C-Quaternary Alkynyl Glycinols via the Ritter Reaction of Cobalt Complexed Alkynyl Glycols

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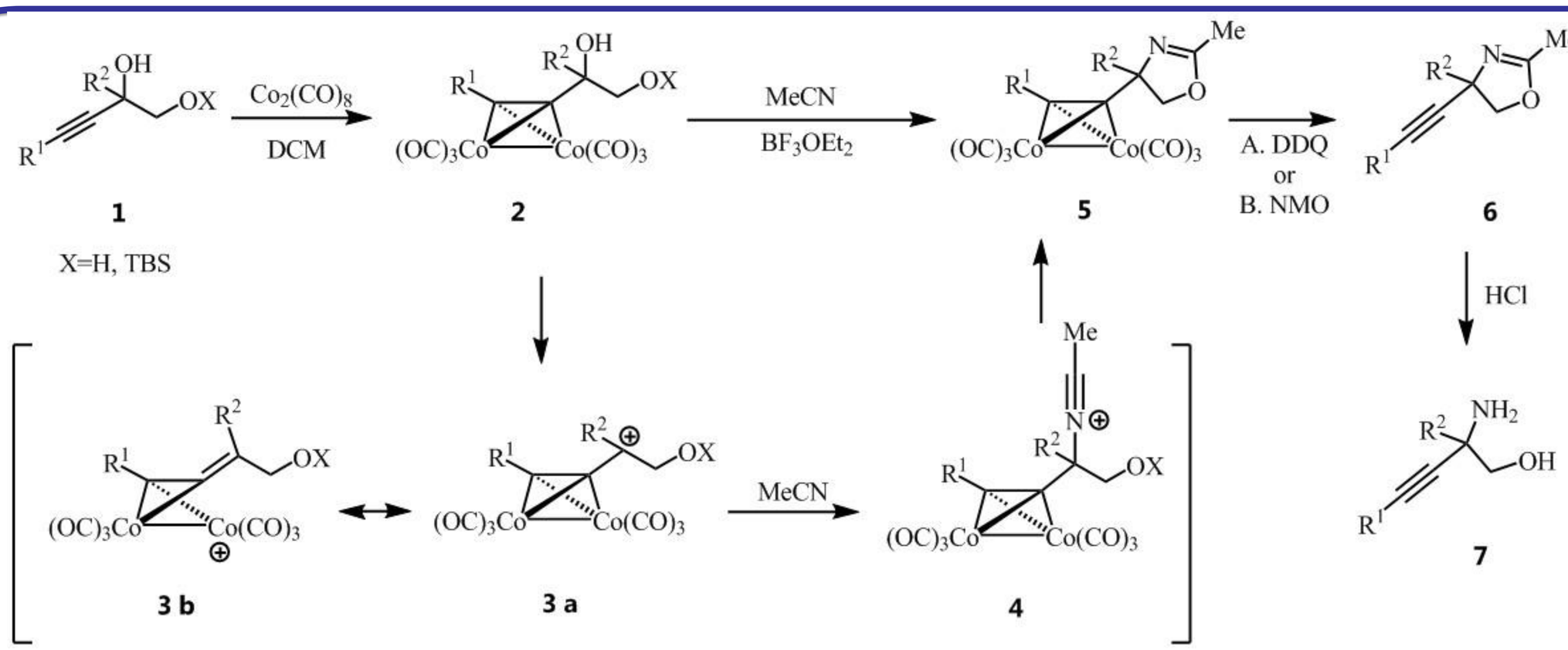
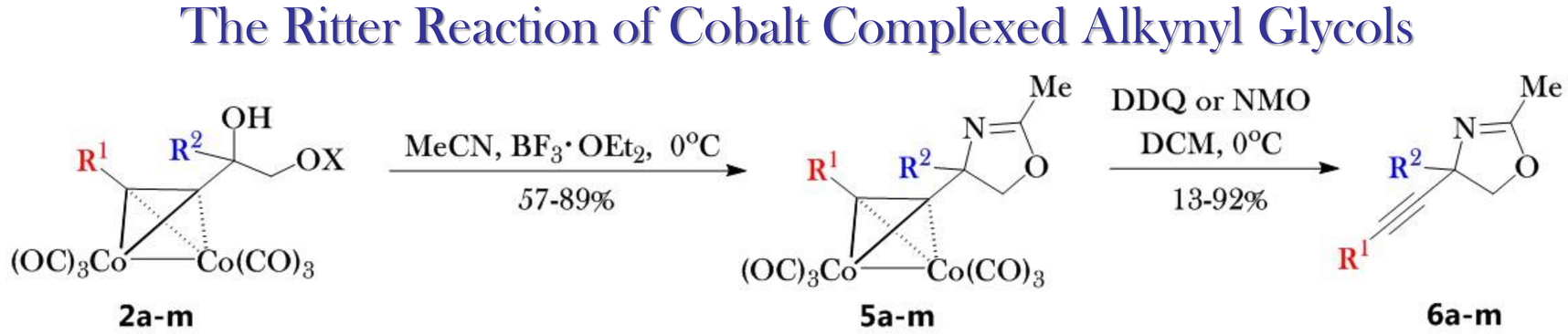


C-Quaternary alkynyl glycinols **7** are versatile building blocks for the construction of complex biologically active molecules. The Ritter reaction of nitriles with diols provides an efficient way to synthesize oxazolines which are hydrolyzed towards the corresponding glycols. It is important that the substrates for the Ritter reaction should have a group which stabilizes the intermediate carbocation. Complexation of dicobalt hexacarbonyl to alkyne signifacally stabilize carbocation at the α-position of the alkyne **3a** by delocalization of positive charge into $Co_2(CO)_6$ (mesomeric structure **3b**). It was observed that the cyclization reaction also proceeds with TBS protected alcohols **2** (X=TBS).

The Ritter Reaction of Cobalt Complexed Alkynyl Glycols



R^1= Me, Pent, TMS, ^{t}Bu, Ph, CH_2OBn, 3-ClPh, 4-MeOPh
R^2= H, Me, CH_2OH, CH_2OTBS

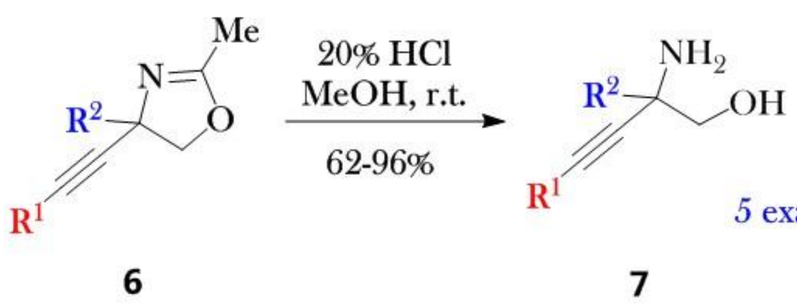
Aryl, alkyl and TMS substituted cobalt carbonyl complexed propargylic alcohols are good substrates for Ritter reaction. Substrates with phenyl substituent in R^2 position proved to be unreactive as they stabilize the formed carbocation. The cyclization could proceed even with substrates bearing TBS protected alcohol. Use of $BF_3{\cdot}Et_2O$ instead of classic Ritter conditions (H_2SO_4, AcOH), was preferable giving higher yields in most of the substrates. Lewis acid for Ritter reaction of diols with acetonitrile can be further investigated.

Cleavage of Cobalt Complex

The incompatibility of the known Co alkyne complex cleavage methods with the reactivity of oxazoline **6** led to the development of a novel method for the cleavage of Co complex ***5*** with DDQ. This, in most cases, gave better results in comparison to the commonly used reagents (CAN, EDA, NMO, TMAO). In turn, NMO was the reagent of choice for the de-complexation of Co-complexes derived from triols (R^2=CH_2OH, X=TBS), avoiding the oxidation of the free hydroxyl group from DDQ.

Synthesis of Glycinols

Selected oxazolines **(6d,g,h,l,m)** were transformed to amino alcohols **7** by using acidic hydrolysis in mild conditions (20% HCl, MeOH, r.t.). The hydrolysis proceed with good yields of product **7d,g,h,l,m** formation which were purified by the trituration with EtOAc.



R^1= Me, Pent, Ph, CH_2OBn
R^2= Me, CH_2OH

Summary

Ritter reaction of diols or triols with acetonitrile gave access to oxazolines in good yields and substrate scope. $BF_3{\cdot}Et_2O$ was the Lewis acid of choice and the cyclization took place even with TBS protected alcohols. The Ritter reaction was promoted by carbocation stabilization from the $Co_2(CO)_6$ complex formed. A novel method with DDQ was developed for the cleavage of the Co-complex, giving higher yields compared to commonly used reagents. NMO was the reagent of choice for the cleavage of the Co-complex in substrates derived from triols. Finally selected oxazolines were transformed to corresponding glycinols in mild conditions. DOI: 10.1039/c7ra03965d

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