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# Pd–Catalyzed Domino Alkyne Dimerization/Double [2+2] Allenyne Cycloaddition

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## 1. ABSTRACT

An efficient and controlled Pd–catalyzed synthesis of attached-ring bis(dihydropyran) fused cyclobutenes via alkyne dimerization followed by double [2+2] cyclization of the resulting bis(allenyne) in a domino sequence has been accomplished.

## 2. INTRODUCTION

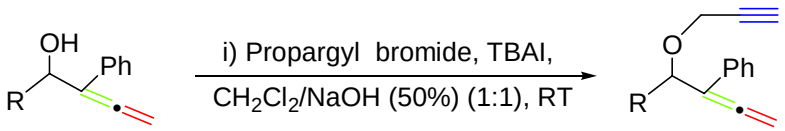
During the last few years the chemistry of allenes has been widely studied, showing an interesting reactivity and selectivity.[1] Thus, the chemistry of allenes has been applied for the preparation of natural and non-natural products of interest. In particular, [2+2] cycloaddition reactions of allenes with alkynes have attracted recent attention.[2] However, stereo- and positional selectivity problems are significant with only one report on the [2+2] cyclization of bis(allenynes), namely, a monocyclization to afford a [5.4] system.[3] In continuation of our interest in allene chemistry,[4] we present the first examples of a double [2+2] cycloaddition in allenynes. The results of our investigation to prepare attached-ring bis(dihydropyran) fused cyclobutenes using alkyne dimerization as well as double cyclization of the resulting bis(allenyne) in a domino sequence, form the subject of this report.

## 3. RESULTS AND DISCUSION

The starting α-allenols required for our study were prepared from the corresponding aldehydes as previously described.[5] Treatment of compounds **1a–d** with propargyl bromide under phase-transfer conditions afforded allenynes **2a–d** in good yields (Scheme 1).

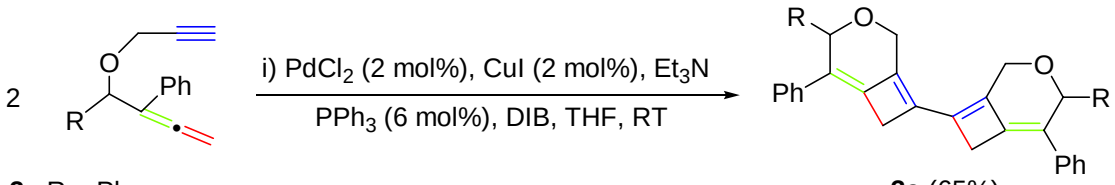
Having obtained the starting materials, we began this work by investigating the Glaser, Eglinton and Hay dimerization protocols in allenyne **2a**, however, a complicated mixture of side products were obtained. To our delight, we found that the Pd-catalyzed oxidative dimerization of alkynes with a stoichiometric amount of (diaceoxyiodo)benzene as oxidant, afforded the unexpected dimeric bis(3-oxabicyclo[4.2.0]octadiene) **3a** in good yield. Similarly, allenynes **2b–d**, provided the corresponding tetracycles **3b–d** in reasonable yields (Scheme 2). These results could be explained through an unprecedented Pd-catalyzed domino alkyne dimerization/[2+2]

allenyne bis(cycloaddition). Interestingly, tetracycles **3** were obtained as single regioisomers involving both external allenic double bonds in the double [2+2] cycloaddition step.[6]




**1a** **2a** (68%)
**1b** **2b** (62%)
**1c** **2c** (72%)
**1d** **2d** (54%)

**Scheme 1**. Synthesis of allenynes **2** from allenes **1** under phase-transfer conditions.

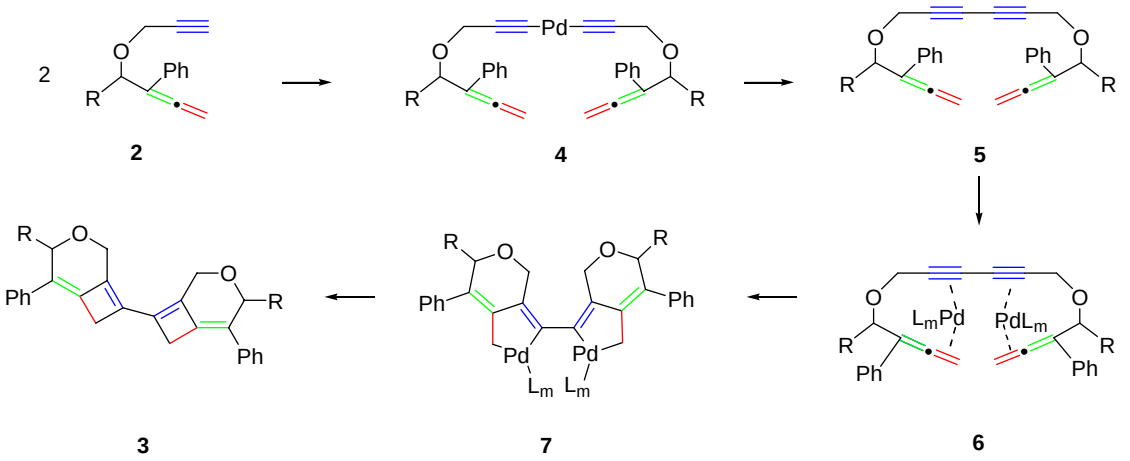



**2a** R = Ph
**2b** R = 4-MeOC$_6$H$_4$
**2c** R = 4-MeC$_6$H$_4$
**2d** R = 2-BrC$_6$H$_4$

**3a** (65%)
**3b** (55%)
**3c** (55%)
**3d** (49%)

**Scheme 2**. Pd-catalyzed domino alkyne dimerization/[2+2] allenyne bis(cycloaddition).

As judge by $^{13}$C NMR data, compounds **3** appear to be diastereomeric mixtures. In addition, no signal corresponding to alkenyl cyclobutene protons was observed, indicating that substitution occurred at the external double bond of the allene moiety. The dimeric nature of these polycycles has been revealed from the analysis of the mass spectra, which correspond to twice the mass of the starting materials. The $C_2$-symmetrical dimer nature of adducts **3** was confirmed by the simplicity of the $^1$H and $^{13}$C NMR spectra. Formation of compounds **3** could be explained via a metal-catalyzed [2+2] allenyne bis(cyclization) after homodimerization of the starting allenyne. Scheme 3 shown a possible mechanistic explanation involving formation of dialkynylpalladiums type **4**, which are then transformed to the corresponding diynes type **5**. The double [2+2] cycloaddition should be explained in terms of the formation of a π-complex **6** with both the triple bond and the external double bond of the allene moiety on substrates **5**. These π-complexes **6** may undergo migratory C–C coupling to afford palladacyclopentenes type **7** followed by reductive elimination to give bis(cyclobutenes) **3**. The regioselectivity observed in compounds **3** could be explained in terms of the stereoelectronic effects of the aryl substituent (phenyl group) in allenynes **2**, restrinting the cyclization towards the internal allenic double bond.




**Scheme 3**. Mechanistic explanation for the palladium-promoted alkyne dimerization/[2+2] bis(cycloaddition) of allenynes **2**.

## 4. CONCLUSIONS

In conclusion, an efficient Pd-catalyzed synthesis of attached-ring bis(dihydropyran) fused cyclobutenes in a totally controlled fashion using alkyne dimerization as well as double [2+2] cyclization of the resulting bis(allenyne) in a domino sequence has been accomplished.

## 5. GENERAL EXPERIMENTAL PROCEDURE

**General Methods.** $^{1}$H NMR and $^{13}$C NMR spectra were recorded on a Bruker Avance AVIII-700 with cryoprobe, Bruker Avance-300, Varian VRX-300S or Bruker AC-200. NMR spectra were recorded in $CDCl_3$ solutions, except otherwise stated. Chemical shifts are given in ppm relative to TMS ($^{1}$H, 0.0 ppm), or $CDCl_3$ ($^{13}$C, 76.9 ppm). Low and high resolution mass spectra were taken on an AGILENT 6520Accurate-Mass QTOF LC/MS spectrometer using the electronic impact (EI) or electrospray modes (ES) unless otherwise stated. Specific rotation $[\alpha]_D$ is given in $10^{-1}$ deg cm$^2$ g$^{-1}$ at 20 °C, and the concentration (*c*) is expressed in g per 100 mL. All commercially available compounds were used without further purification.

***O*-Propargylation of α-allenic alcohols under phase-transfer conditions. General procedure for the synthesis of allenynes 2a–d.** Tetrabutyl ammonium iodide (16.0 mg, 0.043 mmol), 50% aqueous sodium hydroxide (50 mL) and propargyl bromide (6.9 mmol) were sequentially added at room temperature to a solution of the appropriate α-allenic alcohol (4.3 mmol) in dichloromethane (50 mL). The reaction was stirred for 14 h and then water was added (25 mL), before being partitioned between dichloromethane and water. The aqueous phase was extracted with dichloromethane (3 x 25 mL), the combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue using hexanes/ethyl acetate mixtures as eluent gave allenynes **2** in analytically pure form.

**Allenyne 2a.** From 504 mg (2.27 mmol) of the corresponding allenol, and after chromatography of the residue using hexanes/ethyl acetate (8:1) as eluent gave compound **2a** (400 mg, 68%) as a pale yellow oil. $^{1}$H NMR (300 MHz, $CDCl_3$, 25 $^{o}$C): δ = 7.34 (m, 3H), 7.18 (m, 7H), 5.58 (br s, 1H), 5.06 (m, 2H), 4.17 (qd, *J* = 15.9, 2.5 Hz, 2H), 2.39 (t, *J* = 2.5 Hz, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$, 25 $^{o}$C): δ = 209.9, 139.4,

134.0, 128.3, 128.2, 127.8, 127.3, 127.1, 126.9, 106.2, 79.5, 79.3, 79.1, 74.8, 55.8; IR ($CHCl_3$): ν = 3305, 2992, 1944 $cm^{-1}$; HRMS (ES): calcd (%) for $C_{19}H_{16}O$ [*M* + H]$^+$: 261.1279; found: 261.1274.

**Palladium-catalyzed domino alkyne homocoupling/double [2+2] allenyne cycloaddition. General procedure for the synthesis of attached-ring bis(dihydropyran-fused cyclobutenes) 3a–d.** The appropriate allenyne **2** (0.5 mmol) was added to a well stirred suspension of (diacetoxyiodo)benzene (0.3 mmol), $Et_3N$ (0.6 mmol), $PdCl_2$ (0.01 mmol), CuI (0.01 mmol) and $PPh_3$ (0.03 mmol) in THF (1.5 mL) at RT. After disappearance (typically overnight) of the starting material (TLC), the reaction mixture was filtered through a celite plug and the filtrate was concentrated under reduced pressure. Chromatography of the residue using ethyl acetate/hexanes mixtures gave analytically pure compounds.

**Bis(dihydropyran-fused cyclobutene) 3a.** From 50 mg (0.19 mmol) of allenyne **2a**, and after chromatography of the residue using hexanes/ethyl acetate (8:1) as eluent gave compound **3a** (64 mg, 65%) as a yellow oil. $^1$H NMR (700 MHz, $CDCl_3$, 25 $^o$C): δ = 7.39 (m, 16H), 7.23 (m, 4H), 5.82 (s, 2H), 4.29 and 4.05 (d, *J* = 16.0 Hz, each 2H), 3.72 (m, 4H); $^{13}$C NMR (175 MHz, $CDCl_3$, 25 $^o$C): δ = 141.5, 138.1, 138.0, 135.9, 135.2, 133.0, 131.0, 130.9, 129.3, 129.0, 128.5, 128.4, 126.8, 125.5, 122.0, 121.9, 75.2, 75.1, 56.9, 56.8, 38.9, 38.8; IR ($CHCl_3$): ν = 3065 $cm^{-1}$; HRMS (ES): calcd (%) for $C_{38}H_{31}O_2$ [*M* + H]$^+$: 519.2324; found: 519.2329.

## 6. ACKNOWLEDGEMENTS

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## 7. REFERENCES

1. For selected reviews, see: a) Brasholz, M.; Reissig, H.-U.; Zimmer, R. *Acc. Chem. Res.* **2009**, *42*, 45. b) Bongers, N.; Krause, N. *Angew. Chem. Int. Ed*. **2008**, *120*, 2208. c) Widenhoefer, R. A. *Chem. Eur. J*. **2008**, *14*, 5382. d) Ma, S. *Chem. Rev.* **2005**, *105*, 2829. e) *Modern Allene Chemistry*; Krause, N., Hashmi, A. S. K., Eds.; Wiley-VCH: Weinheim, Germany, 2004. f) Zimmer, R.; Dinesh, C. U.; Nandanan, E.; Khan, F. A. *Chem. Rev.* **2000**, *100*, 3067. g) Hashmi, A. S. K. *Angew. Chem. Int. Ed.* **2000**, *39*, 3590.
2. For a review of [2+2] cycloaddition on allenes, see: a) Alcaide, B.; Almendros, P.; Aragoncillo, C. *Chem. Soc. Rev*., **2010**, DOI:10.1039/B913749A.
3. a) Cao, H.; Van Ornum, S. G.; Deschamps, J.; Flippen- Anderson, J.;Laib, F.; Cook, J. M. *J. Am. Chem. Soc*. **2005**, *127*, 933. b) Hao, H.; Flippen-Anderson, J.; Cook, J. M. *J. Am. Chem. Soc*. **2003**, *125*, 3230.
4. a) Alcaide, B.; Almendros, P.; Martínez del Campo, T.; Quirós, M. T. *Chem. Eur. J*. **2009**, *15*, 3344. b) Alcaide, B.; Almendros, P.; Carrascosa, R.; Martínez del Campo, T. *Chem. Eur. J*. **2009**, *15*, 2496. c) Alcaide, B.; Almendros, P.; Martínez del Campo, T.; Soriano, E.; Marco-Contelles, J. L. *Chem. Eur. J*. **2009**, *15*, 1901. d) Alcaide, B.; Almendros, P.; Carrascosa, R.; Redondo, M. C. *Chem. Eur. J*. **2008**, *14*, 637.
5. Isaac, M. B.; Chan, T.-H. *J. Chem. Soc., Chem. Commun.* **1995**, 1003.

6. Attached-ring bis(dihydropyran) fused cyclobutenes **3** possess as well a pyran moiety, which is present in a wide variety of natural products and biologically relevant compounds. For reviews on pyran rings. See: a) Larrosa, I.; Romea, P.; Urpí, F. *Tetrahedon* **2008**, *64*, 2683. b) Clarke, P. A. Santos, S. *Eur. J. Org. Chem*. **2006**, 2045. c) Faulkner, D. *J. Nat. Prod. Rep*. **2000**, *17*, 7.