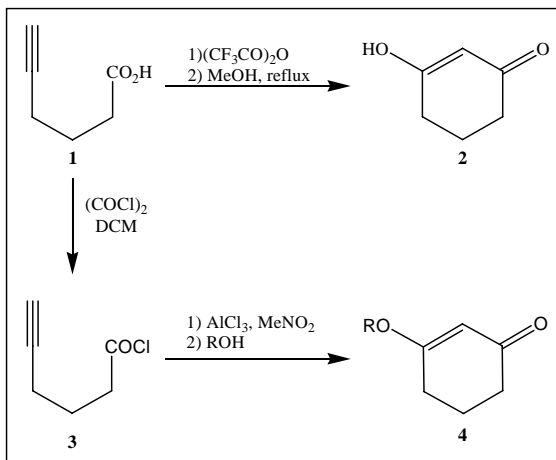


Methodology Development: Alkynoic Acid Cyclization

An important chemical research area is the development of new reactions. Outlined here is the development of the tethered alkynoic acid cyclization. This work is based on the reported cyclization of 5-hexynoic acid **1** to 1,3-cyclohexadione **2**.¹ This process has been employed to make acyclic 1,3-diones,²⁻⁴ but only the Ferrier and Tedder account¹ shows the formation of cyclic 1,3-diones. The goal of this project is to develop a useful transformation for the preparation of a variety of cyclic 1,3-diketones and their derivatives.



Specific aims:

1. Optimize reaction conditions of the 5-hexynoic acid system to raise the yield from the reported 25% to a synthetically useful level. We have found that conversion of the acid to the corresponding acyl chloride followed by treatment with AlCl₃ has led to formation of the related enoether **4**. These results are consistent with those reported by Smit^{3,4} to prepare acyclic 1,3-diones from alkynes.
2. Explore geometric constraints of the reaction with respect to tether length. Ferrier and Tedder¹ reported that attempts to use this reaction to form 5- and 7-membered rings failed to give the desired products. It is anticipated that by utilizing our improved cyclization conditions it will be possible to vary the tether length leading to formation of different sized rings.
3. Explore the effect of steric interactions of the reaction with respect to alkyne substitution. Experiments will focus on the cyclization of molecules containing an internal alkyne substituent such as 5-heptynoic acid, where four potential cyclization products are possible. Examination of these products will allow for a more complete understanding of what preferences the reaction shows.
4. Explore the effect of heteroatomic moieties. To determine if the reaction conditions will tolerate heteroatomic groups substrates containing nitrogen, oxygen and sulfur groups will be subjected to cyclization conditions.

References:

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