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REGULAR ARTICLE

Preparative, mechanistic and tautomeric investigation of 1-phenyl and 1-methyl derivative of 3-methyl-5-pyrazolone

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Abstract. 1-Phenyl and 1-methyl derivative of 3-methyl-5-pyrazolone were prepared quantitatively *via* a scalable solvent-free reaction of corresponding hydrazine derivative with ethyl acetoacetate. Different mechanisms have been proposed for the reaction of hydrazine derivatives (methyl or phenyl) with ethyl acetoacetate and also the tautomeric aspects of the targeted compounds have been discussed.

Keywords. pyrazolone; edaravone; tautomer; 1-phenyl-3-methyl-5-pyrazolone; 1,3-dimethyl-5-pyrazolone.

1. Introduction

The pyrazolone ring is a building block in heterocyclic synthesis and a prominent structural motif found in numerous pharmaceutically active compounds. Some of their derivatives have been widely used owing to anticancer, antioxidant, herbicidal, insecticidal, anti-convulsant antihelmintic, anti-inflammatory, and antiviral activity.[1,2]

1-phenyl-3-methyl-5-pyrazolone, named Edaravone (Radicava), is a novel antioxidant[3] and an intravenous medication used to help with recovery following a stroke and to treat amyotrophic lateral sclerosis (ALS),[4] the synthesis of Edaravone has been numerously reported by the reaction of phenyl hydrazine and ethyl acetoacetate under different reaction conditions with yields of 93-100%.[5–11] Phenyl hydrazine hydrochloride, yielding 75-85% of Edaravone, has also been considered as an alternative starting compound,[12,13] other methods have been proposed using diketene as starting material, affording the targeted compound with the yield of 93%[14] (Scheme 1). 1,3-dimethyl-5-pyrazolone is another important pyrazolone derivative, the synthesis of which has also been widely investigated.[15–23] It is also an important intermediate in the preparation of some medicinal compounds.[16,18,21] Methyl hydrazine and ethyl acetoacetate are common compounds for the synthesis of 1,3-dimethyl-5-pyrazolone. Experimental procedures using these compounds and ethanol or methanol as solvent at a temperature range of 0-78 °C for 1-16 h have afforded 1,3-dimethyl-5-pyrazolone with yields of 66-100%.[15–20] Sulfate salt of methyl hydrazine, yielding 76-83% of 1,3-dimethyl-5-pyrazolone, has also been considered as an alternative starting compound.[21–23] Furthermore, another method has been proposed using diketene[14] as starting material, affording the targeted compound with a yield of 98% (Scheme 1). Other methods considering the green approach have also been reported.[24] To our knowledge, solvent-free synthesis has not yet been reported for the preparation of 1,3-dimethyl-5-pyrazolone.

The reaction of aryl or alkyl hydrazine with differently substituted β-diketones have revealed the formation of two different reaction products, the proportional amount of which depends on the hydrazine and β-diketones substitutions that determine the regioselectivity of nucleophilic and electrophilic centers.[25,26]

Concerning the mechanism of the reaction, it has been previously stated that methylation of hydrazine increase the nucleophilicity of the substituted nitrogen and decrease the reactivity of the adjacent center. Thus, the substituted nitrogen is a more reactive site under kinetic control conditions, while the nucleophilic reaction of the non or less substituted nitrogen

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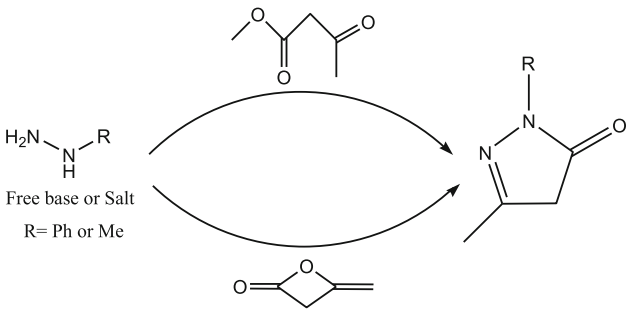
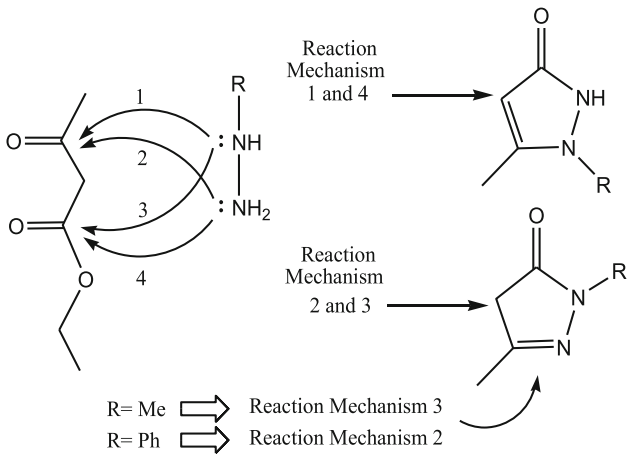


Scheme 1. Different reaction conditions reported for the synthesis of 1-phenyl and 1-methyl derivative of 3-methyl-5-pyrazolone.[5–23].

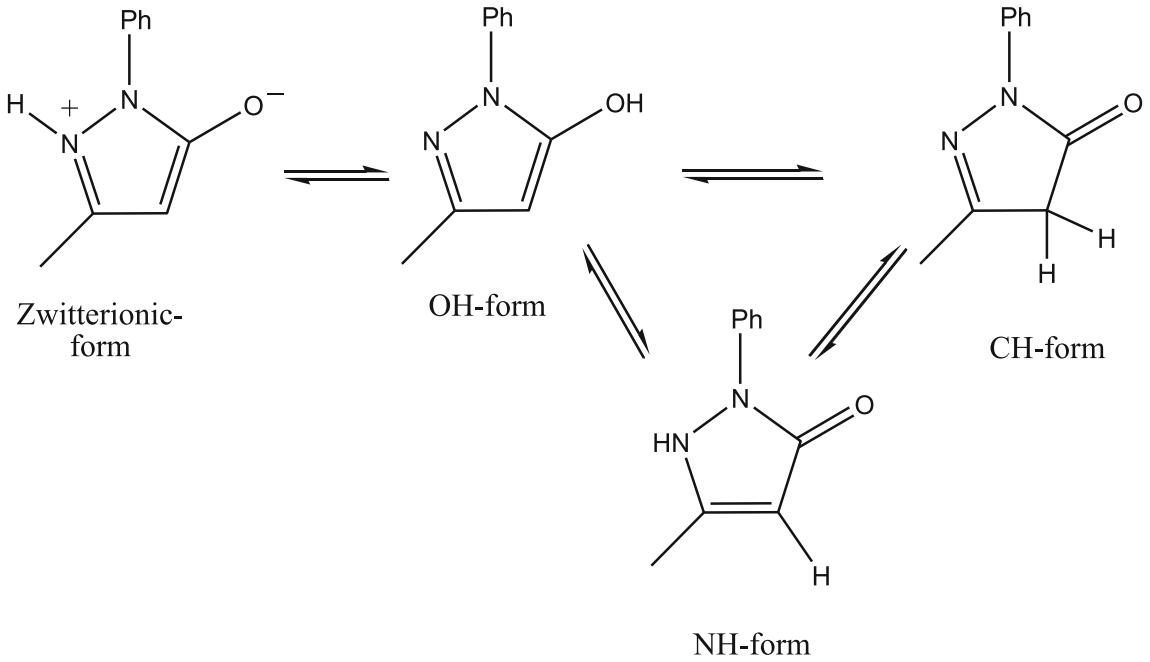
was observed under thermodynamic control conditions.[27]

Microwave-assisted synthesis of Edaravone (with a yield of 67%) has been performed by the regioselective nucleophilic attack of the least hindered nitrogen atom of phenyl hydrazine on the ketone moiety of ethyl acetoacetate followed by intramolecular cyclization involving the ester and the second nitrogen atom of phenyl hydrazine.[28] This was supported by the isolation of hydrazine intermediate (isolated after the reaction time of 1 min) as a side product during the reaction of 2,4-dinitrophenyl hydrazine with ethyl acetoacetate showing that the regioselectivity of the reaction is governed by the higher reactivity of ketone moiety over ester and least hindered nitrogen atom of 2,4-dinitrophenyl hydrazine.

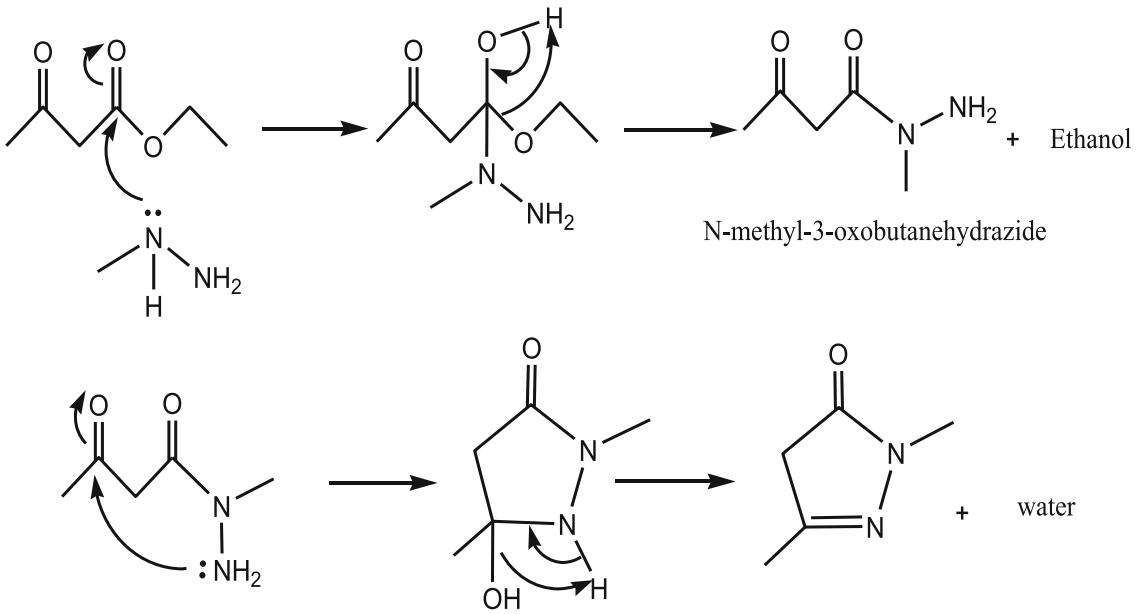


Scheme 3. Plausible mechanisms for the reaction between hydrazine derivatives and ethyl acetoacetate.

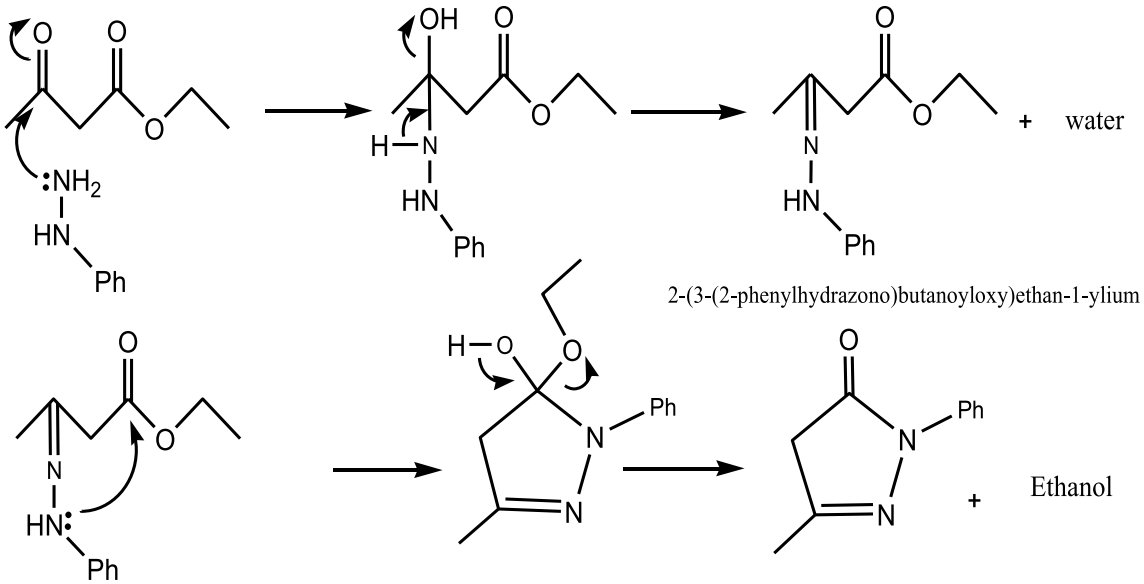
The tautomerism of pyrazolone-5-one has been extensively studied and reviewed.[29–35] Concerning Edaravone, it can exist under different tautomeric forms; zwitterionic, OH, CH and NH forms (Scheme 2). Based on ^{1}H NMR spectroscopy, two major tautomeric forms, NH-form and CH-form, have been observed for Edaravone in DMSO and $CHCl_3$, respectively.[36] In another study based on ^{1}H NMR and IR spectroscopy, it has been stated that Edaravone exists as CH-form in $CHCl_3$, dioxane and CCl_4, OH-form in pyridine and zwitterionic form in solid-state.[37]



Scheme 2. Tautomeric forms of 1-phenyl-3-methyl-5-pyrazolone (Edaravone).



Scheme 4. Mechanism of reaction between methyl hydrazine and ethyl acetoacetate in the preparation of 1,3-dimethyl-5-pyrazolone.



Scheme 5. Mechanism of reaction between phenyl hydrazine and ethyl acetoacetate in the preparation of 1-phenyl-3-methyl-5-pyrazolone.

2. Experimental

2.1 *Chemicals and apparatus*

All solvents and chemical materials were of analytical grades (supplied by Aldrich and Merck) and used without any further purification. NMR analyses were performed by three instruments (Bruker DPX-250, Bruker Avance-300 and Bruker Ascend-400 spectrometer). $CDCl_3$ and DMSO-d_6 were used as solvents, the proton and carbon chemical shifts were recorded in δ (ppm) from TMS.

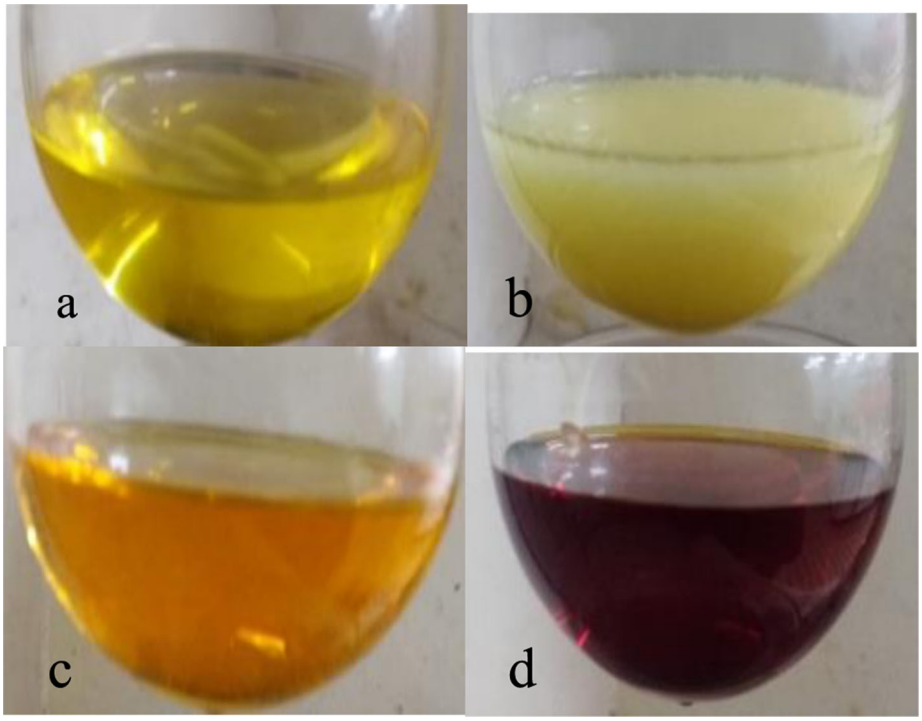


Figure 1. Reaction mixture of methyl hydrazine and ethyl acetoacetate (a) after dropwise addition of methyl hydrazine to ethyl acetoacetate at 0 °C, (b) the mixture **a** at rt, (c) the mixture **b** at 80 °C, (d) after stirring the mixture **c** at 80 °C for 1 h and at 90 °C for 0.5 h.

2.2 *Synthesis of 1-phenyl-3-methyl-5-pyrazolone*

Ethyl acetoacetate (28.1 mL, 28.63 g, 0.22 mol) was placed in a 100 mL one necked flask equipped with a magnetic stirrer and immersed in an ice-water bath (0 °C). Then, phenyl hydrazine (19.66 mL, 21.63 g, 0.20 mol) was dropwise added (1 mL/min). After the addition of phenyl hydrazine, the flask cap has been tightly closed and the reaction was continued for 1 h at 80 °C, and for 30 min at 90 °C. Finally, water, ethanol and excess ethyl acetoacetate were vacuum stripped and the formed solids were washed with diethyl ether (20 mL) giving pale yellow solids (34.8 g, R= ∼100%). M.p. 126-128 °C. ^{1}H NMR (400 MHz, CDCl3, δ ppm): 2.18 (s, 3H), 3.42 (s, 2H), 7.17 (t, 1H, *J*=6.7 Hz), 7.38 (t, 2H, *J*=6.7 Hz), 7.84 (d, 2H, *J*=7.5 Hz).^{13}C NMR (100 MHz, $CDCl_3$, δppm): 16.6, 42.6, 118.4, 124.6, 128.4, 137.6, 156.1, 170.2.

2.3 *Synthesis of 1,3-dimethyl-5-pyrazolone*

Ethyl acetoacetate (28.1 mL, 28.63 g, 0.22 mol) was placed in a 100 mL one necked flask equipped with a magnetic stirrer and immersed in an ice-water bath (0 °C). Then, methyl hydrazine (10.5 mL, 9.21g, 0.20 mol) was dropwise added (1 mL/min). After the addition of methyl hydrazine, the flask cap has been tightly closed and the reaction was continued for 1 h at 80 °C, and for 30 min at 90 °C. Finally, water, ethanol and ethyl acetoacetate excess were vacuum stripped and the formed solids were washed with diethyl ether giving pale brown solids (22.4 g, R= ∼100%) M.p. 113-117 °C. ^{1}H NMR (400 MHz, CDCl3, δ ppm): 2.04 (s, 3H), 3.13 (s, 2H), 3.22 (s, 3H).^{13}C NMR (100 MHz, $CDCl_3$, δppm): 16.9, 31.0, 41.4, 155.6, 172.3.

3. Results and Discussion

Quantitative preparation of 1-phenyl-3-methyl-5-pyrazolone and 1,3-dimethyl-5-pyrazolone have been performed by the reaction of ethyl acetoacetate with phenyl hydrazine and methyl hydrazine, respectively.

Two active nucleophile centers of methyl and phenyl hydrazine along with two active electrophile centers of ethyl acetoacetate can leads to different reaction products following different mechanisms (Schemes 3, 4, 5). The reaction proceeds *via* stepwise elimination of water and ethanol or *vice versa*.

Thus, the mechanism of the reaction between ethyl acetoacetate and methyl hydrazine or phenyl hydrazine can be envisaged as is shown in Schemes 4 and 5. Concerning methyl hydrazine, N-methyl-3-oxobutanehydrazine is formed in the first step of the reaction liberating ethanol after which, in the second step, 1,3-

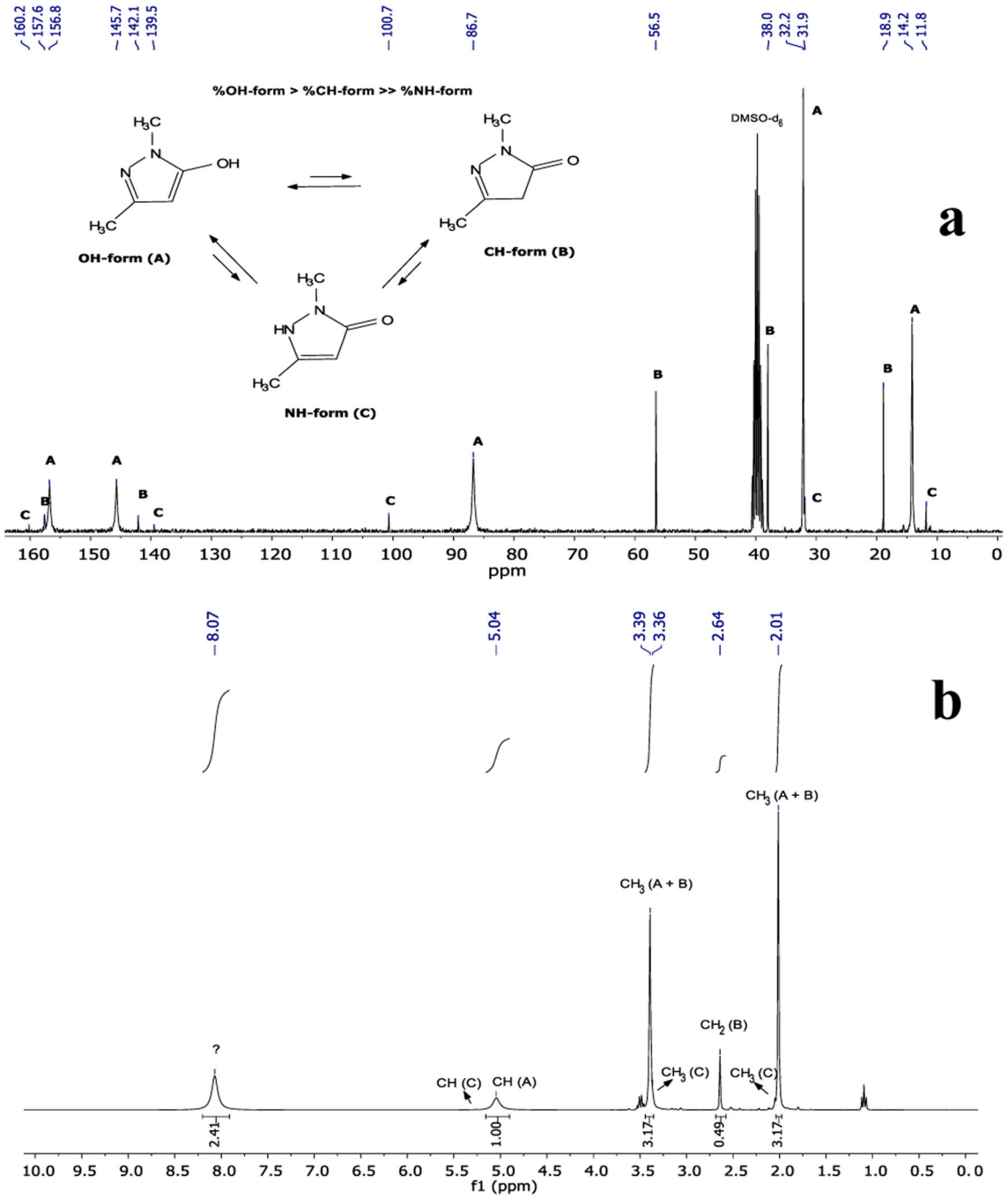


Figure 2. ^{13}C NMR (a) and ^{1}H NMR (b) spectra (in DMSO-d_6 by Bruker Ascend-400 instrument) of the precipitate formed after addition of methyl hydrazine to ethyl acetoacetate and before heating the reaction mixture.

dimethyl-5-pyrazolone is produced by intramolecular cyclization liberating water (Scheme 4). About phenyl hydrazine, 2-(3-(2-phenyl hydrazinyl)butanoyloxy)ethan-1-ylium is formed in the first step, liberating water after which and by intramolecular cyclization (liberating ethanol), 1-phenyl-3-methyl-5-pyrazolone is produced (Scheme 5).

Regarding the course of the reaction between ethyl acetoacetate and methyl hydrazine (Figure 1), and to identified the first step reaction intermediate,

Table 1. Observed (in DMSO-d_6) and predicted (by MestReNova software) chemical shifts and effective transverse relaxation times (T^*_2) of carbon in different tautomeric forms of 1,3-dimethyl-5-pyrazolone.

Tautomeric form		^{13}C NMR (in DMSO-d_6) δ (ppm) Carbon No. 1	2	3	4	5
A	Observed	14.2	32.2	86.7	145.7	156.8
	Predicted	13.6	33.0	90.9	146.9	154.7
	T^*_2 (ms)	32.2	69.8	11.6	12.0	13.1
B	Observed	18.9	38.0	56.5	142.1	157.6
	Predicted	16.6	32.5	45.7	152.7	167.2
	T^*_2 (ms)	209.5	139.6	209.5	139.6	209.5
C	Observed	11.8	31.9	100.7	139.5	160.2
	Predicted	14.8	33.6	85.1	148.9	169.6
	T^*_2 (ms)	~210	~140	~210	~140	~210

N-methyl-3-oxobutanehydrazine (Scheme 4), the formed precipitates - after addition of methyl hydrazine to ethyl acetoacetate and before heating the reaction mixture (Figure 1b) - was filtered and analyzed *via* ^{13}C and ^{1}H NMR (Figure 2, Table 1).

^{13}C NMR and ^{1}H NMR spectra of the formed precipitates in DMSO-d_6 (after addition of methyl hydrazine to ethyl acetoacetate), does not show the signals corresponding to N-methyl-3-oxobutanehydrazine intermediate, instead, it corresponds to the presence of three tautomeric forms of 1,3-dimethyl-5-pyrazolone (OH, CH and NH forms) with preponderance of OH-form (%OH-form > %CH-form >> %NH form). OH-form is characterized by broadened ^{13}C NMR signals and fast effective transfers relaxation time (T^*_2) compared to two other tautomeric forms (Table 1). It seems that in ^{1}H NMR spectrum, the signals corresponding to CH_3 groups in OH-form (A) and CH-form (B) are superimposed. Thus comparing the CH_2's signal integral of CH-form (B) with superimposed CH_3's signal integral of OH-form and CH-form (A+B) show a proportional amount of 70±5, 20±5, 2±5 for OH, CH and NH form respectively. ^{13}C NMR and ^{1}H NMR spectra of 1,3-dimethyl-5-pyrazolone in $CDCl_3$ showed signals corresponding to CH-form (Figure 3).

The preponderance of OH-form in DMSO-d_6 compared to $CDCl_3$ can perhaps be justified by the possibility of hydrogen bonding between oxygen atom in DMSO-d_6 and hydrogen atom of OH group in OH-form. The same justification can be also made for the minor presence of NH-form in DMSO-d_6.

^{13}C and ^{1}H NMR spectra of 1-phenyl-3-methyl-5-pyrazolone in DMSO-d_6 (Figure 4) also correspond to the presence of three tautomeric forms (OH, CH and NH forms). The preponderance of OH-form has also been observed for 1-phenyl-3-methyl-5-pyrazolone in DMSO-d_6. Proportional amount of 81±5, 13±5, 6±5 for OH, CH and NH form respectively have been estimated by comparing the integral of proton at *ortho* position of phenyl group (doublet signals between 7.74 and 7.93 ppm). ^{13}C and ^{1}H NMR spectra of 1-phenyl-3-methyl-5-pyrazolone in $CDCl_3$ showed only signals corresponding to CH-form (Figure 5).

4. Conclusions

The solvent-less reaction of ethyl acetoacetate with phenyl hydrazine or methyl hydrazine has been described affording, quantitatively, 1-phenyl-3-methyl-5-pyrazolone or 1,3-dimethyl-5-pyrazolone, respectively, with a minimum time of reaction (1.5 h) and simple workup procedures. Meanwhile, discussing plausible mechanisms for the reaction between hydrazine derivatives and ethyl acetoacetate, different mechanisms have been proposed for methyl hydrazine and phenyl hydrazine. Concerning the tautomeric forms of 1,3-dimethyl-5- pyrazolone and 1-phenyl-3-methyl-5-pyrazolone, ^{13}C and ^{1}H NMR spectra show

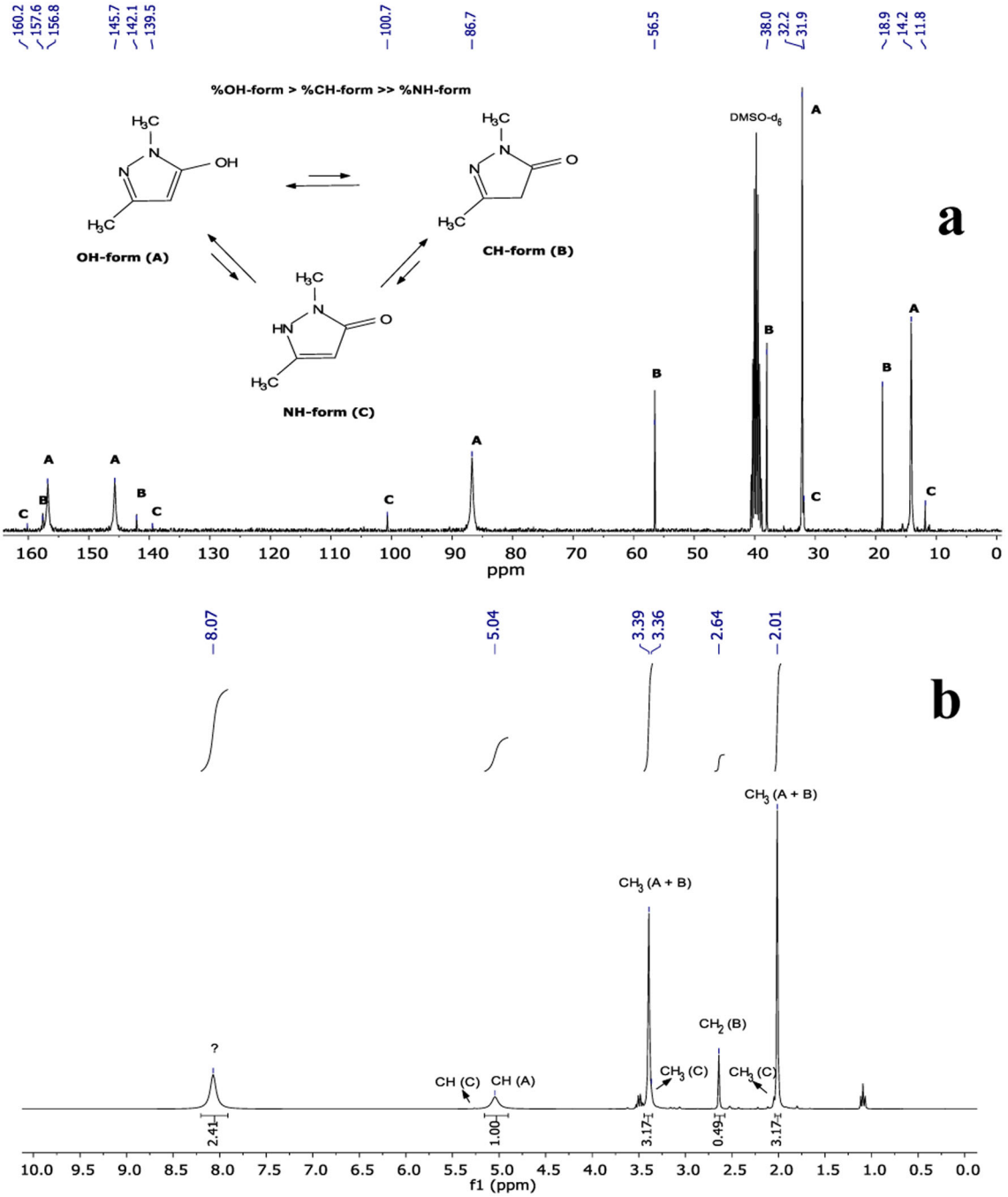


Figure 3. ^{13}C NMR (a) and ^{1}H NMR (b) spectra of 1,3-dimethyl-5-pyrazolone (in $CDCl_3$ by Bruker Ascend-400 instrument).

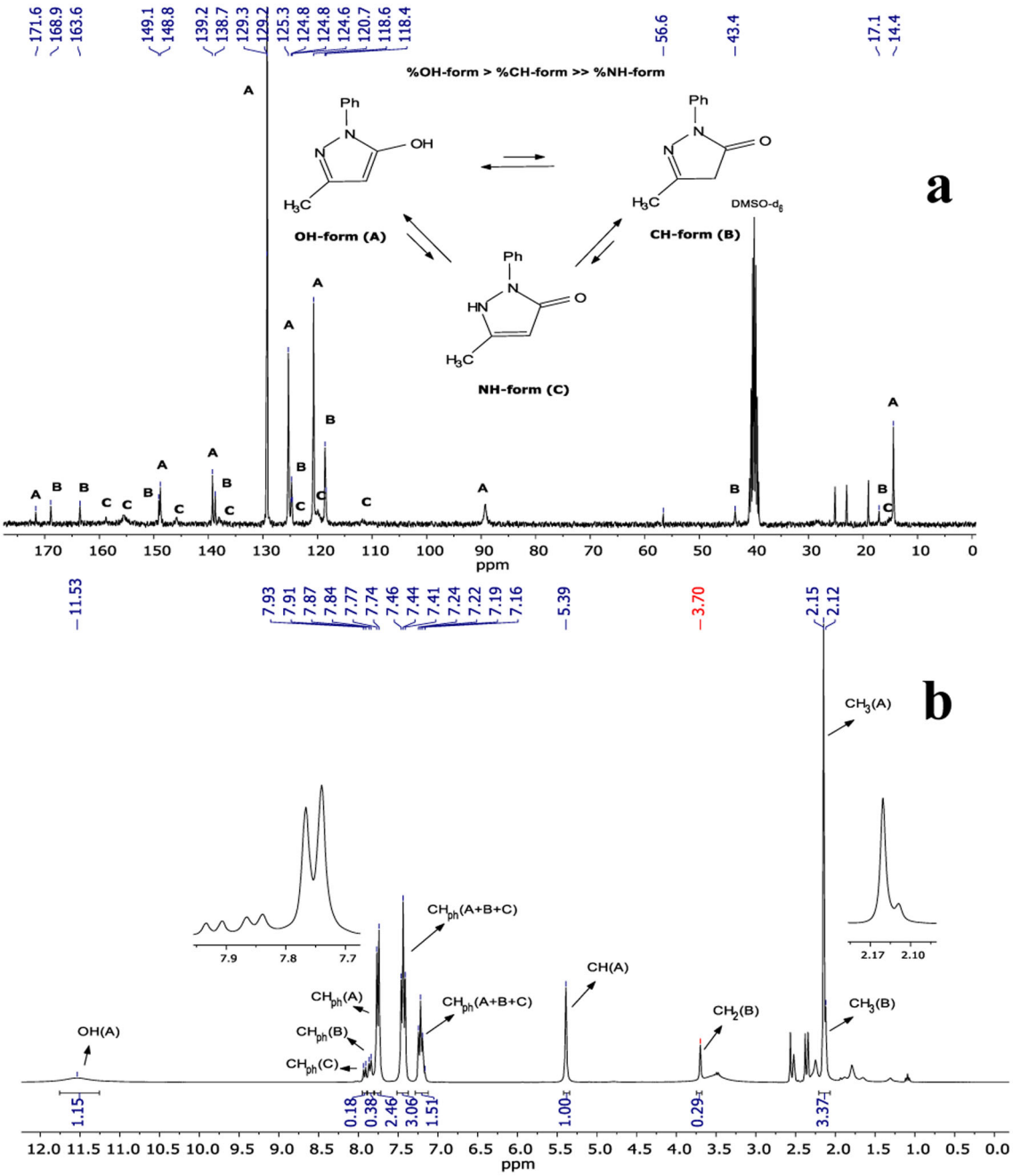


Figure 4. ^{13}C NMR (a) and ^{1}H NMR (b) spectra of 1-phenyl-3-methyl-5-pyrazolone (in DMSO-d_6 by Bruker Avance-300 instrument).

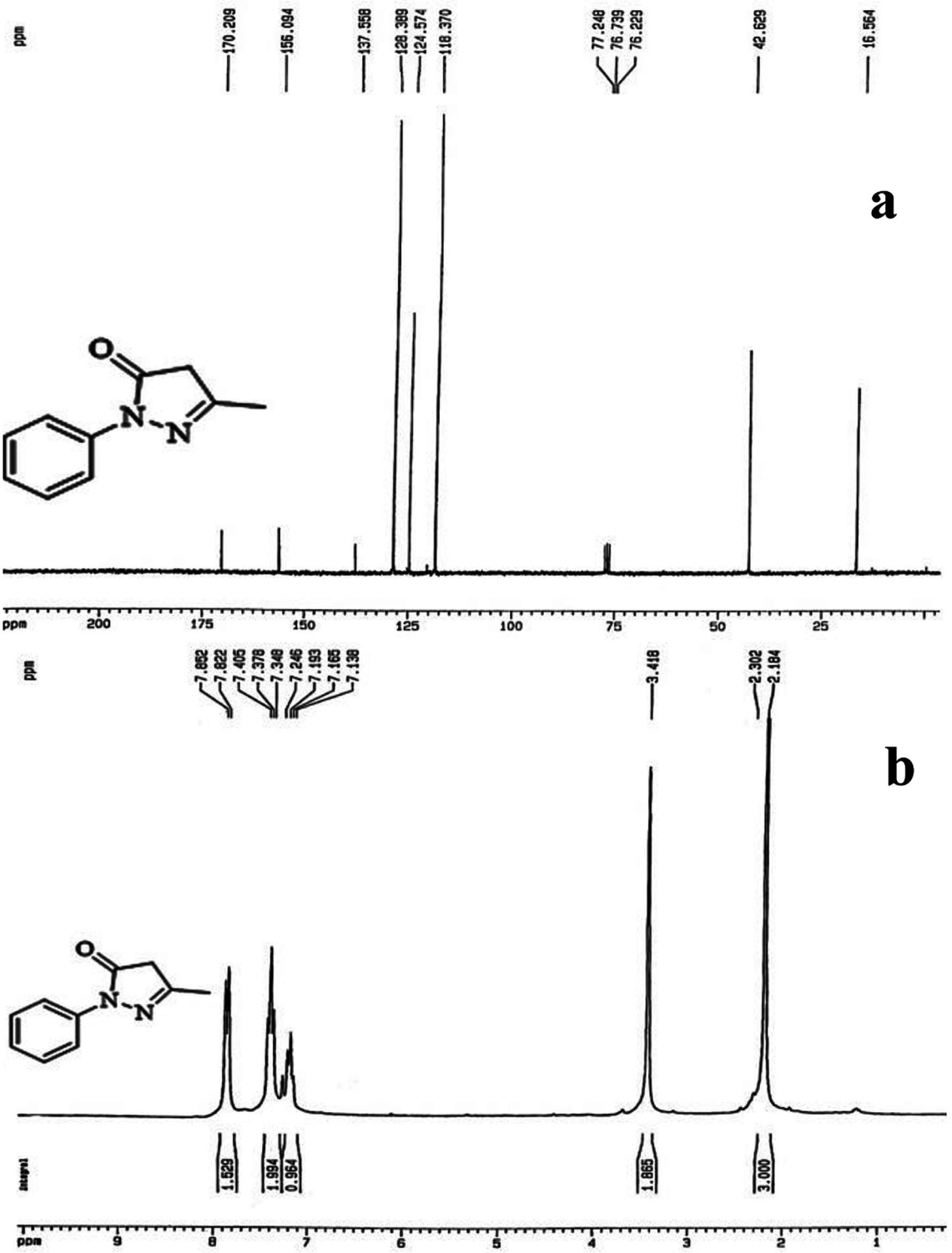


Figure 5. ^{13}C NMR (a) and ^{1}H NMR (b) spectra of 1-phenyl-3-methyl-5-pyrazolone (in $CDCl_3$ by Bruker DPX-250 instrument).

that it exists under CH-form in $CDCl_3$, while in DMSO-d_6, different forms coexist with the proportional amount of OH-form > CH-form >> NH-form.

Supplementary Information (SI)

Figures S1-S4 are available at www.ias.ac.in/chemsci.

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