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Synthesis of 3-Hexyl-4-cyan-6,7-dimethoxy Isocoumarin

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4-(2-Amino-propanamideyl)-3,4,5,6,7,8,9,10-octahydro-5,6,8-trihydroxy-3-methyl-isocoumarin, which was isolated from *Flaveria bidentis* (L) Kuntze, had herbicidal activity and its structure was modified in this research in order to get the isocoumarin compouds with higher herbicidal activity. The reaction starts with 2-amino-4,5-dimethoxy benzoate and then diazo iodination, esterfication, heck coupling, cyclization reaction and cyna substitution reaction were tested to obtain 3-hexyl-4-cyan-6,7-dimethoxy isocoumarin. The isocoumarin derivative is an appropriate precursor for the synthesis of new herbicide.

Keywords: Isocoumarin, Herbicidal activity, Diazo iodination, Esterfication, Heck coupling, Cyclization reaction.

INTRODUCTION

Isocoumarin compounds were widely existed in the umbelliferae, asteraceae, rutaceae, leguminosae, moraceae, rosaceae, rubiaceae, solanaceae and other natural plants. Research and application of coumarin and its derivatives in the field of medicine was very active, especially for the development of anti-cancer drugs[1]. In addition, coumarin was an important pesticide intermediate. The bromine, tribromo-substituted derivatives of hydroxymethyl coumarin could effectively kill the newly hatched larvae of Aedes aegypti[2]. Coumarin was also an important allelopathic compound. The furanocoumarins had a high herbicidal activity and it could inhibit the germination of wild mustard at the concentration of 10^{-9} mol/L[3]. The coumarin and 7-methoxycoumarin had been isolated from lavender and they could inhibit the growth of annual ryegrass[4]. The 4-(hydroxymethyl)-7-substituted coumarin could inhibit the mung bean[5]. It has been found that coumarin could inhibit bidens and barnyard grass as well as the synthesis of plant cellulose[6]. In the previous study, we had isolated a high herbicidal activity substance named 4-(2-amino-propanamideyl)-3,4,5,6,7,8,9,10-octahydro-5,6, 8-hydroxy-3-methyl-isocoumarin (**1**) (Fig. 1) from *Flaveria bidentis* (L) Kuntze. However, the OH group in the molecule might be unstable in plants. So under the condition of retaining the precursor of isocoumarin, we try to modify its structure to get a compound with a higher herbicidal activity by the following two routes to synthetize the 3-hexyl group, 4-cyano-6,7-dimethoxy isocoumarin (**11**).

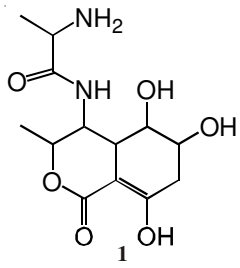

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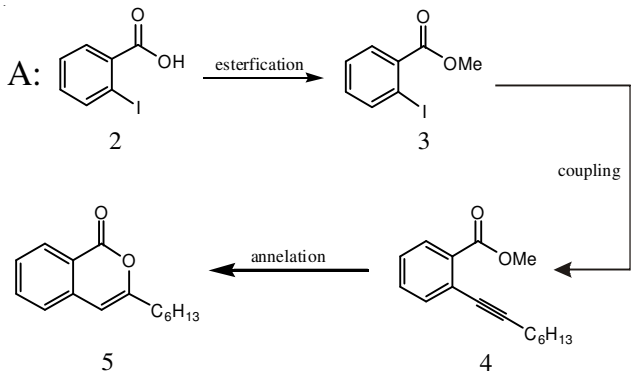
Fig. 1.

EXPERIMENTAL

Route A: The synthesis of **5** was shown in **Scheme-I**. The reaction was carried out under the joint action of K_2CO_3, $(CH_3)_2CO$, CH_3I at room temperature and began with **2** *via* column chromatography separation and purification to give **3**. Compound **3** occurred sonogashira cross coupling reaction with



Scheme-I: General route for the synthesis of 3-hexyl isocoumarin

$CH_3(CH_2)_4CH_2CCH$ in the $Pd(OAc)_2$, DABCO, KOH, PEG 400 catalytic system under the action and argon atmosphere to obtain **4**. Then $FeCl_3$ promoted **4** in CH_3CN to occurred electrophilic cyclization reaction under the argon atmosphere of 80 °C. However, it was difficult to obtained **11** when we used 6 as a starting material. Thus we developed route B (**Scheme-II**) to yield **11**.

4,5-Dimethoxy-2-iodo-benzoic acid (7): 36.5 % aqueous HCl (105 mL) was added dropwise to a mixture of **6** (59.16 g, 300 mmol) in water (300 mL), which was stirred with cooling in an ethanol bath of -10 °C. After that a solution of $NaNO_2$ (22.2 g, 321.7 mmol) in H_2O (108 mL) was added dropwise to the reaction mixture at -2 to 0 °C and srirred for 20 min and then a solution of KI (99.6 g, 600 mmol) in water (120 mL) was added to the mixture with a rapid dropwise and stirred for 0.5 h at -2 to 0 °C. The resulting mixture was slowly poured into a 2000 mL beaker in a water bath of 90 °C, stirred for about 0.5 h. The solid deposited was isolated by filtration, washed with water (100 mL × 3) at room temperature. The resulting solid was dissolved with anhydrous CH_3OH (630 mL) by heating. The CH_3OH solution was filtered again and then dried over Na_2SO_4 and concentrated under reduced pressure to give compound **7** (83.40 g, 90.24 % yield) as a slightly red solid. m.p. 106-108 °C. ^{1}H NMR (300 MHz, DMSO): δ 7.36 (s, 1H, ArH), 7.33 (s, 1H, ArH), 3.82-3.77 [m, 6H, $(OCH_3)_2$]. ^{13}C NMR (300 MHz, DMSO): δ 167.6, 150.9, 148.4, 125.0, 123.2, 113.7, 84.3, 55.1, 55.7. MS, *m/z* (%): 308 (M^+, 75), 350 (100).

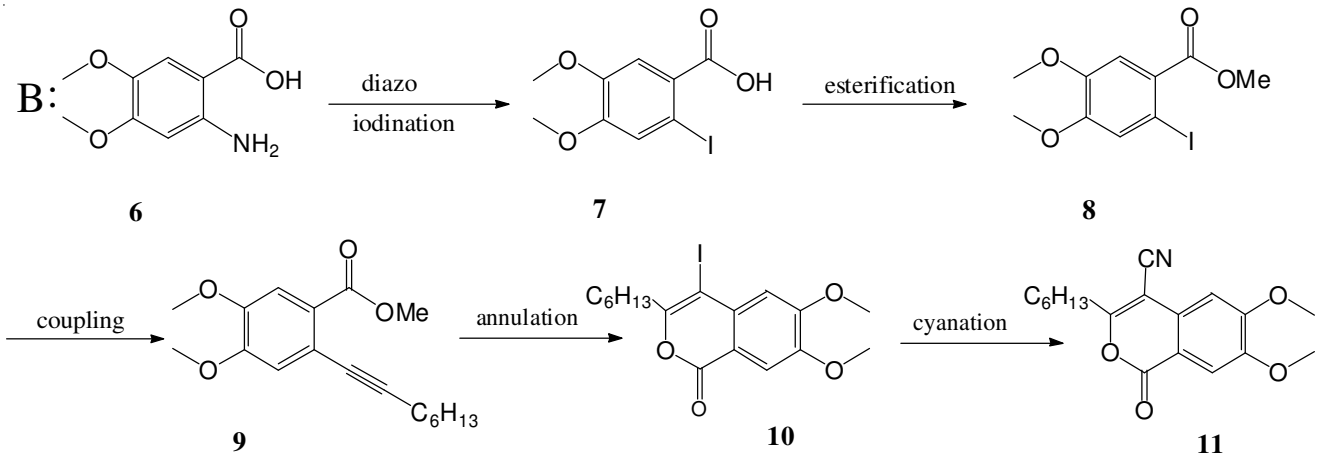
HPLC analysis showed that the purity of **7** was higher than 98 %. This product was used in the next step without any further purification and characterization.

4,5-Dimethoxy-2-iodo-benzoate (8): A solution of 98 % H_2SO_4 (30 mL) was slowly added to a solution of **7** (40.8 g, 132.4 mmol) in CH_3OH (380 mL) and the mixture heated under reflux for 6.5 h. The reaction mixture was evaporated CH_3OH (340 mL) under reduced pressure, filtered and then the solid was dissolved in ethyl acetate (200 mL). The ethyl acetate solution was added water (200 mL), K_2CO_3 (12 g, 86.8 mmol) and stirred for about 10 min. After that the mixture solution was extracted twice with ethyl acetate (50 mL). The organic layers combined were washed with water (200 mL × 3) and dried over Na_2SO_4 and concentrated under reduced pressure to give compound **8** (40.09 g, 95.91 % yield) as a greenish solid[7]. m.p. 107-109 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.44 (s 1H, ArH), 7.39 (s, 1H, ArH), 3.94-3.90 [m, 9H, $(OCH_3)_3$]. ^{13}CNMR (300 MHz, $CDCl_3$): δ 165.9, 151.9, 148.7, 126.1, 123.8, 113.9, 84.6, 56.2, 56.0, 52.2. MS, *m/z* (%): 322 (M^+, 100).

O-octynyl 4,5-dimethoxybenzoate (9): A Et_3N (250 mL, 1787.7 mmol) solution of **8** (50.04 g, 164.4 mmol), C_8H_{14} (20 g), $C_{36}H_{30}Cl_2P_2Pd$ (1.0006 g, 1.43 mmol) and CuI (0.5063 g, 2.66 mmol) was stirred in a water bath of 55 °C for 6 h. The reaction mixture was filtered twice and then the liquid was dissolved in ethyl acetate (300 mL). The ethyl acetate phase was washed with water (200 mL × 3) and dried over and concentrated under reduced pressure to give compound **9** (41.62 g, 88.01 % yield) as a yellow solid[8]. m.p. 47-49 °C. ^{1}H NMR (300 MHz $CDCl_3$): δ 7.44 (s, 1H, ArH), 6.95 (s, 1H, ArH), 3.91 [s, 9H, $(OCH_3)_3$], 2.47 (t, *J* = 6.9 Hz, 2H, ≡C-CH_2), 1.70-1.60 (m, 2H, CH_2), 1.53-1.43 [m, 2H, (CH_2)], 1.38-1.25 [m, 4H, $(CH_2)_2$], 0.89 (t, *J* = 6.6 Hz, 3H, CH_3). ^{13}C NMR (300 MHz, $CDCl_3$): δ 166.5, 151.5, 148.0, 124.3, 118.5, 116.1, 112.7, 94.6, 79.4, 56 (2C), 51.9, 31.4, 28.8, 28.7, 22.6, 19.9, 14.0. MS, *m/z* (%): 304.2 (M^+, 100).

3-Hexyl-4-iodo-6,7-dimethoxy isocoumarin (10): A solution of ICl (2 g, 12.3 mmol) was slowly added to a CH_2Cl_2 (60 mL) solution of 9 (4 g, 13.14 mmol) and the mixture was stirred at room temperature for 45 min. The reaction mixture was washed with water (50 mL × 3) and dried over Na_2SO_4 and concentrated under reduced pressure. The solid was dissolved in CH_3OH (28 mL) under heating and cooled to 5-7 °C and then filtered and repeated dissolution process twice to give **10** (3.668 g, 67.06 % yield) as a colorless solid[9-10]. m.p. 111-113 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.64 (s, 1H, ArH), 7.15 (s, 1H, ArH), 4.06 [s, 3H, (OCH_3)], 3.99 [s, 3H, (OCH_3)], 2.90 (t, *J* = 8.1 Hz, 2H, CH_2), 1.76-1.68 (m, 2H, CH_2), 1.43-1.30 [m, 6H, $(CH_2)_3$], 0. 90 (t, *J* = 6.9 Hz, 3H, CH_3). ^{13}C NMR (300 MHz, $CDCl_3$): δ 155.8, 125, 111.9, 109.6, 106.1, 56.8, 56.5, 56.3, 37.3, 31.5, 31.4, 28.7, 28.7, 27.3, 22.5, 22.4, 14 MS, *m/z* (%): 416.2 (M^+, 100).

3-Hexyl-4-cyano-6,7-dimethoxy isocoumarin (11): A DMF (100 mL) solution of 10 (4.15 g, 1 mmol) and Cu_2CN_2 (1.088 g, 6.1 mmol) was heated under reflux for 6 h. The reaction mixture was filtered at the temperature of 90 °C, concentrated DMF under reduced pressure and the solid deposited in the bottle at a low temperature was added the solution of 98 % H_2SO_4 (1 mL) in water (10 mL) and stirred in a water bath of 60 °C for about 0.5 h. Then the mixture was



Scheme-II: Route for the synthesis of 3-hexyl-4-formyl-6,7-dimethoxy-isocoumarin

cooled to 25 °C and filtered to give **11** (3.01 g, 95.73 %) as a gray solid[11]. m.p. 153-155 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.62 (s, 1H, ArH), 7.03 (s, 1H, ArH), 4.06 [s, 3H, (OCH_3)], 3.99 [s, 3H, (OCH_3)], 2.85 (t, J = 7.5 Hz, 2H, CH_2), 1.83-1.75 (m, 2H, CH_2), 1.44-1.25 [m, 6H, $(CH_2)_3$], 0. 90 (t, J = 6.9 Hz, 3H, CH_3). ^{13}C NMR (300 MHz, $CDCl_3$): δ 167.9, 159.8, 156.1, 150.5, 128.9, 114.6, 111.7, 109.8, 104.5, 91.8, 56.6, 56.5, 33.6, 31.3, 28.6, 27.3, 22.4, 14.0. MS, *m/z* (%): 315.2 (M^+, 100).

Conclusion

2-Amino-4,5-dimethoxy benzoate was used as the initiator and then diazo iodination, esterfication, heck coupling, cyclization reaction and cyna substitution reaction were experimented to got 3-hexyl-4-cyan-6,7-dimethoxy isocoumarin. In summary, we have explored a feasible and versatile approach to compound **11**. Each step of the reaction is easily performed and has a considerable yield except the synthesis of compound **10**. It should be noted that the route B is general and should be applied to the synthesis of a large variety of isocoumarin derivatives. A key step of this approach involves the reaction of cyano-substituted iodine and it lays a foundation for the subsequent reaction.

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