

Note

Synthesis and bioactivity of some new [3-[4-methylphenoxy-methyl]-4-phenyl-[1,2,4]-triazole-5-thio]acetanilide derivatives

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Received 13 January 2006; accepted (revised) 13 November 2006

The synthesis of some triazole derivatives starting from 4-methyl-phenoxycetyl hydrazide is described. In this process, the method for the synthesis of 2-chloroacetanilide had been improved and good yields have been obtained. The chemical structure of all compounds have been elucidated by IR, ^1H NMR, ^{13}C NMR and elemental analysis studies. All of the compounds have been investigated for plant growth regulating activity. It had been found that they remarkably enhance root elongation.

Keywords: 1,2,4-triazole derivatives, biology activity, 3-[4-methylphenoxy-methyl]-4-phenyl-[1,2,4]triazole-5-thio]acetanilide, 4-methylphenoxycetyl hydrazide

IPC: Int.Cl.⁸ C07D

During the last few decades, a considerable attention has been devoted to synthesis of 1,2, 4-triazole derivatives possessing such comprehensive bioactivities as antimicrobial¹⁻³, anti-inflammatory⁴, analgesic⁵, antitumoral⁶, antihypertensive⁷, anticonvulsant^{8,9} and antiviral activities¹⁰. The 1,2,4-triazoles show such broad spectrum of biological activities, possibly due to the presence of >N-C-S moiety^{11,12}. Therefore 5-mercapto-[1,2,4]triazoles derivatives have found applications as antibacterials, antitumour and anti-inflammatory agents, pesticides and herbicides¹³.

It was reported that the incorporation of various substituents and the halogen atom into the heterocyclic ring systems augment the biological activities considerably¹⁴⁻¹⁶ and the acylamide agents have good bioactivity¹⁷. In view of the above findings, and in continuation of our earlier work on the synthesis and biological activity of triazole and aryloxyacetic acid derivatives^{18,19}, we have synthesized a series of 1,2,4-triazole derivatives via fusing

the 1,2,4-triazole and acylamide together and studied their plant growth regulating activities.

The reaction sequence leading to the formation of title compounds are shown in **Scheme I**. 4-Methyl - phenoxycetyl hydrazide **1** was prepared in good yield according to our previous work¹⁹, when reacted with phenylisothiocyanate gives the corresponding thiosemicarbazide **2**. Compound **2** was readily cyclized to 4-phenyl-3-(4-methyl-phenoxymethyl)-5-mercapto-1,2,4(H)-triazole **3** hr by heating with NaOH for 4 hr^{3,20,21}. Further, [3-(4-methyl-phenoxymethyl)-4-phenyl-[1,2,4]triazole-5-thio]acetanilides **5a-h** were synthesized from compound **3** and 2-chloroacetanilide **4a-h** by heating with NaOH in ethanol for 1.5 hr. This method has the advantages of simple operation that shorten reaction times and high yield.

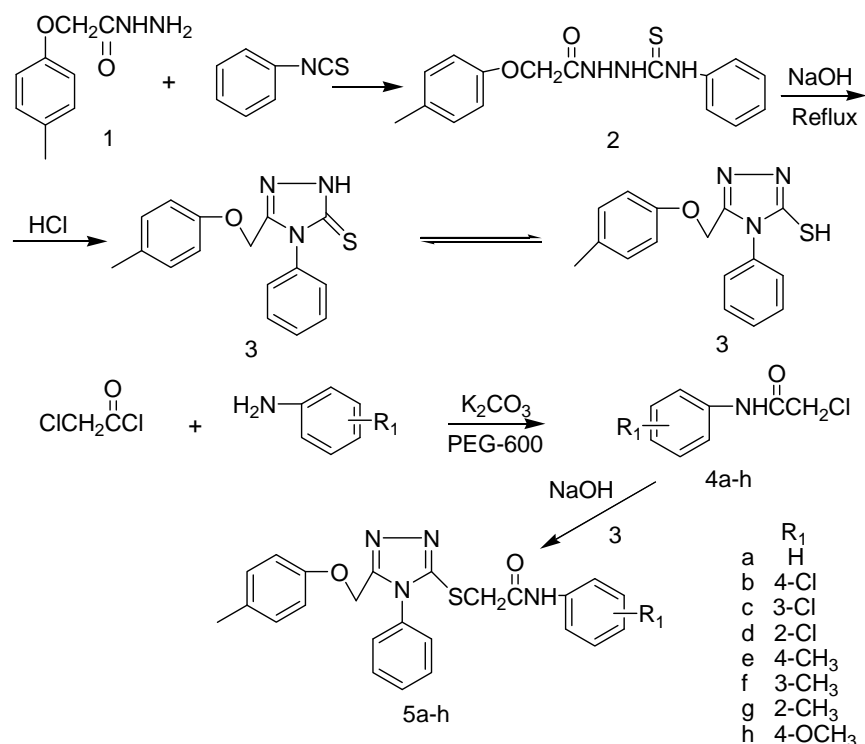
2-Chloroacetanilide **4a-h** could be produced in low yields from 21 to 62% according to the work²². So the condition was improved and the reaction was carried out by making chloroacetyl chloride reacting with aniline in the presence of K_2CO_3 and PEG-600 at the temperature of 0°C . Under this improved condition, **4a-h** could be synthesized in good yields from 74 to 93%.

Experimental Section

Melting points were measured on a X-4 digital melting-point apparatus and were uncorrected. The infrared spectra were performed on a Digilab FTS-3000 FT-IR spectrophotometer as KBr pellets. ^1H NMR and ^{13}C NMR spectra were recorded on a Varian Mercury plus-400 MHz spectrometer. Elemental analysis data were obtained on a PE-2400CHN instrument.

3-[4-Methyl-phenoxymethyl]-4-phenyl-[1, 2, 4]triazol **3**

Equimolar amounts of aryloxyacetyl hydrazide **1** and phenyl isothiocyanate were refluxed in ethanol for 3 hr to produce **2**. Then the precipitate **2** was dissolved in 2 moles/L sodium hydroxide, heated under reflux for 4 hr. After cooling, the solution was acidified with hydrochloric acid. The crude product was precipitated,



Scheme I

filtered and washed with distilled water. Pure compounds were obtained by recrystallization from DMF and H₂O. Yield 91%, m.p. 198-200°C. IR: 3441 (NH), 2914 (CH₂), 1584 (C=N), 1326 cm⁻¹ (C=S). ¹H NMR (400 MHz, DMSO-*d*₆): δ 2.19 (s, 3H, CH₃), 4.92 (s, 2H, OCH₂), 6.59-7.53 (m, 9H, ArH), 14.07 (s, 1H, NH). ¹³C NMR (400 MHz, DMSO-*d*₆): δ 20.41, 60.88, 114.50, 116.24, 128.05, 129.27, 129.52, 133.47, 148.21, 151.02, 154.15, 168.61.

2-Chloroacetanilide 4a-h

Phenylamine (10 mmol), K₂CO₃ (7 mmol) and PEG-600 (1.5 mmol) were added into 20 mL CH₂Cl₂, at the temperature of 0°C. The mixture was stirred for 10 min, then 10 mmol chloroacetyl chloride was slowly added dropwise with constant stirring. After the chloroacetyl chloride was dripped off, the mixture was kept to react for another 1 hr. After evaporating the solvent in vacuum, the crude products were obtained after the precipitation was washed thrice with 10 mL distilled water for three times. Pure products could be obtained by recrystallization from ethanol (Table I).

4-Phenyl-3-(4-methylphenoxymethyl)-5-merc-*apto*-1,2,4(H)-triazoles 5a-h

Table I — Physical Data of 2-chloroacetanilide

R	Entry	Yields %	Mp °C	Lit Mp ^{22,23} °C
-H	4a	84.3	135	136-137
4-Cl	4b	93.2	169-170	169
3-Cl	4c	83.3	99-100	101
2-Cl	4d	76.5	71-72	74
4-CH ₃	4e	87.5	160-162	163
3-CH ₃	4f	81.4	92-93	93
2-CH ₃	4g	73.6	108-109	111
4-OCH ₃	4h	87.7	120-121	121

The synthesis of **5** was carried out by adding NaOH (3 mmol) to a mixture of **3** (3 mmol) and 15 mL ethanol, then it was stirred at ambient temperature until **3** completely dissolved. In succession, **4** (3 mmol) was added, and the mixture was refluxed for 1.5 hr. After the mixture was cooled to the ambient temperature, the crude product was filtered and washed with 10 mL distilled water of three times. The pure products were acquired by recrystallization from DMF-EtOH-H₂O.

5a: Yield 85.2%, m.p. 154-56°C. IR: 3244, 3189 (NH), 1680 (C=O), 1603 (C=N), 1553 (N=C-S), 691 cm⁻¹ (C-S-C). ¹H NMR (400 MHz, CDCl₃): δ

2.28 (s, 3H, ArCH₃), 3.97 (s, 2H, SCH₂), 5.02 (s, 2H, OCH₂), 6.74-7.62 (m, 13H, ArH), 10.34 (s, 1H, NH). ¹³C NMR (400 MHz, CDCl₃): δ 20.41, 36.12, 59.76, 114.63, 119.65, 124.07, 126.66, 128.81, 129.84, 129.93, 130.52, 131.21, 132.05, 138.17, 152.37, 154.00, 155.15, 166.40. Anal. Calcd For C₂₄H₂₂N₄O₂S: C, 66.59; H, 4.73; N, 12.81. Found: C, 66.95; H, 5.15; N, 13.01.

5b: Yield 93.2%, m.p. 164-65°C. IR: 3235, 3178 (NH), 1675 (C=O), 1556 (N=C-S), 691 cm⁻¹ (C-S-C). ¹H NMR (400 MHz, (CDCl₃)): δ 2.26 (s, 3H, ArCH₃), 3.94 (s, 2H, SCH₂), 5.03 (s, 2H, OCH₂), 6.75-7.57 (m, 13H, ArH), 10.52 (s, 1H, NH). ¹³C NMR (400 MHz, (CDCl₃)): δ 20.44, 36.11, 59.77, 114.67, 120.90, 126.68, 128.83, 128.97, 129.99, 130.64, 130.70, 131.34, 132.02, 136.82, 152.48, 154.13, 155.15, 166.51. Anal. Calcd For C₂₄H₂₁N₄O₂SCl: C, 62.09; H, 4.28; N, 12.21. Found: C, 61.99; H, 4.55; N, 12.05.

5c: Yield 86.0%, m.p. 143-45°C. IR: 3235, 3173 (NH), 1682 (C=O), 1594 (C=N), 1547 (N=C-S), 688 cm⁻¹ (C-S-C). ¹H NMR (400 MHz, CDCl₃): δ 2.25 (s, 3H, ArCH₃), 3.97 (s, 2H, SCH₂), 5.03 (s, 2H, OCH₂), 6.74-7.76 (m, 13H, ArH), 10.54 (s, 1H, NH). ¹³C NMR (400 MHz, CDCl₃): δ 20.41, 36.20, 59.75, 114.64, 117.68, 119.68, 124.07, 126.65, 129.75, 129.94, 130.03, 130.59, 131.27, 131.99, 134.42, 139.34, 152.43, 154.02, 155.12, 166.55. Anal. Calcd For C₂₄H₂₁N₄O₂SCl: C, 62.27; H, 4.28; N, 11.93. Found: C, 61.99; H, 4.55; N, 12.05.

5d: Yield 71.8%, m.p. 192-93°C. IR (KBr): 3335 (NH), 1679 (C=O), 1591 (C=N), 1532 (N=C-S), 694 cm⁻¹ (C-S-C). ¹H NMR (400 MHz, CDCl₃): δ 2.26 (s, 3H, ArCH₃), 4.08 (s, 2H, SCH₂), 5.04 (s, 2H, OCH₂), 6.74-7.53 (m, 13H, ArH), 9.96 (s, 1H, NH). ¹³C NMR (400 MHz, CDCl₃): δ 20.44, 35.78, 59.90, 114.70, 122.25, 123.98, 124.93, 126.70, 127.31, 129.26, 129.95, 130.49, 130.57, 131.17, 132.20, 134.97, 152.58, 153.19, 155.24, 166.86. Anal. Calcd For C₂₄H₂₁N₄O₂SCl: C, 61.97; H, 4.58; N, 11.99. Found: C, 61.99; H, 4.55; N, 12.05.

5e: Yield 91.5%, m.p. 160-61°C. IR (KBr): 3252, 3191 (NH), 1672 (C=O), 1610 (C=N), 1549 (N=C-S), 695 cm⁻¹ (C-S-C). ¹H NMR (400 MHz, CDCl₃): δ 2.26 (s, 3H, OArCH₃), 2.31 (s, 3H, NArCH₃), 3.95 (s, 2H, SCH₂), 5.02 (s, 2H, OCH₂), 6.74-7.54 (m, 13H, ArH), 9.96 (s, 1H, NH). ¹³C NMR (400 MHz, CDCl₃): δ 20.42, 20.83, 36.07, 59.78, 114.66, 119.67, 126.70, 129.30, 129.92, 129.96, 130.52, 131.22, 132.09, 133.67, 135.62, 152.36, 154.04, 155.18, 166.25. Anal.

Calcd For C₂₅H₂₄N₄O₂S: C, 67.36; H, 5.13; N, 12.70. Found: C, 67.55; H, 5.44; N, 12.60.

5f: Yield 71.2%, m.p. 152°C. IR (KBr): 3247, 3200 (NH), 1674 (C=O), 1610 (C=N), 1565 (N=C-S), 690 cm⁻¹ (C-S-C). ¹H NMR (400 MHz, CDCl₃): δ 2.26 (s, 3H, OArCH₃), 2.33 (s, 3H, NArCH₃), 3.94 (s, 2H, SCH₂), 5.03 (s, 2H, OCH₂), 6.74-7.54 (m, 13H, ArH), 10.21 (s, 1H, NH). ¹³C NMR (400 MHz, CDCl₃): δ 20.43, 21.43, 36.10, 59.80, 114.66, 116.83, 120.24, 124.96, 126.70, 128.68, 129.96, 130.02, 130.55, 131.25, 132.08, 138.08, 138.74, 152.39, 154.08, 155.19, 166.43. Anal. Calcd For C₂₅H₂₄N₄O₂S: C, 67.71; H, 5.38; N, 12.58. Found: C, 67.55; H, 5.44; N, 12.60.

5g: Yield 82.5%, m.p. 174-75°C. IR: 3375 (NH), 1675 (C=O), 1590 (C=N), 1537 (N=C-S), 694 cm⁻¹ (C-S-C). ¹H NMR (400 MHz, CDCl₃): δ 2.26 (s, 3H, OArCH₃), 2.34 (s, 3H, NArCH₃), 4.00 (s, 2H, SCH₂), 5.03 (s, 2H, OCH₂), 6.73-8.00 (m, 13H, ArH), 9.76 (s, 1H, NH). ¹³C NMR (400 MHz, CDCl₃): δ 18.26, 20.42, 35.77, 59.78, 114.66, 122.04, 124.68, 126.44, 126.65, 128.90, 129.88, 129.94, 130.40, 130.54, 131.21, 132.08, 136.21, 152.52, 153.94, 155.15, 166.81. Anal. Calcd For C₂₅H₂₄N₄O₂S: C, 67.57; H, 5.50; N, 12.66. Found: C, 67.55; H, 5.44; N, 12.60.

5h: Yield 86.8%, m.p. 184-85°C. IR: 3258, 3194 (NH), 1678 (C=O), 1610 (C=N), 1553 (N=C-S), 690 cm⁻¹ (C-S-C). ¹H NMR (400 MHz, CDCl₃): δ 2.25 (s, 3H, ArCH₃), 3.76 (s, 3H, OCH₃), 3.97 (s, 2H, SCH₂), 5.02 (s, 2H, OCH₂), 6.74-7.52 (m, 13H, ArH), 10.18 (s, 1H, NH). ¹³C NMR (400 MHz, CDCl₃): δ 20.39, 36.06, 55.34, 59.73, 113.91, 114.62, 121.25, 126.66, 129.89, 129.92, 130.48, 131.18, 131.38, 132.06, 152.30, 153.98, 155.15, 156.11, 166.06. Anal. Calcd For C₂₅H₂₄N₄O₃S: C, 64.95; H, 5.07; N, 12.39. Found: C, 65.20; H, 5.25; N, 12.16.

Biological activity

All the synthesized compounds were investigated for plant growth regulation activity. Method of plate culture was adopted and the compound solutions were prepared in the concentration of 200, 100, 50 and 10 ppm, whereafter, rape seeds were cultured in a 10 cm petri dish with 10 mL of different solution and a circular filter paper. Then, the roots were allowed to grow at room temperature, the roots length was gained after 4 days, the percentage plant growth activity was calculated according to the following equation:

$$\text{Percentage plant growth activity} = (N - N_1) / N_1 \times 100\%$$

Table II — Plant growth regulating activity data

Compd	% Plant growth activity ^a			
	200ppm	100ppm	50ppm	10ppm
5a	-37.3	-28.9	4.5	35.7
5b	-32.8	-10.4	8.3	33.9
5c	-30	-12.2	13.7	47.6
5d	-32.2	-22.3	18.4	67.6
5e	-41.7	-9.2	-4.5	33.9
5f	-35.3	0	13.4	44.9
5g	-41.8	-10.7	10.4	50.6
5h	-29.8	15.5	27.7	55.4
Heteroauxing	-95.8	-71.7	-55.1	-25.9

^aThe solution was prepared in the proportion of H₂O:DMF=99.5:0.5, and 0.1g Tween-80 was added to promote the compound to dissolved

where N is the root length cultured in compound solution, and N₁ is the root length cultured in the distilled water under the same condition (**Table II**).

From the results summarized in **Table II**, it is apparent that most of the compounds exhibit inhibition activity at high concentration of 200 ppm, while displayed enhancing root elongation activity at a low concentration of 10 ppm.

When compared with heteroauxing it is seen that the compounds have weak inhibition of root elongation at high concentration of 100 ppm, while they show remarkable enhancement in root elongation at the low concentration.

When compared with **5a**, it is observed that introduction of different functional group into the aniline ring at different position leads to an increase of the root elongation activity. The order in enhancement in root elongation activity is *p*-substitution > *m*-substitution > *o*-substitution.

Acknowledgement

This work was supported by NSFC (20671077), the Key Project of Chinese Ministry of Education (205161) Gansu provincial Natural Science Foundation of China (3ZS061-A25-027) Scientific Research Fund for youth of gansu province in China

(3YS051-A25-010) Scientific Research Fund of Gansu Provincial Education Department (0601-24) and Key Laboratory of Eco-Environment-Related Polymer Materials (Northwest Normal University) Ministry of Education, which are gratefully acknowledged.

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