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Generating Complexity from Simplicity: Pd-Catalyzed or Cu-Promoted Domino Alkyne Homocoupling/Double [2+2] Allenyne Cycloaddition

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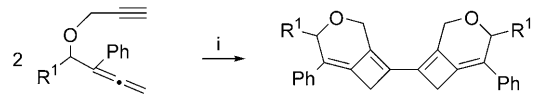
The allene moiety has developed from almost a rarity to an established member of the weaponry utilized in modern organic synthetic chemistry.[1] In particular, [2+2] cycloaddition reactions of allenes with alkynes have attracted recent attention.[2] However, stereo- and positional selectivity problems are significant. Although much effort has been devoted to these fields, [2+2] cycloaddition of bis(allenynes) has rarely been mentioned; only Cook et al. have reported the formation of a monocyclized [5.4] system.[3] The main cause of this lack might be attributed to both the difficulty of preparing the starting diyne-diallenes as well as to additional chemo- and regioselectivity problems. In a 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(heterocyclic) fused cyclobutenes using alkyne homocoupling as well as double cyclization of the resulting bis(allenyne) in a domino sequence are described herein.

Allenyne **1a** was chosen as a model substrate for alkyne homocoupling.[5] To screen the reactivity of the allenyne moiety, the dimerization was studied by using **1a** in the presence of a copper catalyst. The starting allenyne was recovered, together with a complicated mixture of side products when Glaser, Eglinton, or Hay protocols were applied.[6] By contrast, difficulties were surmounted when Pd-catalyzed oxidative homocoupling of alkynes with a stoichiometric amount of oxidant were applied. To our delight, the unexpected dimeric bis(3-oxabicyclo[4.2.0]octadiene) **2a** was obtained in good yield by adopting a modified oxidative acetylenic coupling using a Pd–Cu bimetallic catalytic system and (diacetoxyiodo)benzene (Scheme 1). These results could be explained through an unprecedented Pd–Cu bimetallic catalyzed domino alkyne homocoupling/[2+2] allenyne bis(cycloaddition). Interestingly, total regioselectivity towards both external allenic double bonds was observed. Similar behavior was observed for alicyclic allenynes **1b–d**, providing tetracycles **2b–d** in reasonable yields (Scheme 1).[7] However, variations in concentrations considerably altered results. If the reaction was performed at a lower concentration of 0.33 mol L^{-1}, the conversion dropped dramatically, and in most cases the reaction failed completely; not even a homodimerization of the alkyne moiety was detected. Dimers **2** are acid-sensitive, making the storage in a $CDCl_3$ solution impractical because the acid present in the deuterated solvent induces ring opening and polymerization.



1a R^1 = Ph — **2a** (65%)
1b R^1 = 4-$MeOC_6H_4$ — **2b** (55%)
1c R^1 = 4-MeC_6H_4 — **2c** (55%)
1d R^1 = 2-BrC_6H_4 — **2d** (49%)

Scheme 1. Synthesis of attached-ring bis(dihydropyran-fused cyclobutenes) **2a–d**. Reagents and conditions: i) 2 mol% $PdCl_2$, 2 mol% CuI, Et_3N, 6 mol% PPh_3, DIB, THF, RT. THF = Tetrahydrofuran; DIB = (Diacetoxyiodo)benzene.

To assess the scope, the even more challenging enantiopure 2-azetidinone-tethered allenynes **3** were tested as bis(cyclization) substrates. The starting allenynes **3a–d** were readily obtained beginning from the appropriate 4-oxoazetidine-2-carbaldehyde via a regiocontrolled indium-mediated Barbier-type carbonyl-allenylation reaction.[8] Initial attempts, by employing the above Pd–Cu bimetallic catalytic

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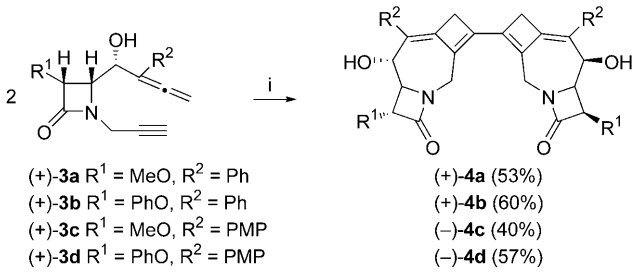
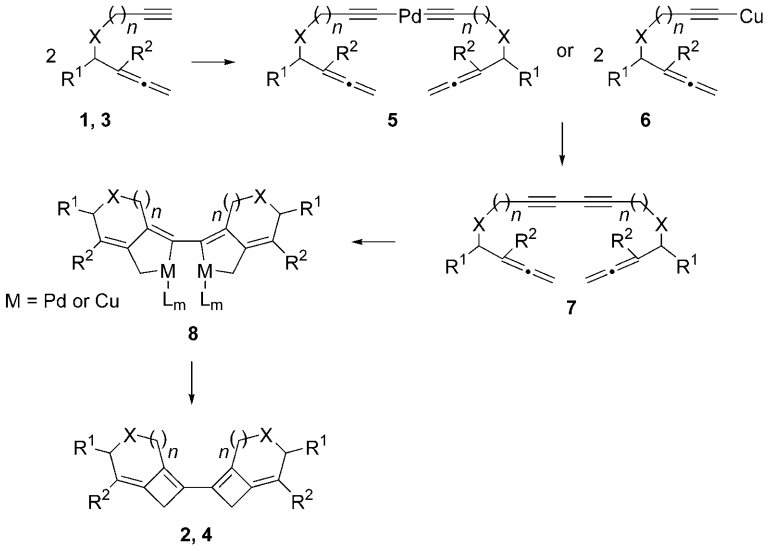
system failed to give the desired product even when the reaction temperature was raised to 80 °C. Different additives and metal sources were screened with compound **3a** as test substrate. Using modified classical copper promoted conditions, however, we were pleased to find that the homodimerization/[2+2] bis(cyclization) sequence proceeded smoothly to afford the desired product **4a**. Copper(II) acetate with potassium carbonate was the best combination. The process was highly solvent dependent, and the best results were obtained in acetonitrile. However, reaction times for complete conversion were considerably longer than with allenynes **1** (10 h for allenyne **1a** and 72 h for allenyne **3a**). At short reaction times at room temperature, the bis(β-lactam)-1,3-diyne homodimer was detected in appreciable amounts. Accordingly, hot solutions of allenynes **3** were exposed to the above disclosed conditions and efficiently afforded bis(cycloadduct) **4a** after 2 h. Taking into account the repeatability, the reproducibility, and the reliability of the copper-promoted conditions, the modified Eglinton protocol was selected as the method of choice.[9] In this way, enantiopure attached-ring bis(tricyclic) β-lactams **4a–d** were conveniently prepared in good overall yields by domino alkyne homocoupling/double [2+2] bis(allenyne) cycloaddition (Scheme 2).



Scheme 2. Synthesis of enantiopure attached-ring bis(tricyclic) β-lactams **4a–d**. Reagents and conditions: i) $Cu(OAc)_2$, K_2CO_3, MeCN, RT→110 °C. PMP = 4-$MeOC_6H_4$.

Interestingly, the exposure of allenynes **1a–d** to the copper-promoted conditions of Scheme 2 afforded bis(hydropyran-fused cyclobutenes) **2a–d** in similar yields. Compounds **4** are remarkable since they bear a challenging dimeric tricyclic 2-azetidinone structure having both a strained cyclobutene as well as a seven-membered ring.[10–13] No loss of stereochemical integrity at the stereogenic centers under the domino conditions was detected. Besides, the depicted distal cycloadducts were the only isomers isolated, showing allenynes **1** and **3** the same regiochemical preference. Substrates **1a–d** and **3a–d** had aryl groups at the inside position of the allene. Unfortunately, when related allenynes **1** and **3** not bearing aryl groups (R^2 = Me or R^2 = H) were used, the reaction stopped at the alkyne homocoupling step.

Dimers **2a–d** arising from racemic monomers **1a–d** appear to be diastereomeric mixtures as seem to suggest the ^{13}C NMR data. NMR data of compounds **2** and **4** suggested a fused cyclic structure. However, no signal for alkenyl cyclobutene protons was detected, indicating that substitution occurred at the former terminal acetylenic end. The observed masses from the mass spectra correspond to twice the mass of the starting compounds, thus revealing the dimeric nature of these polycycles. In addition, the simplicity of the proton and carbon NMR spectra point to the C_2-symmetrical dimmer nature of adducts **2** and **4**. Such dimeric polycycles could be formed either from a metal-promoted [2+2] allenyne mono(cyclization) followed by dimerization of the so-formed cyclobutene derivative or from a metal-promoted [2+2] allenyne bis(cyclization) after homodimerization of the starting allenyne. The first hypothesis could be safely ruled out because we were able to isolate small amounts of diallenynyl diazetidinones of type **7** by the above-mentioned copper-promoted conditions at short reaction times. A tentative mechanistic proposal for the metal-promoted alkyne homocoupling/[2+2] allenyne bis(cycloaddition) of allenynes is depicted in Scheme 3. It may involve the formation of dialkynylpalladium complexes of type **5** or copper(I) acetylides of type **6**, which are then transformed to the corresponding diynes **7**.[14] For the double [2+2] allenyne cyclization, it is believed that initially the metal salt regioselectively forms a π complex with both the triple bond and a double bond of substrates **6**. Such π complexes may undergo migratory C–C coupling to give pallada- or cupracyclopentenes of type **8**. Following this step, intermediates **8**



Scheme 3. Mechanistic explanation for the metal-promoted alkyne homocoupling/[2+2] allenyne bis(cycloaddition) of allenynes **1** and **3**.

would undergo rapid reductive elimination to give bis(cyclobutenes) **2** and **4** as the final products.[15] The observed high regioselectivity of the reaction could be explained in terms of the regioselective formation of metallacycles of type **8**, which would be controlled by the stereoelectronic effects of the aryl substituent (R^2) in allenynes **1** and **3**. Cyclization towards the internal allenic double bonds is probably restricted by the steric hindrance between the metal ligand moiety and the aryl substituent at the putative quaternary stereocenter.

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

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[1] For selected reviews, see: a) M. Brasholz, H.-U. Reissig, R. Zimmer, *Acc. Chem. Res.* **2009**, *42*, 45; b) N. Bongers, N. Krause, *Angew. Chem.* **2008**, *120*, 2208; *Angew. Chem. Int. Ed.* **2008**, *47*, 2178; c) R. A. Widenhoefer, *Chem. Eur. J.* **2008**, *14*, 5382; d) S. Ma, *Chem. Rev.* **2005**, *105*, 2829; e) *Modern Allene Chemistry* (Eds.: N. Krause, A. S. K. Hashmi), Wiley-VCH, Weinheim, **2004**; f) R. Zimmer, C. U. Dinesh, E. Nandanan, F. A. Khan, *Chem. Rev.* **2000**, *100*, 3067; g) A. S. K. Hashmi, *Angew. Chem.* **2000**, *112*, 3737; *Angew. Chem. Int. Ed.* **2000**, *39*, 3590.

[2] For selected references on allene/alkyne [2+2] cyclization, see: a) C. Mukai, Y. Hara, Y. Miyashita, F. Inagaki, *J. Org. Chem.* **2007**, *72*, 4454; b) H. Ohno, T. Mizutani, Y. Fado, K. Miyamura, T. Tanaka, *Angew. Chem.* **2005**, *117*, 5243; *Angew. Chem. Int. Ed.* **2005**, *44*, 5113; c) K. M. Brummond, D. Chen, *Org. Lett.* **2005**, *7*, 3473; d) C. H. Oh, A. K. Gupta, D. I. Park, N. Kim, *Chem. Commun.* **2005**, 5670; e) Y. Horino, M. Kimura, S. Tanaka, T. Okajima, Y. Tamaru, *Chem. Eur. J.* **2003**, *9*, 2419; f) Q. Shen, G. B. Hammond, *J. Am. Chem. Soc.* **2002**, *124*, 6534.

[3] a) H. Cao, S. G. Van Ornum, J. Deschamps, J. Flippen-Anderson, F. Laib, J. M. Cook, *J. Am. Chem. Soc.* **2005**, *127*, 933; b) H. Cao, J. Flippen-Anderson, J. M. Cook, *J. Am. Chem. Soc.* **2003**, *125*, 3230.

[4] a) B. Alcaide, P. Almendros, T. Martínez del Campo, M. T. Quirós, *Chem. Eur. J.* **2009**, *15*, 3344; b) B. Alcaide, P. Almendros, R. Carrascosa, T. Martínez del Campo, *Chem. Eur. J.* **2009**, *15*, 2496; c) B. Alcaide, P. Almendros, T. Martínez del Campo, E. Soriano, J.L. Marco-Contelles, *Chem. Eur. J.* **2009**, *15*, 1901; d) B. Alcaide, P. Almendros, R. Carrascosa, M. C. Redondo, *Chem. Eur. J.* **2008**, *14*, 637; e) B. Alcaide, P. Almendros, T. Martínez del Campo, *Angew. Chem.* **2007**, *119*, 6804; *Angew. Chem. Int. Ed.* **2007**, *46*, 6684; f) B. Alcaide, P. Almendros, T. Martínez del Campo, *Angew. Chem.* **2006**, *118*, 4613; *Angew. Chem. Int. Ed.* **2006**, *45*, 4501.

[5] Allenynes **1a–d** were prepared from the corresponding α-allenols by treatment with propargyl bromide under phase-transfer conditions (see the Supporting Information for details). The starting α-allenols required for our study were prepared from the corresponding aldehydes as previously described: M. B. Isaac, T.-H. Chan, *J. Chem. Soc. Chem. Commun.* **1995**, 1003.

[6] a) C. Glaser, *Ber. Dtsch. Chem. Ges.* **1869**, *2*, 422; b) G. Eglinton, A. R. Galbraith, *Chem. Ind. (London)*, **1956**, 737; c) A. S. Hay, *J. Org. Chem.* **1962**, *27*, 3320.

[7] Attached-ring bis(heterocyclic)fused cyclobutenes **2** 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) I. Larrosa, P. Romea, F. Urpí, *Tetrahedron* **2008**, *64*, 2683; b) P. A. Clarke, S. Santos, *Eur. J. Org. Chem.* **2006**, 2045; c) D. J. Faulkner, *Nat. Prod. Rep.* **2000**, *17*, 7.

[8] B. Alcaide, P. Almendros, C. Aragoncillo, *Chem. Eur. J.* **2002**, *8*, 1719.

[9] B. Alcaide, P. Almendros, R. Carrascosa, R. Rodríuez-Acebes, *Eur. J. Org. Chem.* **2008**, 1575.

[10] Tricyclic β-lactam antibiotics which are generally referred to as trinems are a new class of synthetic antibacterial agents featuring good resistance to β-lactamases and dehydropeptidases; a) O. Kanno, I. Kawamoto, *Tetrahedron* **2000**, *56*, 5639; b) S. Hanessian, B. Reddy, *Tetrahedron* **1999**, *55*, 3427; c) "The Chemistry of Trinems": C. Ghiron, T. Rossi in *Targets in Heterocyclic Systems-Chemistry and Properties, Vol. 1* (Eds.: O. A. Attanasi, D. Spinelli), Societa Chimica Italiana, Rome, **1997**, pp. 161–186.

[11] For a report on the increased antibacterial activity of β-lactam heterodimers in comparison with their monomeric components, see: D. D. Long, J. B. Aggen, B. G. Christensen, J. K. Judice, S. S. Hegde, K. Kaniga, K. M. Krause, M. S. Linsell, E. J. Moran, J. L. Pace, *J. Antibiot.* **2008**, *61*, 595.

[12] The importance of cyclobutane containing compounds both as target molecules as well as useful building blocks for the construction of more complex structures, has been widely demonstrated. For a recent selected review, see: *The Chemistry of Cyclobutanes* (Eds.: Z. Rappoport, J. F. Liebman), Wiley-VCH, Weinheim, **2005**.

[13] Medium-sized rings represent some of the most difficult challenges for cyclization strategies; the combination of developing ring strain and the requirement to restrict rotations around 7–9 flexible bonds ensures unfavorable enthalpic and entropic contributions to ΔG. For reviews, see: a) C. Galli, L. Mandolini, *Eur. J. Org. Chem.* **2000**, 3117; b) G. Illuminati, L. Mandolini, *Acc. Chem. Res.* **1981**, *14*, 95.

[14] Dialkynylpalladium complexes of type **5** are transformed to diynes **7** via a reductive elimination, whereas copper(I) acetylides **6** are rapidly oxidized by the transfer of a single electron to copper(II). Decomposition of the resultant copper(II) acetylide and recombination of the free radicals would give the homocoupled products **7**.

[15] Under Pd-catalyzed conditions, it is necessary for the catalytic cycle that Pd^0 is reoxidized to Pd^{II}, making further reductive elimination possible; this is achieved by the addition of DIB which does not interfere with the course of the reaction.

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