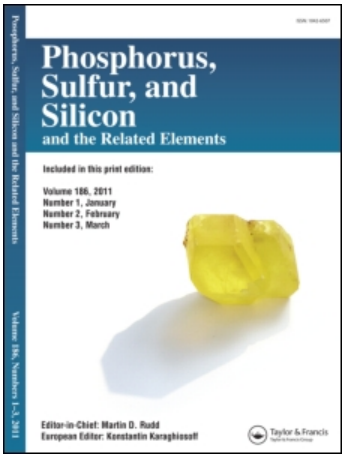

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Cyanoacetanilides Intermediates in Heterocyclic Synthesis, Part 3: Novel Syntheses of Thiazolinone and Thiazolo[3,2-a]Pyridine Derivatives

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Cyanoacetanilides Intermediates in Heterocyclic Synthesis, Part 3: Novel Syntheses of Thiazolinone and Thiazolo[3,2-a]Pyridine Derivatives

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Thiazolo[3,2-a]pyridines ***6a–c***, ***10***, ***13***, *and* ***14*** *have been synthesized via simple methods from the readily accessible 2-[N-(4-ethoxyphenyl)-acetamide-2-yl]-4,5-dihydro-4-thiazolinone* **2**. *The structure of the synthesized compounds was established by analytical and spectral data.*

Keywords Cyanoacetanilide; thiazolinone; thiazolo[3,2-a]pyridine derivatives

INTRODUCTION

Antimicrobial,[1] antifungal,[2] anticonvulsant,[3] anticancer,[4] and antituberculosis[5] activities of thiazolinone derivatives were reported. Thiazolo[3,2-a]pyridines have been reported to possess antibacterial,[6] bactericide,[7] coronary dilator, antihypertensive, and muscle relaxant[8] activities. In view of these observations and in continuation of our interest in the synthesis and chemistry of thiazolo[3,2-a]pyridines,[9–11] we report here the synthesis of some novel thiazolo[3,2-a]pyridines

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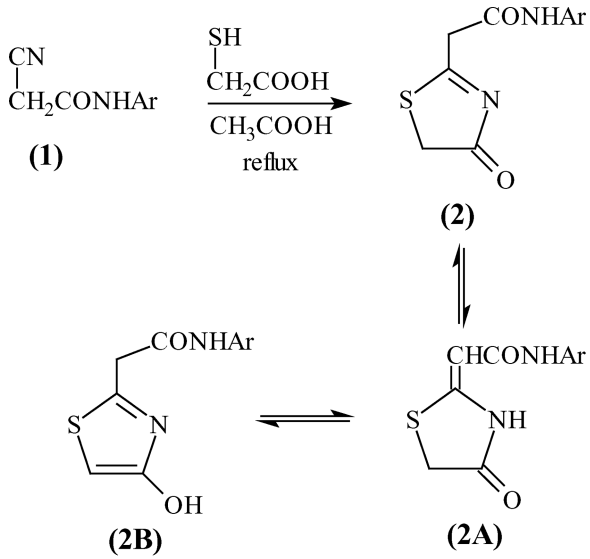
from the readily accessible 2-[*N*-(4-ethoxyphenyl)acetamide-2-yl]-4,5-dihydro-4-thiazolinone **2**.

RESULTS AND DISCUSSION

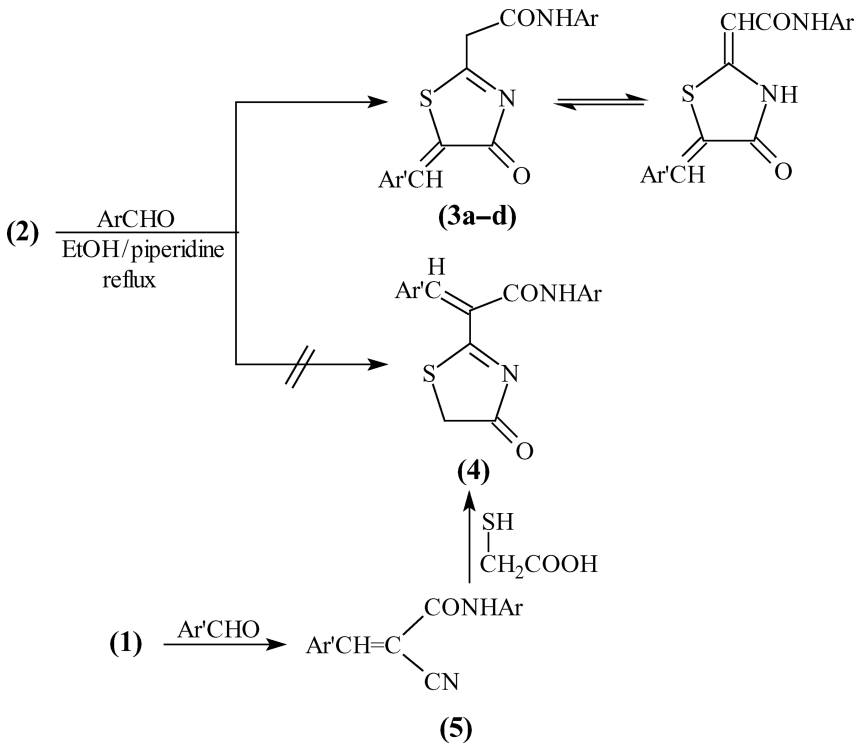
Cyclocondensation of cyanoacetanilide derivative **1** with sulfanylacetic acid in glacial acetic acid at a reflux temperature furnished the novel thiazolinone derivative **2** in good yield (95%; Scheme 1). The structure of compound **2** was supported by its analytical and spectral data. The infrared spectrum of compound **2** revealed a characteristic band for NH (3282 cm^{-1}) and C=O (thiazolinone; 1702 cm^{-1}) function groups. On the basis of ^1H NMR spectrum, compound **2** proved to exist predominantly in the tautomeric form **2A** rather than the tautomeric form **2B**. So, the ^1H NMR of the reaction product recorded in DMSO-d_6 displayed a signal at δ 5.76 ppm for an methylidene-H in addition to ethoxy, thiomethylene, two NH, and aromatic protons. Formation of compound **2** is assumed to proceed via the initial nucleophilic addition of the mercapto function group to the cyano function, followed by intramolecular cyclization by the elimination of the water molecule to afford **2**.

The reactivity of compound **2** towards aromatic aldehydes as electrophilic reagents was investigated. Thus, when compound **2** was



Ar = $C_6H_4OC_2H_5$-4

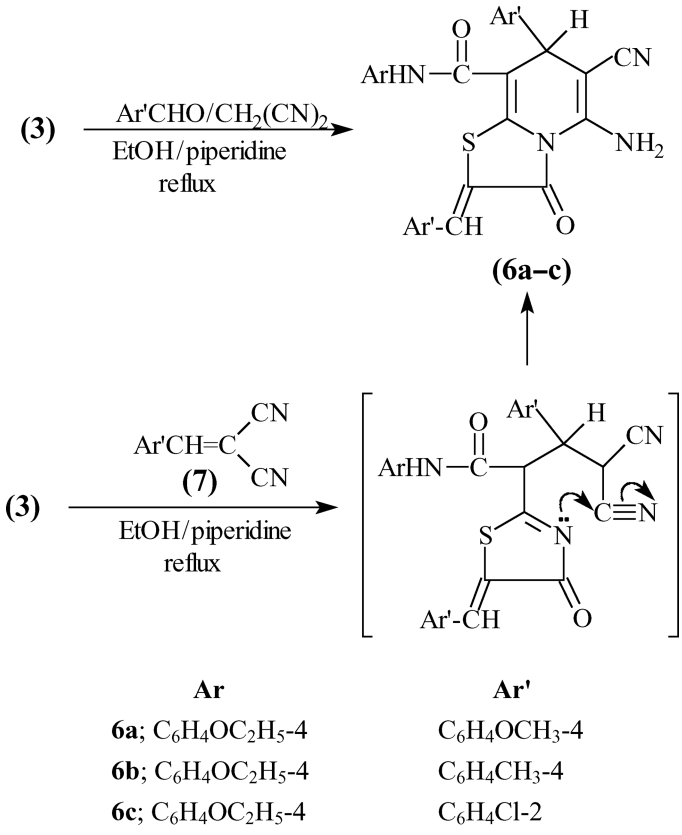
SCHEME 1



Ar	**Ar′**
3a; $C_6H_4OC_2H_5$-4	$C_6H_4CH_3$-4
3b; $C_6H_4OC_2H_5$-4	$C_6H_4OCH_3$-4
3c; $C_6H_4OC_2H_5$-4	C_6H_4Br-4
3d; $C_6H_4OC_2H_5$-4	C_6H_4Cl-2
4; $C_6H_4OC_2H_5$-4	$C_6H_4CH_3$-4

SCHEME 2

condensed with aromatic aldehyde in ethanol under reflux in the presence of piperidine, two possible structures, **3** and **4**, can be formulated (Scheme 2). The methylidene derivative **3** was established by ^{1}H NMR spectra and the other possible structure **4** was eliminated. The ^{1}H NMR spectrum of compound **3b** in DMSO-d_6 revealed the lack of a singlet characteristic for thiomethylene, which was present in the parent compound and exhibited signals for ethoxy, methylidene, NH, and aromatic protons. In the mass spectrum of compound **3b**, a molecular ion peak was observed at m/z = 396 (8.9%) with a base peak at m/z = 137, which is characteristic for a $H_2NC_6H_4OC_2H_5$-4 moiety. Compound **4** was isolated



Ar	Ar'
6a; $C_6H_4OC_2H_5$-4	$C_6H_4OCH_3$-4
6b; $C_6H_4OC_2H_5$-4	$C_6H_4CH_3$-4
6c; $C_6H_4OC_2H_5$-4	C_6H_4Cl-2

SCHEME 3

by cyclocondensation of **5** with sulfanylacetic acid in dioxane in the presence of piperidine under reflux.

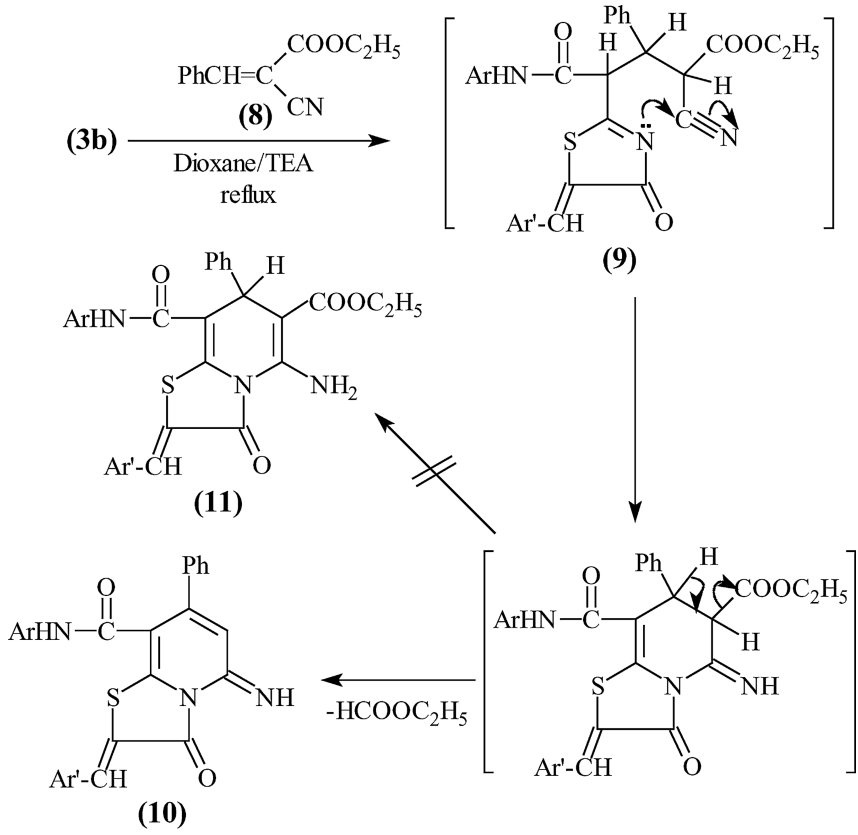
Ternary condensation of compound **3**, aromatic aldehyde, and malononitrile (1:1:1 molar ratio) in ethanol in the presence of piperidine under reflux yielded the novel thiazolo[3,2-a]pyridines **6a–c** in high yields. The structures of these compounds were elucidated by elemental analyses and spectral data. For example, the infrared spectrum of compound **6a** exhibited 4 absorption bands at 3410, 3250, 3200, and 1710 cm^{-1} that were assignable the NH_2, C≡N, and C=O (thiazolinone) groups, respectively. The ^1H NMR spectrum of compound **6a**, for example, dislpayed a signal at δ 5.1 ppm that was attributed to pyridine-H in addition to the presence of amino, NH, methylidene, ethoxy, methoxy, and aromatic protons. A molecular ion peak at m/z 580 (2.7%) was observed in the mass spectrum of compound **6a** with a base peak at m/z 137

($H_2NC_6H_4OC_2H_5$-4 moiety). A further conformation of the synthesized compound **6** was achieved by an independent synthetic route by treatment of compound **3** with arylmethylidenemalononitrile **7** (1:1 molar ratio) in refluxing ethanol in the presence of a catalytical amount of piperidine. Also, cyclocondensation of compound **2**, aromatic aldehyde, and malononitrile (1:2:1 molar ratio) under reflux in ethanol and in the presence of an equimolecular amount of piperidine yielded the thiazolopyridines **6.**

On the other hand, reaction of compound **3b** with **8** in refluxing dioxane containing triethylamine afforded the corresponding 5-imino-2-(4-methoxybenzylidene)-3-oxo-7-phenyl-2,3-dihydro-5H-thiazolo[3,2-a]-pyridine-8-carboxylic acid (4-ethoxyphenyl)amide **10**. The other possible structure, **11**, was readily rolled out for the reaction product on the basis of analytical and spectral data. Its infrared spectrum showed absorption bands at 3242, 3134 cm^{-1} (2NH), and 1692 cm^{-1} (C=O; thiazolinone); also, the absence of nitrile absorption of the reaction product corroborated the assigned structure **10**. The ^1H NMR spectrum of **10** displayed signals for 2NH, methylidene, and aromatic and pyridine protons, and the lack of ester moiety of the reaction product supported the assigned structure **10**. Formation of thiazolopyridine **10** takes place as depicted in Scheme 4 via the Michael addition of the active methylene group of **3b** to the double bond in benzylidene derivative **8** to form the acyclic intermediate **9**, which readily undergoes intramolecular cyclization followed by the elimination of ethyl formate to afford **10**.

Cyclization of compound **3b** with ethyl cyanoacetate by refluxing in ethanol in the presence of a catalytic amount of triethylamine yielded the new thiazolopyridine derivative **13**. The other possible structure **12** was eliminated on the basis of analytical and spectral data. Its infrared spectrum showed absorption bands for the NH_2 and C=O (thiazolidinone) function groups. Also, its ^1H NMR spectrum in DMSO-d_6 showed the proton of the pyridine ring at δ 5.76 ppm in addition to NH_2, NH, methylidene, OCH_3, OC_2H_5, and aromatic protons. The formation of the thiazolopyridine **13** takes place through the nucleophilic addition of the active methylene of **3b** to the nitrile group, followed by intramolecular cyclization by elimination of ethanol to afford **13** (Scheme 5). Also, the reaction product that was isolated was established to be **13** rather than **12** based on its independent synthesis by cyclization of **3b** with cyanoacetamide under reflux in ethanol in the presence of triethylamine.

Finally, thiazolopyridine **14** was obtained by cyclization of compound **4** with malononitrile under reflux in ethanol in the presence of a few drops of piperidine as a catalyst. The structure of **14** was confirmed on the basis of its elemental analysis and spectroscopic data. The formation



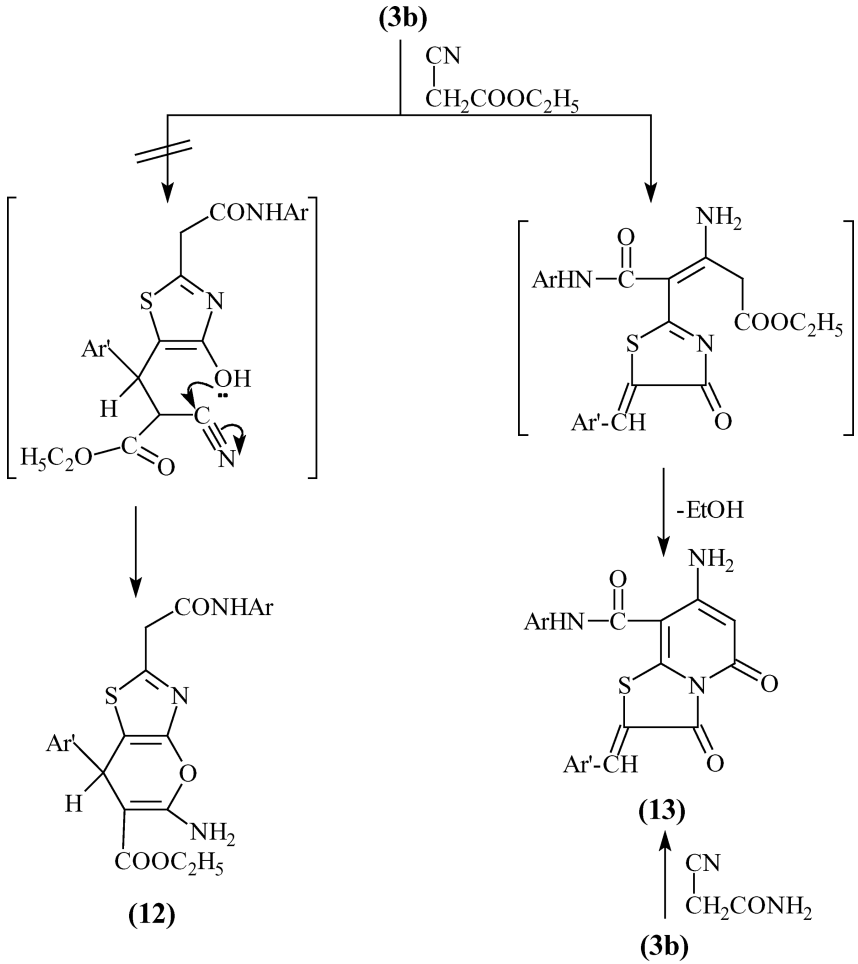
10; Ar = $C_6H_4OC_2H_5$-4 Ar' = $C_6H_4OCH_3$-4

SCHEME 4

14 is assumed to proceed via the addition of active methylene of malononitrile at the ethylenic bond followed by cyclization through a nucleophilic attack of the endocyclic nitrogen to the cyano group to give the cyclized product **14** (Scheme 6).

EXPERIMENTAL

Melting points are uncorrected. IR spectra were recorded (KBr) on a Perkin Elmer 1650 spectrophotometer. ^{1}H NMR spectra were recorded on a Varian Gemini spectrometer 200 (200 MHz) using DMSO-d_6 as a solvent and TMS as internal standard. Chemical shifts are expressed as δ ppm units. Microanalytical data were obtained from the Microanalytical Data Unit at Cairo University. Physical data for the synthesized



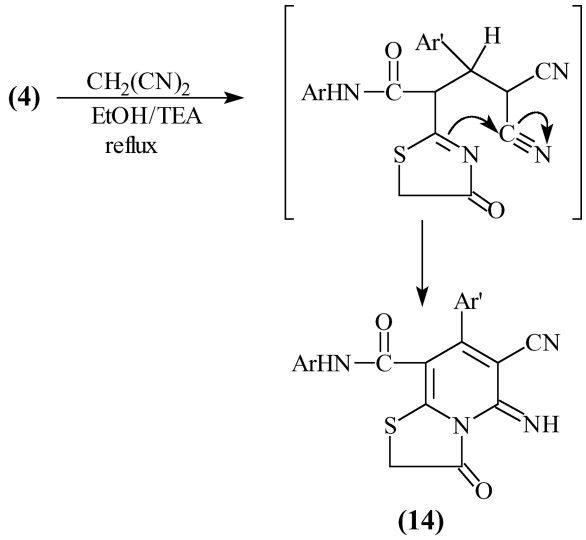
13; Ar = $C_6H_4OC_2H_5$-4 Ar' = $C_6H_4OCH_3$-4

SCHEME 5

compounds are given in Table I. Also, the spectral data are collected in Table II. Compounds (**1**),[12] (**5**),[13] (**7**),[13] and (**8**)[13] were synthesized as previously described.

2-[*N*-(4-Ethoxyphenyl)acetamide-2-yl]-4,5-dihydro-4-thiazolinone (2)

A mixture of compound **1** (0.01 mole) and sulfanylacetic acid (0.01 mole) in acetic acid (20 mL) was heated under reflux for 3 h, allowed to cool,



(14)

14; Ar = $C_6H_4OC_2H_5$-4 Ar' = $C_6H_4CH_3$-4

SCHEME 6

and poured into cold water (50 mL). The solid product was collected and recrystallized to give **2**.

^{13}C NMR (**2**): 15.38, 32.71, 63.78, 93.36, 115.04, 120.78, 133.56, 154.18, 154.67, 165.58, 174.74.

5-Arylmethylidene-2-[N-(4-ethoxyphenyl)acetamide-2-*yl*]-4,5-dihydro-4-thiazolinons (3a–d)

General Procedure

A mixture of compound **2** (0.01 mole), aromatic aldehyde (0.01 mole), and piperidine (0.5 mL) in ethanol (30 mL) was heated under reflux for 4 h, allowed to cool, and poured into cold water (50 mL). The solid product was collected and recrystallized to give **3**.

MS (3b). 396 (M^+; 8.9%), 397 (M+1; 2.6%), 398 (M+2; 1.0%), 260 (14.4%), 164 (13.1%), 165 (9.0%), 149 (10%), 108 (23%), 137 (100%), and 68 (13.6%).

MS (3c). 446 (M^+; 4.2%), 310 (10%), 262 (2%), 137 (100%), 135 (20%), 109 (32%), 108 (35%), 107 (15%), 80 (15%), and 68 (16%).

TABLE I Characteristics Data for the Synthesized Compounds

Compound number	Yield (%)	Solvent Cryst.	M.p. (°C)	Molecular formula (Mol. Wt.)	Elemental analyses Calcd./Found %		
					C	H	N
2	95	Ethanol	220–222	$C_{13}H_{14}N_2O_3S$ (278.33)	56.10 56.10	5.07 5.10	10.06 10.20
3a	82	Benzene	381–382	$C_{21}H_{20}N_2O_3S$ (380.47)	66.30 66.10	5.30 5.10	7.36 7.30
3b	76	Benzene	280–282	$C_{21}H_{20}N_2O_4S$ (396.47)	63.62 63.60	5.08 5.10	7.07 7.00
3c	78	Benzene	286–287	$C_{20}H_{17}BrN_2O_3S$ (445.34)	53.94 53.90	3.85 3.70	6.29 6.30
3d	80	Benzene	267–268	$C_{20}H_{17}ClN_2O_3S$ (400.89)	59.92 59.90	4.27 4.20	6.99 6.90
4	68	Ethanol	220–222	$C_{21}H_{20}N_2O_3S$ (380.47)	66.30 66.40	5.30 5.30	7.36 7.30
6a	83	Dioxane	208–208	$C_{32}H_{28}N_4O_5S$ (580.67)	66.19 66.20	4.86 4.80	9.65 9.60
6b	74	Dioxane	240–242	$C_{32}H_{28}N_4O_3S$ (548.67)	70.05 70.10	5.14 5.00	10.21 10.30
6c	69	Dioxane	258–259	$C_{30}H_{22}Cl_2N_4O_3S$ (589.50)	61.12 61.20	3.76 3.70	9.50 9.70
10	72	Ethanol	275–277	$C_{30}H_{25}N_3O_4S$ (523.62)	68.82 68.80	4.81 4.80	12.23 12.20
13	75	Ethanol	288.9	$C_{24}H_{21}N_3O_5S$ (463.52)	62.19 62.20	4.57 4.60	17.27 17.30
14	87	Ethanol	255–257	$C_{24}H_{20}N_4O_3S$ (444.52)	64.85 64.80	4.54 4.60	12.60 12.50

MS (3d). 400 (M^+; 5.2%), 402 (3.6%), 328 (1.9%), 264 (8.8%), 266 (3.2%), 168 (12%), 137 (100%), 109 (28.6%), 108 (33%), and 68 (18%).

N-(4-Ethoxyphenyl)-2-(4-oxo-4,5-dihydrothiazol-2-yl)-3-(p-tolyl)-acrylamide (4)

A mixture of compound **5** (0.01 mole), sulfanylacetic acid (0.01 mole), and piperidine (0.02 mole) in dioxane (30 mL) was heated under reflux for 4 h, allowed to cool, and poured into cold water (50 mL) and acidified with HCl. The solid product was collected and recrystallized to give **4**.

TABLE II Spectral Data of the Synthesized Compounds

Compound number	IR/ν_{max} (cm^{-1})	^1H NMR (DMSO-d_6) (δ/ppm)
2	3282, 3132 (2NH), 2986 (CH-aliph), 1702 (C═O; thiazolinone), 1646 (C═O; amide).	1.29 (t, 3H, CH_3), 3.67 (s, 2H, SCH_2), 3.98 (q, 2H, CH_2), 5.76 (s, 1H, methylidene-H), 8.80, 7.45 (2d, 4H, Ar-H), 9.59 (s, 1H, NH), 11.43 (hump, 1H, NH).
3a	3282, 3238 (2NH), 3064 (CH-arom), 2986 (CH-aliph), 1702 (C═O; thiazolinone), 1646 (C═O, amide).	1.20 (t,3H,CH_3), 2.1(s,3HCH_3,), 4.1(q,2H,CH_2), 5.9 (s,1H,methylidene-), 6.7, 7.1 (2d,4H,AB-system), 9.91 (s,1H,NH), 11.9 (hump,1H,NH).
3b	3246, 3136 (2NH), 3064 (CH-arom), 2970 (CH-aliph), 1692 (C═O; thiazolinone), 1644 (C═O; amide).	1.30 (t, 3H, CH_3), 3.80 (s, 3H, OCH_3), 4.02 (q, 2H, CH_2), 5.95 (s, 1H, methylidene-H), 6.84, 7.10 (2d, 4H, AB-system), 7.42 (s, 1H, methylidene-H), 7.50, 7.60 (2d, 4H, AB-system), 9.87 (s, 1H, NH), 11.8 (hump, 1H, NH).
3c	3244, 3134 (2NH), 3062 (CH-arom), 2972 (CH-aliph), 1694 (C═O; thiazolinone), 1644 (C═O; amide)	1.30 (t, 3H, CH_3), 4.00 (q, 2H, CH_2), 5.99 (s, 1H, methylidene-H), 6.8, 7.76 (2d, 4H, AB-system), 7.50 (s, 1H, methylidene-H), 7.53–7.59 (m, 4H, Ar-H), 9.92 (s, 1H, NH), 12.0 (hump, 1H, NH).
3d	3300, 3200 (2NH), 2976 (CH-aliph), 1692 (C═O; thiazolinone), 1656 (C═O; amide).	1.3 (t, 3H, CH_3), 4.0 (q, 2H, CH_2), 5.7(s, 1H, methylidene-H), 6.9–7.1 (m, 8H, Ar-H), 7.60 (s, 1H, methylidene-H), 9.7 (s, 1H, NH), 10.0 (hump, 1H, NH).
4	3230 (NH), 2982 (CH-aliph), 1704 (C═O; thiazolinone), 1654 (C═O; amide).	1.30 (t, 3H, CH_3), 4.00 (q, 2H, CH_2), 5.99 (s, 1H, methylidene-H), 6.8, 7.76 (2d, 4H, AB-system), 7.50 (s, 1H, methylidene-H), 7.53–7.59 (m, 4H, Ar-H), 9.92 (s, 1H, NH), 12.0 (hump, 1H, NH).
6a	340, 3250 (NH_2), 2970 (CH-aliph), 2200 (C≡N), 1710 (C═O; thiazolinone), 1647 (C═O; amide).	1.31 (t, 3H, CH_3), 3.72, 3.78 (2s, 6H, 2OCH_3), 3.97 (q, 2H, CH_2), 5.1 (s, 1H, pyridine-H), 6.82-7.69 (m, 15H, Ar-H, methylidene-H and NH_2), 11.47 (s, 1H, NH).
6b	3370, 3210 (NH_2), 2985 (CH-aliph), 2210 (C≡N), 1705 (C═O; thiazolinone), 1650 (C═O; amide).	1.29 (t, 3H, CH_3), 2.26, 2.36 (2s, 6H, 2CH_3), 3.97 (q, 2H, CH_2), 5.13 (s, 1H, pyridine-H), 6.82–7.61 (m, 15H, Ar-H, methylidene-H and NH_2), 9.21 (s, 1H, NH).

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

Compound number	IR/ν_{max} (cm^{-1})	^1H NMR (DMSO-d_6) (δ/ppm)
6c	3400, 3210 (NH_2), 2984 (CH-aliph), 2208 (C≡N), 1715 (C═O; thiazolinone), 1656 (C═O; amide).	1.28 (t, 3H, CH_3), 3.94 (q, 2H, CH_2), 5.5 (s, 1H, pyridine-H), 7.38–7.83 (m, 15H, Ar-H, methylidene-H and NH_2), 9.23 (s, 1H, NH).
10	3242, 3134 (2NH), 3062 (CH-arom), 2892 (CH-aliph), 1692 (C═O; thiazolinone), 1644 (C═O).	1.31 (t, 3H, CH_3), 3.84 (s, 3H, OCH_3), 4.00 (q, 2H, CH_2), 5.97 (s, 1H, pyridine-H), 6.85, 7.11 (2d, 4H, AB-system), 7.45 (s, 1H, methylidene-H), 7.53, 7.59 (2d, 4H, AB-system), 9.69, 12.06 (2s, 2H, 2NH).
13	3298, 3204 (NH_2), 2950 (CH-aliph), 1704 (C═O; thiazolinone), 1660, 1608 (C═O).	1.31 (t, 3H, CH_3), 3.69 (s, 3H, OCH_3), 3.99 (q, 2H, CH_2), 5.76 (s, 1H, pyridine-H), 6.82, 7.47 (2d, 8H, Ar-H), 6.92 (s, 1H, methylidene-H), 9.67 (s, 2H, NH_2), 10.12 (s, 1H, NH).
14	3398, 3292, 3204 (2NH/ OH), 2212 (C≡N), 1656 (C═O).	1.36 (t, 3H, CH_3), 2.43 (s, 3H, CH_3), 3.24 (s, 2H, SCH_2), 4.12 (q, 2H, CH_2), 7.10, 7.27 (2d, 4H, Ar-H), 7.31, 7.41 (2d, 4H, Ar-H), 7.65 (hump, 2H, 2NH).

5-Amino-2-arylmethylidene-7-aryl-8-carboxylic Acid (4-Eathoxy-phenyl)amide-3-oxo-2,3-dihydro-7H-thiazolo[3,2-a]pyridine-6-carbonitriles (6a–c)

General Procedure

Method (A). A mixture of compound **3** (0.01 mole), aromatic aldehyde (0.01 mole), malononitrile (0.01 mole), and piperidine (0.01 mole), in ethanol (30 mL) was heated under reflux for 1 h. The solid product, which was produced when heated, was collected and recrystallized to give **6**.

Method (B). A mixture of compound **3** (0.01 mole), arylmethylidene malononitrile **7** (0.01 mole), and piperidine (0.01 mole) in ethanol (40 mL) was heated under reflux for 1 h. The solid product, which was produced when heated, was collected to give **6**.

Method (C). A mixture of compound **2** (0.01 mole), aromatic aldehyde (0.02 mole), malononitrile (0.01 mole), and piperidine (0.5 mL) in

ethanol (30 mL) was heated under reflux for 1 h. The solid product, which was produced when heated, was collected and recrystallized to give **6**.

MS (6a). 580 (M^+, 2.7%), 581 (M+1, 2.3%), 513 (3.5%), 457 (4.5%), 419 (5.7%), 310 (4.9%), 267 (6.6%), 223 (3.1%), 186 (5.9%), 137 (100%), 129 (10%), 108 (19%), and 68 (10%).

MS (6c). 589 (11.5%), 477 (28%), 424 (23%), 392 (20%), 339 (25%), 170 (20%), 137 (100%), 278 (24%), 264 (19%), 236 (14%), 136 (15%), 134 (23%), 108 (38%), 168 (46%), and 68 (16%).

5-Imino-2-(4-methoxybenzylidene)-3-oxo-7-phenyl-2,3-dihydro-5*H*-thiazolo[3,2-a]pyridine-8-carboxylic Acid (4-ethoxyphenyl)amide (10)

A mixture of compound **3b** (0.01 mole), benzylidene **8** (0.01 mole), and triethylamine (0.01 mole) in dioxane (30 mL) was heated under reflux for 10 h, allowed to cool, and poured into cold water (50 mL) and acidified with HCl. The solid product was collected and recrystallized to give **10**.

7-Amino-2-(4-Methoxybenzylidene)-3,5-dioxo-2,3,5-trihydro-thiazolo[3,2-a]pyridine-5*H*-8-carboxylic Acid (4-ethoxyphenyl)-amide (13)

A mixture of compound **3b** (0.01 mole), ethyl cyanoacetate or cyanoacetamide (0.01 mole), and triethylamine (0.01 mole), in ethanol (40 mL) was heated under reflux for 24 h. The solid product, which was produced on heating, was collected and recrysallized to give **13**.

6-Cyano-5-imino-3-oxo-7-(4-methylphenyl)-2,3-dihydro-5*H*-thiazolo[3,2-a]pyridine-8-carboxylic Acid (4-ethoxyphenyl)amide (14)

A mixture of compound **4** (0.01 mole), malononitrile (0.01 mole), and triethylamine (0.01 mole) in ethanol (30 mL) was heated under reflux for 12 h and allowed to cool. The solid product was collected and recrystallized to give **14**.

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