Modification of the Fritsch–Buttenberg–Wiechell rearrangement: a facile route to unsymmetrical butadiynes

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Abstract—A modification of the Fritsch–Buttenberg–Wiechell rearrangement has been used to form unsymmetrically substituted 1,3-butadiynes from 1,1-dibromo-olefin precursors. The reaction proceeds via lithium–halogen exchange, followed by migration of the aryl or alkynyl moiety to provide the butadiyne framework. The facile formation of the dibromo-olefins in three steps from commercially available aryl aldehydes or carboxylic acid chlorides makes this procedure an attractive alternative to traditional methods for butadiyne synthesis. © 2001 Elsevier Science Ltd. All rights reserved.

The rigid and conjugated nature of the 1,3-butadiyne moiety makes it a useful building block that has been employed in the formation of new photonic materials,[1] oligomers and polymers,[2] macrocycles,[3] as well as supramolecular scaffolds.[4] In addition, this functional group has a rich history as a precursor for single crystal polydiacetylene formation via topochemical polymerization.[5]

The synthesis of symmetrically substituted butadiynes is relatively straightforward using Hay[6] or Eglinton/Galbraith[7] conditions, which proceed via oxidative homocoupling of terminal acetylenes with Cu(I)/Cu(II) catalysis.[8] Hay or Eglinton/Galbraith conditions are not suitable, however, for the synthesis of unsymmetrical substituted butadiynes, as mixtures of products are usually encountered. The cross-coupling of terminal acetylenes with alkynyl bromides or iodides, the Cadiot–Chodkiewicz[9] coupling, often provides a useful method for accessing unsymmetrical diynes. The predominant limitation of this and related methods,[10] however, is that they all require the prior synthesis of a terminal alkyne as one coupling partner and an alkynyl halide as the other.

Palladium catalyzed cross-coupling reactions of terminal alkynes with aryl halides or triflates, such as the Sonogashira reaction,[11] are an alternative route into the formation of aromatic 1,3-butadiynes. Using $PdCl_2(PPh_3)_2$ or $Pd(PPh_3)_4$, these reactions generally work quite well with aryl iodides and with electron-deficient aryl bromides. With unactivated aryl bromides, however, rigorous conditions are often necessary.
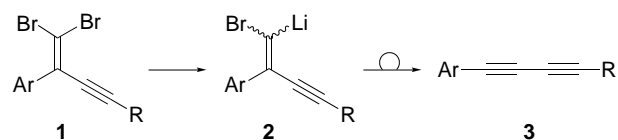

The Fritsch–Buttenberg–Wiechell (FBW) rearrangement is a well precedented technique for the formation of alkynes.[12,13] We recently reported a modification of this method and demonstrated that it is suitable for the formation of a variety of polyynes via alkyne migration in carbene/carbenoid intermediates.[14,15] The high propensity for alkyne and/or aryl migration suggested that dibromo-olefins such as **1** would serve well as precursors to diynes **3**. This reaction would involve a sequence of lithium halogen exchange to give the carbene/carbenoid intermediate **2** followed by rearrangement to **3**. We now report the successful synthesis of a range of unsymmetrical 1,3-butadiynes[16] via this method. In contrast to other methods of butadiyne formation that rely on arylyne or aryl halide precursors, the method described herein utilizes aryl aldehydes or aryl carbonyl chlorides as starting materials. As a result, this route is particularly useful for the formation of electron-rich aryl diynes that are unactivated toward palladium catalyzed alkynylations.

The general synthetic route to trimethylsilyl protected aryl 1,3-butadiynes is outlined in Scheme 1.[17] An excess of trimethylsilyl acetylene (1.25 equiv.) is lithiated with *n*-BuLi (1.2 equiv.) at −78°C in Et_2O to give the acetylide **4**. The aryl carboxaldehyde (1 equiv.) is added at −78°C, and the reaction mixture was slowly warmed
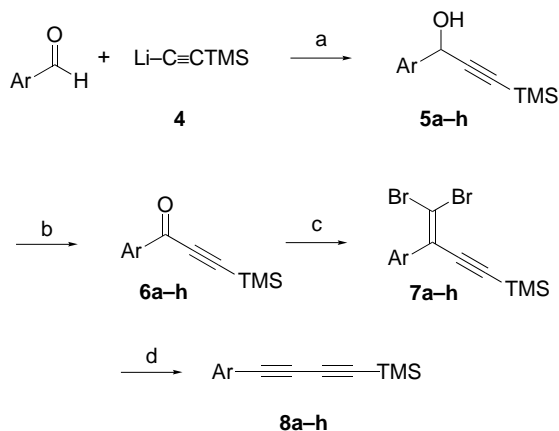
Scheme 1. *Reagents and conditions*: (a) Et_2O, −78°C; (b) PCC, Celite, mol. sieves (4 Å), CH_2Cl_2, rt; (c) PPh_3 (2 equiv.), CBr_4, CH_2Cl_2 @ rt or C_6H_6 @ reflux; (d) *n*-BuLi, −78 to −40°C, hexanes.

Table 1. Synthesis of diynes **8a–h**

compd	Ar	5 yield (%)[a]	6 yield (%)	7 yield (%)	8 yield (%)
a	CH₃O o-tolyl	90	—	59[b,c]	43
b	CH₃O m-tolyl	76	76[d]	48[b,c]	75
c	CH₃O p-tolyl	97	—	47[b,c]	88
d	naphthyl	63[d]	—	44[b,c]	93
e	pyrenyl	96	83[d]	28[b,e]	79
f	furyl	85	—	30[b,c]	54
g	thienyl	97	—	85[b,c]	67
h	ferrocenyl (Fe)	95	36[d] / 94[f]	29[b,e]	28

[a] Isolated yield from reaction without purification by chromatography.
[b] Isolated yield from alcohol without isolation of intermediate ketone.
[c] Reaction in CH_2Cl_2 at rt. [d] Isolated yield after column chromatography.
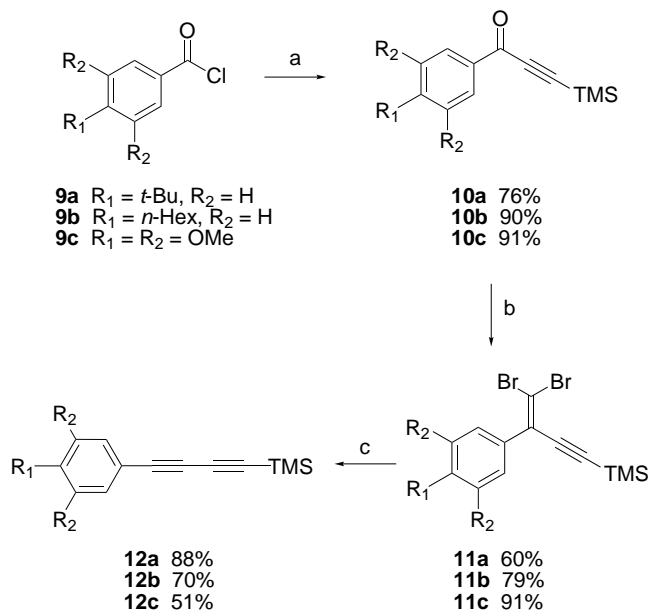[e] Reaction in C_6H_6 at 80 °C. [f] Using $BaMnO_4$ in CH_2Cl_2.

to ca. −10°C until the reaction was judged complete by TLC. The reaction is cooled again to −78°C and quenched with aqueous NH_4Cl.[18] As a result of the slight excess of acetylide, complete reaction with the aldehyde can generally be effected, and the resultant alcohols **5** can be isolated pure and in high yield following aqueous work-up.

Oxidation of alcohol **5** to ketone **6** with PCC is accomplished at rt in CH_2Cl_2, with reaction times of less than 1 h for most derivatives. Concentration of the reaction mixture, followed by filtration through a short plug of silica affords the crude ketones **6a–h**, which are of sufficient purity to be carried on to the dibromo-olefination step.[19] They can, however, be isolated pure by flash chromatography, as demonstrated for ketones **6b** and **6e**. The oxidation of ferrocenyl alcohol **5h** was particularly difficult with PCC, affording only 36% yield. Using $BaMnO_4$ as the oxidant,[20] however, ketone **6h** could be obtained in 94% yield. The well-established dibromo-olefination method using PPh_3/CBr_4 was employed to provide derivatives **7**.[21] For sterically unhindered ketones, the dibromo-olefins can be formed at rt in CH_2Cl_2 in 1–2 h. For ketones **6e** and **6h**, however, reactions were sluggish at rt in CH_2Cl_2, and they were therefore carried out in benzene at reflux. In all cases, the dibromo-olefinic product is considerably less polar than the ketone precursor, as well as any by-products of the reaction, and can be easily purified by column chromatography.
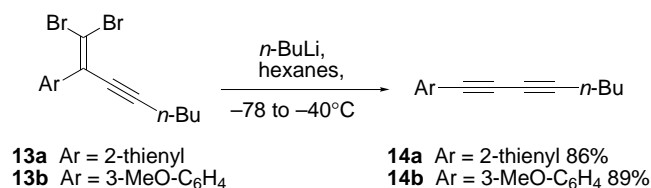
To date, the conversion of the dibromo-olefins to the desired diynes **8** has been more successful in hexanes, as opposed to more polar solvents such as Et_2O or THF.[22] Thus, diyne formation is effected by the dropwise addition of *n*-BuLi to a hexanes solution of **7** cooled to −78°C. The mixture is subsequently warmed to ca. −40°C over 0.5 h to ensure complete rearrangement of the carbenoid intermediate and then quenched at −78°C. If anhydrous reaction conditions have been maintained, the diyne is generally the sole product observed by TLC analysis.[23] The diynes can thus be isolated pure in good to excellent yields by passing the concentrated reaction mixture through a plug of silica to remove more polar, baseline material.[24]

Scheme 2 outlines an alternative pathway to aryl 1,3-diynes that exploits readily available aryl acid chlorides. Friedel–Crafts acylation of acid chlorides **9a–c** with bis(trimethylsilyl)acetylene in the presence of $AlCl_3$ afforded ketones **10a–c** in excellent yields.[25] Dibromo-olefination of **10a–c** generated **11a–c** in 60–91% yields. Subjecting dibromides to *n*-BuLi at −78°C according to the standard protocol affords 4-*t*-butylphenyl diyne **12a**[24] in 88% yield, 4-hexylphenyl diyne **12b** in 70% yield, and the trimethoxy aryl diyne **12c** in 51% yield.

This method for diyne synthesis is also extendable to systems other than those with trimethylsilylethynyl substituents. As shown in Scheme 3, rearrangement of alkyl substituted dibromo-olefins **13a** and **13b** affords 1,3-diynes **14a** and **14b** in high yields.[26]

9a R$_1$ = *t*-Bu, R$_2$ = H
9b R$_1$ = *n*-Hex, R$_2$ = H
9c R$_1$ = R$_2$ = OMe

10a 76%
10b 90%
10c 91%

12a 88%
12b 70%
12c 51%

11a 60%
11b 79%
11c 91%

Scheme 2. *Reagents and conditions*: (a) TMSC≡CTMS, AlCl$_3$, CH$_2$Cl$_2$, 0 to 25°C; (b) PPh$_3$ (2 equiv.), CBr$_4$, CH$_2$Cl$_2$; (c) *n*-BuLi, hexanes, −78 to −40°C.

13a Ar = 2-thienyl
13b Ar = 3-MeO-C$_6$H$_4$

14a Ar = 2-thienyl 86%
14b Ar = 3-MeO-C$_6$H$_4$ 89%

Scheme 3.

In summary, the modified FBW rearrangement described herein provides a facile route to a range of aryl diyne systems. This synthetic route offers several attractive features versus more commonly employed palladium coupling methods including (1) the wide range of commercially availability of aryl aldehydes and carboxylic acid precursors, (2) applicability to electron-rich aryl groups, (3) generally rapid reaction times and easy purification/isolation.[27]

Acknowledgements

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17. All new compounds have been completely characterized by ^{1}H and ^{13}C NMR, IR, MS and either HRMS or combustion analysis. Typical procedure for diyne formation: To the appropriate dibromo-olefin (0.368 mmol) in dry hexanes (10 mL) at −78°C was added dropwise over 10 min 1.1 equiv. of *n*-BuLi (0.16 mL, 2.5 M in hexanes, 0.40 mmol). The mixture was warmed to approximately −40°C for 30 min, re-cooled to −78°C, and quenched with a satd aq. solution of NH_4Cl. The organic layer was separated, washed with satd aq. NH_4Cl, and dried over magnesium sulfate. Solvent removal in vacuo and passage through a short plug of silica gel yielded the desired diyne.

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19. For synthetic convenience, the CH_2Cl_2 solutions resulting from oxidation, after passage through a plug of silica, were normally carried on directly to dibromo-olefination.

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22. A full investigation of the mechanistic aspects of this reaction is underway, including solvent effects.

23. Using TLC to monitor these reactions is problematic, as warming of the sample in the capillary tube used for TLC application can lead to the inaccurate observation that the reaction had reached completion.

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26. Dibromo-olefins **13a** and **13b** were prepared from 1-hexyne and the appropriate aryl carboxaldehyde, in the same manner as that described in Scheme 1.

27. It is worth noting that in most of the cases outlined in Table 1 and Scheme 2, the complete sequence of reactions, from the carboxaldehyde (or acid chloride) to the desired aryl diyne could be completed by a graduate student in a single day (<12 h).