Hexacarbonyl Dicobalt Complexed *N*-Prop-2-ynyl-2-azetidinones: a New Entry to *N*-Unsubstituted-β-Lactams through a Nicholas-type Reaction

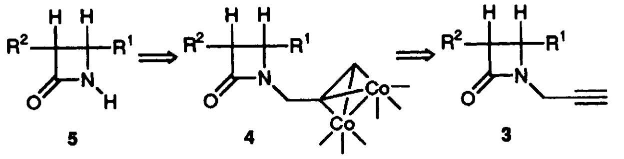
Benito Alcaide,* Javier Pérez-Castells, Belén Sánchez-Vigo, Miguel A. Sierra*

Dpto. de Química Orgánica I, Facultad de Química, Universidad Complutense, 28040-Madrid, Spain

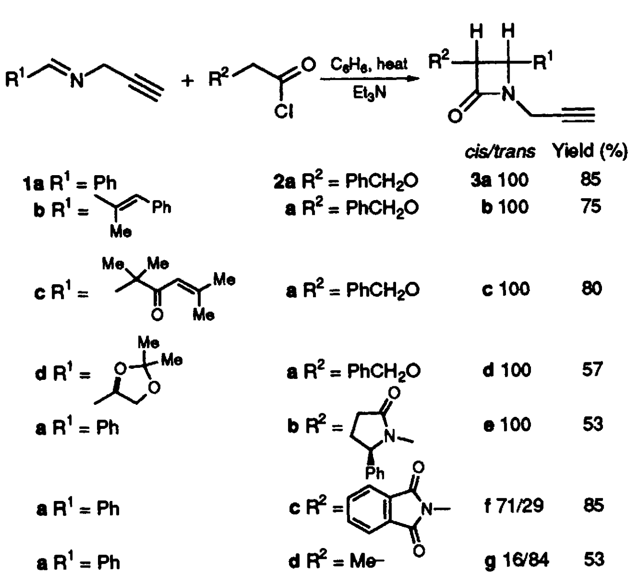
Sequential one-pot treatment of easily obtained *N*-prop-2-ynyl-2-azetidinones with $Co_2(CO)_8$ and DMSO–H_2O gives under mild conditions *N*-unsubstituted-β-lactams in good yields and with total retention of stereochemistry.

N-Unsubstituted-2-azetidinones play an essential role as key intermediates in the synthesis of many biologically active antibiotics.[1] The oxidative cleavage by cerium(IV) ammonium nitrate (CAN)[2] of an activated aromatic moiety attached to the lactam nitrogen is the most widely used method to obtain these compounds.[3] However, this method has shortcomings, especially with labile compounds or when incompatible functionalities are present. In this context, we devised an approach to these important compounds under neutral conditions (Scheme 1). The key step is a Nicholas-type[4] reaction of $Co_2(CO)_6$-*N*-prop-2-ynyl-β-lactam complexes and nucleophiles.

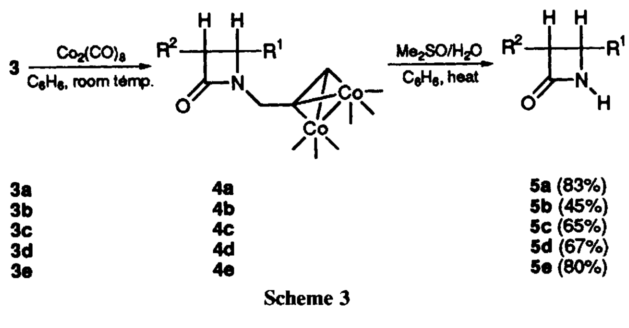
To test the feasibility of this approach, a number of *N*-prop-2-ynyl-β-lactams **3a–g** were prepared (in 53–90% yields) by the reaction of *N*-prop-2-ynyl imines **1a–d**† with different acid chlorides in the presence of Et_3N‡ (Scheme 2). Thus, a series of *N*-prop-2-ynyl-2-azetidinones possessing versatile groups at C-3 and C-4 were obtained. Building of azetidinones **3** proceeded with total *cis*-stereoselectivity except for compound **3g**, in good agreement with the accepted mechanism for the Staüdinger reaction.[5] Chiral β-lactams **3d–e** were obtained as single diastereoisomers.§



Scheme 1



Scheme 2



Scheme 3

Complexes **4** are formed in essentially quantitative yields by treating 2-azetidinones **3** with $Co_2(CO)_8$ in benzene at room temp. These complexes react *in situ* with DMSO–H_2O, in boiling benzene, to form *N*-unprotected-2-azetidinones **5** in good yields¶ (Scheme 3). The stereochemistry of the starting compound **3** is preserved through the deprotection process. Furthermore, the process is compatible with different functionalities, such as double bonds, carbonyl and ketal groups which are specially sensitive to the standard synthetic routes towards NH-2-azetidinones.[2,3] Owing to the smooth and neutral conditions employed, this method appears to be compatible with labile functional groups.

The mechanistic pathways involved in the reaction above are currently under investigation. The process is likely to occur through a variant of the well known Nicholas reaction.[4] However, formation of key intermediates in the Nicholas reaction, namely (propynyl)$Co_2(CO)_6^+$ complexes (isolated or generated *in situ*), requires protic or Lewis acids.[6] This is the first example of a Nicholas-type reaction without acid catalysis.|| Furthermore, in this process an amide nitrogen is displaced by nucleophiles, which is quite unusual in this class of reactions.

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Footnotes

† Imines **1a–d** (70–90% yields) were obtained in analytically pure form by condensation of equimolar amounts of the corresponding aldehyde and commercial prop-2-ynyl amine in the presence of $MgSO_4$.

‡ A solution of acid chloride **2** (1.5 mmol) in anhydrous benzene (5 ml) was added dropwise *via* syringe to a boiling solution of imine **1** (1 mmol) and Et_3N (3 mmol) in benzene (5 ml) under argon. The mixture was refluxed until complete reaction (TLC). Then, the reaction mixture was diluted with CH_2Cl_2 (20 ml) and successively washed with aqueous $NaHCO_3$ (saturated solution, 2 × 10 ml) and water (2 × 10 ml), and dried ($MgSO_4$). After filtration and evaporation of the solvent under reduced pressure, residues were purified by crystallisation (hexane–EtOAc) or flash chromatography (hexane–EtOAc) to yield analytically pure **3**.

§ All new compounds exhibited satisfactory spectroscopic (^1H and ^{13}C NMR, IR) and analytical (combustion) data. The ratio of *cis–trans* isomers was determined by integration of well-resolved signals in the ^1H NMR (300 MHz) spectra of the crude reaction mixtures.

¶ $Co_2(CO)_8$ (1.15 mmol) was added to a solution of compound **3** (1 mmol) in anhydrous benzene (20 ml), and the resulting solution was stirred under argon at room temp. until complete disappearance of the starting β-lactam. Water (3 mmol) and Me_2SO (3 mmol) were added, and the resulting solution was refluxed until complete consumption of complex **4** (TLC). The solvent was evaporated *in vacuo*, and the residue was chromatographed (silica gel, hexane–EtOAc) to yield compounds **5** in analytically pure form.

|| Yields of compounds **5** are similar to those obtained under standard conditions when water is substituted by other nucleophiles such as benzylic alcohol.

References

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