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Synthesis and Herbicidal Activity of 3-Hexyl-4-R-6,7-dimethoxy Isocoumarin

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According to Suzuki reaction, four kinds of 3-hexyl-4-R-6,7-dimethoxy isocoumarin derivatives have been designed and synthesized with the 3-hexyl-4-iodo-6,7-dimethoxy isocoumarin as raw materials. Their structures were characterized by ^{1}H NMR, ^{13}C NMR and mass spectrometry. The herbicidal activity of target compounds was studied through a small cup test. The results showed that the inhibition rates of compounds **1** and **2** on the root of *Amaranthus retroflexus L* were higher than 80 % at the concentration of 250 mg/L, while the inhibition rate of compound 3 to the stem of *Setaria viridis (L.) Beauv.* was over 80 % at the concentration of 500 mg/L. Compounds **1**, **2** and **3** were safe to the sorghum growth at the same concentration.

Keywords: Derivatives of 3-hexyl-4-R-6,7-dimethoxy isocoumarin, Synthesis, Herbicidal activity, Crop safety.

INTRODUCTION

Coumarin compounds are widely distributed in Apiaceae, Asteraceae, Ruta, Fabaceae, Sankoh, Rosaceae, Rubiaceae, Solanaceae and other natural plants [1]. The research and application of coumarin and its derivatives are extremely active in the field of medicine and they are also the important pesticide intermediates [2]. Apostolakos *et al.* [3] found that coumarin had an inhibition on the growth of *Beggars-ticks* and *Barnyardgrass* and could inhibit the synthesis of cellulose.

Isocoumarin is also the basic structure of natural products, whose derivatives have the physiological and biological activity of antibacterial [4], anti-inflammatory [5], anticancer [6], inhibition of proteases [7] and weeding [8]. It has become a hot topic in recent years and has a variety of synthetic methods [9,10].

We have already isolated the 4-(2-amino-propionyl-amino)-3,4,5,6,7,8,9,10-octahydro-5,6,8-three hydroxy-3-methyl isocoumarin from *Flaveria bidentis (L) Kuntze* [11]. Under the premise of retaining the parent structure of isocoumarin, we changed its structure in order to obtain some compounds having higher herbicidal activity.

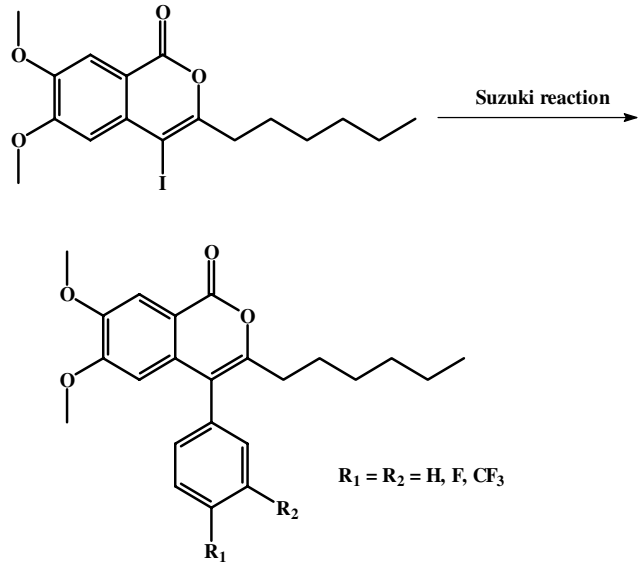
Suzuki coupling reaction, discovered by Suzuki [12], a relatively new cross-coupling reaction, was showing that palladium could catalyze aryl boronic acid and aryl halides. Suzuki reaction is widely used in the field of synthesis since 1981. In 1989, Beletskaya *et al.* [13] developed a new Suzuki coupling reaction system which was palladium catalyzed in the pure water without additional ligands. The author made the iodobenzoate and iodophenol reacted with benzene boronic in the conditions of $Pd(OAc)_2$ as the catalyst and Na_2CO_3 as the alkali.

On the basis of previous work, we got 3-hexyl-4-iodo-6,7-dimethoxy isocoumarin [14]. Using the 3-hexyl-4-iodo-6,7-dimethoxy isocoumarin as the raw material, we successfully synthesized four kinds of 3-hexyl-4-R-6,7-dimethoxy isocoumarin derivatives according to the Suzuki reaction principle. The test methods and steps are as follows,

In this study, iodide isocoumarin 3-hexyl-4-iodo-6,7-dimethoxy isocoumarin and R-boronic acid reacted on the basic of Suzuki reaction. The iodine was substituted by the R-phenyl and then 3-hexyl-4-(R-)-6,7-dimethoxy isocoumarin was synthesized, the reaction route is shown in **Scheme-I**.

EXPERIMENTAL

Synthesis of 3-hexyl -4-R-6,7-dimethoxy isocoumarin: 3-Hexyl-4-iodo-6,7-dimethoxy isocoumarin (0.01 mol), boric acid compound 0.012 mol and *tetrakis*(triphenylphosphine)-palladium (0.0001 mol) were put into a single jar and then add 10 mL benzene and 10 mL tetrahydrofuran. Dissolved 0.02 mol sodium carbonate to a saturated aqueous sodium carbonate with 15 mL water, then added it to the single jar. Installing the condenser and pump funnel and then using the pump to suction after sealing. When the solution is not bulging bubble, nitrogen was pumped until the balloon mustered at



Scheme-I

the top of condenser. The procedure was repeated twice, then begin stirring and heating, keeping temperature to 90 °C and refluxing overnight. TLC is used to track the reaction. The reaction solution was poured into a separatory funnel to remove the aqueous layer after the reaction was completed. The organic layer was washed three times with 30 mL water, then the organic solvent was removed by rotary evaporation under reduced pressure to get the crude red oil. The pure product of 3-hexyl-4-R-6,7-dimethoxy isocoumarin was obtained after the crude red oil was separated by column chromatography.

3-Hexyl-4-(4-fluorophenyl)-6,7-dimethoxy isocoumarin (1): White solid, yield, 52.28 %, m.p.: 57-59 °C. ^{1}H NMR (400 MHz, TMS/$CDCl_3$) δ, ppm (*J*, Hz): 0.82-0.86 (3H, t, *J* = 8.00, C-CH_3); 1.15-1.29 (2H, m, CH_2); 1.60-1.67 (2H, m, CH_2); 2.31-2.35 (2H, m, CH_2); 3.73 (3H, s, O-CH_3); 3.98 (3H, s, O-CH_3); 6.28 (1H, s, H_{Ar}); 7.18-7.24 (1H, m, $H_{Ar\text{-}F}$); 7.24-7.28 (1H, m, $H_{Ar\text{-}F}$); 7.71 (1H, s, H_{Ar}). ^{13}C NMR (400 MHz, $CDCl_3$) δ: 14.13 (-CH_3); 22.92 (C-16); 26.44 (C-13); 28.44 (C-14); 31.10 (C-15); 32.48 (C-12); 56.11 (-OCH_3); 108.35 (C-1); 109.64 (C-4); 114.78 (C-2); 115.39 (C-27); 115.55 (C-25); 118.82 (C-10); 130.70 (C-3); 130.76 (C-28); 130.83 (C-24); 131.47 (C-23); 150.87 (C-5); 151.26 (C-6); 160.22 (C=O); 162.27 (C-26); 164.64 (C-9).

3-Hexyl-4-(3-fluorophenyl)-6,7-dimethoxy isocoumarin (2): White solid, yield: 57.82 %, m.p.: 111-112 °C. ^{1}H NMR (400 MHz, TMS/$CDCl_3$) δ, ppm (*J*, Hz): 0.82-0.91 (3H, m, C-CH_3); 1.15-1.27 (2H, m, CH_2); 1.64-1.70 (2H, m, CH_2); 2.32-2.36 (2H, m, CH_2); 3.72 (3H, s, O-CH_3); 4.00 (3H, s, O-CH_3); 6.24 (1H, s, H_{Ar}); 7.51-7.53 (1H, d, *J* = 8, $H_{Ar\text{-}F}$); 7.60 (1H, s, $H_{Ar\text{-}F}$); 7.67-7.69 (1H, d, *J* = 4, $H_{Ar\text{-}F}$); 7.74 (1H, m, H_{Ar}). ^{13}C NMR (400 MHz, $CDCl_3$) δ: 13.89 (-CH_3); 22.37 (C-20); 27.64 (C-17); 28.69 (C-18); 31.30 (C-15); 31.36 (C-16); 55.91 (-OCH_3); 56.33 (-OCH_3); 105.18 (C-1); 109.68 (C-4); 113.19 (C-23); 114.72 (C-2); 122.52 (C-10); 125.04 (C-24); 127.52 (C-25); 129.52 (C-27); 131.50 (C-22); 133.92 (C-26); 135.69 (C-3); 149.37 (C=O); 154.74 (C-5)155.07 (C-6); 162.28 (C-9).

3-Hexyl-4-(4-trifluoromethylphenyl)-6,7-dimethoxy isocoumarin (3): White solid, yield: 55.38 %, m.p.: 78-80 °C. ^{1}H NMR (400 MHZ, TMS/$CDCl_3$), δ, ppm (*J*, Hz): 0.82-0.86 (3H, t, *J* = 8.00, C-CH_3); 1.14-1.26 (2H, m, CH_2); 1.60-1.68 (2H, m, CH_2); 2.30-2.34 (2H, m, CH_2); 3.73 (3H, s, O-CH_3); 3.99 (3H, s, O-CH_3); 6.24 (1H, s, H_{Ar}); 7.45 (1H, d, *J* = 4, $H_{Ar\text{-}F}$); 7.72 (1H, s, H_{Ar}); (1H, d, *J* = 4, $H_{Ar\text{-}F}$); ^{13}C NMR (100 MHz, $CDCl_3$), δ: 13.92 (-CH_3); 22.40 (C-16); 27.63 (C-13); 28.70 (C-14); 31.33 (C-12,15); 56.01 (-OCH_3); 56.32 (-OCH_3); 105.19 (C-2); 109.62 (C-10); 113.14 (C-1); 114.85 (C-4); 124.00 (-CF_3); 125.92 (C-27); 125.95 (C-29); 130.67 (C-28); 131.11 (C-26, 30); 133.73 (C-3); 138.68 (C-25); 149.36 (-C=O); 154.50 (C-5); 155.09 (C-6); 162.37 (C-9).

3-Hexyl-4-(3-trifluoromethylphenyl)-6,7-dimethoxy isocoumarin (4): White solid, yield: 50.33 %, m.p.: 102-104 °C. ^{1}H NMR (400 MHz, TMS/$CDCl_3$) δ, ppm (*J*, Hz): 0.81-0.91 (3H, m, C-CH_3); 1.14-1.36 (2H, m, CH_2); 1.61-1.77 (2H, m, CH_2); 2.31-2.37 (2H, m, CH_2); 3.74 (3H, s, O-CH_3); 3.99

TABLE-1
INHIBITORY EFFECT OF FOUR COMPOUNDS ON THE ROOT AND STEM OF *Setaria viridis (L.) Beauv* AND *Amaranthus retroflexus L*

Compound	Testing standards	IC_{50}	Toxicity regression equation	r^2
1	*Setaria viridis- root*	275.707	Y = -4.712 + 1.931X	0.937
	Setaria viridis- stem	498.270	Y = -4.928 + 1.827X	0.954
	Amaranthus- root	40.109	Y = -1.641 + 1.025X	0.925
	Amaranthus- stem	188.161	Y = -2.114 + 0.929X	0.935
2	*Setaria viridis- root*	165.231	Y = -2.003 + 0.902X	0.937
	Setaria viridis- stem	205.290	Y = -3.683 + 1.592X	0.924
	Amaranthus- root	101.026	Y = -4.659 + 2.325X	0.968
	Amaranthus- stem	273.177	Y = -4.450 + 1.826X	0.975
3	*Setaria viridis- root*	219.251	Y = -1.961 + 0.838X	0.990
	Setaria viridis- stem	41.782	Y = -1.471 + 0.908X	0.987
	Amaranthus- root	163.882	Y = -1.710 + 0.773X	0.959
	Amaranthus- stem	908.012	Y = -4.712 + 1.931X	0.960
4	*Setaria viridis- root*	550.623	Y = -1.902 + 0.694X	0.978
	Setaria viridis- stem	677.564	Y = -3.556 + 1.256X	0.970
	Amaranthus- root	1794.123	Y = -4.064 + 1.249X	0.986
	Amaranthus- stem	989.471	Y = -5.375 + 1.794X	0.978
Atrazine	*Setaria viridis- root*	32.170	Y = -2.883 + 1.922X	0.991
	Setaria viridis- stem	25.778	Y = -2.456 + 1.765X	0.969
	Amaranthus- root	29.829	Y = -2.824 + 1.930X	0.992
	Amaranthus- stem	32.147	Y = -3.420 + 2.268X	0.997

(3H, s, O-CH_3); 6.30 (1H, s, H_{Ar}); 7.01-7.10 (1H, m, H_{Ar-F}); 7.15-7.20 (1H, m, H_{Ar-F}); 7.44-7.54 (1H, m, H_{Ar-F}); 7.72 (1H, m, H_{Ar}); ^{13}C NMR (400 MHz, $CDCl_3$) δ: 13.97 (-CH_3); 22.42 (C-20); 27.62 (C-17); 28.72 (C-18); 31.41 (C-16, 19); 55.95 (-OCH_3); 56.34 (-OCH_3); 105.34 (C-1); 109.56 (C-4); 113.15 (C-2); 114.97 (C-28); 116.43 (C-24)117.74 (C-10); 126.42 (C-25); 127.78 (C-23); 130.52 (C-26); 133.99 (C-3); 136.91 (C-22); 149.27 (27); 154.42 (C-5)155.00 (C-6); 162.39 (C-7); 164.19 (C-9).

The herbicidal activity and crop safety of the four compounds were measured using the small cup method and the atrazine was the control agent. Foxtail and Amaranthus were selected as the test weeds and Sorghum as the test crop. Four compounds showed different inhibitory effect on the root and stem of Foxtail and Amaranthus, while they showed safe to sorghum (Table-1).

Conclusion

According to Suzuki reaction principle, four derivatives of 3-hexyl-4-R-6,7-dimethoxy isocoumarin using 3-hexyl-4-iodo-6,7-dimethoxy isocoumarin as raw materials were synthesized. The test procedure is simple and the yield of product is about 50 %. Three compounds showed a good herbicidal activity and had a different inhibitory effect on *Setaria viridis (L.) Beauv* and *Amaranthus retroflexus L.* It should be noted that this synthesis route is versatile and is suitable for the synthesis of a variety of different isocoumarin derivatives. So one can study their structure-activity relationships and biological activity, which will lay the foundation for the further study of the mechanism.

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