Three-component condensation of 4-aminoisothiazole derivatives with aldehydes and Meldrum´s acid. Synthesis of 6,7-dihydro-4*H*-isothiazolo[4,5-*b*]pyridin-5-ones

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A convenient method was developed for the synthesis of previously unknown substituted 6,7-dihydro-4H-isothiazolo[4,5-b]pyridin-5-ones based on the three-component condensation of 4-aminoisothiazole hydrochlorides, Meldrum's acid, and aromatic aldehydes.

Key words: 4-aminoisothiazoles, three-component condensation, Meldrum's acid, decarboxylation, 6,7-dihydro-4H-isothiazolo[4,5-b]pyridin-5-ones.

Aminoisothiazole derivatives have bactericidal properties,¹ inhibit cyclin-dependent kinases (CDK) and glycogen synthase kinase 3 (GSK-3),² and are used for the synthesis of antibiotics.^{3,4} Hence, the synthesis of new fused heterocyclic systems containing the 4-aminoisothiazole moiety is an important problem.

Previously, we have developed a general approach to the synthesis of 4,7-dihydro-5*H*-thieno[2,3-*b*]pyridin-6ones **1a**,⁵ 6,7-dihydro-4*H*-thiazolo[4,5-*b*]pyridin-5-ones **1b**,^{6,7} 6,7-dihydro-4*H*-thieno[3,2-*b*]pyridin-5-ones **1c**,⁸ and 6,7-dihydro-4*H*-selenazolo[4,5-*b*]pyridin-5-ones **1d**⁹ based on the three-component condensation of labile heterocyclic amines **2** with aldehydes **3** and Meldrum's acid **4** (Scheme 1).

In this method, the generation of aminoheterocycles 2 directly in the reaction mixture plays a key role. The generation is performed by either the *in situ* decarboxylation of vicinal aminocarboxylic acids 5, which are formed by the alkaline hydrolysis of readily available esters, 5,6,8 or by the neutralization of stable hydrochlorides 6 with anhydrous sodium acetate. 7,9

In the present study, we extended the previously developed approach based on the three-component condensation of 4-aminoisothiazole derivatives 7, which are formed *in situ* from the corresponding hydrochlorides 8, with aromatic aldehydes 3 and Meldrum's acid 4 to the synthesis of 6,7-dihydro-4H-isothiazolo[4,5-b]pyridin-5-ones 9 (Scheme 2, Table 1).

Labile amines 7 can be generated *in situ* with the use of either hydrochlorides **8**, which are prepared by the acid hydrolysis of ethyl 4-aminoisothiazole-5-carboxylates **10** (see Ref. 10) followed by the decarboxylation, or potassium 4-aminoisothiazole-5-carboxylates **11**,¹¹ which are formed by the alkali treatment of esters **10** (Scheme 3).



Our studies showed that 4-aminoisothiazole hydrochlorides 8 are the reagents of choice for the synthesis of the target 6,7-dihydro-4H-isothiazolo[4,5-b]pyridin-5-ones 9.

Fused pyridinones **9** were synthesized in acetic acid in the presence of anhydrous sodium acetate, which served as the base for the generation of free 4-aminoisothiazole **7**. It should be noted that the reaction with the use of amino

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Com-	Substituents		M.p./°C	Yield (%)	Found (%)			Molecular formula
pound	R	Ar		(70)	Calculated			
					С	Η	Ν	
9a	4-Cl-C ₆ H ₄	4-Cl-C ₆ H ₄	267—269	45	<u>57.43</u> 57.61	$\frac{3.13}{3.22}$	<u>7.30</u> 7.46	$C_{18}H_{12}Cl_2N_2OS$
9b	4-Cl-C ₆ H ₄	$3-MeO-C_6H_4$	169—171	37	<u>61.33</u> 61.54	$\frac{4.21}{4.08}$	<u>7.38</u> 7.55	$C_{19}H_{15}ClN_2O_2S$
9c	4-Cl-C ₆ H ₄	2-F-C ₆ H ₄	186—188	29	<u>60.53</u> 60.25	<u>3.49</u> 3.37	<u>7.99</u> 7.81	C ₁₈ H ₁₂ ClFN ₂ OS
9d	4-Cl-C ₆ H ₄	Ph	222—224	34	<u>63.64</u> 63.43	<u>3.72</u> 3.84	$\frac{8.07}{8.22}$	C ₁₈ H ₁₃ ClN ₂ OS
9e	Ph	4-MeO-C ₆ H ₄	177—179	43	<u>67.61</u> 67.84	<u>4.92</u> 4.79	<u>8.15</u> 8.33	$C_{19}H_{16}N_2O_2S$
9f	Ph	$2,3-(MeO)_2C_6H_3$	164—166	41	<u>65.77</u> 65.56	<u>5.09</u> 4.95	<u>7.79</u> 7.64	$C_{20}H_{18}N_2O_3S$
9g	Ph 4-($NH_2C(O)CH_2O)-C_6H_4$	190—192	33	<u>63.57</u> 63.31	<u>4.65</u> 4.52	<u>10.93</u> 11.07	$C_{20}H_{17}N_3O_3S$
9h	Ph	2-F-C ₆ H ₄	144—146	30	<u>66.38</u> 66.65	<u>4.16</u> 4.04	<u>8.81</u> 8.64	$C_{18}H_{13}FN_2OS$
9i	СООН	Ph	226-228	43	<u>57.16</u> 56.92	<u>3.80</u> 3.67	<u>10.04</u> 10.21	$C_{13}H_{10}N_2O_3S$
9j	СООН	4-Cl-C ₆ H ₄	156—159	46	<u>50.79</u> 50.57	<u>3.05</u> 2.94	<u>9.25</u> 9.07	$C_{13}H_9ClN_2O_3S$
9k	СООН	$4-F-C_6H_4$	179—181	42	<u>53.69</u> 53.42	<u>3.00</u> 3.10	<u>9.74</u> 9.58	$C_{13}H_9FN_2O_3S$
91	СООН	$3-Cl-C_6H_4$	123—124	51	<u>50.77</u> 50.57	<u>3.82</u> 2.94	<u>9.23</u> 9.07	$C_{13}H_9ClN_2O_3S$
9m	СООН	$3-MeO-C_6H_4$	118-120	35	<u>55.51</u> 55.26	<u>4.11</u> 3.97	<u>9.40</u> 9.21	$C_{14}H_{12}N_2O_4S$

Table 1. Yields, melting points, and elemental analysis data for compounds 9a-m

Scheme 2



7: R = 4-Cl-C₆H₄ (**a**); Ph (**b**); CO₂H (**c**)

acid **8c** was performed in the presence of a twofold excess of the starting compound **8c** and sodium acetate because of instability of amino acid **8c**. The proposed scheme of the synthesis of 6,7-dihydro-4H-isothiazolo[4,5-b]pyridin-5-ones **9** involves the Michael addition of 4-aminoisothiazole **7** to arylmethylidene derivative **12**, which is

Scheme 3



8–10: R = 4-Cl-C₆H₄ (a), Ph (b), CO₂H (8c), CO₂Et (10c), CO₂K (11c)

formed *in situ* from aldehydes and Meldrum's acid, followed by the intramolecular cyclization accompanied by the elimination of CO_2 and acetone molecules (Scheme 4).

The newly synthesized compounds are crystalline solids, whose structures were confirmed by elemental analy-

Scheme 4



sis and ¹H NMR spectroscopy (see Tables 1 and 2). The ¹H NMR spectra of reaction products **9** show characteristic signals for the methine protons at $\delta 4.67-5.00$ and for the nonequivalent protons of the methylene unit at $\delta 2.81-3.02$, which agree well with the data published in the literature for related compounds.^{5–9}

To sum up, we developed a new general method for the synthesis of the previously unknown substituted 6,7-di-hydro-4H-isothiazolo[4,5-b]pyridin-5-ones based on the

three-component condensation of 4-aminoisothiazole hydrochlorides, Meldrum's acid, and aromatic aldehydes.

Experimental

The ¹H NMR spectra were recorded on a Bruker Avance II 300 instrument (300 MHz) in DMSO-d₆. The melting points were measured on a Boetius hot-stage apparatus and are uncorrected. The course of the reactions was monitored and the purity

Table 2. ¹H NMR spectra (DMSO-d₆, δ , *J*/Hz) of compounds **9a**-m

Com- poundR $H-C-H$ $H-C-H$ CHArN9a7.56 (d, 2 H, C ₆ H ₄ , J=8); 7.74 (d, 2 H, C ₆ H ₄ , J=8); 7.56 (d, 2 H, C ₆ H ₄ , J=8); 7.56 (d, 2 H, C ₆ H ₄ , J=8); 7.56 (d, 2 H, C ₆ H ₄ , J=8); 7.56 (d, 2 H, C ₆ H ₄ , J=8); 7.74 (d, 2 H, C ₆ H ₄ , J=8); 7.81 (J=0,7) 7.81 (J=16,6) 7.74 (J=16,6) 7.74 (J=16,6) 7.74 (J=16,7) 7.78 (M, 2 H, Ph) 7.74 (J=16,6) 7.74 (J=16,6) 7.74 (J=16,6) 7.74 (J=16,7) 7.78 (H, 2 H, C ₆ H ₄ , J=9); 7.76 (H, 2 H, C ₆ H ₄ , J=9); 7.76 (H, 2 H, C ₆ H ₄ , J=9); 7.76 (H, 2 H, C ₆ H ₄ , J=9); 7.76 (H, 2 H, C ₆ H ₄ , J=9); 7.76 (H, 2 H, C ₆ H ₄ , J=9); 7.76 (H, 2 H, C ₆ H ₄ , J=9); 7.76 (H, 2 H, C ₆ H ₄ , J=9); 7.76 (H, 2 H, C ₆ H ₄ , J=9); 7.76 (H, 2 H, C ₆ H ₄ , J=9); 7.76 (H, 2 H, C ₆ H ₄ , J=9);	H 1 H)
$\begin{array}{c ccccccccccccccccccccccccccccccccccc$, I H)
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	
$\begin{array}{cccccccccccccccccccccccccccccccccccc$.23
9b7.56 (d, 2 H, C_6H_4, J = 8); 7.74 (d, 2 H, C_6H_4, J = 8); 	
$\begin{array}{cccccccccccccccccccccccccccccccccccc$.19
9c7.56 (d, 2 H, C_6H_4, J = 8); 7.74 (d, 2 H, C_6H_4, J = 8) 7.56 (d, 2 H, C_6H_4, J = 8) 7.56 (d, 2 H, C_6H_4, J = 8); 7.74 (d, 2 H, C_6H_4, J = 8) 7.74 (d, 2 H, C_6H_4, J = 9); 7.68 - 7.78 (m, 2 H, Ph) 7.74 (J = 16, 6)3.72 (J = 16, 9) (J = 16, 9) (J = 6, 9) 7.28 (d, 2 H, C_6H_4, J = 9); 3.75 (s, 3 H, MeO)3.74 (s, 3 H, MeO) 7.1-7.45 (m, 4 H, C_6H_3);100 100 100 100 100 100 100 100 101 1019c7.41-7.58 (m, 3 H, Ph); 7.41-7.58 (m, 3 H, Ph); 2.812.812.934.926.70-6.80 (m, 1 H, C_6H_3);100 100 100	
9c7.56 (d, 2 H, C_6H_4, J = 8);2.833.025.007.1-7.45 (m, 4 H, C_6H_4)107.74 (d, 2 H, C_6H_4, J = 8)(J = 16, 8)(J = 16, 7)(J = 7, 8)9d7.56 (d, 2 H, C_6H_4, J = 8);2.902.904.757.23-7.45 (m, 4 H, C_6H_5)107.74 (d, 2 H, C_6H_4, J = 8)(J = 0, 7)(J = 0, 7)(J = 7, 7)79e7.43-7.56 (m, 3 H, Ph);2.812.914.676.94 (d, 2 H, C_6H_4, J = 9);107.68-7.78 (m, 2 H, Ph)(J = 16, 6)(J = 16, 9)(J = 6, 9)7.28 (d, 2 H, C_6H_4, J = 9);109f7.41-7.58 (m, 3 H, Ph);2.812.934.926.70-6.80 (m, 1 H, C_6H_3);10	
$\begin{array}{cccccccccccccccccccccccccccccccccccc$.25
9d $7.56 (d, 2 H, C_6H_4, J=8);$ 2.90 2.90 4.75 $7.23-7.45 (m, 4 H, C_6H_5)$ 10 $7.74 (d, 2 H, C_6H_4, J=8)$ $(J=0, 7)$ $(J=0, 7)$ $(J=7, 7)$ 9e $7.43-7.56 (m, 3 H, Ph);$ 2.81 2.91 4.67 $6.94 (d, 2 H, C_6H_4, J=9);$ 10 $7.68-7.78 (m, 2 H, Ph)$ $(J=16, 6)$ $(J=16, 9)$ $(J=6, 9)$ $7.28 (d, 2 H, C_6H_4, J=9);$ 10 $3.75 (s, 3 H, MeO)$ 9f $7.41-7.58 (m, 3 H, Ph);$ 2.81 2.93 4.92 $6.70-6.80 (m, 1 H, C_6H_3);$ 10	
$\begin{array}{cccccccccccccccccccccccccccccccccccc$.20
9e7.43-7.56 (m, 3 H, Ph); 7.68-7.78 (m, 2 H, Ph)2.81 $(J = 16, 6)$ 2.91 $(J = 16, 9)$ 4.67 $(J = 6, 9)$ 6.94 (d, 2 H, C ₆ H ₄ , J = 9); 7.28 (d, 2 H, C ₆ H ₄ , J = 9); 3.75 (s, 3 H, MeO)10 9f9f7.41-7.58 (m, 3 H, Ph); 2.81 2.81 2.93 2.93 4.92 4.67 $6.70-6.80 (m, 1 H, C6H3);6.70-6.80 (m, 1 H, C6H3);1010$	
7.68-7.78 (m, 2 H, Ph) $(J = 16, 6)$ $(J = 16, 9)$ $(J = 6, 9)$ 7.28 (d, 2 H, C ₆ H ₄ , J = 9); 3.75 (s, 3 H, MeO)9f7.41-7.58 (m, 3 H, Ph);2.812.934.926.70-6.80 (m, 1 H, C ₆ H ₃);10).11
9f 7.41-7.58 (m, 3 H, Ph); 2.81 2.93 4.92 3.75 (s, 3 H, MeO) 6.70-6.80 (m, 1 H, C ₆ H ₃); 10	
9f 7.41–7.58 (m, 3 H, Ph); 2.81 2.93 4.92 $6.70-6.80$ (m, 1 H, C ₆ H ₃); 10	
).11
7.65–7.79 (m, 2 H, Ph) $(J = 16, 8)$ $(J = 16, 7)$ $(J = 7, 8)$ 6.98–7.11 (m, 2 H, C ₆ H ₃);	
3.81 (s, 3 H, MeO);	
3.82 (s, 3 H, MeO)	
9g 7.45–7.60 (m, 3 H, Ph); 2.86 2.93 4.72 $6.85-7.02$ (m, 1 H, C ₆ H ₄); 10	.13
7.68–7.81 (m, 2 H, Ph) $(J = 16, 8)$ $(J = 16, 7)$ $(J = 7, 8)$ 7.26–7.44 (m, 3 H, C ₆ H ₄);	
6.85 - 7.02 (m, 2 H, NH ₂);	
4.41 (s, 2 H, CH ₂)	
9h 7.45–7.57 (m, 3 H, Ph); 2.84 3.02 5.00 $7.15-7.44$ (m, 4 H, C_6H_4) 10	.19
7.67–7.81(m, 2 H, Ph) $(J = 16, 7)$ $(J = 16, 7)$ $(J = 7, 7)$	
9i 13.20–14.25 (br.s, 1 H) 2.86 2.98 4.81 7.22–7.41 (m, 5 H, Ph)	.17
(J = 16, 8) $(J = 16, 7)$ $(J = 7, 8)$	
9j 12.40–13.01 (br.s, 1 H) 2.86 2.96 4.83 $7.34 (d, 2 H, C_6H_4, J=8);$ 9	.17
(J = 16, 8) $(J = 16, 7)$ $(J = 7, 8)$ 7.44 (d, 2 H, C ₆ H ₄ , J = 8)	
9k 13.20–14.68 (br.s, 1 H) 2.86 2.95 4.82 $7.14-7.27$ (m, 2 H, C ₆ H ₄); 9	.16
(J = 16, 8) $(J = 16, 7)$ $(J = 7, 8)$ $7.31-7.45$ (m, 2 H, C ₆ H ₄)	
91 13.20–14.68 (br.s, 1 H) 2.89 2.99 4.84 $7.24-7.49$ (m, 4 H, C ₆ H ₄) 9	.19
(J = 16, 8) $(J = 16, 7)$ $(J = 7, 8)$	
9m 13.20–14.68 (br.s, 1 H) 2.91 2.91 4.76 6.80–6.97 (m, 1 H, C ₆ H ₄); 9	.15
(J = 0, 8) $(J = 0, 8)$ $(J = 8, 8)$ 7.23-7.35 (m, 3 H, C ₆ H ₄);	
3.74 (s, 3 H, MeO)	

of the reaction products was checked by TLC on Merck Silica gel 60 F254 plates using an ethyl acetate—hexane mixture as the eluent.

Esters 10 and aminoisothiazole hydrochlorides 8a-c were synthesized according to methods described in the literature.¹⁰

3,7-Diaryl-6,7-dihydro-4*H***-isothiazolo[4,5-***b***]pyridin-5-ones 9a—h (general procedure). A mixture of 4-aminoisothiazole hydrochloride 8a,b (2 mmol), anhydrous sodium acetate (0.16 g, 2 mmol), Meldrum's acid (0.32 g, 2.3 mmol), and the corresponding aldehyde (2.15 mmol) in acetic acid (7 mL) was refluxed for 2 h and concentrated** *in vacuo***. The residue was recrystallized from aqueous ethanol, filtered off, and washed on a filter with aqueous ethanol and water.**

7-Aryl-5-oxo-6,7-dihydro-4*H*-isothiazolo[4,5-*b*]pyridine-3carboxylic acids 9i—m (general procedure). A mixture of hydrochloride 8c (0.72 g, 4 mmol), anhydrous sodium acetate (0.33 g, 4 mmol), Meldrum's acid (0.32 g, 2.2 mmol), and the corresponding aldehyde (2 mmol) in acetic acid (7 mL) was refluxed for 2 h and concentrated *in vacuo*. The residue was dissolved in aqueous ethanol, and then concentrated hydrochloric acid (0.5 mL) was added to the solution. The precipitate that formed was filtered off and dissolved in a 0.6 *M* NaOH solution (10 mL). The alkaline solution was filtered from insoluble impurities and neutralized with concentrated hydrochloric acid. The precipitate that formed was filtered off and washed on a filter with water.

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