Tetrahedron Letters 52 (2011) 4164–4167

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Condition-controlled selective synthesis of coumarins and flavones from 3-(2-hydroxyphenyl)propiolates and iodine

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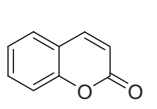
ARTICLE INFO

Article history:
Received 13 May 2011
Accepted 31 May 2011
Available online 12 June 2011

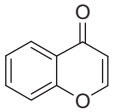
ABSTRACT

2*H*-Chromen-2-ones (coumarins) and 4*H*-chromen-4-ones (flavones) were selectively prepared via the reaction of 3-(2-hydroxyphenyl)propiolates with iodine in toluene and *N*,*N*-dimethylformide, respectively.

Both 2*H*-chromen-2-ones (coumarins) and 4*H*-chromen-4-ones (flavones)[1] are of paramount importance because of their bioactivities in nature.[2] Coumarins are widely used in the pharmaceutical company as precursors in the synthesis of a variety of anticoagulant pharmaceuticals and some even more efficient rodenticides that work by the same anticoagulant mechanism. Coumarins also possess clinical values in the treatment of lymphedema.[3] Industry of flavones has grown enormously due to its acknowledged effects against atherosclerosis, osteoporosis, diabetes mellitus, and certain cancers.[4] Both structures contain benzopyrone, but in different connection as shown below. General synthetic methods leading to coumarin skeleton include the well-known Perkin reaction between salicylaldehyde and acetic anhydride,[5] Pechmann condensation,[6] and others.[7] Synthetic ways leading to the flavone skeleton are the Allan–Robinson reaction[8] where *o*-hydroxyaryl ketones react with aromatic anhydrides, the Auwers synthesis,[9] the Algar–Flynn–Oyamada reaction[10] where a chalcone undergoes an oxidative cyclization and others.[11] In this Letter, we would like to report an iodine-mediated annulation of methyl 3-(2-hydroxyphenyl)propiolates, which furnishes coumarin or flavone skeleton with high selectivity under different reaction conditions.



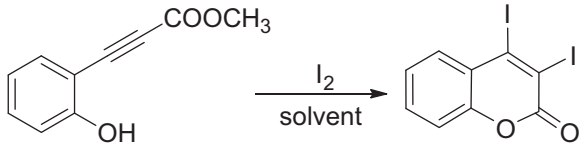
2*H*-chromen-2-one
coumarin



4*H*-chromen-4-one
flavone

In order to construct a fused heterocyclic structure, such as benzofuran, we selected methyl 3-(2-hydroxy-phenyl)propiolate (**1a**) as substrate because the hydroxyl group of this substrate is adjacent to triple bond.[12] When iodine was used as Lewis acid to activate the triple bond,[13] the hydroxyl group could nucleophilically attack the electron-deficient triple bond intramolecularly. A fused product could thus be constructed. However, when **1a** reacted with iodine in acetonitrile, 3,4-diiodo-2*H*-chromen-2-one (**2a**) was obtained instead of obtaining the expected benzofuran. In order to have the optimized reaction condition, we altered the ratio of iodine to substrate, the solvent, and the reaction temperature, individually (Table 1). Increasing molar ratio of iodine to **1a** would benefit the reaction (Table 1, entries 1–3). *N*,*N*-Dimethylacetamide (DMAc) worked for the reaction (Table 1, entry 4). However, when the mixture of **1a** and iodine was refluxed in dichloromethane (DCM), only trace amount of **2a** was detected by TLC after 36 h (Table 1, entry 5). When the reaction mixture was refluxed in commercial toluene for 28 h, **2a** was isolated in a yield of 42% (Table 1, entry 6). To our delight, the yield was dramatically increased to 92% when the fresh-distilled toluene was

Table 1
Formation of coumarin skeleton from **1a** and iodine under various reaction conditions



1a **2a**

Entry	Solvent	*T* (°C)	I_2 (equiv)	Time (h)	Yield[a] (%)
1	CH_3CN	82	1	72	74
2	CH_3CN	82	1.5	48	64
3	CH_3CN	82	2	48	82
4	DMAc	110	2	48	43
5	DCM	40	2	36	Trace
6	Toluene	110	2	28	42
7	Toluene[b]	90	2	12	92

[a] Isolated yield.
[b] Fresh-distilled toluene.

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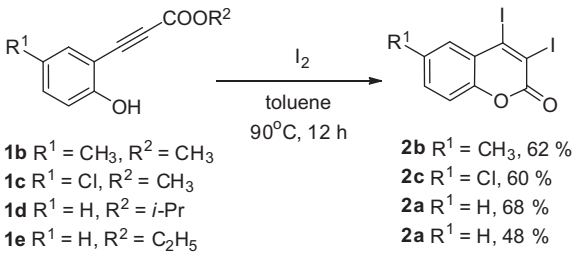
doi:10.1016/j.tetlet.2011.05.150



Scheme 1. Synthesis of coumarin skeleton.

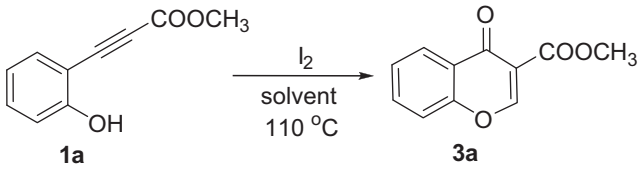
used as the solvent (Table 1, entry 7). Under the optimized reaction conditions, substrates (**1b–d**) afforded the corresponding products in yields between 48% and 68% (Scheme 1).[14]

Dimethylformamide (DMF) has been widely used as formylation reagent for many years. The typical example is the Vilsmeier reaction where the combination of DMF and phosphoryl trichloride is used.[15] Later on, lots of combinations were developed, such as the mixture of DMF, thionyl chloride and alkaline iodide,[16] the mixture of DMF and phosphine–halogen complexes[17], and the mixture of DMF and iodine pentafluoride.[18] When the reaction of **1a** and iodine was performed in DMF, an interesting product was obtained. Instead of obtaining **2a**, methyl 4-oxo-4*H*-chromene-3-carboxylate (**3a**) was constructed efficiently. As we can see from Table 2, the most suitable ratio of iodine to **1a** was found to be 1.5:1 (Table 2, entries 1–7). Due to the fact that DMF was not only used as a polar solvent but also did participate in the reaction, we tested this reaction in toluene, but with a 2:1 ratio of DMF to **1a** (Table 2, entry 8). The yield significantly decreased to 25% even though the reaction was refluxed and lasted for 72 h. Substrates with methyl (**1b**) and chloro (**1c**) afforded the corresponding products (**3b** and **3c**) in yields of 61% and 76%, respectively, while the ester with different alcohol parts (**1d**, **1e**, and **1f**) did not affect the reaction. Thus, **3d**, **3e**, and **3f** were prepared smoothly (Scheme 2).[19] Structures of **3** were analyzed by spectroscopy and further confirmed by X-ray analysis of **3c** (Fig. 1).[20]

According to the reference method, the final step for the preparation of the starting material (**1**) was the deprotection of methoxymethyl (MOM) of the corresponding phenols. However, deprotection of **4a** and **4b** failed to get the desired products. Considering the nucleophilicity of the lone pair electrons of the phenolic oxygen of these MOM-protected compounds,[21] we directly reacted **4a** and **4b** with iodine in DMF, respectively. To our surprise, compounds with flavone skeleton (**3g** and **3h**) could also be constructed in yields of 89% and 81%, respectively (Scheme 3).[22] However, any effort on the transformation of MOMs of **1a–1f** to **3a–3f** failed although the starting material (**1a–1f**) disappeared based on TLC tracking.

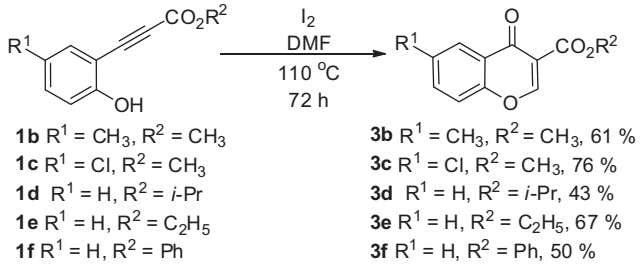
At the beginning, we believed that the triple bond was hydrated first to form β-ketoester as a key intermediate for formylation by DMF and sequential cyclization. Therefore, we used methyl 3-(2-hydroxyphenyl)-3-oxopropanoate (**5**) as substrate to run the reaction under the same condition. However, instead of getting the desired product with flavone skeleton, iodation on the activated methylene and the sequentially intramolecular esterification occurred. 3,3-Diiodochroman-2,4-dione (**6**) was obtained in high yield. In order to test the necessity of the adjacent hydroxy group and the ester group in the substrate, ethyl 3-phenylpropiolate (**7**) and 2-(phenylethynyl)phenol (**8**) were used as substrates to react with iodine in DMF, individually. Both reactions did not occur based on TLC tracking. In the presence of *n*-butanol, **7** did not react with iodine in DMF as well, which implied that the intermolecular reaction did not happen. When dimethylacetamide (DMAc) was used as solvent instead of DMF, **2a** was isolated (Table 1, entry 4). DMAc did not participate in the reaction while DMF did.

Table 2
Formation of flavone **3a** from **1a** and iodine under various reaction conditions



Entry	Solvent	I_2 (equiv)	Time (h)	Yield[a] (%)
1	DMF	0	72	ND
2	DMF	0.25	72	13
3	DMF	0.5	72	48
4	DMF	1	72	54
5	DMF	1.2	72	54
6	DMF	1.5	72	66
7	DMF	2	48	42
8	Toluene[b]	1.5	72	25

[a] Isolated yield.
[b] 2 equiv DMF relative to **1a** was used.



Scheme 2. Synthesis of flavones **3** from **1**.

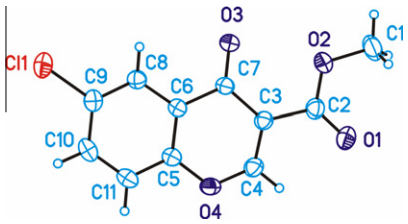
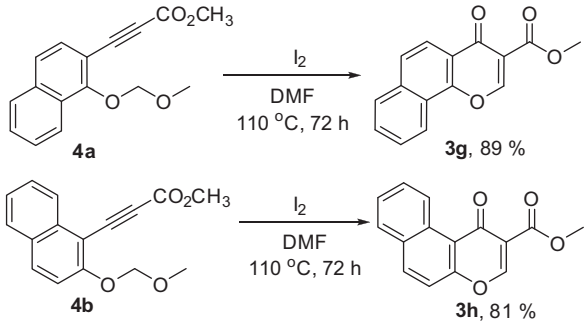
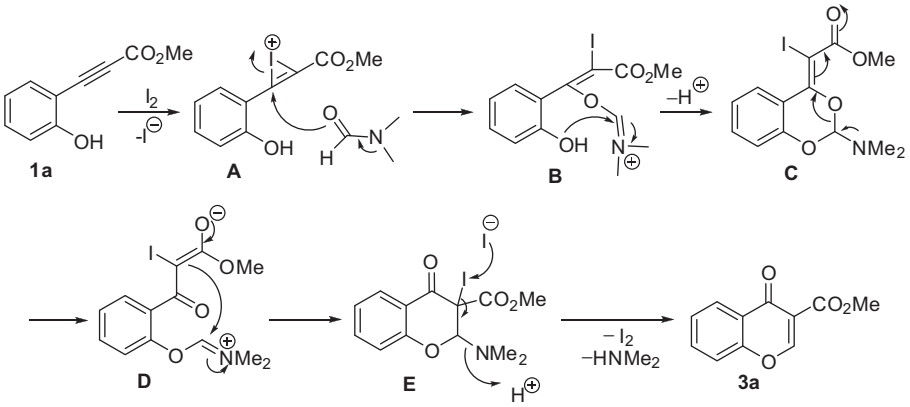


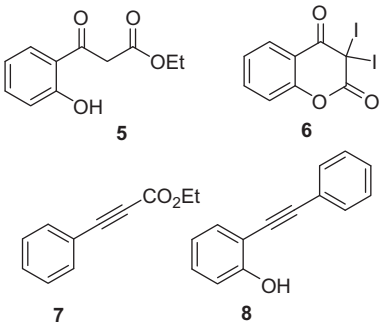
Figure 1. X-ray diffraction of **3c**.



Scheme 3. Synthesis of flavone **3** skeleton from **4**.



Scheme 4. Possible mechanism for the formation of flavone.



Based on these results, we postulated a possible mechanism for this transformation (Scheme 4). Activated by iodine, the triple bond became electron-deficient as described in the previous report.[23] Both oxygen and nitrogen in DMF are electron-rich due to its resonance nature. By nucleophilic attack from oxygen of DMF on the iodonium intermediate (**A**), iminium intermediate (**B**) was afforded, which could be intramolecularly attacked by the *ortho* hydroxy group. Via electron push-pull effect, the fused ring (**C**) was opened and a new iminium intermediate (**D**) was formed which further cyclized to **E**. Subsequent exclusion of iodine and dimethylamine led to the formation of flavone skeleton (**3a**) successfully.

In this Letter, we reported the selective reaction between 3-(2-hydroxyphenyl)propiolate and iodine in toluene and DMF, respectively. The reaction of 3-(2-hydroxyphenyl)propiolate and iodine in toluene afforded coumarins, while the reaction of 3-(2-hydroxyphenyl)propiolate and iodine in dimethylforamide gave flavones. Assisted by iodine, DMF participated in the reaction, implying that the combination of DMF and iodine might be an efficient formylating reagent in both laboratory and industry.

Acknowledgment

We thank the National Natural Science Foundation of China (Nos. 21032005, 20872128) for the financial support of this research.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.05.150.

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14. Typical procedure for the synthesis of **2a**: Iodine (2 mmol) was added to the solution of methyl 3-(2-hydroxyphenyl)propiolate **1a** (1 mmol) in fresh-distilled toluene (10 mL). The mixture was stirred at 90 °C for 12 h. The resulting reaction solution was quenched with saturated $Na_2S_2O_3$ solution (20 mL) and extracted with 3 × 10 mL of ethyl acetate. The extract was dried over anhydrous Na_2SO_4 and evaporated in vacuo. The residue was purified by silica gel column chromatography with hexane–EtOAc. Compound **2a**: yellow solid, mp 187–190 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62–7.52 (m, 2H), 7.39–7.32 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.2, 151.4, 133.0, 132.5, 127.5, 125.1, 120.7, 120.1, 117.0 ppm; HRMS (ESI) calcd for $C_9H_4O_2I_2$ ($[M+Na]^+$), 420.8205; found, 420.8193.
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19. Typical procedure for the synthesis of **3a**: Iodine (1.5 mmol) was added to the solution of methyl 3-(2-hydroxyphenyl)propiolate **1a** (1 mmol) in DMF (10 mL). The mixture was stirred at 110 °C for 72 h. The resulting reaction solution was quenched with saturated $Na_2S_2O_3$ solution (25 mL) and extracted with 3 × 10 mL of ethyl acetate. The extract was dried over anhydrous Na_2SO_4 and evaporated in vacuo. The residue was purified by silica gel column chromatography with hexane–EtOAc. **3a**: White solid, mp 79–82 °C, ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.70 (s, 1H), 8.30 (d, J = 7.9 Hz, 1H), 7.72 (t, J = 7.7 Hz, 1H), 7.49 (dd, J = 16.4, 8.1 Hz, 2H), 3.94 (s, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) 173.4, 164.1, 162.1, 155.6, 134.2, 126.6, 126.3, 125.14, 118.1, 116.1, 52.4 ppm. HRMS (ESI) calcd for $C_{11}H_8O_4$ ($[M+Na]^+$), 227.0315; found, 227.0312.

20. CCDC: 790082 contains the supplementary crystallographic data for compounds **3c**. These data can be obtained free of charge via http://www.ccdc.cam.ac.uk/data_request/cif, or by emailing data _reques t@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.
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22. Synthesis of **3g**: Iodine (1.5 mmol) was added to the solution of **4a** (1 mmol) in DMF (10 mL). The mixture was stirred at 110 °C for 72 h. The resulting reaction solution was quenched with saturated $Na_2S_2O_3$ solution (25 mL) and extracted with 3 × 10 mL of ethyl acetate. The extract was dried over anhydrous Na_2SO_4 and evaporated in vacuo. The residue was purified by silica gel column chromatography with hexane–EtOAc. Compound **3g**: yellow solid, mp 122–126 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.03 (d, J = 8.7 Hz, 1H), 8.67 (s, 1H), 8.12 (d, J = 9.0 Hz, 1H), 7.91 (d, J = 8.0 Hz, 1H), 7.77 (t, J = 7.8 Hz, 1H), 7.64 (t, J = 7.4 Hz, 1H), 7.51 (d, J = 9.0 Hz, 1H), 3.97 (s, 3H) ppm; ^{13}C NMR (101 MHz, DMSO-d_6) 175.3, 164.1, 159.2, 156.8, 136.2, 131.0, 130.4, 129.6, 128.3, 127.3, 127.1, 118.6, 118.5, 117.0, 52.5 ppm. HRMS (ESI) calcd for $C_{15}H_{10}O_4$ ([M+Na]$^+$), 277.0471; found, 277.0468.
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