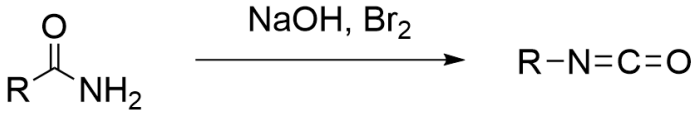
Exercise session – 24/11/2022

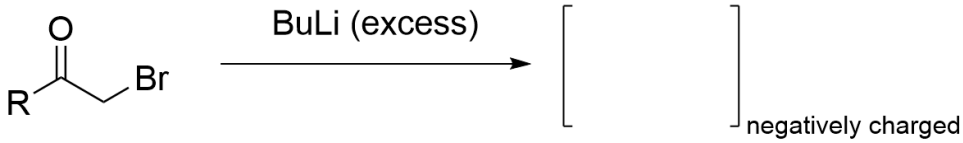
Alkynolate chemistry : Applications and mechanism investigations

Part I: Discovery of alkynolate - *J. Am. Chem. Soc.* **1982**, 104, 321-323

[Q1a] Give the name of this rearrangement and its mechanism:

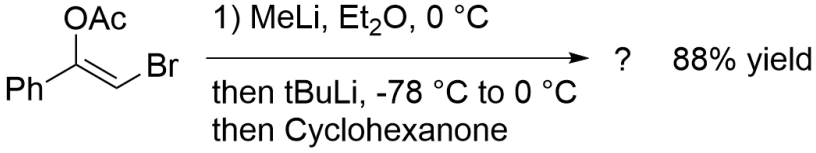


[Q1b] Kowalski & al discovered a new type of rearrangement:



Find the structure of the key intermediate (explain why excess of BuLi is necessary)

[Q1c] Write the mechanism to find the structure of the major product:



[Q1d] When the previous reaction is carried in THF, the yield drops to 70% and a new product is formed in 12% yield. There is now a new benzylic signal in ^{1}H NMR. Provide a mechanism for this new side product.

[Q1e] How would you improve the yield of this side product? (2 major changes are needed)

[Q1f] After optimization, when switching cyclohexanone to benzaldehyde, another product is formed, which shows conjugation of the two phenyl rings. Propose a mechanism.

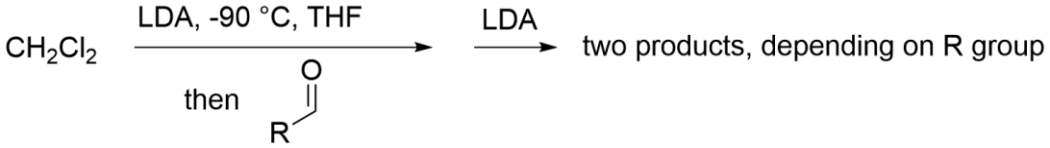
[Q1g] Try to find another way to reach the alkynolate by passing by the same double negatively charged precursor but with a different starting material. Propose a synthesis of this starting material.

[Q1h] How could you determine the mechanism of the rearrangement? The starting material must be pinacolone derivative and needs to be synthesized from scratch.

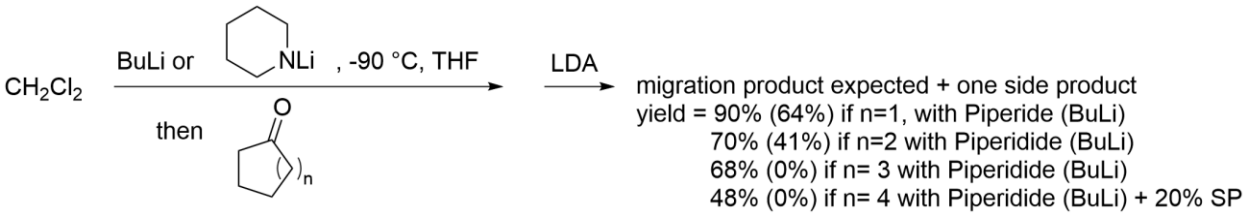
Part II: Relationship with carbene chemistry and application to a homologation reaction - *J. Am. Chem. Soc.* **1985**, 107, 1429-1430

[Q2a] Villieras and Normant's work (Cocorico) showed that α-haloenolates are versatile building blocks that can be used as nucleophiles and electrophiles.

One way to make them is by rearrangement (of an intermediate that you will name):

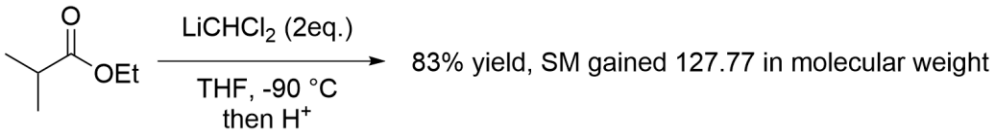


[Q2b] When replacing aldehydes with cyclic ketones, the migration product is still observed, and a new side product is formed (Villiéras. C. Bacquet and J.F. Normant, *C.R. Acad. Sci. Paris* **1973** *Ser. C*, t.276 433) :



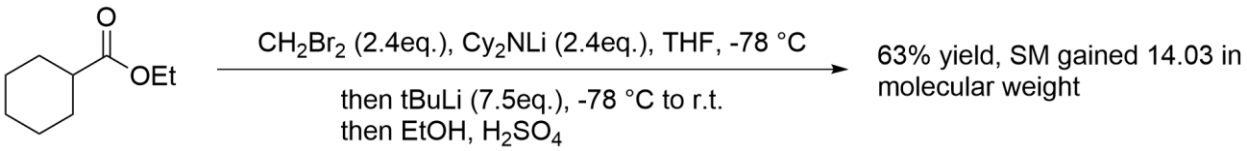
For the bromo analogs, the yields drops (60% starting from cyclopentanone and 53% w/cyclohexanone).

[Q2c] It is possible to replace ketones and aldehydes by esters. However, a completely different reactivity is observed:



Provide a mechanism. Make the connection with **[Q1g]**

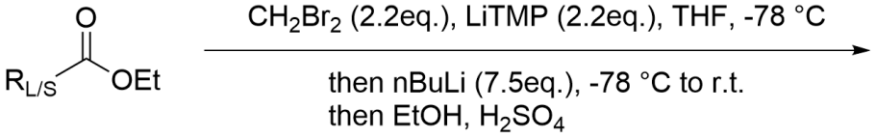
[Q2d] Modification of Normant's procedure by Kowalski gave a different product. Provide a mechanism for the formation of this new product.



Part III: Deep dive into the homologation mechanism - *J. Org. Chem.* **1992**, 57, 7194-7208

[Q3a] Write a mechanism when R is bulky or not, considers these feedbacks:

- When R isn't bulky, quenching **after addition to nBuLi at -78 °C** gives an **analog** of **[Q2c]**.
- When R isn't bulky, **after addition of nBuLi** and **warming to r.t.**, another reaction occurs leading to the **key intermediate precursor of this reaction**. (precursor --> key intermediate)
- When R is bulky, quenching **prior to addition to nBuLi** gives the same results as **[Q2c]**
- When R is bulky, **after addition of nBuLi** the same precursor as **warming to r.t.** with non-bulky group is formed.



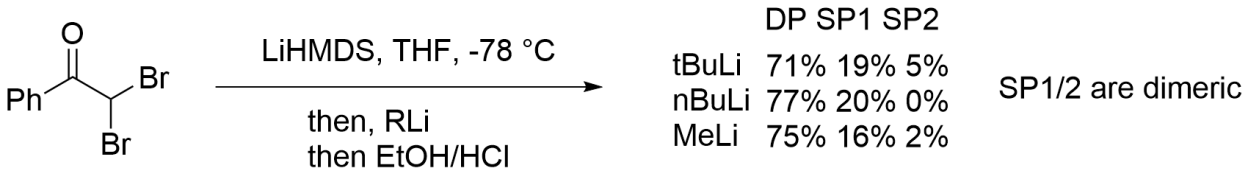
Give your conclusion on the necessity (or not) to differentiate bulky and non bulky group for this procedure.

Remark : it is possible to quench the reaction with chlorosilanes to yield siloxyacetylenes.

[Q3b] Addition of acidic ethanol solution **to** the key intermediate gives a complex mixture. Why?

[Q3c] "*Although this chemistry worked for a wide variety of esters with primary, secondary, tertiary, aryl, alkenyl, and alkynyl R groups, the yields (53-75%) and scale of reactions (2-5 mmol) were only moderate*"

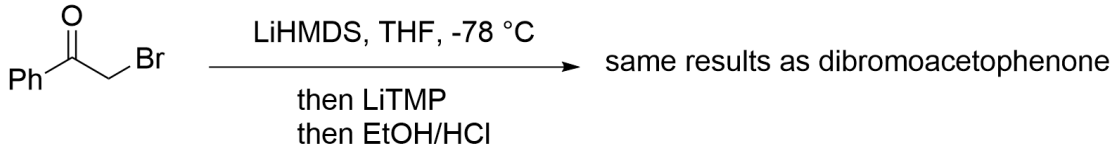
Provide a mechanism to explain the formation of the dimeric side products.



[Q3d] How would you detect formation of SP1 precursor?

[Q3e] How would you avoid the formation of these dimeric compounds? (read **[Q3a]** until the end)

[Q3f] Converting bromoacetphenone to the corresponding rearranged product works well when using LiTMP rather than nBuLi.



However, when using the same procedure to avoid the dimeric side products, only a complex mixture is observed.

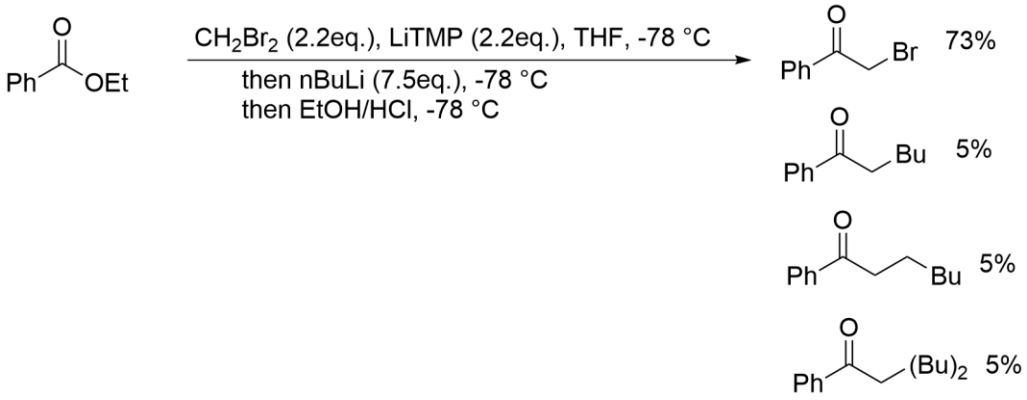
How would you prove that the use of LiTMP is problematic when trying to avoid dimeric side products?

[Q3g] During formation of the key intermediate precursor, either E o Z configuration can be obtained. How would you determine the ratio?

[Q3h] The enolate formation is highly regioselective with a 97:3 ratio in favor of the Z isomer. Is this result concordant with the mechanism of the rearrangement?

[Q3i] How would you prove the importance of the enolate geometry for this reaction?

[Q3j] The ynolate reactivity has been studied, the enolate reactivity too. This only leaves tetrahedral intermediate left:



How would you prove that these side products do not arise directly from the bromo-enolate?

Suggest another control experiment to understand where the butyl side chains come from.

[Q3k] Propose a new intermediate that would explain the formation of these side products, considering that carbenoids are known to undergo addition by organometallic reagents. And how to solve this problem.