

Three-component condensation of 2,4-diaminothiazoles with aldehydes and Meldrum's acid. The synthesis of 7-aryl- and 7-alkyl-6,7-dihydro-4*H*-thiazolo[4,5-*b*]pyridin-5-ones

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7-Aryl- and 7-alkyl-6,7-dihydro-4*H*-thiazolo[4,5-*b*]pyridin-5-ones were obtained by three-component condensation of 5-unsubstituted 2-amino-4-iminothiazolidine hydrochlorides with aromatic or aliphatic aldehydes and Meldrum's acid.

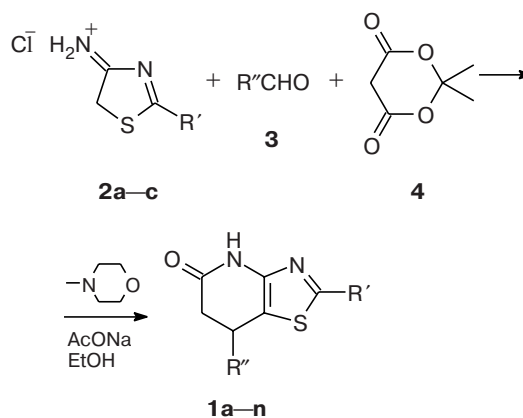
Key words: 2-amino-4-iminothiazolidinium chlorides, three-component condensation, Meldrum's acid, 7-aryl- and 7-alkyl-6,7-dihydro-4*H*-thiazolo[4,5-*b*]pyridin-5-ones.

We have proposed a convenient route to 4,7-dihydro-5*H*-thieno[2,3-*b*]pyridin-6-ones through unstable 2-aminothiophenes.¹ Here we applied this approach to the synthesis of earlier unknown 7-aryl- and 7-alkyl-6,7-dihydro-4*H*-thiazolo[4,5-*b*]pyridin-5-ones **1** (Scheme 1). Three-component condensation involves reactions of labile 2,4-diaminothiazoles generated from stable 2-amino-4-iminothiazolidinium chlorides **2** with aromatic (or aliphatic) aldehydes **3** and Meldrum's acid (**4**). 2,4-Diaminothiazoles are known to be ambident nucleophiles: they react with appropriate substrates at both the amino N atom in position 4 and the C(5) atom of the thiazole ring to form a new ring annulated with the thiazole fragment.

The resulting novel heterocyclic system can be regarded as modified 2,4-diaminothiazole, whose known derivatives exhibit a high specific biological activity in inhibition of cycline-dependent kinases.^{2–5} The sole relevant example described in the literature includes the annulation of 2-amino-4-iminothiazolidinium chloride with ethyl acetoacetate or pentane-2,5-dione, giving the corresponding 2-amino-5,7-dimethylthiazolo[4,5-*b*]pyridines and 2-amino-7-methyl-4*H*-thiazolo[4,5-*b*]pyridin-5-ones.⁶

We used stable 5-unsubstituted 2-amino-4-iminothiazolidinium chlorides **2**. The synthesis of such salts is described for either a primary or tertiary amino group (amino, 1-piperidyl, 4-morpholino, *etc.*) as a substituent in position 2.⁶ In this case, 5-unsubstituted 2,4-diaminothiazoles are difficult to use as the starting reagents because of their instability.⁷ Moreover, when dissolved, they are in equilibrium with their tautomer 2-amino-4-iminothiazolidine; the imino form is dominant,^{8,9} which makes them prone to hydrolysis.

Scheme 1



Compound	R'	R''
1a	NH ₂	Me ₂ CHCH ₂
1b	NH ₂	3-Pyridyl
1c	NH ₂	3,4-(MeO) ₂ C ₆ H ₃
1d	NH ₂	2,5-(MeO) ₂ C ₆ H ₃
1e	NH ₂	2-Thienyl
1f	NH ₂	4-PhCH ₂ O-C ₆ H ₄
1g	NH ₂	CH(CH ₂) ₅
1h	NH ₂	4-Cl-C ₆ H ₄
1i	N(CH ₂) ₅	4-Cl-C ₆ H ₄
1j	N(CH ₂) ₄ O	4-Cl-C ₆ H ₄
1k	N(CH ₂) ₅	2-MeO-C ₆ H ₄
1l	N(CH ₂) ₄ O	2,4-(MeO) ₂ C ₆ H ₃
1m	N(CH ₂) ₅	2,4-(MeO) ₂ C ₆ H ₃
1n	N(CH ₂) ₄ O	2,5-Cl-C ₆ H ₃

The condensation was carried out in boiling ethanol in the presence of a small excess of AcONa and a catalytic amount of *N*-methylmorpholine (see Scheme 1, Table 1).

Table 1. Yields, melting points, and elemental analysis data for compounds **1a–n**

Compound	M.p./°C	Yield (%)	Found Calculated (%)					Molecular formula
			C	H	N	S	Cl	
1a	228–230	44	53.04 53.31	6.64 6.71	18.52 18.65	14.38 14.23	—	C ₁₀ H ₁₅ N ₃ OS
1b	292 (decomp.)	56	53.43 53.64	4.62 4.09	22.34 22.75	13.27 13.02	—	C ₁₁ H ₁₀ N ₄ OS
1c	224–227	48	54.79 55.07	4.89 4.95	13.91 13.76	10.32 10.50	—	C ₁₄ H ₁₅ N ₃ O ₃ S
1d	231–232	46	54.80 55.07	4.89 4.95	13.86 13.76	10.34 10.50	—	C ₁₄ H ₁₅ N ₃ O ₃ S
1e	260 (decomp.)	53	47.47 53.64	3.57 4.09	16.51 22.75	25.79 13.02	—	C ₁₀ H ₉ N ₃ OS ₂
1f	325	55	64.65 64.94	4.82 4.88	12.14 11.96	9.18 9.12	—	C ₁₉ H ₁₇ N ₃ O ₂ S
1g	271–273	67	57.55 55.07	6.89 4.95	16.34 13.76	12.48 10.50	—	C ₁₂ H ₁₇ N ₃ OS
1h	285	47	51.32 51.52	3.53 3.60	14.81 15.02	11.66 11.46	12.45 12.67	C ₁₂ H ₁₀ ClN ₃ OS
1i	199–201	57	58.92 58.70	5.24 5.22	11.87 12.08	9.15 9.22	10.37 10.19	C ₁₇ H ₁₈ ClN ₃ OS
1j	178–180	62	55.06 54.93	4.64 4.61	11.90 12.01	9.22 9.17	10.08 10.13	C ₁₆ H ₁₆ ClN ₃ O ₂ S
1k	134–136	49	62.76 55.07	6.13 4.95	12.07 13.76	9.45 10.50	—	C ₁₈ H ₂₁ N ₃ O ₂ S
1l	124–126	54	57.73 57.58	5.67 5.64	11.38 11.19	8.50 8.54	—	C ₁₈ H ₂₁ N ₃ O ₄ S
1m	183–185	51	60.83 61.10	6.18 6.21	11.37 11.25	8.73 8.59	—	C ₁₉ H ₂₃ N ₃ O ₃ S
1n	244–246	65	49.77 50.01	3.89 3.93	11.12 10.93	8.40 8.34	18.32 18.45	C ₁₆ H ₁₅ Cl ₂ N ₃ O ₂ S

Apparently, the first step involves the formation of free 2,4-diaminothiazoles **5** under the action of sodium acetate (with a release of an equimolar amount of AcOH) and the formation of arylmethylidene derivatives of Meldrum's acid (**6**) (catalyzed by N-methylmorpholine or its acetate). This is followed by conjugated addition of 2,4-diaminothiazole to compound **6** and cyclization with a release of CO₂ and acetone (Scheme 2).

Compounds **1** are crystalline solids. Their structures were proved by elemental analysis, NMR spectroscopy, and mass spectrometry. The mass spectra of compounds **1** contain characteristic molecular ion peaks. The structure of compound **1h** was confirmed by 2D C—H correlation experiments. The signals for the proton-bearing C atoms in the ¹³C NMR spectra and for the corresponding protons in the ¹H NMR spectra were assigned from HSQC data.¹⁰ The signals for the quaternary C atoms were assigned from HMBC data.¹¹ The observed correlations allowed identification of all the protons and all the C atoms (except for the fragment C—NH₂ because the corresponding signal shows no cross peaks).

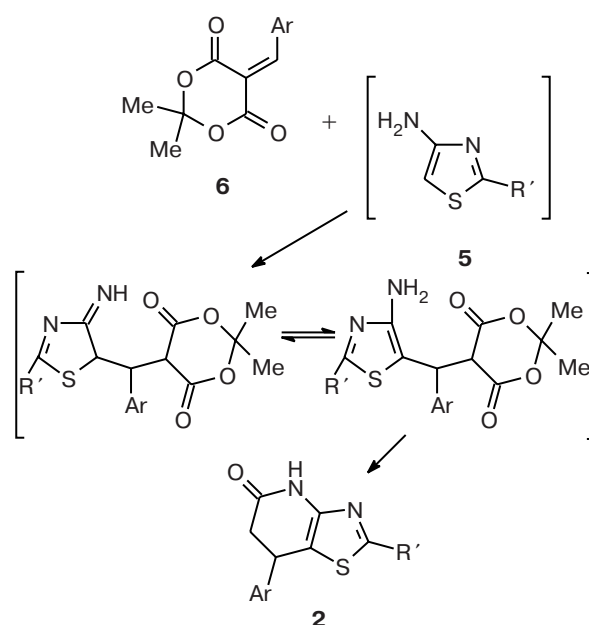
Scheme 2

Table 2. ^1H NMR spectra (DMSO- d_6 , δ , J/Hz) of compounds **1a–n**

Compound	Ar	H—C—H (dd, 1 H)	H—C—H	CH	R	NH (br.s, 1 H)
1a	0.85 (m, 6 H, CH_3); 1.25 (m, 2 H, CH_2); 1.65 (m, 1 H, CH)	2.2 (dd, $J = 7, 16$)	2.6 (dd, 1 H, $J = 7, 16$)	2.9 (m, 1 H, CH)	6.95 (s, 2 H, NH_2)	10.05
1b	7.35 (m, 1 H, Py); 7.55 (m, 1 H, Py); 8.45 (m, 2 H, Py)	2.5 (dd, $J = 7, 16$)	2.95 (dd, 1 H, $J = 7, 16$)	4.25 (dd, 1 H, $J = 7$)	7.05 (s, 2 H, NH_2)	10.30
1c	3.70 (s, 6 H, OCH_3); 6.65 (m, 1 H, H(Ar)); 6.85 (m, 2 H, H(Ar))	2.55 (dd, $J = 8, 16$)	2.8 (dd, 1 H, $J = 8, 16$)	4.1 (dd, 1 H, $J = 8$)	7.0 (s, 2 H, NH_2)	10.20
1d	3.65 (s, 3 H, OCH_3); 3.80 (s, 3 H, OCH_3); 6.45 (m, 1 H, H(Ar)); 6.80 (m, 1 H, H(Ar)); 6.95 (m, 1 H, H(Ar))	2.55 (dd, $J = 6, 16$)	2.95 (dd, 1 H, $J = 8, 16$)	4.35 (dd, 1 H, $J = 6.8$)	7.05 (s, 2 H, NH_2)	10.20
1e	6.85 (m, 1 H, H(Het)); 6.95 (m, 1 H, H(Het)); 7.35 (m, 1 H, H(Het))	2.6 (dd, $J = 7, 16$)	3.0 (dd, 1 H, $J = 7, 16$)	4.45 (dd, 1 H, $J = 7$)	7.05 (s, 2H, NH_2)	10.25
1f	5.05 (s, 2 H, OCH_2); 6.95 (m, 4 H, H(Ar)); 7.40 (m, 5 H, H(Ar))	2.45 (dd, $J = 7, 15$)	2.85 (dd, 1 H, $J = 7, 15$)	4.13 (dd, 1 H, $J = 7$)	7.0 (s, 2H, NH_2)	10.20
1g	0.80–1.80 (m, 11 H, C_6H_{11})	2.35 (m, CH)	2.65 (m, 2 H, CH_2)	2.65 (m, 2 H, CH_2)	6.95 (s, 2 H, NH_2)	10.00
1h*	7.15 (d, 2 H, H(Ar), $J = 8$); 7.35 (d, 2 H, H(Ar), $J = 8$)	2.5 (dd, $J = 7, 16$)	2.9 (dd, 1 H, $J = 7, 16$)	4.3 (dd, 1 H, $J = 7$)	7.05 (s, 2 H, NH_2)	10.25
1i	7.2 (d, 2 H, H(Ar), $J = 6$); 7.35 (d, 2 H, H(Ar), $J = 6$)	2.55 (dd, $J = 7, 16$)	2.9 (dd, 1 H, $J = 7, 16$)	4.3 (dd, 1 H, $J = 7$)	1.55 (s, 6 H, CH_2); 3.3 (s, 4 H, NCH_2)	10.45
1j	7.15 (d, 2 H, H(Ar), $J = 6$); 7.3 (d, 2 H, H(Ar), $J = 6$)	2.55 (dd, $J = 7, 17$)	2.9 (dd, 1H, $J = 7, 17$)	4.3 (t, $J = 7$)	3.25 (m, 4 H, NCH_2); 3.65 (m, 4 H, OCH_2)	10.40
1k	3.85 (s, 3 H, OMe); 6.95 (m, 3 H, H(Ar)); 7.25 (m, 1 H, H(Ar))	2.55 (dd, $J = 4, 16$)	2.95 (dd, 1 H, $J = 8, 16$)	4.45 (dd, 1 H, $J = 4.8$)	1.55 (s, 6 H, CH_2)	10.30
1l	6.45 (m, 1 H, H(5)(Ar)); 6.55 (m, 1 H, H(3)(Ar)); 6.8 (m, 1 H, H(6)(Ar))	2.5 (dd, $J = 5, 17$)	2.9 (dd, 1 H, $J = 7, 17$)	4.35 (dd, 1 H, $J = 5, 7$)	3.25 (m, 4 H, NCH_2); 3.65 (m, 4 H, OCH_2)	10.25
1m	6.4 (m, 1 H, H(5)(Ar)); 6.55 (m, 1 H, H(3)(Ar)); 6.8 (m, 1 H, H(6)(Ar))	2.5 (m, CH)	2.9 (m, 1 H, CH)	4.35 (m, 1 H, CH)	1.55 (s, 6 H, CH_2); 3.3 (s, 4 H, NCH_2)	10.20
1n	7.3 (m, 1 H, C_6H_3); 7.45 (m, 2 H, H(Ar))	2.75 (dd, $J = 7, 17$)	3.0 (dd, 1 H, $J = 10, 17$)	5.2 (dd, 1 H, $J = 7, 10$)	3.2 (m, 4 H, NCH_2); 3.65 (m, 4 H, CH_2OCH_2)	10.45

* The ^{13}C NMR spectrum of compound **1h**: 35.51 (C(7)), 93.45 (C(7a)), 128.58, 128.62 (C(2'), C(3')), C(5'), C(6')), 131.35 (C(4)), 142.75 (C(1')), 143.61 (C(4a)), 167.64 (C(2)), 168.64 (C(5)).

Thus, three-component condensation of 2-amino-4-iminothiazolidine hydrochlorides with aromatic or aliphatic aldehydes and Meldrum's acid provides a convenient route to substituted dihydrothiazolo[4,5-*b*]pyridinones.

Experimental

^1H and ^{13}C NMR spectra were recorded on Bruker Avance II 300 and Bruker DRX-500 instruments in DMSO- d_6 . Mass spectra were recorded on a FINNIGAN MAT INCOS 50

instrument (direct inlet probe, EI, 70 eV). Melting points were measured on a Boetius hot stage and are given uncorrected. The course of the reactions was monitored and the purity of the products was checked by TLC on Silica gel 60 F254 plates (Merck) with ethyl acetate–hexane as an eluent.

Compounds **2a–c** were prepared as described earlier.¹²

Synthesis of 6,7-dihydro-4-thiazolo[4,5-*b*]pyridin-5-ones (1a–n). Ethanol (6–10 mL) was added to a mixture of 2-amino-4-iminothiazolidine hydrochloride **2** (3 mmol), Meldrum's acid (0.5 g, 3.2 mmol), AcONa (0.25 g, 3 mmol), an appropriate aldehyde (3 mmol), and *N*-methylmorpholine (3 drops). The reaction mixture was refluxed for 4 h. The precipitate that formed was filtered off, washed with ethanol (2×5 mL), water (5 mL), and again ethanol (5 mL), and dried to a constant weight.

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