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A case study of the iodine-mediated cyclization of C_2'-OH- and C_2-OH-chalcones toward the synthesis of flavones: Reinvestigation of the mechanisms

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Abstract

Synthesis of flavones from chalcones via the iodine-mediated cyclization required at least one hydroxy group at their C_2'-positions. On the contrary, the ring oxidative cyclization from C_2-OH-chalcones under the same condition was unusual and reported only once. We evaluated the aforementioned method and found different results. The mechanisms in detail were discussed.

KEYWORDS

chalcone, Claisen-Schmidt condensation, flavone, iodine-mediated cyclization

1 | INTRODUCTION

Flavones distributed widely in plant kingdoms and exhibited a broad spectrum of biological activity.[1] Chalcones could be served as important intermediates to synthesize flavones.[2] A variety of conditions were employed on synthesis of flavones from chalcones, such as I_2/dimethyl sulfoxide (DMSO), SiO_2/I_2, NH_4I, PIDA/MeOH, SiO_2-SeO_2/MW, etc.[3] Among these oxidative cyclization methods, the most common and convenient strategy was mediated by iodine in DMSO. In this regard, chalcones with a hydroxyl group at their C_2' positions were essential (Figure 1, path a). On the other hand, chalcones with a C_2-OH group for the synthesis of flavones mediated either by iodine in various solvents or in solvent-free condition (neat) were also reported[4] (Figure 1, path b).

With the ongoing project in the synthesis of flavones for evaluation of their biological activities, we have synthesized a series of chalcones containing with either C_2'-OH or C_2-OH or both and with different substituents on arenes. Chalcones reported in this article were synthesized by Claisen-Schmidt condensation from the corresponding ketones and aldehydes. During this course, we observed that the C_2-OH positions in chalcones studied in this article were not practical in formation of corresponding flavones as described in the literature[4] (via *infra*). The very low yields of expected flavones or a complicated mixture were received. We, therefore, intend to evaluate this strategy.

2 | RESULTS AND DISCUSSION

Chalcones **1** and **2** were prepared from 2-hydroxyacetophenone and 4-bromo-2-hydroxyacetophenone to condense with the corresponding aldehydes, respectively. Compounds **1** and **2** were conducted by the iodine-mediated cyclization in

Yu-Tzu Huang and Cing-Ling Kuo contributed equally to this study.

DMSO to lead to the expected flavones **3**[5] and **4** in 96 and 73% yields, respectively (Scheme 1).

We are inspired by a reported procedure in the synthesis of flavones from C_2-OH-chalcones mediated by either iodine in various solvents or molecular iodine.[4] In order to testify whether either C_2'-OH or C_2-OH of chalcones is more favorable in formation of flavones, we, therefore, synthesized compounds **5** and **10,** which possessed with both hydroxyl groups at their C_2'- and C_2-positions for evaluation, respectively (Scheme 2).

However, when compound **5** was treated with $I_{2(cat)}$/DMSO, neither expected products **8** nor **9** were received but 2-acylbenzofuran **6** was isolated as major component in 16% yield. Compound **6** was further methylated to afford **7** in 65% yield. When compound **10** was treated with the aforementioned condition, the similar result was received as mentioned in compound **5**. The 2-acylbenzofuran **11** was isolated as major component in 15% yield and no expected compounds **8** and **9** were obtained. We also tried compounds **5** and **10** in treatment of molecular iodine under solvent-free condition as described in the literature.[4] Unfortunately, the results were complicated by thin layer chromatography (TLC) indication in both cases. Therefore, our proposal to synthesize flavones **8** and **9** from compounds **5** and **10**, respectively, was not successful at least in this study.

Benzofurans are oxygen-containing heterocycles distributed in nature and possessed a wide variety of biological activities.[6] The synthesis of 2-acylbenzofurans from chalcones under similar strategy (I_2/TBHP/NaN_3) was reported previously.[7] We suspected the intramolecular hydrogen bonding between C_2'-OH with carbonyl groups of **5** and **10,** which enforced the formation of 2-acylbenzofurans **6** and **11**, respectively (Figure 2, intermediate **13**, s-cis conformation). On the contrary, we rationalized that the hydrogen bonding between C_2'-OH and C_2-OH groups retarded in favor of formation of **8** and **9** (Figure 2, intermediate **14**, *s-trans* conformation).

We intended to evaluate whether compounds **15** and **16** were cyclized in the presence of either $I_{2\ (cat)}$/DMSO or I_2 (cat, solvent-free condition) (Scheme 3). We observed that both compounds **15** and **16** under $I_{2\ (cat)}$/DMSO condition led to a complicated mixture by TLC indication. When compound **15** was treated with I_2 under solvent-free condition, compound **3** was isolated as major component in 23% yield. The aforementioned condition was also applied on compound **16** to afford only **4** as major compound in 16% yield.

The plausible mechanism for synthesis of **3** and **4** from **15** and **16**, respectively, was depicted in Figure 3. Whereas the *E* conformation of compounds **15** and **16** must be mediated by iodine to be converted into their *Z*-isomers (**17** → **19** then **19** → **21**) before obtaining **3** and **4**, respectively. We found that synthesis of flavones from the C_2-OH of chalcones either **15** or **16** was not so efficient as

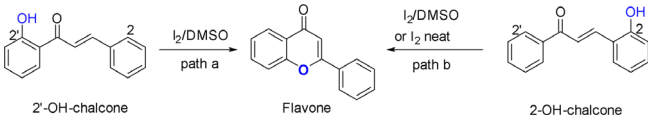
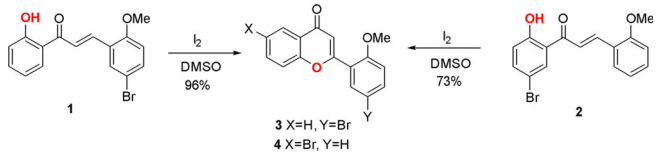


FIGURE 1 General strategy in synthesis of flavone from chalcone via the iodine-mediated cyclization



SCHEME 1 The iodine-mediated cyclization in synthesis of flavones **3** (from **1**) and **4** (from **2**)

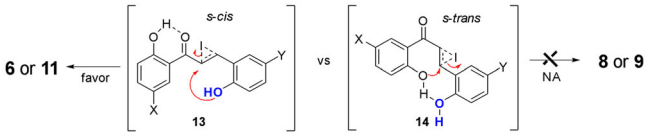
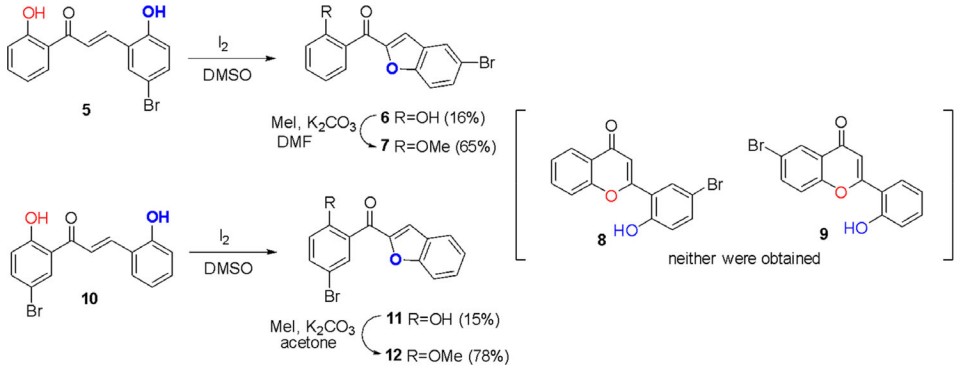


FIGURE 2 Plausible mechanisms in favor of formation of **6** or **11** over **8** or **9** from **5** and **10**, respectively



SCHEME 2 The iodine-mediated cyclization in synthesis of 2-acylbenzofurans **6** (from **5**) and **11** (from **10**)

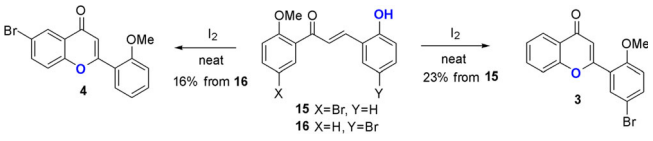
described in the reported protocol[4] in our present study. Further, the repeated column chromatography and recrystallization were needed in order to remove the contaminated impurity from **3** and **4** to result in their low yields. We suspect that iodine is not efficiently enough to isomerize the double bonds of compounds **15** and **16** in both cases.

3 | EXPERIMENTAL

All chemicals were purchased from Sigma-Aldrich and Alfa-Aesar companies and used without further purification. ^{1}H and ^{13}C spectra were recorded on a Bruker 600 MHz instrument. The chemical shifts were reported in part per million (ppm) as residual solvent as internal standard ($CDCl_3$: ^{1}H, 7.26 ppm; ^{13}C, 77.0 ppm). Silica gel used for purification was purchased from Fuji silysia chemical, LTD (Chromatorex GS60-40/75). The melting points were determined by MP-2D apparatus and uncorrected. High resolution mass spectrometry (HRMS) data were recorded on Bruker UltraFlex II for ESI.

3.1 | 2-(5-Bromo-2-methoxyphenyl)-4*H*-chromen-4-one (3)

Compound **1** (0.050 g, 0.15 mmol) and iodine (0.0095 g, 0.0075 mmol) in DMSO (1.0 ml) were heated at 130–140°C in a sealed tube for 24 hr. At the end of reaction, the mixture was diluted with $Na_2S_2O_3$ (sat'd) and extracted with ether. The organic layer was separated, dried ($MgSO_4$), and purified by flash column chromatography (EtOAc:Hexane = 1:10–1:5; EtOAc:Hexane = 1:4, R_f = 0.8) to afford **3** (0.0478 g, 0.145 mmol) as a white solid. Yield: 96%. Mp 160–165°C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.21 (dd, J = 7.9, 1.6 Hz, 1H), 8.01 (d, J = 2.5 Hz, 1H), 7.69 (td, J = 8.6, 1.6 Hz, 1H), 7.56–7.54 (m, 2H), 7.41 (td, J = 8.1, 1.0 Hz, 1H), 7.13 (s, 1H), 6.92 (d, J = 8.9 Hz, 1H), 3.92 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 178.7, 159.0, 157.1, 156.4, 134.8, 133.7, 131.7, 125.6 (2x), 125.1, 123.7, 122.5, 118.0, 113.6, 113.1, 56.0. HRMS (ESI) calcd. For $C_{16}H_{12}BrO_3$ $[M + H]^+$ 330.9970. Found: 330.9964.



SCHEME 3 Synthesis of **3** (from **15**) and **4** (from **16**) via molecular iodine under solvent-free condition

3.2 | 6-Bromo-2-(2-methoxyphenyl)-4*H*-chromen-4-one (4)

Compound **2** (0.0738 g, 0.222 mmol) and iodine (0.0040 g, 0.0158 mmol) in DMSO (1.33 ml) were heated at 140°C in a sealed tube for 26 hr. At the end of reaction, the mixture was diluted with ether and H_2O. The organic layer was separated, dried ($MgSO_4$), and purified by flash column chromatography (Hexane:CH_2Cl_2 = 1:1; Hexane: CH_2Cl_2 = 1:10, R_f = 0.35) to afford **4** (0.0534 g, 0.161 mmol) as a light brown-yellow solid. Yield: 73%. Mp 146–149°C (161–164°C).[5] ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.34 (d, J = 2.5 Hz, 1H), 7.87 (dd, J = 7.8, 1.7 Hz, 1H), 7.74 (dd, J = 8.9, 2.4 Hz, 1H), 7.48 (ddd, J = 9.1, 7.5, 1.8 Hz, 1H), 7.41 (d, J = 8.8 Hz, 1H), 7.15 (s, 1H), 7.10 (d, J = 7.7, 1.1 Hz, 1H), 7.04 (d, J = 8.3 Hz, 1H), 3.93 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 177.5, 161.1, 158.0, 155.2, 136.44, 132.7, 129.2, 128.2, 125.1, 120.8,

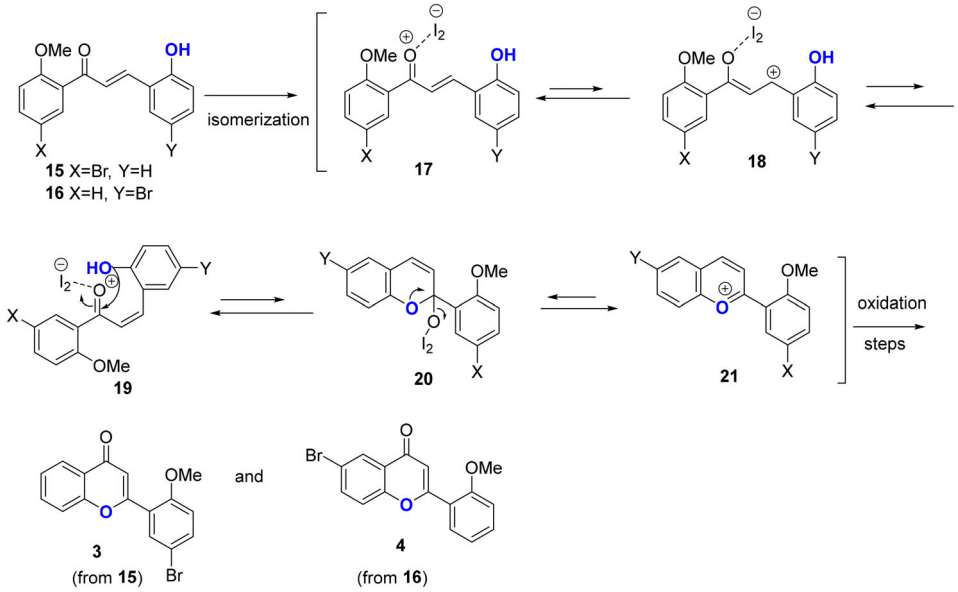


FIGURE 3 Plausible mechanism in synthesis of **3** (from **16**) and **4** (from **15**)

120.4, 120.0, 118.3, 112.6, 111.8, 55.7. HRMS (ESI) calcd. For $C_{16}H_{12}BrO_3$ $[M + H]^+$ 330.9970. Found: 330.9960.

3.3 | (5-Bromobenzofuran-2-yl)(2-hydroxyphenyl)methanone (6)

Compound **5** (0.3208 g, 1.0052 mmol) was treated with the same procedure as described in preparation of **3**. Purification by flash column chromatography (EtOAc:Hexane = 0:1–1:20–1:10; EtOAc:Hexane = 3:10, R_f = 0.7) afforded **6** (0.0510 g, 0.161 mmol) as a yellow solid. Yield: 16%. Mp 130–133°C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 11.95 (s, 1H), 8.35 (d, J = 8.0 Hz, 1H), 7.89 (s, 1H), 7.62–7.60 (br s, 2H), 7.57 (d, J = 7.5 Hz, 1H), 7.55 (t, J = 9.0 Hz, 1H), 7.26 (s, 1H), 7.08 (d, J = 8.3 Hz, 1H), 7.02 (t, J = 7.7 Hz, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 186.4, 163.6, 154.6, 153.1, 136.9, 131.7, 131.4, 128.6, 125.7, 119.3, 118.8, 118.7, 117.3, 115.4, 114.0. HRMS (ESI) calcd. For $C_{15}H_{10}BrO_3$ $[M + H]^+$ 316.9813. Found: 316.9809.

3.4 | (5-Bromobenzofuran-2-yl)(2-methoxyphenyl)methanone (7)

Compound **6** (0.0362 g, 0.114 mmol) and K_2CO_3 (0.0350 g, 0.25324 mmol) were dissolved in dimethylformamide (DMF) (1.0 ml) then followed by addition of MeI (0.0243 g, 0.17122 mmol). This mixture was stirred at ambient temperature for 1.5 hr then neutralized with 2 N HCl and diluted with ether and H_2O. The organic layer was separated, dried ($MgSO_4$), and concentrated. The solid was recrystallized from EtOAc and hexane to afford **7** (0.0245 g, 0.0740 mmol, EtOAc:Hexane = 3:10, R_f = 0.45) as a white solid. Yield: 65%. Mp 118–119°C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.81 (s, 1H), 7.56 (d, J = 8.8 Hz, 1H), 7.52 (t, J = 8.1 Hz, 1H), 7.49 (d, J = 9.2 Hz, 1H), 7.48 (d, J = 9.5 Hz, 1H), 7.25 (s, 1H), 7.07 (t, J = 7.4 Hz, 1H), 7.03 (d, J = 8.4 Hz, 1H), 3.8 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 184.7, 157.7, 154.6, 154.0, 132.9, 131.2, 129.8, 129.1, 127.5, 125.8, 120.5, 116.8, 115.0, 114.1, 111.7, 55.8. HRMS (ESI) calcd. For $C_{16}H_{12}BrO_3$ $[M + H]^+$ 330.9970. Found: 330.9970.

3.5 | Benzofuran-2-yl(5-bromo-2-hydroxyphenyl)methanone (11)

Compound **10** (0.4000 g, 1.250 mmol) was treated with the same procedure as described in preparation of **6**. Purification by flash column chromatography (EtOAc:Hexane = 1:10–1:8; EtOAc:Hexane = 1:5, R_f = 0.8) afforded **11** (0.0600 g, 0.1410 mmol) as a yellow solid. Yield: 15%. Mp 119–120°C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 12.0 (s, 1H), 8.55 (d, J = 2.4 Hz, 1H), 7.78 (d, J = 7.9 Hz, 1H), 7.73 (d, J = 0.6 Hz, 1H), 7.63 (dd, J = 8.9 Hz, 2.4 Hz, 1H), 7.55 (td, J = 9.2, 1.1 Hz, 1H), 7.38 (td, J = 7.9, 0.6 Hz, 1H), 6.99 (d, J = 8.9 Hz, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 185.5, 162.5, 156.2, 151.8, 139.1, 133.9, 128.9, 126.6, 124.4, 123.4, 120.5, 120.1, 117.3, 112.6, 110.9. HRMS (ESI) calcd. For $C_{15}H_{10}BrO_3$ $[M + H]^+$ 316.9813. Found: 316.9807.

3.6 | Benzofuran-2-yl(5-bromo-2-methoxyphenyl)methanone (12)

Compound **11** (0.0447 g, 0.141 mmol) was treated with the same procedure as described in preparation of **7** in which acetone was replaced of DMF. Purification by flash column chromatography (EtOAc:Hexane = 1:10–1:8; EtOAc:Hexane = 1:10, R_f = 0.3) afforded **12** (0.0362 g, 0.110 mmol) as a yellow gum. Yield: 78%. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.70 (d, J = 8.0 Hz, 1H), 7.61–7.59 (m, 3H), 7.49 (td, J = 8.4 Hz, 1.1 Hz, 1H), 7.35 (d, J = 0.7 Hz, 1H), 7.32 (td, J = 7.8, 0.7 Hz, 1H), 6.92 (d, J = 9.0 Hz, 1H), 3.79 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 183.2, 156.7, 156.2, 152.5, 135.0, 132.1, 129.6, 128.7, 127.1, 124.0, 123.5, 116.8, 113.6, 112.6, 56.1. HRMS (ESI) calcd. For $C_{16}H_{12}BrO_3$ $[M + H]^+$ 330.9970. Found: 330.9966.

4 | CONCLUSIONS

We carefully investigated the iodine-mediated cyclization of chalcones **3**/**4** and **15**/**16** in comparison of their yields. We found that the C_2'-OH groups of **3** and **4** are more efficient than C_2-OH groups of **15** and **16** in the cyclization toward the synthesis of flavones and affords higher yields. In this regard, the iodine-mediated cyclization of chalcones **5** and **10,** which contained both C_2'-OH and C_2-OH afforded benzofurans **6** and **11** instead of expected flavones **8** and **9** in low yields in our present study.

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CONFLICT OF INTEREST

The authors declare no potential conflict of interest.

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SUPPORTING INFORMATION

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