Pd–Ag catalyzed selective dicoupling of α-trialkylsilyl α,ω-diynes; the first one-pot synthesis of dienediynes

Ulla Halbes-Létinois, Patrick Pale *

Laboratoire de synthèse et réactivité organique, Institut Le Bel, Université L. Pasteur, 4 rue B. Pascal, 67000 Strasbourg, France.

Dedicated to Professor Jean-Pierre Genêt on the occasion of his 60th birthday and for his contributions to organic and organometallic chemistries

Abstract

Using Pd and Ag as catalysts, the first one-pot synthesis of dienediynes have been achieved. Sequential dicoupling reactions afforded a regioselective access to dienediynes starting from any and especially non-symmetrical α,ω-diynes. Good to excellent yields were obtained in dimethylformamide at room temperature.
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1. Introduction

The cross-coupling of alkynes with different partners, especially alkenyl triflates, is nowadays a widely used process in organic synthesis [1,2], especially for the synthesis of conjugated polyunsaturated natural products [3,4]. A double coupling reaction with α,ω-diynes would be an interesting sequence allowing for a rapid synthesis of conjugated dienediynes (DEDY), which could be applied to the synthesis of DEDY natural products such as the chromophore of Neocarzinostatin [5], the more recent N1999A2 [6] (Scheme 1) or analogs [7] (see also Ref. [2a]).

However, coupling non-symmetrical α,ω-diynes would lead to a mixture of regioisomeric DEDY. Therefore, several questions have to be addressed as a prelude to any synthetic applications: How can be achieved a rapid and efficient dicoupling? How can we control the selectivity of such dicoupling?

We present here an approach, which offers an answer to those questions and allows for the first one-pot synthesis of dienediynes.

This approach is based on the judicious use of methods developed for coupling sensitive terminal alkynes with vinyl triflates [8,9] and for the direct coupling of silyl protected alkynes [10]. Starting from a monosilylated α,ω-diyne, it should be possible to apply one method for the coupling at one end of the diyne and then the other for the coupling at the other end (Scheme 2). Moreover, since both methods require the same Pd and Ag catalysts, a one-pot process could be envisaged by sequentially adding a vinyl triflate with the appropriate activator and then another vinyl triflate with the corresponding reagent to a mixture of monoprotected diyne and catalysts.

2. Results and discussion

Unprecedented, the feasibility of such sequenced dicoupling was first investigated with a simple α,ω-diyne, the commercially available 1,7-octadiyne. Monoprotection with a trimethylsilyl group led to the corresponding 1-trimethylsilyl-1,7-octadiyne **1** which was then first submitted to our conditions developed for terminal alkynes [8]. The expected enediynes **3a**–**b** were obtained in good to excellent yields either from the simple vinyl triflate **2a** [11] or from the functionalized vinyl triflate **2b** [12] (Scheme 3). Only the free alkyne

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* Corresponding author. Tel./fax: +33-3-9024-1517.
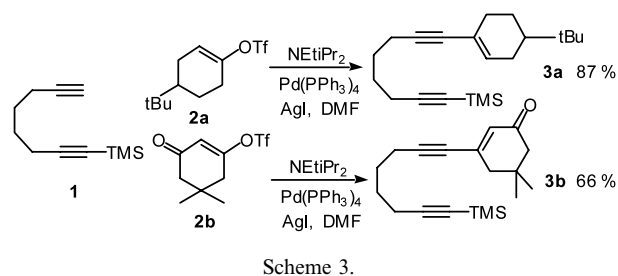*E-mail address:* ppale@chimie.u-strasbg.fr (P. Pale).
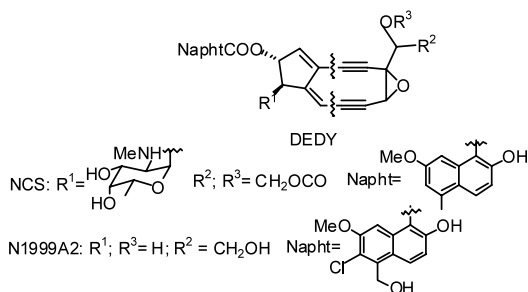
Scheme 1.

Scheme 3.

function was substituted as evidenced by the presence in the products of the characteristic spectroscopic signals of the trimethylsilyl acetylene moiety (2117 cm^{-1} for IR, 0.01 and 106 ppm in ^{1}H- and ^{13}C-NMR, respectively).

These products were then engaged in our coupling reaction developed for 1-trialkylsilyl-1-alkynes [10]. Coupling the enediyne **3a** with the vinyl triflate **2a** or the enediyne **3b** with the activated vinyl triflate **2b** cleanly provided the symmetrical DEDY **4aa**, **4bb** in good overall yields (Table 1, entries 1 and 3). The non-symmetrical DEDY **4ab** was cleanly obtained by coupling either **3a** with **2b** or **3b** with **2a**. Interestingly, the overall yields obtained were similar whatever the order of events (Table 1, entries 2 and 4).

Gratifyingly, the reverse order of reactions gave as expected first the non-protected enediynes **5a–b** and then the same DEDY as above with similar overall yields (Scheme 4). As with the reverse order of events, only one diyne is eventually obtained in each reaction.

This two steps sequence provides thus a rapid and efficient access to DEDY. With these results in hands, we then investigated a one-pot process. To a DMF solution of **1** were successively added the catalysts, the vinyl triflate **2a** and diisopropylethylamine and, when the consumption of **1** was total as judged by TLC monitoring, then **2a** and the solid TBAF–hydrate were added. The expected dienediyne **4aa** was isolated as the sole product with a yield similar to the one obtained through the step-by-step procedure. The same one pot procedure proved also as efficient for the direct forma-

tion of **4ab** and **4bb** with again yields similar to the step-by-step procedure (Scheme 5).

These results represent the first one-pot synthesis of conjugated dienediynes. They also clearly demonstrate that both Pd and Ag catalysts are still active during this one pot reaction.

To address the regioselectivity problem, the α-silylated non-symmetrical α,ω-diyne **6** was prepared [13,14] and submitted either to the vinyl triflates **2a** or **2b** in step-by-step procedure or in the one pot process. As in the preceding case, the first coupling left untouched the silylated acetylenic end and then the latter was cleanly converted to the corresponding enyne (Scheme 6). The expected DEDY were selectively obtained in good overall yields. Gratifyingly, the one-pot procedure proved even better since the expected DEDY were obtained with an excellent 71% yield. Therefore, this sequence solved the regioselectivity problem associated with the dicoupling strategy.

3. Conclusion

The results presented here demonstrated that two successive Pd/Ag-catalyzed coupling reactions of α-trialkylsilyl–α,ω-diynes allow to regioselectively prepare dienediynes. Furthermore, a one-pot process has been achieved, providing the first one-pot synthesis of dienediynes. The scope and limitations of this one-pot dicoupling reaction is now under investigation, as well as further developments toward dienediyne antibiotics.
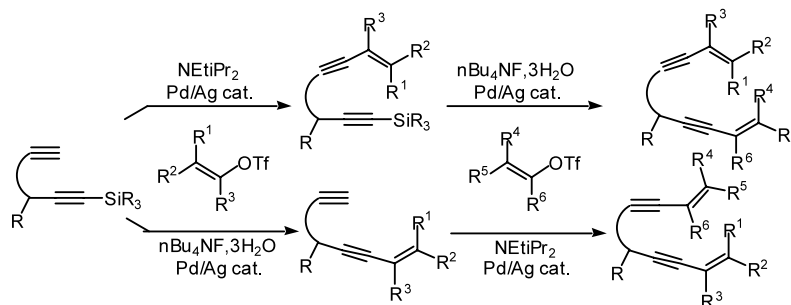
Scheme 2.

Table 1
Sequenced DEDY synthesis [a,b]
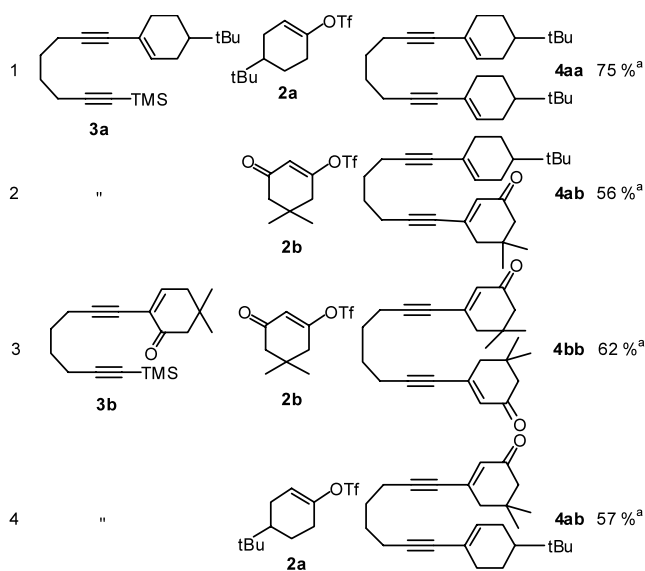
4. Experimental

4.1. Typical procedure for the one pot DEDY synthesis

#### 4.1.1. 1,8-bis(4-Tertbutylcyclohex-1-enyl)-1,7-octadiyne (4aa)

4-*tert*-Butyl-1-cyclohexenyl trifluoromethanesulfonate (**2a**) (200 mg, 0.63 mmol) was dissolved in dimethylformamide (10 ml). Diisopropylethylamine (154 μl, 0.89 mmol), tetrakis(triphenylphosphane) palladium (81 mg, 0.07 mmol) and silver iodide (33 mg, 0.14 mmol) were then successively added at room temperature (r.t.) under argon. The resulting solution was stirred 10 min. in the dark, then 1-trimethylsilyl-1,7-octadiyne (124 mg, 0.7 mmol) was added. The reaction mixture was stirred in the dark while the consumption of the starting materials was monitored by TLC. When the starting enol triflate has disappeared as judged by TLC, a second equivalent of 4-*tert*-butyl-1-cyclohexenyl trifluoromethanesulfonate (**2a**) (200mg, 0.63 mmol) was added, followed by a solution of TBAF.3H$_2$O (330 mg, 1.5 equivalents) in 10 ml DMF. The reaction was further monitored by TLC until the alkyne or the second equivalent of triflate was consumed. The mixture was then quenched with water (20 ml) and extracted with ether (3 × 15 ml). The combined organic extracts were washed with water (3 × 10 ml), dried over MgSO$_4$ and concentrated. The crude product was purified by flash
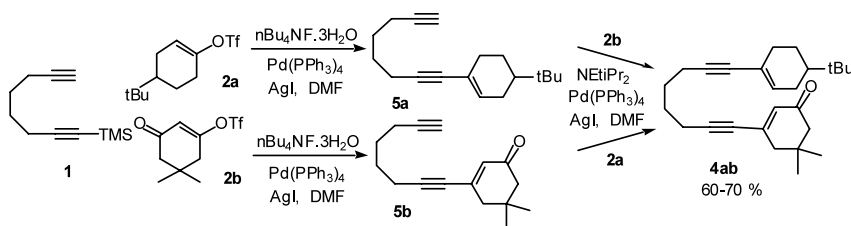
Scheme 4.
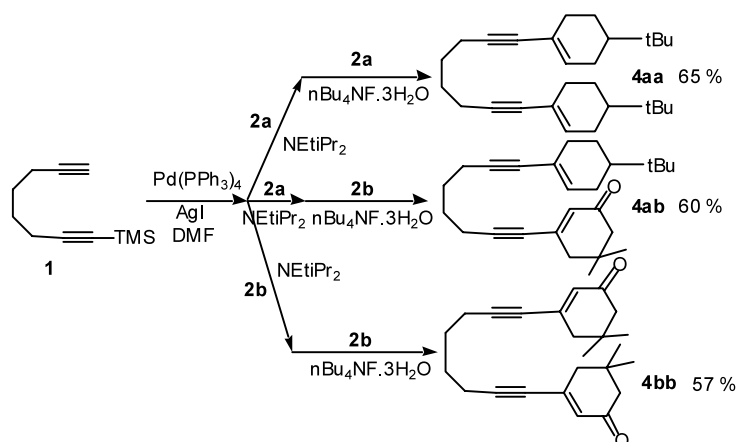
Scheme 5.
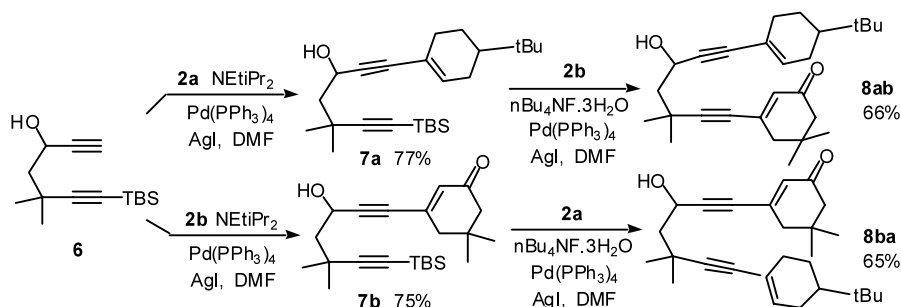
Scheme 6.

chromatography (silica gel–petroleum ether 100%) giving the expected dienediyne as a colorless liquid.

^{1}H (CDCl$_3$): $\delta = 0.81$ (9H, s, $H_{4''}$); 1.00–1.24 (4H, m, $H_{4',6'}$); 1.60 (4H, m, $H_{4,5}$); 1.68–1.87 (4H, m, $H_{3',6'}$); 1.93–2.09 (6H, m, $H_{3',5'}$); 2.26 (4H, t, $J = 3.8$, $H_{3,6}$); 5.97 (2H, t, $J = 1.5$, H_2); ^{13}C: $\delta = 18.9$ (C_3); 27.1 (C_3); 27.2 ($C_{b,c,d}$); 27.6 ($C_{4'}$); 31.1 (C_5); 32.1 (C_6); 32.2 (C_a); 43.3 (C_4); 76.3 ($C_{1'}$); 82.3 ($C_{1'}$); 87.1 ($C_{2'}$); 120.8 (C_1); 133.5 (C_2). IR: 3052; 2961; 2253; 1422; 1366; 1284; 1142; 999. MS: 378 [M$^+$], 289; 245; 149; 85; 57. HRMS: Found 378.3794; Calc. 378.3287.

4.1.2. 1,8-bis(5,5-Dimethyl-3-oxocyclohex-1-enyl)-1,7-octadiyne (4bb)

^{1}H (CDCl$_3$): $\delta = 0.98$ (12H, s, $H_{5'a}$); 1.63 (4H, m, $H_{4,5}$); 2.17 (4H, s, $H_{4'}$); 2.23 (4H, d, $J = 1.6$, $H_{6'}$); 2.39 (4H, t, $J = 6$, $H_{3,6}$); 6.09 (1H, d, $J = 1.6$, $H_{2'}$). ^{13}C: $\delta = 19.4$ (C_3); 27.4 ($C_{4,5}$); 28.5 ($C_{5'a}$); 33.7 ($C_{5'}$); 44.7 ($C_{6'}$); 51.1 ($C_{4'}$); 81.1 (C_1); 100.1 (C_2); 131.1 ($C_{2'}$); 142.0 ($C_{1'}$); 199.1 ($C_{3'}$); IR (neat): 2961, 2253, 1658, 1384,1265.

4.1.3. 1-(4-tert-Butylcyclohex-1-enyl)-8-(5,5-dimethyl-3-oxocyclohex-1-enyl)-1,7-octadiyne (4ab)

^{1}H (CDCl$_3$): $\delta = 0.88$ (9H, s, $H_{4''a}$); 0.98 (6H, s, $H_{5'a}$); 1.11–1.21 (2H, ma, $H_{4'',6''}$); 1.65–1.69 (4H, m, $H_{4,\,5}$); 1.76–1.87 (2H, ma, $H_{5'',6''}$); 1.93–2.09 (3H, m, $H_{5'',\,3''}$) 2.17 (2H, s, $H_{6'}$); 2.23 (1H, d, $J = 1.8$, $H_{4'}$); 2.29 (2H, t, H_6); 2.42 (2H, t, H_3); 6.01 (1H, m, $H_{2''}$); 6.14 (1H, m, $H_{2'}$). ^{13}C: $\delta = 18.0$ ($C_{5'}$); 18.9 (C_6); 19.5 (C_3); 23.9 ($C_{5''}$); 27.2 ($C_{7''a}$); 27.3 ($C_{5''}$); 28.1 ($C_{5'a}$); 30.4 (C_4); 31.0 (C_5); 31.2 ($C_{6''}$); 32.2 ($C_{7''}$); 43.4 ($C_{4''}$); 44.8 ($C_{4'}$); 51.1 ($C_{6'}$); 80.7 (C_1); 82.0 (C_8); 87.2 (C_7); 102.0 (C_2); 120.9 ($C_{1''}$); 130.1 ($C_{3'}$); 133.4 ($C_{2''}$); 142.0 ($C_{2'}$); 199.3 ($C_{1'}$).

IR: 3052; 2961; 2253; 1422; 1366; 1284; 1142; 999. MS: 364 (M +), 307; 293; 277; 270; 201; 149; 127; 85.

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[12] Readily obtained by treatment of dimedone with triflic anhydride in the presence of base.

[13] The TBS group was used for convenience during the synthesis of **6**. As demonstrated earlier [10b], it does not affect the reactivity during the coupling step.

[14] The diyne **6** was conveniently obtained from the commercially available 3-methylbut-1-yn-3-ol through the following sequence: Bromination then malonate displacement followed by decarboxylation and reduction provided 3,3-dimethylpent-4-ynol. Silylation then oxidation and ethynyl bromomagnesium addition yielded **6**.