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An acetylene zipper—Sonogashira reaction sequence for the efficient synthesis of conjugated arylalkadiynols

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ABSTRACT

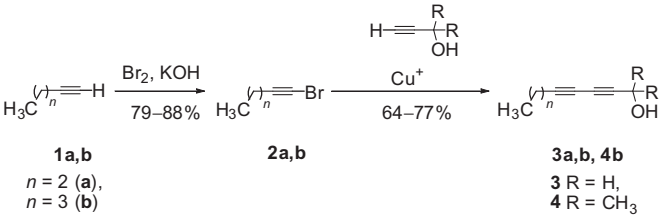
We describe a new approach to the preparation of unsymmetrical arylalkadiynols, which is based on the isomerization of readily available internal alkadiynols into their terminal isomers followed by Sonogashira cross-coupling. The influence of the reaction conditions on the efficiency of the 'acetylene zipper' of alkadiynols is investigated. Unstable terminal diynols are used without isolation in Pd/Cu-catalyzed cross-couplings with iodoarenes bearing either electron-withdrawing or electron-donating substituents.

A significant number of natural products contain a diacetylenic moiety. These diacetylenes display a broad spectrum of interesting biological properties.[1] In addition, diacetylenes, especially unsymmetrical examples, represent important building blocks in organic synthesis,[2] in particular for the preparation of enynes[2c] and fused heterocycles,[2e] as well as in supramolecular chemistry,[3] biochemistry, and materials science.[2d,4] Since the development of the Cadiot–Chodkiewicz heterocoupling[5] of 1-haloalk-1-ynes with terminal alkynes, this approach and its modifications,[6] including Pd-catalyzed transformations,[6a,7] remain a popular method for the synthesis of unsymmetrical diacetylenes. Another general approach to these structures is based on the selective desilylation of 1,4-bis(trimethylsilyl)buta-1,3-diyne followed by alkylation and/or cross-coupling reactions.[8,9] Alternative methods allowing access to an expanded collection of functionalized unsymmetrical diynes and polyynes have been also proposed. For example, the four-step synthesis of unsymmetrical 1-aryl(hetaryl/vinyl)-buta-1,3-diynes using Fritsch–Buttenberg–Wiechell[10] rearrangement of the corresponding ethynyl substituted 1,1-dibromoolefins was described by Tykwinski et al.[11] We have previously reported a convenient synthesis of 1-aryl(hetaryl)-alka-1,3-diynes by Sonogashira[12] cross-coupling of alka-1,3-diynes. The latter were generated from internal isomers via 'diacetylene zipper' reactions using lithium 2-aminoethylamide (LAETA) as a 'super base'.[13]

In connection with our investigations on the cyclizations of functionalized buta-1,3-diynylarenes with the aim to obtain enediyne systems fused to heterocyclic cores,[14] we have extended this approach to the synthesis of arylalkadiynols. While the Sonogashira cross-coupling is a very popular procedure for the alkynylation of aryl or vinyl halides,[15] terminal diacetylenes are rarely employed in this reaction, mainly due to their poor availability and low stability. Terminal conjugated diacetylenes bearing a hydroxyl group at the opposite end of the molecule are even more versatile synthetic intermediates, as they can be utilized for the synthesis of macrocyclic enediynes.[14d,e] Herein, we report the efficient preparation of arylalkadiynols using a sequential 'acetylene zipper' reaction—Sonagashira coupling procedure. This method allows us to avoid isolation of very unstable terminal alkadiynols.

Internal diacetylenic alcohols **3** and **4** were prepared in two-steps from commercially available terminal acetylenes **1a**,**b** and propargyl alcohol (for primary alkadiynols **3a**,**b**) or 2-methylbut-3-yn-2-ol (for tertiary alcohol **4b**) (Scheme 1).

Our initial efforts were focused on the optimization of the conditions for the crucial prototropic isomerization of internal alkadiy-



Scheme 1. Synthesis of internal alkadiynols **3** and **4**.

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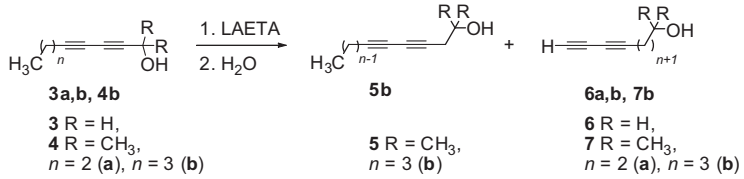


Scheme 2. Isomerization of the internal alkadiynols.

nols (Scheme 2). Since terminal diynes decompose significantly during isolation, ^{1}H NMR spectroscopy was employed for analysis of the products (see Supplementary data). Isomerization of tertiary alcohol **4b** under conditions previously described for alkadiynes,[13] in THF with a four-fold excess of LAETA (Table 1, entry 1) did not give the expected terminal isomer **7b**. NMR data indicated that the conjugated system of triple bonds had shifted only by one position giving the isomer **5b**, isolated in a good yield. Formation of homopropargylic isomers was previously observed for acetylene alcohols[16a] and explained by their higher thermodynamic stability under 'acetylene zipper' conditions.[16b] In contrast to alkadiynes, alcohols **3** and **4** are deprotonated by LAETA to give alkoxide ions and can form aggregates.[17] Taking into account that diamines were usually used as solvents for 'acetylene zipper' reactions of alkynols,[16a,18] we hypothesized that employing ethylenediamine (EDA) as a co-solvent might help to enhance the yield of the isomerization. Indeed, the desired terminal diacetylene **7b** appeared in the reaction mixture when EDA was used (Table 1, entry 2). A twofold increase in the amount of EDA led to no significant change in the ratio of isomers **5b** and **7b** (Table 1, entry 3).

The best result was obtained when a 1:2 mixture of EDA/THF was used. Under these conditions, conversion of the internal diacetylene into the terminal isomer was complete and the desired diynol **7b** was obtained as the major product (Table 1, entry 4). This observation indicates that the presence of EDA in the solvent mixture was crucial for the success of the diynol 'zipper' reaction. It was previously known that organolithium reagents as well as N-lithiated species such as amides adopt oligomeric structures, and additives are often used to enhance their reactivity. In particular, the addition of amines promotes the breakdown of agglomerates of organolithium compounds.[19] Apparently, an excess of EDA is necessary for achieving decomposition of LAETA–alkoxide aggregates, which leads to an increase in the efficiency of triple bond isomerization. Under optimized conditions, isomerization of primary alkadiynols **3a**,**b** gave only terminal isomers **6a**,**b** (Table 1, entries 5 and 6). Reducing the concentration of amide from 1.4 to 1.2 M did not affect the outcome of the reaction, and only the terminal isomer **6a** was observed in the reaction mixture after 10 min (Table 1, entry 7). Also, it should be mentioned that *retro*-Favorsky reaction (elimination of acetone from dimethylpropargyl alcohols with release of terminal alkadiynes) did not occur under the given conditions.

With an efficient method for the preparation of terminal diacetylenes in hand, we turned our attention to the optimization of the prototropic isomerization–Sonogashira cross-coupling sequence. The 'zipper' reaction was conducted under the conditions of entry 4 in Table 1. The reaction mixtures were quenched with water to decompose the lithium diacetylides, and were extracted with Et_2O. Solutions of alkadiynols **6**, **7** were used in the coupling step without further purification. Aryl iodides **8**–**12**, with either electron-withdrawing or electron-donating substituents, or both, were used in the second step to test the scope and limitations of this approach with respect to the preparation of arylalkadiynols (Scheme 3, Table 2). Since tertiary alcohol **7** is more stable than primary analogs **6**, we employed the former in the initial experiments. Pd/Cu-catalyzed cross-coupling is usually carried out with an excess of the terminal acetylenes due to competitive Glaser homocoupling in the presence of Cu(I) salts.[15] Additionally, we found that complete conversion of the more reactive iodoarene **8** required three equivalents of the starting internal alcohol **4**, apparently due to the low stability of terminal alkadiynols. The Sonogashira cross-coupling reaction was complete in five hours, giving product **13b** in good yield (Table 2, entry 1). As expected, the reaction of terminal alcohol **7** with 2-iodothioanisole (**9**) proceeded slowly, and was accompanied by significant polymerization. 2-(Methylsulfanylphenyl)nona-5,7-diyn-1-ol (**14b**) was isolated in moderate yield after 24 h (Table 2, entry 2). In the case of primary alcohol **3b**, a fivefold excess of diacetylene over iodoarenes **8** and **9** was used, and the reactions led to the desired arylalkadiynols **15b** and **16b** in similar yields (entries 3 and 4).

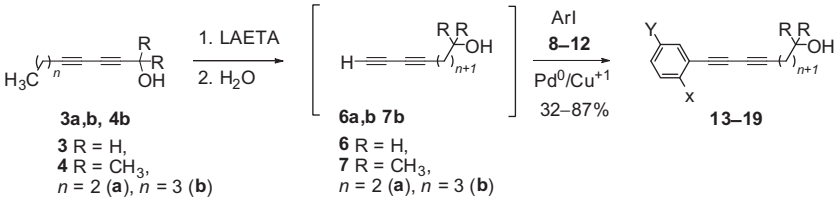
Next, we attempted the synthesis of arylalkadiynols bearing amino groups at the *ortho*-position relative to the diacetylene moiety. While it is known that Sonogashira coupling proceeds faster with electron-poor aryl halides, we were surprised to observe no conversion of starting iodide 10 containing a dimethylamino group (Table 2, entry 5). However when the DIPA–DMF[21] system was employed instead of conventional Et_3N–THF for the cross-coupling, product **17b** was formed in a satisfactory yield (Table 2, entry 6). The yield of arylalkadiynol **16b** was also improved by using the DIPA–DMF system (entry 7). An increase in the yield was obtained by reducing the LAETA concentration during the first step of the procedure. When the 'diacetylene zipper' of diynols **3a**,**b** was performed under the conditions of entry 7 (Table 1), the target aryldiynols **16a**,**b** **18a**, and **19a** were obtained in very good yields (Table 2, entries 8–11).[22] It was also found that these conditions allowed for the reduction of the amount of starting internal alcohol from 5 to 3.5 equiv, and for the scale-up of the synthesis to 7.5 g of diynols 3 without any loss of efficiency.

In summary, we have developed an efficient two-step protocol for the preparation of arylalkadiynols. This approach employs the prototropic isomerization of internal diacetylenic alcohols followed by Sonogashira cross-coupling of the terminal isomers with iodoarenes. The optimized conditions described here allow the preparation of arylalkadiynols bearing either electron-withdraw-

Table 1
Isomerization of alkadiynols **3** and **4** (see Scheme 2)[a]

Entry	Alkadiynol	EDA:THF (v/v)	Ratio of isomers (by ^{1}H NMR)[b]
1	**4b**	0:1	**5b**[c] /—
2	**4b**	1:8	**5b**/**7b** (1:1)
3	**4b**	1:3.5	**5b**/**7b** (1:1)
4	**4b**	1:2	**7b**
5	**3b**	1:2	**6b**
6	**3a**	1:2	**6a**
7	**3a**	1:2	**6a**

[a] Reaction conditions: 15–25 °C, 10 min, ratio LAETA: **3**(**4**) was 4:1; c_{LAETA} = 1.38 M for entries 1–6, for entry 7 c_{LAETA} = 1.20 M.
[b] The ratio of isomeric alcohols was determined by the relative intensity of the characteristic signals in the ^{1}H NMR spectra: δ 1.97 (terminal proton of isomer **7b** ≡CH) and δ 2.42 (methylene group of isomer **5b** ≡$CH_2C(CH_3)_2OH$).
[c] Isolated in 86% yield.



Scheme 3. Synthesis of arylalkadiynols by sequential 'diacetylene zipper reactions' of alkadiynols **3** and **4** and Pd/Cu-catalyzed cross-coupling (see Table 2).

Table 2
Synthesis of arylalkadiynols **13–19** (Scheme 3)[20]

Entry[a]	ArI	X	Y	Alkadiynols (ratio **3,4**: ArI)	R (*n*)	Base	Solvent	Product (yield %)
1	**8**	NO_2	H	**4b** (3:1)	CH_3 (3)	Et_3N	THF	**13b** (70)
2	**9**	SMe	H	**4b** (3:1)	CH_3 (3)	Et_3N	THF	**14b** (32)
3	**8**	NO_2	H	**3b** (5:1)	H (3)	Et_3N	THF	**15b** (61)
4	**9**	SMe	H	**3b** (5:1)	H (3)	Et_3N	THF	**16b** (52)
5	**10**	NMe_2	COOMe	**3b** (5:1)	H (3)	Et_3N	THF	**17b** (0)
6	**10**	NMe_2	COOMe	**3b** (5:1)	H (3)	DIPA	DMF	**17b** (61)
7	**9**	SMe	H	**3b** (5:1)	H (3)	DIPA	DMF	**16b** (64)
8	**9**	SMe	H	**3b** (3.5:1)	H (3)	DIPA	DMF	**16b** (89)
9	**9**	SMe	H	**3a** (3.5:1)	H (2)	DIPA	DMF	**16a** (87)
10	**11**	NMe_2	COOEt	**3a** (3.5:1)	H (2)	DIPA	DMF	**18a** (82)
11	**12**	NH_2	H	**3a** (3.5:1)	H (2)	DIPA	DMF	**19a** (85)

[a] The first step of the sequence was carried out under the conditions of entry 4 (Table 1) for entries 1–7; the conditions of entry 7 (Table 1) were applied for entries 8–11. DIPA = 1-(2-hydroxypropylamino)propan-2-ol.

ing or donor substituents, in good yields on a multi-gram scale, from readily available starting materials.

Acknowledgments

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Supplementary data

Supplementary data (experimental details, NMR, MS spectra, of synthesized compounds and copies of NMR spectra)associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.02.066.

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22. *Procedure for the synthesis of* ***16a***. Under argon, Li (1.48 g, 0.21 mol) was added gradually to a mixture of dry ethylenediamine (12.80 mL, 0.21 mol + 59.0 mL) and THF (118.4 mL). The mixture was stirred untill the starting dark blue color faded and a yellowish suspension of the lithium salt (c_{LAETA} = 1.2 M) was obtained. Then the mixture was cooled to 16 °C and internal diynol **3a** (6.5 g, 0.053 mol) was added dropwise at 16–20 °C (carefully controlled), and the resulting mixture stirred for 10 min. The mixture was poured onto ice and extracted with Et_2O (3 × 100 mL). The combined organic layers were washed with a saturated solution of NH_4Cl (1 × 100 mL), and brine (1 × 100 mL) and dried over anhydrous Na_2SO_4, concentrated (to 1/2 vol) under reduced pressure and used in the next step.
Under argon, the obtained solution of the terminal diynol **6a** was added to a mixture of iodoarene 9 (3.80 g, 0.015 mol), $Pd(PPh_3)_2Cl_2$ (0.53 g, 0.76 mmol), PPh_3 (0.40 g, 1.52 mmol) and DIPA (8.08 g, 60.8 mmol) in DMF (80 mL) and stirred at 40 °C over 30 min. Then CuI (0.2 g, 1.05 mmol) was added and the mixture was stirred overnight at 40 °C. The mixture was washed with NH_4Cl (2 × 100 mL), H_2O (1 × 100 mL), and brine (2 × 100 mL) and extracted with EtOAc (3 × 100 mL). The combined organic layers were dried over anhydrous Na2SO4 and the solvents evaporated. The crude product was purified by flash chromatography (5:1 hexane/EtOAc, silica gel, R_f = 0.18) to yield **16a** (3.23 g, 87%) as a yellow oil.