.[9]

Since the Suzuki–Miyaura reaction of 1,1-dibromoalkenes with alkyl,[11] alkenyl,[11,12] alkynyl,[13] aryl[14a,b] and heteroaryl[14b] boronic acids and organotrifluoroborates[11] 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.

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 [Pd_2dba_3, TFP, Na_2CO_3, 1,4-dioxane, H_2O, 65 °C, and 4–6 h][14a] (Scheme 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

Keywords: Alkynes; Alkenes; 1,1-Dibromoalkenes; Suzuki–Miyaura reaction; Palladium catalysts.
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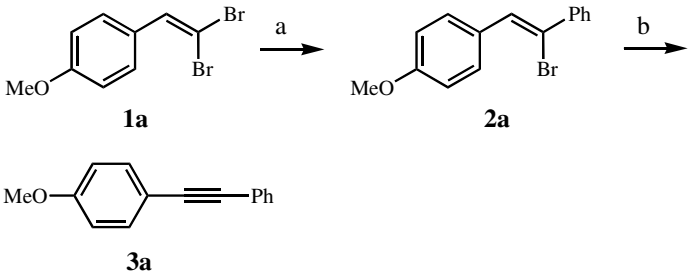


Scheme 1. Reagents and conditions: (a) $PhB(OH)_2$, Pd_2dba_3 (2.5%), TFP (15%), Na_2CO_3 (2.0 equiv), 1,4-dioxane, H_2O, 65 °C and 4 h; (b) Table 1.

Table 1. Dehydrobromination of **2a**[a]

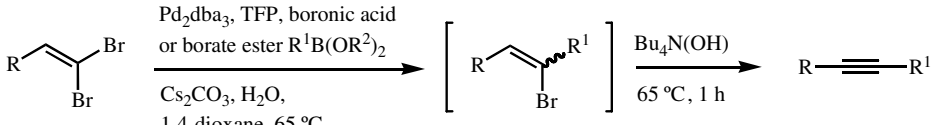
Entry	Base (equiv)	*T*/*t* (°C/h)	Conv.[b] (%)	Yield[c] (%)
1	NaOH (10.0)	25/24	0	—
2	NaOH (10.0)	65/15	65	—
3	NaOH (10.0)/$Bu_4N(HSO_4)$ (1.0)	65/4	100	72
4	$Bu_4N(OH)\cdot 30H_2O$ (5.0)	65/1	100	>95

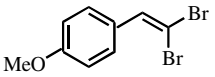
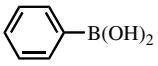
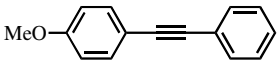
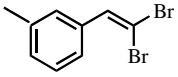
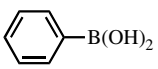
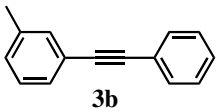
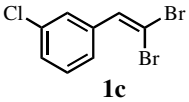
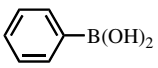
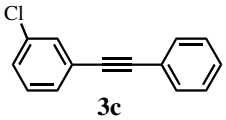
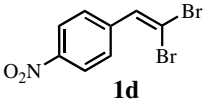
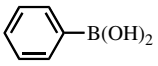
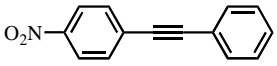
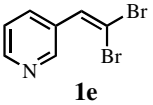
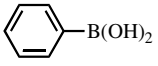
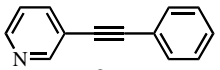
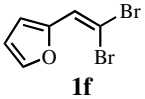
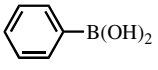
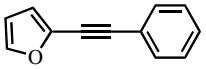
[a] The reaction was carried out at 1.0 mmol scale with Na_2CO_3 (2.0 equiv) in a mixture of 1,4-dioxane (5 mL) and H_2O (2 mL).
[b] Determined by ^1H NMR.
[c] Isolated yields after flash chromatography.

were 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 $Bu_4N(HSO_4)$ greatly improved the reaction, but the yield was moderate (entry 3). Finally, nearly quantitative yield was obtained when $Bu_4N(OH)\cdot 30H_2O$ 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 then examined. Thus, the Suzuki–Miyaura coupling of **1a** with phenylboronic acid (1.05 equiv) was accomplished using tris(2-furyl)phophine (TFP, 15 mol %) and tris(dibenzylideneacetone)dipalladium (Pd_2dba_3, 2.5 mol %) in 1,4-dioxane and aqueous cesium

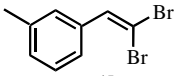
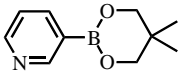
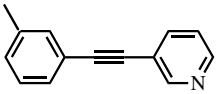
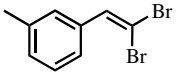
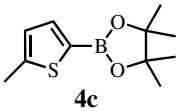
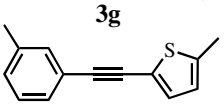
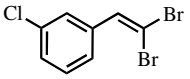
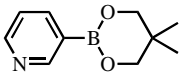
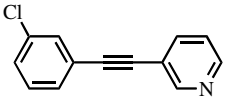
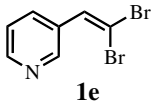
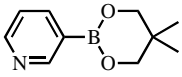
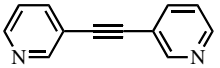
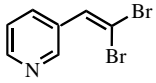
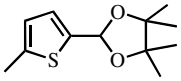
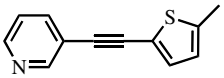
Table 2. Synthesis of alkynes from 1,1-dibromoalkenes[a]



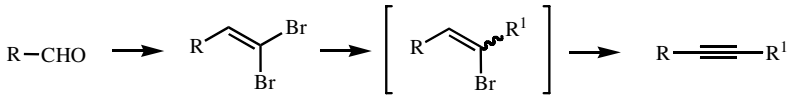
Entry	Dibromide	Boronic acid or borate ester	Product	Yield[b] (%)
1	 **1a**	 **4a**	 **3a**	56
2	 **1b**	 **4a**	 **3b**	76
3	 **1c**	 **4a**	 **3c**	89
4	 **1d**	 **4a**	 **3d**	82
5	 **1e**	 **4a**	 **3e**	67
6	 **1f**	 **4a**	 **3f**	79

(*continued on next page*)

Table 2 (*continued*)

Entry	Dibromide	Boronic acid or borate ester	Product	Yield[b] (%)
7	 **1b**	 **4b**	 **3g**	48
8	 **1b**	 **4c**	 **3h**	35
9	 **1c**	 **4b**	 **3i**	63
10	 **1e**	 **4b**	 **3j**	82
11	 **1e**	 **4c**	 **3k**	67

[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 mL), 65 °C, 6–12 h; then $Bu_4N(OH)\cdot 30H_2O$ (4 g, 5.0 equiv), 65 °C, 1 h.
[b] Isolated yields after flash chromatography.



Scheme 2.

carbonate (2.0 equiv)[15] at 65 °C and once all the dibromide has been converted (6 h and TLC monitoring), $Bu_4N(OH)\cdot 30H_2O$ was added. After stirring for a 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,[16] the corresponding alkynes were obtained in moderate to good yields with both electron rich (Table 1, entries 1 and 2) and deficient 1,1-dibromoalkenes (entries 3–5). These results did not change substantially when both π-excessive and π-deficient heteroaromatic substituents (entries 5 and 6) were used. Some representative examples of 1,1-dibromoalkenes were finally cross-reacted with the electron deficient boronate ester **4b** (entries 7,9 and 10) and electron rich boronate ester **4c** (entries 8 and 11) to give the corresponding alkynes in satisfactory yields.

In summary, the palladium catalyzed Suzuki–Miyaura coupling of 2-aryl- or 2-heteroaryl-1,1-dibromoalkenes with aryl or heteroaryl boronic acids or borate esters and the subsequent one-pot dehydrobromination of the intermediate coupled products afford internal alkynes in moderate to good yields. Given the easy availability of a variety of organoboron compounds, this protocol represents a valuable alternative to the Stille reaction to prepare this important class of compounds. The last but not the least, 1,1-dibromoalkenes are easily obtainable in high yields from the related aldehydes[6,17] and so the total process offers a convenient and simple route for aldehyde to internal alkynes homologation (Scheme 2). Further studies on this subject are currently in progress.

Acknowledgements

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15. Cesium carbonate was preferred to Na_2CO_3 because of afforded clearer products. For an example of comparative study on the use of bases in the Suzuki–Miyaura cross-coupling, see: Molander, G. A.; Felix, L. A. *J. Org. Chem.* **2005**, *70*, 3950.
16. *Typical procedure for the preparation of alkynes* **3a–k**: A mixture of 1-(2,2-dibromovinyl)-4-nitrobenzene (**1d**) (0.307 g, 1.0 mmol), $PhB(OH)_2$ (0.128 g, 1.05 mmol) and Cs_2CO_3 (0.706 g, 2.0 mmol) in 1,4-dioxane–H_2O (5 mL + 2.0 mL) was degassed by bubbling nitrogen for few minutes. Then, $Pd_2(dba)_3$ (23 mg, 0.025 mmol) and tris(2-furyl)phosphine (TFP) (35 mg, 0.15 mmol) were added and the resulting mixture was heated at 65 °C under nitrogen for 12 h. Then $Bu_4N(OH)\cdot 30H_2O$ (4.0 g, 5.0 mmol) was added and stirring was continued at 65 °C for a further 1 h. The mixture was diluted with ethyl acetate (50 mL) and washed with brine (2×15 mL). The organic phase was dried (Na_2SO_4), the solvent was evaporated and the residue was purified by flash chromatography (petroleum ether/EtOAc = 8:2) to give 1-nitro-4-(2-phenylethynyl)benzene (**3d**) as a yellow solid: 0.191 g (82% yield).[18]
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