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Clove (Eugenia Caryophyllata) Extraction and Synthesis of New Pyrazole Derivatives from Eugenol

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S. Hamri [α], K. Rhazri [σ], A. Hafid [ρ], H. Ouchetto [ω], Y. Hajbi [¥] & M. Khouili [§]

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I. Introduction

According to the literature, the majority of natural products derived from plants by different extraction methods. In bibliography, eugenol extracted from clove, is cited as a substance similar to an odorous oil, having the same functional groups as those of the family of natural allyl phenols such as chavicol (A), estragol (B), and osmorhyzol (C) (fig. 1).[1]

This is also the main component of the oil of clove (Eugenia caryophyllata), also present in many herbs like cinnamon.[2]

Eugenol **1** is used as raw material in the manufacture of several drugs. Thus, in dentistry, it is employed as an antiseptic, disinfectant and also widely used as an analgesic.[3, 4] This is also the major active ingredient of rhizoma Acori graminei (RAG). Cited in the literature as a medicinal herb that has been used for epilepsy and forgetting in East Asia for centuries, down cytotoxicity $A\beta_{1\text{-}40}$-induced PC-12 cells in vitro.[10]

In cosmetic and food products, it is used as a flavoring, antimicrobial, and antioxidant agent.[5] In addition to these antioxidant properties,[6] it protects neurons in culture from toxic events.[7] It has activities of anti-convulsive[8] and hypothermic[9] agent.

Complex heterocyclic systems such as: isomerization in polar protic solvents,[11] the conversion into ferulic acid,[12] oxidation[13] and enzymatic glycosylation of eugenol by cultured cells of *E. perriniana*.[14] Much of the synthetic strategy is devoted to the preparation of heterocyclic compounds derived from medicinal plants.

As part of our research, we have synthesized new pyrazole derivative structure from eugenol **1**. In this case, the 4-allyl-2 methoxyphenol (eugenol) **1** has a high reactivity, attributed to the functional groups of the aromatic ring. Recently, considerable attention has been focused on the development of new methodologies to synthesize many kinds of substituted pyrazolic subunit.[15] Indeed, these compounds are now widely recognized as important materials showing interesting biological activities and also as intermediate on heterocyclic chemistry. Many pyrazoles derivatives known to exhibit a wide range of biological properties such as antihyperglycemic, analgesic, anti-inflammatory, antibacterial, hypoglycaemic, sedative-hypnotic activity.[16] Although many pyrazoles have pharmacological activities,[17] those who have found a practical application, their activities are due more to the various substituents that the intrinsic activity of the pyrazole ring itself.

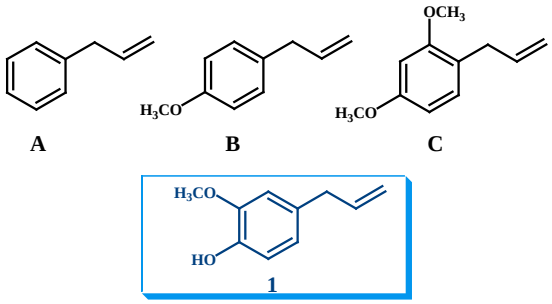

Fig. 1 : Names of allyl phenols natural

According to studies cited in the literature and those carried out in our laboratory for building five-membered pyrazole cycles prompted us to explore new methodologies for the synthesis of substituted 1-aryl-pyrazoles.[18]

According to studies cited in the literature and those carried in our laboratory for the construction of five-membered pyrazole cycles, we looked at the development of new methodologies for the synthesis of substituted 1-aryl-pyrazoles namely the 1,3-dipolar cycloaddition.[18] This is a process for the synthesis of several classes of azoles, such as isoxazoles, triazoles

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and pyrazoles.[19] Pyrazoles are part of heterocyclic structures most commonly used for the development of new drugs.[20, 21] Subsequently, David J. Babinski et *al.* have synthesized heterocyclic compounds containing the pyrazole skeleton, following a synthetic strategy based on pericyclic reactions for the preparation of pyrazoles 3,4,5-tri-substituted by a tandem catalytic cross-coupling/electrocyclization enol triflates and diazoacetates.[19-f]

Our investigation of this system is part of a current study on the synthesis of new pyrazole derivatives via 1,3-dipolar cycloaddition reaction. In this paper, we present the synthesis of 1-aryl-4,5-dihydro-1*H*-pyrazoles from eugenol, previously extracted of cloves, and different dipoles *N*-aryl-*C*-ethoxycarbonitrilimines.

II. Results and Discussion

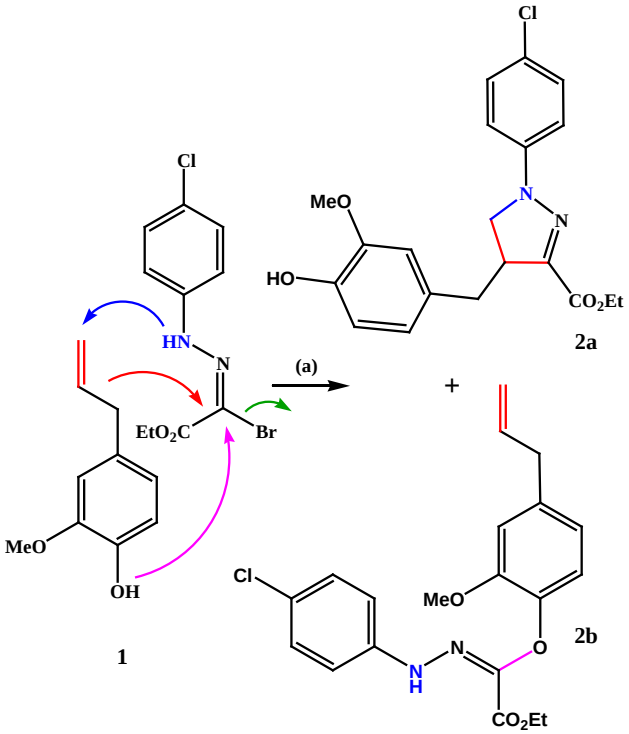
Clove (buds) was purchased commercially for extraction of essential oil eugenol. *Eugenia caryophyllata* buds were converted into powder by crushing and extracted by steam distillation of water for 4 hours.

The eugenol **1** will then be separated from the water by extraction with diethyl ether. The diethyl ether solution will then be dried and evaporated at a temperature not exceeding 40°C, to afford the eugenol oil. This oil was then purified by chromatography and identified by NMR ^{1}H and ^{13}C.[22]

Thereafter, new cycloaddition reactions with 4-allyl-2-methoxyphenol **1** as a dipolarophile were developed using the *N*-aryl-*C*-ethoxycarbonitrilimine derivative: the (*Z*)-ethyl 2-bromo-2-(2-(4-chlorophenyl)-hydrazono)acetate, who act as a dipole. The synthesis of the latter, was performed under conditions described by Hamilton et al.,[23] according to one reaction of diazonium chloride aniline with ethyl diazoacetate treated with a solution of bromine.

The 1,3-dipolar cycloaddition of 4-allyl-2-methoxy-phenol **1** with allyl group formed the corresponding pyrazole **2a**. Unfortunately, we have noted the presence of compound **2b** according *O*-alkylation reaction.[24] To avoid this side reaction, the 1,3-dipolar cycloaddition reaction was carried in different non-polar solvents.

The desired derivative **2a** (1-aryl-4,5-dihydro-1*H*-pyrazoles) was formed predominantly in relation to the derivative **2b** (*N*-aryl-*C*-ethoxy-carbonitrilimines). The latter product is derived from the condensation of phenol on the dipole *via* a nucleophilic substitution (*SN*) reaction (Scheme 1). The conversion rate, according to the results (Table 1), increases with the temperature without any degradation. We noted that the best conversion was obtained after 48 hours, when the reaction was carried out in refluxing toluene.

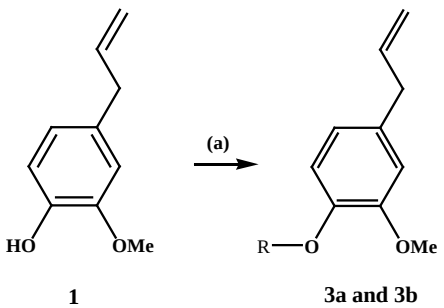


Scheme 1 : Reagents and conditions: (a) Et_3N, solvent, reflux, 48h

Table 1 : Reaction yields depending on solvent

Solvent	**2a** yield (%)	**2b** yield (%)
THF	6	11
Toluene	30	16
Xylene	20	1

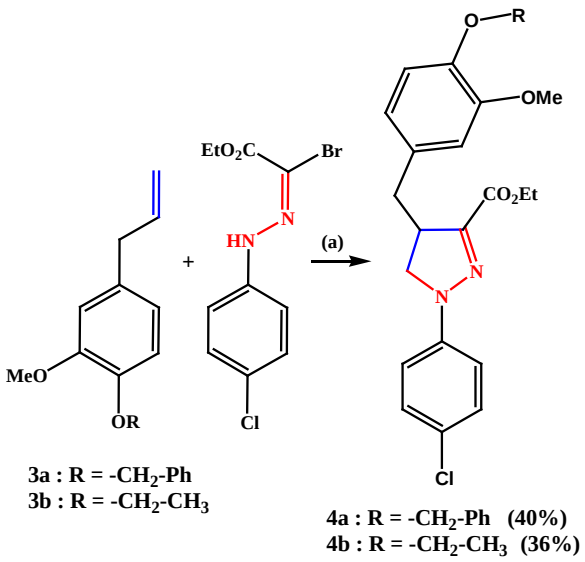
To control the dipolar cyclization reaction and avoid the formation of the ether-oxides, first we initially protected the phenol by a simple nucleophilic substitution reaction with various alkyl halides, which also allow us studying the donor effect of the system. The *SN* reaction was carried out with K_2CO_3 in acetone (Scheme 2).



Scheme 2 : Reagents and conditions: (a) RX, K_2CO_3, Acetone, reflux, 4 h

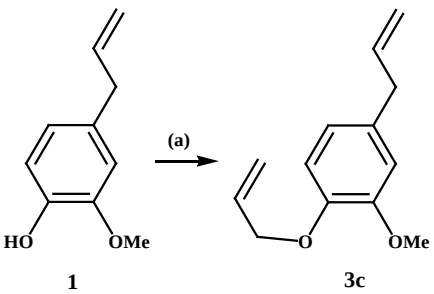
Table 2 : Synthesis, yields of compounds 3a and 3b

R	Compound	Yield (%)
Benzyl	**3a**	92
Ethyl	**3b**	90



Scheme 3 : Reagents and conditions: (a) Et_3N, Toluene, reflux, 48 h

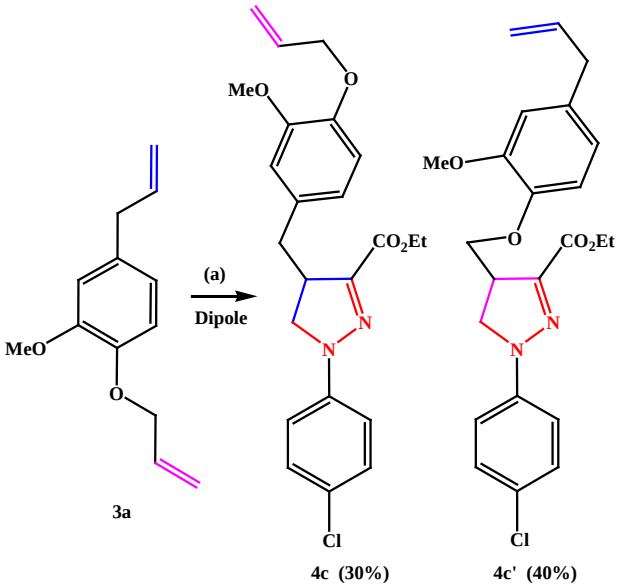
The desired compounds, **3a and 3b**, were isolated in good yields (Scheme 2, Table 2) and were subjected to condensation reaction with *N*-aryl-*C*-ethoxy-carbonitrilimine to afford only derivatives of 1-aryl-4,5-dihydro-1*H*-pyrazole, **4a** and **4b**, with average yields. This modest result is presumably due to the degradation of the *N*-aryl-*C*-ethoxycarbonitrilimine (Scheme 3).



Scheme 4 : Reagents and conditions: (a) allyl chloride, K_2CO_3, Acetone, reflux, 4 h

We envisioned the protection of the phenol with allyl group so as to examine the effect of the presence of two dipolarophile systems in our condensation reaction.

Thus, the eugenol **1** was engaged in *SN* reaction in presence of allyl chloride, according the conditions described for the preparation of **3a** and **3b**, to afford the compound **3c** in good yield (91%) (Scheme 4).The resulting allyl **3a** was heated in toluene at reflux for 48 hours in the presence of a dipole: the (*Z*)-ethyl 2-bromo-2-(2-(4-chlorophenyl)-hydrazono) acetate, to give two dipolar cycloadducts **4c** (30%) and **4c'** (40%). (Scheme 5) we noted that this 1,3-dipolar cycloaddition is not regioselective.



Scheme 5 : Dipole: (*Z*)-ethyl 2-bromo-2-(2-(4-chlorophenyl)-hydrazono) acetate; (a) Et_3N, Toluene, reflux, 48 h

III. Experimental Section

Melting points were taking for samples in capillary tubes with an electro-thermal apparatus and are uncorrected. ^1H NMR and ^{13}C NMR were recorded on a Bruker Avance DPX250 spectrometre (300 MHz ^1H, 75 MHz ^{13}C) using trimethylsilane as the internal standard, chemical shifts were reported in parts par million (ppm, δ units). Coupling constants were reported in units of hertz (Hz). Flash chromatography was performed on silica gel 60 (40–63 mesh). Thin layer chromatography (TLC) was carried out on Merck silica gel 60F254 precoated plates. Visualization was made with ultraviolet light. All organic solvents were distilled immediately prior to use.

a) General procedure for preparation of compound 2a and 2b

To a solution of 4-allyl-2-methoxyphenol 1 (1.22 mmol) in dry THF, toluene or xylene (10 mL); was added (3.4 mmol) the (*Z*)-ethyl 2-bromo-2-(2-(4-chlorophenyl)-hydrazono) acetate, and 0.52 mL of the triethylamine. The mixture was heated at solvent reflux for 48 hours. After cooling, the reaction mixture was extracted three times with dichloromethane. Organic phase was dried, evaporated and the crude was purified by column chromatography (eluent: ethyl acetate - hexane, 2: 8) to give **2a** and **2b**.

b) Ethyl-5-(4-hydroxy-3-methoxybenzyl)-1-(4 chlorophenyl)-4,5-dihydro-1H-pyrazole-3-carboxylate 2a

This compound was obtained as a yellow solid. Yields from: THF (6%), toluene (30%), xylene (20%). Mp: 124-126°C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.23 (d, J = 9.1 Hz, 4H), 6.85 (d, J = 8.2 Hz, 1H), 6.65 (dd, J = 1.9 and 8.2 Hz,1H), 6.55 (d, J = 1.9 Hz ,1H), 5.55 (s, 1H), 4.82-4.55 (m, 1H), 4.3 (q, J = 7.2 Hz, 2H), 3.82 (s, 3H), 3.19-2.62 (m, 4H), 1.35 (t, J = 7 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 162.86, 146.75, 144.82, 140.96, 139.68, 129.39, 127.84, 126.36, 122.25, 116.03, 114.73, 112.02, 62.22, 61.35, 56.08, 36.97, 36.52, 14.45.

c) (4-Allyl-2-methoxy-phenoxy)-[(4-chloro-phenyl)-hydrazono]acetic acid ethyl ester 2b:

This compound was obtained as a yellow oil. Yields from: THF (11%), toluene (16%), xylene (1%). ^{1}H NMR (300MHz, $CDCl_3$): δ 9.80 (s, 1H), 7.40 (d, J = 8.4 Hz, 2H), 7.10 (d, J = 8.4 Hz, 2H), 6.80-6.61 (m, 3H), 5.94-5.76 (m, 1H), 5.15-5.01 (m, 2H), 4.22 (q, J = 7.1 Hz, 2H), 3.87 (s, 3H), 3.39-2.22 (m, 2H), 1.25 (t, J = 6.8 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): 158.6, 154.0, 151.3, 141.2, 140.0, 136.5, 131.1, 129.7, 124.3, 122.8, 117.7, 116.8, 114.5, 61.4, 56.2, 48.4, 13.8.

d) General procedure for preparation of compounds 3a-c

To a solution of 4-allyl-2-methoxyphenol **1** (0.3 g, 1.7 mmol) in dry acetone (10 ml) was added K_2CO_3 (0.67 g, 4.88 mmol). The reaction was stirred in oil bath at 50-80°C. After 1 hour, 1.7 mmol of the corresponding haloalkyl groups or allyl chloride was added to a previous solution and the mixture was heated for 4 hours. After complete conversion of the starting material, the reaction was evaporated to dryness and the residue was purified by column chromatography (eluent: ethyl acetate - hexane, 1: 9) to give the corresponding compounds **3a-c**.

e) 4-Allyl-1-(benzyloxy)-2-methoxybenzene 3a

The compound was obtained as a yellow oil (92%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.50-7.19 (m, 5H), 6.78-6.58 (m, 3H), 6.10-5.90 (m,1H), 5.07 (s, 2H), 5.20-5.00 (m, 2H), 3.80 (s, 3H), 3.40-3.20 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 149.6, 146.5, 137.6, 137.4, 133.3, 128. 7, 127.7, 127.3, 120.46, 115.6, 114.3, 112.4, 71.2, 55.9, 39.8.

f) 4-Allyl-1-methoxy-2-ethoxybenzene 3b

The compound was obtained as a yellow oil (90%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.60-6.70 (m, 3H), 5.90-5.80 (m, 1H), 5.00-4.90 (m, 2H), 4.00 (q, J = 6 Hz, 2H), 3.80 (s, 3H), 3.30-3.16 (m, 2H), 1.33 (t, J = 6 Hz, 3H, O-CH_2-CH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 149.3, 146.7, 137.7, 132.6, 120.0, 115.5, 112.4, 112.2, 64.4, 55.8, 39.8, 14.9.

g) 4-Allyl-1-allyloxy-2-methoxybenzene 3c

The compound was obtained as a yellow oil (91%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.90-6.70 (m, 3H), 6.20-5.90 (m, 2H), 5.48 (dd, J = 3.3 and 1.5 Hz, 1H), 5.4 (dd, J = 3.3 and 1.5 Hz, 1H), 5.36-5.24 (m, 2H), 5.15-5.05 (m, 2H), 4.69-4.51 (m, 2H), 3.85 (s, 3H), 3.38-3.26 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): 149.7, 146.8, 136.5, 133.6, 130.8, 122.4, 117.2, 116.4, 115.2, 114.1, 72.3, 56.2, 48.2.

h) General procedure for preparation of 4a-c

To a solution of each compounds **3a-c** in dry toluene (10 mL) was added 1.2 equivalents of *N*-aryl-*C*-ethoxycarbonitrilimine and appropriate quantity of triethylamine. The mixture was stirred at reflux for 48 hours. After cooling, the mixture was extracted with dichloromethane. Organic phase was evaporated and purified by column chromatography (eluent: ethyl acetate - hexane, 2: 8) to give the corresponding compounds.

i) Ethyl-5-(4-Benzyloxy)-3-methoxybenzyl)-1-(4-chlorophenyl)-4,5-dihdro-1H-pyrazole-3-caboxylate 4a

This compound was obtained as a yellow solid (40%). Mp: 102-104°C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.28-7.13 (m, 5H), 7.00 (d, J = 8.1 Hz, 2H), 6.80 (d, J = 7.9 Hz, 2H), 6.60 (d, J = 7.8 Hz, 1H), 6.57-6.48 (m, 1H), 6.00 (d, J = 7.8 Hz, 1H), 5.20 (s, 2H), 4.87-4.75 (m, 1H), 4.20 (q, J = 7.3 Hz, 2H), 3.75 (s, 3H), 3.40-3.20 (m, 2H), 1.40-1.60 (m, 2H), 1.10 (t, J = 7 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 172, 160, 150, 146, 142, 140, 136, 132, 129, 127, 120, 119, 117, 111, 65, 63, 56, 40, 15, 13.

j) Ethyl-5-(4-ethoxy-3-methoxybenzyl)-1-(4-chloro-phenyl)-4,5-dihydro-1H-pyrazole-3-carboxylate 4b

This compound was obtained as a yellow solid (36%). Mp: 124-126°C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.33 (d, J = 9.1 Hz, 2H), 7.2 (d, J = 9.1 Hz, 2H), 6.80 (d, J = 8.7 Hz, 1H), 6.68-6.56 (m, 1H), 5.99 (d, J = 8.7 Hz, 1H), 5.07-4.92 (m, 1H), 4.18 (q, J = 6.9 Hz, 2H), 4.00 (q, J = 7.2 Hz, 2H), 3.8 (s, 3H), 3.36-3.25 (m, 2H), 1.4-1.6 (d, J = 7.2 Hz, 2H), 1.44 (t, J = 7.2 Hz, 3H), 1.10 (t, J = 6.9 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 158.9, 149, 146, 142, , 136, 132, 130, 129, 120, 119, 115, 113, 112, 64, 63, 55, 40, 14.8, 13.6.

k) Ethyl-5-(4-(allyloxy)-3-methoxybenzyl)-1-(4-chlorophenyl)-4,5-dihydro-1H-pyrazole-3-carboxylate 4c

This compound was obtained as a yellow oil (30%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.3 (d, J = 9.1 Hz, 2H), 7.2 (d, J = 9.1Hz, 2H), 6.82 (d, J = 8.1Hz, 1H), 6.68 (dd, J = 2.1 and 8.1 Hz, 1H), 6.6 (d, J = 2.1 Hz, 1H), 6.18-6.02 (m, 1H), 5.4 (dd, J = 1.5 and 17.4 Hz, 1H), 5.3 140 (dd, J = 1.5 and 10.2 Hz, 1H), 4.80-4.70 (m, 1H), 4.65-4.58 (m, 2H), 4.32 (q, J = 7.2, 2H), 3.85 (s, 3H), 3.22-2.65 (m, 4H), 1.38 (t, J = 7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 163.08, 149.93, 147.46, 141.18, 139.9, 133.65, 129.18, 126.6, 121.81, 118.34, 116.26, 114.05, 113.38, 70.29, 62.34, 61.56, 56.37, 37.14, 36.79, 14.67.

l) Ethyl-5-((4-allyl-2-methoxyphenoxy)methyl)-1-(4-chlorophenyl)-4,5-dihydro-1H-pyrazole-3-carbox-ylate 4c'

This compound was obtained as a yellow oil (40%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.25 (d, *J* = 9.6Hz, 2H), 7.2 (d, *J* = 9.6 Hz, 2H), 6.75-6.65 (m, 3H), 6.2-5.88 (m, 1H), 5.12-5.05 (m, 2H), 4.95-4.85 (m, 1H), 4.38 (q, *J* = 7.2 Hz, 2H), 4.86-3.60 (m, 2H), 3.82 (s, 1H), 3.42-3.30 (m, 4H), 1.4 (t, *J* = 7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 162.91, 150.26, 146.29, 141.37, 140.61, 135.02, 129.64, 126.66, 120.93, 116.15, 115.40, 113.08, 68.79, 61.62, 60.54, 56.18, 40.13, 36.29, 14.67.

IV. Extraction of Eugenol

Commercially available plant material (buds) was purchased for the essential oil extraction. The buds of Eugenia caryophyllata were extracted by steam distillation for 4h. The distillation was extracted with diethyl ether, dehydrated with anhydrous sodium sulfate and solvent removed and by evaporation using a rotator evaporator at 40°C. The residual oil obtained was used for chemical analysis, further purification and biological assays. The extracted oil was purified by normal phase chromatography on silica gel with the eluent of n-hexane ; ethyl acetate (10 : 1). The eluate was collected in 30 fractions of 30ml, Fractions collected were evaporated and of the residual obtained is colorless oil was identified by ^{1}H-NMR (250 MHz, $CDCl_3$), ^{13}C-NMR (62,5MHz, $CDCl_3$).

V. Conclusion

New structure pyrazole derivatives have been prepared by 1,3-dipolar cycloaddition with eugenol as the starting material. The latter was extracted from cloves by steam distillation. The cycloaddition reaction with the compound (*Z*)-ethyl 2-bromo-2-(2-(4-chlorophenyl)-hydrazono) acetates, used as a dipole, was carried out with modest yields. In the case of the presence of dipolarophile: 4-allyl-1 (allyloxy)-2-methoxybenzene, the reaction proceeded with full conversion and 70%, with the formation of the two possible regioisomeric products, are: ethyl 4-(4-(allyloxy)-3-methoxybenzyl)-1-(4-chlorophenyl)-4,5-dihydro-1*H*-pyrazole-3-carboxylate (**4c**) and ethyl 4- ((4-allyl-2-methoxyphenoxy)methyl)-1-(4-chlorophenyl)-4,5-dihydro-1*H*-pyrazole-3-carboxylate (**4c'**). The two regioisomeric products were obtained in good yields. This method was used to prepare a variety of substituted 1-(4-aryl)-4,5-dihydro-1*H*-pyrazole. All synthesized compounds were purified and identified by conventional spectroscopic methods.

VI. Acknowledgements

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References Références Referencias

1. (a) Gilbertson, G.; Koenig, R. *Anal. Chem.* **1981**, *53*, 61R–77R. (b) Marotti, M.; Piccaglia, R.; Giovanelli, E. J. *Agric. Food Chem.* **1996**, *44*, 3926. (c) Markowitz, K.; Moynihan, M.; Liv, M.; Kim, S. *Oral Surg. Oral Phatol.* **1992**, *73*, 729. (d) Asha, M. K.; Prashanth, D.; Murali, B.; Padmaja, R.; Amit, A. *Fitoterapia* **2001**, *72*, 669. (e) Kamatou, G. P.; Vermaak, I.; Viljoen, A. M. *Molecules* **2012**, *17*, 6953. (f) Delogu, G.; Fabbri, D.; Dettori, M. A.; Forni, A.; Casalone, G. Tetrahedron: *Asymmetry* **2004**, *15*, 275.
2. Usta, J.; Kreydiyyeh, S.; Barnabe, P.; Bou-Moughlabay, Y.; Nakkash-Chmaisse, H. *Hum. Exp. Toxicol.* **2003**, *22*, 355.
3. (a) Hattori, M.; Hada, S.; Watahiki, A.; Ihara, H.; Shu, Y.-Z.; Kakiuchi, N.; Mizuno, T.; Namba, T. *Chem. Pharm. Bull.* **1986**, *34*, 3885; (b) Himejima, M.; Kubo, I. *J. Nat. Prod.* **1992**, *55*, 620; (c) Fujisawa, S.; Atsumi, T.; Satoh, K.; Sakagami, H. *J. Dent. Res.* **2003**, *82*, 43.
4. Ohkubo, T.; Shibata M. *J. Dent. Res.* **1997**, *76*, 848.
5. (a) Yanishlieva, N. V.; Marinova, E. M. *Eur. J. Lipid Sci. Technol.* **2001**, *103*, 752; (b) Suppakul, P.; Miltz, J.; Sonneveld, K.; Biger, S. *J. Agric. Food Chem.* **2003**, *51*, 3197.
6. Fujisawa, S.; Atsumi, T.; Kadoma, Y.; Sakagami, H. *Toxicology* **2002**, *177*, 39.
7. Wie, M. B.; Won, M. H.; Lee, K. H.; Shin, J. H.; Lee, J. C.; Suh, H. W.; Song, D. K.; Kim, Y. H. *Neurosci. Lett.* 1997, *225*, 93.
8. Sayyah, M.; Valizadeh, J.; Kamalinejad, M. *Phytomedicine* **2002**, *9*, 212.
9. Won, M. H.; Lee, J. C.; Kim, Y. H.; Song, D. K.; Suh, H. W.; Oh, Y. S.; Kim, J. H.; Shin, T. K.; Lee, Y. J.; Wie, M. B. *Neurosci. Lett.* **1998**, *254*, 101.
10. (a) Irie, Y.; Keung, W. M. *Brain Res.* **2003**, *963*, 282. (b) Irie, Y.; Itokazu, N.; Anjiki, N.; Ishige, A.; Watanabe, K.; Keung, W. M. *Brain Research* **2004**, *1011*, 243.
11. Sumeet, K. S.; Vivek, K. S.; Raksh, V. J. *Journal of Molecular Catalysis A: Chemical* **2006**, *245*, 200.
12. Nicholas, J. W.; Narbad, A.; Craig, B. F.; Williamson, G. *Current Opinion in Biotechnology* **2000**, *11*, 490.
13. Souza, B.; Dayse, P.; Alini, T. F.; Heiddy, M. A.; Gisele, C. S.; Olsen Mara, H. N.; Lucio, C. F. C. F.; Antunes O. A. C. *Catalysis Communications* **2007**, *8*, 1041.
14. Kei, S.; Yoko, K.; Tomohisa, N.; Hatsuyuki, H.; Nobuyoshi, N.; Hiroki, H. *Phytochemistry* **2006**, *7*, 2256.
15. (a) Camacho, M. E.; Leon, J.; Entrena, A.; Velasco, G.; Carrion, M. D.; Escames, G.; Vivo, A.; Castroviejo, D. A.; Gallo, M. A.; Espinosa, A. *J. Med. Chem.*, **2004**, *47*, 5641. (b) Goodell, J. R.; Puig-Basagoiti, F.; Forshey, B. M.; Shi, P. Y.; Ferguson,

D. M. *J. Med. Chem.*, **2006**, *49*, 2127. (c) Schenone, S.; Brullo, C.; Bruno, O.; Bondavalli, F.; Mosti, L.; Maga, G.; Crespan, E.; Carraro, F.; Manetti, F.; Tintori, C.; Botta, M. *Eur. J. Med. Chem.*, **2008**, *43*, 2665.

16. (a) Cottineau, B.; Toto, P.; Marot, C.; Pipaud, A.; Chenault, J. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 2105. (b) Lee, K. Y.; Kim, J. M.; Kim, J. N. *Tetrahedron Lett.* **2003**, *44*, 6737. (c) John, W. L.; Patera, R. M.; Plummer, M. J.; Halling, B. P.; Yuhas, D. A. *Pest. Sci.* **1994**, *42*, 29.
17. Goodman, L. S.; Gilman, A. *The Pharmacological Basis of Therpeutics; Macmillan: New York,* **1980**.
18. (a) Patel, H. V.; Vyas, K. A.; Fernandes, P. S. *Indian J. Chem.* **1990**, *29B*, 966. (b) Patel, H. V.; Vyas, K. A.; Fernandes, P. S. *Indian J. Chem.* **1990**, *29B*, 836. (c) Patel, H. V.; Vyas, K. A.; Fernandes, P.S. *Indian J. Chem.* **1989**, *28B*, 470. (d) Patel, H. V.; Vyas, K. A.; Fernandes, P.S. *Indian J. Chem.* **1989**, *28B*, 56. (e) Fadel S.; hajbi Y.; Rakib E.M.; Khouili M.; Pujol M.D.; Guillaumet G.; *Synth. Commun.* **2004**, *34*, 2195. (f) S. Fadel, S . Hamri, Y. Hajbi, F. Suzenet, A. Hafid, E.M. Rakib, M. Khouili, M. D. Pujol, G. Guillaumet *ARKIVOC*, **2011**, *ii*, 240.
19. (a) Padwa, A.; Pearson, W. H. Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry Toward Heterocycles and Natural Products; *Wiley & Sons: Hoboken, NJ,* **2003**. (b) Pérez, P.; Domingo, L. R.; Aurell, M. J.; Contreras, R.*Tetrahedron* **2003**, *59*, 3117. (c) Dang, Q.; Brown, B. S.; Erion, M.D. *J. Org. Chem.* **1996,** *61,* 5204. (d) Moura N. M. M.; Giuntini F.; Faustino M. A. F.; Neves M. G. P. M. S.; Tomé A. C.; Silva A. M. S.; Rakib E. M.; Hannioui A.; Abouricha S.; Röder B.; Cavaleiroa J. A. S. *ARKIVOC* **2010,** *v*, 24. (e) Shawali A. S.; Farghaly T. A.; Aldahshoury A. I. R. *ARKIVOC* **2010**, ix, 19. (f) Babinski, D. J.; Aguilar, H. R.; Still, R.; Frantz, D. E. *J. Org. Chem.* **2011**, *76*, 5915.
20. (a) Shawali, A. S.; Samy, N. A. *The Open Bioactive Compd. J.* **2009**, *2*, 8. (b) Shawali, A. S. *Current Org. Chem.* **2010**, *14*, 784.
21. (a) Haque, T. S.; Tadesse, S.; Marcinkeviciene, J.; Rogers, M. J.; Sizemore, C.; Kopcho, L. M.; Amsler, K.; Ecret, L. D.; Zhan, D. L.; Hobbs, F.; Slee, A.; Trainor, G. L.; Stern, A. M.; Copeland, R. A.; Combs, A. P. *J. Med. Chem.* **2002**, *45*, 4669. (b) Pfifferkorn, J. A.; et al. *J. Med. Chem.* **2008**, *51*, 31. (c) Sweeney, Z. K.; et al. *J. Med. Chem.* **2008**, *51*, 7449.
22. Bouali J.; Rhazri K.; Hamri S.; Zaiter J.; Ouchetto H.; Hafid A.; El Batal H.; Hasib A.; Khouili M. *Chemical and Process Engineering Research* **2013**, *12*, 19-27.
23. Sharp B.; Hamilton C. S. *J. Amer. Chem. Soc.* **1946**, *68*, 588.
24. a) Enayati, A. A.; Vatandoosty, H.; Ladonniy, H.; Townson, H.; Hemingway, *J. Medical and Veterinary Entomology* **2003**, *17*, 138. (b) Lynd, A.; Ranson, H.; McCall, P. J.; Randle, N. P.; Black IV, W. C.; Walker, E. D.; Donnelly, M. J. *Malaria Journal* **2005**, *4*:16, 1. (c) Takken, W. *Tropical Medicine and International Health* **2002**, 7:12, 1022. (d) Khambay, B. P. S. *Pesticide Outlook* **2002**, *13*(2), 49. (e) Darriet, V.; Chandre, F.; Hougard, J. M. *Journal of the American Mosquito Control Association* **2004**, *20*: 438. (f) Gazzaeva, R.; Mochalov, S.; Archegov, B.; Zefirov, N. *Chemistry of Heterocyclic Compounds* **2005**, *41*, 272. (g) Gnad, F.; Rieser, O. *Chem. Rev.* **2003**, *103*, 1603. (h) Pietruszka, J. *Chem. Rev.* **2003**, *103*, 1051. (i) Bakunov, S. A.; Rukavishnikov, A. V.; Tkachev, A. V. *Synthesis* **1994**, 935. (j) Lee, P. H.; Kim, J. S.; Kim, Y. C.; Kim, S. *Tetrahedron Letters* **1993**, *34*, 7583. (k) Hammond, G. B.; Cox, M. B.; Wiemer, D. F. *J. Org. Chem.* **1990**, *55*, 128. (l) Arlt, D.; Jautelat, M.; Lantzsch, R. *Angew. Chem. Int.Ed. Engl.* **1981**, *20*, 703.