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THIAZOLE ANALOGS OF CHALCONES, CAPABLE OF FUNCTIONALIZATION AT THE HETEROCYCLIC NUCLEUS

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The synthesis of new amino and alkoxy derivatives of thiazole-5-carbaldehyde, on the basis of which α,β-unsaturated ketones of the thiazole series were synthesized, are described in this paper. The possibility of obtaining chalcones and variation of substitution reactions in the thiazole ring has been shown.

Keywords: 2,4-dichoro-5-formylthiazole, chalcone, substitution of a chlorine atom, crotonic condensation.

At the time of its discovery in 1896, chalcone (1,3-diphenylpropen-1-one) [1] interest in the chemistry of its substituted and heterocyclic analogs did not decrease. A retrospective review in Dhar's monograph [2] showed that most attention was concentrated on investigation of the reactivity of the propenone fragment of chalcone. In the reviews [3, 4] this was illustrated in examples of the cyclocondensations with 1,2-, 1,3-, and 1,4-dinucleophiles. At the same time reactions with the participation of the aromatic or heterocyclic nuclei were less studied.

In the present work we have studied the problem of synthesis of heterocyclic analogs of chalcone with substituents in the heteroaromatic nucleus capable of further transformations not involving the propenone unit. It is known [2, 3] that the most useful method for the synthesis of chalcones is the crotonic condensation with compounds containing formyl and acetyl groups.

Starting with this problem we turned our attention to papers [5, 6], in which is proposed an original and accessible method for the synthesis of 2,4-dichloro-5-formylthiazole **1**. Compound **1** contains at least three reactive centers: two chorine atoms and a formyl group, which is suggested by a series of reactions occurring either at the aldehyde group (reduction, formation of oximes and acetals) [7-9], or with participation of the chlorine atoms (substitution reactions with amines and thiols, dehalogenation) [9]. On the other hand, the chemistry of thiazole arouses interest because among its derivatives there are a large number of compounds which possess physiological activity (among natural compounds, for example, the triazole ring is the active center of thiamine, vitamin B_1).

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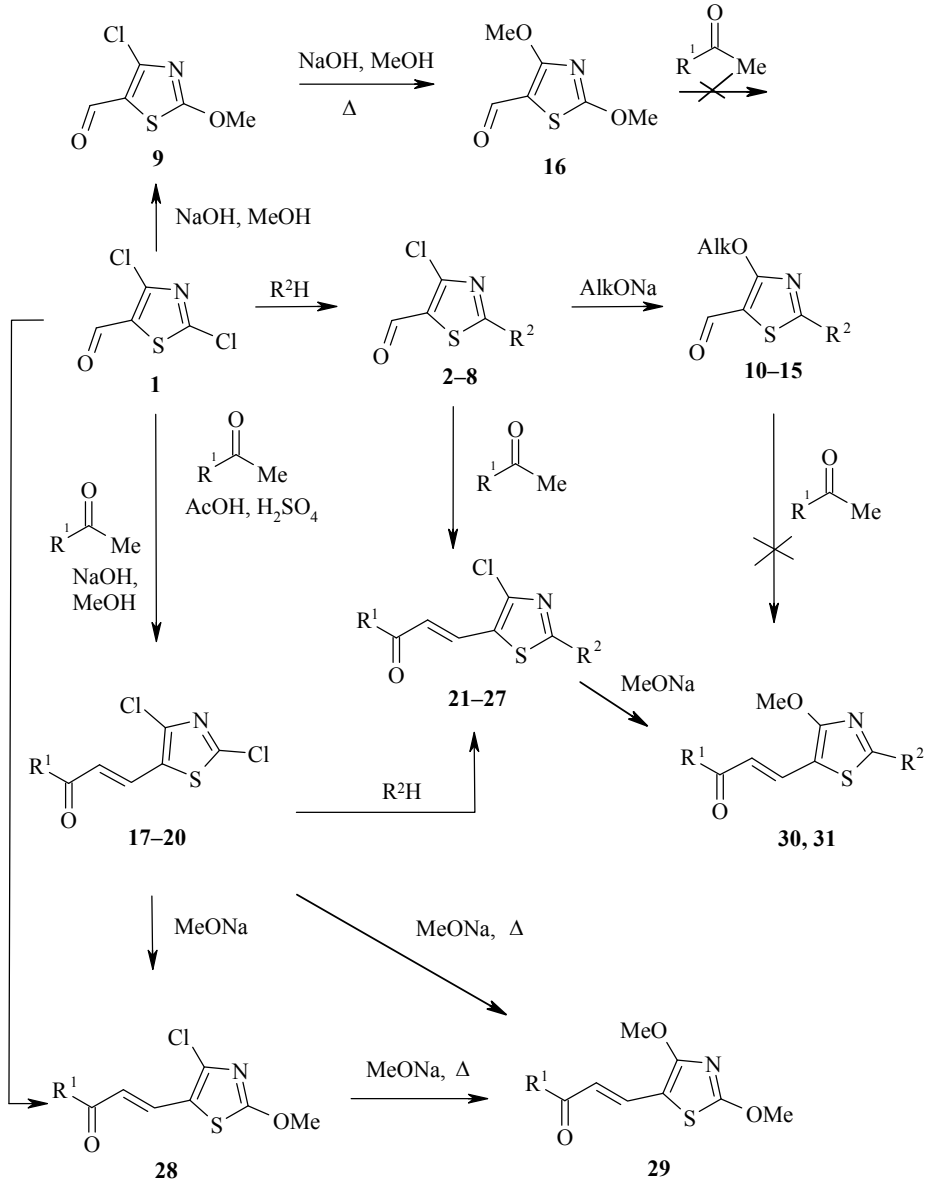
We reproduced the synthesis of aldehyde **1**, starting from 1,3-thiazolidine-2,4-dione, and carried out a number of its chemical transformations with participation of the chlorine atoms. To begin with it should be noted that there is a difference in chemical reactivity between the chlorine atoms. The chlorine atom in the *meso* position is considerably more prone to nucleophilic substitution; even at room temperature in CCl_4 solution it is substituted by secondary amino groups in high yield: Dimethyl- and diethylamino-, piperidino-, morpholino- and piperazinyl-, to form compounds **2- 6.**



2 $R^2 = NMe_2$; **3** $R^2 = NEt_2$; **4** R^2 = piperidino; **5** R^2 = morpholino; **6** R^2 = 4-(1-formylpiperazinyl); **7** R^2 = OPh; **8** R^2 = SPh; **10** $R^2 = NMe_2$, Alk = Me; **11** $R^2 = NMe_2$, Alk = Et; **12** R^2 = piperidino, Alk = Me; **13** R^2 = piperidino, Alk=Et; **14** R^2 = morpholino, Alk = Me; **15** R^2 = morpholino, Alk = Et; **17** R^1 = Ph; **18** $R^1 = 4\text{-}ClC_6H_4$; **19** $R^1 = 4\text{-}BrC_6H_4$; **20** $R^1 = 4\text{-}MeOC_6H_4$; **21** R^1 = Ph, $R^2 = NMe_2$; **22** R^1 =Ph, $R^2 = NEt_2$; **23** R^1 = Ph, R^2 = piperidino; **24** $R^1 = 4\text{-}ClC_6H_4$, R^2 = piperidino; **25** R^1=Ph, R^2= morpholino; **26** $R^1 = 4\text{-}ClC_6H_4$, R^2= morpholino; **27** $R^1 = 4\text{-}MeOC_6H_4$, R^2 = morpholino; **28** R^1 = Ph; **29** R^1 = Ph; **30** R^1 = Ph, R^2= piperidino; **31** R^1 = Ph, R^2= morpholino

We varied the conditions for carrying out the syntheses: the best results were obtained with using a two-fold excess of the amine (the second equivalent of the amine was bound to the HCl) or by using potassium carbonate as a catalyst [9]. It should be noted that substitution of the chlorine at position 4 was not observed, even prolonged maintenance at room temperature of a reaction mixture containing a 10-fold excess of the secondary amine, which indicates its low nucleophilicity.

The chlorine atom in position 2 is also readily substituted by phenoxy and phenylsulfanyl groups (to form compounds **7** and **8**), in this case only potassium carbonate permits the production of the required products in excellent yields (~ 80%). In addition, in the ^{1}H NMR spectrum of unpurified product **8** additional signals of aromatic protons and the proton of an aldehyde group were obserwed which, in our view, is explained by partial substitution of the chlorine atom in position 4 by a phenylsulfanyl group. This agrees with the mass spectrum of the unpurified product in which, along with signal of the molecular ion peak of compound **8**, a peak of the impurity with *m/z* = 329 was observed, which disappeared on recrystallization. Phenol did not undergo this side reaction which is probably a result of its lower nucleophilicity. As expected, introduction of an alkoxy group in position 2 of compound **1** occurs considerably more easily. 4-Chloro-2-methoxy-1,3-thiazole-5-carbaldehyde (**9**) was formed in the presence of 1 equivalent of sodium hydroxide in methanol at room temperature. Substitution of the chlorine atom at position 4 proceeds with a twofold excess of alkali on mild (~50°C) heating to give the dimethoxy-substituted product **16**.

It should be noted the difference in mobility of the chlorine atoms in positions 2 and 4 of the thiazole ring even appears in that the 2,4-dichloro derivative **1** is a strong lachrymator, while this property is lost in 2-R-substituted 4-chloro-5-formylthiazole.

TABLE 1. Physicochemical Characteristics of Aldehydes of the Thiazole Series

Compound	Empirical formula	Found, % / Calculated, %		mp, °C	Yield, %
		N	S		
1	C_4HCl_2NOS	7.67 / 7.69	17.63 / 17.61	40	50
2	$C_6H_7ClN_2OS$	14.71 / 14.69	16.84 / 16.82	91	85
3	$C_8H_{11}ClN_2OS$	12.83 / 12.81	14.69 / 14.66	112	85
4	$C_9H_{11}ClN_2OS$	12.17 / 12.14	13.93 / 13.90	96	90
5	$C_8H_9ClN_2O_2S$	12.07 / 12.04	13.79 / 13.78	195	95
6	$C_9H_{10}ClN_3O_2S$	16.19 / 16.18	12.39 / 12.35	165	95
7	$C_{10}H_6ClNO_2S$	5.87 / 5.84	13.41 / 13.38	50	70
8	$C_{10}H_6ClNOS_2$	5.52 / 5.48	25.10 / 25.07	78	75
9	$C_5H_4ClNO_2S$	7.72 / 7.69	18.09 / 18.05	35	75
10	$C_7H_{10}N_2O_2S$	15.08 / 15.04	17.24 / 17.22	112	85
11	$C_8H_{12}N_2O_2S$	14.03 / 13.99	16.03 / 16.01	131	80
12	$C_{10}H_{14}N_2O_2S$	12.42 / 12.38	14.20 / 14.17	74	85
13	$C_{11}H_{16}N_2O_2S$	11.69 / 11.66	13.37 / 13.34	134	80
14	$C_9H_{12}N_2O_3S$	12.29 / 12.27	14.08 / 14.05	220	85
15	$C_{10}H_{14}N_2O_3S$	11.59 / 11.56	13.25 / 13.23	205	80
16	$C_6H_7NO_3S$	8.11 / 8.09	18.54 / 18.51	40	80

It should also be noted that in the case of aldehydes **2**, **4**, and **5**, which contain a secondary amino group in position 2, substitution of the remaining chlorine in position 4 is effected by the sodium alkoxide in the corresponding alcohol at room temperature. The methoxy- and ethoxy-substituted thiazolecarbaldehydes **10**-**15** were obtained in this way. In contrast, all attempts at hydrolysis in the presence of aqueous solutions of alkali resulted in resinification.

The composition and structures of the first synthesized aldehydes were confirmed by elemental and spectroscopic analyses (Tables 1 and 2).

Formylthiazoles we obtained were subjected to the Claisen-Schmidt reaction with acetophenone with the objective of obtaining the corresponding α,β-unsaturated ketones. It appeared that a direct reaction of 2,4-dichlorothiazole-5-carbaldehyde **1** with acetophenone in methanol in conditions of alkaline catalysis gave 3-(4-chloro-2-methoxy-1,3-thiazol-5-yl)-1-phenyl-2-propenone (**28**) in comparatively low yield (25%).

Taking into account the high mobility of the chlorine atoms in the 2,4-dichloro-5-formylthiazole we used acid catalysis for the condensation. The best results were obtained by using acetic and sulfuric acids, the optimum results were obtained with an equivalent amount of sulfuric acid relative to the aldehyde. As a result we obtained the corresponding 1-aryl-3-(2,4-dichloro-1,3-thiazol-5-yl)-2-propen-1-ones **17-20**. With the objective of increasing the rate of the reaction we used ultrasonic oscillation, which decreased the reaction time to 24 h.

In contrast 2-amino-substituted 4-chloro-1,3-thiazole-5-carbaldehydes **2-4** readily underwent condensation with aromatic ketones with alkaline catalysis to give the chalcones **21-23** in good yields (48-52%). 4-Chloro-2-morpholino-1,3-thiazole-5-carbaldehyde (**5**) was the exception. It did not give the desired products in these conditions with acetophenone. The thiazole-5-carbaldehydes **10-16**, with an alkoxy substituent at position 4, did not undergo analogous reactions. This is possibly explained by the electronic and steric effects of the alkoxy groups on the reactivity of the formyl groups.

TABLE 2. Spectroscopic Characteristics of Aldehydes of the Thiazole Series

Compound	IR spectrum, $\nu_{C=O}$, cm^{-1}	^1H NMR spectrum, δ, ppm (*J*, Hz)
1	1625	9.60 (1H, s, CHO)
2	1620	3.15 (6H, s, $N(CH_3)_2$); 9.65 (1H, s, CHO)
3	1628	1.27 (6H, t *J* = 7.0, $N(CH_2C\underline{H}_3)_2$); 3.56 (4H, q, *J* = 7.0, $N(C\underline{H}_2CH_3)_2$); 9.45 (1H, s, CHO)
4	1625	1.61 (6H, s, piperidine); 3.50 (4H, s, piperidine); 9.45 (1H, s, CHO)
5	1635	3.54-3.87 (4H, m, morpholine); 3.67-3.72 (4H, m, morpholine); 9.68 (1H, s, CHO)
6	1660, 1670	3.28-3.33 (2H, m, piperazine); 3.55-3.70 (6H, m, piperazine); 8.10 (1H, s, CHO); 9.65 (1H, s, CHO)
7	1663	7.35-7.55 (5H, m, H Ar); 9.85 (1H, s, CHO)
8	1665	7.60-7.85 (5H, m, H Ar); 9.78 (1H, s, CHO)
9	1610	4.07 (3H, s, OCH_3); 9.51 (1H, s, CHO)
10	1620	3.1 (6H, s, $N(CH_3)_2$); 3.99 (3H, s, OCH_3); 9.43 (1H, s, CHO)
11	1619	1.31 (3H, t, *J* = 7.0, $OCH_2C\underline{H}_3$); 3.1 (6H, s, $N(CH_3)_2$); 4.39 (2H, q, *J* = 7.0, $OC\underline{H}_2CH_3$); 9.45 (1H, s, CHO)
12	1615	1.59 (6H, s, piperidine); 3.53 (4H, s, piperidine); 3.97 (3H, s, OCH_3); 9.47 (1H, s, CHO)
13	1615	1.30 (3H, t, *J* = 7.0, $OCH_2C\underline{H}_3$); 1.57 (6H, s, piperidine); 3.55 (4H, s, piperidine); 4.40 (2H, q, *J* = 7.0, $OC\underline{H}_2CH_3$); 9.48 (1H, s, CHO)
14	1627	3.53-3.60 (4H, m, morpholine); 3.63-3.66 (4H, m, morpholine); 3.98 (3H, s, OCH_3); 9.5 (1H, s, CHO)
15	1632	1.3 (3H, t, *J* = 7.0, $OCH_2C\underline{H}_3$); 3.45-3.48 (4H, m, morpholine); 3.63-3.65 (4H, m, morpholine); 4.42 (2H, q, *J* = 7.0, $OC\underline{H}_2CH_3$); 9.5 (1H, s, CHO)
16	1617	3.95 (3H, s, OCH_3); 4.17 (3H, s, OCH_3); 9.51 (1H, s, CHO)

TABLE 3. Physicochemical Characteristics of Chalkones of the Thiazole Series

Compound	Empirical formula	Found, % / Calculated, %		mp, °C	Yield, %
		N	S		
17	$C_{12}H_7Cl_2NOS$	4.97 / 4.93	11.33 / 11.28	95	55
18	$C_{12}H_6Cl_3NOS$	4.45 / 4.40	10.11 / 10.06	105	50
19	$C_{12}H_6BrCl_2NOS$	3.94 / 3.86	8.90 / 8.83	124	40
20	$C_{13}H_9Cl_2NO_2S$	4.51 / 4.46	10.25 / 10.21	116	53
21	$C_{14}H_{13}ClN_2OS$	9.59 / 9.57	10.97 / 10.95	185	48
22	$C_{16}H_{17}ClN_2OS$	8.78 / 8.73	10.15 / 9.99	112	50 (80)*
23	$C_{17}H_{17}ClNO_2S$	8.47 / 8.42	9.69 / 9.63	181	52 (85)*
24	$C_{17}H_{16}Cl_2N_2OS$	7.69 / 7.63	8.77 / 8.73	155	90
25	$C_{16}H_{15}ClN_2O_2S$	8.49 / 8.37	9.70 / 9.58	190	87
26	$C_{16}H_{14}Cl_2N_2O_2S$	7.65 / 7.59	8.78 / 8.68	193	90
27	$C_{17}H_{17}ClN_2O_3S$	7.73 / 7.68	8.88 / 8.79	184	85
28	$C_{13}H_{10}ClNO_2S$	5.15 / 5.01	11.58 / 11.46	122	80
29	$C_{14}H_{13}NO_3S$	5.15 / 5.09	11.73 / 11.65	134	80
30	$C_{18}H_{20}N_2O_2S$	8.62 / 8.53	9.81 / 9.76	175	75
31	$C_{17}H_{18}N_2O_3S$	8.56 / 8.48	9.78 / 9.70	168	70

* From compound **17**

We attempted to solve this problem by substituting the chlorine atoms in the alredy created molecule 3-(2,4-dichloro-1,3-thiazol-5-yl)-1-phenyl-2-propen-1-one (**17**) under conditions previously used for 2,4-dichloro-1,3-thiazole-5-carbaldehyde (**1**). It was shown that the chlorine atom in position 2 was readily replaced by amino (including morpholino) and methoxy groups under the influence of the corresponding amines or sodium methoxide.

Analogously to the reactions of derivatives of thiazole-5-carbaldehydes, the chlorine atom at position 4 in the thiazole ring of chalcones **23** and **25** is capable of nucleophilic substitution by the methoxy group to give compounds **30** and **31**.

EXPERIMENTAL

IR spectra (KBr) were measured with a Specord IR-75 spectrophotometer and ^{1}H NMR spectra of DMSO-d_6 solutions with TMS as internal standard were measured with Varian VX-200 instrument (200 MHz). Monitoring of the course of reactions and purity of the compounds obtained was carried out by TLC on Silufol-254 plates, using the following eluents: 1:1 acetone–hexane (compounds **1-8**), 1:1 ethyl acetate–toluene (compounds **9-15**), 1:1 chloroform–hexane (compounds **16**, **28-31**), and pure chloroform (compounds **17-27**).

TABLE 4. Spectroscopic Characteristics of Chalcones of the Thiazole Series

Compound	IR spectrum, $\nu_{C=O}$, cm^{-1}	^1H NMR spectrum, δ, ppm (*J*, Hz)
17	1662	7.64 (1H, d, *J* = 15.4, HC=CH); 7.73 (1H, d, *J* = 15.4, HC=CH); 7.55-8.12 (5H, m, H Ar)
18	1665	7.63 (1H, d, *J* = 15.4, HC=CH); 7.71 (1H, d, *J* = 15.4, HC=CH); 7.61-8.13 (4H, m, H Ar)
19	1675	7.62 (1H, d, *J* = 15.4, HC=CH); 7.68 (1H, d, *J* = 15.4, HC=CH); 7.75-8.04 (4H, m, H Ar)
20	1658	3.86 (3H, s, OCH_3); 7.63 (1H, d, *J* = 15.4, HC=CH); 7.73 (1H, d, *J* = 15.4, HC=CH); 7.07-8.13 (4H, m, H Ar)
21	1642	3.10 (6H, s, $N(CH_3)_2$); 7.09 (1H, d, *J* = 14.7, HC=CH); 7.65 (1H, d, *J* = 14.7, HC=CH); 7.48-8.05 (5H, m, H Ar)
22	1638	1.18 (6H, t, *J* = 6.9, $N(CH_2C\underline{H}_3)_2$); 3.49 (4H, q, *J* = 6.9, $N(C\underline{H}_2CH_3)_2$); 7.04 (1H, d, *J* = 14.7, HC=CH); 7.72 (1H, d, *J* = 14.7, HC=CH); 7.49-8.03 (5H, m, H Ar)
23	1640	1.62 (6H, s, piperidine); 3.54 (4H, s, piperidine); 7.02 (1H, d, *J* = 14.7, HC=CH); 7.72 (1H, d, *J* = 14.7, HC=CH); 7.50-8.02 (5H, m, H Ar)
24	1639	1.61 (6H, s, piperidine); 3.53 (4H, s, piperidine); 7.03 (1H, d, *J* = 14.6, HC=CH); 7.71 (1H, d, *J* = 14.6, HC=CH); 7.56-8.05 (4H, m, H Ar)
25	1648	3.48-3.53 (4H, m, morpholine); 3.66-3.71 (4H, m, morpholine); 7.09 (1H, d, *J* = 14.6, HC=CH); 7.72 (1H, d, *J* = 14.6, HC=CH); 7.48-8.05 (5H, m, H Ar)
26	1650	3.52-3.57 (4H, m, morpholine); 3.70-3.75 (4H, m, morpholine); 7.08 (1H, d, *J* = 14.6, HC=CH); 7.72 (1H, d, *J* = 14.6, HC=CH); 7.54-8.06 (4H, m, H Ar)
27	1655	3.48-3.53 (4H, m, morpholine); 3.61-3.66 (4H, m, morpholine); 3.82 (3H, s, OCH_3); 7.12 (1H, d, *J* = 14.6, HC=CH); 7.68 (1H, d, *J* = 14.6, HC=CH); 7.01-8.05 (4H, m, H Ar)
28	1645	4.10 (3H, s, OCH_3); 7.41 (1H, d, *J* = 15.3, HC=CH); 7.68 (1H, d, *J* = 15.3, HC=CH); 7.50-8.10 (5H, m, H Ar)
29	1620	3.99 (3H, s, OCH_3); 4.12 (3H, s, OCH_3); 7.41 (1H, d, *J* = 15.1, HC=CH); 7.75 (1H, d, *J* = 15.1, HC=CH); 7.50-7.80 (5H, m, H Ar)
30	1635	1.61 (6H, s, piperidine); 3.54 (4H, s, piperidine); 3.97 (3H, s, OCH_3); 6.54 (1H, d, *J* = 14.7, HC=CH); 7.80 (1H, d, *J* = 14.7, HC=CH); 7.46-7.93 (5H, m, H Ar)
31	1627	3.51-3.55 (4H, m, morpholine); 3.67-3.72 (4H, m, morpholine); 3.98 (3H, s, OCH_3); 6.61 (1H, d, *J* = 14.6, HC=CH); 7.81 (1H, d, *J* = 14.6, HC=CH); 7.43-7.94 (5H, m, H Ar)

2,4-Dichloro-1,3-thiazole-5-carbaldehyde (1). DMF (24 g, 0.33 mol) was added dropwise to a suspension of 1,3-thiazolidine-2,4-dione (35.1 g, 0.3 mol) in phosphorus oxytrichloride (180 ml, 1.8 mol). The mixture was stirred for 1 h at room temperature, then for 1 h at 80-90°C, after which the mixture was raised to boiling point and heated for another 4 h. The reaction mixture was poured onto ice (1.5 kg), the aldehyde **1** was separated by steam distillation. It crystallized on cooling, yield 272.3 g (50%); mp 40°C.

4-Chloro-2-dimethylamino-1,3-thiazole-5-carbaldehyde (2). A solution of dimethylamine (9 g, 0.2 mol) in carbon tetrachloride (50 ml) was added dropwise with stirring and cooling to a solution of 2,3-dichloro-5-formyl-1,3-thiazole (18.2 g, 0.1 mol) in CCl_4 (100 ml) and kept at room temperature for 24 h. The solvent was removed under reduced pressure, the residue was diluted with water, and the precipitate of aldehyde **2** was filtered off to give a yield of 16.2 g (85%); mp 91°C.

4-Chloro-2-diethylamino-1,3-thiazole-5-carbaldehyde (3). A solution of diethylamine (14.6 g, 0.2 mol) in carbon tetrachloride (50 ml) was added dropwise with stirring and cooling to a solution of 2,3-dichloro-5-formyl-1,3-thiazole (18.2 g, 0.1 mol) in CCl_4 (100 ml). The mixture was stirred for a further 2 h and then kept overnight. The solvent was evaporated, the residue was diluted with water, and the precipitate of aldehyde **3** was filtered off to give a yield of 18.6 g (85%); mp 112°C.

2-Piperidino- (4), 2-Morpholino- (5) and **2-(Formylpiperazin-4-yl)-substituted (6) 4-Chloro-1,3-thiazole-5-carbaldehydes** were prepared analogously (Table 1).

4-Chloro-2-phenoxy-1,3-thiazol-5-carbaldehyde (7). Anhydrous potassium carbonate (13.8 g, 0.1 mol) was added to a solution of aldehyde **1** (9.1 g, 0.05 mol) in acetonitrile (200 ml), then at room temperature with stirring a solution of phenol (4.7 g, 0.05 mol) in acetonitrile (20 ml) was added. The mixture was stirred for 16 h, the inorganic precipitate was filtered off and the filtrate evaporated. The residue was recrystallized from hexane. Yield 8.4 g (70%); mp 50°C.

4-Chloro-2-phenylsulfanyl)- 1,3-thiazole-5-carbaldehyde (8) was prepared analogously (Table 1).

4-Chloro-2-methoxy-1,3-thiazole-5-carbaldehyde (9). NaOH (1 g) was added to a stirred solution of aldehyde **1** (5 g, 0.027 mol) in methanol (100 ml) at room temperature, stirring was continued for 8 h, after which the solvent was evaporated. The residue was dissolved in dichloromethane, washed with a small quantity of water, the organic layer was separated and dried over sodium sulfate. The solvent was evaporated and the residue – compound **9** as a brownish oily liquid – crystallized on standing to solid with mp 35°C.

4-Methoxy-2-morpholino-1,3-thiazole-5-carbaldehyde (14). A solution of MeONa (5.4 g, 0.1 mol) in methanol (50 ml) was added dropwise with stirring to a solution 4-chloro-2-morpholino-1,3-thiazole-5-carbaldehyde (23.25 g, 0.1 mol) in methanol (200 ml). The reaction mixture was kept for 10 h, the solvent was removed under reduced pressure, and the residue was washed with a small amount of water. The precipitated product was filtered off and recrystallized from heptane. Yield 19.4 g (85%); mp 74°C.

4-Methoxy-2-dimethylamino- and **4-Methoxy-2-piperidino-1,3-thiazole-5-carbaldehydes** (**10** and **12**, Table 1) and also (with ethanol and sodium ethoxide) the **4-ethoxy analogs 11, 13,** and **15** were made analogously.

2,4-Dimethoxy-1,3-thiazole-5-carbaldehyde (16). A. Sodium hydroxide (0.68 g, 0.0175 mol) was added at 50°C to a stirred solution of 4-chloro-2-methoxy-1,3-thiazole-5-carbaldehyde (3 g, 0.017 mol) in methanol (100 ml) and the reaction was continued for another 6 h. The solvent was evaporated, the residue was dissolved in dichloromethane and washed with a small amount of water. The organic layer was separated, dried over sodium sulfate, and the solvent evaporated at reduced pressure to give compound **16** as a deep-brown oily liquid which crystallized on standing to give a solid with mp 40°C. Yield 2.35 g (80%).

B. Sodium hydroxide (2.4 g, 0.06 ml) was added at 50°C with stirring to a solution of 2,4-dichloro-1,3-thiazol-5-carbaldehyde (5 g, 0.027 mol) in methanol (100 ml) and kept under these conditions for another 6 h. The solvent was evaporated, the residue was dissolved in dichloromethane and washed with a small amount of water. The organic layer was separated and dried over sodium sulfate, the dichloromethane was evaporated under reduced pressure to give compound **16** as dark-brown oily liquid, which crystallized on standing to a solid with mp 40°C. Yield 3.74 g (80%).

3-(2,4-Dichloro-1,3-thiazol-5-yl)-1-phenyl-2-propen-1-one (17). A. Conc. H_2SO_4 (0.3 ml) was added to a solution of aldehyde **1** (1 g, 0.0054 mol) and acetophenone (0.66 g, 0.0054 mol) in acetic acid (20 ml) and kept at room temperature for 3 d. The precipitate was filtered off and recrystallized from acetic acid. Yield 0.84 g (55%); mp 95°C.

Chalcones 18-20 were made analogously (Table 3).

3-(4-Chloro-2-dimethylamino-1,3-thiazol-5-yl)-1-phenyl-2-propen-1-one (21). B 3-5 Drops of (20%) aqueous sodium hydroxide solution were added to a solution of aldehyde **2** (1 g, 0.0052 mol) and acetophenone (0.63 g, 0.0052 mol) in ethanol (10 ml) and the solution was kept overnight. The precipitate which formed was filtered off, washed with 5% aqueous acetic acid, and recrystallized from ethanol to give compound **21** (0.73 g, 48%); mp 185°C.

Chalcones 22 and 23 were made analogously (Table 3).

3-(4-Chloro-2-morpholino-1,3-thiazol-5-yl)-1-(4-chlorophenyl)-2-propen-1-one (26). C. Morpholine (2.73 g, 0.0314 mol) in acetonitrile (10 ml) was added dropwise with stirring to a solution of

3-(2,4-dichloro-1,3-thazol-5-yl)-1-(4-chlorophenyl)-2-propen-1-one (**18**) (5 g, 0.0157 mol) in acetonitrile (50 ml). The mixture was stirred for 3 h and kept overnight. The solvent was evaporated , the residue washed with water, the precipitate filtered off and recrystallized from ethanol. Yield 4.92 g (85%); mp 182°C.

Chalcones 22-25 and **27** were obtained analogously (Tables 3 and 4).

3-(4-Chloro-2-methoxy-1,3-thaizol-5-yl)-1-phenyl-2-propen-1-one (28). D. A solution of sodium methoxide (0.19 g, 0.0035 mol) in methanol (10 ml) was added to a solution of chalcone **17** (1 g, 0.0035 mol) in methanol (20 ml) at room temperature with stirring and kept for 4 h. The solvent was evaporated and the residue was recrystallized from ethanol. Yield 0.49 g (50%); mp 122°C.

3-(2,4-Dimethoxy-1,3-thiazol-5-yl)-1-phenyl-2-propen-1-one (29). E. A solution of sodium methoxide (0.4 g, 0.0074 mol) in methanol (10 ml) was added to a solution of chalcone **17** (1 g, 0.0035 mol) in methanol (20 mol) and the mixture was heated at 50°C for 5 h. The solvent was evaporated and the residue was recrystallized from ethanol. Yield 0.43 g (45%); mp 134°C.

Chalcones 30 and 31 were obtained analogously from chalcones **23** and **25** (Tables 3 and 4).

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