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Synthesis of Fused Tricyclic β-Lactams by the Pauson-Khand Cyclization of Enyne-2-azetidinones

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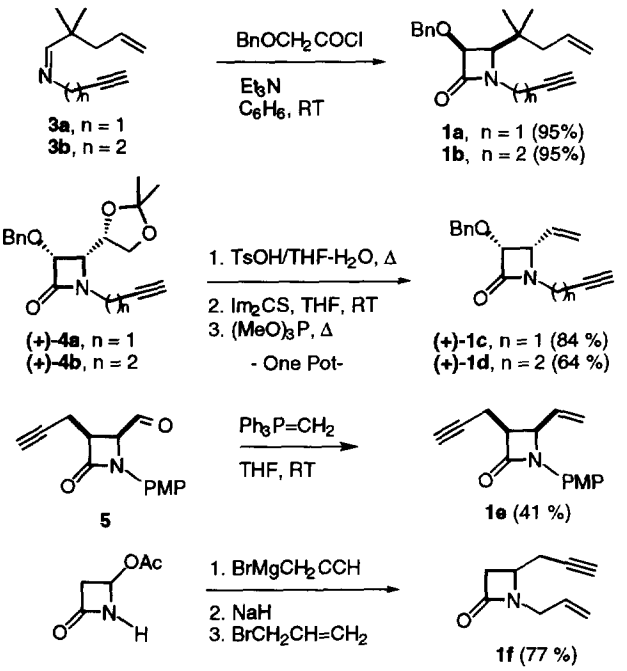
Abstract: Reaction of enyne-β-lactams **1** with $Co_2(CO)_8$ followed by in situ thermal or TMANO decomposition of the formed alkyne-$Co_2(CO)_6$ complexes gives tricyclic β-lactams **2** as single stereoisomers, in good to excellent yields. These are the first examples of an intramolecular Pauson-Khand reaction on an enyne system tethered to a four membered ring.

The intramolecular cyclization of enynes mediated by $Co_2(CO)_8$ (the Pauson-Khand, P-K, reaction) ranks among the best methods to increase molecular complexity in a single synthetic step.[1] Recently, a new family of β-lactam antibiotics named tribactams has been reported as superlative antibacterial agents.[2] Their impressive biological activity and increased stability towards enzymatic degradation may make tribactams the antibiotics of choice for the beginning of the 21st century. As a result policyclic β-lactams have become interesting targets for synthesis. Synthetic approaches to tribactams[3] and policyclic 2-azetidinones[4] rest, in general, in the stepwise building of the final system from monocyclic, easily available, β-lactams. The simultaneous building of two of the three rings on a performed monocyclic 2-azetidinone would be a conceptually different, more straightforward approach to these compounds. Following this idea the Pauson-Khand cyclization of enyne-2-azetidinones, **1**, to yield tricyclic β-lactams, **2**, is reported here.

Substrates for cyclization, enyne-2-azetidinones, **1**, were prepared using standard methodology (Scheme 1). Racemic compounds **1a-b** were obtained in almost quantitative yields, as single *cis*-diastereomers, by cyclization of benzyloxyacetyl chloride and imines **3a-b** in the presence of Et_3N. Optically pure 2-azetidinones **4a-b**[5] were transformed into 4-vinyl-β-lactams **1c-d** by successive treatment with *p*-toluenesulfonic acid, 1,1-thiocarbonyldiimidazol[6] and, finally, reaction with $(MeO)_3P$.[7] 4-Vinyl-2-azetidinone **1e** was prepared in racemic form by standard Wittig olefination of *cis*-2-azetidinone aldehyde **5**.[8] Finally, reaction of commercial 4-acetoxy-2-azetidinone with propargylmagnesium bromide,[9] followed by *N*-alkylation with allyl bromide gave the last cyclization substrate, 2-azetidinone **1f**. These approaches illustrate the simplicity with which different enyne-2-azetidinones are available for cyclization.

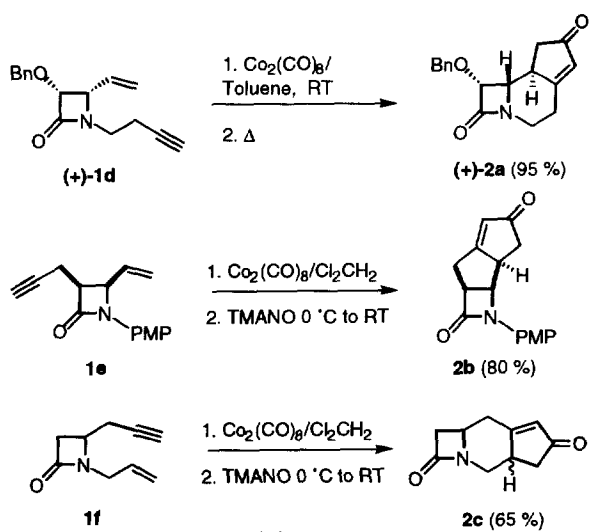
Treatment of compounds **1** with $Co_2(CO)_8$ formed the alkyne-$Co_2(CO)_6$ complexes in quantitative yield without novelty.[10] The behaviour of these complexes towards P-K cyclization strongly depends on the structure of the 2-azetidinone **1** and the size of the ring to be formed. Thus, alkyne-$Co_2(CO)_6$ complexes derived from **1a** and **1b** gave complex reaction mixtures in the presence of trimethylamine *N*-oxide (TMANO).[11] From these mixtures the corresponding 2-azetidinones with the former triple bond reduced

to a double bond,[12] were isolated in low yields. Extensive decomposition to a plethora of unindentified compounds was obtained also from the alkyne-$Co_2(CO)_6$ complex derived from **1c**. The ^{1}H-NMR spectra of the crude mixtures from these reactions show, in some cases, the presence of *NH*-2-azetidinones which could not be isolated. Thermal decomposition of complexes derived from 2-azetidinones **1a-c** (boiling benzene or toluene) as well as the use of other cyclization promotors such as *N*-methylmorfoline-*N*-oxide,[13] and wet silica-gel,[14] gave analogous results. The presence of *NH*-2-azetidinones in the reaction mixtures may be explained through a Nicholas-type reaction[15] as we previously reported.[16] Clearly neither seven[17] or eigth membered ring nor propargyl groups attached to the lactam nitrogen are compatible with our approach to tricyclic β-lactams.



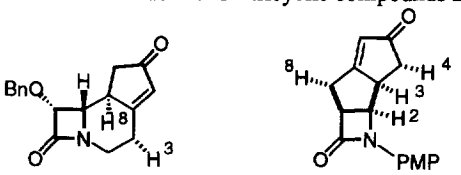
Scheme 1

A totally different result was obtained with the alkyne-$Co_2(CO)_6$ complexes derived from 2-azetidinones **1d-f**. Treatment with TMNAO gave the desired tricyclic compounds **2a-c**, respectively.[18] Compounds **2b** and **2c** were obtained in almost quantitative yield after filtration of the metal residue through Celite. Better yields of tricycle **2a** were obtained when thermal decomposition (boiling toluene) was used instead of TMNAO (Scheme 2). A single diastereomer of the final product was produced in all cases. Cyclization of the complex derived from enantiomerically pure 2-azetidinone **1d** gave a single enantiomer of the tricyclic final product, **2a**. Analytically pure compounds were obtained by simple crystallization of the reaction crudes. The stereoselectivity of these reactions is notable, specially in the formation of compound **2c** with the director chiral center two bonds away from the reactive center.[19]



Scheme 2

The structure of tricyclic compounds **2** was assigned from mono- and bidimensional NMR experiments. Once the unambiguous assignment of the methyne groups in compounds **2a-c** by ^{1}H-^{13}C heteronuclear correlation (HETCOR) was made, the relative stereochemistry of compounds **2a-b** could be elucidated from NOE experiments, as depicted in the Figure 1. However, the NOE experiments for **2c** were not conclusive and the stereochemistry of the newly formed chiral center remains uncertain.



2a H3-H8 (8%)

2b H2-H3 (10 %)
H3-H4 (5 %)
H2-H8 (4.5 %)

Figure 1. NOE increments on compounds **2a-b**

The results above show that the P-K cyclization is viable to prepare different types of fused tricyclic systems simply by switching the positions of the reactive enyne system. Limitations to this approach are the size of the central ring which should be six or smaller and the exclusion of propargyl groups attached to the lactam nitrogen.[17] The ability to obtain compounds with different ring conectivities and the total stereoselectivity observed in these reactions surpass other approaches to policyclic 2-azetidinones which have been developed with an specific ring system as target.[3,4]

In conclusion, the approach to tricyclic β-lactams reported in here represents a straight and stereoselective entry to this class of emerging potentially antibacterial compounds. Furthermore, to the best of our knowledge, these are the first examples of a Pauson-Khand reaction on an enyne system tethered to a four membered ring. Efforts to develop this chemistry to prepare more sophisticated policyclic β-lactams are now in progress.

Acknowledgments. Support for this work under grant PB93-0442 (DGYCIT, Spain) is acknowledged. C. Polanco thanks the UCM for a pre-doctoral grant.

References and Notes

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5. Enantiomerically pure 2-azetidinones **4a-b** are obtained from the corresponding protected *D*-gliceraldehyde acetonide imines, **3c-d**, through Staüdinger reaction with benzyloxyacetyl chloride as single *cis*-enantiomers. The stereochemical outcome of this type of β-lactams has been determined both experimental and theoretically. For the experimental approach see: (a) Hubschwerelen, C.; Schmid, G. *Helv. Chim. Acta* **1983**, *66*, 2206. (b) Welch, J. T.; Araki, K.; Kawecki, R.; Wichtowski, J. A. *J. Org. Chem.* **1993**, *58*, 2454-2462. (c) Wagle, D. R.; Garai, C.; Chiang, J.; Monteleone, M. G.; Kurys, B. E.; Strohmeyer, T. W.; Hedge, V. R.; Manhas, M. S.; Bose, A. K. *J. Org. Chem.* **1988**, *53*, 4227-4236, and

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17. Strictly speaking, the possibility to obtain seven membered rings is not totally discarded since a propargyl group attached to the lactam nitrogen is present in compound **1a.**
18. A representative experimental procedure for the preparation of compound **2b** follows: Solid $Co_2(CO)_8$ (0.21 g, 0.6 mmol) was added to a solution of 2-azetidinone **1e** (0.12 g, 0.5 mmol) in anhydrous CH_2Cl_2 (7 mL) under argon. The dark solution obtained was stirred at room temperature until complete complex formation as judged by TLC (ca 1 h) The resulting solution of $Co_2(CO)_6$-alkyne complex was cooled to 0 °C and solid anhydrous TMANO (0.04 g, 0.5 mmol) was added. The reaction flask was open to the air and was warmed to room temperature by immediate removal of the ice bath. After 30 m, the reaction was again cooled to 0 °C, and 0.04 g (0.5 mmol) of solid anhydrous TMANO was added, and the solution was warmed again to room temperature by immediate removal of the ice bath. This sequence was repeated until a total of 3 mmol (0.24 g) of TMANO anh. was added. After that the solution was stirred for 1h at room temperature. During this period a purple precipitate was formed. TLC analysis indicated the complete disappearance of the starting material and the formation of a more polar, UV active spot. The crude mixture was diluted with EtOAc (20 mL) and filtrated through a short path of Celite. The solvent was removed under vacuum and a colorless solid was obtained. Crystallization (EtOAc/hexane) yields 0.11 g (80%) of compound **2b** as colorless crystalline solid. Mp 159-160 °C.
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