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Synthesis of 3,4-substituted cyclopentenones via an intramolecular Pauson–Khand reaction of N–O linked enynes

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Abstract

Differentially 3,4-disubstituted cyclopentenones are constructed via a novel Pauson–Khand cyclization/cleavage strategy of N–O linked enynes. © 2000 Published by Elsevier Science Ltd.

The Pauson–Khand cycloaddition has recently emerged as a premier method for the construction of cyclopentenones and cyclopentane containing natural products.[1] Intermolecular examples of this formal [2+2+1] cycloaddition generally provide a mixture of regioisomers.[2] Intramolecular reactions generally overcome this regioselectivity issue, however, not all synthetic targets are amenable to an intramolecular approach.[3] In these instances, a cleavable and sometimes 'traceless' tether can provide an intramolecular cyclization that can be subsequently cleaved. In an attempt to apply this approach to a general methodology for natural product synthesis, we utilized a cleavable tether strategy that provides additional functionality for further synthetic modification.

The use of cleavable tethers was first applied to the radical-mediated synthesis of *C*-glycosides[4] (silyloxy tether) and palladium-catalyzed cycloadditions[5] (ester tether). Since these first examples, both tethered and cleavable functional groups have been recognized for their entropic benefits and have become more widespread in synthetic endeavors.[6] Many natural products contain cyclopentane rings with adjacent heteroatom functionality. Examples include palau'amine[7,8] styloguanidines,[9] axinellamines,[10] and agelastatin.[11] Utilization of a cyclization/cleavage strategy for the construction of a five-membered ring **2** through an intramolecular Pauson–Khand reaction with a novel tethered enyne **3** was envisioned (Scheme 1). This nitrogen–oxygen linkage, in addition to controlling the regiochemistry of the transformation, can allow for cleavage to give the monocyclic compound **1** that contains discriminant functionalities, in this case an amino and hydroxyl group.

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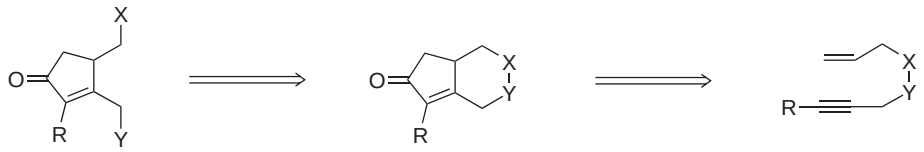
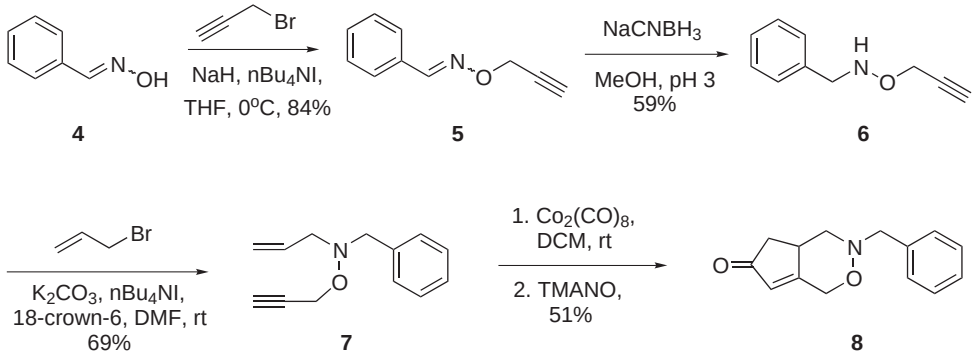
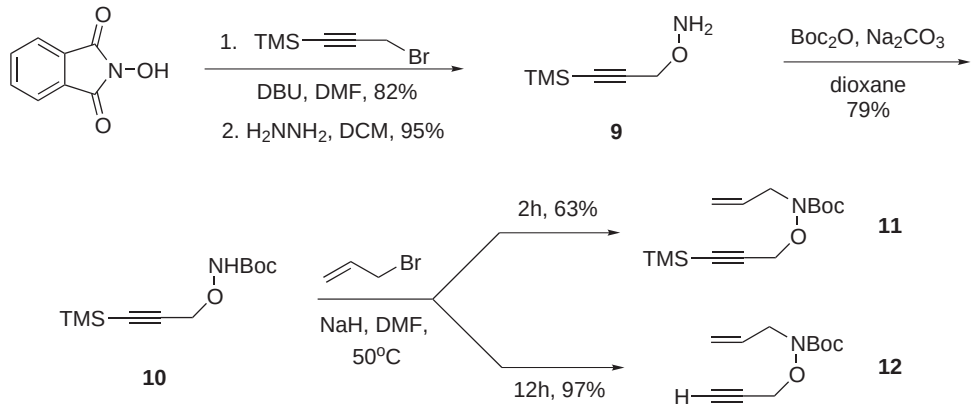


Scheme 1. Retrosynthesis of the N–O linked cyclization/cleavage strategy

Construction of the benzyl-protected N–O linked enyne **7** was initiated from benzaldehyde oxime **4**. Treatment of **4** with NaH and propargyl bromide at 0°C furnished the oxime ether **5** in 84% yield (Scheme 2). Reductive amination under acidic conditions, followed by allylation of the hydroxylamine **6**, furnished the Pauson–Khand precursor **7** in moderate yield. Cycloaddition of **7** mediated by dicobalt octacarbonyl and trimethylamine *N*-oxide furnished the Pauson–Khand product **8** in 51% yield.[12] This transformation validated the feasibility of an intramolecular Pauson–Khand reaction using a novel N–O linkage.



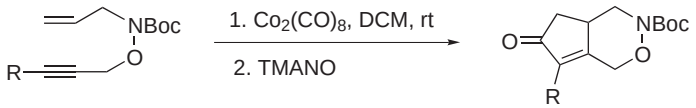
Scheme 2. Synthesis of benzyl protected enyne **7** and cyclopentenone **8**



Scheme 3. Synthesis of *t*-butoxycarbonyl-protected enynes **11** and **12**

An analogous *t*-butoxycarbonyl-protected enyne would further expand the scope of this N–O cleavable tether approach. Alkylation of *N*-hydroxy phthalimide with TMS–propargyl bromide, followed by treatment with hydrazine gave TMS–propargyl hydroxylamine **9** in 78% yield over two steps. Hydroxylamine **9** could be protected as its Boc-carbamate **10** by treatment with Boc-anhydride in the presence of Na_2CO_3 (79%). Further alkylation with allyl bromide in the presence of NaH in DMF at 50°C for 2 h led to the formation of **11** in 63% yield, while allowing the reaction to proceed for 12 h yielded **12** in 97% yield (Scheme 3).

Pauson–Khand cycloadditions of **11** and **12** to cyclopentenones **13** and **14**[13] (Scheme 4) were accomplished under identical conditions as those for the benzyl-protected enyne **7**. It is interesting to note that comparable yields were observed for the cycloaddition of substrates **7** and **12** (51 and 59%, respectively), while the silyl-protected alkyne substrate **11** gave the highest yield overall (76%).

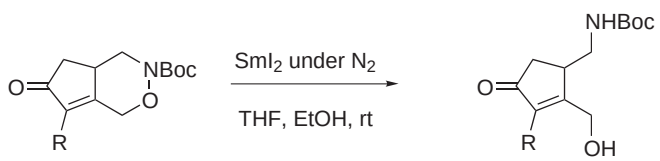


11: R = TMS
12: R = H

13: R = TMS, 76%
14: R = H, 59%

Scheme 4. Pauson–Khand reaction of *t*-butoxycarbonyl-protected enynes **11** and **12**

General utility of this methodology will require mild and efficient cleavage of the N–O bond. Treatment of both **13** and **14** with activated Zn/AcOH, nickel boride (NiB_2), and hydrogenation with various catalysts afforded none of the desired products (**15** and **16**). However, treatment with SmI_2 in THF/EtOH facilitated smooth cleavage of the backbone to give differentially 3,4-substituted cyclopentenones **15** and **16** in 83% and 76% yields, respectively (Scheme 5). These and other cyclopentenones could prove to be valuable intermediates in the synthesis of complex natural products.



13: R = TMS
14: R = H

15: R = TMS, 83%
16: R = H, 76%

Scheme 5. Cleavage of N–O tether of cyclopentenones **13** and **14**

In conclusion, we have designed a new N–O tethered enyne approach, compatible with existing Pauson–Khand reaction conditions, to provide novel cyclopentenones. Selective cleavage of the N–O backbone produces differentially 3,4-substituted cyclopentenones. Further work expanding the application and scope of this methodology is currently underway and will be reported shortly.

Acknowledgements

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12. **General Procedure**: 1.2 equivalents of $Co_2(CO)_8$ are added to a stirred solution of 1.0 equivalent of enyne **3** in 30 mL of anhydrous dichloromethane. After stirring for 1 h at rt and verification of the reddish-brown cobalt–alkyne complex by TLC, 8.4 equivalents of anhydrous trimethylamine *N*-oxide are added in portions to the dark solution. We have found that cooling the solution below 0°C prior to addition of the *N*-oxide helps to control the exothermic character of the reaction and facilitates greater yields of product. Further stirring (2 h) followed by filtration of the crude mixture through a silica gel plug with ethyl acetate and column chromatography on SiO_2 (Hex/EtOAc, 4:1 gradient to 1:1) furnishes UV active cyclopentenone **2**.
13. **Characterization of *tert*-butyl 6-oxo-4,4a,5,6-tetrahydro-cyclopenta[*d*][1,2]-oxazine-3(1*H*)-carboxylate 14.** R_f 0.26 (1:1, Hex/EtOAc); IR (neat) 2978, 2932, 1715, 1634, 1443, 1393, 1368, 1320, 1245, 1159, 1089, 855 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.06 (s, 1H), 4.73 (d, 1H, $J=13.3$ Hz), 4.66 (d, 1H, $J=13.3$ Hz), 4.41 (m, 1H), 3.11 (m, 1H), 3.07 (bs, 1H), 2.55 (m, 1H), 2.06 (m, 1H), 1.51 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 206.0, 171.9, 154.3, 128.8, 82.5, 70.1, 52.9, 38.2, 37.8, 28.2; HRMS (FAB) calcd for $C_{12}H_{17}NO_4$ 239.1158, found 239.1156.