Synthesis of tri- and tetraynes using a butadiynyl synthon[†]

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Using a one-pot protocol, triynes and tetraynes are formed from the reaction of a dibromovinyl triflate and a terminal alkyne under palladium-catalyzed cross-coupling conditions.

Conjugated polyynes are useful building blocks for conjugated structures,^{1,2} and they show significant potential for new optical materials.³ They are also commonly isolated as natural products with significant biological activity.⁴ While the conjugated acetylenic framework of an unsymmetrical 1,3-diyne can be formed through a plethora of different transformations,⁵ that of 1,3,5-hexatriyne is typically more difficult to achieve. Two methods are commonly employed, the Cadiot–Chodkiewicz coupling⁶ and the Fritsch–Buttenberg–Wiechell (FBW) rearrangement,^{7,8} while other protocols also exist.^{9,10}

To broaden the scope of the FBW rearrangement toward polyyne formation, the use of vinyl triflate 1 as a butadiynyl synthon was explored,¹¹ and a general method was sought toward the formation of 1,1-dibromoolefins 2 (Scheme 1). In the course of subjecting 1 to Sonogashira coupling conditions¹² in the presence of a terminal alkyne, we have discovered that the product of the reaction was not the expected olefin 2, but rather the triyne 3. It was immediately clear that this transformation offered a route to polyynes not accessible though a typical elimination reaction because the formation of 3 did not require the use of a strong base. Herein, the results of an initial study to optimize this protocol are presented.

The requisite precursor 1 is readily available from dibromoolefin 4^{13} via deprotonation with LiHMDS followed by quenching the resultant enolate with either *N*-phenyltriflamide or triflic anhydride (Scheme 2). Yields in both cases are quite good, and the reaction could be scaled to several grams without a decrease of yield.¹⁴

Initial attempts toward the Sonogashira coupling of triflate 1 to form 2 utilized typical conditions with either $PdCl_2(PPh_3)_2$ or $Pd(PPh_3)_4$ in the presence of a variety of bases. These exploratory reactions led only to mixtures of products resulting from an indiscriminate cross-coupling of the alkyne with both the triflate and dibromoolefin groups.

As the reactivity of **1** was explored further, a catalyst system of $Pd(OAc)_2$ (10 mol%), and PPh_3 (20 mol%) was attempted in DMF, using an excess (4 equiv.) of phenylacetylene at 70 °C. A trace of triyne **3a** was formed (Table 1, entry 1), and when the phosphine ligand was changed to P(p-tolyl)₃, **3a**





Scheme 2 Synthesis of dibromovinyl triflate 1.

was isolated in 37% yield under the same conditions after 12 h (entry 2). Several additional attempts with $P(p-tolyl)_3$ and other acetylenes revealed that the yields were typically low (*e.g.*, entry 7), although a 60% yield was obtained in the case of triyne **3d** (entry 10).

Switching to the even more active phosphine ligand, $P(Cy)_{3}$,¹⁵ significantly improved the yield of **3a**, and, at the same time, reduced the reaction time to only 2 h at r.t. (entry 3). Finally, the use of $P(^{t}Bu)_{3}$ gave a comparable yield to that found for $P(Cy)_3$, but further reduced the reaction time to 30 min (entry 4) and allowed for a reduction of the excess of the terminal acetylenes to 2 equivalents. The trend of comparable yields and shorter reaction times for $P(^{t}Bu)_{3}$ vs. $P(Cy)_{3}$ was maintained for a number of different polyynes, including electron rich (entries 6 and 16) and electron deficient aromatic substituents (entries 9, 12 and 14). It is worth noting that triynes 3c-h have not previously been available via a FBW rearrangement because either the electrophilic aryl substituent was not tolerant to the strong base required (3c-e and 3h) or the aniline substituent hampered the formation of the requisite dibromoolefin (3f and 3g). Reactions of both trimethylsilylacetylene and its more polar analogue (entry 20) have so far been unsuccessful but are subject to further investigations.¹⁶

With a reasonably optimized set of conditions in hand,[‡] this one-pot reaction was tested with several terminal diynes, and unsymmetrical tetraynes 3k-m were, thus, produced (entries 21–23). The formation of 3l is particularly noteworthy because it demonstrates the compatibility of this reaction with an acetylene terminated with the acetone adduct, a commonly used alkyne protecting group.¹⁷

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1 +	H— <u>—</u> R ——	→ [/] Pr	₃Si— <u>—</u> —	3	=	—R
Entry	R	Product	PR ₃ (20 mol%)	$T/^{\circ}C$	t/h	Yield (%)
1 2 3 4		$3a^a$ $3a^a$ $3a^a$ $3a^b$	PPh ₃ P(<i>p</i> -tolyl) ₃ P(Cy) ₃ P('Bu) ₃	70 70 r.t. r.t.	24 12 2 0.5	Trace 37 57 62
5 6		3b ^a 3b ^b	$P(Cy)_3$ $P('Bu)_3$	r.t. r.t.	16 1	50 62
7 8 9	₹CN	$3c^a 3c^a 3c^b$	$\begin{array}{l} P(p\text{-tolyl})_3 \\ P(Cy)_3 \\ P(^tBu)_3 \end{array}$	70 r.t. r.t.	6 2 1	31 52 59
10 11 12		3d ^a 3d ^a 3d ^b	$\begin{array}{l} P(p\text{-tolyl})_3 \\ P(Cy)_3 \\ P(^tBu)_3 \end{array}$	70 r.t. r.t.	6 2 2	60 70 68
13 14	₹NHAc	$3e^a$ $3e^b$	$P(Cy)_3$ $P('Bu)_3$	r.t. r.t.	24 12	48 53
15 16	₹NH2	3f ^a 3f ^b	$\begin{array}{l} P(Cy)_3 \\ P('Bu)_3 \end{array}$	r.t. r.t.	24 6	32 33
17	ξ-√N ⁱ Pr₂	$3g^a$	P(Cy) ₃	r.t.	24	48
18	§СНО	3h ^b	P(^t Bu) ₃	r.t.	12	40
19	₹CF3	3i ^b	P(^t Bu) ₃	r.t.	4	31
20	§−siCN	3j ^b	P(^{<i>t</i>} Bu) ₃	r.t.	24	0
21		3 k ^b	P(^t Bu) ₃	r.t.	24	26
22	§ — <u></u> —	31 ^b	P(^t Bu) ₃	r.t.	24	45
23	┋───	3m ^b	P(^t Bu) ₃	r.t.	24	15

 Table 1
 One-pot synthesis of tri-and tetraynes by Pd-catalyzed reactions between 1 and terminal alkynes

^{*a*} Reaction was run with R–C \equiv CH (4 equiv.), Pd(OAc)₂ (10 mol%), PR₃ (20 mol%), CuI (20 mol%), ^{*i*}Pr₂NH (4 equiv.), under nitrogen. ^{*b*} Reaction was run with R–C \equiv CH (2 equiv.), Pd(OAc)₂ (10 mol%), PR₃ (20 mol%), CuI (20 mol%), ^{*i*}Pr₂NH (4 equiv.), under nitrogen.

Spectroscopic analysis of all tri- and tetraynes were consistent with their proposed structures and with data that was previously reported (*e.g.*, **3c**). Definitive proof of polyyne formation was also provided by X-ray crystallographic characterization of **3d** (Fig. 1).§ As observed with other polyynes in the solid state,¹⁸ the triyne segments of **3d** takes on a gentle bowing conformation, with bond angles of 177–178°.

To extend the potential usefulness of this procedure toward even longer polyynes, the reaction of 1 with substrates **5a–d** bearing a 1,1-dibromovinyl moiety was explored (Scheme 3). The products of this reaction, **6**, might then be suitable for



Fig. 1 ORTEP drawing of triyne 3d.



Scheme 3 Synthesis of polyynes bearing a dibromovinyl moiety.

further elaboration. Specifically, in the case of **6a–c**, a subsequent FBW reaction,⁷ could be used to form penta- and hexaynes terminated with triisopropyl groups. While the yields of these transformations tended to be somewhat lower (*ca.* 30–50%) than those in Table 1, the rapid formation of advanced polyyne intermediates still make this an attractive alternative to the stepwise approach used in the past.

In summary, we have presented an efficient new synthetic route toward polyynes by using a Pd-catalyzed cross-coupling reaction of terminal alkynes with an α, α -dibromovinyl triflate. A variety of triyne and tetrayne derivatives were prepared to demonstrate that this protocol is a valuable alternative to a traditional FBW rearrangement, because it tolerates base sensitive functional groups. Further studies toward elucidating the scope and mechanism¹⁹ of this reaction are currently in progress.

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Notes and references

‡ General procedure for the Pd-catalyzed cross coupling reaction of a terminal alkyne with α, α -dibromovinyl triflate 1: To compound 1 (0.5 mmol) dissolved in 10 ml of DMF was added the appropriate terminal alkyne (1 to 2 mmol) and 'Pr₂NH (2 mmol). The solution was deoxygenated for 1 h, and P('Bu)₃ (0.25M solution in toluene), Cul (20 mol%), and Pd(OAc)₂ (10 mol%) were added. After stirring at r.t. for the time specified, a saturated aqueous solution of NH₄Cl was added, and the resulting mixture was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with brine (10 mL) and dried over anhydrous MgSO₄. Evaporation of the solvent followed by purification *via* silica-gel column chromatography gave the corresponding polyyne.

§ Crystal data for 3d: C₂₁H₂₅NO₂Si, M = 351.51; monoclinic crystal system; space group $P2_1/c$ (no. 14), a = 20.1591(16), b = 7.3496(6),

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