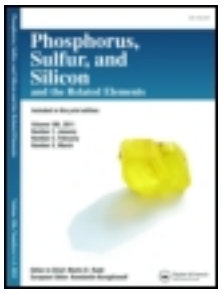

Phosphorus, Sulfur, and Silicon and the Related Elements

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NOVEL AND FACILE SYNTHESIS OF THIOPHENE, THIAZOLE, 2H-PYRAN-2-ONE BENZIMIDAZO[1,2-a]PYRIDINE AND PYRIDINE DERIVATIVES CONTAINING ANTIPYRINE MOIETY

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NOVEL AND FACILE SYNTHESIS OF THIOPHENE, THIAZOLE, 2H-PYRAN-2-ONE BENZIMIDAZO[1,2-a]PYRIDINE AND PYRIDINE DERIVATIVES CONTAINING ANTIPYRINE MOIETY

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Several new thiophene, thiazole, 2H-pyran-2-one, benzimidazo[1,2-a]-pyridine and pyridine derivatives were synthesised from active methylene reagents, 4-chloroacetylantipyrine and enaminones as starting materials.

Keywords: 2H-Pyran-2-one; benzimidazopyridine; pyridine; thiazole; thiophene

Thiophene and thiazole derivatives carrying antipyrinyl moiety possess diverse pharmacological properties.[1–8] These pharmacological activities have been attracted special attention to synthesize a new class of thiophene and thiazole derivatives carrying antipyrinyl moiety because of their applications in the field of pharmaceuticals[1–8] and biodegradable agrochemicals.[9,10] This article reports the synthesis of thiophene and thiazole derivatives using readily available starting materials.

RESULTS AND DISCUSSION

It has been found that, active methylene nitriles **1a–d** were treated with phenyl isothiocyanate in dimethylformamide (DMF) under basic conditions in KOH/DMF to give the non-isolable intermediates **4**. These were reacted with 4-chloroacetyl-1-phenyl-2,3-dimethyl-3-pyrazolin-5-one **(2)** to give the enamine derivatives **5a–d**. Structures **5** were supported by their elemental analysis and spectral data.

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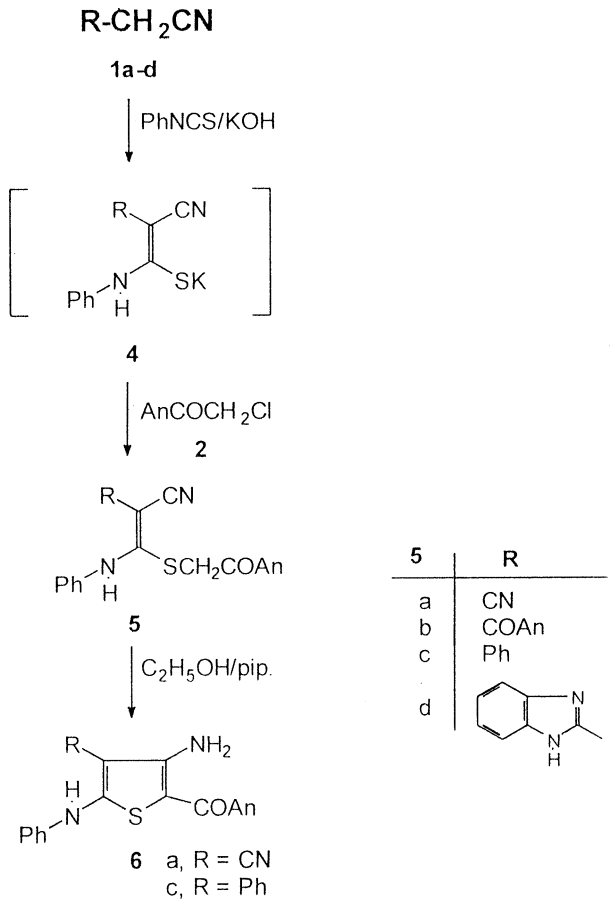
Compounds **5a**,**c** were converted into 3-aminothiophene derivatives **6a**,**c**. ^{1}H-NMR spectra of **6** clearly indicate the absence of signals at $\delta \simeq 4.0$ ppm attributable to methylene groups which in good agreement with the thiophene structures **6** (Scheme 1).

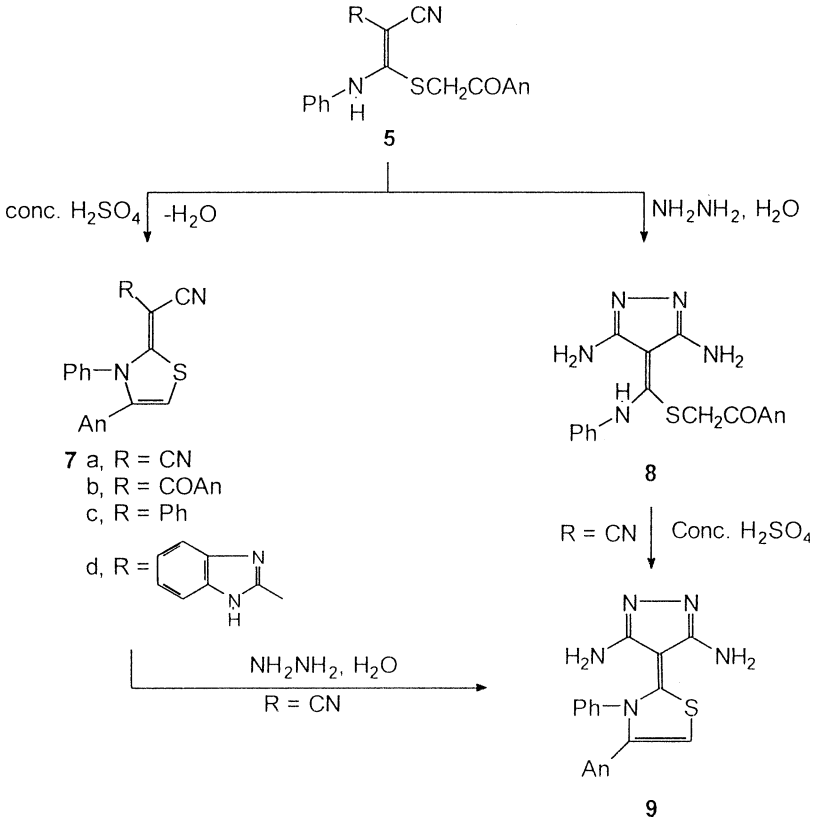


SCHEME 1

On the other hand, the enaminonitriles **5a–d** can be converted into thiazole derivatives **7a–d** by stirring with concentrated sulphuric acid. The elemental analysis and spectral data of the reaction products were compatible only with the thiazole structures **7**.

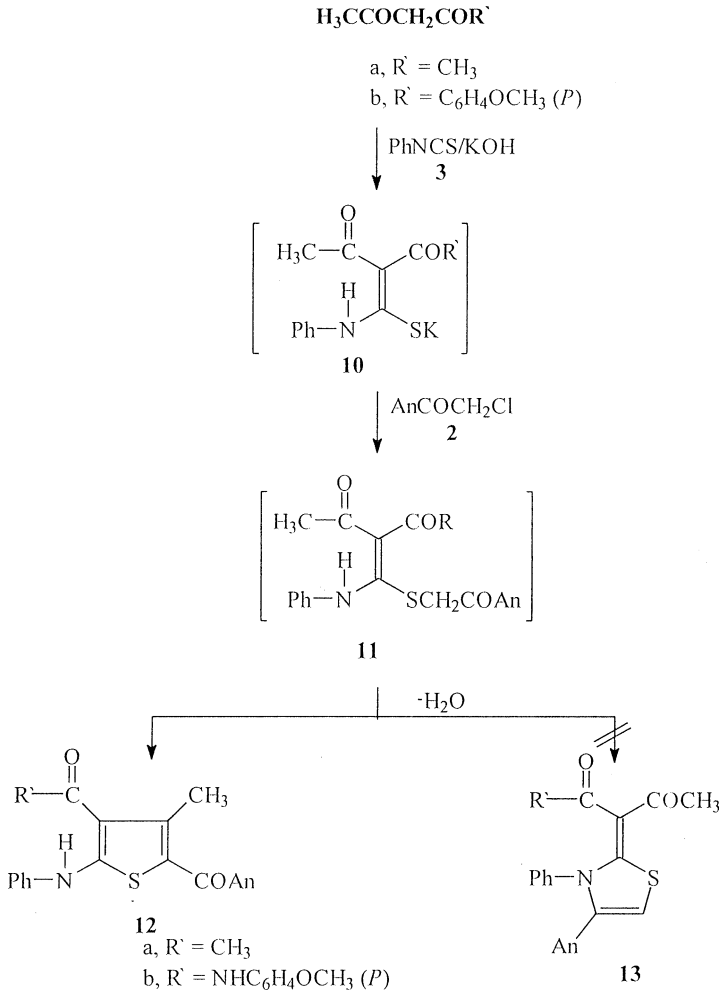
Treatment of thiazole **7a** with hydrazine hydrate afforded the pyrazole derivative **9**. IR spectra of **9** clearly indicate the absence of cyano group and the presence of amino group. The same products **9** was

synthesized by an independent method *via* reacting the enaminonitrile **5a** with hydrazine hydrate to give the pyrazole derivative **8** followed by cyclization of the later by the effect of concentrated sulphuric acid (Scheme 2).



SCHEME 2

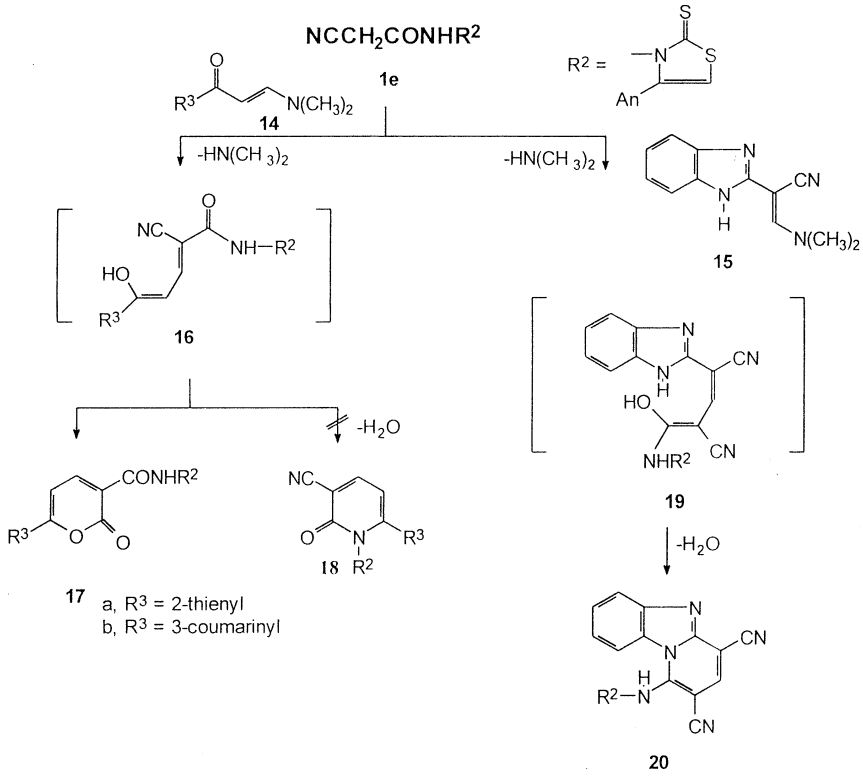
Also, it has been found that, mixture of both acetylacetone **(2a)** or acetoacetanilide **(3b)** and phenyl isothiocyanate in dimethylformamide containing equivalent amount of potassium hydroxide give the intermediates **10**. These were alkylated with 4-chloroacetylantipyrine **(2)** to yield products with water elimination. Structures **12** and **13** were considered for the reaction products. The thiazole structures **13** were ruled out based on ^{1}H-NMR spectra which clearly showed the absence of signals at $\delta \simeq 6.5$ ppm due to thiazole H-5. Thus, the thiophene structures **12** were assigned as reaction products. Compounds **12a**,**b** were thought to be formed *via* sequence demonstrated in (Scheme 3).



SCHEME 3

In addition, the chemical reactivity of active methylene nitrile **1e**[4] towards a variety of chemical reagents have been investigated. Thus, compound **1e** was allowed to react with the enaminones **14** in ethanol and in the presence of acetic acid as catalyst to afford α-pyrones **17** or the pyridines **18**. Structures **17** were supported by IR spectra which revealed the absence of cyano groups. Compounds **17** were assumed to be formed *via* first addition of the active methylene in **1e** to the activated double bond in **14** and eliminate one molecule of dimethylamine to give the intermediates **16** which readily cyclized to afford the α-pyrones **17**.

In a similar manner, **1e** was subjected to react with the enaminonitrile **15** to yield benzimidazo[1,2-a]pyridine **20**. Compound **20** was identified as a reaction product by its elemental and spectral analysis (Scheme 4).



SCHEME 4

Compound **1e** condensed with aromatic aldehydes to afford the arylidenes **21**. Structures **21** were established as reaction products from ^{1}H-NMR spectrum of **21a** which displays the absence of a signal attributable to the exocyclic methylene group and the presence of ylidenic proton at $\delta = 8.3$ ppm (see Tables I and II).

Refluxing thiazole **1e** with arylidenemalononitriles **22** in ethanol containing catalytic amount of piperidine resulted in the formation of the pyridines **24** or the 4H-pyrans **25**. Structures **24** were proposed as reaction products based on their elemental and spectral data. If the reaction product is **25**, ^{1}H-NMR spectrum would show signals at $\delta \simeq 4.5$–5.0 ppm for pyran H-4. Moreover, compounds **24** were also synthesized

TABLE I Analytical Data and Physical Characteristics of Novel Compounds

Compd no.	Molecular formula (M.wt)	m.p. (°C)	Yield	Elemental analysis (found) C	H	N
5a	$C_{23}H_{19}N_5SO_2$ (429.5)	208–210	80	64.12 (64.14)	4.46 (5.20)	16.31 (16.36)
5b	$C_{34}H_{30}N_6SO_4$ (618.73)	198–200	78	66.03 (66.34)	4.89 (5.03)	13.58 (13.41)
5c	$C_{28}H_{24}N_4SO_2$ (480.59)	182–184	70	69.98 (69.79)	5.03 (5.35)	11.66 (11.47)
5d	$C_{29}H_{24}N_6SO_2$ (520.62)	190–192	65	66.90 (66.84)	4.65 (4.73)	16.14 (16.27)
6a	$C_{23}H_{19}N_5SO_2$ (429.50)	>300	70	64.12 (64.45)	4.46 (4.51)	16.31 (16.24)
6c	$C_{28}H_{24}N_4SO_4$ (480.59)	240–242	60	69.98 (70.03)	5.03 (5.14)	11.66 (11.56)
7a	$C_{23}H_{17}N_5SO$ (411.49)	520–252	70	67.13 (67.26)	4.16 (4.38)	17.02 (17.11)
7b	$C_{34}H_{28}N_6SO_3$ (600.70)	230–232	70	67.98 (67.89)	4.70 (4.83)	13.99 (14.05)
7c	$C_{28}H_{22}N_4SO$ (462.58)	220–222	65	72.70 (72.64)	4.79 (5.03)	12.11 (12.16)
7d	$C_{29}H_{22}N_6SO$ (502.6)	232–234	63	69.30 (69.61)	4.41 (4.81)	16.72 (16.14)
8	$C_{23}H_{23}N_7SO_2$ (461.55)	250–252	60	59.85 (60.03)	5.02 (5.13)	21.24 (21.34)
9	$C_{23}H_{21}N_7SO$ (443.53)	>300	60	62.29 (62.11)	4.77 (4.81)	22.11 (22.24)
12a	$C_{25}H_{23}N_3SO_3$ (445.54)	225–227	70	67.40 (67.60)	5.20 (5.40)	9.43 (9.50)
12b	$C_{31}H_{28}N_4SO_4$ (552.65)	154–156	62	67.37 (67.53)	5.11 (5.31)	10.14 (10.22)
17a	$C_{24}H_{18}N_4S_3O_4$ (522.62)	170–172	63	55.16 (55.44)	3.34 (3.57)	10.72 (10.36)
17b	$C_{29}H_{20}N_4S_2O_6$ (584.63)	185–187	60	59.58 (59.64)	3.45 (3.37)	9.58 (9.45)
20	$C_{27}H_{18}N_8S_2O$ (534.62)	190–192	62	60.66 (60.51)	3.39 (3.52)	20.99 (20.83)
21a	$C_{24}H_{18}BrS_2N_5O_2$ (552.48)	210–212	70	52.18 (52.37)	3.28 (3.24)	12.68 (12.53)
21b	$C_{24}H_{18}CIS_2N_5O_2$ (508.02)	232–234	63	56.74 (56.67)	3.57 (3.38)	13.79 (13.63)
21c	$C_{22}H_{17}N_5S_3O_2$ (479.60)	210–212	62	55.10 (55.33)	3.57 (3.67)	14.60 (14.57)
24a	$C_{27}H_{18}BrN_7S_2O_2$ (616.53)	250–252	65	52.60 (52.54)	2.94 (3.11)	15.90 (15.87)
24b	$C_{25}H_{17}N_7S_3O_2$ (543.65)	180–182	60	55.23 (55.47)	3.15 (3.22)	18.04 (18.21)

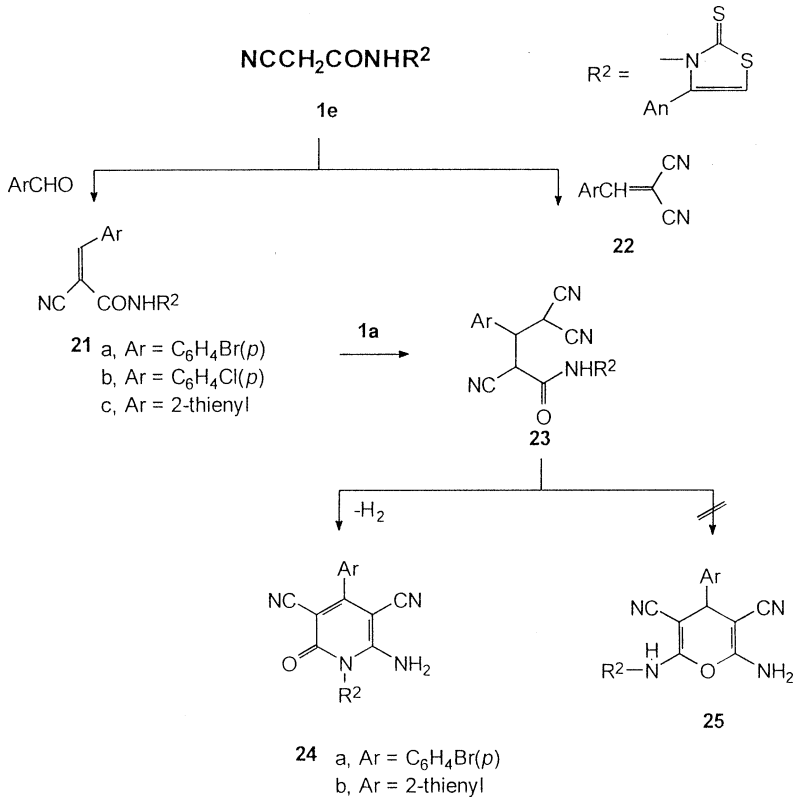
TABLE II Spectral Data of Newly Synthesized Compounds

Compd no.	IR (cm^{-1})	^{1}H-NMR (δ_H)
5a	3100 (NH), 2205 (CN), 1680, 1670 (CO)	2.59 (s, 3H, CH_3), 3.37 (s, 3H, N—CH_3), 4.6 (s, 2H, CH_2), 7.0–7.6 (m, 10H, aromatic H), 8.3 (s, 1H, NH).
5b	3570 (NH), 2210 (CN), 1680, 1670 (CO)	2.33, 2.5 (2S, 6H, $2CH_3$), 3.07.3.31 (2S, 6H, 2N—CH_3), 4.21 (s, 2H, CH_2),7.18–7.51 (m, 15H, aromatic H), 10.3 (s, 1H, NH).
5c	3540 (NH), 2207 (CN), 1680, 1665 (CO)	2.61 (s, 3H, CH_3), 3.36 (s, 3H, N—CH_3), 4.3 (s, 2H, CH_2), 6.8–7.7 (m, 15H, aromatic H), 9.2 (s, 1H, NH).
5d	3560 (NH), 2205 (CN), 1680, 1660 (CO)	2.53 (s, 3H, CH_3), 3.4 (s, 3H, N—CH_3), 4.4 (s, 2H, CH_2). 6.9–7.8 (m, 14H, aromatic H), 8.4, 9.8 (2S, 2H, 2NH).
6a	3410, 3300 (NH_2,NH), 2215 (CN), 1680, 1670 (CO).	2.38 (s, 3H, CH_3), 3.33 (s, 3H, N—CH_3), 7.15–7.61 (m, 15H, aromatic H), 7.8, 10.2 (2S, NH, NH_2).
6c	3390, 3290, 3230 (NH_2,NH), 2208 (CN), 1680, 1660 (CO).	2.36 (s, 3H, CH_3), 3.36 (s, 3H, N—CH_3), 6.97.6 (m, 15H, aromatic H), 9.2, 10.1 (2S, NH, NH_2).
7a	2190 (CN), 1665 (CO).	2.7 (s, 3H, CH_3), 3.0 (s, 3H, N—CH_3), 7.0–7.6 (m, 11H, aromatic H).
7b	2215 (CN), 1685, 1665 (CO)	2.3, 2.45 (2S, 6H, $2CH_3$), 3.2, 3.33 (2S, 6H, 2N—CH_3), 7.2–7.7 (m, 15H, aromatic H).
7c	2210 (CN), 1660 (CO)	2.4 (s, 3H, CH_3), 3.35 (s, 3H, N—CH_3), 6.7–7.7 (m, 11H, aromatic H).
8	3400, 3350 (NH_2, NH), 1785, 1660 (CO)	2.51 (s, 3H, CH_3), 3.2 (s, 3H, N—CH_3), 4.37 (s, 2H, CH_2), 6.9–7.6 (m, 10H, aromatic H), 7.8 (s, 2H, NH_2), 8.6 (s, 2H, NH_2). 9.3 (s, 1H, NH).
9	3480, 3370 (NH_2, NH), 1665 (CO)	2.43 (s, 3H, CH_3), 3.34 (s, 3H, N—CH_3), 6.65–7.67 (m, 11H, aromatic H). 8.7, 9.6 (2S, 4H, $2NH_2$).
12a	3460 (NH), 1685, 1675, 1660 (CO)	2.47, 2.5, 2.6 (3S, 9H, $3CH_3$), 3.33 (s, 3H, N—CH_3), 7.15–7.6 (m, 10H aromatic H), 11.7 (s, 1H, NH).
12b	3510,3460 (NH),1680,1675 1665 (CO).	2.4, 2.48 (2S, 6H, $2CH_3$), 3.7 (s, 3H, OCH_3), 6.95–7.7 (m, 14H, aromatic H), 9.3, 10.2 (2S, 2H, 2NH).
17a	3450 (NH), 1743 (CO), 1702 (CO), 1650 (CO).	2.35 (s, 3H, CH_3), 3.33 (s, 3H, N—CH_3), 6.64 (s, 1H, thiazole H-5), 6.92 (d, J = 8Hz, 1H, pyrone, H-5), 7.2–8.0 (m, 8H, aromatic H), 8.2 (d, J = 8Hz, 1H, pyrone H-4), 9.6 (s,1H, NH).
20	3460 (NH), 2227, 2218 (2CN), 1654 (CO)	2.35 (s,3H,CH_3), 3.35 (s, 3H, N—CH_3), 7.41–8.01 (m, 11H, aromatic H), 10.1 (s, 1H, NH).
24a	3447 (NH), 2200 (CN), 1710 (CO), 1660 (CO)	2.4 (s, 3H, CH_3), 3.2 (s, 3H, N—CH_3), 6.7 (s.1H, thiazole H-5), 7.3–7.52 (m, 9H, aromatic H), 8.3 (s, 1H, CH), 9.7 (s, 1H, NH).

TABLE II Spectral Data of Newly Synthesized Compounds *(Continued)*

Compd no.	IR (cm^{-1})	^{1}H-NMR (δ_H)
214a	3448, 3387 (NH_2), 2216 (CN), 1730 (CO, 1670 (CO)	2.34 (s, 3H, CH_3), 3.3 (s, 3H, N—CH_3), 7.1–7.74 (m, 10H, aromatic H); 8.3 (s, 2H, NH2).
24c	3460, 3390 (NH2), 2220 (CN), 1715 (CO), 1636 (CO)	2.28 (s, 3H, CH3), 3.4 (s, 3H,N—CH3), 7.35–7.98 (m, 9H, aromatic H), 8.74 (s,2H, NH2).

via reacting the arylidenes **21** with malononitrile in ethanolic-pyridine. Formation of **24** were suggested to take place via Michael type addition of the active methylene group in **1e** to the π-deficient centre in **22** to give the Michael adduct **23**, which cyclized and readily eliminate one molecule of hydrogen to yield the pyridines **24** (Scheme 5).



SCHEME 5

EXPERIMENTAL

All melting points are uncorrected and measured on Griffin & George MBF 010T (London) apparatus. Recorded yields correspond to the pure products. IR(KBr) spectra were recorded on a Perkin Elmer SP-880 spectrophotometer and ^{1}H-NMR spectra were measured on a Varian 270 MHz spectrometer in DMSO-d_6 as solvent and TMS as an internal standard (chemical shifts are reported in δ units ppm. Microanalysis were performed on LECOCHN-932.

Preparation of the Enaminonitriles 5a–d

A solution of **1a–d** (0.01 mmol) in dimethylformamide (30 ml), phenyl isothiocyanate (0.01 mmol) and potassium hydroxide (0.01 mmol) in water (10 ml) were added. The reaction mixture was stirred for 6 h at room temperature then (0.01 mmol) of **2** was added. The reaction was then stirred over night, poured on cold water and neutralized with dil. HCl. The solid products were collected by filtration and crystallized from ethanol to give **5a–d**.

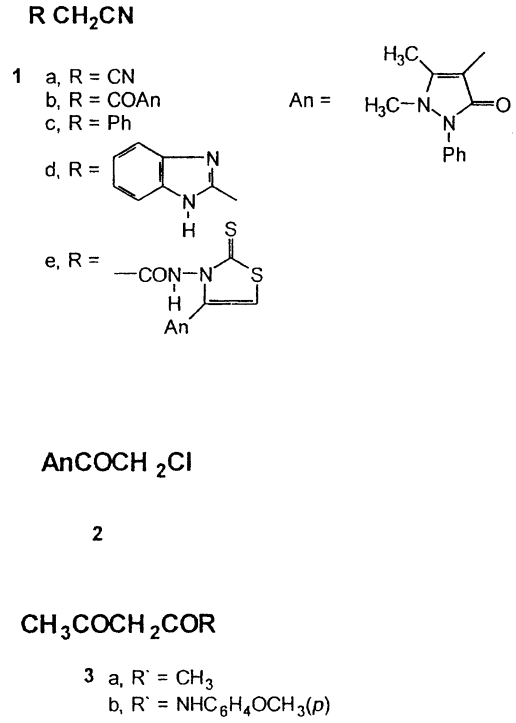


FIGURE 1

Preparation of Thiophene Derivative 6a,c

A solution of (0.01 mmol) of **5a**,**b** in ethanol (50 ml) containing few drops of piperidine was refluxed for 4 h then left to cool. The solid deposited were collected by filtration and crystallized from ethanol to give **6a**,**c**.

Preparation of 3-Phenyl-1,3-thiazolines 7

A solution of **5** (0.01 mmol) in conc. sulphuric acid (10 ml) was stirred for 3 h at room temperature then poured into ice. The precipitates were collected by filtration and crystallized from ethanol-dioxane to give 7.

Reaction of 5 and 7 with Hydrazine Hydrate: General Procedure for Preparation of 8 and 9

A solution of **5** to **7** (0.01 mmol) in ethanol (50 ml) were treated with hydrazine hydrate were refluxed for 1 h and then left to cool. The solid products were collected by filtration and crystallized from ethanol-DMF to give compounds **8** and **9** respectively.

Compound **9** were prepared by stirring 0.01 mmol of **8** with conc. H_2SO_4.

Formation of Thiophenes 12a,b

A solution of (0.01 mmol) of **3a,b** in dimethylformamide (30 ml) containing potassium hydroxide (0.01 mmol) and (0.01 mmol) of phenyl isothiocyanate was stirred overnight. To this solution (0.01 mmol) of **2** was added, then stirred again overnight, poured on ice. The precipitates formed were collected by filtration and crystallized from ethanol to give **12a**,**b**.

Reaction of 1e with the Enamines 14 and 15: Formation of 17 and 20

A solution of **1e** (0.01 mmol) and (0.01 mmol) of **14** or **15** in ethanol (50 ml) containing acetic acid (1 ml) was refluxed for 6 h. The solvent was removed by distillation under reduced pressure and the resulting solutions were left to cool. The solid precipitates were collected by filtration and recrystallized from ethanol to give **17** and **20** respectively.

Condensation of 1e with Aromatic Aldehydes: Formation of 21

A solution of **1e** (0.01 mmol) and the appropriate amounts of aromatic aldehydes (0.01 mmol) in ethanol (50 ml) with (0.1 ml) of piperidene was refluxed for 3 h then left to cool. The resulting solids obtained on standing were collected by filtration and crystallized from ethanol to give **21a–c**.

Formation of Pyridines 24a,c

Method A

A solution of **1e** (0.01 mmol) in ethanol (50 ml) was treated with **4** (0.01 mmol) and few drops of piperidine were heated under reflux for 3 h. The resulting solid products were collected by filtration, recrystallized from ethanol/DMF and then identified as **24a**,**c**.

Method B

A suspension of **21a**,**c** (0.01 mmol) in ethanol (50 ml) was treated with malononitrile (0.01 mmol) and dry pyridine (1 ml). The mixture was refluxed for 5 h and the solvent was concentrated in vacuo and crystallized (m.p. and mixed m.p.s as **24a**,**c**).

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