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Synthesis and Bioactivity of Novel Triazolo [1,5-*a*]Pyrimidine Derivatives[3]

Guangfu Yang, Li Xu, and Aihong Lu

Institute of Organic Synthesis, Central China Normal University, Wuhan 430079, P. R. China; gfyang@ccnu.edu.cn

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ABSTRACT: *In an attempt to discover novel compounds with high herbicidal activity and low toxicity, a series of novel 1,2,4-triazolo[1,5-a]pyrimidine derivatives, α-(5,7-dimethyl-1,2,4-triazolo[1,5-a]pyrimidine-2-thio)acetamides* **3** *and α-(5,7-dimethyl-1,2,4-triazolo[1,5-a]pyrimidine-2-sul-fonyl)acetamides* **4**, *have been designed and synthesized by a three-step synthetic route. The structures of all compounds prepared were confirmed by elemental analyses and by ^1H NMR and mass spectroscopy. The results of preliminary bioassay indicate that the title compounds possess good herbicidal activity against rape (Brassica campestris L.) and barnyardgrass (Echinochloca crusgalli L.)* © 2001 John Wiley & Sons, Inc. Heteroatom Chem 12:491–496, 2001

INTRODUCTION

The chemistry of 1,2,4-triazolo[1,5-*a*]pyrimidine derivatives has been of considerable interest for many years. In 1935, 5-methyl-7-hydroxy-1,2,4-triazolo[1,5-*a*]pyrimidine was found to be an excellent stabilizer for photographic emulsions. Since then, various derivatives of 1,2,4-triazolo-[1,5-*a*] pyrimidine have found applications in pharmaceutical, agricultural, and other areas.

A recent review [1] discusses the synthesis and properties of 1,2,4-triazolo[1,5-*a*]pyrimidine derivatives. The 1,2,4-triazolo[1,5-*a*]pyrimidine-2-sulfonamide derivatives have shown excellent herbicidal and plant growth regulation activity [2–4]. Recently, we became interested in the syntheses of novel 1,2,4-triazolo[1,5-*a*]pyrimidines. Some of the compounds we synthesized have shown potential herbicidal and fungicidal activities [3–6]. As a continuation of our research, we wish to report herein the preparation of α-(5,7-di-methyl-1,2,4-triazolo[1,5-*a*] pyrimidine-2-thio)acetamides **3a–n** and α-(5,7-dimethyl-1,2,4-triazolo[1,5-*a*]pyrimidine-2-sulfonyl)acetamides **4a–g**. The purpose of the present work is to find novel compounds with good biological activity, such as herbicidal activity.

RESULTS AND DISCUSSION

Synthesis and Structure Characterization of the Title Compounds

The title compounds were synthesized *via* two different routes outlined in Schemes **1** and **2**, respectively.

In method A, as shown in Scheme **1**, α-(5,7-dimethyl-1,2,4-triazolo[1,5-*a*]pyrimidine-2-thio)acetic acids **2a–b** were synthesized by treating 2-mercapto-5,7-dimethyl-1,2,4-triazolo[1,5-*a*]pyrimidine **1** with $ClCH_2COOH$ or $CH_3CHBrCOOH$ in the presence of sodium hydroxide. In the presence of dicyclohexylcarbodiimide (DCC), these compounds were reacted with various aromatic amines in dimethylformamide (DMF) at room temperature to afford α-(5,7-dimethyl-1,2,4-triazolo[1,5-*a*]pyrimidine-

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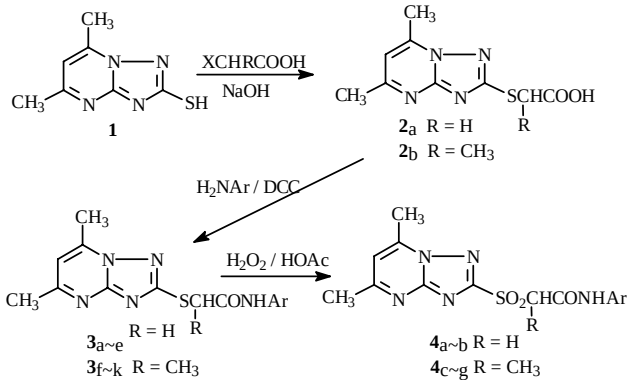
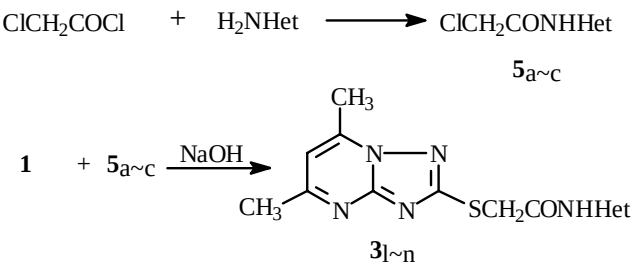


SCHEME 1 (Method A)



SCHEME 2 (Method B)

2-thio)acetamides **3a–k**. In view of the stability of the amide group, the H_2O_2/HOAc system was selected as the oxidizing reagent to transform α-(5,7-dimethyl-1,2,4-triazolo[1,5-*a*]pyrimidine-2-thio)acetamides **3** to the corresponding sulfones. A representative example, **3c,** has been taken to study the influence of the reaction temperature and the catalyst on the oxidation reaction of α-(5,7-dimethyl-1,2,4-triazolo[1,5-*a*]pyrimidine-2-thio)acetamides to the corresponding sulfones, and the results are summarized in Table 1. With an increase in the reaction temperature, the yield of sulfone increases. The best yield (67.5%) was obtained when the reaction was carried out at ca. 55–60°C in the presence of sodium tungstate dihydrate as catalyst [5]. In summary, the optimum conditions for the oxidation reaction of α-(5,7-dimethyl-1,2,4-triazolo[1,5-*a*]-pyrimidine-2-thio)acetamides to the corresponding sulfone **4** were ca. 55–60°C and included the presence of sodium tungstate dihydrate as catalyst.

TABLE 1 The Influence of Reaction Conditions on the Oxidation of **3c**

No.	Reaction Temperature (°C)	Catalyst[a]	Reaction Time (hours)	Yield(%)
1	25–30	No	5	No reaction
2	25–30	Yes	5	23.8
3	35–40	Yes	5	47.6
4	45–50	Yes	5	51.3
5	55–60	Yes	5	67.5
6	55–60	No	5	58.7
7	65–70	Yes	5	49.5
8	75–80	Yes	5	Complex

[a]$NaWO_4 \cdot 2H_2O$ as a catalyst.

Attempted coupling reactions of α-(5,7-dimethyl-1,2,4-triazolo[1,5-*a*]pyrimidine-2-thio)acetic acids **2a–b** with heterocyclic amines in DMF in the presence of DCC were unsuccessful. However, the convenient synthetic route depicted in Scheme **2** gave fruitful results. Thus, chloroacetyl chloride was reacted with heterocyclic amines to give chloroacetamides **5a–c,** which were then treated with 2-mercapto-5,7-dimethyl-1,2,4-triazolo[1,5-*a*] pyrimidine **1** in the presence of sodium hydroxide to obtain the target compounds **3l–n** in good yields.

All the products **3** and **4** were purified by recrystallization from ethanol. The structures of the products **3** and **4** were confirmed by ^{1}H NMR, mass spectral, and elemental analyses. The experimental data for **3** and **4** are listed in Tables 2 and 3. The ^{1}H NMR spectrum of **3h,** a representative example in this series, shows the presence of a doublet and a quartet at δ 1.70 and δ 4.60 due to the presence of α-CH_3 and methyne protons with $J = 7.98$. The NH protons appeared as a broad peak at δ 10.20. The singlets at δ 2.71, δ 2.80, and δ 6.90 were due to 5-methyl, 7-methyl, and 6-methyne protons, respectively. The aromatic protons displayed a multiplet at δ 7.20–7.60. In the ^{1}H NMR spectra of **4,** the chemical shifts of the methylene and the methyne protons linked with sulfonyl were shifted to lower field due to the strong inductive effect of the sulfonyl group and appeared in the range of δ 4.65–4.80. The proton of NH of each compound **4** showed broad peaks at δ 9.15–10.70. The ^{1}H NMR resonances of the protons in the heterocycle moiety and aromatic ring moiety have a similar regularity to **3** and can be clearly assigned. In addition, the EI-MS spectra of **3** and **4** exhibited the anticipated molecular ion peaks. All the fragmentation ions were consistent with their structures and can be clearly assigned. For example, compound **3h,** under electron impact, gave the molecular ion peak *m/z* (%): 361(23.9), and the other conspicuous peaks: 235(100), 208(83.70), 175(96.90), 149(84.30), 108(11.00), 107(32.40), and 67(22.20), while **4b** gave the molecular ion peak *m/z* (%): 379(26.40), and other major fragmentation ion peaks: 315(9.90), 273(100), 253(73.70), 190(24.10), and 162(59.80).

TABLE 2 Physical Constants of Compounds **3** and **4**

					Analysis (%) Calcd/Found		
No.	*Ar (Het)*	*R*	*m.p. (°C)*	*Yields (%)*	*C*	*H*	*N*
3a	2,6-$Cl_2C_6H_3$	H	197–199	70.2	47.12/47.14	3.40/3.19	18.32/18.23
3b	2-ClC_6H_4	H	172–174	69.4	51.79/51.96	4.02/4.37	20.14/20.55
3c	2-$CH_3C_6H_4$	H	195–198	65.4	58.71/58.43	5.19/4.87	21.40/21.71
3d	3,4-$Cl_2C_6H_3$	H	165–166	47.6	47.12/47.46	3.40/3.12	18.32/18.66
3e	3-$CH_3OC_6H_4$	H	193–195	83.6	55.97/55.69	4.95/4.78	20.40/20.74
3f	2-$CH_3C_6H_4$	CH_3	174–176	80.0	59.82/60.13	5.57/5.19	20.52/20.87
3g	4-$CH_3C_6H_4$	CH_3	175–176	77.9	59.82/59.74	5.57/5.79	20.52/20.73
3h	4-ClC_6H_4	CH_3	163–165	81.5	53.11/53.35	4.42/4.68	19.36/19.71
3i	2-ClC_6H_4	CH_3	153–155	67.9	53.11/52.98	4.42/4.59	19.36/19.67
3j	3-$CH_3C_6H_4$	CH_3	126–128	67.6	59.82/60.13	5.57/5.34	20.52/20.77
3k	3-ClC_6H_4	CH_3	134–136	82.8	53.11/53.38	4.42/4.71	19.36/19.57
3l	4,6-CH_3OPm-2-[a]	H	233–235	85.7	48.00/48.23	4.53/4.35	26.13/26.39
3m	Ben-2-[b]	H	197–198	82.4	51.89/51.64	3.78/3.99	22.70/22.98
3n	4,6-CH_3Pm-2-[c]	H	192–194	80.0	52.47/52.75	4.95/4.78	28.57/28.79
4a	2-ClC_6H_4	H	182–184	32.0	47.43/47.71	3.68/3.45	18.44/18.72
4b	4-ClC_6H_4	H	186–188	57.0	47.43/47.65	3.68/3.84	18.44/18.59
4c	4-$CH_3C_6H_4$	H	184–187	41.0	53.48/53.15	4.73/4.97	19.49/19.64
4d	3-ClC_6H_4	H	170–171	60.0	47.43/47.15	3.68/3.47	18.44/18.71
4e	2-$CH_3C_6H_4$	H	160–161	67.5	53.48/53.67	4.73/4.95	19.49/19.81
4f	4-ClC_6H_4	CH_3	188–190	62.6	48.79/48.53	4.06/3.87	17.78/17.96
4g	4-$CH_3C_6H_4$	CH_3	186–187	70.2	54.69/54.83	5.09/5.36	18.76/19.04

[a]4,6-Dimethoxylpyrimidinyl-2-.
[b]Benzothiazolyl-2-.
[c]4,6-Dimethylpyrimidinyl-2-.

Biological Studies

The herbicidal activity of some compounds **3** and **4** against rape (*Brassica campestris L.*) and barnyard grass (*Echinochloca crusgalli L.*) was measured according to the modified method described previously [7]. A set amount of each sample was dissolved in acetone into which a drop of an emulsifier, Sorpol-144, was added. Then, the solution was diluted with water until it reached the concentration required (100 ppm). The amounts of acetone and the emulsifier were set as low as possible but were still sufficient to make a uniform emulsion even at high concentrations. Biological assays were carried out in vials ($\Phi = 3.5$ cm) containing 4 mL of solution. Five seeds of rape (or barnyard grass) were placed in the solution. The vials were kept at 25°C, with light of 42,000 lux for 12 hours each day. After incubation for 72 hours, the shoot length was measured for the five seeds in each vial and averaged and used as an index of herbicidal activity on a 0–100 rating scale. The scale is based on measurement of shoot length as compared to an untreated control. With this scale, 0 represents no inhibition and 100 represents complete inhibition. The herbicidal activity of some compounds **3** and **4** are listed in Table 4. The herbicidal activities given in Table 4 indicate most of the compounds showed an inhibition effect (>50%) against rape and barnyardgrass, and the inhibitory rate of compounds **3b, 3j, 3k**, and **3l** to rape exceeded 90%. In addition, the herbicidal activity of compounds **4** is much weaker than that of compounds **3**. Further studies on the structure activity relationships of these compounds are underway.

EXPERIMENTAL

Instruments

Melting points were determined with a Yanaco MT-500 apparatus and are uncorrected. ^{1}H NMR spectra were taken on a BRUKER AC-P200 spectrometer using $CDCl_3$ as solvent and tetramethylsilane (TMS) as internal standard. Mass spectra were recorded on a Hewlett-Packard 5988 instrument. Elemental analyses were carried out on a Yana MT-3 instrument. All solvents and materials were reagent grade and purified as required. 2-Mercapto-5,7-dimethyl-1,2,4-triazolo-[1,5-*a*]pyrimidine **1** was prepared as described in a published procedure [8].

General Procedure for the Syntheses of α-(5,7-dimethyl-1,2,4-triazolo[1,5-a] pyrimidine-2-thio) acetic acids **2a–b**

A solution of 9 g (0.05mol) of 2-mercapto-5,7-dimethyl-1,2,4-triazolo[1,5-*a*]pyrimidine **1** and 4 g

TABLE 3 Spectral and Analytical Data of Compounds **3** and **4**[a]

No.	*^{1}HNMR (TMS, $CDCl_3$, or DMSO-d_6, δ, ppm)*	*MS (m/z, %)*
3a	[a] 2.52 (s, 3H, CH_3), 2.64 (s, 3H, CH_3), 4.20 (s, 2H, SCH_2), 7.05 (s, 1H, 6-H), 7.14–7.56 (m, 3H, C_6H_3), 10.27 (s, 1H, NH).	382(M^+, 2.9), 194 (100), 193 (31.5), 180 (5.4), 149 (40.8), 108 (34.4), 107 (25.1), 67 (36.4)
3b	[b] 2.61 (s, 3H, CH_3), 2.70 (s, 3H, CH_3), 4.08 (s, 2H, SCH_2), 6.78–8.40 (m, 5H, 6-H + C_6H_3), 9.57 (s, 1H, NH).	347(M^+, 12.8), 221 (59.8), 194 (100), 193 (46.3), 180 (7.2), 149 (64.9), 108 (38.6), 107 (28.1), 67 (27.5)
3c	[b] 2.19 (s, 3H, CH_3), 2.61 (s, 3H, CH_3), 2.70 (s, 3H, CH_3), 3.99 (s, 2H, SCH_2), 7.05 (s, 1H, 6-H), 7.20–7.89 (m, 4H, C_6H_4), (s, 1H, NH).	327 (M^+, 49.4), 221 (56.5), 194 (100), 193 (55.2), 9.30 180 (7.9), 149 (86.7), 108 (52.8), 107 (60.7), 67 (41.8)
3d	[b] 2.64 (s, 3H, CH_3), 2.67 (s, 3H, CH_3), 3.93 (s, 2H, SCH_2), 6.81 (s, 1H, 6-H), 7.42–7.83 (m, 3H, C_6H_3), 10.14 (s, 1H, NH).	382 (M^+, 16.0), 221 (78.5), 194 (100), 193 (57.9), 180 (11.6), 149 (77.3), 108 (49.6), 107 (41.1), 67 (36.9)
3e	[a] 2.49 (s, 3H, CH_3), 2.61 (s, 3H, CH_3), 3.69 (s, 3H, OCH_3), 4.20(s, 2H, SCH_2), 7.02 (s,1H,6-H), 6.48–7.32 (m,4H,C_6H_4), 10.29 (s, 1H, NH).	343 (M^+, 54.7), 221 (100), 194 (75.5), 193 (65.7), 180 (12.6), 149 (90.6), 108 (59.2), 107 (59.1), 67 (35.7)
3f	[a] 1.70 (d, 3H, α-CH_3), 2.30 (s, 3H, CH_3), 2.65 (s, 3H, CH_3), 2.75 (s,3H, CH_3), 4.70 (q, 1H, SCH), 6.88 (s, 1H, 6-H), 7.00–8.00 (m, 4H, C_6H_4), 9.40 (s, 1H, NH).	341 (M^+, 14.7), 279 (33.2), 278 (100), 235 (32.2), 208 (38.2), 207 (28.0), 180 (10.8), 175 (53.2), 149 (39.0), 107 (24.1), 77 (67.1), 67 (11.2)
3g	[a] 1.70 (d, 3H, α-CH_3), 2.30 (s, 3H, CH_3), 2.65 (s, 3H, CH_3), 2.75 (s, 3H, CH_3), 4.55 (q, 1H, SCH), 6.80 (s, 1H, 6-H), 7.30 (2d, 4H, C_6H_4), 9.80 (s, 1H, NH).	341 (M^+, 21.1), 235 (100), 208 (44.4), 207 (55.0), 180 (12.4), 175 (77.4), 149 (57.4), 108 (8.9), 107 (35.9), 67 (14.1)
3h	[a] 1.70 (d, 3H, α-CH_3), 2.71 (s, 3H, CH_3), 2.80 (s, 3H, CH_3), 4.60 (q, 1H, SCH), 6.90 (s, 1H, 6-H), 7.40 (2d, 4H, C_6H_4), 10.20 (s, 1H, NH).	361 (M^+, 23.9), 235 (100), 208 (83.7), 207 (69.5), 175 (96.9), 149 (84.3), 108 (11.0), 107 (32.4), 67 (22.2)
3i	[a] 1.64 (d, 3H, α-CH_3), 2.68 (s, 3H, CH_3), 2.73 (s, 3H, CH_3), 4.71 (q, 1H, SCH), 6.72 (s, 1H, 6-H), 6.80–8.40 (m, 4H, C_6H_4), 9.51 (s, 1H, NH).	361 (M^+, 3.1), 234 (68.1), 208 (14.1), 207 (99.7), 180 (20.7), 179 (20.4), 175 (11.3), 174 (100), 149 (8.3), 148 (89.3), 107 (15.0), 67 (11.1)
3j	[a] 1.65 (d, 3H, α-CH_3), 2.25 (s, 3H, CH_3), 2.61 (s, 3H, CH_3), 2.67 (s, 3H, CH_3), 4.71 (q, 1H, SCH), 6.74 (s, 1H, 6-H), 6.81–7.50 (m, 4H, C_6H_4), 9.81 (s, 1H, NH).	341 (M^+, 1.5), 234 (89.8), 208 (9.8), 207 (67.4), 206 (47.3), 180 (7.6), 179 (17.3), 175 (10.9), 174 (100), 148 (90.9), 67 (12.1)
3k	[a] 1.65 (d, 3H, α-CH_3), 2.67 (s, 3H, CH_3), 2.73 (s, 3H, CH_3), 4.47 (q, 1H, SCH), 6.75 (s, 1H, 6-H), 6.84–7.74 (m, 4H, C_6H_4), 10.20 (s, 1H, NH).	361 (M^+, 5.88), 234 (49.9), 208 (11.4), 207 (90.6), 206 (36.4), 180 (6.7), 179 (21.3), 175 (11.6), 174 (100), 148 (95.7), 106 (42.0), 67 (11.6)
3l	[b] 3.90 (s, 6H, 2×OCH_3), 2.52 (s, 3H, CH_3), 2.67 (s, 3H, CH_3), 4.59 (s, 2H, SCH_2), 5.88 (s, 1H, Py-H), 7.15 (s, 1H, 6-H), 10.65 (s, 1H, NH).	375 (M^+, 54.6), 302 (42.1), 221 (13.4), 220 (58.5), 194 (100), 193 (46.4), 180 (11.6), 149 (72.5), 108 (92.5), 107 (64.0), 67 (78.7)
3m	[b] 2.58 (s, 3H, CH_3), 2.64 (s, 3H, CH_3), 4.22 (s, 2H, SCH_2), 7.14 (s, 1H, 6-H), 7.26–8.08 (m, 4H, C_6H_4), 12.80 (s, 1H, NH).	370 (M^+, 17.4), 297 (5.3), 221 (22.8), 194 (100), 193 (42.0), 149 (52.4), 108 (52.8), 107 (26.7), 67 (19.9)
3n	[b] 2.30 (s, 6H, 2 × CH_3), 2.70 (s, 3H, CH_3), 2.75 (s, 3H, CH_3), 4.50 (s, 2H, SCH_2), 7.00 (s, 1H, Py-H), 7.16 (s, 1H, 6-H), 10.92 (s, 1H, NH).	[c]
4a	[b] 2.70 (s, 3H, CH_3), 2.85 (s, 3H, CH_3), 4.70 (s, 2H, SCH_2), 7.05 (s, 1H, 6-H), 7.10–8.25 (m, 4H, C_6H_4), 9.15 (s, 1H, NH).	379 (M^+, 12.8), 344 (39.9), 273 (88.2), 253 (56.6), 238 (100), 190 (18.3), 162 (33.2), 149 (4.91), 127 (24.5), 108 (11.0), 107 (15.3), 67 (29.0)
4b	[b] 2.60 (s, 3H, CH_3), 2.75 (s, 3H, CH_3), 4.80 (s, 2H, SCH_2), 7.30 (s, 1H, 6-H), 7.50 (2d, 4H, C_6H_4), 10.70 (s, 1H, NH).	379 (M^+, 26.4), 315 (9.90), 273 (100), 253 (73.7), 190 (24.1), 162 (59.8), 127 (34.7), 67 (33.0)
4c	[b] 2.22 (s, 3H, CH_3), 2.61 (s, 3H, CH_3), 2.73 (s, 3H, CH_3), 4.65 (s, 2H, SCH_2), 6.90–7.50 (m, 5H, 6-H + C_6H_4), 10.29 (s, 1H, NH).	359 (M^+, 2.51), 253 (4.3), 252 (31.1), 189 (11.0), 161 (64.3), 106 (100), 66 (40.9)
4d	[b] 2.64 (s, 3H, CH_3), 2.74 (s, 3H, CH_3), 4.71 (s, 2H, SCH_2), 7.30 (s, 1H, 6-H), 7.40–7.70 (m, 4H, C_6H_4), 10.59 (s, 1H, NH).	379 (M^+, 2.4), 272 (23.9), 252 (25.9), 189 (28.6), 162 (10.9), 161 (100), 126 (22.2), 66 (41.4)
4e	[b] 2.16 (s, 3H, CH_3), 2.67 (s, 3H, CH_3), 2.73 (s, 3H, CH_3), 4.80 (s, 2H, SCH_2), 6.90–7.44 (m, 5H, 6-H + C_6H_4), 9.60 (s, 1H, NH).	359 (M^+, 2.2), 344 (100), 225 (93.0), 190 (4.2), 162 (9.0), 67 (11.0)
4f	[b] 1.56 (d, 3H, α-CH_3), 2.64 (s, 3H, CH_3), 2.70 (s, 3H, CH_3), 4.68 (q, 1H, SCH), 7.20–7.62 (2d, 4H, C_6H_4), 7.38 (s, 1H, 6-H), 10.58(s, 1H, NH).	393 (M^+, 17.5), 273 (79.1), 190 (31.9), 176 (45.1), 148 (16.1), 108 (12.6), 107 (51.8), 67 (100)
4g	[b] 1.56 (d, 3H, α-CH_3), 2.22 (s, 3H, CH_3), 2.64 (s, 3H, CH_3), 2.70 (s, 3H, CH_3), 4.68 (q, 1H, SCH), 6.90–7.50 (m, 5H, 6-H + C_6H_4), 10.32 (s, 1H, NH).	373 (M^+, 11.6), 266 (12.4), 253 (12.9), 176 (44.2), 175 (41.9), 108 (16.0), 107 (100), 106 (66.8), 77 (30.9), 67(82.0)

[a][a] $CDCl_3$, [b] DMSO-d_6, [c] undetected.

TABLE 4 Herbicidal Activity of Some Compounds **3** and **4**

Compounds No.	**3a**	**3b**	**3c**	**3f**	**3g**	**3h**	**3i**	**3j**	**3k**	**3l**	**4a**	**4b**	**4c**	**4d**
Concentration (ppm)	100	100	100	100	100	100	100	100	100	100	100	100	100	100
Rape	48.4	94.0	64.4	69.0	72.9	48.9	87.2	96.0	92.7	100	61.5	43.1	38.8	41.5
Barnyard	50.4	65.7	62.7	68.0	60.0	39.0	76.4	89.4	78.0	81.5	65.2	52.8	48.4	48.4

(0.1 mol) of NaOH in 200 mL of water was heated at reflux for 0.5 hour. Then, 4.7 g (0.05 mol) of $ClCH_2COOH$ (or $CH_3BrCHCOOH$) was added, and the resulting mixture was refluxed for 5 hours. The reaction mixture was cooled to room temperature, adjusted to pH = 2–3 using aq. HCl, and filtered. The filter cake was recrystallized from DMF to afford the pure products as white needles. **2a:** Yield 90%, m.p. 248–250°C. ^{1}H NMR δ ($CDCl_3$) 2.66 (s, 3H, CH_3), 2.72 (s, 3H, CH_3), 3.96(s, 2H, CH_2), 6.80(s, 1H, CH), 12.31(s, 1H, COOH). **2b:** yield 91%, m.p. 232–233°C. ^{1}H NMR δ($CDCl_3$) 1.68 (d, 3H, CH_3), 2.68 (s, 3H, CH_3), 2.73 (s, 3H, CH_3), 4.61(q, 1H, CH), 6.83(s, 1H, CH), 12.50 (s, 1H, COOH).

General Procedure for the Syntheses of α-(5,7-Dimethyl-1,2,4-triazolo[1,5-a] pyrimidine-2-thio) Acetamides **3a–k** *(Method A)*

A mixture of 5 mmol of **2,** 5 mmol of aromatic amine, and 1 g of DCC in 20 mL of DMF was stirred at room temperature for 5–6 hours. The mixture was filtered, and the filter cake was washed with water and recrystallized from ethanol to afford the pure products as white crystals. The physical data for compounds **3a–k** are listed in Table 2.

General Procedure for the Syntheses of α-(5,7-Dimethyl-1,2,4-triazolo[1,5-a] pyrimidine-2-sulfonyl)acetamides **4a–g**

To a vigorously stirred mixture of 4.41 mmol of **3**, 20 mL of acetic acid, and 0.04 g (0.13 mmol) of sodium tungstate dihydrate, was slowly added 1.5 g (13.23 mmol) of hydrogen peroxide as a 30% aqueous solution, maintaining the reaction mixture temperture at 35–40°C. Stirring was continued at 55–60°C for an additional 5 hours. The excess hydrogen peroxide was destroyed by the addition of an aqueous solution of sodium sulfite, the resulting mixture was filtered, and the filter cake recrystallized from ethanol to give the pure products as colorless crystals. The physical data for compounds **4a–g** are listed in Table 2.

General Procedure for the Syntheses of N-4,6-Dimethoxypyrimidinyl-2-chloroacetamide **5a** *and N-Benzothiazolyl-2-chloroacetamide* **5b**

To a stirred, cold (0°C) solution of 3.1 g (0.02 mol) of 2-amino-4,6-dimethoxypyrimidine (or 2-aminobenzothiazole) in 20 mL of dichloromethane was added dropwise a solution of 2 mL of chloroacetyl chloride in 5 mL of dichloromethane at 0°C with stirring. The resulting mixture was stirred at room temperature for 3 hours. The mixture was filtered, and the filter cake was washed with water and recrystallized from ethanol to give the pure products. **5a:** yield 70.4%, white solid, m.p. 240–241°C. Anal. calcd for $C_8H_{10}N_3O_3Cl$ (231.5): C, 41.46; H, 4.32; N, 18.14. Found: C, 41.73; H, 4.11; N, 18.51. **5b:** yield 71.7%, slight yellow solid, m.p. 161–162°C. Anal. calcd for $C_9H_7N_2OSCl$ (226.5): C, 47.68; H, 3.09; N, 12.36. Found: C, 47.42; H, 3.37; N, 12.72.

Procedure for the Syntheses of N-4,6-Dimethyl-pyrimidinyl-2-chloroacetamide **5c**

To a solution of 12.3 g (0.1 mol) of 2-amino-4,6-dimethylpyrimidine and 9 g (0.11 mol) of CH_3COONa in 100 mL of acetone, a solution of 8.1 mL (0.1 mol) of chloroacetyl chloride in 5 mL of acetone was added dropwise at 0°C with stirring. The resultant mixture was refluxed for 2 hours and poured into 400 mL of saturated NaCl solution. After extraction with chloroform three times (3 × 50 mL), the separated organic phase was washed with water and dried. After the filtrate had been evaporated under reduced pressure, the residue was recrystallized from an ethyl acetate/petroleum ether mixture (1:1) to give the pure products as a slight yellow solid, yield 43%, m.p. 112–113°C. Anal. calcd for $C_8H_{10}N_3OCl$ (199.5): C, 48.12; H, 5.01; N, 21.05. Found: C, 48.47; H, 4.89; N, 21.42.

General Procedure for the Syntheses of α-(5,7-dimethyl-1,2,4-triazolo[1,5-a] pyrimidine-2-thio)acetamides **3l–n** *(Method B)*

A mixture of 1.8 g (0.01 mol) of **1,** 0.4 g (0.01 mol) of NaOH, and 0.01 mol of **5** in 10 mL of DMF was stirred at room temperature for 2 hours. Then, the reaction mixture was filtered, and the solid was recrystallized

from ethanol to give the pure product. The physical data for compounds **3l–n** are also listed in Table 2.

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