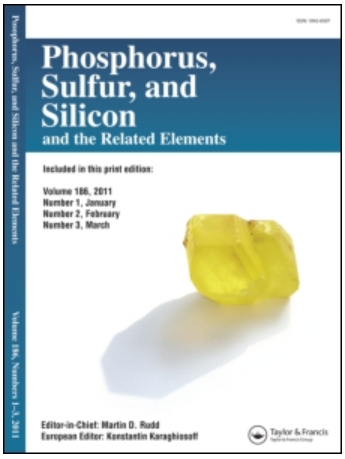

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SYNTHESIS THROUGH REACTIONS OF NUCLEOPHILES WITH ACRYLONITRILES; PART 13: A DIRECT ONE-POT SYNTHESIS OF THIAZOLOPYRIDINES

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SYNTHESIS THROUGH REACTIONS OF NUCLEOPHILES WITH ACRYLONITRILES; PART 13: A DIRECT ONE-POT SYNTHESIS OF THIAZOLOPYRIDINES

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Several new thiazolopyridines have been synthesized by a one-pot method through the ternary condensation of aldehydes with malononitrile and thioglycolic acid. Structure and reaction pathway are also reported.

Key words: Heterocycles; thiazolopyridines; antibacterial activity.

Recently, we have described the synthesis of several heterocyclic compounds by a simple method.[1–5] In an extension of our studies, the present paper describes a quick synthetic method for thiazolopyridines from readily available starting materials. Thiazolopyridines are biologically important as antiinflammatory and antibacterial agents.[6,7] In spite of this; there are limited publication of the synthesis of thiazolopyridines.[8–12]

Thus it has been found that the ternary condensation of pyridine-3-carboxaldehyde **1a** with malononitrile and thioglycolic acid in a 2:2:1 molar ratio in ethanol and in the presence of piperidine as a basic catalyst afforded 5-amino-6,8-dicyano-3-oxo-2-(3-pyridylmethylene)-7-(3-pyridyl)-2,3-dihydro-7H-thiazolo[3,2-a] pyridine **Va**.

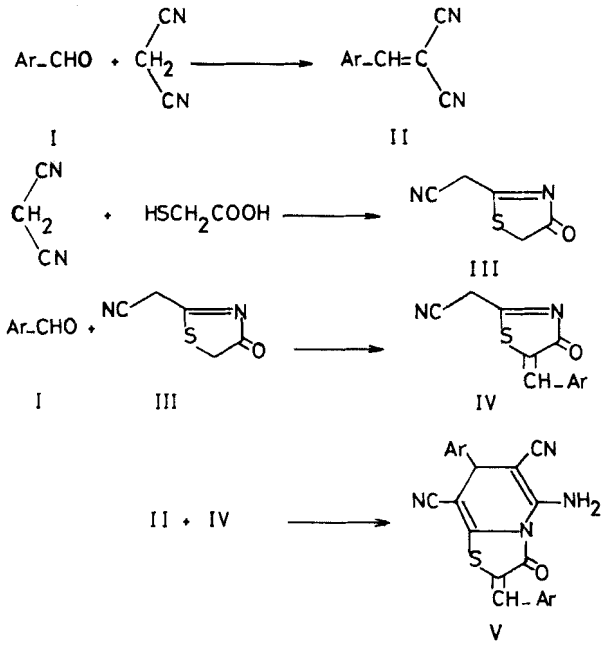
Structure **Va** was established for the reaction product based on agreement of the analytical and spectral data (cf. Experimental). The reaction pathway is considered to proceed as shown in Scheme I.

Structure proof was obtained through another route by treatment of α-cyano-β-(3-pyridyl) acrylonitrile (**IIa**) with thioglycolic acid in molar ratio 2:1 in the presence of a catalytic amount of piperidine (cf. Experimental, Method B).

Similarly by using thiophene-2-carboxaldehyde (**1b**) and/or furfural (**1c**) as (π-excessive heterocyclic aldehydes) instead of the (π-deficient heterocyclic aldehyde) **1a** under conditions as given above, the corresponding thiazolo[3,2-a] pyridines (**Vb, c**) were produced (cf. Scheme I). Thiazolopyridines (**Vb, c**) were also prepared from the corresponding acrylonitriles (**11b, c**).[9]

In the same manner 1-naphthaldehyde (**1d**) submitted to the same reaction conditions afforded the corresponding thiazolo [3,2-a]-pyridine (**Vd**).

In order to generalize this one-pot synthesis, we found that the substituted benzaldehyde (**1e-I**) under the identical reaction conditions afforded the corresponding thiazolo[3,2-a]pyridines (**Ve-I**).



I,II,IV,V	Ar	I,II,IV,V	Ar
a	3-pyridyl	g	$C_6H_4NO_2$-p-
b	2-thienyl	h	2,4-di-$MeOC_6H_3$
c	2-furyl	i	2,5-di-$MeOC_6H_3$
d	1-naphthyl	j	3,4-di-$MeOC_6H_3$
e	C_6H_4-OCH_3-o-	k	C_6H_5
f	C_6H_4-Cl-o-	l	$C_6H_4CH_3$-p-

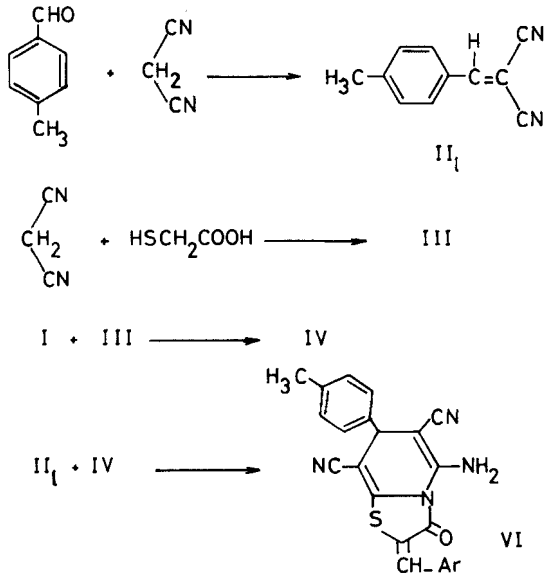
SCHEME I

Compounds (**Ve-I**) were unambiguously prepared by another route from the corresponding acrylonitrile (**11e-I**). Structures (**11b-I**) were established in a similar manner as described above (cf. Experimental).

In order to investigate the possible utility of this one-pot method to prepare polyfunctionally thiazolopyridines having two different aryl moieties, we succeeded in preparing thiazolopyridines (**VIa-d**) by using one mole of *p*-tolualdehyde and one mole of arylaldehyde instead of the two moles of aldehyde under the previous reaction conditions.

Thiazolopyridenes (**Va-I**) were eliminated as another possible expected structures for the reaction product based on analytical and spectral data as well as m.p's (c.f. Experimental). As an example (**VIb**) shows in its H-NMR spectrum the presence of only one signal with three protons for the methyl group at 2.38 ppm which must be two methyl groups in case of (**VI**) and must disppear in case of (**VIb**).

Structure proof for such a structure was obtained through its synthesis from the acrylonitrile derivative **II I**, (c.f. Scheme II, Experimental, Method B) Formation of (**V1a-d**) is shown as follows:



I,II,IV,VI	Ar
a	3-pyridyl
b	C_6H_5
c	C_6H_4-Cl-o-
d	1-naphthyl

SCHEME II

EXPERIMENTAL

All melting points are uncorrected. The IR spectra were recorded with (KBr) wafers on a Shimadzu-408 spectrophotometer, the ^{1}H-NMR spectra in DMSO on a Varian A-60 spectrometer. Chemical shifts are expressed in δ ppm using TMS as the internal standard. Microanalytical data were obtained from the microanalytical data unit at Cairo University.

Synthesis of **Va-l**

Method A: A solution of aldehyde **1a-l** (0.02 mole), malononitrile (0.02 mole) and thioglycolic acid (0.01 mole) in ethanol (50 ml) and a catalytic amount of piperidine was heated under reflux for three hours. The solvent was then evaporated. The solid product so formed was collected by filtration and crystallized from the proper solvent.

Method B: A solution of **IIa-l** (0.02 mole) and thioglycolic acid (0.01 mole) in ethanol (50 ml) and a catalytic amount of piperidine was heated under reflux for three hours. The solvent was then evaporated. The solid product so formed was collected by filtration and crystallized from the proper solvent.

5-Amino-6,8-dicyano-3-oxo-2-(3-pyridylmethylene)-7-(3-pyridyl)-2,3 dihydro-7H-thiazolo[3,2-a]pyridine. **Va**: Yield 68% (method A), and 59% (method B), m.p. 234–236°C (Ethanol/DMF); yellow crystals.

IR: 3400–3200 (NH_2), 2980 (CH), 2200 (CN), 1700 (CO) and 1650–1600 cm (C=C).

H-NMR: 5.0 (s, 1H, pyridine H-6); 7.5–8.7 (m, 1OH, 2H NH_2 and 8H of aromatic pyridyl protons), 9.2 (s, 1H, arylidene protons).

Found: C 62.6, H 3.4, N 21.8, S 8.46%.

Calc. for $C_{20}H_{12}N_6OS$ (384): C 62.5, H 3.1, N 21.9, S 8.3%.

5-Amino-6,8-dicyano-3-oxo-2-(2-thienylmethylene)-7-(2-thienyl)-2,3 dihydro-7H-thiazolo[3,2-a]pyridine. **Vb**: Yield 88% (method A) and 83% (method B), m.p. 216–218°C Lit.[9] m.p. 214–216°C (Ethanol/DMF); yellow crystals.

5-Amino-6,8-dicyano-3-oxo-2-(2-furylmethylene)-7-(2-furyl)-2,3-dihydro-7-H-thiazolo[3,2-a]pyridine. **Vc**: Yield 85% (method A) and 86% (method B), m.p. 228–230°C, Lit.[9] m.p. 230–232°C (Ethanol/DMF); brown crystals.

5-Amino-6,8-dicyano-3-oxo-2-(1-Naphthylmethylene)-7-(1-Naphthyl)-2,3-dihydro-7H-thiazolo[3,2-a]pyridine. **Vd**: Yield 82% (method A) and 76% (method B), m.p. 264–266°C (Ethanol/DMF); pale yellow crystals.

IR: 3400–3320 (NH_2); 2980 (CH); 2200 (CN); 1700 (CO); and 1660 (C=C).

Found: C 74.5, H 3.5, N11.5, S 6.5%.

Calc. for $C_{30}H_{18}N_4OS$ (482): C 74.7, H 3.7, N 11.6, S 6.6%.

5-Amino-6,8-dicyano-3-oxo-2-(2-anisylmethylene)-7-(2-anisyl)-2,3-dihydro-7H-thiazolo[3,2-a]pyridine. **Ve**: Yield 70% (method A) and 73% (method B), m.p. 218–220°C (Ethanol/DMF); brown crystals.

IR: 3400–3350 (NH_2); 2980, 2950 (CH, CH_3); 2200 (CN); 1720 (CO); 1660 (C=C).

Found: C 65.3, H 3.9, N 12.6, S 7.3%.

Calc. for $C_{24}H_{18}N_4O_3S$ (442): C 65.1, H 4.1, N 12.7, S 7.2%.

5-Amino-6,8-dicyano-3-oxo-2-(2-chloro-phenylmethylene)-7-(2-chlorophenyl)-2,3-dihydro-7H-thiazolo[3,2-a]pyridine. **Vf**: Yield 78% (method A) and 64% (method B); m.p. 264–266°C (Ethanol/DMF); yellow crystals.

IR: 3400–3350 (NH_2); 2200 (CN); 1720 (CO); and 1610 (C=C).

H-NMR: 5.1 (s, 1H, pyridine H-6); 7.2–7.8 (m, 9H, aromatic and arylidene protons); 8.2 (2H, NH_2 protons).

Found: C 58.5, H 2.9, N 12.1, S 7.15.

Calc. for $C_{22}H_{12}Cl_2N_4OS$ (451): C 58.5, H 2.7, N 12.4, S 7.1%.

5-Amino-6,8-dicyano-3-oxo-2-(4-Nitro-phenylmethylene)-7-(4-Nitrophenyl)-2,3-dihydro-7H-thiazolo[3,2-a]pyridine. **Vg**: Yield 75% (method A) and 65% (method B); m.p. 255–257°C (Ethanol/DMF); brown crystals.

IR: 3400–3350 (NH_2); 2980–2950 (CH); 2200 (CN); 1730 (CO); 1660 (C=C).

Found: C 55.8, H 2.5, N 17.8, S 6.83%.

Calc. for $C_{22}H_{12}N_6O_5S$ (472): C 55.9, H 2.5, N 17.8, S 6.8%.

5-Amino-6,8-dicyano-3-oxo-2-(2,4-dimethoxy-phenylmethylene)-7-(2,4 dimethoxy-phenyl)-2,3-dihydro-7H-thiazolo[3,2-a]pyridine. **Vh:** Yield 85% (method A) and 75% (method B); m.p. 214–216°C ($CHCl_3$); yellow crystals.

IR: 3400–3350 (NH_2); 2950–2850 (CH, CH_3); 2200 (CN); 1710 (CO); 1650 (C=C).

Found: C 62.0, H 4.2, N 11.10, S 6.70%.

Calc. for $C_{26}H_{22}N_4O_5S$ (502): C 62.20, H 4.40, N 11.20, S 6.40%.

5-Amino-6,8-dicyano-3-oxo-2-(2,5-dimethoxy-phenylmethylene)-7-(2,5 dimethoxy-phenyl)-2,3-dihydro-7H-thiazolo[3,2-a]pyridine **Vi**: Yield 80% (method A) and 74% (method B); m.p. 232–234°C ($CHCl_3$), yellow crystals.

IR: 3450–3350 (NH_2); 2980–2950 (CH and CH_3); 2200 (CN); 1700 (CO); 1650–1640 (C=C).

H-NMR: 3.3–3.8 (m, 12H, 4-CH_3O—); 4.8 (s, 1H, pyridine CH); 7–7.2 (m, 8H, aromatic and NH_2 protons); 7.8 (s, 1H, CH).

Found: C 62.10, H 4.30, N 11.10, S 6.70%.

Calc. for $C_{26}H_{22}N_4O_5S$ (502): C 62.20, H 4.4, N 11.2, S 6.4%.

5-Amino-6,8-dicyano-3-oxo-2-(3,4-dimethoxy-phenylmethylene)-7-(3,4 dimethoxy-phenyl)-2,3-dihydro-7H-thiazolo[3,2-a]pyridine. **Vj**: Yield 79% (method A) and 64% (method B): m.p. 236–238°C ($CHCl_3$), yellow crystals.

IR: 3450–3350 (NH_2); 2980–2950 (CH and CH_3); 2200 (CN); 1700 (CO); 1650–1640 (C=C).

Found: C 62.1, H 4.3, N 11.1, S 6.7%.

Calc. for $C_{26}H_{22}N_4O_5S$ (502): C 62.2, H 4.4, N 11.2, S 6.4%.

5-Amino-6,8-dicyano-3-oxo-2-(phenylmethylene)-7-phenyl-2,3-dihydro-7H-thiazolo[3,2-a]pyridine. **Vk**: Yield 80% (method A) and 75% (method B); m.p. 245–248°C Lit.[10] m.p. 244–245°C.

5-Amino-6,8-dicyano-3-oxo-2-(4-tolylmethylene)-7-(4-tolyl)-2,3-dihydro-7H-thiazolo[3,2-a]pyridine. **VI**: Yield 78% (method A) and 70% (method B); m.p. 237–239°C. Lit.[10] m.p. 239–240°C.

5-Amino-6,8-dicyano-3-oxo-2-(3-pyridylmethylene)-7-(4-tolyl)-2,3-dihydro-7H-thiazolo[3,2-a]pyridine. **VIα**: Yield 70% (method A) and 63% (method B); m.p. 260°C (Ethanol/DMF); yellow crystals.

IR: 3400–3350 (NH_2); 2980 (CH); 2200 (CN); 1700 (CO); and 1650–1600 (C=C).

5-Amino-6,8-dicyano-3-oxo-2-(phenylmethylene)-7-(4-tolyl)-2,3-dihydro-7H-thiazolo[3,2-a]pyridine. **VIb**: Yield 80% (method A) and 70% (method B); m.p. 250–252°C (Ethanol/DMF); yellow crystals.

IR: 3400–3350 (NH_2); 2980 (CH); 2200 (CN); 1700 (CO); and 1650–1600 cm (C=C).

H-NMR: 2.38 (s, 3H, CH_3); 4.45 (s, 1H, H-7); 7.2–7.6 (m, 11H, aromatic and NH_2 protons); 7.9 (s, 1H, arylidene proton).

5-Amino-6,8-dicyano-3-oxo-2-(2-chloro-phenylmethylene)-7-(4-tolyl 2,3-dihydro-7H-thiazolo[3,2-a]pyridine. **VIc:** Yield 73% (method A) and 70% (method B); m.p. 245–247°C (Ethanol/DMF); yellow crystals.

IR: 3400–3350 (NH_2); 2200 (CN); 1700 (CO); 1650–1600 (C=C).

5-Amino-6,8-dicyano-3-oxo-2-(1-Naphthylmethylene)-7-(4-tolyl)-2,3-dihydro-7H-thiazolo[3,2-a]pyridine. **VId**: Yield 70% (method A) and 65% (method B); m.p. 248–250°C (Ethanol/DMF); yellow crystals.

IR: 3400–3350 (NH_2); 2200 (CN); 1700 (CO); and 1660–1600 (C=C).

Biological Activity of the Synthesized Compound

Some of the prepared compounds were tested for antibacterial activity. Two different microbial groups were used for this purpose: (a) Gram negative bacteria (*E. coli* and *Serratia*; *G − ve*); (b) Gram positive bacteria (*Bacillus cereus* and *Micrococcus luteus*; *G + ve*).

The biological assay was determined according to the Table I.

TABLE I

Antibacterial activity [a][b]

	G − ve		*G + ve*	
Compound	*E. coli*	*Serratia*	*Bacillus cereus*	*Micrococcus luteus*
Va	− *ve*	+ +*ve*	+ *ve*	− *ve*
Vb	+ *ve*	+ *ve*	− *ve*	− *ve*
Vf	+ *ve*	+ *ve*	+ *ve*	− *ve*
Vh	+ *ve*	− *ve*	+ *ve*	− *ve*
Vi	+ *ve*	+ *ve*	− *ve*	− *ve*
VI	− *ve*	+ + *ve*	− *ve*	− *ve*
VIa	− *ve*	+ + *ve*	− *ve*	− *ve*
VIb	− *ve*	+ + *ve*	− *ve*	+ *ve*
VIc	+ + *ve*	+ *ve*	− *ve*	+ *ve*
VId	+ *ve*	+ *ve*	− *ve*	+ *ve*

[a]Diameter of the zone of inhibition: − = 0.6 to 1 cm; + = 1 to 1.5 cm; + + = 1.5 to 2 cm.

[b]The solvent was DMF. Filter paper disc method a. Assay plates were incubated at 25 one day for the bacteria used.

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