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Novel Synthesis of Pyrano[2,3-d]Thiazole, Thiazolo[3,2-a]Pyridine, and Pyrazolo [3',4':4,5] Thiazolo[3,2-a]Pyridine Derivatives

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Novel Synthesis of Pyrano[2,3-d]Thiazole, Thiazolo[3,2-a]Pyridine, and Pyrazolo [3',4':4,5] Thiazolo[3,2-a]Pyridine Derivatives

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Cyclocondensation of 2-cyanomethyl-4-thiazolidinone (1) with tetracyanoethylene (2) furnished pyrano[2,3-d]thiazole derivative (4). Benzo[e]pyrano[2,3-d]thiazole derivative (6) was obtained by cyclization of compound (1) with salicylaldehyde. In a similar manner, condensation of compound (1) with 2-hydroxy-1-naphthaldehyde in refluxing ethanol yielded naphthol[e]pyrano[2,3-d]thiazole derivative (7). Interaction of compound (9) with benzylidenemalononitriles (10) (1 : 1 molar ratio) at reflux temperature in ethanol in the presence of piperidine afforded thiazolo[3,2-a]pyridines (12a–c). Treatment of compound (12a) with hydrazines furnished pyrazolo[3',4':4,5] thiazolo[3,2-a]pyridines (14a,b). The reaction of compound (1) with benzyli-denecyanoacetate (16) yielded 5-hydroxythiazolo[3,2-a]pyridine derivative (21). Cyclization of bis(thiazolinone) (23) with benzylidenemalononitriles (10) produced bis(thiazolopyridine) derivatives (25a,b).

Keywords Pyrano[2,3-d]thiazole; thiazolinone; thiazolo[3,2-a]pyridine

INTRODUCTION

Pyrano[2,3-d]thiazoles are reported to possess antimicrobial, bactericidal and fungicidal¹ properties. Thiazolo[3,2-a]-pyridine derivatives have also been reported to show antimicrobial,² antifungal,³ anticancer,⁴ and antihypertensive⁵ activities. In continuation of our work,^{6–8} we report here the synthesis of versatile hitherto unknown pyrano[2,3-d]thiazole, thiazolo[3,2-a]pyridine and pyrazolo[3',4':4,5]thiazolo[3,2-a]pyridine derivatives.

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RESULTS AND DISCUSSION

Treatment of 2-cyanomethyl-4-thiazolinone (**1**) with tetracyanoethylene (**2**) in ethanol in the presence of triethyl-amine at reflux temperature afforded the novel pyrano[2,3-d]-thiazole derivative (**4**) and not thiazolo[3,2-a]pyridine (**5**). The molecular structure of (**4**) was established on the basis of elemental analysis and spectral data. Its infrared spectrum showed no absorption band assignable to C=O group and indicated the presence of NH₂ group. On the basis of ¹HNMR spectrum the latter product was recommended to exist predominantly in the form (**4A**) rather than methylene form (**4**). Its ¹HNMR indicated the presence of methylene-H at $\delta = 6.83$ ppm besides the expected signals for NH₂ and NH protons. In addition, the mass spectrum of compound (**4**) revealed a molecular ion peak at $m/z = 268$ (10.0%) and the base peak

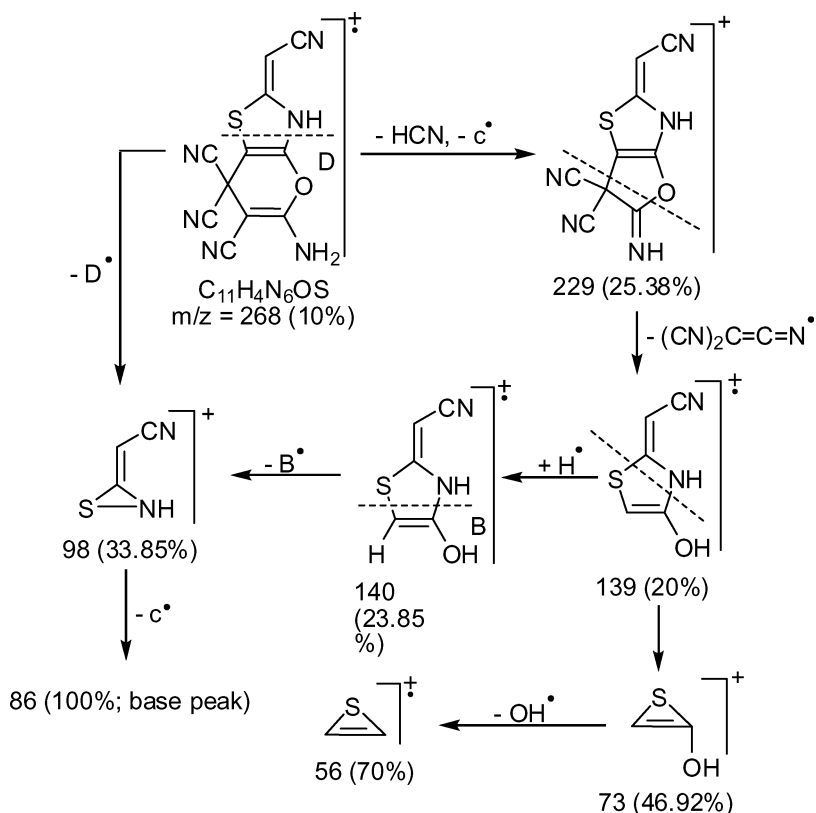
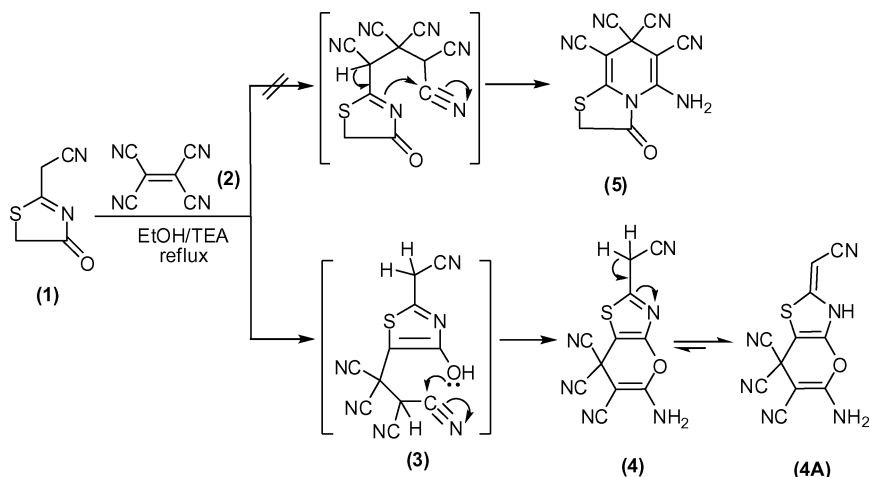


CHART 1 Fragmentation pattern of compound **4**.



SCHEME 1

was found in the spectrum at $m/z = 86$, Chart 1. The formation of (4) is assumed to proceed through an initial Michael addition of the active methylene function group of (1) at C₅ to the activated double bond in (2) to form the non-isolable acyclic intermediate (3) followed by intramolecular cyclization via the addition of hydroxy group to one of the two cyano groups and tautomerization to form (4), Scheme 1.

Cyclization of compound (1) with salicylaldehyde in ethanol under reflux in the presence of piperidine yielded the benzo[e]pyrano[2,3-d]thiazole derivative (6). Assignment of benzopyranothiazole (6) was based on the basis of elemental and spectral data. Its infrared spectrum exhibited the absence of any C=O stretching absorption while it showed the presence of OH group stretching at 3168 cm^{-1} . Also, its mass spectrum showed a molecular ion peak at $m/z = 244$ (1.98%) together with base peak at $m/z = 63$, Chart 2. The formation of (6) is assumed to proceed through the in situ intramolecular cyclization of the non-isolable intermediate (5) via nucleophilic addition of the hydroxy group to the carbonyl group, Scheme 2. In a similar manner, compound (1) underwent cyclocondensation on treatment with 2-hydroxy-1-naphthaldehyde in refluxing ethanol in the presence of piperidine to yield the naphtho[e]pyrano[2,3-d]-thiazole derivative (7). Its mass spectrum revealed a molecular ion peak at $m/z = 294$ (2.57%) and the base peak was observed in the spectrum at $m/z = 66$, Chart 3.

The benzylidene derivative (9) was obtained in a good yield by refluxing of compound (1) with 4-nitro-4'-carbox-aldehyde diphenylether (8) in ethanol in the presence of piperidine. The molecular structure of

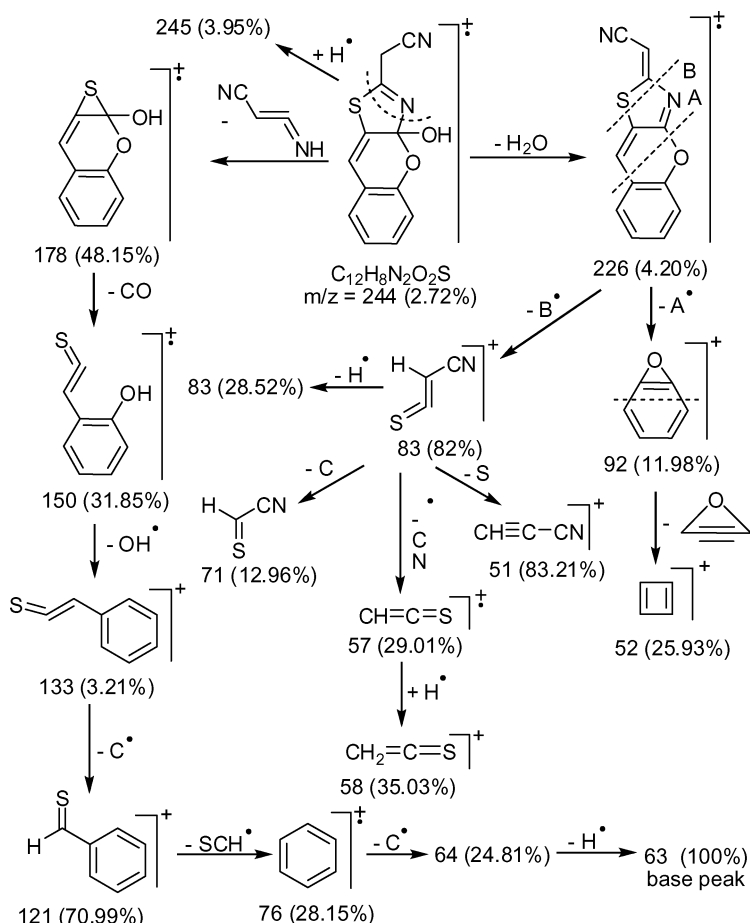
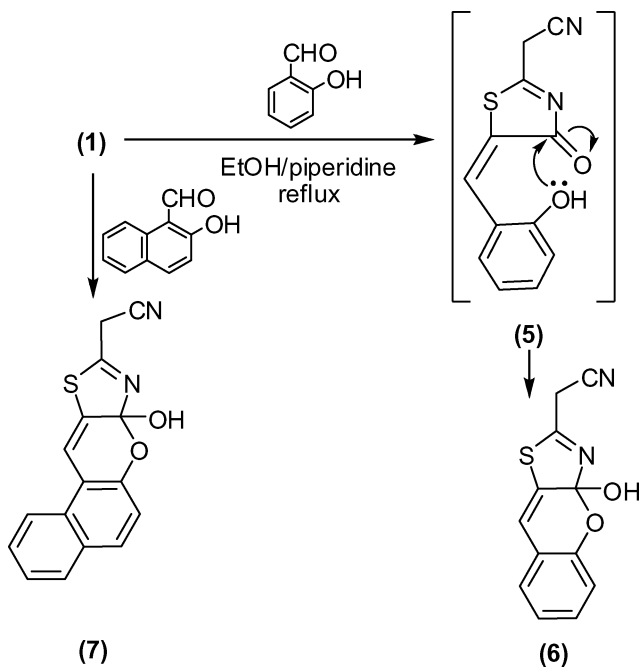


CHART 2 Fragmentation pattern of compound 6.

compound (**9**) was confirmed by its analytical and spectral data. Its mass spectrum showed a molecular ion peak at $m/z = 365$ (25.73%) and the base peak was found in the spectrum at $m/z = 66$. Cyclocondensation of compound (**9**) with benzylidenemalononitriles (**10**) (1 : 1 molar ratio) in ethanol in the presence of piperidine at reflux temperature afforded the novel thiazolo[3,2-*a*]pyridine derivatives (**12a–c**). The molecular structure of thiazolopyridines (**12**) was elucidated through their elemental analysis and spectral data. Mass spectrum of compound (**12a**) exhibited a molecular ion peak at $m/z = 656$ (1.38%) and the base peak was observed in the spectrum at $m/z = 76$ (phenyl group).



SCHEME 2

Also, mass spectrum of compound (12b) showed a molecular ion peak at $m/z = 553$ (4.95%) together with base peak at $m/z = 57$. The formation of (12) is assumed to proceed via Michael addition of the active methylene group in (1) at C₂ to the activated double bond of (10) to form the acyclic intermediate (11) followed by intramolecular cyclization⁶ through the addition of the endocyclic nitrogen of thiazole to the cyano function group and tautomerization to yield (12), Scheme (3). The behavior of compound (12a), which contains α,β -unsaturated ketone, towards hydrazines was examined. Treatment of compound (12a) with hydrazine hydrate in refluxing ethanol furnished the pyrazolo[3',4':4,5]thiazolo[3,2-a]pyridine derivative (14a). The molecular structure of compound (14a) was assigned on the basis of its elemental analysis and spectral data. Its infrared spectrum indicated the absence of carbonyl group stretching absorption that might be expected to appear at the range of ν 1700–1730 cm^{-1} . In addition, its ¹HNMR of compound (14a; DMSO-*d*₆) revealed the presence of a pyridine H-7 proton at $\delta = 4.81$ ppm besides the expected signals for the NH₂, NH and aromatic protons. Also, mass spectrum of compound (14a) showed a molecular ion peak at $m/z = 668$ (2.07%) together

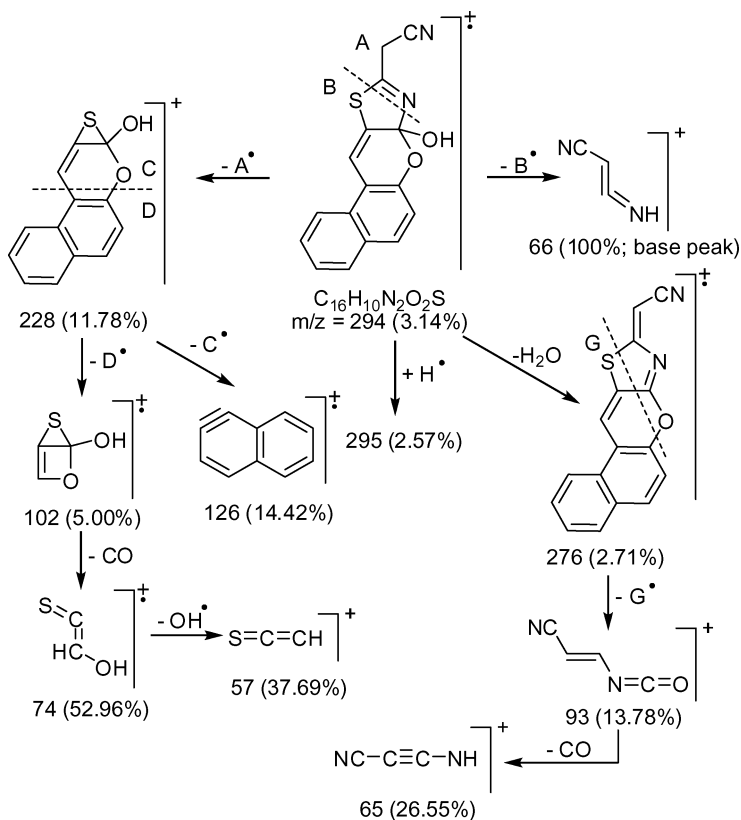
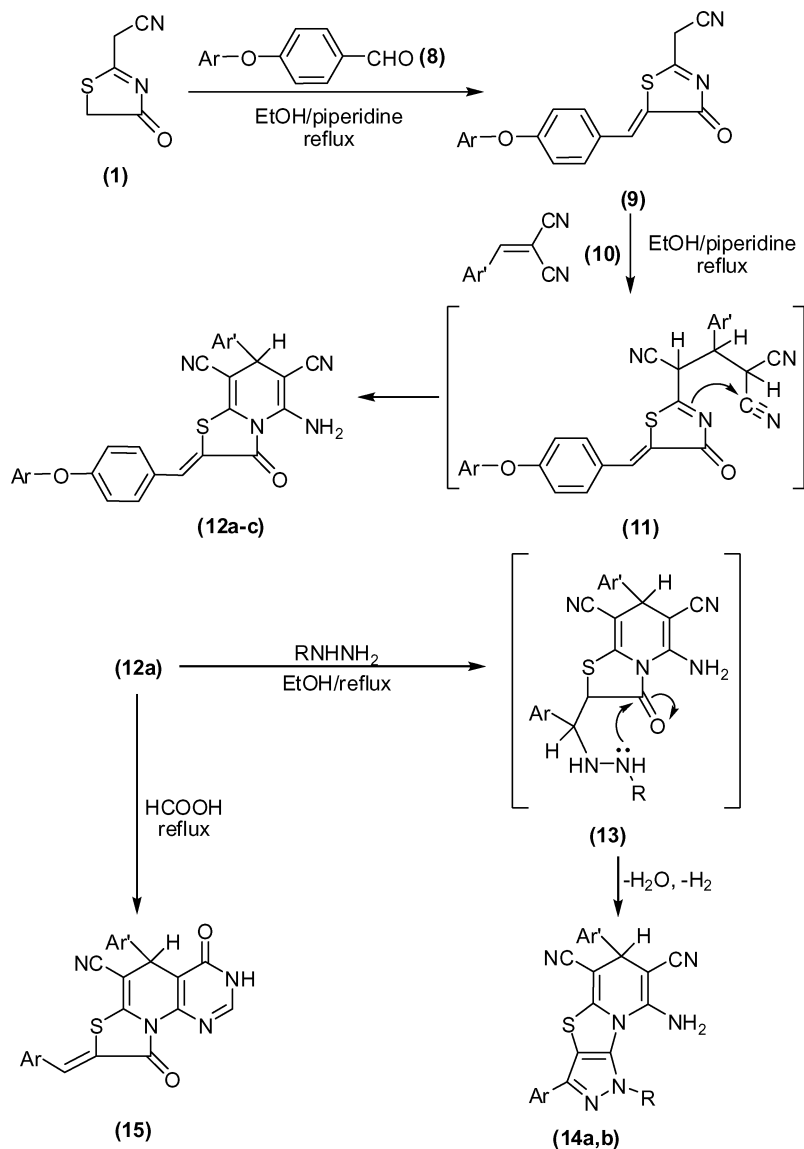


CHART 3 Fragmentation pattern of compound **7**.

with base peak at $m/z = 257$. The formation of (**14a**) is assumed to proceed via Michael addition of hydrazine to the activated double bond of (**12a**) to form the non-isolable acyclic intermediate (**13**) followed by intramolecular cyclization through dehydration and auto-oxidation under the experimental conditions. In a similar manner, compound (**12a**) was allowed to react with benzoyl hydrazine in ethanol at reflux temperature to give the pyrazolo[3',4':4,5]thiazolo[3,2-a]pyridine derivative (**14b**). Refluxing of compound (**12a**) with formic acid⁸ afforded the corresponding thiazolo[2',3':1,6]pyrido[2,3-d]pyrimidine derivative (**15**), Scheme 3.

The reaction of compound (**1**) with equimolar amount of benzyldienecyanoacetate (**16**) in refluxing ethanol in the presence of piperidine afforded the 5-hydroxy-thiazolo[3,2-a]-pyridine derivative (**21**). Both elemental and spectral data supported the proposed structure (**21**) and



9; Ar = C₆H₄NO₂-4

12a; Ar = C₆H₄NO₂-4,

12b; Ar = C₆H₄NO₂-4,

12c; Ar = C₆H₄NO₂-4,

14a; Ar = Ar' = C₆H₄NO₂-4,

14b; Ar = Ar' = C₆H₄NO₂-4,

15; Ar = C₆H₄NO₂-4,

Ar' = C₆H₄OC₆H₄NO₂-4

Ar' = C₆H₄Cl-2

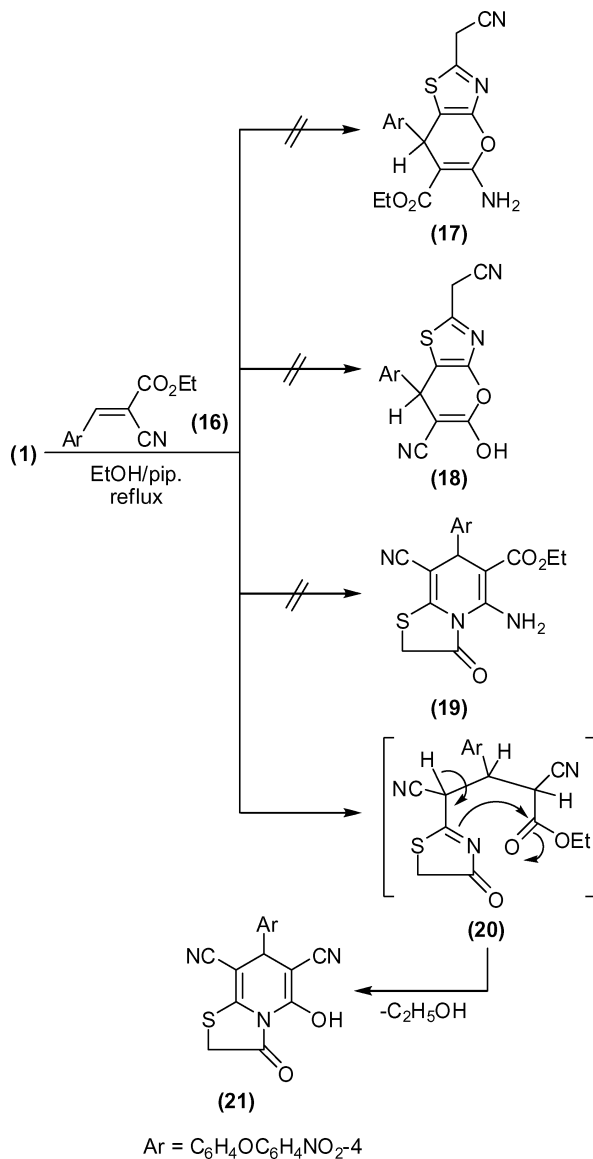
Ar' = C₁₀H₇-1

R = H

R = COC₆H₅

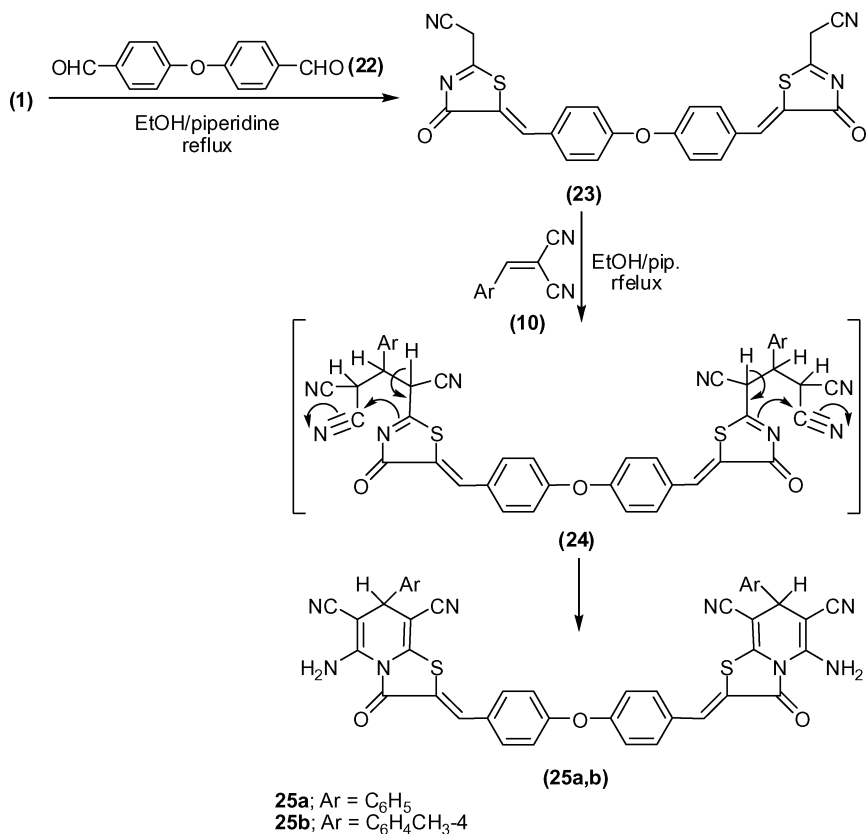
Ar' = C₆H₄OC₆H₄NO₂-4

SCHEME 3



SCHEME 4

ruled out the other possible structures (17), (18), and (19). The infrared spectrum of compound (21) revealed absorption bands at 3400, 2208, and 1700 cm^{-1} due to hydroxyl, cyano and carbonyl function groups, respectively. Also, its ^1H NMR spectrum ($\text{DMSO}-d_6$) indicated the absence



SCHEME 5

of ethoxycarbonyl moiety and showed the presence of methylene, hydroxyl, and aromatic protons. In addition, its mass spectrum exhibited a molecular ion peak at $m/z = 432$ (2.22%), and the base peak was found in the spectrum at $m/z = 76$ which is characteristic for C₆H₄ moiety. The formation of (21) is assumed to proceed via the Michael addition of active methylene group in (1) at C₂ to the activated double bond of (16) to form Michael adduct (20) followed by intramolecular cyclization through elimination of ethanol, Scheme 4.

Condensation of compound (1) with 4,4'-bis(carboxaldehyde) diphenylether (22) in ethanol in the presence of piperidine furnished bisbenzylidene derivative (23). Its mass spectrum revealed a molecular ion peak at $m/z = 470$ (23%). Cyclocondensation of compound (23) with benzylidenemalononitriles (10) (1 : 2 molar ratio) at reflux temperature in the presence of piperidine yielded the bis(thiazolopyridine)

derivatives (**25a,b**) on the basis of their elemental and spectral data. Mass spectrum of compound (**25a**) showed a molecular ion peak at $m/z = 778$ (1.78%), which is characteristic for the molecular formula $C_{44}H_{26}N_8O_3S_2$. The formation of (**25**) is assumed to proceed via the in situ intramolecular cyclization⁶ of the non-isolable Michael adduct (**24**), Scheme 5.

CONCLUSION

2-Cyanomethyl-4-thiazolinone (**1**) was used as starting material for the synthesis of some novel pyrano [2,3-d] thiazole, thiazolo [3,2-a] pyridine and pyrazolo [3',4':4,5] thiazolo [3,2-a] pyridine derivatives through its reaction with some electrophilic reagents.

EXPERIMENTAL

Melting points are recorded on a Fisher-John melting points apparatus and are uncorrected. IR spectra were recorded on a Shimadzu 470 spectrometer using KBr pellets. ¹HNMR spectrum were recorded on a Varian Gemini spectrometer 200 (200 MHz) using TMS as internal standard and mass spectra on a Jeol-JMS-600 mass spectrometer. Elemental analyses were performed on a Perkin-Elmer 240 C micro-analyzer. The physical and spectral data are collected in Tables I and II, respectively.

Synthesis of 5-Amino-2-cyanomethylene-2, 3-dihydropyrano-[2,3-d]thiazole-6,7,7-tricarbonitrile (**4**)

A mixture of compound **1**⁸ (0.01 mol) and tetracyano-ethylene **2** (0.01 mol) and triethylamine (0.01 mol) in ethanol (40 mL) was heated under reflux for 1 h., the solid product, which was produced on heating was collected and recrystallized to give **4**.

Synthesis of 2-Cyanomethylene-3a-hydroxy-benzo[e] pyrano-[2,3-d]thiazole (**6**), 2-Cyanomethylene-3a-hydroxy-naphtho[e]-pyrano[2,3-d]thiazole (**7**)—General Procedure

A mixture of compound **1** (0.01 mol), ortho hydroxy-carboxaldehyde (0.01 mol), and piperidine (0.01 mol) in ethanol (40 mL) was heated under reflux for 3 h., the solid product which produced on heating was collected and recrystallized to give **6** and **7**.

TABLE I Physical and Analytical Data for the Synthesized Compounds

Compd. no.	M.p. (°C)	Yield (%)	Solvent cryst.	Molecular formula (Mol. Wt.)	Elemental analyses		
					C%	H%	N%
4	>300	63	DMF	C ₁₁ H ₄ N ₆ OS (268)	49.25	1.49	31.34
					49.20	1.40	31.20
6	>300	71	DMF	C ₁₂ H ₈ N ₂ O ₂ S (244)	59.01	3.27	11.47
					59.10	3.20	11.40
7	>300	65	DMF	C ₁₆ H ₁₀ N ₂ O ₂ S (294)	65.30	3.40	9.52
					65.20	3.30	9.60
9	210–212	82	Dioxane	C ₁₈ H ₁₁ N ₃ O ₄ S (365)	59.17	3.01	11.50
					59.10	3.20	11.40
12a	236–238	84	AcOH	C ₃₄ H ₂₀ N ₆ O ₇ S (656)	62.19	3.04	12.80
					62.10	3.10	12.70
12b	240–241	60	AcOH	C ₂₈ H ₁₆ ClN ₅ O ₄ S (553.5)	60.70	2.89	12.64
					60.60	2.80	12.40
12c	252–254	74	AcOH	C ₃₂ H ₁₉ N ₅ O ₄ S (569)	67.48	3.33	12.30
					67.40	3.20	12.20
14a	270–272	79	AcOH	C ₃₄ H ₂₀ N ₈ O ₆ S (668)	61.07	2.99	16.76
					61.10	2.90	16.70
14b	292–293	70	AcOH	C ₄₁ H ₂₄ N ₈ O ₇ S (772)	63.73	3.10	14.50
					63.60	3.00	14.40
15	152–153	62	AcOH	C ₃₅ H ₂₀ N ₆ O ₈ S (684)	61.40	2.92	12.28
					61.30	2.80	12.20
21	166–168	61	Dioxane	C ₂₁ H ₁₂ N ₄ O ₅ S (432)	58.33	2.77	12.96
					58.20	2.70	12.80
23	>300	78	Dioxane	C ₂₄ H ₁₄ N ₄ O ₃ S ₂ (470)	61.27	2.97	11.91
					61.20	2.80	11.80
25a	290–292	70	AcOH	C ₄₄ H ₂₆ N ₈ O ₃ S ₂ (778)	67.86	3.34	14.39
					67.80	3.30	14.30
25b	272–274	55	AcOH	C ₄₆ H ₃₀ N ₈ O ₃ S ₂ (806)	68.48	3.72	13.89
					68.40	3.60	13.80

Synthesis of 2-Cyanomethylene-5-[4-(4-nitrophenoxy)benzylidene]-4-thiazolinone (9)

A mixture of compound **1** (0.01 mol), compound **8**⁹ (0.01 mol) and piperidine (0.01 mL) in ethanol (40 mL) was heated under reflux for 1 h., the solid product which produced on heating was collected and recrystallized to give **9**.

TABLE II Spectral Data of the Synthesized Compounds

Compd. No.	IR / ν_{\max} (cm ⁻¹)	¹ H NMR (DMSO- <i>d</i> ₆) (δ / ppm)
4	3400, 3324, 3176 (NH/ NH ₂), 2926 (CH-aliph.), 2202 (C≡N).	4.23 (hump, 2H, NH ₂ ; exchange-able), 6.83 (s, 1H, methyldene-H), 7.34 (s, 1H, NH, exchange-able).
6	3364, 3168 (OH/NH), 2204 (C≡N).	Insoluble
7	3240 (OH), 2208 (C≡N), 1638 (C=N).	Insoluble
9	3076 (CH-arom.), 2926 (CH- aliph.), 2198 (C≡N), 1720 (C=O).	4.05 (s, 2H, CH ₂), 7.15–8.30 (m, 9H, Ar-H + methyldene-H).
12a	3382, 3284 (NH ₂), 2198 (C≡N), 1720 (C=O).	4.69 (s, 1H, pyridine-H), 7.41–7.62 (m, 16H, Ar-H), 7.78 (s, 1H, methyldene-H), 7.87 (s, 2H, NH ₂ ; exchangeable).
12b	3334, 3200 (NH ₂), 2200 (C≡N), 1714 (C=O).	—
12c	3382, 3300 (NH ₂), 2196 (C≡N), 1718 (C=O).	4.71 (s, 1H, pyridine-H), 7.15–8.32 (m, 18H, Ar-H + methyldene-H + NH ₂).
14a	3330, 3204 (NH ₂), 2210 (C≡N).	4.49 (s, 1H, pyridine-H), 6.83–8.39 (m, 18H, Ar-H + NH ₂), 11.96 (s, 1H, NH; exchangeable).
14b	3328, 3198 (NH ₂), 2214 (C≡N).	4.59 (s, 1H, pyridine-H), 7.09–8.36 (m, 23H, Ar-H + NH ₂).
15	3386 (NH), 2200 (C≡N), 1718, 1660 (2 C=O).	4.98 (s, 1H, pyridine-H), 7.15–8.30 (m, 18H, Ar-H + methyldene-H + pyrimidine-H), 11.62 (s, 1H, NH; exchangeable).
21	3400 (OH), 2208 (C≡N), 1720 (C=O).	4.10 (s, 2H, CH ₂), 4.96 (s, 1H, pyridine-H), 7.09–8.31 (m, 8H, Ar-H), 8.68 (s, 1H, OH; exchangeable).
23	2198 (C≡N), 1708 (C=O).	4.05 (s, 4H, 2CH ₂), 7.23–7.99 (m, 10H, Ar-H + methyldene-H)

(Continued on next page)

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

Compd. No.	IR / ν_{\max} (cm ⁻¹)	¹ H NMR (DMSO- <i>d</i> ₆) (δ / ppm)
25a	3390, 3300 (NH ₂), 2200 (C≡N), 1722 (C=O).	—
25b	3472, 3350 (NH ₂), 2200 (C≡N), 1716 (C=O).	1.61 (s, 6H, 2CH ₃), 4.43 (s, 1H, pyridine-H), 6.91–7.71 (m, 22H + Ar-H + methyldene-H + 2 NH ₂).

Synthesis of

5-Amino-3-oxo-2-[4-(4-nitrophenoxy)benzylidene]-7-aryl-2,3-dihydro-7H-thiazolo[3,2-a]pyridine-6,8-dicarbonitriles (12a–c) — General Procedure

A mixture of compound **9** (0.01 mol), benzylidene malononitrile **10** (0.01 mol) and piperidine (0.01 mol) in ethanol (40 mL) was heated under reflux for 3 h. The solid product which produced on heating was collected and recrystallized to give **12**.

Synthesis of 8-Amino-3,6-bis[4-(4-nitrophenoxy)phenyl]-1H, 6H-pyrazolo[3',4':4,5]thiazolo[3,2-a]pyridine-5,7-dicarbonitrile (14a), and 8-Amino-1-benzoyl-3,6-bis[4-(4-nitrophenoxy)phenyl]-6H-pyrazolo[3',4':4,5]thiazolo[3,2-a]pyridine-5,7-dicarbonitrile (14b) — General Procedure

A mixture of compound **12a** (0.01 mol) and hydrazine hydrate or benzoyl hydrazine (0.01 mol) in ethanol (30 mL) was heated under reflux for 1 h. The solid product which produced on heating was collected and recrystallized to give **14a** and **14b**, respectively.

Synthesis of 8-[4-(P-nitrophenoxy)benzylidene]-5-[4-(4-nitrophenoxy)phenyl]-3,4,8,9-tetrahydro-5H-4,9-dioxo-thiazolo[2',3':1,6]pyrido[2,3-d]pyrimidine-6-carbonitrile (15)

A mixture of compound **12a** (0.01 mol) in formic acid (10 mL) was heated under reflux for 24 h. The reaction mixture was concentrated and the solid product was collected, washed with water and recrystallized to give **15**.

Synthesis of 6,8-Dicyano-5-hydroxy-7-[4-(4-nitrophenoxy)-phenyl]2,3-dihydro-3-oxo-7H-thiazolo[3,2-a]pyridine (21)

A mixture of compound **1** (0.01 mol), arylidene **16** (0.01 mol) and piperidine (0.01 mol) in ethanol (40 mL) was heated under reflux for 0.5 h. The solid product which produced on heating was collected and recrystallized to give **21**.

Synthesis of 4,4'-[2-Cyanomethyl-4,5-dihydro-5-methylidene-4-thiazolinone-5-yl]diphenylether (23)

A mixture of thiazolidinone **1** (0.02 mol), 4,4'-bis(carbox-aldehyde)-diphenylether **22**⁹ (0.01 mol), and piperidine (0.01 mol) in ethanol (40 mL) was heated under reflux for 3 h. The solid obtained after cooling was filtered and dried and recrystallized to give **23**.

Synthesis of 4,4'-Bis[5-amino-7-aryl-2-methylidene-2,3-dihydro-7H-3-oxo-thiazolo[3,2-a]pyridine-6,8-dicyano-2-yl]diphenylether Derivatives (25a,b)—General Procedure

A mixture of **23** (0.01 mol), arylidenemalononitrile **10** (0.02 mol) and piperidine (0.01 mol) in ethanol (40 mL) was heated under reflux for 3 h. The solid product which produced on heating was collected and recrystallized to give **25a,b**.

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