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

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The effect of some active methylene containing heterocyclic compounds, namely barbituric, thiobarbituric acids and 3-mehtyl-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 from their IR, ^{1}H NMR and mass spectra.

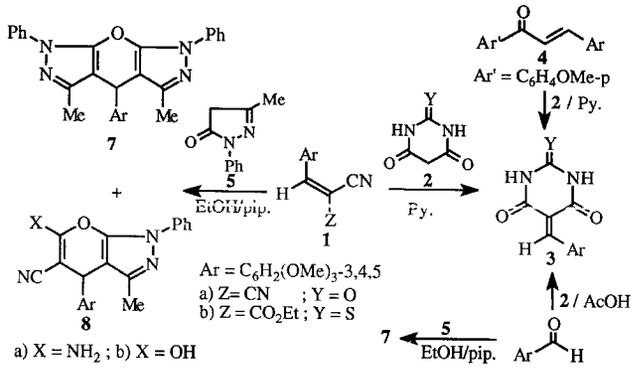
INTRODUCTION

Recently, it has been reported that[1] the reaction of chalcones with barbituric or thiobarbituric acid may afford pyranopyrimidine derivatives in the presence of P_2O_5 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] arylidene derivative[4] or simple substitution product.[5]

The present work studies the behaviour of α-cyanocinnamonitrile derivative **1a,b** and chalcone **4** toward barbituric and/or thiobarbituric acid **2a,b**. Thus, when compound **1a,b** and/or compound **4** was submitted to react with compound **2a,b** in refluxing pyridine afforded the arylidine derivative **3a,b** [cf. Scheme I].

Scheme I



The structure of compounds **3a,b** was explored 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 structure. This structure gets further support from mass spectroscopy. It has been observed that electron impact (EI) spectra have many common features. The first of which is that the highest recorded peak representing the molecular ion peak (*m/z* 306 & 322). The second is the similarity in their EI fragmentation patterns. The common fragmentation pathways are represented in Chart 1.

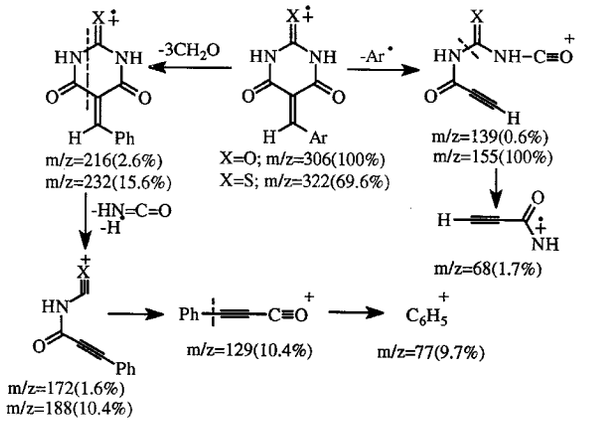


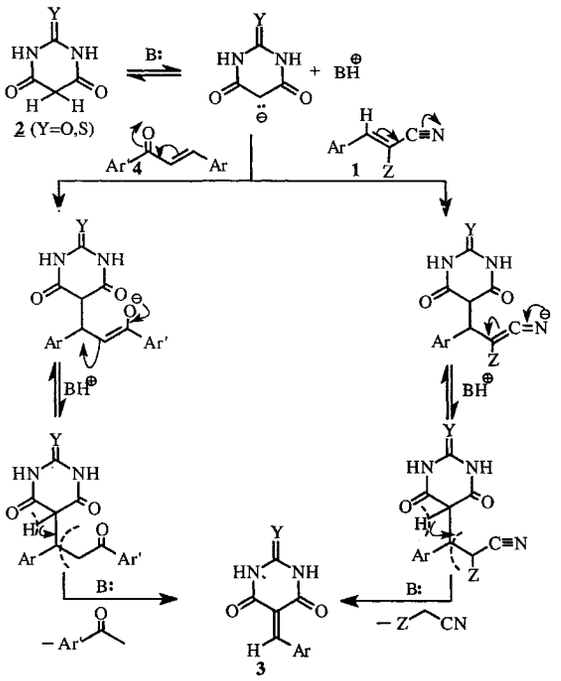
Chart 1

Furthermore, the arylidene derivatives **3a,b** show identity (IR, TLC, m.p and m.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 represented by Scheme II.

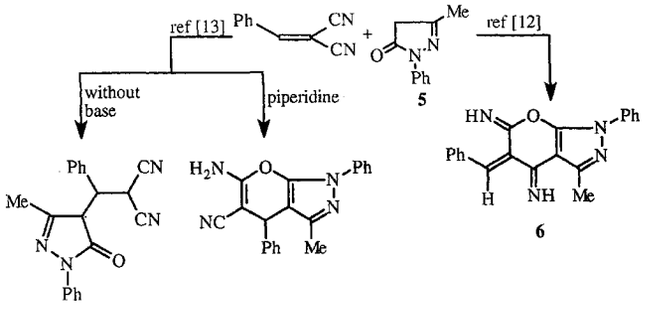
The diverse biological activities of fused pyrazoles have stimulated considerable research in this field.[6-11] It has been reported[12] that the pyrazolone derivative **5** reacted with α-cyanocinnamonitrile in the presence of piperidine to yield the 1:1 adduct **6**.

On the other hand, it has been also claimed[13] that the above mentioned reaction afforded two products instead of compound **6** [cf. Scheme III].

Scheme II



Scheme III



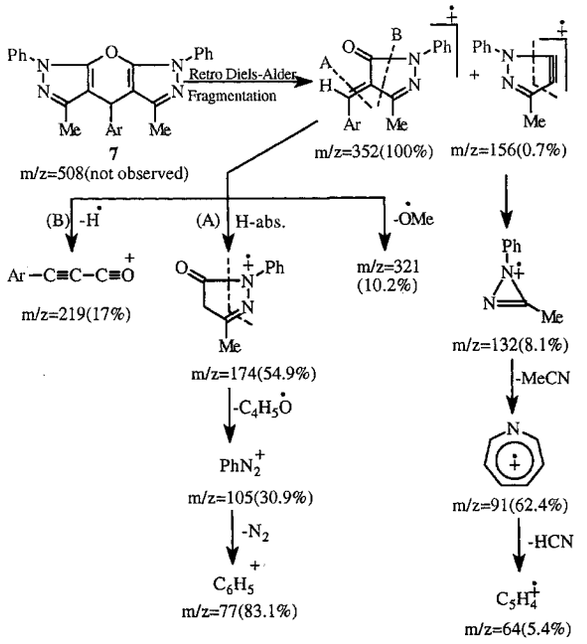


Chart 2

Because of the striking biological activity of fused pyrazoles, and to extend the present work, equimolar amounts of **1a** and **5** were refluxed in absolute ethanol in the presence of piperidine as a catalytic base. After 15 minutes an insoluble fraction was isolated as colourless crystals, 13%, and detected to be the oxino bispyrazole **7** and the reaction was completed for 3 h. Removal of most of the solvent and acidification with diluted acetic acid afforded the 1:1 adduct **8a** or **8b** as pale yellow crystals; 44% and 46% yield, respectively [cf., Scheme I]. The structure of **7** is 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** is represented in Chart 2 which is in accordance with the proposed structure. Furthermore, the bis-pyrazole derivative **7** shows identity (IR, m.p. and mixed m.p., TLC) 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 I].

Structure of the adduct **8a** is based upon:

(i) The elemental analysis which gave satisfactory results.

(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 ^1H 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; 3 OMe) 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. Successive loss 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 Chart 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 ^1H 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 Chart 4.

The formation of the oxino bis-pyrazole derivative **7**

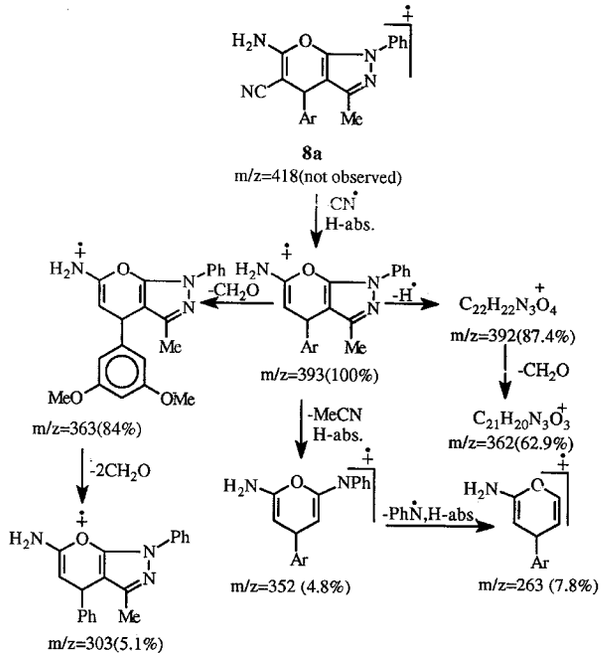


Chart 3

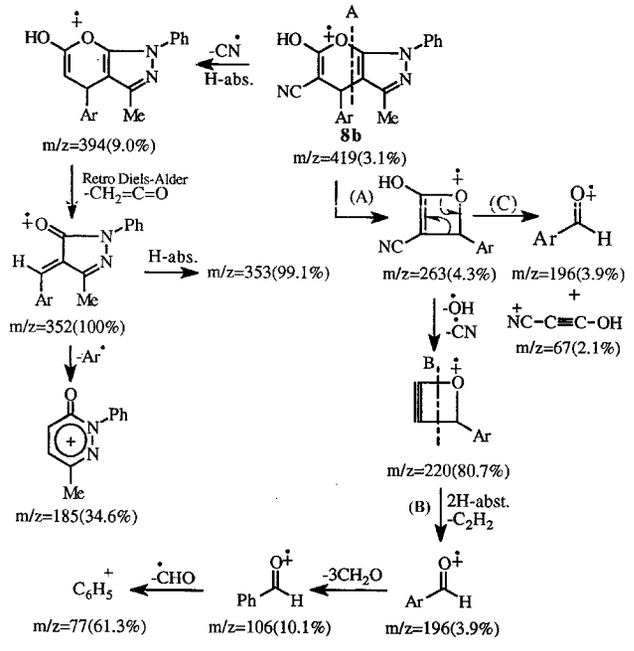
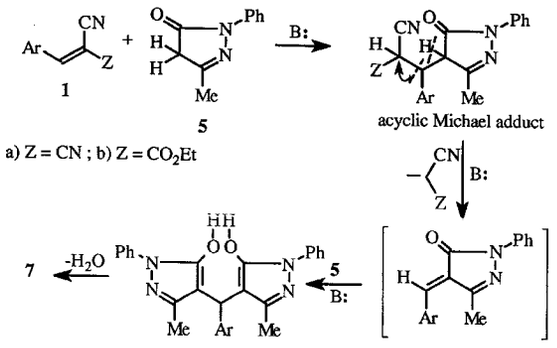


Chart 4

from the reaction of **1a** and/or **1b** with 3-methyl-1-phenyl-pyrazolone **5** probably proceeds via the initial Michael addition to afford acyclic Michael's 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 cyclodehydration step to yield the isolated bis-pyrazole derivative **7** [cf. Scheme IV].

Scheme IV



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.

EXPERIMENTAL

Melting points are not corrected. The IR spectra were recorded in a Pye-Unicam SP 1200 spectrophotometer using KBr wafer technique.

The ^{1}H NMR spectra were determined 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 controlled by TLC.

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

A mixture of **1a** (2.44 g, 0.01 mol) and/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 3 h. 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** and/or **3b** [cf. Table 1].

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

A mixture of chalcone **4** (3.28 g, 0.01 mol), and barbituric acid (1.28 g, 0.01 mol) and/or thiobarbituric acid (1.44 g,

Table 1. Physical Characteristics of the New Compounds

Compd.	Mol. F.	Mol. Wt.*	M.P °C	Yield %	Solvent of Recryst.**	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.

0.01 mol) in pyridine (30 mL) was refluxed for 3 h. 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) and/or **3b** (42.4% yield).

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

A mixture of barbituric acid (1.28 g, 0.01 mol) or thiobarbituric acid (1.44 g, 0.01 mol) and 3,4,5-trimethoxybenzaldehyde (1.96 g, 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) and/or **3b** (86.1% yield).

Reaction of 1a with 3-methyl-1-phenylpyrazol-5-one 5; Formation of 4H-3,5-dimethyl-1,7-diphenyl-4-(3,4,5-trimethoxyphenyl)oxino[2,3-c:6,5-′c] bis-pyrazole 7 and 4H-6-amino-5-cyano-3-methyl-1-phenyl-4-(3,4,5-trimethoxyphenyl)pyrano[2,3-c]pyrazole 8a and/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** (2.4 g, 0.01 mol) and/or **1b** (2.91 g, 0.01 mol) and 3-methyl-1-phenylpyrazol-5-one **5** (1.74 g, 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 **7**. The filtrate was refluxed up to 3 h. 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** and/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 (1.96 g, 0.01 mol) and 3-methyl-1-phenylpyrazol-5-one **5** (1.74 g, 0.01 mol) in absolute ethanol (30 mL) in the presence of a catalytic amount of piperidine was refluxed for 15 minutes. The insoluble product was filtered off, dried and recrystallized from the proper solvent to give **7**.

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Key Words

Barbituric and thiobarbituric acids; Pyrazolone; Activated nitriles.

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