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Synthesis of 3-Hexyl-4-carboxylic acid-6,7-dimethoxy Isocoumarin

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In this work, 3-hexyl-4-carboxylic acid-6,7-dimethoxy isocoumarin was synthesized by the direct method and indirect methods with 3-hexyl-4-cyano-6,7-dimethoxy as the raw material. In the direct method, 3-hexyl-4-cyano-6,7-dimethoxy was directly hydrolyzed into 3-hexyl-4-carboxylic acid-6,7-dimethoxy isocoumarin with the mixture of concentrated sulfuric acid and glacial acetic acid as the reaction solvent. While in the indirect method, 3-hexyl-4-cyano-6,7-dimethoxy isocoumarin was firstly hydrolyzed into 3-hexyl-4-carboxamide-6,7-dimethoxy isocoumarin, which was then hydrolyzed into 3-hexyl-4-carboxylic acid-6,7-dimethoxy isocoumarin. By comparing the two methods, it could be concluded that the direct method had the advantages of simple operation, high conversion rate and no special catalyst, so it was a more ideal method to synthesize 3-hexyl-4-carboxylic acid-6,7-dimethoxy isocoumarin.

Keywords: Synthesis, 3-Hexyl-4-carboxylic acid-6,7-dimethoxy isocoumarin.

INTRODUCTION

Isocoumarin is a kind of natural lactone compound and its body skeleton is benzopyrone. Isocoumarin and its derivatives have a variety of biological activity and the researches are more focused on medicine [1]. The reports have shown that isocoumarin and its derivatives have antitumor effects and certain therapeutic effect on mice with alzheimer's disease [2,3]. The isocoumarin derivatives extracted from natural products often have low activity. Thus, in order to improve the biological activity of the obtained compounds, we need to modify their structures.

Heynekamp *et al.* [4] synthesized several new isocoumarin derivatives by changing the 3-methoxy into long-chain or cyclic ether and joining benzamide in 7 site of 3-methoxy-4-chloro-isocoumarin and the bioassay results shown that some of the compounds could enhance the inhibition of isocoumarin to pancreatic cancer.

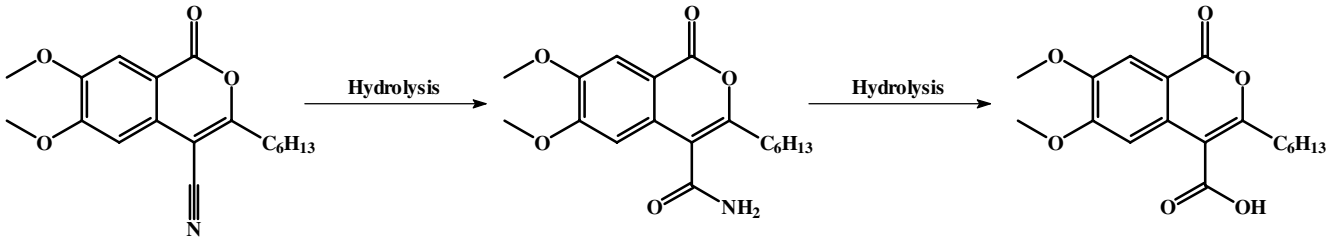
Some isocoumarin compounds with antibacterial activity were modified by Brasholz *et al.* [5]. As a result, the compounds not only had antibacterial activity but also had anticancer activity. At present, the researches on isocoumarin are more concentrated on anticancer [6,7] and antibacterial activities [8] and there is less research about herbicidal activities.

Our group obtained one herbicidal compound from *Flaveria bidentis* (L.) kuntze and the compound was identified as isocoumarins. To obtain the compound with higher herbicidal activity, we synthesized 3-hexyl-4-cyano-6,7-dimethoxy isocoumarin by using 2-amino-4, 5-dimethoxy benzoic acid as the starting material [9]. In this study, we synthesized 3-hexyl-4-carboxylic acid-6,7-dimethoxy isocoumarin by the direct method and indirect methods with the 3-hexyl-4-cyano-6,7-dimethoxy as the raw material. The study will lay a foundation for synthesizing isocoumarin derivatives with herbicidal activity.

EXPERIMENTAL

Synthesis of 3-hexyl-4-carboxylic acid-6,7-dimethoxy isocoumarin by indirect method: With the action of acetaldehyde oxime and copper catalyst, 3-hexyl-4-cyano-6,7-dimethoxy isocoumarin was first hydrolyzed into 3-hexyl-6,7-dimethoxy-4-carboxamide isocoumarin [10], which then hydrolyzed into 3-hexyl-6,7-dimethoxy-4-carboxylic acid isocoumarin (**Scheme-I**).

Synthesis of 3-hexyl-6,7-dimethoxy-4-carboxamide isocoumarin: 3-Hexyl-4-cyano-6,7-dimethoxy isocoumarin (10 mmol) and CuI (1 mmol) were put into a 50 mL three-necked flask and then DMF (10 mL) was added as solvent. The mixture was stirred and acetaldoxime (15 mmol) was added into the mixture. The reaction mixture was heated under reflux for 0.5 h. After cooling, the black solid was filtered off with suction through a frit. Then 30 mL water was added into the filtrate and the resulting precipitate was filtered off to give the gray-white solid. The crude product was purified by column



Scheme-I

chromatography to get white powder (ethyl acetate:petroleum ether = 3:1).

Yield: 88.2 %, m.p.: 159-162.1 °C, MS: 333.17. ^{1}H NMR (400 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 0.82-0.90 (3H, t, *J* = 16.00 Hz, C-CH_3); 1.24-1.30 (2H, m, CH_2); 1.32-1.39 (2H, m, CH_2); 1.67-1.78 (2H, m, CH_2); 2.61-2.65 (2H, m, CH_2); 3.88 (3H, s, O-CH_3); 3.93 (3H, s, O-CH_3); 6.38 (1H, s, NH_2); 6.84 (1H, s, H_{Ar}); 7.30 (1H, s, H_{Ar}); ^{13}C NMR (400 MHz, $CDCl_3$), δ: 14.00 (C-17); 22.46 (C-16); 27.60 (C-13); 28.94 (C-14); 31.44 (C-15); 32.01 (C-12); 56.05 (C-24); 56.27 (C-23); 104.41 (C-11); 109.02 (C-10); 112.38 (C-4); 130.35 (C-3); 149.45 (C-9); 155.26 (C-6); 155.35 (C-5); 161.87 (C=O); 167.74 (C=O).

Optimization of synthesis of 3-hexyl-4-carboxamide-6,7-dimethoxy isocoumarin: The different solvents and reaction time were compared in this study (Table-1).

In addition, because of the catalytic effect of CuO was not very good, we screened a series of copper catalyst to optimize reaction result (Table-2).

The yields of compounds **3**, **4**, **5** and **6** were 83.71, 89.91, 87.66 and 89.91 %, respectively.

According to the reaction results, it is found that the best reaction condition with CuI as catalyst is: 3-hexyl-4-cyano-6,7-dimethoxy isocoumarin (1 equivalent), CuI (0.1 equivalent), acetaldoxime (1.5 equivalent), DMF as solvent, refluxing for 0.5 h.

Synthesis of 3-hexyl-4-carboxylic acid-6,7-dimethoxy isocoumarin: 3-Hexyl-4-carboxamide-6,7-dimethoxy isocoumarin (0.01 mol) was dissolved in 10 mL of dimethyl sulfoxide and 10 mL of 30 % aqueous hydrochloric acid was added in succession. Then aqueous solution of sodium nitrite was slowly dropped under ice-alcohol bath. After 4 h of stirring under the temperature lower than 0 °C, 50 mL of water were added and the mixture was stirred for 10 min under a low temperature. The resulting precipitate was filtered off with suction through a frit and the crude product was obtained. The crude product was purified by column chromatography to get pure product (ethyl acetate:dichloromethane = 3:2).

MS: 334.1495, ^{1}H NMR (400 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 0.83-0.87 (3H, t, *J* = 8.00 Hz, C-CH_3); 1.26-1.38 (2H, m, CH_2); 1.59-1.65 (2H, m, CH_2); 2.53-2.56 (2H, m, CH_2); 3.87 (3H, s, O-CH_3); 3.88 (3H, s, O-CH_3); 6.87 (1H, s, H_{Ar}); 7.46 (1H, s, H_{Ar}); 10.09 (1H, s, COOH); ^{13}C NMR (400 MHz, CDCl3), δ: 14.33 (C-17); 22.40 (C-16); 27.35 (C-13); 28.62 (C-14); 31.35 (C-15); 31.54 (C-12); 56.21 (C-24, 23); 105.54 (C-1); 112.81 (C-10); 113.32 (C-4); 114.42 (C-2); 129.66 (C-3); 147.83 (C-25); 153.13 (C-5); 154.87 (C-6); 161.20 (C=O); 167.26 (C=O).

Synthesis of 3-hexyl-4-carboxylic acid-6,7-dimethoxy isocoumarin by direct method: Using 3-hexyl-4-cyano-6,7-dimethoxy isocoumarin as raw materials, 3-hexyl-4-carboxylic acid-6,7-dimethoxy isocoumarin was directly generated under

TABLE-1
RESULTS OF REACTION UNDER DIFFERENT SOLVENTS AND REACTION TIME WITH CuO AS CATALYST

Number	Catalyst (%)	Acetaldoxime (eqv)	Solvent	Reaction time (h)	Conversion rates (%)
1	10	1	Water	24	–
2	10	1	Methanol	24	–
3	10	1	Dichloromethane	24	3.84
4	10	1	Ethyl acetate	24	–
5	10	1	DMF	24	44.46
6	10	1	DMF	12	49.25
7	10	1	DMF:Water (3:1)	12	40.11
8	10	1.5	DMF	12	52.41
9	10	2	DMF	12	53.19
10	10	4	DMF	12	56.88
11	20	1	DMF	12	43.24

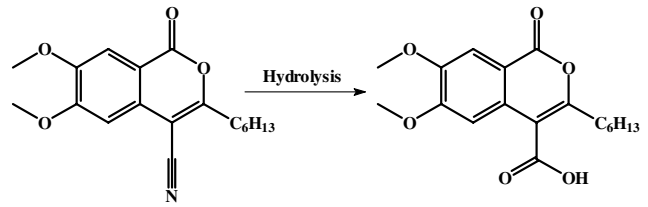
TABLE-2
REACTION EFFICIENCY UNDER DIFFERENT CATALYSTS

Number	Catalyst (%)	Acetaldoxime (eqv)	Solvent	Reaction time (h)	Conversion rates (%)
1	CuO	1.5	DMF	12.0	51.35
2	CuI	1.5	DMF	12.0	69.84
3	CuI	1.5	DMF	0.5	85.69
4	CuBr	1.5	DMF	1.0	83.4
5	CuCl	1.5	DMF	1.0	79.32
6	Cu_2O	1.5	DMF	1.5	75.31

TABLE-3
EFFICIENCY OF HYDROLYSIS REACTION UNDER DIFFERENT PROPORTION OF CONCENTRATED SULFURIC ACID AND GLACIAL ACETIC ACID

Number	Solvent (concentrated sulfuric acid: glacial acetic acid)	Reaction temperature (°C)	Reaction time (h)	HPLC (%)	
				Formamide	Formic acid
1	1:1	90	1.0	41.53	–
2	6:4	90	3.0	55.46	6.81
3	7:3	90	6.0	51.71	29.08
4	8:2	90	4.0	13.11	83.4
5	9:1	90	4.0	6.77	88.97
6	9:1	70	12.0	19.28	42.37
7	9:1	80	5.0	24.63	58.82
8	9:1	100	2.5	5.51	80.49

the conditions of sulfuric acid and glacial acetic acid as solvent and high temperature. The reaction scheme is as the following:



3-Hexyl-4-cyano-6,7-dimethoxy isocoumarin (10 mmol) and 10 mL of 90 % concentrated sulfuric acid and glacial acetic acid were put into three-necks flask. The reaction mixture was heated under 90 °C. The reaction was detected by TLC. After reaction, the temperature was cooled to room temperature and the reaction liquid was dropped slowly into ice water with the temperature lower than 30 °C.

50 mL of ethyl acetate was added into the above solution and the mixture was stirred for a moment. The pH was adjusted to 4-5. The aqueous layer was then extracted three times with 20 mL of ethyl acetate. The aqueous layer was discarded and the grey solid was obtained from the organic layer after rotary evaporation. The grey solid was purified by column chromatography (petroleum ether:ethyl acetate = 1:4).

The melting point of the products obtained by the direct method and indirect method was 156 °C. The products obtained by the two methods were also detected by HPLC and the result shown that the retention time was consistency.

Optimization of the direct method to synthesis 3-hexyl-4-carboxylic acid-6,7-dimethoxy isocoumarin: We studied the effect of different proportions of glacial acetic acid and concentrated sulfuric acid and different temperatures on the yield of 3-hexyl-4-carboxylic acid-6,7-dimethoxy isocoumarin (Table-3).

Conclusion

In this study, 3-hexyl-4-carboxylic acid-6,7-dimethoxy isocoumarin was synthesized by the direct method and indirect methods with 3-hexyl-4-cyano-6,7-dimethoxy as the raw material. By comparing the two methods, it is concluded that the direct method of preparation of 3-hexyl-4-carboxylic acid-6,7-dimethoxy isocoumarin had the advantages of simple operation, high conversion rate and no special catalyst required. This study will lay a foundation for developing the new isocoumarin derivates with herbicidal activity.

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