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Integrated
Research Advances

Synthetic applications of LithiumDiisopropylamide (LDA): A brief review

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ABSTRACT

LDA is a hindered non-nucleophilic base. It abstracts hydrogen from less hindered site as compared to other bases. LDA prefers the formation of thermodynamically favoured product compared to other bases. LDA is a region-selective reagent. It has wide applications in organic synthesis. This review is focused on the synthesis and applications of LDA in organic synthesis.

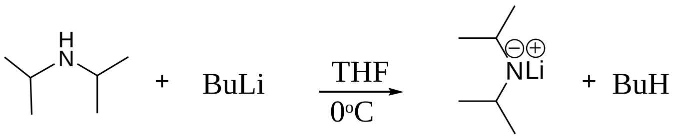
Keywords: LDA, Alkylation, Base

INTRODUCTION

Lithium Diisopropylamide (LDA) is a Chemical Compound. LDA is a colorless solid and its molecular formula is $[(CH_3)_2CH]_2NLi$. LDA is used as a strong base and it has good solubility in non-polar organic solvents. LDA is also a non-nucleophilic as well as highly polar in nature.[1]

Preparation

LDA (3) isprepared with the reaction of diisopropylamine (1) with butyllithium (2) in presence of tetrahydrofuran (THF) at 0°C to -75°C. (scheme-1).[2]

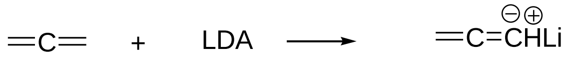


1 2 3 LDA

Scheme-1

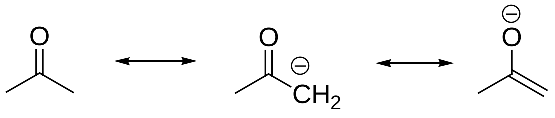
Applications

1) LDA is hindered non-nucleophilic strong base.
2) LDA is a poor nucleophile and does not give nucleophilic substitution even with alkyl halides and tosylates (R-O-Ts). It does not give nucleophilic addition with aldehydes,ketones and nitriles. [2]
3) In THF its structure is primarily that of a solvated dimer.[3,4]
4) LDA forms a temperature-dependent oligomer equilibrium, in non- polar solvents such as toluene. At room temperature trimers and tetramers are the most likely structures. With increasing temperature theaggregation extends to pentameric and higher oligomeric structures.[5]
5) Solid LDA is pyrophoric but its solutions are generally not.[6]
6) It is strong base that it abstracts hydrogen from active carbon[2] (Scheme-2,3)



4 5 6

Scheme-2



7 8 9

Scheme-3

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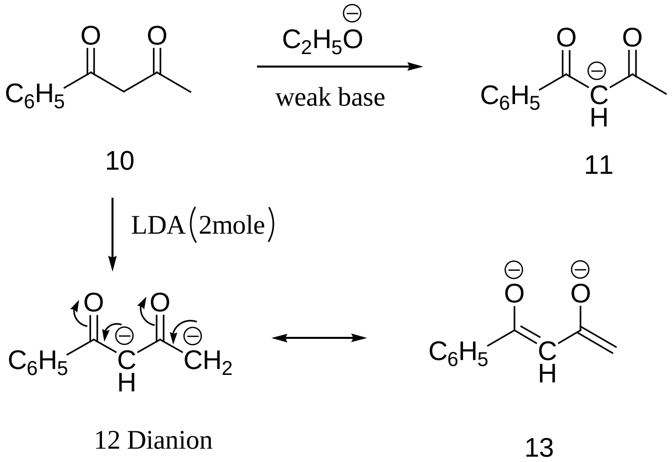
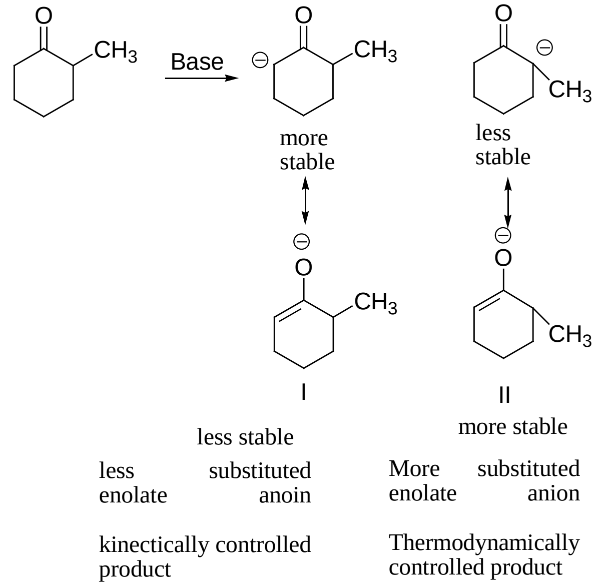
7) A compound possessing two activated *CH* groups of different acidity forms dianion in a very good yield (Scheme-4).[2]



Scheme-4

8) For a ketone with two sets of non-equivalent α-hydrogens,formation of enolate anion has high degree ofregioselectivity and regioselectivity depends on experimental condition (Scheme-5).



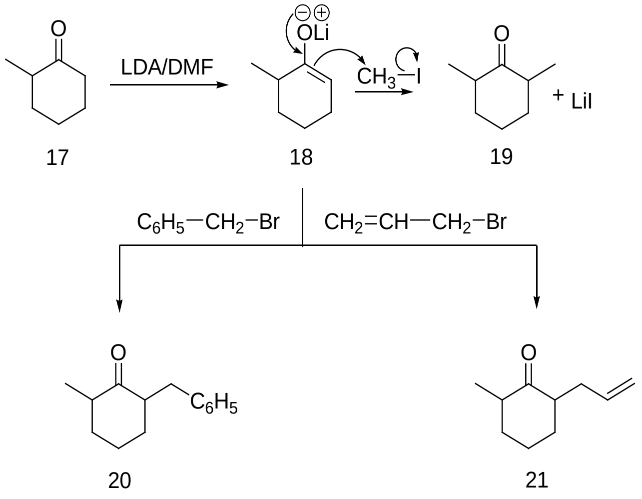
Scheme-5

Highly hindered strong bases,such as LDA favour formation of the kinetic,less substituted enolate,whereas unhindered weak bases such as NaH,KH,sodium and potassium salt of primary,secondary and tertiary alcohols (i.e., sodium and potassium alkoxide) generate the more substituted, thermodynamic enolate.[2]

Lithium enolates of ketones from LDA are very useful compounds for organic synthesis. Some of the reactions are mentioned below:

Direct Alkylation and Acylation of ketones

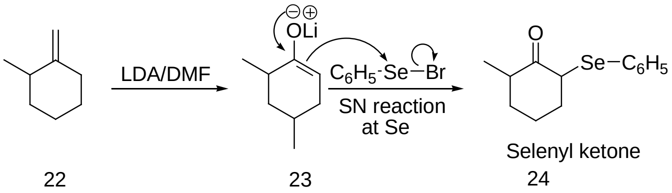
The alkylation reaction is SN2. Enolate anions are strong bases,successful alkylation occurs only when primary alkyl,primary benzyl and primary alkyl halides are used in this reaction. With secondary and tertiary,elimination becomes the main course of the reaction.(Scheme-6)[2]



Scheme-6

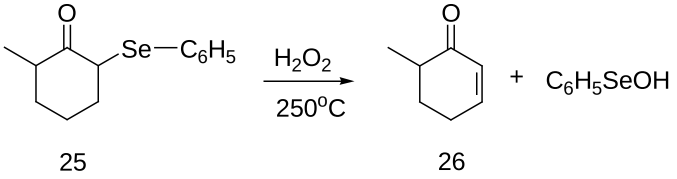
α-Selenation

Lithium enolate obtained by LDA react with benzene selenyl chloride or bromide to yield products containing aPhSe- group at the α-position (Scheme-7).



Scheme-7

Selenyl ketone on oxidation with hydrogen peroxide at room temperature gives an α,β-unsaturated ketone (Scheme-8).[2]



Scheme-8

CONCLUSIONS

LDA is hindered non-nucleophilic strong base. LDA abstracts hydrogen from active carbon and generate enolate anion. It forms temperature-dependent complex that consists few monomer units. Solid LDA is fire-bearing in air at or below 55°C but its solution is not.

ACKNOWLEDGMENTS

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