HL ISSN: 2231 – 3087(print) / 2230 – 9632 (Online)
http://heteroletters.org Vol. 2: (3), 2012, 263-269

REGIOSELECTIVE REACTIONS OF 3-ALKYL-1-PHENYL-2-PYRAZOLIN-5-ONES WITH ACYL HALIDES IN THE PRECENCE OF NONOSIZED MAGNESIUM HYDROXIDE AS A HIGHLY EFFECTIVE HETEROGENOUS BASE CATALYST

Hassan Sheibani* and Bahman Massomi Nejad

Department of Chemistry, Shahid Bahonar University of Kerman, Kerman 76169, Iran
E-mail: hsheibani@mail.uk.ac.ir

Abstract- 4-Acyl-3-alkyl-1-phenyl-2-pyrazolin-5-one derivatives were prepared by the regioselective acylation of 3-alkyl-1-phenyl-2-pyrazolin-5-ones in the presence of base catalysts such as calcium hydroxide [$Ca(OH)_2$], magnesium hydroxide [$Mg(OH)_2$] and nanosized magnesium hydroxide. In the presence of nanosized magnesium hydroxide, excellent yields of products were obtained and reaction times were significantly reduced.

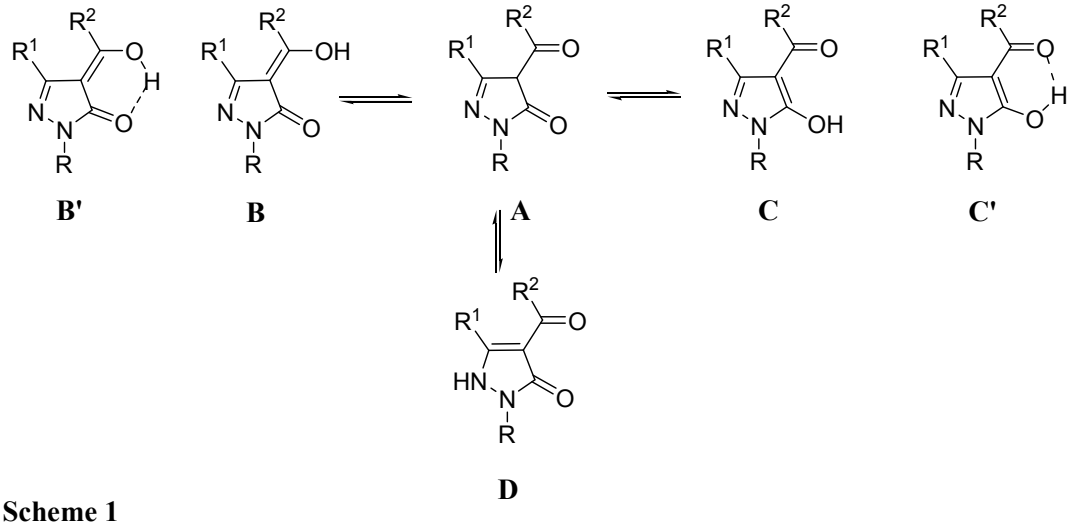
KEYWORDS
3-alkyl-1-phenyl-2-pyrazolin-5-ones, regioselective reaction, acyl halides, calcium hydroxide [$Ca(OH)_2$], magnesium hydroxide [$Mg(OH)_2$].

Introduction

The *N*-aryl-3-substituted 5-pyrazolone derivatives are very useful intermediates in the synthesis of biologically active compounds[1] and for the construction of condensed heterocyclic systems[2, 3]. These compounds are very useful intermediates in the synthesis of substituted pyrazolones, generally, which were prepared by the condensation of 3-methyl-1-phenyl-5-pyrazolone with some electrophiles such as acyl halides[4] and aromatic aldehydes[5]. 4-Acyl-3-alkyl-1-phenyl-2-pyrazolin-5-ones are effective chelating and extracting reagents for many metal ions[6] and are used as starting materials for the synthesis of condensed heterocyclic systems[7]. These compounds have often been known as analogues of β-diketone ligands and employed in their anionic chelating σ-donor forms in complexes of different metal acceptors and their complexes are generally more stable than the corresponding β-diketonates[8].

Acyl pyrazolones have played a key role in coordination compounds that have found wide application in several fields, from new materials[9] to catalysts[10], as precursors for CVD in the microelectronic industry[11], as potential antitumourals[12], and as thermal stabilizers for rigid some polemers[13]. These compounds exist in several tautomeric forms, such as the keto-enol (forms A, B and C), the NH (form D), which the isomers B and C having the possibility to be stabilized via an intramolecular hydrogen bond (B′, C′) (Scheme 1). The tautomerism of such compounds is a challenging field of study because of its importance in chemical reactivity, molecular recognition and biological systems[14, 15]. Holzer and coworkers presented NMR spectroscopic studies that revealed a complex behavior of such compounds in solution with the chelated OH

form B being the main isomer in $CDCl_3$ or C_6D_6, whereas in DMSO-d_6 an equilibrium between the OH form (B and C) and NH form (D) is assumed[16].



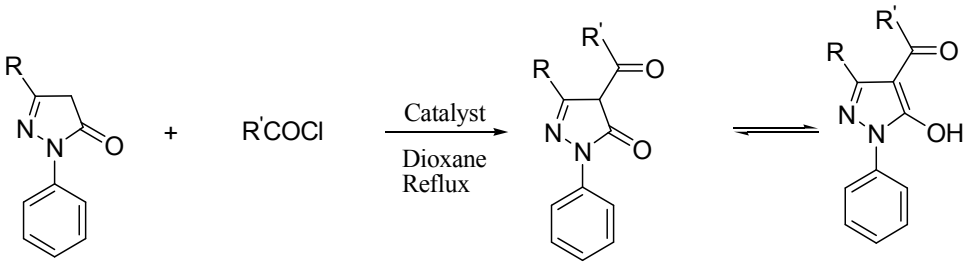
Scheme 1

In order to investigate of the tautomerism and synthetic potential of pyrazolones , we have recently reported the reaction of (chlorocarbonyl)phenyl ketene with pyrazolones led to the formation of 3-hydroxypyrazolo[1,2-*a*]pyrazole-dione/pyrazolo[1,2-*a*]pyrazole-trione derivatives. In these reactions the pyrazolones reacted as 1,2- or 1,3-bisnucleophiles[17].

In continuing our previous work on reactions of 3-alkyl-1-phenyl-2-pyrazolin-5-ones with electrophiles[17,18], we now wish to describe regioselective reactions of 3-alkyl-1-phenyl-2-pyrazolin-5-ones with acyl halides in the presence of base catalysts such as calcium hydroxide [$Ca(OH)_2$] , magnesium hydroxide [$Mg(OH)_2$] and nanosized magnesium hydroxide as a highly effective heterogenous base catalyst to afford 4-acyl-3-alkyl-1-phenyl-2-pyrazolin-5-one derivatives. The spectra data such as IR, ^1H and ^{13}C NMR and mass spectra are also in accordance with the proposed structures. We believe that the operational simplicity of the present process combined with the efficiency of this method will make it potentially attractive for synthesis of these compounds.

RESULTS DISCUSSION

In the present protocol as exhibited in Scheme **2** we studied the chemoselective synthesis of 4-acyl-3-alkyl-1-phenyl-2-pyrazolin-5-one derivatives by the acylation of 3-alkyl-1-phenyl-2-pyrazolin-5-ones in the presence of base catalysts such as calcium hydroxide [$Ca(OH)_2$] , magnesium hydroxide [$Mg(OH)_2$] and nanosized magnesium hydroxide. The products 3a-f were obtained in excellent yields when these reactions were carried out in the peresence of nanosized magnesium hydroxide as base catalyst.



1 **2** **3a-f**

3a: R = CH_3, R' = C_6H_5
3b: R = CH_3, R'= $C_6H_5CH_2$
3c: R = CH_3, R' = CH_3CH_2
3d: R = CH_3, R' = $(CH_3)_2CH$
3e: R = $CH3CH_2CH_2$, R' = C_6H_5
3f: R = $CH3CH_2CH_2$, R' = $C_6H_5CH_2$

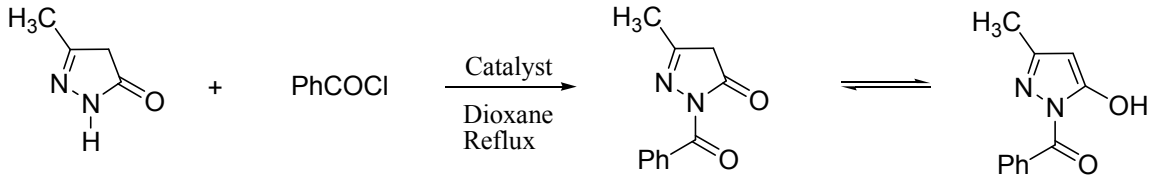
Scheme 2

In order to optimize the reaction conditions for preparing compounds **3**, the effect of base catalyst for preparing compounds **3** under different reaction conditions were investigated.
First we examined the reaction of 3-alkyl-1-phenyl-2-pyrazolin-5-ones **1a** with acylchlorids **2a-e** in an organic solvent (dioxane) at reflux in the presence of calcium hydroxide [$Ca(OH)_2$] as base catalyst. The reactions were too slow and the yields were not high. Second: other reactions were performed in the presence of magnesium hydroxide [$Mg(OH)_2$] in condition reaction same as first method. Finally, these reactions were carried out in the presence of nanosized magnesium hydroxide which found this catalyst to be more active than two other catalysts, and the results of these methods are presented in Table **1.**

Table 1: Synthesis of 3-alkyl-1-phenyl-2-pyrazolin-5-one derivatives **3a-f** in the presence of base catalyst.

Compd No.	R	R'	Commercial $Ca(OH)_2$		Commercial $Mg(OH)_2$		Nanosized $Mg(OH)_2$		[Ref]
			Time (min)	Yield (%)	Time (min)	Yield (%)	Time (min)	Yield (%)	
3a	CH_3	C_6H_5	35	70	40	70	10	95	16
3b	CH_3	$C_6H_5CH_2$	35	75	30	65	10	90	16
3c	CH_3	CH_3CH_2	45	40	40	48	15	94	16
3d	CH_3	$(CH_3)_2CH$	45	40	40	55	15	94	-
3e	$CH_3CH_2CH_2$	C_6H_5	37	37	30	60	10	92	-
3f	$CH_3CH_2CH_2$	$C_6H_5CH_2$	40	40	30	67	10	9	-

Attempts to bring 3-methyl-2-pyrazolin-5-one **4** to react with benzoyl chloride **5** to prepare C acylated product in the presence of base catalysts such as calcium hydroxide [$Ca(OH)_2$] , magnesium hydroxide [$Mg(OH)_2$] and nanosized magnesium hydroxide was unsuccessful. The reaction leads preferentially to N-acylated product with two tautomeric forms **6** (scheme 2).



4 **5** **6**

Scheme 3

The structuers of compounds **3a-c** are known and their melting points and spectral data are in good agreement with those reported in the literature [16]. The structuers of compounds **3c-f** and **6** were established on the basis of spectral data and shown distinctive, expected features. The IR spectra of these compounds measured in potassium bromide pellets show bands at 3400-3100 cm^{-1} and 1730-1620 cm^{-1} related to elongation of the OH and C=O groups, respectively. The ^1H NMR and ^{13}C NMR spectra of compounds **3a** and **3e** exhibited two tautomers. quantitative analysis of mixtures is achieved by evaluating the integration peaks of ^1H NMR spectra.

In summary, we have described Regioselective synthesis of 3-alkyl-1-phenyl-2-pyrazolin-5-ones with acyl halides in the presence of nanosized magnesium hydroxide as a highly effective heterogenous base catalyst. The advantage of these procedures reported here are: high conversions and selectivity, high purity of products and easy workup.

EXPERIMENTAL SECTION

General Procedures. Melting points were measured on a Gallenkamp melting point apparatus and are uncorrected. IR spectra were measured on a Mattson 1000 FT-IR spectrometer. The proton and carbon NMR spectra were recorded with a BRUKER DRX-500 AVANCE spectrometer at 500 and 125.77 MHz, respectively. Mass spectra were recorded on a MS-QP2000A Shimadzu mass spectrometer operating at an ionization potential of 70 eV. Elemental analyses were performed using a Heracus CHN-O-Rapid analyzer.

Preparation of nanosized magnesium hydroxide [$Mg(OH)_2$]

The $Mg(OH)_2$ nanoparticles were synthesized by precipitation of the magnesium hydroxide gels in aqueous solution using $Mg(NO_3)_2$ as salt and liquid ammonia as the precipitating agent. Initially, the pH of 200 ml of distilled water was adjusted to 10.5 by addition of liquid ammonia. To this solution, 0.1 M magnesium nitrate solution was added dropwise with continuous stirring. The rate of addition of the salt solution was kept at 20 ml/h. During the addition, the pH of the mixture decreased due to hydrolysis of the salt. The pH was maintained at 10.5 by controlled addition of liquid ammonia solution. After completion of the precipitation procedure, the mixture was stirred at room temperature for 12 h, filtered, repeatedly washed with distilled water, dried at 120 ºC[18, 19].

General procedure for the preparation of 4-acyl-3-alkyl-1-phenyl-2-pyrazolin-5-one derivatives (3a-f). Method (A): In dioxane with calcium hydroxide [$Ca(OH)_2$]:
Under cooling and vigorous stirring, to a suspension of 3-alkyl-1-phenyl-2-pyrazolin-5-ones (2 mmol) and calcium hydroxide powder (0.148 g, 2 mmol) in 10 mL of dioxane was added a solution of acyl halide (2 mmol) in 5 mL of dioxane, and the mixture was then refluxed for 2 h. After cooling, 2.5 mL of 2 N HCl was added, and the mixture was vigorously stirred for 1 h and was then poured onto 50 mL of water. The precipitated solid was filtered off, washed with water, and recrystallized from ethanol[20]. **Method (B): In the presence of commercial magnesium hydroxide or nanosized magnesium hydroxide [$Mg(OH)_2$]:** The foregoing method was carried out except that calcium hydroxide powder was replaced by commercial magnesium hydroxide or nanosized magnesium hydroxide [$Mg(OH)_2$]compounds (0.116 g, 2 mmol).

4-Benzoyl-3-methyl-*N*-phenyl-pyrazolone (3a). Orange crystals, mp 94-96 °C. IR (KBr, ν_{max}/cm^{-1}): 3271-2928 (broad, OH), 1759, 1668 (C=O), 1630 (C=N). MS, m/z (relative intensity %): 278(40, parent peak), 201(66), 91(100, base peak), 77(75), 65(55), 51(46).
Major tautomer: 4-Benzoyl-3-methyl-1-phenyl-2,1*H*-pyrazol-5(4*H*)-one, **3a, I.** (75%), ^{1}H NMR (500 MHz, DMSO-d_6): 8.06(1H, d,$^3J_{HH}$= 7.9 Hz, Ar)*, 7.95(1H, d,$^3J_{HH}$= 7.8 Hz, Ar)*, 7.76(2H, d,$^3J_{HH}$= 7.8 Hz, Ar)*, 7.72-7.34 (6H, m, Ar)*, 6.32(1H, s, CH), 2.40(3H, m, CH_3) *. ^{13}CNMR (125 MHz, DMSO-d_6): 189.75(C=O), 168.19(C=O),162.84(C=N), (139.24, 138.52, 137.45, 135.98, 135.68, 133.71, 132.95, 131.64, 130.91, 130.37, 130.14, 129.78, 129.41, 129.22, 128.12, 126.72, 123.97, 123.41, 110.31)*,67.23(CH), 15.27(CH_3). * For two tautomers
Minor tautomer: (5-hydroxy-3-methyl-1-phenyl-1*H*-pyrazole-4-yl)(phenyl)methannone, **3a, II**. (25%), 1H NMR (500 MHz, DMSO-d6): 12.69(1H, s,OH), 2.67(3H, s, CH3). ^{13}CNMR (125 MHz, DMSO-d6): 191.15(C=O), 151.00, 145.19, 97.24(C4), 15.09(CH3).

3-Methyl-1-phenyl-4-(2-phenylacetyl)-1*H*-pyrazol-5(4*H*)-one (3b). Yellow crystals, mp 94-96 °C. IR (KBr, ν_{max}/cm^{-1}): 3418-2922 (broad, OH), 1711, 1617 (C=O), 1593 (C=N). ^{1}H NMR (500 MHz, DMSO-d_6): 12.80(1H, s,OH), 7.71(2H, d,$^3J_{HH}$= 7. 9 Hz, Ar), 7.50 (2H, t,$^3J_{HH}$= 7.8 Hz, Ar), 7.32-7.19 (7H, m, Ar), 4.24(2H, s, CH_2), 2.49(3H, m, CH_3). ^{1}3CNMR (125 MHz, DMSO-d6): 190.75 (C=O), 161.29(C5), 152.84(C3), 137.04, 136.90, 130.53, 129.92, 128.97, 127.06, 126.89, 121.61, 104.89(C4),46.53(CH2),14.93(CH3). MS, m/z (relative intensity %): 293(15, parent peak), 201(100, base peak), 91(50), 77(38), 65(32), 51(19).

3-Methyl-1-phenyl-4-propionyl-1*H*-pyrazol-5(4*H*)-one (3c). Pale yellow crystals, mp=63-65°C. IR(KBr, ν_{max}/cm^{-1}): 3114-2875 (broad, OH), 1671, 1620 (C=O), 1593 (C=N). ^{1}H NMR (500 MHz, DMSO-d_6): 7.76-7.15(5H, m, Ar), 6.30(1H, s, CH), 2.75 (2H, q,$^3J_{HH}$= 6.5 Hz, CH_2), 2.35 (3H, s, CH_3), 1.03 (3H, t, $^3J_{HH}$= 6.5 Hz, CH_3). ^{13}CNMR (125 MHz, DMSO-d_6): 195.54 (C=O), 163.4(C5), 149.78(C=N), 139.26, 129.49, 125.18, 120.40, 104.68 (C4), 33.40(CH2),16.68(CH3), 9.59(CH3). MS, m/z (relative intensity %): 230(22, parent peak), 201(67), 131(14), 105(46), 92(27), 77(100, base peak), 51(79), 39(45).

4-(Isobutyryl)-3-methyl-1-phenyl-1*H*-pyrazol-5(4*H*)-one (3d). Pale yellow crystals, mp=80-82 °C. IR (KBr, ν_{max}/cm^{-1}): 3294-2871 (broad, OH), 1692, 1617 (C=O), 1581 (C=N). ^{1}H NMR (500 MHz, DMSO-d_6): 7.86-7.18(5H, m, Ar), 4.00(1H, s, CH), 2.08 (3H, s, CH_3), 1.16 (1H, m, CH), 0.94 (6H, d,CH_3). 13CNMR (125 MHz, DMSO-d6): 200.38 (C=O), 176.88(C5), 159.18(C=N), 136.58, 124.48, 122.92, 112.68, 71.88 (C4), 37.34(CH), 18.07(2CH3),9.51(CH3).

MS, m/z (relative intensity %): 244(47, parent peak), 201(42), 132(20), 92(100, base peak), 77(91), 51(63), 39(56).

4-Benzoyl-3-propyl-*N*-phenyl-pyrazolone (3e). Yellow crystals, mp=110-112 °C. IR (KBr, $\nu_{max/}$ cm^{-1}): 3400-2924 (broad, OH), 1728, 1629 (C=O), 1599 (C=N). MS, m/z (relative intensity %): 306(15, parent peak), 229(42), 201(27), 132(32), 105(100, base peak), 77(61), 51(55), 43(39). Anal. Calcd. For $C_{19}H_{18}N_2O_2$: C, 74.49; H, 5.92; N, 9.14 %. Found : C, 74.11; H. 5.51; N;8.69. Major tautomer: 4-Benzoyl-1-phenyl-3-propyl-2,1*H*-pyrazol-5(4*H*)-one**, 3e, I.** (75%). ^{1}H NMR (500 MHz, DMSO-d_6): 7.96(1H, d,$^3J_{HH}$= 7.4 Hz, Ar)*, 7.75(2H, d,$^3J_{HH}$= 7.4 Hz, Ar)*, 7.72(2H, d,$^3J_{HH}$= 7.9 Hz, Ar)*, 7.64-7.29 (5H, m, Ar)*, 6.34(1H, s, CH), 2.59(2H, t,$^3J_{HH}$= 7.2 Hz, , CH_2), 1.55(2H, m, CH_2), 0.84(3H, t,$^3J_{HH}$= 7.2 Hz, , CH_3), ^{13}CNMR (125 MHz, DMSO-d_6): 190.55(C=O), 168.20(C=O), 152.77(C=N), (139.75, 133.67, 132.68, 131.67, 130.90, 130.14, 130.08, 129.85, 129.60, 129.39, 128.91, 127.09,13.40, 122.27)*,94.27(CH), 30.41, 22.24, 14.57.
* For two tautomers

Minor tautomer: (5-hydroxy-1-phenyl-3-propyl-1*H*-pyrazol-4-yl)(phenyl) methanone, **3e, II**.
(25%). ^{1}H NMR (500 MHz, DMSO-d_6): 11.23(1H, s,OH),2.60(2H, t,$^3J_{HH}$= 7.2 Hz, , CH_2), 1.67(2H, m, CH_2), 0.96 (3H, t,$^3J_{HH}$= 7.2 Hz, , CH_3), ^{13}CNMR (125 MHz, DMSO-d_6): 198.70(C=O),153.00(C=N), 104.67(C5),31.38, 22.79, 14.63(CH_3).

General procedure for the preparation of 1-phenyl-4-(2-phenylacetyl)-3-propyl-1*H*-pyrazol-5(4*H*)-one (3f). Pale yellow crystals, mp=133-136 °C. IR (KBr, $\nu_{max/}$$cm^{-1}$): 3423-2930 (broad, OH), 1740, 1648 (C=O), 1597 (C=N). ^{1}H NMR (500 MHz, DMSO-d_6): 11.43(1H, s,OH), 7.69(2H, d,$^3J_{HH}$= 7. 8 Hz, Ar), 7.50 (2H, t,$^3J_{HH}$= 7.6 Hz, Ar), 7.20-7.32 (6H, m, Ar), 4.24(2H, s, CH_2), 2.79(2H, t, $CH_2$$^3J_{HH}$= 7.4Hz, Ar). 1.63(2H, m, CH_2) , 0.92(3H, t, $CH_3$$^3J_{HH}$= 7.3Hz,).^{13}CNMR (125 MHz, DMSO-d_6): 192.88(C=O), 173.54 (C5), 155.39(C3), 137.00, 130.49, 130.22, 129.90, 129.09, 128.45, 127.02, 121.83, 104.35(C4),46.58(CH_2),30.03(CH_2), 21.70(CH_3),14.56(CH_3). MS, m/z (relative intensity %): 320(18, parent peak), 229(100, base peak), 201(24), 119(45), 107 (25), 91(73), 77(65), 51(51), 43(35). Anal. Calcd. For $C_{20}H_{20}N_2O_2$: C, 74.98; H, 6.29; N, 8.74 %. Found : C, 74.63; H. 5.98; N; 8.32.

General procedure for the preparation of 1-Benzoyl-3-methyl-1*H*-pyrazol-5(4*H*)-one (6). A solution of benzoyl chloride **5** (0.28 g, 2 mmol) in anhydrous dioxane (5 mL) was added dropwise over 5 min to a stirred solution of 3-methyl-1-phenyl-1*H*-pyrazol-5(4*H*)-one **4** (0.196 g, 2 mmol) in dioxane (10 mL) at ambient temperature for 15 min. The solid product was collected and recrystallized from ethanol and water (80/20). 0.38 g.White crystals, 95% yield, mp=174-176 °C. IR (KBr, $\nu_{max/}$$cm^{-1}$): 3453-2990 (broad, OH),1748,1705 (C=O), 1580 (C=N).^{1}H NMR (500 MHz, $CDCl_3$): 10.80(1H,enol form, s,OH), 8.07(2H, d,$^3J_{HH}$= 7. 2 Hz, Ar), 7.73 (1H, t,$^3J_{HH}$= 7.4 Hz, Ar), 7.58 (2H, t,$^3J_{HH}$= 7.7 Hz, Ar), 5.95(1H,keto form, s, CH), 2.23(2H, s, CH_3). ^{13}CNMR (125 MHz, $CDCl_3$): 164.43(C=O), 155.48 (C3), 140.75(C5), 135.01, 131.57, , 130.57, 129.91, 129.31, 95.43(C4),11.86(CH_3) . MS, m/z (relative intensity %): 202(26, parent peak), 105(100, base peak), 97(43), 77(45), 51(38). Anal. Calcd. For $C_{11}H_{10}N_2O_2$: C, 65.34; H, 4.98; N, 13.85 %. Found : C, 65.03; H. 5.08; N; 13.41.

ACKNOWLEDGEMENTS
The authors express appreciation to the Shahid Bahonar University of Kerman Faculty Research Committee Fund for its support of this investigation.

REFERENCES

1. P. Chiba, W. Holzer, M. Landau, G. Bechmann, K. Lorenz, B. Plagens, M. Hitzler, E. Richter and G. Ecker, J. Med. Chem, 41, 4001(1998).
2. J. Elguero, In Comprehensive Heterocyclic Chemistry; Pergamon Press, Oxford, (1984).
3. G.F. Liu, L. Liu, D.Z. Jia, B.H. Peng, X. Hu, K.B. Yu, Heterocyclic. 63, 2079(2004).
4. R.C. Maurya, A. Pandey, J. Chaurasia, H. Martin, J. Mol. Struct. 89, 798(2006).
5. C. Su, Z.C. Chen, Q.G. Zheng, Synthesis. 555(2003).
6. C. Pettinari, F. Marchetti, A. Cingolani, G. Bianchini, A. Drozdov, V. Vertlib, S. Troyanov, J. Organomet. Chem. 5, 651(2002).
7. B. Stanovnik, J. Svete, Pyrazoles. In Science of Synthesis: Houben-Weyl Methods of Molecular Transformations; Thieme: Stuttgart-New York, Vol. 12, pp 15-225(2002).
8. C. Pettinari, R. Pettinari, M. Fianchini, F. Marchetti, B.W. Skelton, A.H. White, Inorg. hem, 44, 7933(2005)
9. G. Vicentini, L.B. Zinner, J. Zukerman-Schpector , K. Zinner, Coord. Chem. Rev, 196, 353(2000).
10. P. Dobrzynski, J. Kasperczylk, M. Bero, Macromolecules, 32 (14), 4735(1999).
11. M.J. Hampden-Smith, T.T. Kodas, Polyhedron, 14(6), 699(1995).
12. B.K. Keppler, C. Friesen, H.Vongerichten, E. Vogel, In: Keppler BK (ed) Metal Complexes In Cancer Chemotherapy. VCH, Weinheim, pp 297–323 (1993).
13. M.W. Sabaa, E.H. Oraby, A.S. Abdul Naby, R.R. Mohamed, Polym. Degrad. Stab, 91, 911(2006).
14. J. Elguero, C. Marzin, A.R. Katritzky, P. Linda, The Tautomerism of Heterocycles. In Advances in Heterocyclic Chemistry, Suppl. 1; Academic Press: New York, pp 313-336 (1976).
15. W.Holzer, R.M, Claramunt, M. Pe´rez-Torralba, D. Guggi, T.H. Brehmer, J. Org. Chem, 68, 7943(2003).
16. W. Holzer, K. Mereiter, B. Plagens, Heterocycles, 50 (2), 799 (1999).
17. M. Abaszadeh, H. Sheibani, K. Saidi, Aust. J. Chem, 63, 92(2010).
18. H. Sheibani, M. Babaie, Synth. Commun, 40, 257(2010).
19. D. Kumar, V.B. Reddy, B.G. Mishra, R.K. Rana, M.N. Nadagouda, R.S. Varma, Tetrahedron, 63, 3093(2007).
20. N. Sutradhar, A. Sinhamahapatra, B. Roy, H.C. H.C. Bajaj, I. Mukhopadhyay, A.B. Panda, Mater. Res. Bull. 46, 2163(2011).

Received on April 16,2012.