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Synthesis and Characterization of novel Pulegone derivatives as substitutes of 4-(1,1 dimethylethyl) cyclohexan-1-ol acetate

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ABSTRACT

A series of novel pulegone derivatives were synthesized employing 1,4-addition of Gringard reagent followed by sodium borohydride reduction and esterification with optimum yields. The structures of synthesized esters were characterized by means of GC-MS, ^{1}H and ^{13}C NMR. The synthesized compounds GRP1, GRP2, GRP3 and GRP4 possesses woody fruity smell which can be used as good substitute of 4-(1, 1-dimethylethyl) cyclohexan-1-ol acetate.

Key words: Pulegone, Chiral Pool, Grignard reaction, Essential oils, ketone

INTRODUCTION

In the present era, the demand for essential oils products has gradually increased particularly in the east and the industrialized countries for their greater variety in their food and trend towards health and wellness. Essential oils also have their greater contribution towards flavours and fragrance[1-2] in the foods as well as in aromatherapy. Various supported studies [3-4] claims that the specific aromas carried by essential oils have curative effects and possess multitude of pharmacological properties, [5-6] such as bactericidal, fungicidal, antiviral, cytotoxic, insecticidal and antioxidant and used extensively in cosmetics,[7-8] medicine,[9] household cleaning products, pharmaecutical[10] and perfumery industry.[11-12] Naturally occurring optical active cyclohexenones, so-called "Chiral pool" such as pulegone, carvone and piperitone are widely used in natural product synthesis because these compounds are bargain priced and readily available in large quantities.[13-14] These naturally occurring compounds have lack of structural diversity due to this "Chiral pool" is in much interest in the development of routes to non-natural enantiomerically pure cyclohexenones.[15] Until recently, the most common method to obtain such non-natural cyclohexenones was the derivatization of cyclohexenones from the chiral pool. For instance, the important synthons 4-methyl-2-cyclohexenone and 5-methyl-2-cyclohexenone can both be obtained enantiomerically pure from (*R*)-pulegone and (*R*)-carvone, [16-19] these methods consist of multistep synthesis with overall low yields. In 1941, Kharash *et.al*. introduced 1,4-addition of Grignard reagent with cyclohexenone in the presence of Cu (I) instead of 1,2-addition.[20]. Cyclohexenone also undergo enatioselective Cu-catalyzed 1,4-addition using Taddol- Derived Phosphine-Phosphite ligands and 2-methyl –THF as a solvent.[21]

Pulegone is natural occurring oxygenated cyclic monoterpene ketone obtained from the essential oil of a variety of plants such as *Nepeta cataria* (Catnip) and *Mentha* species; *Mentha piperita* L. (Peppermint oil) and *Mentha pulegium* L. (Pennyroyal herb) *Mentha piperita* L. contains 4% and *M. pulegium* L. contains 60-90% pulegone as principal component of essential oil[22-25] reported to have antifeedent, pesticidal and insect repellant properties. Commercially, it was used as flavouring agent for toothpastes and mouthwashes, as valuable ingredient for perfumes and various pharmaceuticals and has been utilized in aromatherapy.[26] It has been previously reported in the literature that a, ß-Ethylenic ketone, pulegone undergoes Oppenauer oxidation[27] for the preparation of isopulegone, intramolecular aldol cyclization reaction for efficient synthesis of (+)- conocephalenol,[28] asymmetric synthesis of natural (-)-Pumiliotoxin C,[29] enatioselective synthesis of spiroacetal[30] (2S,4R,6R,8S)-2,4,8-trimethyl-l,7 -dioxaspiro[5.5]undecane employing asymmetric dihydroxylation to introduce additional chirality, reduction reactions[31-34] to yields epimeric alcohols. Pulegone also undergoes magnesium-copper-catalyzed conjugate 1,4-addition of organomagnesium reagents.[35]

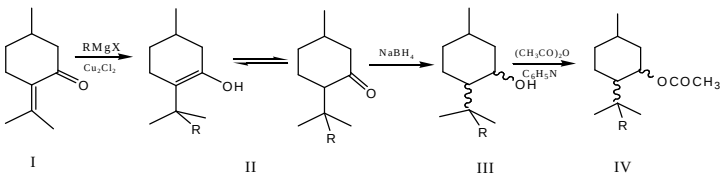
Synthetically prepared 4-(1,1-dimethylethyl)cyclohexan-1-ol acetate, widely used as perfumery product in various industries, but its multistep synthesis results into a high cost product so there is greater need to substitute with other synthetic or natural occurring compound which are readily accessible. In the light of these observations this prompted us to synthesize novel pulegone derivatives as a substititute of 4-(1,1-dimethylethyl)cyclohexan-1-ol acetate. In the present study, modifications of natural occurring a, ß- Ethylenic ketone i.e pulegone, a waste-by-product of mint industries was envisaged to have possible new product as high quality woody fruity smelling fragrant material.

MATERIAL AND METHODS

Pulegone was provided by Hindustan Mint and Agro Products Private Limited, Chandausi, Uttar Pardesh (India). It was subjected to GC-MS and found to be 65% pure, which was further purified up to 96% by using column chromatography. Melting points were recorded on Toshniwal melting point apparatus by open capillary method and are uncorrected. The GC-MS Spectra were recorded on a MS-QP-2010 series Shimadzu, Tokyo, Japan equipped with FID, AOC-20i auto-sampler and BP-20 capillary column 30m x 0.25mm x 0.25µm (polyethylene glycol, TPA treated). The NMR spectra were recorded on a Bruker Avance-300 spectrometer in $CDCl_3$ at ^{1}H (300MHz) and ^{13}C (75.4 MHz) using TMS as internal standard (chemical shift in δ ppm). The purity of the compounds was determined on Pre-coated TLC using suitable solvent system. Dry Cu_2Cl_2 was prepared by the usual method.

Pulegone (I) is subjected to Grignard reaction [36-37] with RMgX using catalytical amount of Cu_2Cl_2 to force 1,4-addition and to form cyclic unsaturated alcohols (II). The reduction of these unsaturated alcohols with $NaBH_4$ yields two pairs of dia-stereoisomers of cyclic saturated alcohols (III) which are separated by column chromatography and then subjected to acetylation using acetic anhydride

Scheme 1



I II III IV

R= methyl, ethyl, propyl,butyl; X= I or Br

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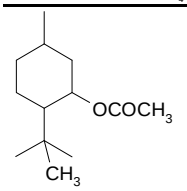
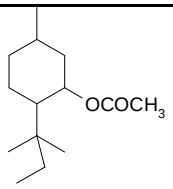
Table 1: Detailed data of the synthesized compounds

Compound	Grignard Reagent	Structure	Molecular formula	Molecular weight	IUPAC Name	%age Yield
GRP 1	CH_3MgI	a	$C_{13}H_{24}O_2$	212.0	2-(1,1-dimethylethyl)-5-methylcyclohexan-1-ol acetate	60
GRP 2	C_2H_5MgBr	b	$C_{14}H_{26}O_2$	226.0	2-(1,1-dimethylpropyl)-5-methylcyclohexan-1-ol acetate	52
GRP 3	C_3H_7MgBr	c	$C_{15}H_{28}O_2$	240.0	2-(1,1-dimethylbutyl)-5-methylcyclohexan-1-ol acetate	47
GRP 4	C_4H_9MgBr	d	$C_{16}H_{30}O_2$	254.0	2-(1,1-dimethylpentyl)-5-methylcyclohexan-1-ol acetate	54



a



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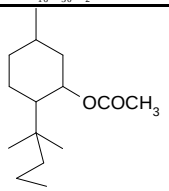
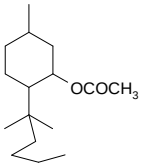


c



d

in presence of pyridine to yield cyclic esters (IV), GRP1, GRP2, GRP3, GRP4. The reaction steps are I→II→III→IV is shown in Scheme-1. Synthesized compounds GRP1, GRP2, GRP3, and GRP4 were characterized by GC-MS, ^1H and ^{13}C NMR.

Synthesis of 2-(1, 1-dimethylethyl) -5-methyl cyclohexan-1-ol acetate (GRP 1)

Step1. Synthesis of 2-(1, 1-dimethylethyl)-5-methyl-cyclohaxen-1-ol (II):
The Grignard reagent (MeMgI) was prepared by adding methyl iodide (2.02ml, 32mmol) to a mixture of preactivated magnesium turnings (0.787g, 32mmol) and dry ether (70ml) under nitrogen atmosphere[9] which is then, reacted with a mixture of pulegone (5.35ml, 32mmol) and cuprous chloride (3.2g, 32mmol), over a 25–30 min period at 0°C with constant stirring. Since the reaction is exothermic in nature so that dry toluene (15ml) was added during the reaction. After completion, the reaction mixture was hydrolyzed by drop wise addition of 2M hydrochloric acid (100ml) with constant stirring. The aqueous layer was extracted three times with 100ml portions of ethyl acetate. The combined organic layers are successively washed with saturated solution of ammonium chloride and dried over anhydrous sodium sulphate. After filtration, the solvents are removed with a Rota evaporator and the reaction product was characterized as 2-(1,1-dimethylethyl)-5-methyl-cyclohexen-1-ol (II) with 85 % yield.

Step2. Synthesis of 2-(1, 1-dimethylethyl)-5-methyl-cyclohexan-1-ol (III):
A mixture of compound (II) (2g,11mmol) and methanol (30ml) were treated with $NaBH_4$ (0.45g,11mmol) at constant stirring. On completion, the reaction mixture was extracted three times with 100 ml portions of ethyl acetate. The organic layer was dried over anhydrous sodium sulphate and further concentrated on Rota evaporator and the reaction product was characterized as 2-(1, 1-dimethylethyl)-5-methyl-cyclohexan-1-ol (III) with 70% yield. The resultant product contains two diastereoisomeric pairs which were resolved on the basis of Rf value by column chromatography using silica gel (60-120 mesh). The column was first eluted with hexane followed by gradually increasing the percentage of ethyl acetate in hexane.

Step3. Synthesis of 2-(1, 1-dimethylethyl)-5-methyl-cyclohexan-1-ol acetate (IV):
Acetic anhydride (0.39ml, 5mmol) and pyridine (2ml) were added to a solution of compound (III) (1g, 5mmol) in chloroform (30mL) with constant stirring. After completion of the reaction, reaction mixture was cooled to 0°C in a dry ice bath. The chloroform was added primarily to prevent freezing of pyridine and the reaction mixture was poured in 10% sulfuric acid with constant stirring for removal of pyridine. The sulphuric acid mixture was extracted twice with chloroform. The chloroform layer was dried over anhydrous sodium sulphate and concentrated on Rota evaporator, the reaction product was characterized as 2-(1,1-dimethylethyl)-5-methyl-cyclohex-1-anol acetate (GRP 1) with 60% yield.

Synthesis of 2-(1, 1-dimethylpropyl) -5-methyl cyclohexan-1-ol acetate (GRP2), 2-(1,1-dimethylbutyl)-5-methyl-cyclohexan-1-ol acetate (GRP 3) and 2-(1,1-dimethylpentyl)-5-methyl-cyclohexan-1-ol acetate (GRP 4) was synthesized from pulegone (2.14ml, 13mmol) and with Grignard reagents, Ethyl bromide (1.0ml, 13mmol), Propyl bromide (1.11ml, 13mmol) and Butyl bromide (1.5 ml, 13mmol) by the method as described for 2-(1,1-dimethylethyl)-5-methyl-cyclohex-1-anol acetate (GRP1). The synthesized compounds differ only in alkyl halide substitution which was summarized in Table 1.

CHARACTERIZATION OF THE SYNTHESIZED COMPOUNDS

1)2-(1-methylethene)-5-methyl-cyclohexan-1-one:
The compound shows its m/z at 152 by GCMS. ^1H NMR ($CDCl_3$, TMS, 300MHz): 1.78 (1H, m, $-CH_2-CH(CH_3)-CH_2$); 0.85 (3H, d, $-CH-CH_3$); 2.15 (2H, t, $-CH_2-CH_2$); 2.57 (2H, d, $-CH-CH_2$); 2.34 (3H, d, J=12.9, $-CH-CH_2$); 1.83 (6H, s, $=C(CH_3)_2$). ^{13}C NMR (75.4MHz, $CDCl_3$, δ, TMS=0); 203.9, 141.7, 131.7, 50.6, 34.9, 31.5, 28.5, 22.7 and 20.6.

2)2-(1,1-dimethylethyl)-5-methyl cyclohexan-1-ol acetate:
The compound shows its m/z at 212 by GCMS. ^1H NMR ($CDCl_3$, TMS, 300MHz): 1.82 (1H, m, $CH_2-CH(CH_3)-CH_2$); 3.81 (1H, q, -CH2-CH(OCOCH3)-CH); 1.53 (1H, q, $-CH_2-CH-CH_2-$); 2.24 (1H, t, $-CH-CH_2-CH$); 0.85 (3H, d, J=13.9, $-CH-CH_3$) and 1.25 (9H, s, $-CH(CH_3)_3$). ^{13}C NMR (75.4MHz, $CDCl_3$, δ, TMS=0); 169.1, 68.5, 48.5, 38.0, 34.4, 29.7, 26.8, 24.4, 22.7, 16.5 and 14.1.

3)2-(1,1-dimethylpropyl)-5-methyl-cyclohexan-1-ol acetate:
The compound shows its m/z at 226 by GCMS. ^1H NMR ($CDCl_3$, TMS, 300MHz): 4.04 (1H, q, -CH2-CH(OCOCH3)-CH); 1.45 (1H, m, $-CH_2-CH(CH_3)-CH_2$); 1.67 (1H, q, $-CH_2-CH-CH_2-$); 1.24 (2H, q, $-CH_2-CH_2-CH$); 0.86 (2H, q, $-CH_2-CH_3$); 2.02 (2H, t, $-CH-CH_2-CH$) and 0.73 (3H, t, $-CH_2-CH_3$). ^{13}C NMR (75.4MHz, $CDCl_3$, δ, TMS=0); 170.0, 66.7, 47.9, 36.4, 32.6, 31.6, 30.3, 24.4, 23.4, 21.4, 21.0, 19.2, 17.4 and 8.17.

4)2-(1,1-dimethylbutyl)-5-methyl cyclohexan-1-ol acetate:
The compound shows its m/z at 240 by GCMS. ^1H NMR ($CDCl_3$, TMS, 300MHz): 4.02 (1H, q, -CH2-CH(OCOCH3)-CH); 1.63 (1H, m, $-CH_2-CH(CH_3)-CH_2$); 0.93 (2H, m, $-CH_2-CH_2-CH_3$); 1.18 (2H, t, $-CH_2-CH_2$); 2.01 (s, 3H, $-OCOCH_3$) and 1.98 (6H, s, $CH_2-C(CH_3)_2$). ^{13}C NMR (75.4MHz, $CDCl_3$, δ, TMS=0); 170.2, 66.5, 49.0, 41.5, 38.9, 32.4, 31.4, 28.0, 25.5, 24.3, 22.7, 20.9 and 14.1.

5)2-(1,1-dimethylpentyl)-5-methyl cyclohexan-1-ol acetate:
The compound shows its m/z at 254 by GCMS. ^1H NMR ($CDCl_3$, TMS, 300MHz): 1.06 (3H, d, $-CH-CH_3$), 1.61(1H, m, $-CH_2-CH(CH_3)-CH_2$), 1.40 (4H, m, $-CH-(CH_2)_2-CH$), 3.90(1H, q, $-CH_2-CH(OCOCH_3)-CH$), 2.01 (s, 3H, $-OCOCH_3$), 1.23(6H, s, $-C(CH_3)_2$), 1.19 (2H, t, $-CH_2-CH_2$), 1.18 (2H, m, $-CH_2-CH_2-CH_2$), 0.96 (3H, t, $-CH_2-CH_3$). ^{13}C NMR (75.4MHz, $CDCl_3$,δ, TMS=0); 169.8, 50.1, 47.1, 37.7, 35.7, 32.2, 27.8, 27.4, 24.3, 22.1, 19.8, 16.9 and 14.0.

RESULT AND DISCUSSION

Inspite of some miner uses, Pulegone is not regarded as a favourite of good perfumer because it possesses an undesired minty odor similar to pennyroyal, peppermint and camphor. But a number of Pulegone derivatives have been found to use as flavouring agents in perfumery as well as in aromatherapy. In the present study, different Pulegone derivatives GRP 1, GRP 2, GRP 3 and GRP 4 were synthesized, which found to possesses woody fruity smell which can be used as a substitute of well known high quality woody smelling fragrant material 4-(1,1-dimethyl ethyl)cyclohexan-1-ol acetate.

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