ORGANIC LETTERS

2001
Vol. 3, No. 16
2607−2610

Synthesis of Bridged Medium-Sized Rings through the Intramolecular Pauson–Khand Reaction

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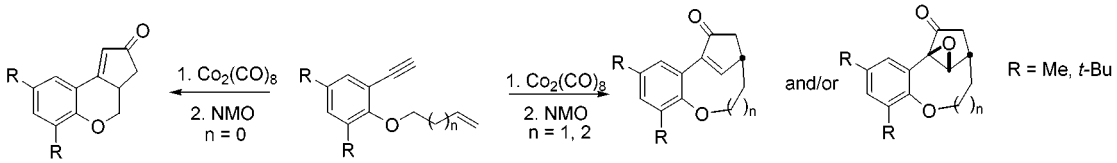
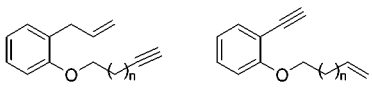
Received June 20, 2001

ABSTRACT



A series of aromatic enynes containing steric buttressing elements were prepared and evaluated in the NMO-mediated Pauson–Khand cyclization. *O*-Allyl systems led to the expected angularly fused products, whereas the *O*-butenyl and *O*-pentenyl derivatives afforded the unprecedented bridge systems.

The Pauson−Khand reaction (PKR) is a powerful method for the construction of cyclopentenones.[1] Over the past few years this transformation has been investigated extensively, resulting in the expansion of the scope of the reaction and the development of catalytic variants.[1] However, despite its obvious synthetic potential, until recently the intramolecular variant of this reaction has been largely restricted to the construction of bicyclo[3.3.0]octenones and bicyclo[4.3.0]-nonenones.[2,3] This limitation would seem to be extremely unfortunate given the large number of biologically active natural products that possess a medium-sized ring annulated to a cyclopentyl moiety, which in principle might be accessible in a direct fashion via an intramolecular PKR.[4] It is well-known that the construction of medium rings is more difficult than the formation of normal rings due to a combination of unfavorable entropic and enthalpic factors.[5] In the absence of a detailed understanding of the mechanism of the PKR, it appeared to us that the incorporation of structural features into the cyclization precursors that would reduce the entropic contribution to the free energy of activation might favor medium ring formation. The *gem*-dimethyl effect has already been shown to be effective in the PKR and other cyclizations by increasing the reactive rotamer population.[6] It was proposed that the construction of substrates such as **1** and **2** might serve a similar purpose (Figure 1). It was envisioned that the introduction of an



1 **2**

Figure 1. Conformationally restricted aryl enynes.

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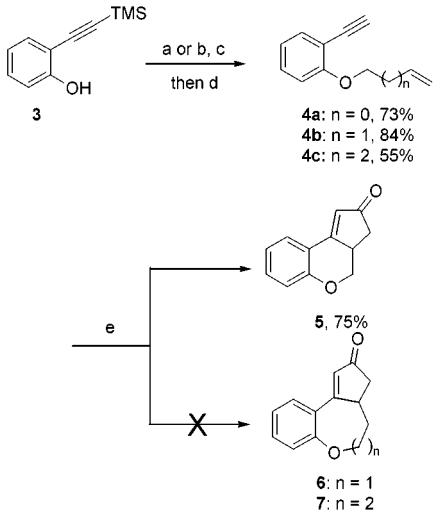
(1) For a recent review of this area, see: Brummond, K. M.; Kent, J. L. *Tetrahedron* **2000**, *56*, 3263.
(2) Krafft, M. E.; Fu, Z.; Bonaga, V. R. *Tetrahedron Lett.* **2001**, *42*, 1427.
(3) Cazes has reported the low yield synthesis of a bicyclo[5.3.0]decene from an allenyne. See: Ahmar, M.; Locatelli, C.; Colombier, D.; Cazes, B. *Tetrahedron Lett.* **1997**, *38*, 5281.

10.1021/ol016308s CCC: $20.00
Published on Web 07/10/2001

aromatic ring into the backbone of the enyne would reduce the conformational degrees of freedom of the side chains, thereby preorganizing the alkyne and alkene for cyclization. After an initial, largely unsuccessful, foray with substrates patterned after **1**,[7] our attention was drawn to the alternate series **2**.[8,9] This Letter details our initial findings in this latter substrate.

The cyclization precursors were readily prepared via alkylation of the TMS-protected 2-ethynylphenol **3**,[10] either directly with the alkyl bromide or through a Mitsunobu protocol (Scheme 1).[8] Desilylation then provided the requisite

Scheme 1[a]



[a] (a) K_2CO_3, acetone, allyl bromide; (b) Ph_3P, DEAD, 3-buten-1-ol, THF; (c) K_2CO_3, NaI, acetone, 5-bromo-1-pentene; (d) K_2CO_3, MeOH, THF; (e) $Co_2(CO)_8$, CH_2Cl_2 then NMO.

enynes **4a**−**c**.[8] After conversion to the corresponding $Co_2(CO)_6$ complexes, the enynes were treated with excess *N*-methylmorpholine oxide (NMO) to initiate the cyclization process. In the case of enyne **4a**, a smooth cyclization reaction was observed, providing the 6,6,5-tricyclic system **5** in 75% yield.[8] On the other hand, both enynes **4b** and **4c** failed to undergo cyclization. While this and other experiments confirmed that the aromatic ring was a suitable scaffold for PKR's, apparently the entropic issues were not addressed in the higher homologues.[8,9]

Some time ago, Sammes and co-workers demonstrated that the introduction of substituents *ortho* to conformationally flexible side chains in aromatic substrates had a beneficial effect on both the rates and yields of the [3 + 2] azide−alkene cycloadditions under study.[11] These "steric buttresses" decreased the conformationally accessible space, and hence the entropic change during the reaction was reduced. This strategy appeared to be a sound one, and therefore it was applied to the substrates in this study (Figure 2).[12]

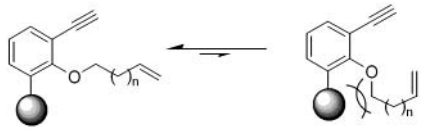


Figure 2. Steric buttressing in aryl enynes.

Initially it was decided to evaluate substrates that contained an *o*-*t*-Bu group as the buttressing element. For the sake of synthetic convenience, 2,4-di-*tert*-butylphenol was employed as starting material, since regiochemical complications could be avoided in the preparation of *o*-ethynylphenol **8**.[13] With this material in hand, the hydroxyl group was alkylated either with the alkyl halide or through a Mitsunobu reaction as before (Scheme 2). After desilylation, the enynes were converted into the corresponding $Co_2(CO)_6$ complex and then treated with NMO. The influence of the *t*-Bu group on these reactions was immediately apparent. In the case of enyne **10a**, it was converted into the expected enone **12a** in 70% yield. However, instead of requiring 8 h for complete consumption of starting material such as **4a**, the reaction of **10a** was complete after 30 min (after the addition of NMO was complete). In a similar fashion, the consumption of the higher homologues **10b** and **10c** was rapid, leading to the formation of new compounds. However, when the products were isolated, it was clear from the NMR data that although the products were cyclic and they possessed carbonyls, they were not the expected cycloadducts **13a** or **16a**.[14] In the case of the PKR of enyne **10b**, two new compounds were isolated in 18% and 36% yields. The determination of the identity of the major cycloadduct proved to be quite challenging as inter alia the mass spectrum revealed that the compound contained one more oxygen atom than expected. Fortunately, this compound provided crystals of suitable quality for analysis by X-ray crystallography. The results obtained from this determination were quite surprising (Figure 3). The

(4) For an attempt to prepare seven-membered rings through the intramolecular Pauson−Khand reaction, see: Mukai, C.; Sonobe, H.; Kim, J. S.; Hanoaka, M. *J. Org. Chem.* **2000**, *65*, 6654. See also Wender, P. A.; McDonald, F. E. *Tetrahedron Lett.* **1990**, *31*, 3691.

(5) (a) Petasis, N. A.; Patane, M. A. *Tetrahedron* **1992**, *48*, 5757. (b) Roxburgh, C. J. *Tetrahedron* **1993**, *49*, 10749.

(6) (a) Jung, M. E. *Synlett* **1999**, 843. (b) Jung, M. E. *Synlett* **1990**, 186.

(7) Seshadri, H. Ph.D. Dissertation, The University of Texas at Arlington, Arlington, TX, 2001.

(8) Lovely, C. J.; Seshadri, H. *Synth. Commun.* **2001**, *31*, xxxx. See also: Blanco-Urgoiti, J.; Casarrubios, L.; Domínguez, G.; Pérez-Castells, J. *Tetrahedron Lett.* **2001**, *42*, 3315.

(9) For studies relating to systems derived from *o*-vinylphenol, see: Pérez-Serrano, L.; Blanco-Urgoiti, J.; Casarrubios, L.; Domínguez, G.; Pérez-Castells, J. *J. Org. Chem.* **2000**, *65*, 3513.

(10) Arcadi, A.; Cacchi, S.; Del Rosario, M.; Fabrizi, G.; Marinelli, F. *J. Org. Chem.* **1996**, *61*, 9280.

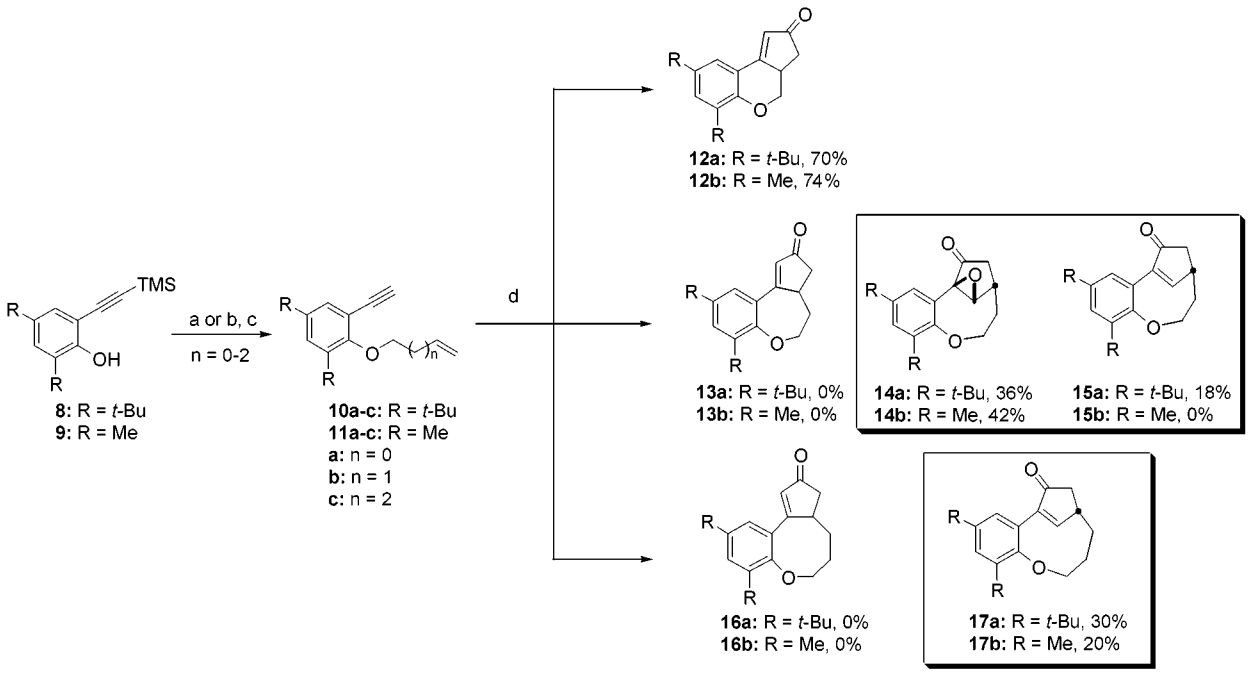
(11) Orlek, B. S.; Sammes, P. G.; Weller, D. J. *Tetrahedron* **1993**, *49*, 8179.

(12) For a review of this approach see Sammes, P. G.; Weller, D. J. *Synthesis* **1995**, 1205.

(13) The *o*-ethynylphenols were prepared by iodination of the corresponding phenol and then Sonogashira cross-coupling of the iodide with TMS-acetylene. See Supporting Information for details.

(14) The absence of a three-proton doublet quickly ruled out migration of the double bond to an internal position followed by cyclization to provide a methylcyclopentenone: see ref 4.

Scheme 2[a]



[a] (a) K_2CO_3, acetone, allyl bromide; (b) Ph_3P, DEAD, 3-buten-1-ol or 4-penten-1-ol, THF; (c) K_2CO_3, NaI, acetone, 5-bromo-1-pentene; (d) K_2CO_3, MeOH, THF; (e) $Co_2(CO)_8$, CH_2Cl_2 then NMO.

mystery of the additional oxygen became immediately clear: the product contained an epoxide moiety **14a**.[15] The greatest surprise however came in the form of the ring size and the mode of ring fusion. The X-ray structure revealed that instead of cyclizing to afford a seven-membered ring, i.e., **13a**, an eight-membered ring was formed. Furthermore, instead of the expected angular ring fusion, the eight- and five-membered rings were bridged. This is, to the best of our knowledge, the first example of the formation of this type of bridged ring system in the PKR.[16] This crystallography result suggested that the minor product was in fact enone **15a**.[17]

An equally unusual result was obtained from the cyclization of enyne **10c**. Again the spectroscopic data suggested a cyclic product was formed, but there were inconsistencies observed in the ^{1}H NMR spectrum with regard to the enone proton, cf. **15a**. The structure of the product was secured through X-ray analysis, and this showed again that a bridged system was formed (Figure 4). In this case, a nine-membered ring was formed bridged to a five-membered ring, **17a**. No epoxide was isolated from this cyclization reaction.

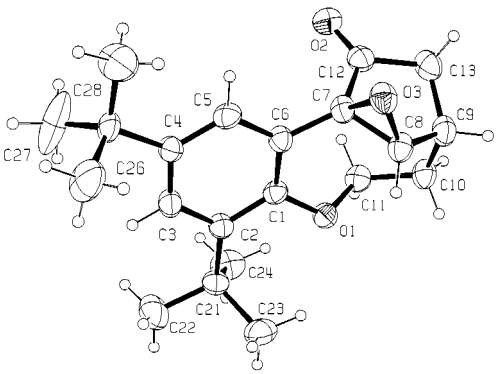


Figure 3. X-ray crystal structure of epoxyenone **14a**.

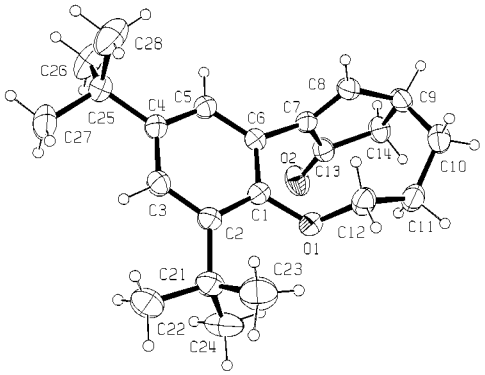


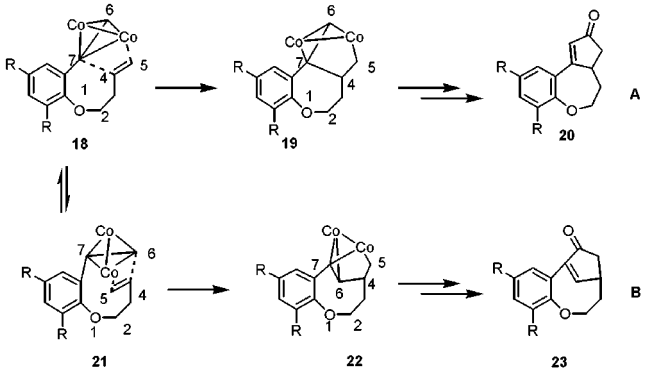
Figure 4. X-ray crystal structure of bridged enone **17a**.

Given that the *t*-Bu substituent facilitated this reaction, we wished to establish whether the steric bulk of this group was excessive. Therefore, substrates containing the smaller methyl group were prepared and evaluated. The necessary precursors were prepared in a largely analogous fashion to enynes **10a**−**c**, from the corresponding *o*-ethynylphenol **9**.[10]

With enynes **11a**−**c** in hand, they were converted into their cobalt complexes and then treated with NMO. In the case of enyne **11a**, the expected normal cyclization product **12b** was obtained in 74% yield. However, the rate of this cyclization was almost identical to that of the unsubstituted system **4a**. This did not appear to bode well for the higher homologues. However, we were pleased to find that both enynes **11b** and **11c** participated in the cyclization to again provide bridged products. In the case of **11b**, the only isolated product was the epoxide **14b**, which was obtained in 42% yield. **11c** provided the bridged enone **17b** in 20% yield.

The mode of cyclization observed in these substrates is highly unusual for the PKR. However these results can be rationalized in terms of the alkene rotamer that undergoes insertion; this is illustrated in Scheme 3 for the cycloaddition

Scheme 3[a]



[a] CO ligands are omitted for clarity.

of the butenyl substrates. The generally accepted mechanistic hypothesis for the formation of the "normal" enone involves the orientation of the alkene terminus away from the cobalt alkyne complex (**18**, Scheme 3A). The alkene inserts into the Co−C7 bond, and new bonds between Co−C5 and C7−C4 are formed, furnishing the seven-membered ring containing metallocycle **19**. Subsequent CO insertion followed by loss of the complexed cobalt cluster furnishes the [5.3.0] bicyclic system **20**. To account for the observed outcome, presumably the alkene orients itself toward the cobalt alkyne complex (**21**, Scheme 3B). The alkene inserts into the Co−C6 bond, and new bonds are formed between Co−C5 and C6−C4, furnishing the eight-membered ring containing metallocycle **22**. This is followed by CO insertion and loss of the cobalt complex, affording the bridged compound **23**.[18]

The driving force behind the unprecedented regiochemistry observed in this cycloaddition is not clear at this point. The buttressing groups seemingly play a crucial role in decreasing the entropic barrier to cycloaddition by bringing the reacting partners closer to each other. They may also limit the space for accommodating the linker between the phenol oxygen and alkene, which then forces insertion through the abnormal rotamer **21**. The insertion of the carbonyl moiety at the internal carbon of the alkyne is unusual in the intramolecular PKR. However, this orientation is normal in the intermolecular variant and so the examples reported in this paper may simply follow typical sterically driven regiochemistry that can be accommodated as a result of the extended tether length. Electronic effects cannot be ruled out however since the phenolic oxygen atom can interact with the alkyne group in these substrates. The net effect of this interaction is to polarize the alkyne, which in turn may influence the regioselectivity of the insertion.[19,20]

In summary, the work reported herein describes the use of steric buttressing to facilitate the formation of medium-sized rings via the PKR. Furthermore, these cyclizations occur to form bridged rings as a result of unusual regioselectivity during alkene insertion. Currently we are investigating the scope of this interesting variant of the PKR and the factors that control this unusual mode of insertion. We will report on this and other aspects of this work in due course.

Acknowledgment. This work was supported by the Robert A. Welch Foundation (Grant Y-1362) and The University of Texas at Arlington (Start-up Funds). The NSF (CHE-9601771) is thanked for partial funding of the purchase of a 500 MHz NMR spectrometer (UTA). Arkansas Science and Technology Authority is gratefully acknowledged for support of the X-ray facility (UA). We would like to thank Prof. Ken Turnbull and Dr. Tony Hudgens (Department of Chemistry and Biochemistry, The University of Arkansas) for providing the experimental protocol for the preparation of 2-iodo-4,6-dimethylphenol.

Supporting Information Available: Experimental procedures and characterization data for all compounds described in this paper. Details of the X-ray analysis of compounds **14a** and **17a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) At this point we are operating under the assumption that the epoxidation of the strained double bond is NMO promoted. However, control experiments indicate that this does not take place by direct reaction of the enone with NMO. For a related observation, see: Muto, R.; Ogasawara, K. *Tetrahedron Lett.* **2001**, *42*, 4143 and references therein.

(16) Krafft has observed bridged products as a result of CO insertion at the internal position of *both* the alkyne and the alkene; see ref 2. See also: Forsyth, G. S.; Kerr, W. J.; Ladduwahetty, T. In *Organometallics in Organic Synthesis*; Bateson, J. H., Mitchell, M. B., Eds.; Academic Press: London, 1994; p 239. We are grateful to Prof. Marie Krafft for bringing this reference to our attention.

(17) Particularly supportive of this assignment is the downfield signal for the β-enone proton (δ = 8.25 vs 6.30−6.47); see ref 8.

(18) Presumably, with the allyl-containing substrates it is geometrically difficult to adopt a conformation related to **21** to produce a bridged adduct.

(19) Krafft, M. E.; Romero, R. H.; Scott, I. L. *J. Org. Chem.* **1992**, *57*, 5277.

(20) Robert, F.; Milet, A.; Gimbert, Y.; Konya, D.; Greene, A. E. *J. Am. Chem. Soc.* **2001**, *123*, 5396.