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Synthesis and Characterization of new Menthopyrazole Compounds derived from Menthone

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ABSTRACT: Menthone, is a monoterpene ketone, occurs in nature and widely present in high concentration in mentha species essential oils. Also, it has become the key to the synthesis of many heterocyclic compounds exhibiting various kinds of biological activity. The objective of the present work is to synthesize new menthone derivative compounds such as menthopyrazole (HPM) and 1-phenylmenthopyrazole (PMP) by condensation of hydroxymethylenementhone with hydrazine and phenylhydrazine, respectively. The structures of these compounds were characterized by FT-IR, ^{1}H NMR and ^{13}C NMR spectra.

KEYWORDS: Menthone, Hydroxymethylenementhone, Menthopyrazole, Hydrazine, Phenylhydrazine.

1 INTRODUCTION

The widespread occurrence of p-menthane compound in many classes of natural products makes them a valuable building block for the synthesis of various biologically organic target molecules [1, 2]. Also, the synthesis of various p-menthane derivatives is extensively studied to obtain eco-friendly corrosion inhibitors [3, 4]. For instance, menthone, named p-menthan-3-one, is a monocyclic monoterpene ketone, frequently found in the essential oils throughout the labiatae family, frequently in the oils of the *mentha species* [5]. In the industry, the menthone is used as a flavoring agent in foods [6] and green corrosion inhibitor of steel in 1M HCl [7]. It has also become the key of starting the synthesis of natural compounds of some substances exhibiting various kinds of biological activity [8]. In our previous study, we report. The new p-menthane derivative having two isoxazolidine moieties and named (3R*,6R*,4' S*,8'R*,3" R*,6"R*)-3, 3"-Diisopropyl-6,6"-dimethyl-2',6' diphenyldispiro [cyclohexane-1,4'-(3. 7-dioxa-2,6-diazabi-cyclo[3.3.0]octane)-8',1"-cyclohexane]-2,2"-dione) was obtained by the reaction of 2-hydroxymethylene menthone and n-diphenylnitrone. The structure of this compound was determined by the X-ray diffraction data [9].

To continue our work, we are focused on the present study on the synthesis of new menthone derivatives, namely menthopyrazole (HMP) and 1-phenylmenthopyrazole (PMP) by the condensation of hydroxymethylenementhone with hydrazine and phenylhydrazine, respectively (schema 1).

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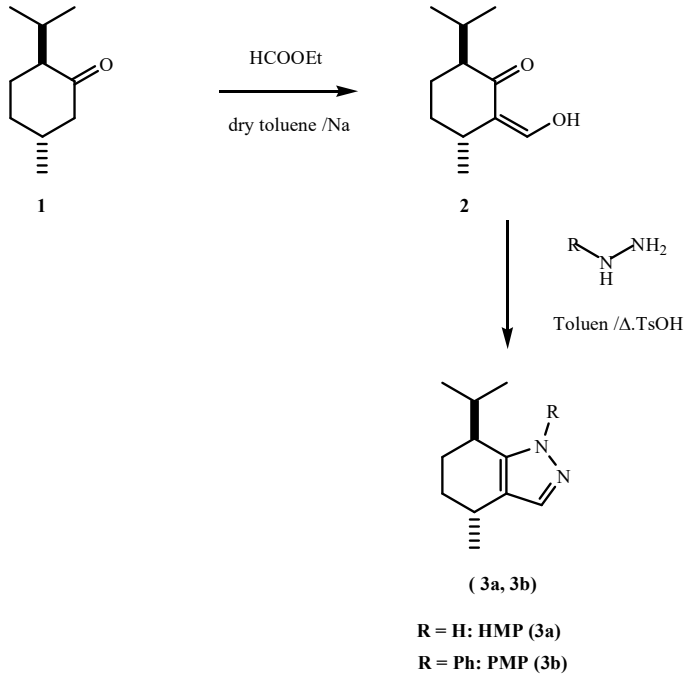


Scheme 1: Generic structure of HMP and PMP

2 RESULTS AND DISCUSSION

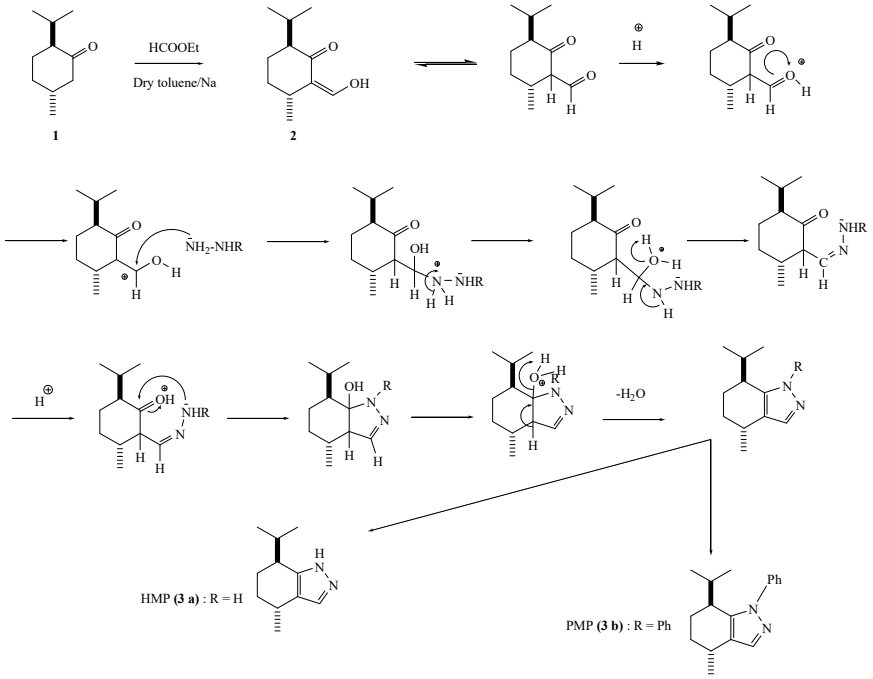
The hydroxymethylenementhone **(2)** easily available from menthone by its formulation using Ethyl format and sodium in dry toluene could be employed as the starting material in the synthesis of menthopyrazole. The aldehyde function of **(2)** exists in the enol form, this is the most stable tautomer as it allows overlapping of the π-electrons of the two double bonds and intramolecular hydrogen bonding. In the second step, we prepared menthopyrazole (HMP) and 1-phenylmenthopyrazole (PMP) by the condensation of commercially available hydrazines (RNH-NH_2) with hydroxymethylenementhone **(2)**. The experimental data are listed in (table 1).

Table 1. Reaction times, yields, boiling or malting points and physical appearance of synthesized products

Product	Time(hour)	Yield (%)	Bp or Mp(°C)	Physical appearance
2	12	80	Bp: 107	Yellowish liquid
3a	11	65	-	Yellowish viscous oil
3b	11	75	Mp: 265	Lightly color less solid

The reaction between α-β-dicarbonyl compound and hydrazine (RNH-NH_2) constitutes the main synthetic approach to the pyrazoles ring and the mechanism of these reactions has been studied several times [10, 11]. In the general case of an asymmetrically substituted α-β-dicarbonyl compound, the reaction can lead to a mixture of pyrazoles isomers, which become identical when R = H, due to the annular tautomerism related to the Mills–Nixon effect [12]. Besides, the reaction of hydroxymethylenenementhone **(2)** with hydrazine and phenyl hydrazine in dry toluene at reflux and catalysis acid in a Dean–Stark apparatus afforded as sole reaction product the corresponding pyrazoles derivatives substituted (3a) and (3b), respectively, which were easily separated by column chromatography and their elucidation were easily be verified by IR, ^{1}H NMR and ^{13}C NMR spectra. Those results are in accordance with those reported by Fernandez and al. [13], who explained this regioselectivity observed by the existence of marked kinetic differences in the dehydration step of the proposed dihydroxypyrazolidines leading to the Δ^2-pyrazoline . Those authors noted also the importance of the catalysis acid for obtaining a single compound. In contrast, the absence of the catalysis acid may lead to the production of another compound named 5-hydroxymenthopyrazole in the case of using the phenyl hydrazine.

The mechanism of the formation of PMP (**3b**) can be explained, firstly, by the nucleophile attack of the –NH_2 of hydrazine via a Michael addition and secondly by the nucleophile attack of PhHN- on the carbonyl group of compound (**2**). This regioselectivity can be explained by the stability that offering the phenyl group, in the pyrazole cycle. Indeed, the experience shows that the arylhydrazines preferentially attack the aldehyde carbon by the nitrogen unsubstituted, which is more subject to the action of deactivation of the aromatic ring than the nitrogen atom directly related to this ring [14] (schema 2).



Scheme 2: The mechanism proposed for the synthesis of pyrazoles

3 EXPERIMENTAL SECTION

3.1 MATERIALS, INSTRUMENTS AND REAGENTS

All chemical reagents used for this study were of analytical grades and obtained from Aldrich Chemical Co. Melting points were measured in a Reichert Kofler Thermopan and is uncorrected.

The IR spectrometer used is a Fourier Transform Spectrometer (Jasco FTIR-4100 type). The spectra were acquired in transmission on KBr pellets. The light beam passes through the sample with a thickness about 2 microns. The analysis was carried out between 4000 cm^{-1} and 400 cm^{-1}.

^{1}H NMR and ^{13}C NMR analysis were obtained using Bruker AC spectrometer apparatus at 300 MHz by dissolving the product in DMSO using TMS as internal standard (chemical shifts in δ values, J in Hz).

3.2 FORMULATION OF MENTHONE

The new menthone derivatives used in this study are synthesized as shown in (schema 1). This process was carried out in two steps. According to the slight modification of the method reported by TanaKa and al.[15], a solution of Mentone **(1)** (26.95 g, 175 mmol) in dry toluene (50 ml) was added to the mixture solution of Ethyl format (26 g, 350 mmol) and a suspension of sodium (8 g, 350 mmol) in dry toluene (200 ml) at ice-bath. After stirring overnight at room temperature, water was added. The organic layer was washed with 5% sodium hydroxide solution. The aqueous layer was acidified with dilute HCl and then extracted with etherEt_2O. The Et_2O layers were dried over $MgSO_4$ anhydrous. Afterward, the solvent was removed to give hydroxymethylenementhone **(2)**.

3.3 CHARACTERIZATION OF HYDROXYMETHYLENEMENTHONE (2)

RI (KBr), υ (cm^{-1}):$\nu_{C=O:}$1689;$\nu_{C=C}$: 1624; ν_{C-H} : 2959; ν_{OH} : 3440.

^{1}H NMR ($CDCl_3$), δ (ppm): =CH-OH (3.34, S) H: p-menthanic ring: (1.4-2.6, m).

^{13}C NMR ($CDCl_3$), δ (ppm): C=O**:** 200; =C (OH)**:** 169.

3.4 SYNTHESIS OF HMP (3A) AND PMP (3B)

The processes for the addition of **(2)** to hydrazines RNH-NH_2 (R= H, Ph) was carried out as follows To a rapidly stirred solution of **(2)** (0.728 g, 4 mmol) freshly prepared under dry toluene and at room temperature was added in a single addition the

corresponding hydrazines R-NH-NH_2 R= H (0.5 ml, 16 mmol), R= Ph (1 ml, 8 mmol) and a catalytic amount of TsOH (40 mg, 0.23 mmol). The reaction mixture was refluxed in a Dean-stark apparatus for 11 h, once eliminated the solvents under reduced pressure, the remaining residue was purified by column chromatography over silica gel using as eluent mixtures of Hexane/EtOAc (8/2) to give the compound HMP, systematic name**:** 7**-**isopropyl-4-methyl-4,5,6,7-tetrahydro-1H-indazole, **(3a** : R= H) and PMP**,** systematic name**:** 7-isopropyl-4-methyl-1-phenyl-4,5,6,7-tetrahydro-1H-indazole, **(3b**: R= Ph**)**, after removing the solvent under reduced pressure.

3.5 CHARACTERIZATION OF HMP: 7-ISOPROPYL-4-METHYL-4,5,6,7-TETRAHYDRO-1H-INDAZOLE (3A)

RI (KBr), υ (cm^{-1}): 3461, 2857, 1585, 1380, 1369, 1205, 1174, 1091, 954 cm^{-l}.

^{1}H NMR ($CDCl_3$) δ (ppm):7.36 (1H, s), 2.76, 2.78 (1H, m), 2.14, 2.13 (2H, m), 1.50 (1H, m), 1.22 (3H, d), 1.04 (3H, d), 0.68 (3H, d).

^{13}C NMR and DEPT ($CDCl_3$), δ (ppm): 18.73 (CH_3), 20.19 (CH_3), 22.3 (CH_3), 26.1 (CH), 29.65 (CH_2), 30.8 (CH), 38.7 (CH), 122 (CH), 132 (C), 144 (C).

3.6 CHARACTERIZATION OF PMP: 7-ISOPROPYL-4-METHYL-1-PHENYL-4,5,6,7-TETRAHYDRO-1H-INDAZOLE (3B)

RI (KBr), υ (cm^{-1}): 950, 2927, 1660, 1460, 1380, 1370, 1044, 866 cm^{-1}**.**

^{1}H NMR ($CDCl_3$) δ (ppm):7.62 (1H, s), 7.4 (5H, m), 3(1H, m), 2.86 (1H, m), 1.79 (2H, m), 1.47 (1H, m), 1.25 (3H, d), 0.94 (3H, d), 0.87 (3H, d).

^{13}C NMR and DEPT ($CDCl_3$), δ (ppm): 18.15 (CH_3), 20.92 (CH_3), 20.78 (CH_3), 20.57(CH_3), 21.56 (CH_2), 29.90 (CH_2), 33 (CH), 37 (CH), 123 (C), 124 (CH), 127 (CH), 129 (CH), 137 (CH), 140 (C), 141 (C).

4 CONCLUSION

In our work, we have synthesized new menthone derivatives in two stages. In the first stage, we synthesized the hydroxymethylenementhone by formulation of menthone. The second stage led us to synthesis the menthopyrazole (HPM) and the 1-phenylmenthopyrazole (PMP), with good yields ranging from 65 to 75%, respectively, by condensation of hydroxymethylenementhone with hydrazine and phenylhydrazine, respectively.The structures of these compounds were confirmed and characterized by the uses of spectroscopic methods of Fourier Transform Infrared (FT-IR) and the Nuclear Magnetic Resonance (NMR) ^{1}H and ^{13}C.

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