1,1,1,-TRIFLUORO METHYL KETONE AND ITS REACTION WITH GRIGNARD REAGENT

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Abstract
1,1,1-Trifluoro propanone undergoes aldol condensation with various catalysts and has been used as a starting material for several compounds. In the present work we have synthesised 4-methyl-1,1,1,5,5,5-hexafluoro-3-penten-2-one and studied its Grignard reaction to form 4-methyl-1,1,1,5,5,5-hexafluoro-2-pentanone.

Keywords: Trifluoro methyl ketone, methyl ketone, Grignard reagent, pentanones

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1. Introduction

Much attention is currently being given to the development of methods to incorporate fluorine into organic molecules. The tremendous popularity of this area stems from the fact that the physiological and chemical properties of small molecules are greatly altered by the incorporation of fluorine atoms. Trifluoroacetone is an organofluorine colourless liquid. Trifluormethyl ketones are exceedingly valuable synthetic targets in their own right and used as synthons in the construction of fluorinated pharmacons. It has an electronegative trifluoromethyl group. Fluorine is the most reactive element and the significant chemical properties of these compounds is due the the fact that C-F bonds are of high strength (bond energy of 116 KCal.mol-1). Furthermore with fluorine there is also the tendency to form strong hydrogen bonds.

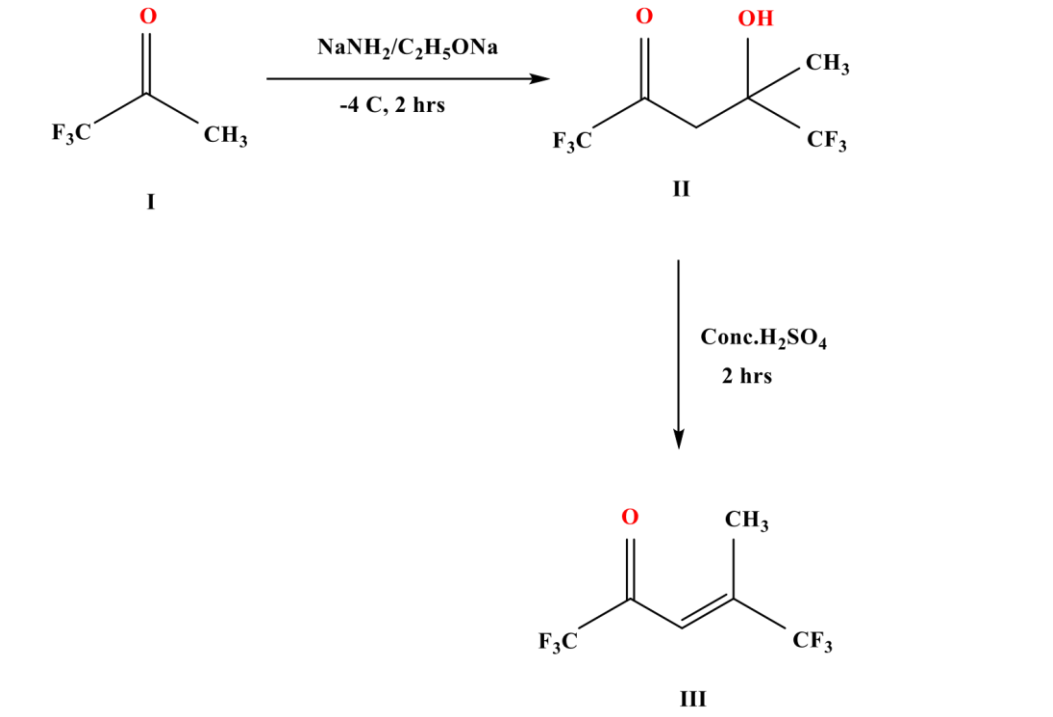
These serve as critical intermediates in constructing trifluoromethylated heterocycles, medicinal compounds and fluorinated analogues of natural products. It is used as an intermediate in many bioactive compounds and also in hypertensive drugs.Many drugs now feature fluorine for these reasons. Trifluoromethyl ketone has been used recently in the synthesis of one of the leading antiretroviral drugs in the treatment of HIV Efavirenz (sustiva). As a consequence of the inductive power of the CF3 group, the carbonyl oxygen of TFMK is far less prone to activation with Lewis acids and therefore less likely to participate in Lewis acid-mediated condensation processes. It acts as a good oxidising agent mainly oxiidising hydroxyl group of secondary alcohols in Oppeneuer oxidation. They are versatile materials which have been used as synthons in a range of fields.

In the present work, we have carried out self aldol condensation of the trifluoromethyl ketone (I) in the presence of a strong base like sodium amide in sodium ethoxide at low temperature to give 1,1,1,5,5,5,-hexafluoro-2-pentanone (II). Compound II was found to give a phenylhydrazone showing the presence of a ketonic group. This compound undergoes undergoes dehydration with conc. H2SO4 to form 4-methyl-1,1,1,5,5,5,hexafluoro-3-penten-2-one (III) as shown in scheme I.

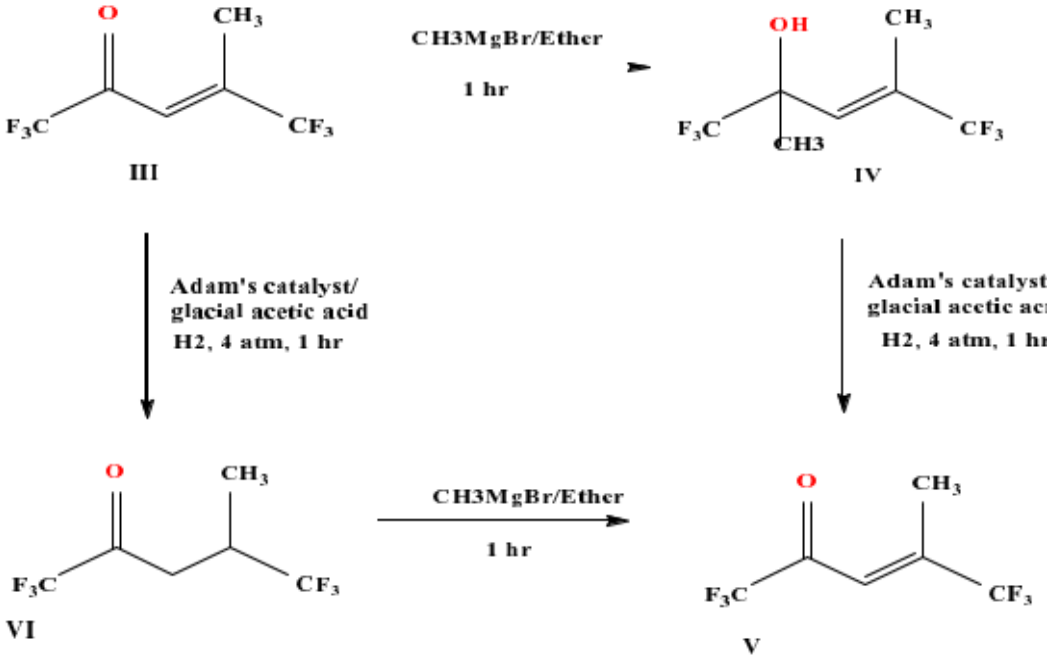
This α, β-unsaturated ketone acts as a very good reactant due to the presence of ketone and ethylenic linkage giving way to a variant reaction. Several reactions take place at carbonyl group, double bond or at both the functional groups. In the present work, we have seen the addition of Grignard reagent to compound III was very interesting. There are 3 possibilities here. First grignard reagent can attack at the carbonyl group. Second it can attach at the olefinic linkages or third, there is a possibility of 1,4-addition. In the second or third case addition followed by ketonization takes place. When compound III on reaction with Grignard reagent, two factors may be responsible for the formation of product . First one being the electronic factor where the reactant carbonyl group increases as electronegativity of trifluoromethyl decreases. Second being the steric factor where the reactivity of carbonyl group decreases as -CF3 groups are bulky.

However, the two -CF3 groups show relatively minor electronic effects and negligible steric effect. As far as the reaction with Grignard reagent is concerned, the inductive effect of -CF3 can be compared to that of -CH3. Hence tertiary alcohol III is formed by 1,2addition reaction. In order to prove the structure of IV, the following reactions were carried out.

Reduction of compound III, selective reduction with catalyst to give 2,4-Dimethyl-4hydroxyl-1,1,1,5,5,5-hexafluoro-2-pentanol (VI) which on reaction with Grignard reagent has undergone 1,2-addition to form 4-Methyl-1,1,1,5,5,5-hexafluoro-2-pentanone (V). This compound V is the same compound that has been formed by treating Compound III with Grignard reaction followed by reduction. This clearly indicates the the addition is 1,2, addition as shown in scheme II. All the compounds were characterised by H1NMR spectra and CH analysis.



Scheme-I: Synthesis of 4-methyl 1,1,1,5,5,5-hexafluoro-3-penen-2-one (III)



Scheme-II: Synthesis of 4-Methyl-1,1,1,5,5,5-hexafluoro-2-pentanone (V)

2. Experimental:

4-Hydroxy-4-methyl-1,1,1,5,5,5-hexafluoro-2-pentanone (II)

10 g (0.089 mole) of 1,1,1-Trifluoro propanone was taken in a 1 L RB flask at -4 º C and 100 mL of sodium ethoxide was added to it under Nitrogen atmosphere for 10 minutes. Then 0.004 g (0.133 mole) of sodium amide was added and stirred at a temperature below 0 º C for 2 hrs. Then the solution was cooled and poured into 1000 ml of ice cold water containing 100 mL of conc.H2SO4. The solid which has precipitated was filtered. The aqueous layer was then neutralised and extracted with ether. The ether solution on distillation gave 10 g of crude product. It was then recrystallised from pet ether-benzene mixture to give 6.3 g of compound II, mol. wt. 224, m.p. 75 º which was characterised by 1HNMR spectroscopy and CH analysis. 1HNMR: δ 1.2 (3H,S), 2.7 (2H, S); CH analysis data: Calculated: C,32.14, H,2.68; Found: C,32.10, H, 2.62.

4-Methyl-1,1,1,5,5,5-hexafluoro-3-penten-2-one (III)

To 5.5 g (0.025 mole) of compound II was added 25 g of 98% H2SO4 (13.3 ml) and stirred for 2 hrs. The resulting solution was then distilled and recrystallised with etherbenzene mixture to give 8 g of crude product which on distillation gave 3.2 g (63 %) of III, mol.wt. 206, b.p.72 º which was characterized by 1HNMR spectroscopy and CH analysis. 1HNMR: δ 2.1 (3H, S), 6.5 (1H, S); CH analysis data: Calculated: C,34.94, H,1.94; Found: C,34.82, H, 2.00.

2,4-Dimethyl-1,1,1,5,5,5-hexafluoro-3-penten-2-ol (IV)

20 ml of ether was taken in a RB flask and 2.0 g (0.009 mole) of compound III was added and stirred vigorously. To it is added 1.5 g (0.009 mole) of methyl magnesium iodide . The stirring was continued for 1 hr. The solution was then cooled and hydrolysed with 5% HCl solution. The aqueous layer was separated, neutralised with Na2CO3 and then extracted with ether solution. On distillation, the ether solution gave 1.8 g (83 %) of compound IV, mol. wt. 222, b.p. 72 º which was characterised by 1HNMR spectroscopy and CH analysis. 1HNMR: δ 1.3 (3H, S), 1.9 (3H, S), 5.7 (1H, S); CH analysis data: Calculated: C,37.84, H,3.60; Found: C,37.82, H, 3.68.

4-Methyl-1,1,1,5,5,5-hexafluoro-2-pentanone (V)

1.5 g (0.007 mole) of compound IV in 5 ml of glacial acetic acid and 0.01 g of Adams catalyst was hydrogenated at 4 atm pressure for 1 hr. The solution was cooled and then filtered to remove catalyst. Distillation of the solution gave 900 mg (64 %) of compound V, mol. wt. 208, b.p. 85 º which was characterised by 1HNMR spectroscopy and CH analysis. 1H NMR: δ 1.1 (3H,d), 2.34 (1H,tq), 2.41-2.45 (2H, d) ; CH analysis data: Calculated: C,34.62, H,2.88; Found: C,34.50, H, 3.02.

2,4-Dimethyl-4-hydroxyl-1,1,1,5,5,5-hexafluoro-2-pentanol (VI)

1.0 g (0.005 mole) of compound III in 5 ml of glacial acetic acid and 0.01 g of Adams catalyst was hydrogenated at 4 atm pressure for 1 hr. The solution was cooled and then filtered to remove catalyst. Distillation of the solution gave 550 mg (51 %) of compound VI, mol wt. 224, b.p. 85 º which was characterised by 1HNMR spectroscopy and CH analysis, 1H NMR: δ 1.1 (3H,s), 2.69-2.70 (2H, s,s); CH analysis data: Calculated: C,32.14, H,2.68; Found: C,32.00, H, 2.72.

Preparation of compound V from VI

To 400 mg (0.002 mole) of compound VI in 20 ml of ether , 0.33 g (0.002 mole) of methyl magnesium iodide was added and stirred for 1 hr. The solution was then cooled and hydrolysed with 5% HCl solution. The aqueous layer was separated, neutralised with Na2CO3 and then extracted with ether solution. On distillation, the ether solution gave 245 g (66 %) of compound V.

Acknowledgments

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