International Journal of Current Engineering and Technology
E-ISSN 2277 – 4106, P-ISSN 2347 – 5161
©2016 INPRESSCO®, All Rights Reserved
Available at http://inpressco.com/category/ijcet

Research Article

New Method of N-phenyl-3-methyl-3 hydroxy-5-pyrazolone production

Sarmad Tailb Najim†, EKhlas A. Salman†* and Wlada Alamery‡

†Chemical Engineering Department, Al-Nahrain University, Iraq
‡Pharmaceutical Department,, ACAI Company, Iraq

Accepted 15 March 2016, Available online 23 March 2016, **Vol.6, No.2 (April 2016)**

Abstract

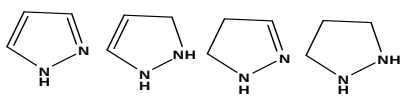
This study involved the optimization of determining parameters in reaction conditions of N-phenyl-3-methyl-3hydroxy-5-pyrozolone process Characterizations were carried out by analyzing the spectrum of Fourier transform infrared (FTIR), (nuclear magnetic resonance) 1H NMR, and 13C-NMR.The optimized reaction conditions were determined by the method has been successfully applied to the assay in pure and pharmaceutical forms in the system, the time taken for a complete reaction, the temperature used for the reaction to occur and the ratio of methyl iodide and phenyl hydrazine unit to ethyl acetoacetate in the final yield of the product. The optimized reaction conditions of 72% yield and 97.8% assay of NPMHP, reaction time of 14 h, reaction temperature of 18°C, These optimization factors allowed good yields of NPMHP providing plenty of opportunities for its multi-applications.

Keywords: *Pyrazole, phenyl-3-methyl-3hydroxy-5-pyrozolone, Reaction Conditions for pyrazoles*

1. Introduction

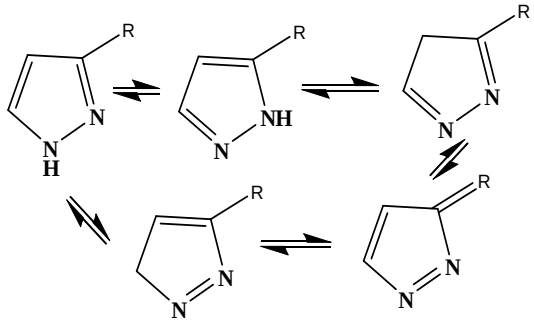
Pyrazoles (1a) in Fig.1 are the important members of heterocyclic compounds with two adjacent nitrogens in a five-membered ring system. Among the two nitrogen atoms; one is basic and the other is neutral in nature. These are aromatic molecules due to their planar conjugated ring structures with six delocalized π-electrons. The aromatic nature arises from the four π electrons and the unshared pair of electrons on the –NH nitrogen. The partially reduced forms of pyrazole are named as pyrazolines (1b or 1c); while completely reduced form is pyrazolidine (1d). [1,2and3]

Pyrazole is a tautomeric substance; the existence of tautomerism cannot be demonstrated in pyrazole itself, but it can be inferred by the consideration of pyrazole derivatives. Unsubstituted pyrazole can be represented in three tautomeric forms (Scheme-1) inFig.2. For the pyrazole derivatives in which two carbon atoms neighboring the nitrogen atoms on the ring have different substituents, five tautomeric structures are possible (Scheme-2), antihyperglycemic, antipyretic, antihelmintic, antioxidant and herbicidal properties antidepressant, a nticonvulsant.



1a 1b 1c 1d

Fig.1 Different types of pyrazoles



Scheme-2

Fig. 2 Different of Pyrazoles Derivatives

The pyrazole ring is present as the core in a variety of leading drugs such as Celebrex, Sildenafil (Viagra), Ionazlac, Rimonabant and Difenamizole etc. Pyrazole analogues have found use as building blocks in organic synthesis for designing pharmaceutical and agrochemicals; and as bifunctional ligands for metal catalysis (Ruiu, *et al*, 2003).

Pyrazoles have illustrious history; in 1883, a German chemist Ludwig Knorr was the first to discover antipyretic action of pyrazole derivative in man, he named the compound antipyrine. When he attempted to synthesize quinoline derivatives with antipyretic activity, Pyrazoles played a crucial role in the development of theoretical studies in heterocyclic chemistry and also useful building blocks in organic chemistry (Zhou, *et al*, 2005) with wide application as dyestuff, analytical reagents and agrochemicals (Ouyang, *et al*, 2008) The pyrazole ring system is a

*Corresponding author: **EKhlas A. Salman**

useful structural moiety found in numerous biologically active compounds. Pyrazole is uses structural unit in the field of the medicinal chemistry (Ciolkowski, *et al*, 2009) and has been reported to exhibit a variety of biological activities such as, analgesic (Shah, *et al*, 2009) anti-inflammatory, antianxiety, antibacterial, antifungal accidentally obtained antipyrine (2,3- dimethyl-1-phenyl-3-pyrazolin-5-one) which has analgesic, antipyretic and antirheumatic activity; which stimulated interest in pyrazole chemistry. The first natural pyrazole derivative was isolated by Japanese workers Kosuge and Okeda in the year 1954, till their discovery it was thought that pyrazoles could not be obtained naturally. They isolated 3-n-nonylpyrazole (2) in Fig.3. From Houttuynia Cordata, a plant of the "piperaceae" family from tropical Asia; which showed antimicrobial activity. They also isolated levo-β-(1-pyrazolyl) alanine (3) an amino acid from watermelon seeds (Citrullus Vxdulgaris)

Antitumour (Mohan, *et al*, 2010), antitubercular, and antiparasitic (Ouyang, *et al*, 2008) etc.Motivated by the afore-mentioned findings and as a continuation of our research to develop novel series of pyrazole derivatives that would act as better and potent anti-inflammatory analgesic agents.(Manjula, *et al*, 2013)
In the present work, substituted 1-Methyl-1-phenylhydrazine were synthesized by treatment of Phenyl Hydrazine and methyl Iodide and reaction N-phenyl-3-methyl-3hydroxy-5-pyrazolone were synthesized by the reaction of ethyl acetoacetate and substituted 1-methyl-1-phenylhydrazine.

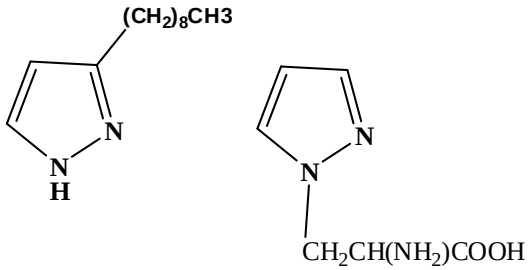


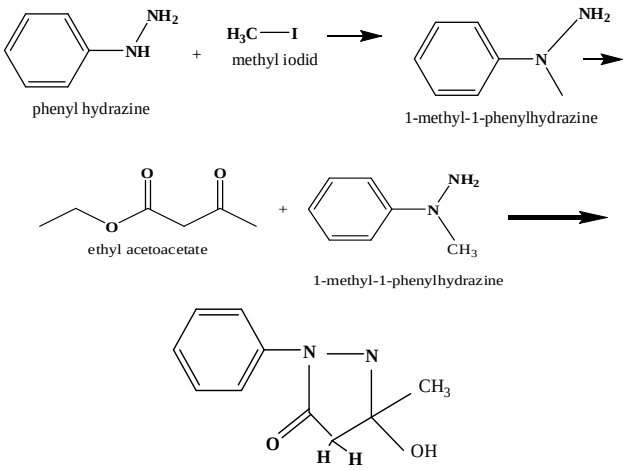
Fig. 3 Different of Pyrazoles Derivatives , (2) 3-n-nonylpyrazole (3) levo-β-(1-pyrazolyl) alanine

2. Experimental Work

The melting points were determined in Fisher-Johns apparatus. The Fourier transform infrared (FTIR) test was recorded on 470- Shimadzu infrared spectrophotometer using the KBr disc technique and expressed in cm-1. 1HNMR spectra was recorded on Bruker DRX-300 in DMSO-d6 as solvent. The chemical shift was given in δ (ppm) downfield fromt etramethylsilane (TMS) as an internal standard. Splitting patterns were designated as follows: s: singlet; d: doublet; m: multiplet. Elemental analysis was carried on Elemental (Vario EL) GmbH and the values were within ±0.4% of the theoretical values as shown in Appendix (A).

2.1 Experimental Procedure

General procedure for the synthesis of NPMHP is that methyl iodide (1.42g, 0.01mol) and (1.08 g (0.01mol)) of phenyl hydrazine were mixed together in an evaporating dish. The mixture was cooled on an iced water bath for 2 to 2.5 hours and stirred from time to time. Then added (1.3g, 0.01mol) from ethyl acetoacetate to 1-methyl-1-phenylhydrazine as shown in equation (1). The product was filtered at the pump then recrystallised from a small quantity of a mixture of equal volume of water and ethanol. The NPMHP was obtained as colourless crystals, melting point 135ºC and yield was 72.6%.



N-phenyl-3-methyl-3hydroxy-5- pyrozolone

Fig.4 Synthesis (N-phenyl-3-methyl-3hydroxy-5-pyrozolone)

An approximately 0.01 M *N-bromosuccinimide* (NBS) solution was prepared by dissolving an accurately weighed quantity of NBS in water with the aid of heat. The solution was cooled to room temperature, standardized iodometrically, kept in coloured bottle, 3–9 ml of pure (NPMHP) solution containing 6–18 mg of (NPMHP) was accurately measured and transferred into a 100 mL titration flask. The total volume was brought to 10 mL by adding 2 : 3 acetic acid. and the solution titrated with 0.01 M NBS using a drop of methyl orange as indicator until the red colour disappeared. A blank titration was run and the necessary volume corrections were made. The amount of (NPMHP) in the measured aliquot was calculated from:

$$\text{Amount(mg)} = \text{VM}_\text{W}\frac{\text{R}}{\text{n}} \quad (1)$$

Table 1 Abbreviations

NPMHP	N-phenyl-3-methyl-3hydroxy-5-pyrozolone
NBS	*N*-bromosuccinimide
V	volume of NBS consumed
Mw	relative molecular mass of (NPMHP)
R	molar concentration of NBS
N	the reaction stoichiometry (number of moles NBS reacting with each mole of (NPMHP)

3. Result and Discussion

The optimization of the reaction conditions for Synthesis of NPMHP, which included yield, assay, reaction time, shaking of the reaction materials, Effect of solvent on the yield, temperature and also study Pharmacologic Signs .

Synthesis of (NPMHP)

White crystals. Yield: 72%. Mp. 135–137 °C). IR (KBr) cm−1: 1620 (C=O), 1419 (C=C) ,3193 (N-H).
^{1}H-NMR (DMSO): 2.09-3.035 (Ar-CH), 7.25–7.914 (10H, Ar-H). ^{13}C-NMR (DMSO-d6) δ= 175.2, 187.2, 279.3 (amu) m/z: Anal. Calcd. For $C_{10}H_{10}N_2O_2$ (190): C, 60.89; H, 4.782; N, 15.25 Found: C, 60.64; H, 4.782; N, 15.25; O, 19.328

Assay (Titrimetry)

The direct titration of the pyrazolone group with standard *N*-bromosuccinimide was only successful for (NPMHP) in glacial acetic acid using methyl orange as the indicator. The concentration of the acetic acid must be not less than 9 N at the end of the titration. The end-point being detected either by methyl orange or potentiometrically. Under the optimized reaction condition, The molar ratio of the reaction was found to be always 1:1 (NPMHP: *N*-bromosuccinimide)

Yield

In this study, it was found that above 72 % of yield, the assay of product increasing. This could indicate that at this stage the main reaction was more dominant to form NPMHP than the side reaction. Fig.5 illustrates the relation between yield and assay of product

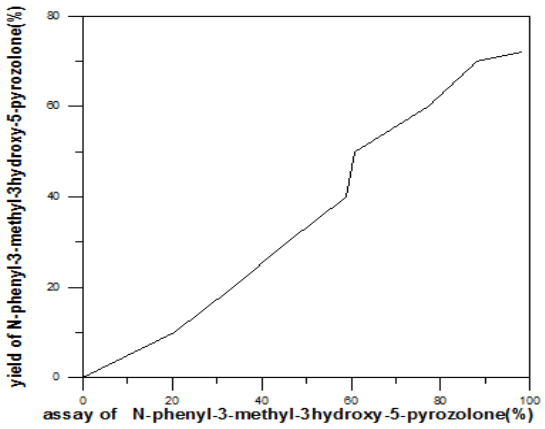


Fig. 5 The effect of assay of NPMHP on yield

Reaction Time

Fig.6. illustrates the effect of shaking on reaction time and yield parameters. The time taken for NPMHP process to take place varied from 20 min to 14 h. Following the sudden initial increase in yield by shaking and decreasing it without shaking, The increase in yield value by shaking at longer reaction times could be due to the fact that the NPMHP reaction reaches the equilibrium state after 14 h of the reaction time.

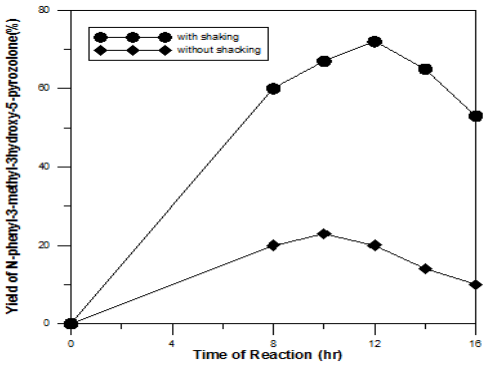


Fig. 6 The effect of time of reaction on yield of NPMHP

Reaction Temperature

The influence of the reaction temperature on the yield and assay of the product is shown in Fig. 7. We found that the exothermic effect of addition of Phenyl Hydrazine to N-H bond in syntheses of larger scale is quite significant. In higher temperatures reaction tends to accelerate rate and can get out of control. The control reaction can be achieved by ice bath control. The control reaction can be achieved by ice bath.

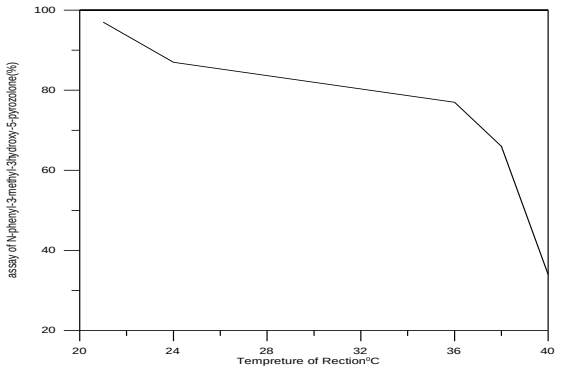


Fig.7 The reaction temperature versus the assay of NPMHP

Solvent

The effect of solvents on the yield also studied with methanol, ethanol, Dichloromethane and acetone .The effect of solvents on the yields was shown in the Table 1, from the table the highest yield of NPMHP obtained from the ethanol that is because the crystal structure and dissolution rate for NPMHP among the differences organic solvents is different

Table 2 The effect of solvents on yield of NPMHP

Solvent	Methanol	Ethanol	Dichloromethane	Acetone
Yield%	40	72	60	35

Pharmacological Evaluation

Animals

Six White rabbits (obtained from ACAI Company), equally divided as to sex, weighing 2250 to 2500 grams, were used in this study. maintained under standard conditions of alternating 12 h light and dark cycles at a constant temperature (26±2ºC and 40–55% relative humidity),and were conditioned for a minimum of 12 days prior to study initiation.

Acute toxicity

The acute toxicity test was carried out according to the Organization for Economic Co-operation and Development (OECD) guidelines to establish the effective dose of test compounds. The acute toxicity of synthesized compounds were determined using White rabbits, equally divided as to sex (2250 to 2500g) those maintained under standard husbandry conditions. The animals were fasted overnight prior to the experiment and fixed dose of 250 mg/kg body weight was administered (oral). The animals were monitored for the next 14 days and no behavioral change was observed.

Dose - Mortality Data

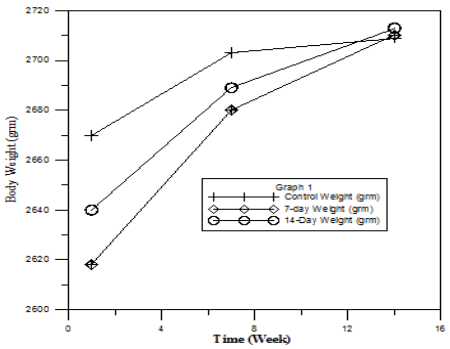
These data tabulated as:-

Table 3 Dose - Mortality Data

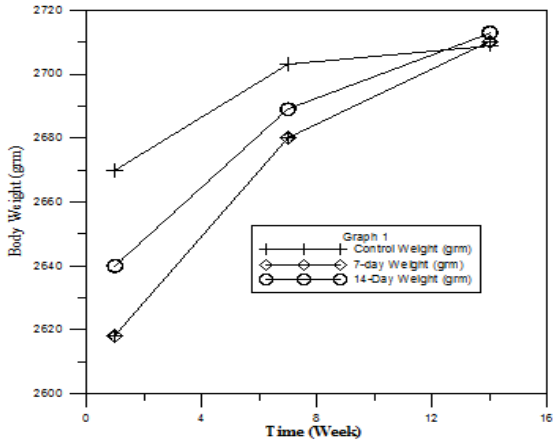
Dosage level mg/kg	Days	Number of Death	Total Mortalities		
			Male	Female	Total
1000	1 2 3 4 5 6 7-14	- - - - - - -	0/3	0/3	0/6

Body Weight

There was mean body weight depression in dosed male and female rabbit when compared with controls Fig. 8. No abnormal clinical signs were recorded. Body weight observation during 14 days.



Male



Female

Fig.8 Body weight for male and female rabbit of NPMHP Dose

Pharmacologic Signs

The following pharmacologic signs were observed during the 14-day observation period as shown in Table 4.

Table 4 Pharmacologic Signs

Males

Days	Normal	Diarrhea	Urine Stained	Soft Stool
1-8	3	-	-	-
9-10	2	1	-	-
11	3	-	-	-
12	2	1	-	-
13-14	3	-	-	--

Females

Days	Normal	Diarrhea	Urine Stained	Soft Stool
1-8	3	-	-	-
9-10	3	-	-	-
11	3	-	-	-
12	3	-	-	-
13-14	3	-	-	--

Conclusion

The developed method is simple, reliable, economical, have a good yield (72%) and excellent assay (98%), developed have the facile synthesis of pyrazole derivatives by a simple cyclization of easily reaction ethyl acetoacetate and phenyl hydrazine under Optimization of Reaction Conditions. This greener synthetic methodology provides a straightforward approach to the synthesis of NPMHP for the determination of NPMHP in pharmaceutical forms And especially the use of (NPMHP) in the treatment of meningitis

References

S. Ruiu, G. A. Pinna, G. Marchese, J. M. Mussinu, P. Saba, S. Tambaro,P. Casti, R. Vargiu, and L. Pani,(2003), Synthesis and characterization of NESS 0327: A novel puta tive antagonist of the CB1 cannabinoid receptor, J. Pharm. Exp. Ther., vol. 306, pp. 363-370.

Wang, S.; Shi, B.; Li, Y.; Wang, Q.; Huang, R., (2003) ,A convenient synthesis of novel 4-(1,2, 4-triazol-1-yl)-2-pyrazolines and their derivatives. Synth. Commun, 33, 1449–1457

G. B. Zhou, P. F. Zhang, and Y. J. Pan,(2005) ,A novel method for synthesis of arylac-etic acids from aldehydes, N-(2,3,4,6-tetra-O-pivaloylated-Dglucopyranosyl)amine and trimethylsilyl cyanide, vol.61, pp. 5671-5677.

Ouyang, G.P.; Cai, X.J.; Chen, Z.; Song, B.A.; Bhadury, P.S.; Yang, S.; Jin, L.H.; Xue, W.;Hu, D.Y.; Zeng, S. (2008),Synthesis and antiviral activities of pyrazole derivatives containing an oxime moiety. J. Agric. Food Chem., 56, 10160–10167.

Ouyang, G.P.; Cai, X.J.; Chen, Z.; Song, B.A.; Bhadury, P.S.; Yang, S.; Jin, L.H.; Xue, W.;Hu, D.Y.; Zeng, S.,(2008), Synthesis and antiviral activities of pyrazole derivatives containing an oxime moiety. J. Agric. Food Chem., 56, 10160–10167.

Adhikari, N.; Saha, N., (2008), Synthesis and spectroscopic characterization of palladium(II) and platinum(II) complexes with substituted pyrazoles. Asian J. Chem., 20, 521–529

Ciolkowski, M.; Paneth, P.; Lorenz, I.P.; Mayer, P.; Rozalski, M.; Krajewska, U.; Budzisz, E.,(2009), Tautomeric forms study of 1H-(2'-pyridyl)-3-methyl-5-hydroxypyrazole and 1H-(2'-pyridyl)-3- phenyl-5-hydroxypyrazole. Synthesis, structure, and cytotoxicactivity of their complexes with palladium(II) ions. J. Enzym. Inhib. Med., 24, 1257–1268.

Shah NK, Patel MP, Patel RG,(2009), Synthesis, characterization and antimicrobial activity of some new quinoline bearing pyrazole nucleus. Indian Journal of Chemistry, 48B: 1170- 1173

Kalirajan, R.; Sivakumar, S.U.; Jubie, S.; Gowramma, B.; Suresh, B.,(2009), Synthesis and biological evaluation of some heterocyclic derivatives of chalcones. Int. J. ChemTech Res. 2009, 1, 27–34.

Gupta, R.; Gupta, N.; Jain, A.,(2010), Improved synthesis of chalcones and pyrazolines under ultrasonic irradiation. Ind. J. Chem., 49B, 351–355.

Mohan S, Ananthan S, Murugan KR., (2010), Synthesis, characterization and biological activity of some novel sulphur bridged pyrazoles. Int J Pharm Sci Res 1(9) 391-398

Hassan, G.S.; Kadry, H.H.; Abou-Seri, S.M.; Ali, M.M.; Mahmoud, A.E.E.,(2011), Synthesis and in vitro cytotoxic activity of novel pyrazolo[3,4-d]pyrimidines and related pyrazole hydrazones toward breast adenocarcinoma MCF-7 cell line. Bioorg. Med. Chem., 19, 6808–6817.

Kulkarni, Naveen V, Kamath A, Budaumpi S, Revankar V, (2011),Pyrazole bridged binuclear transition metal complexes: Synthesis, characterization, antimicrobial activity and DNA binding/cleavage studies. Journal of Molecular structure, 1006(1-3); 580- 588.

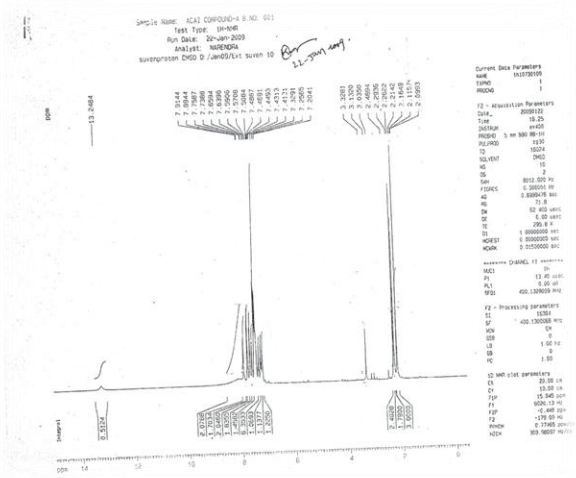
Hamada, N.M.; Sharshira, E.M.,(2011), Synthesis and antimicrobial evaluation of some heterocyclic chalcone derivatives. Molecules, 16, 2304–2312

Rangaswamy, J.; Kumar, H.V.; Harini, S.T.; Naik, N., (2012), Synthesis of benzofuran based 1, 3,5-substitutedpyrazole derivatives: As a new class of potent antioxidants and antimicrobials-A novel accost to amend biocompatibility. Bioorg. Med. Chem. Lett., 22, 4773–4777.

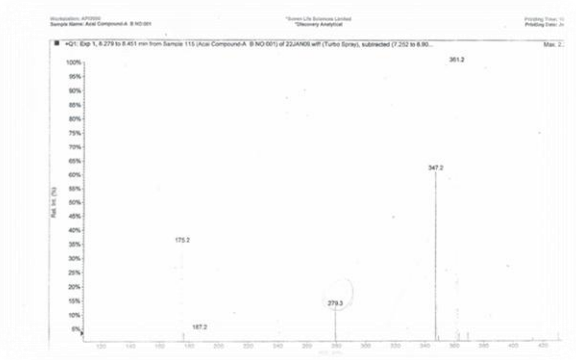
Manjula M, Jayaroopa P, Manjunath BC, Ajay Kumar K, Lokanath NK, (2013). 3-Methyl-1,5-diphenyl-4,5-dihydro-1H-pyrazole. Acta Crysta Sect E E69(Part 4) o602-o602

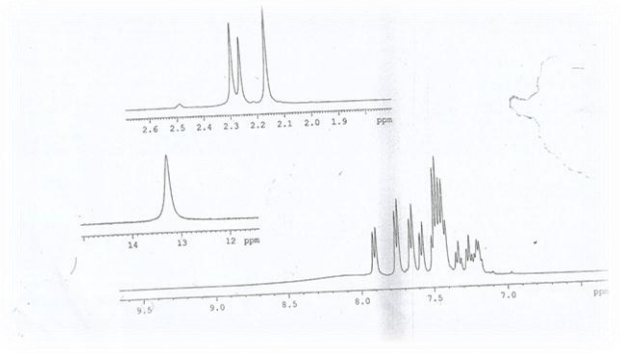
Appendix (A)

A.1.1 H NMR spectral spectras of synthesised compounds (NPMHP)

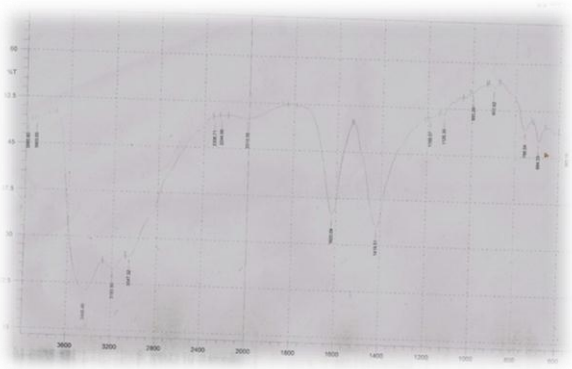


A.2 C NMR spectra spectras of synthesised compounds (NPMHP)

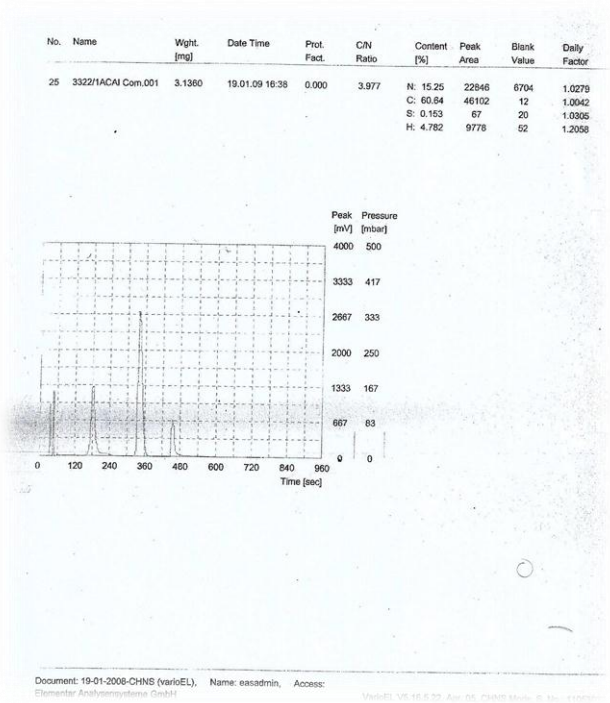




A.3 FTIR spectras of synthesised compounds (NPMHP)



A.4 Analytic Functional Testing



No.	Name	Wght. [mg]	Date Time	Prot. Fact.	C/N Ratio	Content [%]	Peak Area	Blank Value	Daily Factor
25	3322/1ACAI Com.001	3.1360	19.01.09 16:38	0.000	3.977	N: 15.25	22846	6704	1.0279
						C: 60.84	46102	12	1.0042
						S: 0.153	67	20	1.0305
						H: 4.782	9778	52	1.2058

Document: 19-01-2008-CHNS (varioEL), Name: easadmin, Access: