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SYNTHESIS OF ALKENES FROM KETONES VIA ARYLSULPHONYLHYDRAZONES; MECHANISTIC VIEWS; THE ORGANIC CHEMISTRY NOTEBOOK SERIES, A DIDACTICAL APPROACH, Nº 7

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ABSTRACT

This is the seventh chapter in the series published by the same authors: "The Organic Chemistry Notebook Series, a Didactical Approach".

The aim of this series of studies is to help students to have a graphical view of organic synthesis reactions of diverse nature. Here we describe the mechanistic views of the synthesis of alkenes from ketones *via* arylsulphonylhydrazones. These methods employ aliphatic and alicyclic ketones with one α-hydrogen, that react along with toluene-*p*-sulphonylhydrazones and two equivalents of an alkyl-lithium or lithium diisopropylamide. The mechanism views for the transformation of pinacolone into 3,3-dimethyl-1-butene are proposed. The formation of 3-phenylpropene using phenylacetone is explained step by step. An approach is made on the obtaining of alkenes from ketones using derived enol ethers or esters by means of reductive excision or by means of coupling with organocuprates. We have used various series of reactions reviewed by W. Carruthers in 'Some modern methods of organic synthesis', and we have proposed didactical and mechanistic views for them. This theme is included in the chapter "Formation of carbon-carbon double bonds" in the text mentioned above. ***Spanish title****: Síntesis de alquenos a partir de cetonas via arilsulfonilhidrazonas; vistas mecanísticas; De la serie: El cuaderno de notas de química orgánica, un enfoque didáctico, Nº7.*

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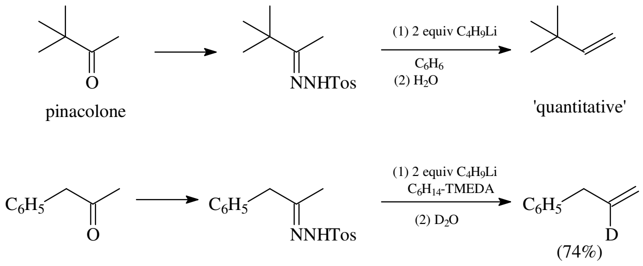
INTRODUCTION

During master classes of organic chemistry it is possible to notice that students are confronted with a lack of knowledge with regard to mechanisms. For instance, oxidation-reduction reactions which are among the most commonly employed constitute a kind of black box for the student's mind. A mechanistic approach of any kind of reaction enhances the capacity of facing new reactions with respect to an understanding of all processes involved in them, and also develops synthetic creativity. As academics we feel concerned with the didactical importance of covering these needs in debutant students in organic synthesis. This, the synthesis of alkenes from ketones via arylsulphonylhydrazones, is the seventh study in: "The Organic Chemistry Notebook Series, a Didactical Approach" [1-6].

REACTIONS AND THEIR MECHANISTIC PROPOSALS, DISCUSSION

Aliphatic and alicyclic ketones with at least one hydrogen in α are employed to synthesize alkenes [7]. The method includes reaction of ketones with toluene-*p*-sulphonylhydrazones and the addition of two equiv of lithium diisopropylamide or alkyl lithium [7-9]. Products present no changes in the carbon framework, and given the adequate mild conditions; the less substituted alkene is obtained [7]. Pinacolone gives an only product: 3,3-dimethyl-

1-butene [7]. See Fig. 1 and 2, and Fig. 3 for a mechanistic explanation. 3-phenylpropene is brought forth by phenylacetone, however no styrene is present after reaction [7] (Fig. 1, 2 and Fig. 4).



(Tos = $p\text{CH}_3\text{C}_6\text{H}_4\text{SO}_2$; TMEDA = tetramethylethylenediamine)

Figure 1. *Alkenes (the less substituted) from ketones via arylsulphonylhidrazones; reviewed by W. Carruthers [7]*

Various steps are applicable to the reaction. First, the anion **1** is formed by action of the first alkyl lithium [7]. Then the second equivalent of alkyl lithium generates another charge and the dianion **2** appears. Localization of the excessive charge in the carbanion of **2**, leads to the fragmentation of the arylsulphonyl moiety [7]. The resulting anionic diazo-alkene becomes a carbanion by means of excision of one molecule of gaseous nitrogen; the carbanion makes a new covalence with one cation Lithium, the other one compensates the charge of the arylsulphonate [7]. The yield can be improved by using tetramethylethylenediamine (TMEDA) [7] as solvent. TMEDA is the additive or solvent necessary to obtain the less substituted alkene from an unsymmetrical ketone [7]. When an ethereal or hydrocarbon solvent is used, the C=C bond occupies a position defined by the stereochemistry of the hydrazone [7]. The second abstraction of the a proton in **1**, happens in a *syn* way to the $\text{ArSO}_2\text{N}^{(-)}$- [7,10].

Intermediate **3** can suffer interchange of the cation Li^+ with H^+ of the solvent (or an alternative source of protons) or being substituted by another electrophile [7]. See Fig. 2 and Fig. 3.

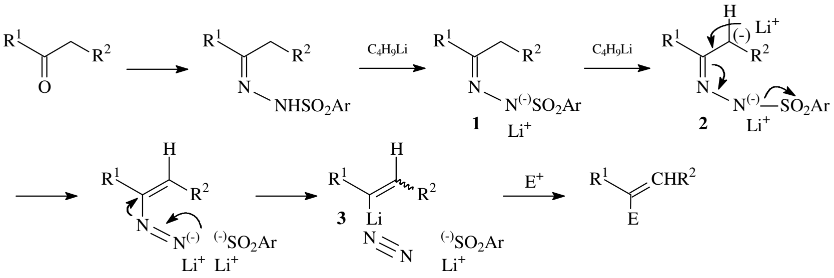


Figure 2. *Alkenes (the less substituted) from ketones via arylsulphonylhidrazones; intermediates description; reviewed by W. Carruthers [7]*

In TMEDA, submitting the reaction to the adding of deuterium oxide is a way to deuterated alkenes (Fig. 1 and Fig. 4) [7]. 2-methylcyclohexanone (**4**, Fig. 5 and 6), gives rise to 2-deuterio-3-methyl cyclohexene, and octan-2-one (**5**, Fig. 5 and 7) to 2-deuterio-1-octene [7]. The preferred form of the 1,2-disubstituted alkene after protonation of the lithium intermediate **3** (Fig. 2) is the *Z*-isomer [7].

The intermediates like **3** (Fig. 2), can be usually treated with other electrophiles like dibromoethane for instance, to give rise to vinyl bromides, or acetaldehyde to give allyl alcohols or carbon dioxide to give acrylic acids [7] (Fig. 5 and 7). The hydrazone more adequate in these reactions is the 2,4,6-triisopropylbenzenesulphonylhydrazone to provide the vinyl-lithium, instead of the *p*-toluensulphonyl [7]. This latter hydrazone suffers lithiation at the *ortho* position of the aromatic ring, provoking thus a diminution of the yields in the substituted alkene [7]. This fact is avoided using the triisopropyl derivative [7,11,12]; see Fig. 5 and 7.

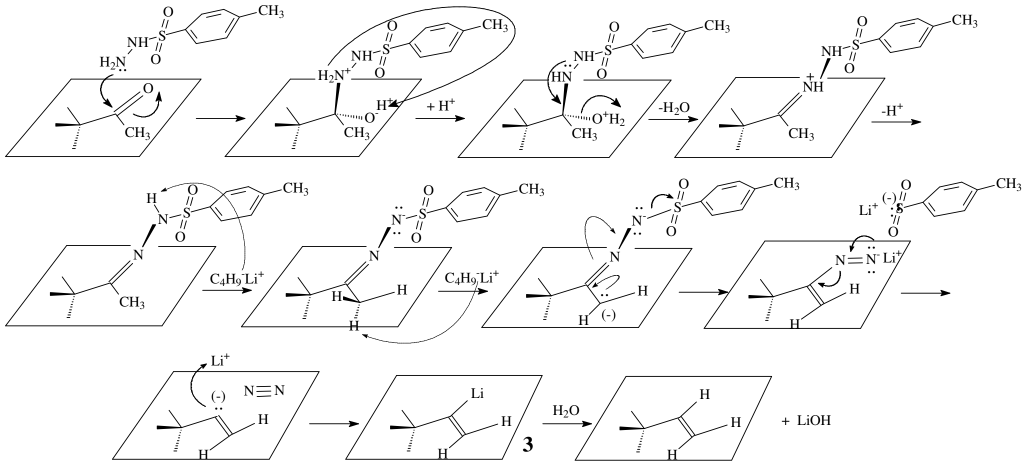


Figure 3. *Pinacolone transformed into 3,3-dimethyl-1-butene via arylsulphonylhydrazone, as only product; mechanistic explanation, based in the mechanism exposed in Fig. 2, reviewed by W. Carruthers [7]*

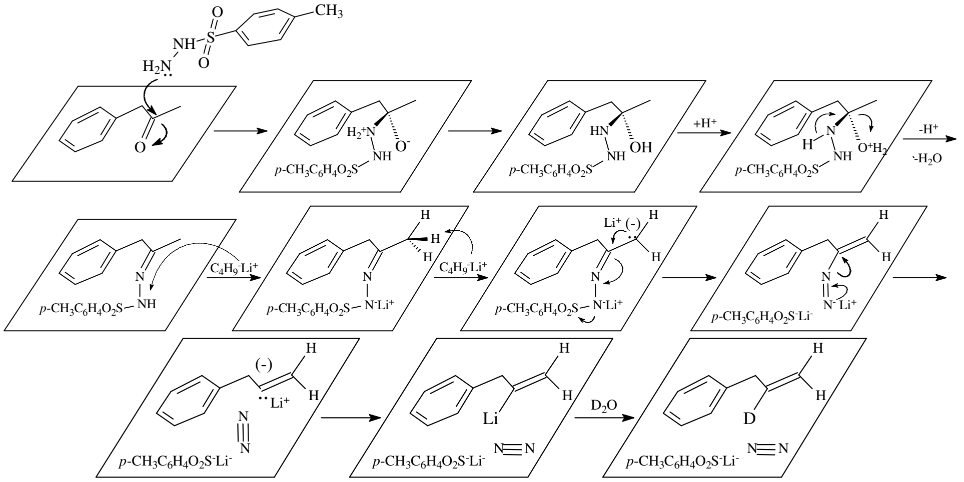


Figure 4. *Phenylacetone transformed into 3-phenyl-2-deuterio-propene via arylsulphonylhydrazone as only product; mechanistic explanation, based in the mechanism exposed in Fig. 2, reviewed by W. Carruthers [7]*

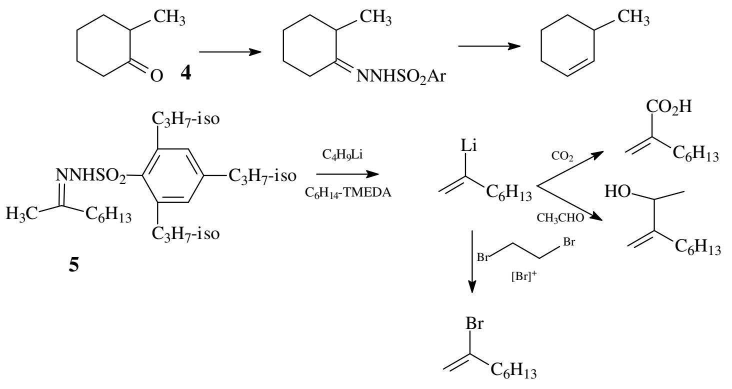


Figure 5. *Conversion of 2-methylcyclohexanone (**4**) into 2-deuterio-3-methylcyclohexene via p-toluensulphonylhydrazone; conversion of octan-2-one (**5**) into 2-deuterio-1-octene via 2,4,6-triisopropylbenzenesulphonylhydrazone; treatment of lithium intermediate with dibromoethane, acetaldehyde, or carbon dioxide; reviewed by W. Carruthers [7]*

Reduction of tosylhydrazones derived from carbonyl compounds into hydrocarbons[7].

This can be achieved by using sodium cyanoborohydride in acid [7]. An alternative to the Wolf-Kishner deoxygenation is the using of catecholborane [7]. When the hydrazones derivatives are $\alpha\beta$-unsaturated, it is possible to form alkenes where the double bond has moved to the original carbonyl position [7]. The reducing agent is usually NaBH($OCOCH_3$) coming from the mixture: $NaBH_4$ and acetic acid [7,13]. A tentative mechanism has been proposed where the formation of the diazene intermediate suffers a migration of hydride (1→5) from N to C [7]. See Fig. 8, 9 and 10.

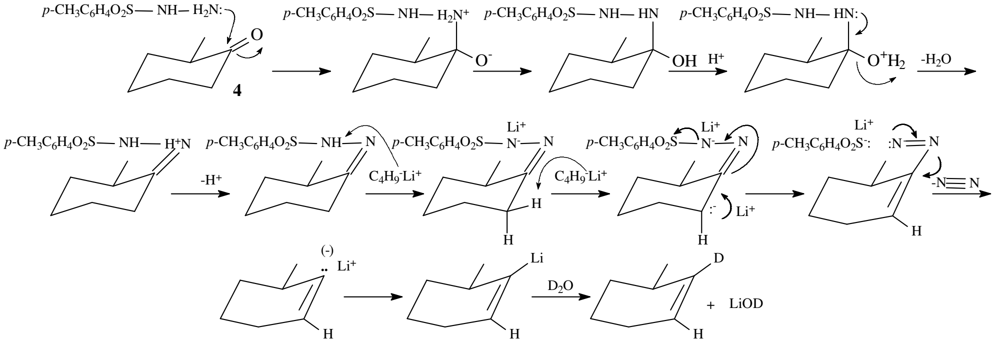


Figure 6. *Conversion of 2-methylcyclohexanone into 2-deuterio-3-methylcyclohexene via p-toluensulphonylhydrazone, based in the mechanism exposed in Fig. 2, reviewed by W. Carruthers [7]; mechanistic view*

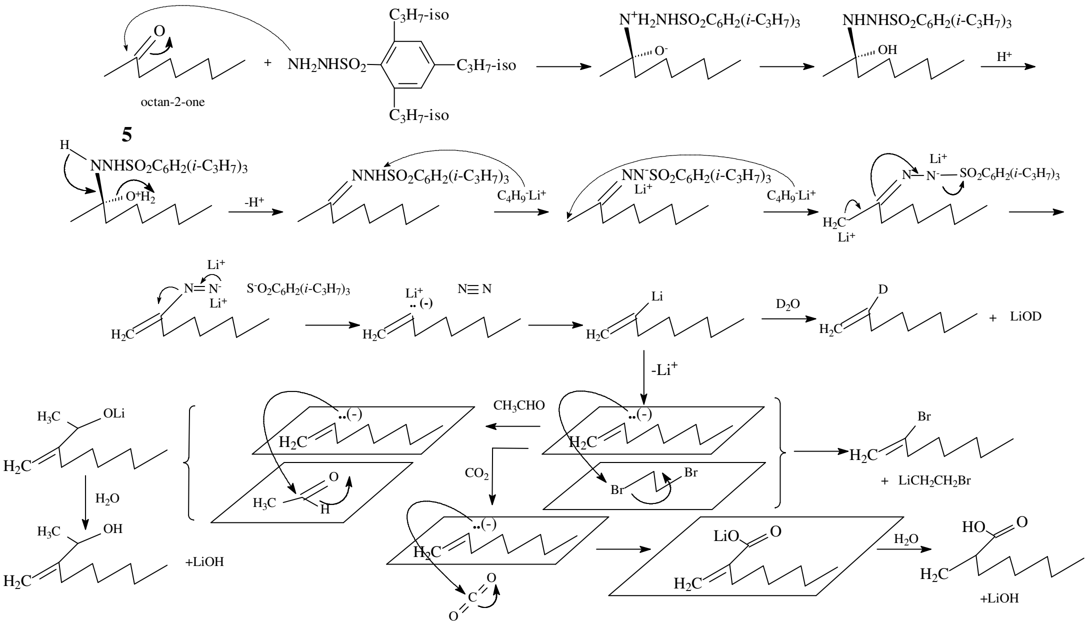


Figure 7. *Conversion of octan-2-one (**5**) into 2-deuterio-1-octene via 2,4,6-triisopropylbenzenesulphonylhydrazone; treatment of the lithium intermediate with dibromoethane, acetaldehyde, or carbon dioxide, based in the mechanism exposed in Fig. 2, reviewed by W. Carruthers [7]; mechanistic view*

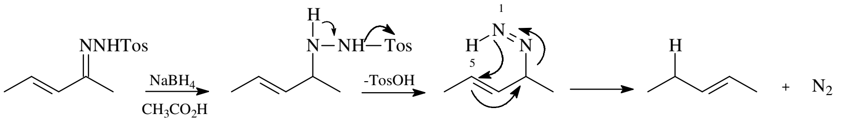


Figure 8. *Mechanism for the reduction of tosylhydrazones derived from carbonyl compounds into hydrocarbons; reviewed by W. Carruthers [7]*

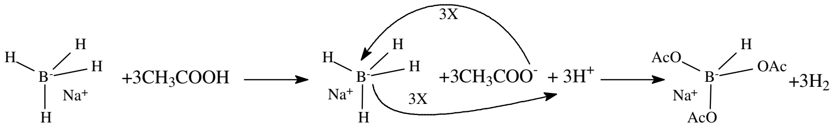


***Figure 9.** Reduction of tosylhydrazones derived from carbonyl compounds into hydrocarbons; acetylation of sodium borohydride to afford sodium boroacetylhydride; mechanistic view*

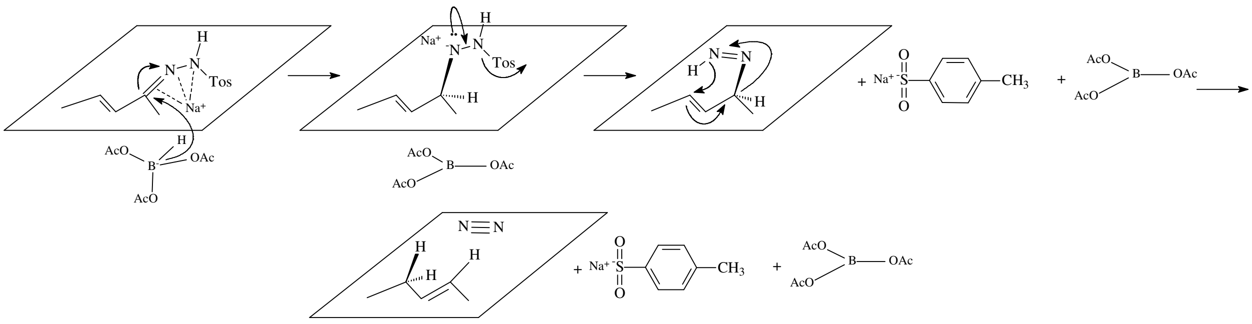


***Figure 10.** Reduction of tosylhydrazones derived from carbonyl compounds into hydrocarbons; action of sodium boroacetylhydride to afford diazene intermediate followed by 1,5-migration of hydride from nitrogen to carbon, according to mechanism of Fig. 8, reviewed by W. Carruthers [7]; mechanistic view*

Moreover, the use of sodium borodeuteride/acetic acid [NaBD$_4$ + 3CH$_3$COOH→ NaBD(CH$_3$COO$^-$)$_3$], or on the other hand the use of carboxyl deuterated acetic acid/sodium borohydride, conducts to the regio-selective introduction of deuterium (one or two units) [7]. When deuterated acetic acid is employed, the interchange at the N-H position with deuterium should be faster than the process of reduction (hydride transfer toward carbon) [7]. See Fig. 11, 12 and 13.

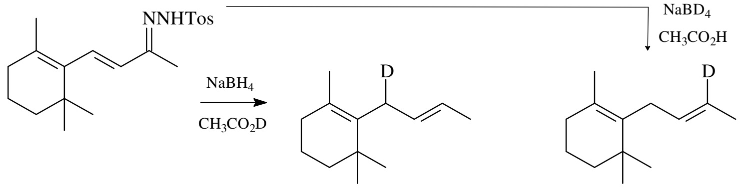


***Figure 11.** Reduction with sodium borodeuteride in acetic acid or carboxyl deuterated acetic acid giving rise to regioselective introduction of deuterium. Reviewed by W. Carruthers [7]*

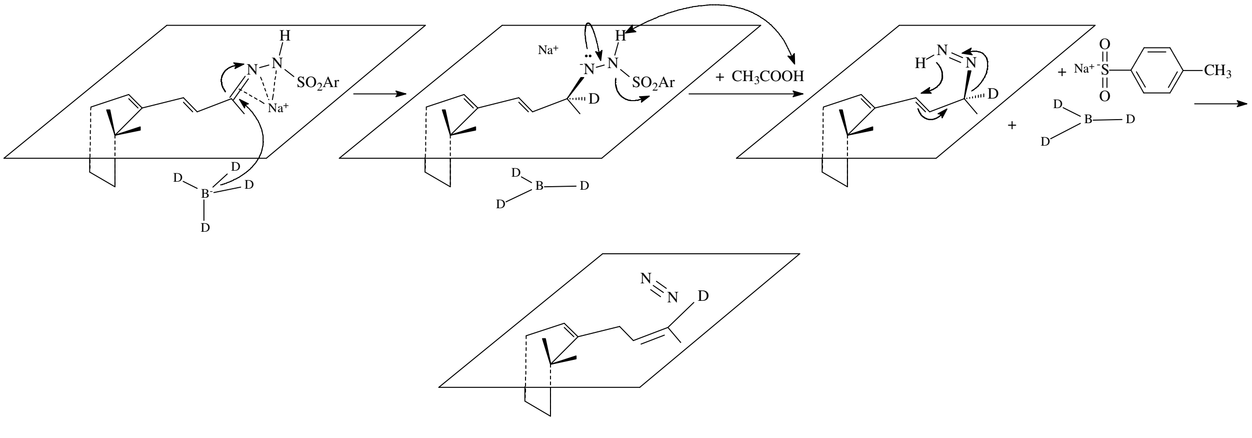


***Figure 12.** Reduction with sodium borodeuteride in acetic acid giving rise to regioselective introduction of deuterium; mechanistic view*

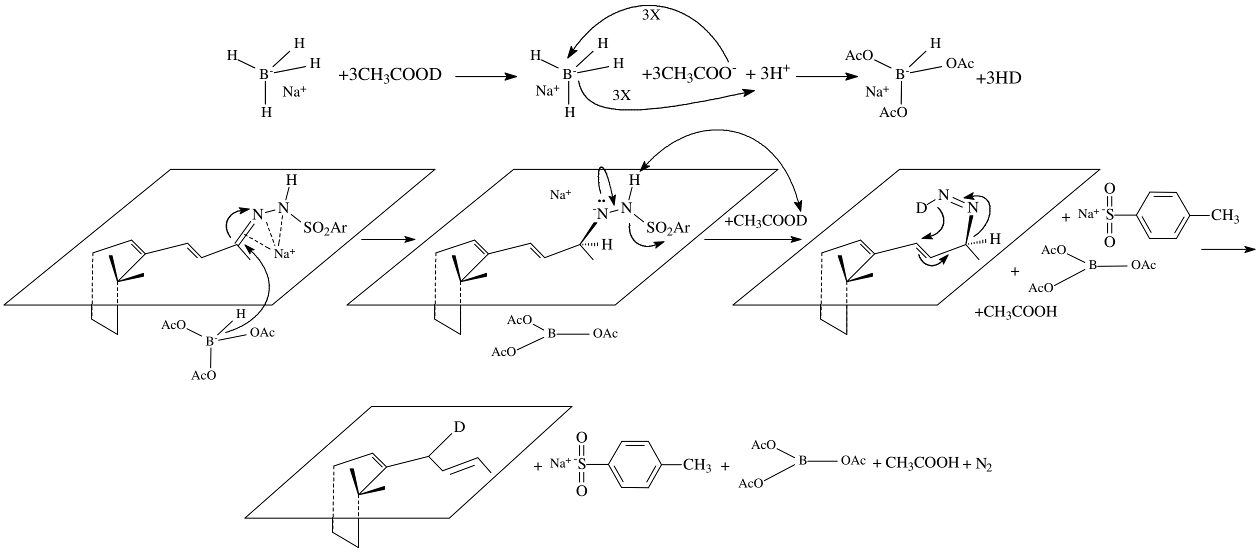


Figure 13. *Reduction with sodium boroacetylhydride in carboxyl deuterated acetic acid giving rise to regioselective introduction of deuterium; mechanistic view*

Ketones are also precursors of alkenes by the way of derived enol ethers or enol esters [7]. This is achieved by reductive cleavage or by coupling with organocuprates [7]. The substrate to be reduced by the using of lithium and amines is the *N*,*N*,*N*',*N*'-tetramethylphosphordiamidates. The cleavage occurs on the C-O bond [7]; with enol derivatives it conducts to the corresponding alkene with good yields [7,14]. See Fig. 14 and 16.

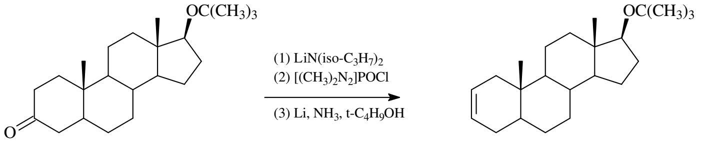


Figure 14. *Reductive cleavage of ketones to form alkenes by the way of derived enol ethers . Reviewed by W. Carruthers [7]*

The enol can be reduced, it means see its oxygen replaced by an anion, rather by a carbanion (alkyl), instead of a hydride (a basic hydrogen), by the reaction of the enol diphenylphosphate or the enol trifluoromethanesulphonate (triflate) with lithium dialkylcuprate [7,15,16]. See Fig. 15. The high stereoselectivity characterizes these reactions [7]. As an example let us examine the transformation of (*Z*)-5-trifluoromethanesulphonyloxy-5-decene into (*E*)-5-methyl-5-decene by using dimethyl cuprate [7]. See Fig. 15

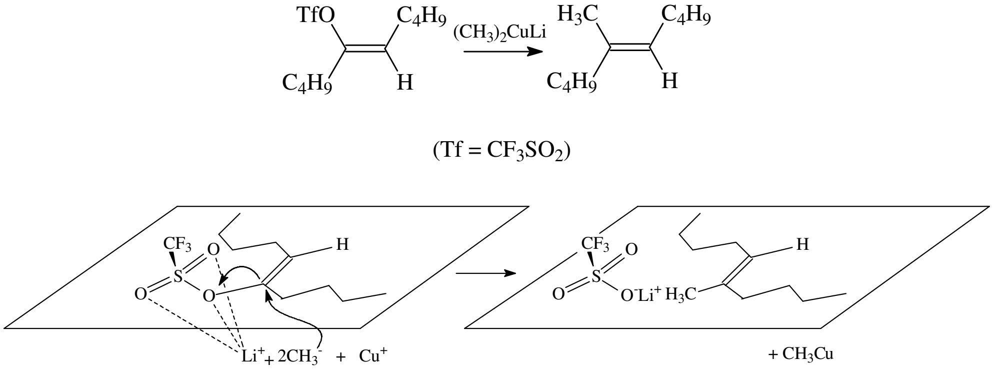


Figure 15. *Replacement or reduction of the enol's oxygen atom by a n alkyl group instead of H. using triflate with lithium dialkylcuprate. Reviewed by W. Carruthers [7]. Mechanistic view*

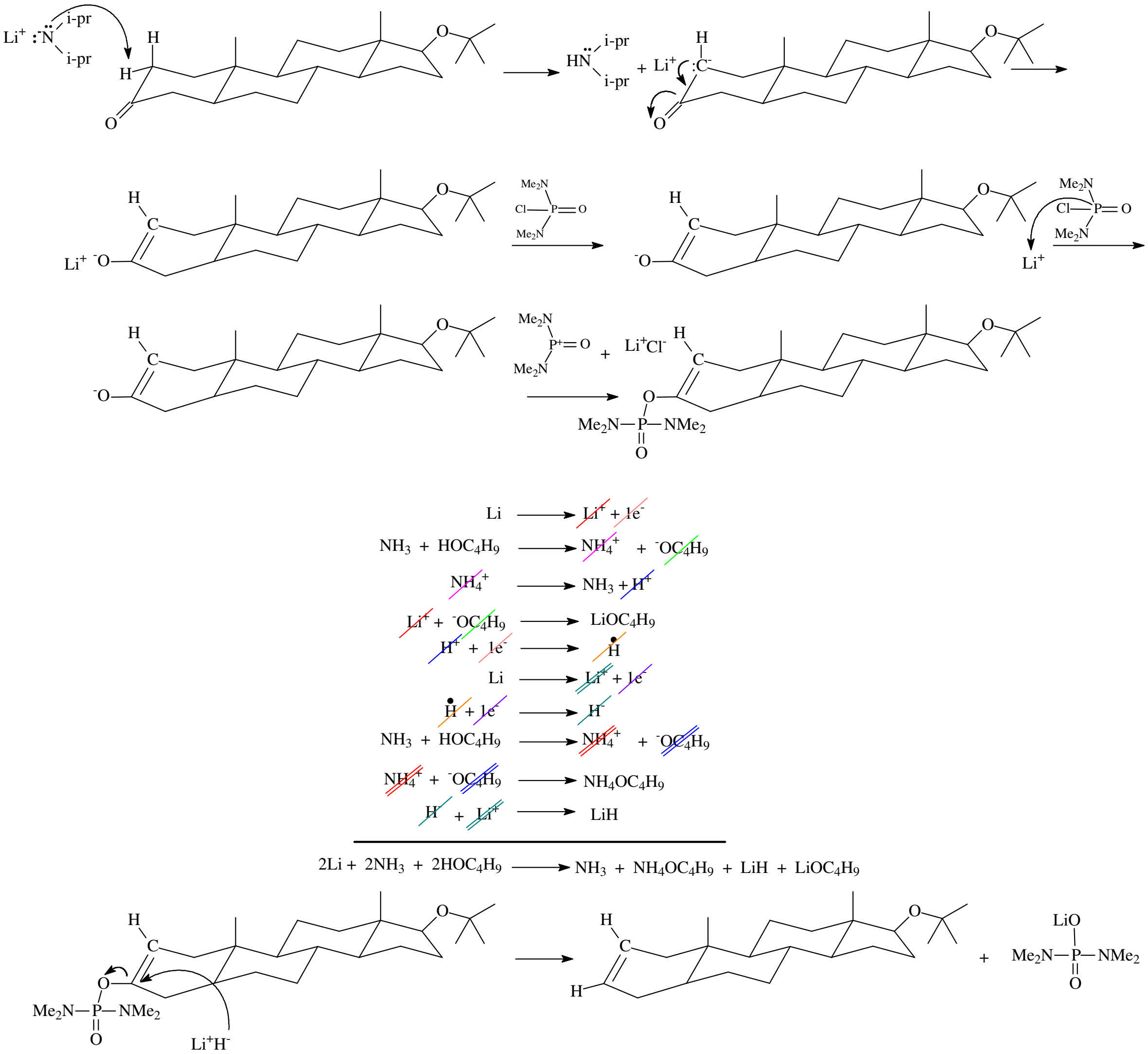


Figure 16. *Reductive cleavage of ketones to form alkenes by the way of derived enol ethers. Mechanistic views.*

In Fig. 16 the basic nitrogen temporally stabilized by the cation Li^+, withdraws the proton in α of carbonyl in the ketone. This is due to its acidic character. A carbanion appears in the place of the α-hydrogen. Because the oxygen supports better than the carbon atom a negative charge in excess, an inductive current generates the migration of the two electrons over the carbon atom for establishing a new C^2=C^3 double bond and placing the negative charge over the oxygen of the ketone now transformed into an enol oxygen. Oxygen is now temporally stabilized by Li^+. This lithium enol interacts now with chloride from phosphorus derivative $\{[(CH_3)_2N]_2POCl\}$ thus generating the corresponding cation with the positive charge reposing on the phosphorus. What is next is the oxidation of two equiv. of Lithium metallic plus the using of two equiv. of ammonia as well as two equiv. of *n*-butanol to give one ammonia, a *n*-butoxylammonium, a lithium-*n*-butoxyl and a lithium hydride. This hydride is responsible of the reduction of the enol into an alkene function.

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