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Behaviour of Some Activated Nitriles Toward Barbituric Acid, Thiobarbituric Acid and 3-Methyl-1-Phenylpyrazol-5-one

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Abstract: The effect of some active methylene containing heterocyclic compounds, namely barbituric acid, thiobarbituric acid and 3-methyl-1-phenylpyrazol-5-one on α-cyano-3,4,5-trimethoxycinnamonitrile and ethyl α-cyano-3,4,5-trimethoxycinnamate (**1a**,**b**) was investigated. The structure of the new products was substantiated by their IR, ^{1}H-NMR and mass spectra.

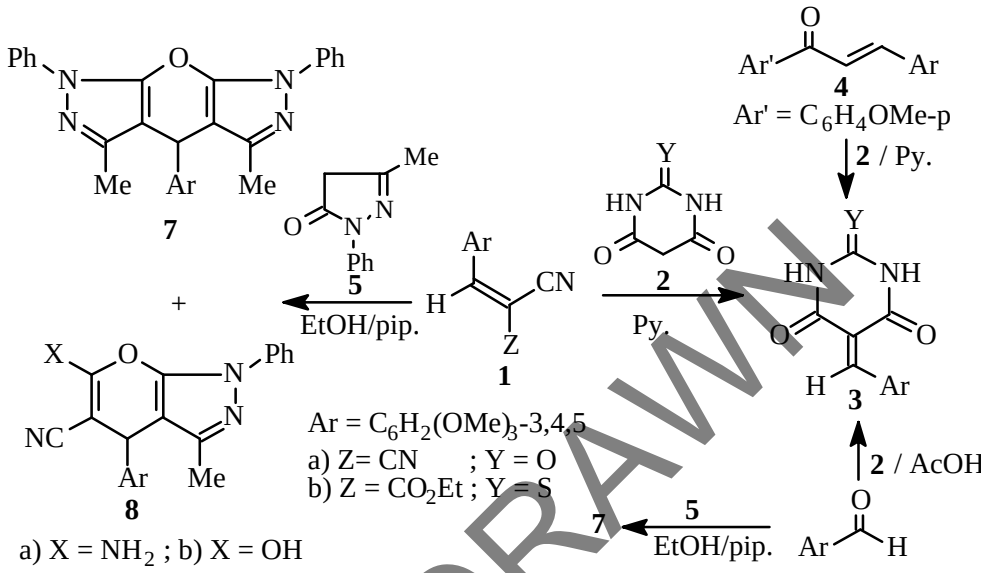
Keywords: Barbituric and thiobarbituric acids, pyrazolone, and activated nitriles.

Introduction

Recently, it has been reported that the reaction of chalcones with barbituric or thiobarbituric acid may afford pyranopyrimidine derivatives in the presence of P_2O_5 [1] or it may proceed via simple substitution with triethanolamine [2] depending on the reaction conditions. Also, the reaction of α-cyanocinnamonitrile with barbituric acid afforded pyranopyrimidine [3], an arylidene derivative [4] or simple a substitution product [5]. The present work studies the behaviour of α-cyano-cinnamonitrile derivatives **1a**,**b** and chalcone **4** toward barbituric or thiobarbituric acid **2a**,**b**. Thus, when compounds **1a**,**b** or compound **4** were reacted with compounds **2a**,**b** in refluxing pyridine they afforded the arylidine derivatives **3a**,**b** [cf. Scheme 1].

Results and Discussion

The proposed structures of compounds **3a**,**b** were confirmed by ^{1}H-NMR, molecular weight determination using field desorption mass spectroscopy as well as the chemical evidence. The ^{1}H-NMR spectrum of **3** (Y=O,S) in DMSO-d_6 displayed signals from low to high field at δ (ppm) 11.5, 11.4 (two s, 2H,2NH), 8.4 (s,1H, olefinic proton), 7.9 (br.s, 2H, aromatic protons) and 3.95 (br. s, 9H, 3 OMe) which agree well with the assigned structures.



Scheme 1.

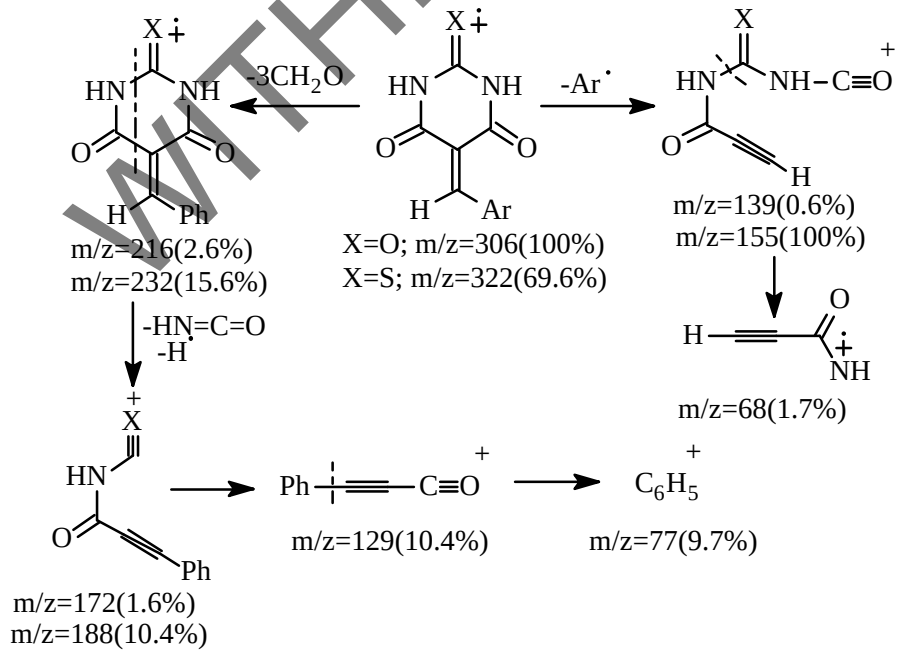
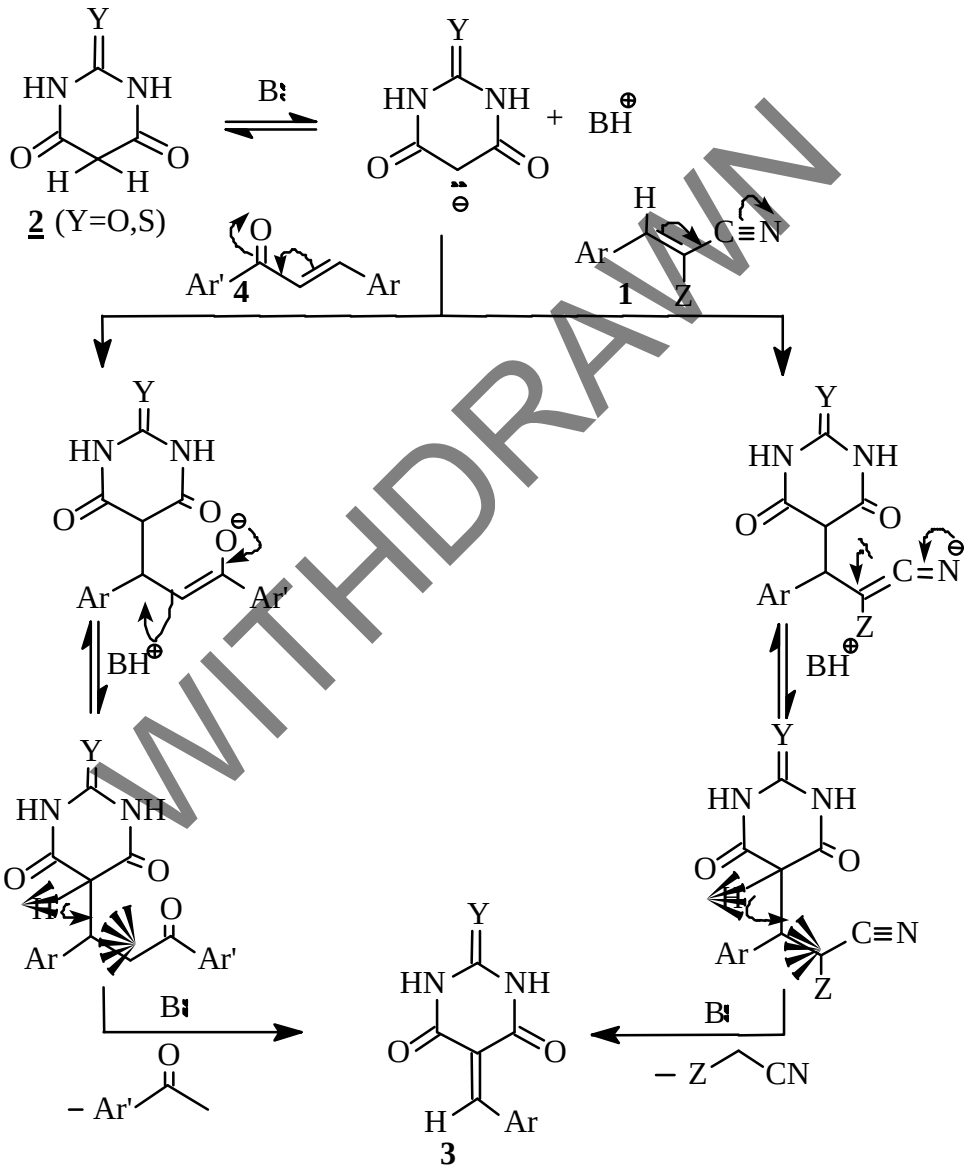


Figure 1.

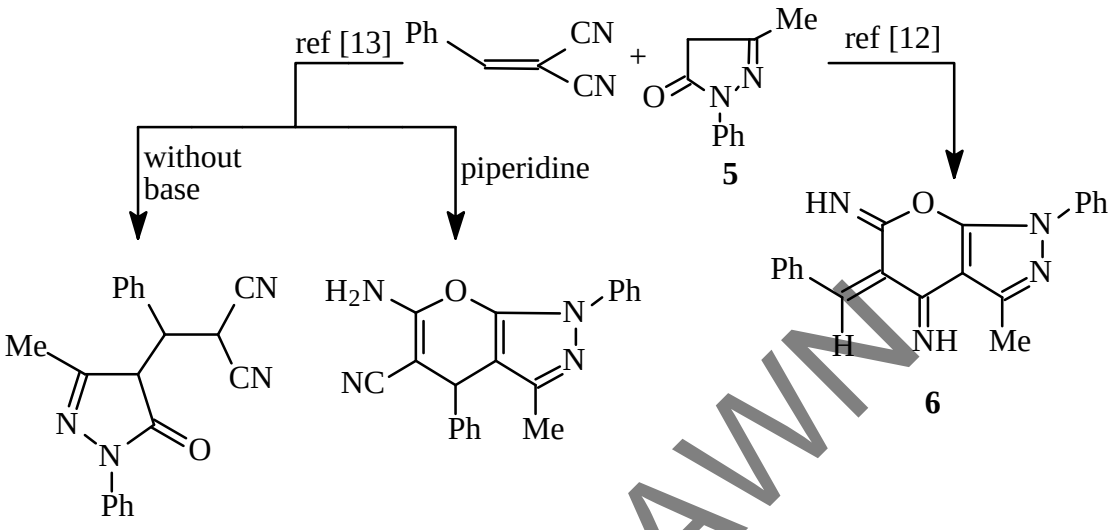
These structures are further supported by mass spectroscopy data. It was observed that their electron impact (EI) spectra have several common features, the first of which is that the highest recorded peak represents the corresponding molecular ion peaks (m/z 306 & 322). The second common feature is the similarity in their EI fragmentation patterns. The common fragmentation pathways are represented in Figure 1.

Furthermore, the arylidene derivatives **3a**,**b** are identical (lR, TLC, m.p and mixed m.p) with an authentic sample prepared by stirring 3,4,5-trimethoxybenzaldehyde with barbituric and/or thiobarbituric acids in refluxing acetic acid. A possible pathway for the formation of the arylidene derivatives may be as represented in Scheme 2.



Scheme 2.

The diverse biological activities of fused pyrazoles have stimulated considerable research in this field [6-11]. It has been reported [12] that the pyrazolone derivative **5** reacted with α-cyano-cinnamonitrile in the presence of piperidine to yield the 1:1 adduct **6**. On the other hand, it has been also claimed [13] that the above mentioned reaction afforded two products instead of compound **6** [cf. Scheme 3].



Scheme 3.

Because of the striking biological activity of fused pyrazoles and to extend the present work, equi-molar amounts of **1a** and **5** were refluxed in absolute ethanol in the presence of piperidine as a basic catalyst. After 15 minutes an insoluble fraction was isolated as colourless crystals (13%) and identified as the oxinobispyrazole **7**. The reaction was then continued for 3h. Removal of most of the solvent and acidification with dilute acetic acid afforded the 1:1 adducts **8a** and **8b** as pale yellow crystals in 44% and 46% yield respectively [cf. Scheme 1]. The structure of **7** was elucidated exclusively from its IR and mass spectral data beside the correct analytical data and chemical evidence. Thus, the IR spectrum of **7** lacks $\nu_{C=O}$ and ν_{CN}. The mass spectrum of **7**, which is represented in Figure 2, is in accordance with the proposed structure. Furthermore, the bispyrazole derivative **7** was identical (TLC, IR, m.p. and mixed m.p) with an authentic sample synthesized by stirring 3,4,5-trimethoxybenzaldehyde with **5** in absolute ethanol in the presence of a catalytic amount of piperidine for 15 minutes [cf. Scheme 1].

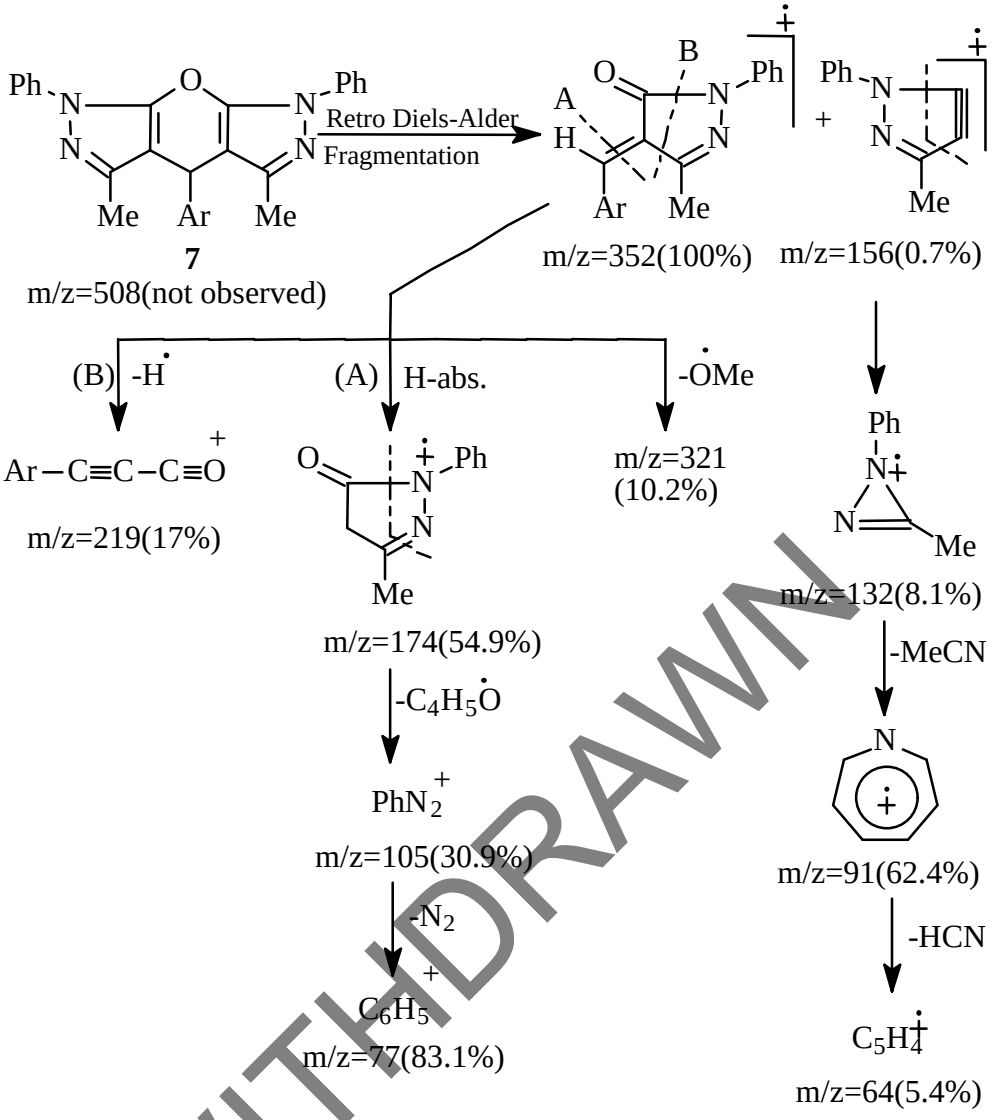


Figure 2.

The proposed structure of the adduct **8a** is based upon:

i) A satisfactory elemental analysis.

ii) The IR displayed ν_{NH_2} at 3485 , 3373 and 3223 cm^{-1}, ν_{CN} at 2205 cm^{-1} and $\nu_{C=N}$ at 1622 cm^{-1}.

iii) The ^{1}H-NMR spectrum (DMSO-d_6) exhibits signals at δ(ppm) 7.9-7.3 (m, 5H, Ph), 6.8 (s, 2H, arom. protons), 5.0 (s, 1H, CHAr), 3.90-3.75 (two s, 9H ; 3OMe) and 2.3 (s, 3H, Me).

iv) EI fragmentation of **8a** involves primary loss of $CN^{\bullet}$ followed by H-abstraction to give the radical cation of m/z=393/100%; base peak). There is also a loss of formaldehyde molecule to give the ion of m/z=363 (84.0%) which is the major daughter ion. Successive losses of two molecules of formaldehyde resulted in the radical cation of m/z = 303 (5.1%). The tentative fragmentation pattern of **8a** is represented in Figure 3.

The IR spectrum of the adduct **8b** lacks ν_{CO} of ester and displayed ν_{OH}(br) centered at 3913 cm^{-1}, ν_{CH} 2941 cm^{-1} ν_{CN} at 2216 cm^{-1}, $\nu_{C=N}$ at 1620 cm^{-1} and $\nu_{C=C}$ at 1595 cm^{-1}. The ^{1}H-NMR spectrum of **8b** (DMSO-d_6) exhibits signals from low to high field at δ(ppm) 7.9-7.4 (m, 5H, ph), 6.9 (s, 2H, aromatic protons), 5.0 (s, 1H, CHAr), 4.0 - 3.8 (two s, 9H, 3 OMe). and 2.4 (s, 3H, Me). The mass spectrum of **8b**, which is in accord with the assigned structure, is represented in Figure 4.

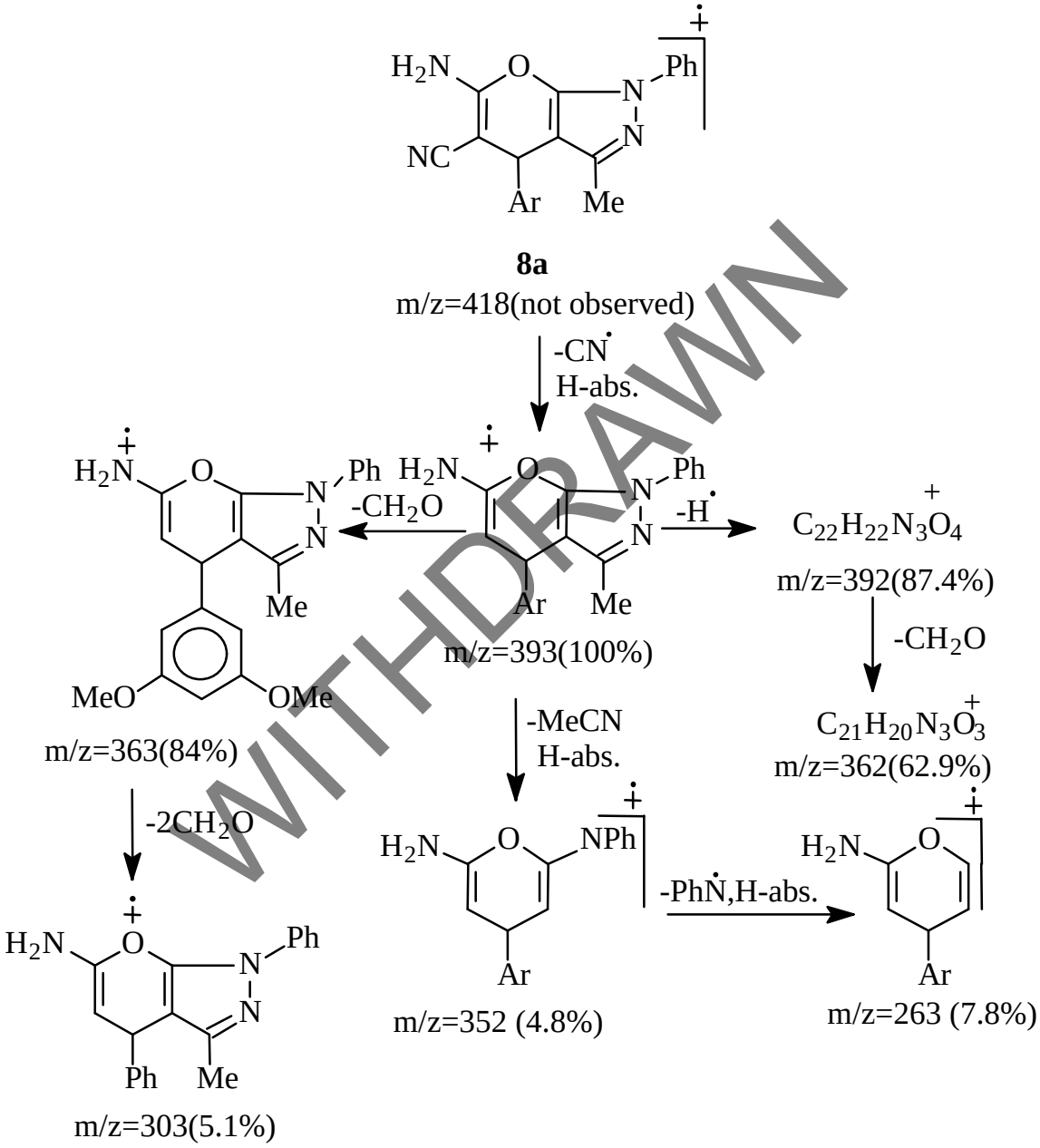


Figure 3.

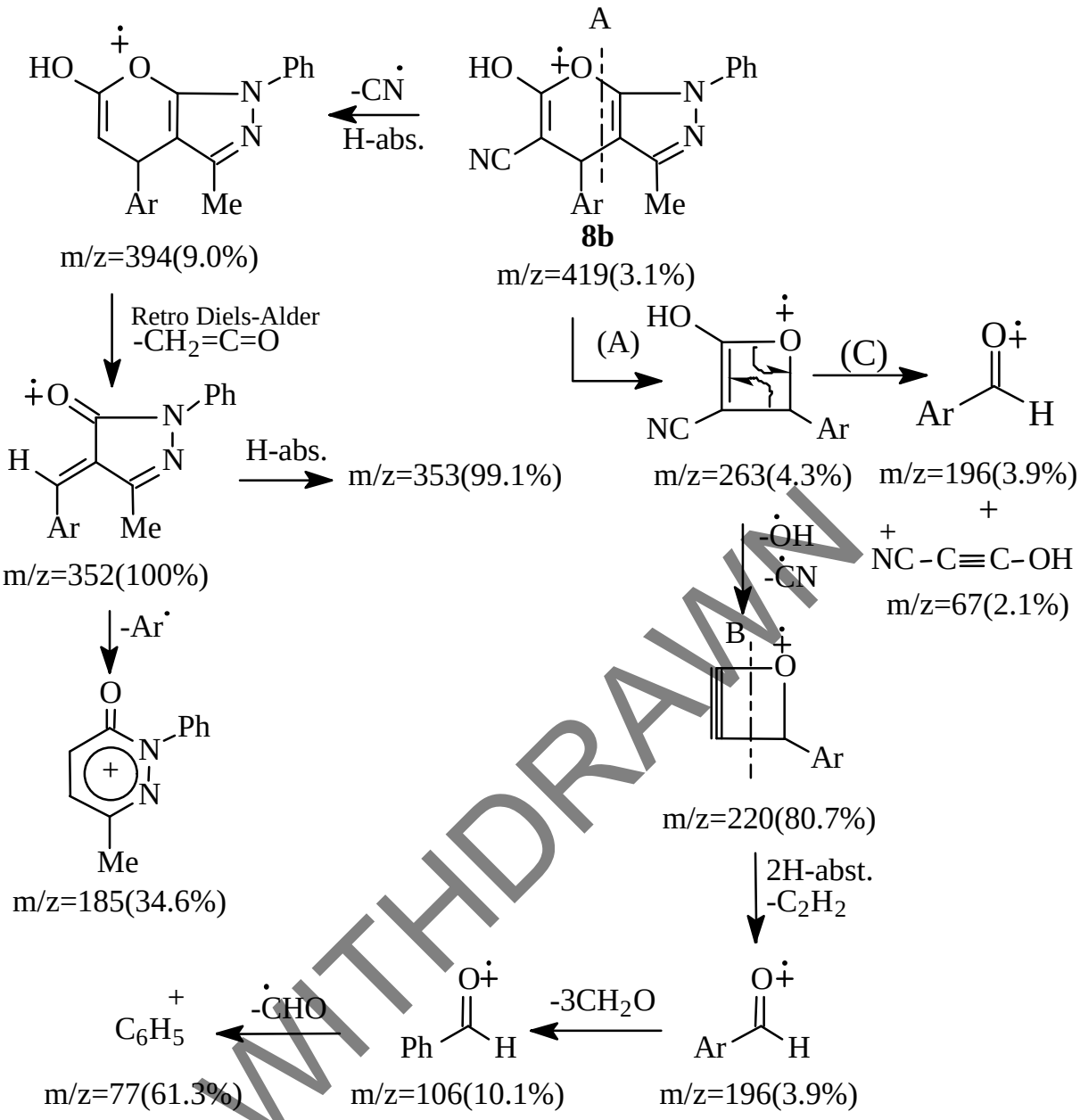
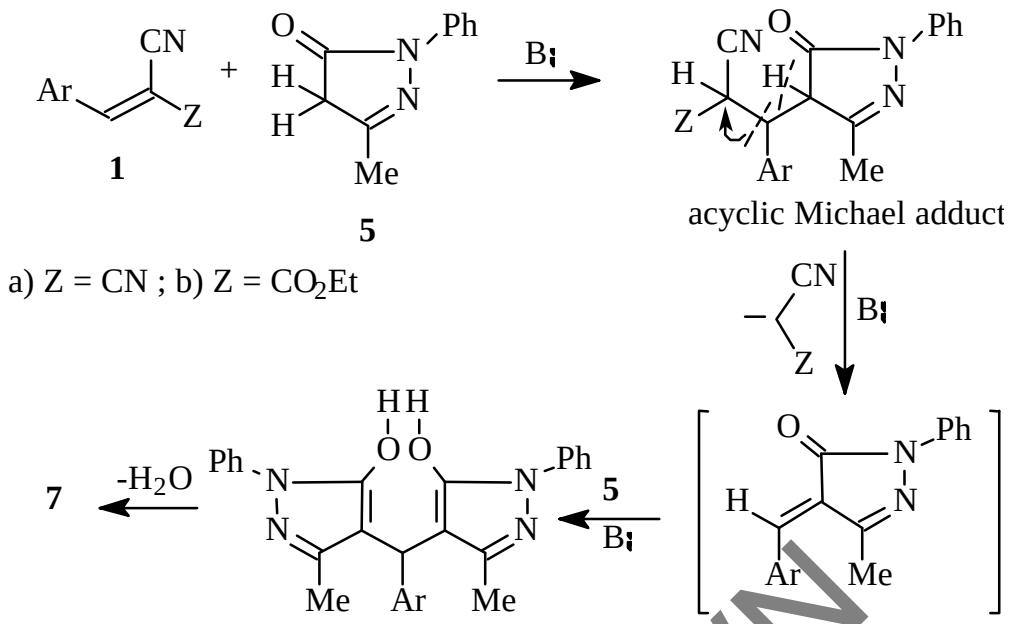


Figure 4.

The formation of the oxino bispyrazole derivative **7** from the reaction of **1a** and/or **1b** with 3-methyl-1-phenylpyrazolone **5** probably proceeds via the initial Michael addition to afford an acyclic Michael adduct which then loses the active methylene moiety, i.e., malononitrile or ethyl cyanoacetate to give the arylidene pyrazolone which could be attacked by a new molecule of **5** followed by a cyclodehydration step to yield the isolated bispyrazole derivative **7** [cf. Scheme 4]. Cyclization of the acyclic Michael adducts via attack of the ring carbonyl either on the cyano or ester functional group yielded the products **8a** and **8b** respectively.



Scheme 4.

Experimental

General

Melting points are not corrected. The IR spectra were recorded in a Pye-Unicam SP 1200 spectrophotometer using the KBr wafer technique. The ^{1}H-NMR spectra were recorded on a Varian GEMINI 200 MHz NMR Spectrophotometer using DMSO-d_6 as solvent and TMS as internal standard. All chemical shifts are in ppm downfield from TMS. The elemental analysis were carried out in the Central Lab., Faculty of Science, Ain Shams University, Abbassiya, Cairo, Egypt. Mass spectra were recorded on Shimadzu GC-MS-QP 1000 EX instrument. The purity of the synthesised compounds was monitored by TLC.

*Reaction of α-cyano-3,4,5-trimethoxycinnamonitrile (***1a***) or ethyl α-cyano-3,4,5-trimethoxycinnamate (***1b***) with barbituric acid or thiobarbituric acid; Formation of 5-(3,4,5-trimethoxybenzylidene)barbituric or thiobarbituric acid (***3a** *or* **3b***)*

A mixture of **1a** (2.44 g; 0.01 mol) or **1b** (2.91 g, 0.01 mol) and barbituric acid (1.28 g, 0.01 mol) or thiobarbituric acid (1.44 g, 0.01 mol) in pyridine (30 mL) was refluxed for 3h. Most of the solvent was distilled off and the reaction mixture was cooled and acidified with ice-cold glacial acetic acid. The solid which deposited was filtered off, washed with cold water, dried and recrystallized from the proper solvent to give **3a** or **3b** [cf. Table 1].

Table 1. Physical characteristics of the new compounds.

Compd.	Mol. Formula	Mol. Wt.*	M.P (°C)	Yield %	Recryst. Solvent**	Colour
3a	$C_{14}H_{14}N_2O_6$	306	236-8	78.6	E.A	Yellow
3b	$C_{14}H_{14}N_2O_5S$	322	196-8	83.11	M	Pink
7	$C_{30}H_{28}N_4O_4$	508	196-8	13	CCl_4	Colourless
8a	$C_{23}H_{22}H_4O_4$	418	170-2	44	CCl_4	Pale yellow
8b	$C_{23}H_{21}N_3O_5$	419	204-6	46	B/L.p	Pale yellow

* All elemental analysis (C,H,N) are in agreement with the calculated values.

** E.A. = Ethyl acetate , M = Methanol , B = Benzene. , L.p = Light petroleum.

Reaction of chalcone **4** *with barbituric or thiobarbituric acid, Formation of* **3a** *or* **3b**

A mixture of chalcone **4** (3.28g; 0.01mol). and barbituric acid (1.28g.; 0.01mol) or thiobarbituric acid (1.44g , 0.01 mol) in pyridine (30 mL) was refluxed for 3h. The reaction mixture was concentrated, cooled, and acidified with ice cold acetic acid. The solid which separated out was filtered off, washed with water, dried and recrystallized from the suitable solvent to give **3a** (26.7% yield) or **3b** (42.4% yield).

Reaction of barbituric or thiobarbituric acid with 3,4,5-trimethoxybenzaldehyde; Formation of an authentic sample of **3a**

A mixture of barbituric acid (1.28g; 0.01mol) or thiobarbituric acid (1.44g; 0.01mol) and 3,4,5-trimethoxybenzaldehyde (1.96g; 0.01 mol) in glacial acetic acid (30 mL) was heated under reflux for 30 minutes. The reaction mixture was concentrated, diluted with ice cold water. The solid deposited was filtered off, dried and recrystallized from the proper solvent to yield **3a** (77.3% yield) or **3b** (86.1% yield).

Reaction of **1a** *or* **1b** *with 3-methyl-1-phenylpyrazol-5-one (***5***); Formation of 4H-3,5-dimethyl-1,7-diphenyl-4-(3,4,5-trimethoxy-phenyl)oxino[2,3-c:6,5-ℓc] bis-pyrazole (***7***) and 4H-6-amino-5-cyano-3-methyl-1-phenyl-4-(3,4,5-trimethoxyphenyl)-pyrano[2,3-c]pyrazole (***8a***) or 4H-5-cyano-6-hydroxy-3-methyl-1-phenyl-4-(3,4,5-trimethoxyphenyl)pyrano[2,3-c]-pyrazole (***8b***)*

A mixture of the arylidene derivative **1a** (2.4g; 0.01mol) or **1b** (2.91g; 0.01 mol) and 3-methyl-1-phenylpyrazol-5-one **5** (1.74g; 0.01 mol) in absolute ethanol (30 ml) was refluxed in the presence of a

catalytic amount of piperidine. After 15 minutes, the colourless insoluble product was filtered off, dried and recrystallized from the proper solvent to give compound **7**. The filtrate was refluxed up to 3h. Most of the solvent was distilled off and the reaction mixture was cooled and acidified with ice cold acetic acid. The deposited solid was filtered off, dried and recrystallized from the suitable solvent to give **8a** or **8b** [cf. Table 1].

Reaction of 5 with 3,4,5-trimethoxybenzaldehyde; Formation of an authentic sample of **7**

A mixture of 3,4,5-trimethoxybenzaldehyde (1.96g; 0.01 mol) and 3-methyl-1-phenylpyrazol-5-one (**5**) (1.74g, 0.01mol) in absolute ethanol (30 mL) was refluxed for 15 minutes in the presence of a catalytic amount of piperidine. The insoluble product was filtered off, dried and recrystallized from the appropriate solvent to give **7**.

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Samples Availability: Available from the authors.