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Iodine mediated synthesis of coumarins from chromenes

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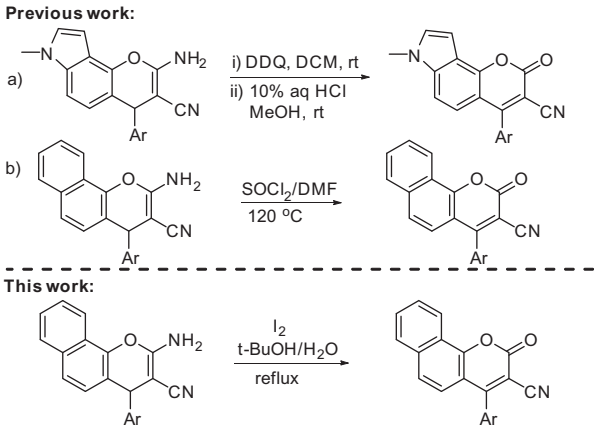
ABSTRACT

Iodine mediated rapid conversion of 2-amino-3-cyano-4-aryl-4*H* chromenes to the corresponding coumarins in the presence of water is described. Several chromenes are obtained in high yields without chromatographic purification. Under anhydrous conditions, 2-iminochromenes are obtained as major products.

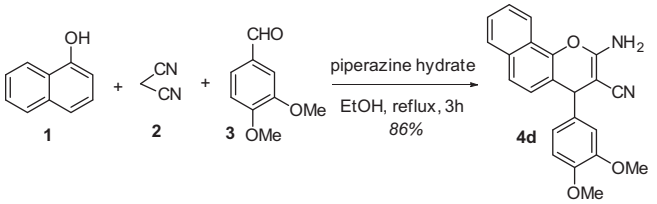
2-Amino-3-cyano-4-aryl-4*H* chromenes and their derivatives are important structural motifs found in various biologically active compounds. They have been found to exhibit potent anticancer, antibacterial, antifungal, and antirheumatic activities.[1] Several 2-amino-3-cyano-4-aryl-4*H* chromenes act as antagonist for anti-apoptotic Bcl-2 proteins. They also act as potent apoptosis inducer by inhibiting tubulin polymerization and vascular disruption. A few chromenes have been found to be active in multidrug resistant MES-SA/DX5 animal tumor cells.[2]

Coumarins are structurally closely related to chromenes and show various biological activities.[3] 3-Cyano-4-aryl coumarins are known as potent apoptosis inducers.[4] 2-Amino-3-cyano-4-aryl-4*H* chromenes can be converted to the corresponding coumarins using literature conditions that are summarized in Scheme 1.[5,6] Cai et al. reported a two-step procedure for coumarin synthesis which relies upon DDQ mediated oxidation of chromenes.[6a] Bavantula et al. reported the synthesis of coumarin under Vilsmeier conditions.[6b] While screening iodine based reagent for difunctionalization of 2-amino-3-cyano-4-aryl-4*H* chromenes, Alla et al. also observed the formation of coumarin.[5e] Herein we report iodine mediated rapid conversion of 2-amino-3-cyano-4-aryl-4*H* chromenes to the corresponding coumarins.

Condensation of an aromatic aldehyde, malononitrile, and α-naphthol in presence of piperazine hydrate produced 2-amino-3-cyano-4*H* chromenes in 86% yield (Scheme 2).[7] The conditions



Scheme 1. Synthetic methods for 3-cyano-4-aryl coumarins.



Scheme 2. Synthesis of 2-amino-3-cyano-4*H* chromene.

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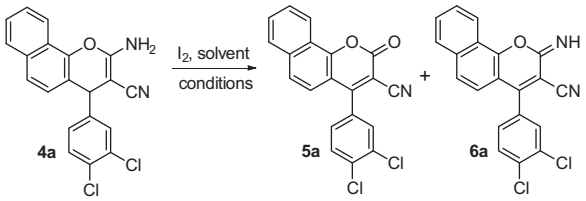
0040-4039/

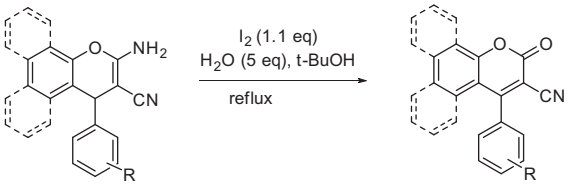
Table 1
Optimization of conditions for coumarin synthesis

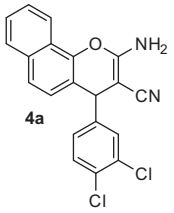
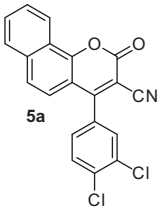
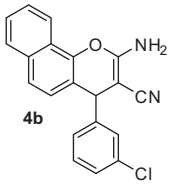
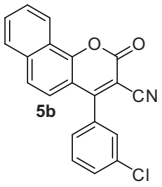
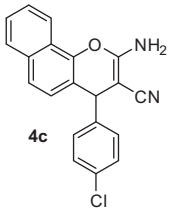
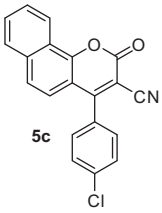


Entry	Solvent	I_2 (equiv)	H_2O (equiv)	conditions	Yield (%)	
					5a	**6a**
a	EtOH	1.1	5.0	rt, 24 h	15[a]	—
b	EtOH	1.1	5.0	Reflux, 2 h	55	—
c	MeOH	1.1	5.0	Reflux, 3 h	45	—
d	*i*-PrOH	1.1	5.0	Reflux, 1 h	65	—
e	THF	1.1	5.0	Reflux, 4 h	63	—
f	Dioxane	1.1	5.0	90 °C, 1 h	70	—
g	CH_3CN	1.1	5.0	Reflux, 2 h	68	—
h	DMSO	1.1	5.0	rt, 6 h	71	—
i	DMF	1.1	5.0	rt, 5 h	73	—
j	DCM	1.1	—	Reflux, 6 h	—	53[b]
k	DCE	1.1	—	Reflux, 4 h	—	68[b]
1	Benzene	1.1	—	Reflux, 3 h	—	65[b]
m	Toluene	1.1	—	Reflux, 2 h	—	72[b]
n	$CHCl_3$	1.1	—	Reflux, 6 h	10	45[b]
o	***t*-BuOH**	**1.1**	**5.0**	**Reflux, 1 h**	**80**	—
p	*t*-BuOH	1.1	10	Reflux, 1 h	72	—
q	*t*-BuOH	2.0	5.0	Reflux, 0.5 h	75	—
r	H_2O	1.1	—	Reflux, 1 h	—	—

[a] Unreacted SM recovered.
[b] Anhydrous solvent was used.

Table 2
Synthesis of coumarins from chromenes



Entry	Chromene	Coumarin	Time (h)	Yield (%)
a			1.0	80
b			1.0	82
c			1.0	84

(*continued on next page*)

Table 2 (*continued*)

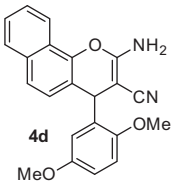
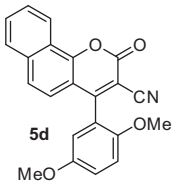
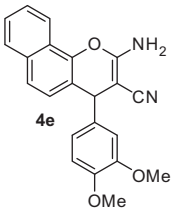
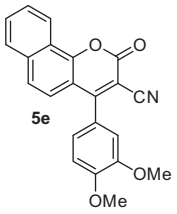
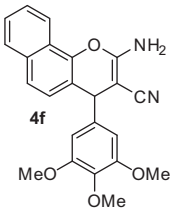
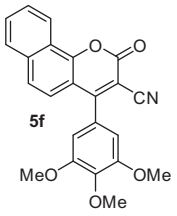
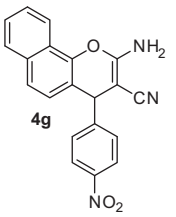
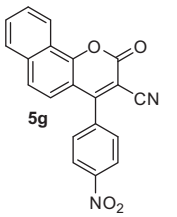
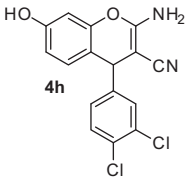
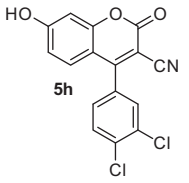
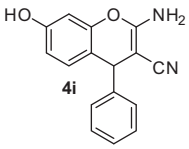
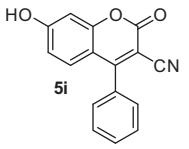
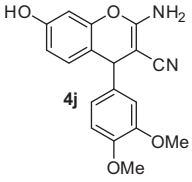
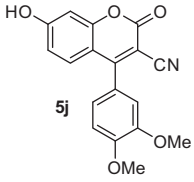
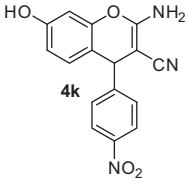
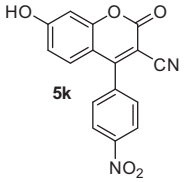
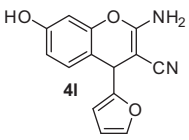
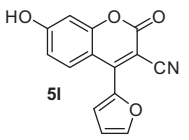
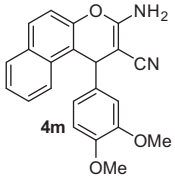
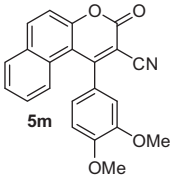
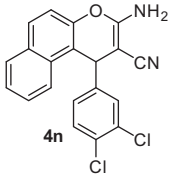
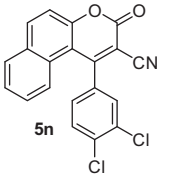
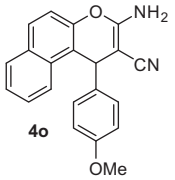
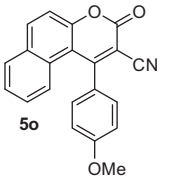
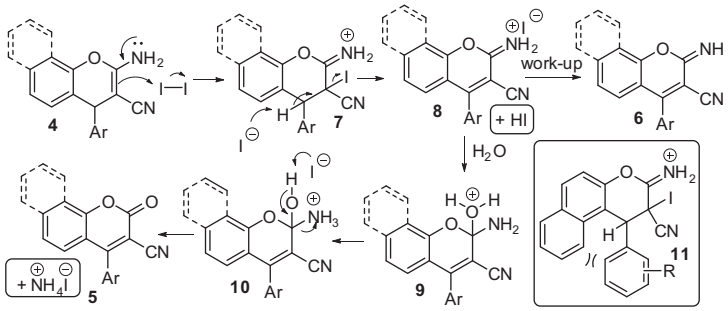
Entry	Chromene	Coumarin	Time (h)	Yield (%)
d			2.0	65
e			2.5	66
f			1.0	56
g			1.5	55
h			1.0	88
i			2.0	79
j			1.0	85
k			3.0	58
l			2.0	78[a]

Table 2 (*continued*)

Entry	Chromene	Coumarin	Time (h)	Yield (%)
m			6.0	30[b]
n			4.0	45
o			4.5	42

[a] Reaction was carried out in DMF at rt.
[b] 20% unreacted SM was recovered.



Scheme 3. Mechanism of iodine mediated coumarin synthesis from chromene.

worked well with β-naphthol as well as resorcinol. During our unsuccessful efforts to protect the amino group of chromene **4a** as its *t*-butyl carbamate with Boc_2O in the presence of 20 mol % iodine in *t*-BuOH at 85 °C, we observed 15% formation of coumarin **5a**. When we run the reaction with 1.1 equiv of iodine in the absence of Boc_2O, complete conversion of chromene to the corresponding coumarin took place and the compound was isolated as a yellow solid after aqueous work-up.

A quick screening of solvents revealed that the reaction worked well in a number of solvents with addition of 5.0 equiv of water (Table 1). Reactions in non-nucleophilic alcoholic solvents provided better results. Using DMSO and DMF as solvents the reaction can be carried out at room temperature (35 °C) (entries h and i, Table 1). Under anhydrous conditions, 2-iminochromene **6a** (entries j–n, Table 1) was obtained as the major product. The coumarin synthesis produced best result in *t*-BuOH as a solvent using 5.0 equiv of water (entry o, Table 1). When the ratio of water was increased, polar unidentified byproducts were observed, leading to diminished yield (entry p, Table 1). Similarly, when 2.0 equiv of iodine was used, reaction was complete within 30 min but the isolated yield of coumarin was lower than that obtained by using 1.1 equiv of iodine (entry q, Table 1). No reaction occurred when water was used as a solvent.

With optimal condition in hand, we tested various chromenes synthesized from aromatic aldehydes, malononitrile, and α-naphthol. As shown in Table 2, high yields were obtained for most of the coumarins. Coumarin **5c** was obtained with 84% yield while coumarin **5g** was obtained with only 55% yield. Coumarin **5f** containing three methoxyl groups in the phenyl ring at 4-position was obtained in moderate yield (56%). Similarly, chromene **4g** which contains a nitro group in the phenyl ring produced coumarin **5g** (entry g, Table 2) in moderate yield (55%). Chromenes derived from resorcinol (entries h–l, Table 2) underwent smooth conversion into corresponding coumarins. Except **5k**, all coumarins were obtained in high yields. In case of chromene **4l** (entry l, Table 2), a complex reaction mixture was obtained when the reaction was carried out in *t*-BuOH under reflux conditions. However, clean reaction was observed using DMF as a solvent at room temperature. Chromenes derived from β-naphthol (entries m–o, Table 2) underwent slow conversion and produced the corresponding coumarins in low yields. Coumarins **5a**–**5c**, **5h**–**5j**, and **5l** were purified by recrystallization and do not require chromatographic purification.[8] The method is compatible with cyano, nitro, ether, ester, and phenolic hydroxyl groups. The method yields best results for chromenes derived from resorcinol. The synthesized coumarins can be stored at room temperature for several weeks.

All chromenes showed intense yellow spot on TLC when visualized under short-UV.

The probable mechanism of iodine mediated coumarin synthesis is depicted in Scheme 3. Electrophilic addition of iodine to chromene leads to intermediate **7**. Iodide mediated elimination of hydroiodic acid would result into intermediate **8**. Loss of a proton from the intermediate **8** will generate iminochromene **6** whereas hydrolysis will generate coumarin **5**. In case of chromenes derived from β-naphthol, formation of iodo-intermediate **11** appears to be difficult due to steric congestion of aryl groups.

In summary, we have developed a rapid and efficient method for the synthesis of pharmaceutically important coumarins from 2-amino-3-cyano-4-aryl-4*H* chromenes mediated by molecular iodine under mild reaction conditions. Several coumarins were isolated without silica gel column chromatography. Thus, the method will be suitable for large scale synthesis. Under anhydrous conditions, the method provides 2-iminochromenes as a major product. The iminium ion intermediate **8** might be useful in functionalization of chromenes. We will explore these and publish a detailed account of this methodology soon.

Acknowledgements

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References and notes

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8. *Experimental procedure for the synthesis of coumarin* **5h**: A mixture of chromene **4h** (300 mg, 0.90 mmol), iodine (253 mg, 1.0 mmol) in *t*-BuOH (5 mL) containing H_2O (81 μL) was heated under reflux for 1 h. TLC analysis indicated complete conversion. The reaction mixture was cooled to rt and quenched with saturated aqueous $Na_2S_2O_3$ solution. *t*-BuOH was removed under reduced pressure and the solid appeared was filtered off. Recrystallization of the solid from hot EtOH produced coumarin **5h** (264 mg, 88% yield) as a yellow solid; data for compound **5d**: light yellow solid, mp 188–189 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.60 (d, J = 7.2 Hz, 1H), 7.86 (dd, J = 1.2, 6.8 Hz, 1H), 7.75–7.66 (m, 2H), 7.61 (d, J = 8.4 Hz, 1H), 7.18 (d, J = 8.8 Hz, 1H), 7.11–7.03 (m, 2H), 6.83 (d, J = 2.8 Hz, 1H), 3.75 (s, 3H), 3.81 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 162.8, 157.5, 153.7, 152.2, 150.2, 136.3, 130.5, 128.0, 127.9, 125.1, 123.3, 122.9, 122.8, 121.7, 117.4, 115.2, 114.0, 113.9, 113.1, 102.0, 56.2, 56.0; HRMS (ES) calcd for $C_{22}H_{16}NO_4$ [M+H]: 358.1079; found 358.1065; compound **5h**: mp 210–211 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.90–7.85 (m, 2H), 7.50 (d, J = 6.8 Hz, 1H), 7.11 (d, J = 8.4 Hz, 1H), 6.87–6.77 (m, 2H), 3.12 (br s, 1H, OH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 165.6, 161.5, 158.0, 156.4, 134.0, 133.4, 132.4, 131.8, 131.0, 130.8, 129.3, 115.4, 115.1, 110.8, 103.4, 96.9; HRMS (ES) calcd for $C_{16}H_8C_{l2}NO_3$ [M+H]: 331.9881; found 331.9861.