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Application of Michael Reaction on 3-Methyl-1-Phenylpyrazolin-5-one with Arylmethylenecyanoacetic Acid Ethyl Esters

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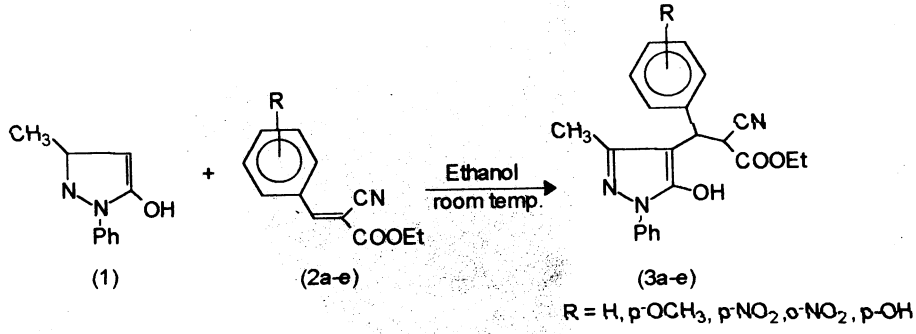
3-Methyl-1-phenylpyrazolin-5-one (1) was reacted with arylmethylenecyanoacetic acid ethyl ester (2) to give 4-[2-cyano-2-ethoxycarbonyl-1-(aryl)ethyl]-3-methyl-1-phenylpyrazolin-5-one. However, when the ethanolic solution of compound (3) was treated with piperidine, arylmethylidenebis(5-hydroxpyrazole) (4) was produced.

Key Words: Michael reaction, 3-Methyl-1-phenylpyrazolin-5-one, Arylmethylenecyanoacetic acid ethyl ester.

INTRODUCTION

Reaction of compound (1) with phenylmethylenemalononitrile in presence of piperidine has been previously reported to yield 4,4′-phenylmethylidene-bis-(5-hydroxy pyrazole)[1], or derivative of pyrazolopyrane ring[2, 3], and also 4-(2,2-dicyano-1-phenylethyl)-3-methyl-1-phenyl pyrazolin-5-one was obtained on reaction of compound (1) with phenylmethylenemalononitrile in absence of piperidine[1].

In this paper, the reaction of compound (1) with compound (2) was carried out in ethanol at room temperature; under this condition Michael addition has been carried out to obtain compound (3), **Scheme-1**.



Scheme-1

EXPERIMENTAL

All chemicals used are of chemically pure grade. Melting points were taken on Griffin apparatus and were uncorrected. The ^{1}H NMR spectra were recorded on Brucker 200 MHz instrument in acetone-d_6 and $CDCl_3$ solution. The chemical shifts are given in δ (ppm) values against TMS as standard. IR spectra were

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measured on Maltson 5000 FT-IR spectrometer as KBr pellets and microanalyses were performed at chemistry laboratory in Raslanoff Company (oil company in Raslanoff, Libya).

Arylmethylenecyanoacetic acid ethyl ester **(2)** was prepared according to the procedure described previously[4].

Preparation of 4-[2-cyano-2-ethoxycarbonyl-1-(phenyl) ethyl]-3-methyl-1-phenylpyrazolin-5-one (3)

To a stirring solution of compound **(1)** (0.01 mole) in 15 mL ethanol was added compound **(2)** (0.01 mole) in 5 portions over a period of 10 min. with continuous stirring at room temperature; a copious white precipitate was formed. It was collected by filtration and re-crystallized from ethanol, affording a white powder, Table-1.

Action of Piperidine on Michael Adducts (Compound 3)

Compound **(3)** (0.01 mole) was suspended in 15 mL of ethanol, then 0.5 mL of piperidine was added. The resulting solution was stirred at room temperature for 1–5 h, during which time a copious white precipitate was formed, which was filtered off and purified by column chromatography using methanol as eluent after evaporation of the solvent; the crude product was re-crystallized from ethanol to afford compound **(4)**, Tables 1 and 2.

TABLE-1
ANALYTICAL AND PHYSICAL DATA OF THE COMPOUNDS (3) AND (4)

Compd.	m.p. (°C)	Yield (%)	Time of stirring (h)	m.f. (mol. mass)	Analyses %, Calcd. (Found)		
					C	H	N
3a	140–142	99	3	$C_{22}H_{21}N_3O_3$ (375.43)	70.38 (69.92)	5.64 (5.63)	11.19 (11.40)
3b	150–153	90.12	3	$C_{23}H_{23}N_3O_4$ (402.46)	68.15 (67.66)	5.72 (5.70)	10.36 (10.10)
3c	160–163	81	1	$C_{22}H_{20}N_4O_5$ (420.43)	62.85 (62.76)	4.79 (4.81)	13.33 (12.96)
3d	142	76	1	$C_{22}H_{20}N_4O_5$ (420.43)	62.85 (62.57)	4.79 (4.80)	13.33 (13.09)
3e	118–119	83	3	$C_{22}H_{21}N_3O_4$ (391.43)	66.04 (65.99)	6.15 (6.16)	9.71 (9.60)
4a	156	42.31	1	$C_{27}H_{24}N_4O_2$ (436.51)	74.31 (73.96)	5.50 (5.80)	12.84 (13.02)
4b	168–170	49.14	2	$C_{28}H_{26}N_4O_3$ (466.54)	72.10 (72.23)	5.58 (5.89)	12.02 (11.83)
4e*	143	43.36	5	$C_{27}H_{24}N_4O_3$ (452.51)	71.68 (70.46)	5.31 (5.19)	12.39 (12.81)

*Compound (3e) contaminated with 0.01 mol of ethanol.

TABLE-2
SPECTROSCOPIC DATA* OF COMPOUND (3) AND (4)

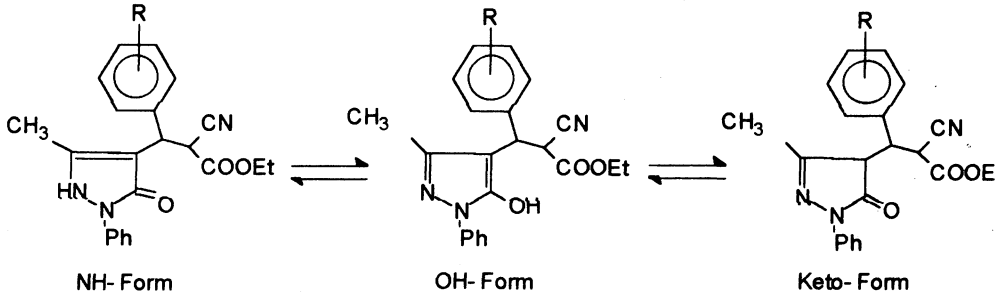
Compd.	Spectroscopic Data (^{1}H NMR and IR)
3a	δ = 1.0, 1.1 (t, t, 6H, $2CH_3$ of ester groups), 2.2, 2.3 (s, s, 6H, $2CH_3$), 4.0 (q, 2H, CH_2 of ester group), 4.1–4.3 (m, 3H, CH_2 and CH), 4.3–4.45 (m, 2H, 2CH), 5.25 (d, 1H, CH), 7.1–7.4 (m, 12H, Ph—H), 7.6–7.8 (m, 8H, Ph—H). ν_{max} (cm^{-1}) = 3063 (Ar—H), 2970 and 2898 (Alkyl-H), 2230 (C≡N), 1737 (C=O ester), 1700 (C=O of pyrazole ring), 1680, 1578 (C=C and/or C=N), 756, 696 (mono substituted aromatic).
3b	δ = 1.0, 1.1 (tt, 6H, $2CH_3$ of ethyl groups), 2.1, 2.3 (s, s, 6H, CH_3), 3.7, 3.75 (s, s, 6H, $2OCH_3$), 4.0 (q, 2H, CH_2 of ethyl group), 4.1–4.25 (m, 3H, CH_2 + CH), 4.3–4.4 (m, 2H, 2CH), 5.2 (d, 1H, CH), 6.8–7.8 (m, 18H, aromatic), 10.05 (s, broad, 1H, NH). ν_{max} (cm^{-1}) = 3010 (Ar—H), 2980 and 2820 (Alkyl-H), 2260 (C≡N), 1740 (C=O), 1580 (C=N and/or C=C), 1010 (C—O), 840, 750, 710 (mono and *para* substituted aromatic).
3c	δ = 1.0, 1.105 (tt, 6H, $2CH_3$ of ethyl ester groups), 2.30, 2.40 (s, s, 6H, $2CH_3$), 4.0 (q, 2H, CH_2 of ethyl group), 4.10–4.30 (m, 3H, CH_2 and CH), 4.55–4.65 (m, 2H, 2CH), 5.30 (d, 1H, CH), 7.10–8.15 (18H, aromatic). ν_{max} (cm^{-1}) = 3059 (Ar—H), 2982 and 2882 (Alkyl-H), 2260 (C≡N), 1740 (C=O ester), 1700 (C=O of pyrazole ring), 1610 (C=N and /or C=C), 1522, 1498 (CH_3), 1108 (C—O), 832, 758, 696 (mono and *para* substituted aromatic).
3d	δ = 1.06, 1.15 (tt, 6H, $2CH_3$ of ethyl ester), 2.21, 2.39 (s, s, 6H, $2CH_3$), 4.0 (q, 2H, CH_2 of ethyl ester group), 4.05–4.15 (m, 3H, CH_2 and CH), 5.0–5.10 (m, 2H, 2CH), 5.3 (d, 1H, CH), 7.21–7.8 (16H, aromatic), 8.21–8.30 (m, 2H, aromatic), 10.34 (s, broad, NH). ν_{max} (cm^{-1}) = 3061 (Ar—H), 2980 and 2836 (Alkyl-H), 2240 (C≡N), 1747 (C=O ester), 1705 (C=O of pyrazole ring), 1640, 1594 (C=N and/or C=C), 1497 (CH_3), 1169 (C—O), 745, 698, 687 (mono and *ortho* substituted aromatic).
3e	δ = 1.0, 1.10 (tt, 6H, $2CH_3$ of ethyl ester groups), 2.20, 2.30 (s, s, 6H, $2CH_3$), 4.0 (q, 2H, CH_2 of ethyl ester group), 4.05–4.20 (m, 3H, CH_2 and CH), 4.25–4.40 (m, 2H, 2CH), 5.20 (d, 1H, CH), 6.9–7.8 (18H, aromatic).
4a	δ = 2.01 (s, 6H, $2CH_3$), 4.78 (s, 1H, CH), 7.07–7.28 (m, 11H, Ph—H), 7.59 (d, 4H, Ph—H).
4b	δ = 2.06 (s, 6H, $2CH_3$), 3.73 (s, 3H, OCH_3), 4.71 (s, 1H, CH), 6.74–7.59 (m, 14H, Ar—H).
4e	δ = 2.40 (s, 6H, $2CH_3$), 4.95 (s, 1H, CH), 6.70 (d, 2H, Ar—H), 7.10–7.25 (tt, 4H, Ar—H), 7.4 (t, 4H, Ar—H), 7.8 (d, 4H, Ar—H).

*The ^{1}H NMR of all compounds in Table -2 in Acetone-d_6 except **4a** and **4b** in $CDCl_3$.

RESULTS AND DISCUSSION

Compound (**3**) was reacted with phenylmethylenemalononitrile to give 4-(2,2-dicyano-1-phenylethyl)-5-hydroxy-3-methyl-1-phenylpyrazole[1]. An analogue of this work was the reaction of equimolar amounts of phenylmethylenecyanoacetic acid ethyl ester (**2a**) with compound (**1**) in ethanol solution at room temperature to give the expected 4-(2-cyano-2-ethoxycarbonyl-1-(phenyl)ethyl)-5-hydroxy-3-methyl-1-phenylpyrazole (**3a**) through Michael addition, by reaction of the methylene group at fourth position of compound (**1**) with olefinic carbon in compound (**2a**), **Scheme-1.** The elemental analysis, Table-1, was succeeded with the structure

of compound **(3a)** in OH form **Scheme-2.** There are no ν(NH) and ν(OH) bands in infrared spectra of compound **3a**, but instead a carbonyl group absorption band at $\nu_{max} = 1700\ cm^{-1}$ appeared in addition to bands characteristic for cyano and carbonyl of ester; so compound **(3a)** existed in keto form and had the suggested structure in solid state, **Scheme-2.**

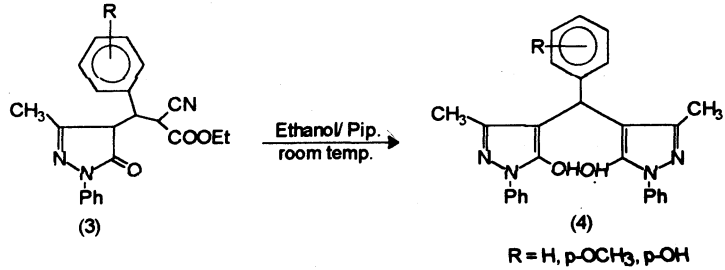


Scheme-2.. Tautomers of Compound **3**

The ^1H NMR spectrum of compound **(3a)** in acetone-d_6, Table-2, showed two triplet and two quartet signals characteristic of two ethyl ester groups, and two singlet signals at δ = 2.30 ppm and 2.20 ppm for two methyl groups of pyrazole ring, 3 protons for 3CH of pyrazole ring and signals at δ = 7.10–7.80 ppm for aromatic protons. This revealed that there is a mixture of two structures although the melting points of these compounds were sharp and gave a single spot on TLC when visualized under UV or with iodine vapour, so that the presence of the mixture is probably due to the tautomeric properties of pyrazolin-5-one ring, which inferred that compound **(3a)** exists in NH- and OH tautomeric forms **(Scheme-2).**

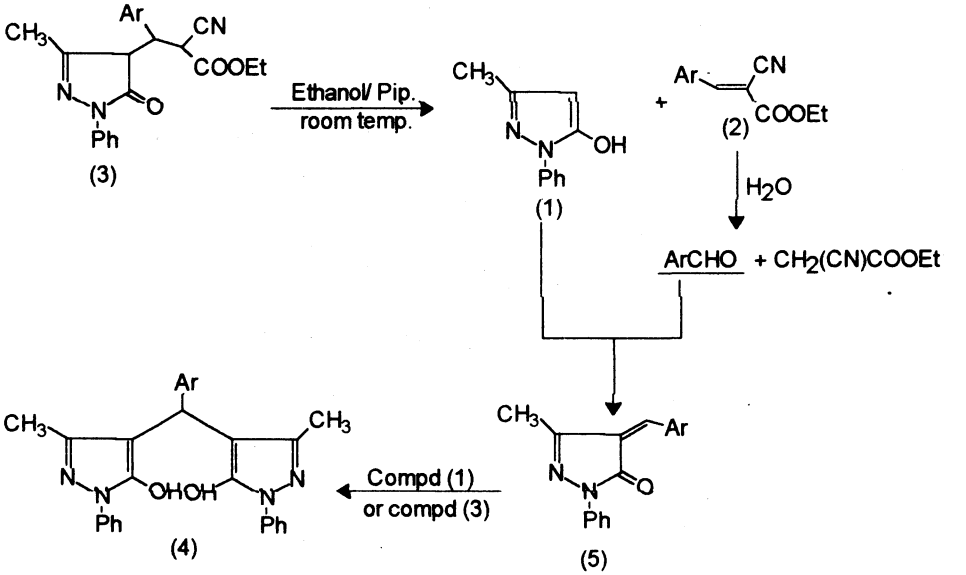
However the same observation was noted, when arylmethylenecyanoacetic acid ethyl esters **(2b–e)** were reacted with 3-methyl-1-phenylpyrazolin-5-one **(1)** to obtain compounds **(3b–e).**

Compound **(3)** was unstable; it converted gradually to corresponding arylmethylene-bis(5-hydroxy-3-methyl-1-phenylpyrazole) **(4),** upon standing in solvent such as methanol, acetone or chloroform, but the conversion of compound **(3)** to the corresponding compound **(4)** was not quantitative, there were a quantity of compound **(3).** In order to make this conversion complete, the ethanolic solutions of compounds **(3a–e)** were treated with piperidine at room temperature; then compounds **(4a), (4b)** and **(4e)** were obtained, but nonisolable mixtures were obtained with compounds **(3c)** and **(3d) (Scheme-3).** The structure of compound (4) substantiated from its ^1H NMR spectra (Table-2).



Scheme-3

The formation of compound (4) under this conditions could be rationalized through retro-Michael reaction to yield compound (1) together with compound (2)[4], which undergoes a cleavage leading to ethylacetate and arylaldehyde[1, 4]. Recombination of arylaldehyde with compound (1) in appropriate form would lead to the formation of 4-arylmethylene-3-methyl-1-phenylpyrazolin-5-one (5)[5, 6]. Reaction of compound (5) with another molecule of compound (1)[5, 6], or with another molecule of compound (3), leads to compound (4) (Scheme-4).



Scheme-4

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