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Original article

Synthesis, characterization and herbicidal activity of new thiazoline derivatives

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ABSTRACT

A series of new thiazoline derivatives 2-alkyl(aryl) imino-4-amino-5-ethoxycarbonyl-3-phenyl-3*H*-thiazoline (**3**) and bis(2-imino-4-amino-5-ethoxycarbonyl-3-phenyl-3*H*-thiazoline alkylene (**4**) have been synthesized by reactions of intermediate 4-amino-5-ethoxycarbonyl-2-methylthio-3-phenyl-3*H*-thiazolinium sulphate (**2**) with alkylamines or arylamine in 64%–89% yields. The structures of **3** and **4** have been confirmed by ^{1}H NMR, EI-MS, IR spectroscopy and elemental analyses. Some compounds exhibited high or moderate herbicidal activities against the roots of rapeseed and barnyard grass at 100 mg/L.

1. Introduction

The chemistry of 2-thiazolines, including new methodologies for their preparation and recent applications in organic synthesis or in the biological field, has been recently reviewed [1,2]. The 2-iminothiazolidine ring system has gained interest for potential use as a potent inhibitor of octopaminergic agonists [3,4], an anthelmintic [5], an anti-inflammatory agent [6,7], a trehalase [8], and an antimalarial agent [9]. Synthesis of the 2-iminothiazoline ring system generally starts from 1,3-bis-thiocarbanilides and phenacyl bromide or the analogous reaction with α-chloroaliphatic ketones [10,11]. However, few 2-iminothiazoline derivatives with bioactivity, in particular herbicidal activity, have been reported.

Recently, we focused our attention on the synthesis of *N*-heterocyclic compounds such as thienopyrimidinones, pyridopyrimidinones, and thiazolopyrimidinones to evaluate their biological activities [12,13]. In this article, a series of new thiazoline derivatives 2-alkyl(aryl)imino-4-amino-5-ethoxycarbonyl-3-phenyl-3*H*-thiazoline (**3**) and bis(2-imino-4-amino-5-ethoxycarbonyl-3-phenyl-3*H*-thiazoline alkylene (**4**) have been synthesized in order to investigate their herbicidal activities.

2. Experimental

Melting points were measured on uncorrrected WRS-1B digital apparatus. IR spectra were recorded on a Nicolet Avatar 360 FTIR spectrometer. MS was determined on a Finnigan Trace MS 2000 spectrometer. ^{1}H NMR spectra were recorded in $CDCl_3$ on a Varian Mercury 400 spectrometer and resonances are given in ppm relative to TMS. Elemental analyses were taken on a Vario EL III instrument. All of the solvents and materials were reagent grade and purified before use.

To a solution of **1** (1.40 g, 5 mmol) in CH_3CN (20 mL) was added dimethyl sulfate (0.95 g, 7.5 mmol) at room temperature. The reaction mixture was heated to 80 °C and stirred for 3 h, then filtered, distilled. The yellow solid was recrystallized from anhydrous C_2H_5OH to give an intermediate **2** (Scheme 1).

To a solution of **2** (3.25 g, 5 mmol) in anhydrous C_2H_5OH (30 mL) was added the *n*-propylamine (0.30 g, 5 mmol). After the reaction mixture was stirred for 10 min, distilled water (30 mL) was added to the reaction solution and stirred for an additional 30 min. The mixture was filtered, distilled, and the solid was recrystallized from anhydrous C_2H_5OH or CH_2Cl_2 to give **3a** (1.00 g, 65% yield). Compounds **3b**–**3i** and **4a**–**4c** were obtained by the reactions of other substituted amines with intermediate **2**.

3. Results and discussion

The intermediate 4-amino-5-ethoxycarbonyl-2-methylthio-3-phenyl-3*H*-thiazolinium sulphate (**2**) was prepared by the reaction of 4-amino-2,3-dihydro-3-phenyl-2-thioxothiazole-5-carboxylate

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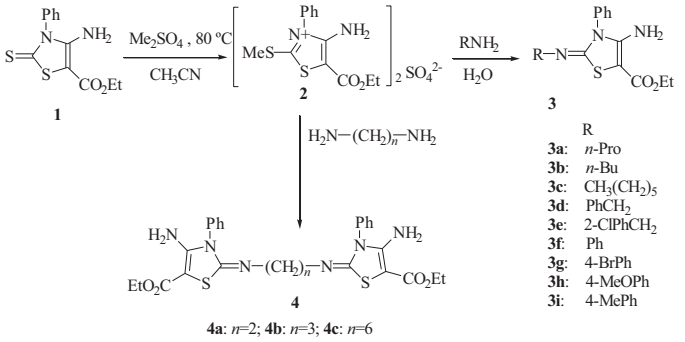

Scheme 1. Synthesis of **3** and **4**.

(**1**) and dimethyl sulfate in CH_3CN at 80 °C. The intermediate **2** was treated with alkylamines or arylamine at room temperature to give 2-alkyl(aryl)imino-4-amino-5-ethoxycarbonyl-3-phenyl-3*H*-thiazoline (**3**) in the presence of H_2O in moderate yields, while **2** was converted to bis(2-imino-4-amino-5-ethoxycarbonyl-3-phenyl-3*H*-thiazoline)alkylene (**4**) by treating with diaminoalkanes at room temperature.

All crude products of **3** and **4** were purified by recrystallization from CH_2Cl_2 or EtOH. The structures of **3** and **4** were confirmed by their spectroscopic data. For example, the IR spectrum of **3a** revealed absorption bands at 1662 cm^{-1} (C=O), 3363 cm^{-1} (N–H) and 2954 cm^{-1} (C–H). The ^1H NMR spectrum of **3a** showed the signal of N–H at δ 5.78, the signal of $-CO_2CH_2-$ at δ 4.23, the triplet of CH_3 ($-CO_2CH_2CH_3$) at δ 1.32, the triplet of CH_3 ($-CH_2CH_2CH_3$) at δ 0.87 and the triplet of CH_2 ($-CH_2CH_2CH_3$) at δ 3.07, The other signals appeared at δ 1.53–1.61 (m, 2H, $-CH_2CH_2CH_3$) and δ 7.27–7.56 (m, 5H, Ar–H). The MS spectrum of **3a** showed the molecule ion peak at *m*/*z* 305 with 54% abundance. The structure of **3a** was also established based on the elemental analysis data.

Selected characterization data. **3a**: Yellow crystal; yield: 65%; mp: 165.5–166.4 °C. ^1H NMR (400 MHz $CDCl_3$): δ 0.87 (t, 3H, J = 7.2 Hz, $CH_2CH_2CH_3$), 1.32 (t, 3H, J = 7.2 Hz, $CO_2CH_2CH_3$), 1.53–1.61 (m, 2H, $CH_2CH_2CH_3$), 3.07 (t, 2H, J = 7.2 Hz, $CH_2CH_2CH_3$), 4.23 (q, 2H, J = 7.2 Hz, $CO_2CH_2CH_3$), 5.78 (s, 2H, NH_2), 7.27–7.56 (m, 5H, Ph-H); EI-MS (70 eV, *m*/*z*) (relative intensity %): 305 (M^+, 54), 275 (52), 230 (23), 118 (100); IR (KBr, cm^{-1}): ν3363 (N–H), 2954 (C–H), 1662 (C=O), 1606, 1527, 1268; elemental anal. calcd. for $C_{15}H_{19}N_3O_2S$ (305.4): C, 58.99; H, 6.27; N, 13.76; S, 10.50; found: C, 58.32; H, 6.33; N, 13.53; S, 10.48. **3b**: Yellow crystal; yield: 63%; mp: 148.6–150.1 °C. ^1H NMR (400 MHz $CDCl_3$): δ 0.89 (t, 3H, J = 7.2 Hz, $CH_2CH_2CH_2CH_3$), 1.28–1.34(m, 5H, $CH_2CH_2CH_2CH_3$, $CO_2CH_2CH_3$), 1.50–1.54 (m, 2H, $CH_2CH_2CH_2CH_3$), 3.09 (t, 2H, J = 7.2 Hz, $CH_2CH_2CH_2CH_3$), 4.23 (q, 2H, J = 7.2 Hz, $CO_2CH_2CH_3$), 5.78 (s, 2H, NH_2), 7.27–7.56 (m, 5H, Ph–H); EI-MS (70 eV, *m*/*z*) (relative intensity %): 319 (M^+, 100), 237 (72), 133 (66); IR (KBr, cm^{-1}): ν3362 (N–H), 2980 (C–H), 1663 (C=O), 1607, 1529, 1268; elemental anal. calcd. for $C_{16}H_{21}N_3O_2S$ (319.4): C, 60.16; H, 6.63; N, 13.16; S, 10.04; found: C, 60.44; H, 6.55; N, 12.86; S, 10.69. **3i**: Yellow crystal; yield: 52%; mp: 156.7–158.2 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 1.26 (t, 3H, J = 7.2 Hz, $CO_2CH_2CH_3$), 2.30 (s, 3H, CH_3), 4.18 (q, 2H, J = 7.2 Hz, $CO_2CH_2CH_3$), 5.78 (s, 2H, NH_2), 6.85–7.61 (m, 9H, Ph–H); EI-MS (70 eV, *m*/*z*) (relative intensity %): 353 (M^+, 45), 119 (100), 77 (17); IR (KBr, cm^{-1}): ν3469, 3330 (N–H), 3051 (Ar–H), 2978 (C–H), 1662 (C=O), 1524, 1524, 1272; elemental anal. calcd. for $C_{19}H_{19}N_3O_2S$ (353.4): C, 64.57; H, 5.42; N, 11.89; S, 9.07; found: C, 64.91; H, 5.78; N, 11.94; S, 9.01. **4a**: Yellow crystal; yield: 73%; mp: 169.5–170.6 °C. ^1H NMR (400 MHz $CDCl_3$): δ 1.33 (t, 6H, J = 7.2 Hz, $2CO_2CH_2CH_3$), 3.28 (s, 4H, $2CH_2$), 4.24 (q, 4H, J = 7.2 Hz, $2CO_2CH_2CH_3$), 5.78 (s, 4H, $2NH_2$), 7.27–7.52 (m, 10H, Ph-H); EI-MS (70 eV, *m*/*z*) (relative intensity %): 553 (M^+, 61), 289 (50), 275 (100), 262 (56), 230 (80); IR (KBr, cm^{-1}): ν3341 (N–H), 3069 (Ar–H), 2972 (C–H), 1674 (C=O), 1579, 1544, 1269; elemental anal. calcd. for $C_{26}H_{28}N_6O_4S_2$ (552.7): C, 56.50; H, 5.11; N, 15.21; S, 11.60; found: C, 56.47; H, 5.19; N, 15.43; S, 11.28. **4b**: Yellow crystal; yield: 69%; mp: 184.2–186.1 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 1.33 (t, 6H, J = 7.2 Hz, $2CO_2CH_2CH_3$), 1.78 (t, 2H, J = 6.8 Hz, CH_2), 3.10 (t, 4H, J = 6.4 Hz, $2CH_2$), 4.24 (q, 4H, J = 7.2 Hz, $2CO_2CH_2$ CH_3), 5.78 (s, 4H, $2NH_2$), 7.35–7.57 (m, 10H, Ph–H); EI-MS (70 eV, *m*/*z*) (relative intensity %): 567 (M^+, 100), 290 (73), 160 (46); IR (KBr, cm^{-1}): ν3319 (N–H), 3053 (Ar–H), 2979 (C–H), 1661 (C=O), 1610, 1526, 1269, 1118; elemental anal. calcd. for $C_{27}H_{30}$ $N_6O_4S_2$ (566.7): C, 57.22; H, 5.34; N, 14.83; S, 11.32; found: C, 57.78; H, 5.62; N, 14.29; S, 11.27. **4c**: Yellow crystal; yield: 54%; mp: 185.4–187.1 °C. ^1H NMR (400 MHz $CDCl_3$): δ 1.27 (s, 4H, $2CH_2$), 1.33 (t, 6H, J = 7.2 Hz, $2CO_2CH_2CH_3$), 1.51 (d, 4H, J = 6.4 Hz, $2CH_2$), 3.07 (t, 4H, J = 7.2 Hz, $2CH_2$), 4.24 (q, 4H, J = 7.2 Hz, $2CO_2CH_2CH_3$), 5.78 (s, 4H, $2NH_2$), 7.32–7.56 (m, 10H, Ph-H); EI-MS (70 eV, *m*/*z*) (relative intensity %): 609 (M^+, 89), 289 (56), 277 (100), 77 (49); IR (KBr, cm^{-1}): ν3354 (N–H), 3049(Ar–H), 2927(C–H), 1662 (C=O), 1612, 1527, 1267, 1122; elemental anal. calcd. for $C_{30}H_{36}N_6O_4S_2$ (608.8): C, 59.19; H, 5.96; N, 13.80; S, 10.53; found: C, 59.57; H, 6.52; N, 13.79; S, 10.22.

The herbicidal activity of **3** and **4** against *Brassica napus* (rapeseed) and *Echinochloa crusgalli (L.)* Beav (barnyard grass) has been investigated at the dosage of 100 mg/L and 10 mg/L according to the reported method [14] and compared with distilled water, and 2,4-dichlorophenoxy acetic acid (2,4-D), a commercially available herbicide. Some compounds exhibited high or moderate herbicidal activities against the roots of rapeseed and barnyard grass at 100 mg/L (see Table 1). For example, **3d** showed higher

Table 1
Herbicidal activity of **3** and **4** (*in vitro* relative inhibition rate %).

Compd.	Barnyard grass				Rapeseed			
	Stalk		Root		Stalk		Root	
	A	B	A	B	A	B	A	B
3a	9.7	35.5	50.0	68.1	4.3	26.1	40.0	48.0
3b	19.4	22.6	25.0	34.4	0	39.1	0	29.3
3c	33.3	33.3	76.7	86.0	64.0	89.0	43.4	92.5
3d	40.7	44.4	74.4	83.7	20.0	92.0	47.2	98.1
3e	12.9	26.5	18.8	19.4	−13.0	34.8	−9.3	38.6
3f	31.6	43.3	69.8	86.0	52.0	64.0	37.7	71.7
3g	31.6	48.1	76.7	88.4	44.0	72.0	32.1	90.6
3h	42.2	61.9	74.4	90.7	66.0	92.0	64.0	94.3
3i	25.9	49.6	79.1	88.4	44.0	44.0	34.0	79.2
4a	15.4	34.6	37.9	58.6	52.0	52.0	39.7	76.9
4b	3.8	34.6	31.0	58.6	12.0	36.0	7.7	41.0
4c	19.2	38.5	34.5	69.0	12.0	32.0	21.8	50.0
2,4-D	33.3	43.5	90.0	97.5	87.5	91.2	88.8	98.0

A: the dosage of 10 mg/L; B: the dosage of 100 mg/L.

inhibition rate (98.1%/92.0%) against the root/stalk growth of rapeseed. But the herbicidal activity decreased obviously at the dosage of 10 mg/L.

4. Conclusion

In conclusion, we have developed a facile method for the preparation of new 2-alkyl(aryl)imino-4-amino-5-ethoxycarbonyl-3-phenyl-3*H*-thiazoline (**3**) and bis(2-imino-4-amino-5-ethoxycarbonyl-3-phenyl-3*H*-thiazoline alkylene (**4**) by the reactions of intermediate 4-amino-5-ethoxycarbonyl-2-methylthio-3-phenyl-3*H*-thiazolinium sulphate (**2**) with alkylamines or arylamine at room temperature. The structures of compounds **3** and **4** have been confirmed by ^{1}H NMR, EI-MS, IR spectroscopy and elemental analyses. Some target compounds possess good herbicidal activity against the roots of *Rape* and *Barnyard grass* at 100 mg/L.

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