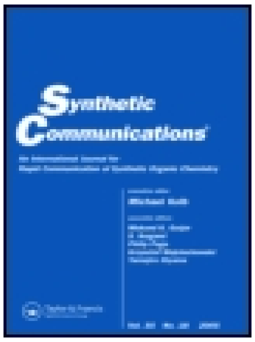

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Iodine-mediated direct synthesis of 3-iodoflavones

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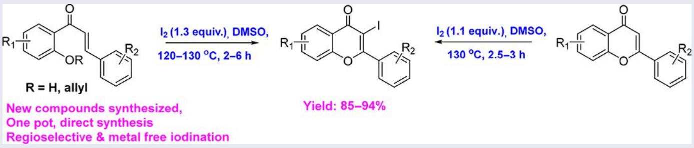
ABSTRACT

Molecular iodine has been used for the regioselective, one pot, direct synthesis of 3-iodoflavones from 2′-allyloxy chalcones, 2′-hydroxy chalcones and flavones. Allyl deprotection, cyclization dehydrogenation and α-iodination of 2′-allyloxychalcones has been achieved in a single step to offer 3-iodoflavones.

GRAPHICAL ABSTRACT



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KEYWORDS
2-Allyloxy chalcone; 3-iodoflavone; chromenone; deallylation; molecular iodine

Introduction

Flavones are available naturally and can also be prepared by chemical syntheses.[1] These are known to exhibit some of the important bioactivities like COX-2 inhibitors, antiviral, tyrosine, and protein kinase C inhibition, antitubulin, antihypertensive, anti-inflammatory, and anticancer.[2] Haloflavones particularly iodoflavones are highly significant in synthetic organic chemistry.[3] Flavones and their haloderivatives have been studied widely and intensively in recent decades.[4]

Flavonoids, iodoflavonoids, and iodothioflavonoids are potential intermediates in diversity oriented synthesis, metal catalyzed coupling reactions[5] and 2,3-diaryl flavonoids. In general, there are two distinct methods to obtain the 3-iodoflavones, (i) from acyclic compounds-like chalcones and (ii) from chromones. Both of these reported synthetic methods suffer from the drawbacks, such as use of unstable and moisture sensitive reagents, such as ICl[5] and LDA.[6] A transition metal containing activator-like cerium(IV) ammonium nitrate (CAN)[7] (Fig. 1) or the strong acid, such as H_2SO_4[8] is needed whereas iodine mediated synthesis has not been explored to its capacity,[9] where molecular iodine is used as the iodinating reagent. A two-step process (i) α-metallation[3,5] and (ii) electrophilic iodination[3] is required when unsubstituted flavones are used as substrates. Therefore, the problem of regioselective iodination and use of multiple synthetic operations need to be dealt with further. Therefore, owing to the pharmaceutical and

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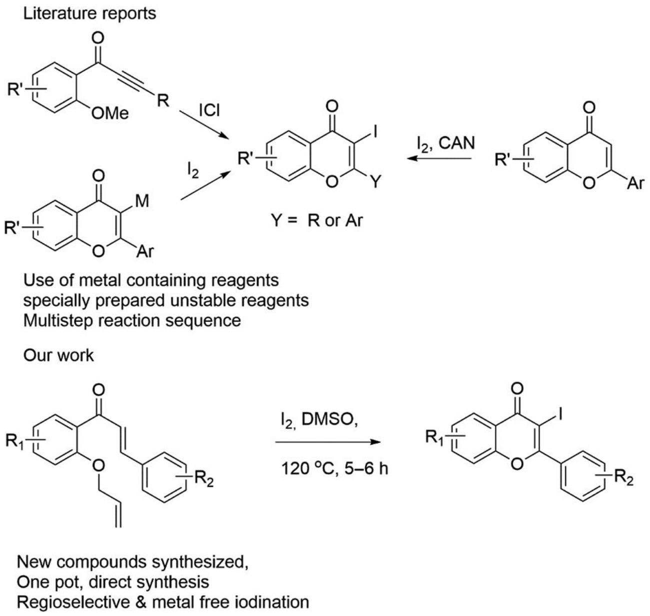


Figure 1. Synthesis of 3-iodoflavones. *Note*: CAN, cerium(IV) ammonium nitrate; DMSO, dimethyl sulfoxide.

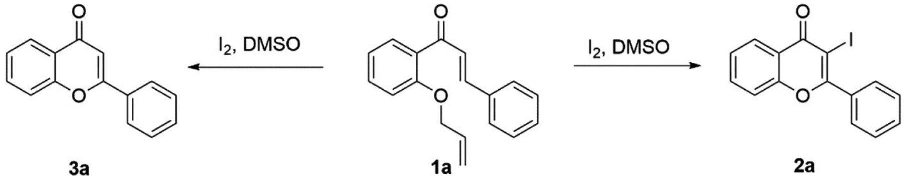
synthetic importance of iodoflavones, development of a direct and regioselective synthetic method is highly desirable.

Molecular iodine is an economic, safe and easily available reagent for an organic transformation. Moderate Lewis acidic nature of iodine facilitates it's usage in organic synthesis.[10] In continuation to our efforts to explore the iodine chemistry for the new and useful organic transformations, it was always our priority to minimize the use of metals and other toxic chemicals used in the synthetic chemistry. Aromatization/dehydrogenation followed by selective iodination of partially saturated aliphatic rings,[11] O-deallylation,[12] and oxidative cyclizations[13] have been performed under the metal-free environment. Specifically, the use of substoichiometric amount of I_2 in dimethyl sulfoxide (DMSO) offered the deallylation of allyl phenyl ethers.[14] But in our recent invention, use of stoichiometric I_2 resulted in O-deallylation, and aromatic iodination of allyl phenyl ethers.[15] Whereas recently the 2′-allyloxychalcones and 2′-hydroxychalcones unexpectedly offered the corresponding iodoflavones instead of aromatic iodination using molecular iodine. This obtained result has been described in the present manuscript.

Results and discussion

As a continuation to our ongoing efforts toward the exploration of the utility of molecular iodine in the synthetic organic chemistry,[11–15] we thought to examine the response of 2′-allyloxychalcones under some varied reaction conditions using I_2/DMSO system. Accordingly when a 0.5 equiv. of molecular iodine was added to the solution of 2′-allyloxychalcone **1a** in DMSO solvent and heated at 120 °C for 30 min. we got the corresponding flavone **3a** in 96% yield (Table 1, entry a).[16] We thought to increase the reaction time under similar stoichiometric conditions, we got mixture of flavone **3a** (58%) and 3-iodoflavone **2a** (31%) after 6 h (Table 1, entry b). This result prompted

Table 1. Optimization of the reaction conditions for the synthesis of 3-iodoflavone.



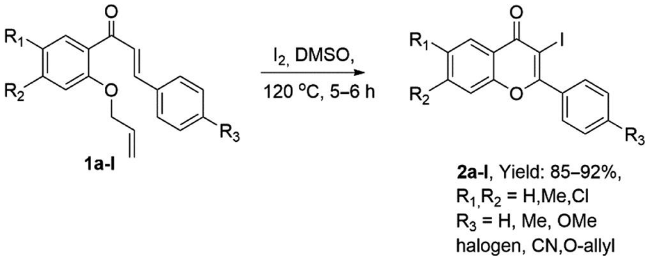
Entry	I_2 (equiv.)	Temperature (°C)	Time (h)	Yield[a] (%) 2a	Yield[a] (%) 3a
a	0.5	120	0.5	–	96
b	0.5	120	6	31	58
c	1.0	120	6	71	20
d	1.3	120	6	92	–
e	1.5	120	6	92	–

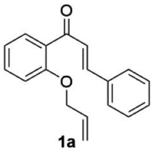
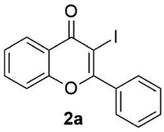
[a] Yield refers to an isolated yield after column chromatography.
DMSO, dimethyl sulfoxide.

us to increase the quantity of I_2, accordingly use of 1 equiv. of molecular iodine resulted in the increased yield (71%) of the 3-iodoflavone **2a** and 20% of unsubstituted flavone **3a** when stirred for 6 h under the same temp and solvent conditions (Table 1, entry c). From these obtained results it was evident that increase in the equivalence of molecular I_2 is required further to obtain the desired 3-iodoflavone exclusively. Accordingly, when 1.3 equiv. I_2 was used 3-iodoflavone was obtained in excellent yield (92%) without any traces of unsubstituted flavone (Table 1, entry d). However, further increase in the quantity of the I_2 (1.5 equiv.) did not cause any additional advantage to this method (Table 1, entry e).

The conversion of 2′-benzyloxychalcones[17] to the corresponding flavones is already known in the literature but, it has not been extended to the preparation of 3-iodoflavones. We have converted 2′-allyloxychalcones to 3-iodoflavones under the optimized reaction condition (Table 1, entry d). Various 2′-allyloxychalcones **1a–l** have been examined under the optimized reaction condition to obtain the corresponding 3-iodoflavones **2a–l** in good to excellent yields (Table 2, entries 1–12). However, there was no particular trend observed

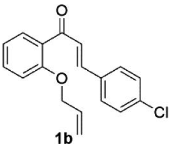
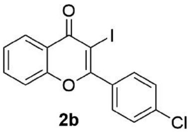
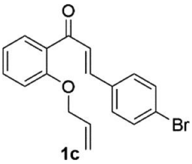
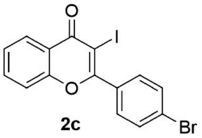
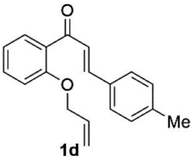
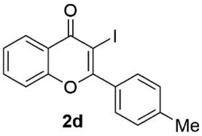
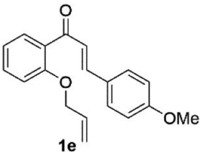
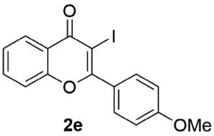
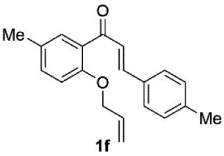
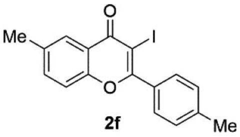
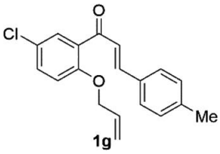
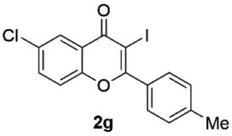
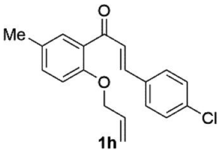
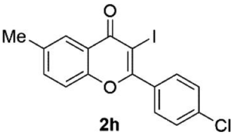
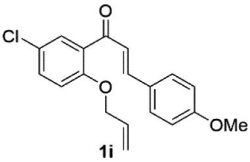
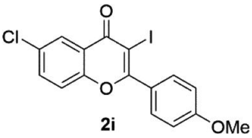
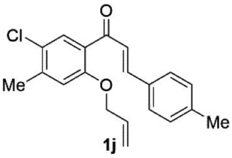
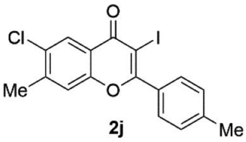
Table 2. Synthesis of 3-iodoflavones from 2′-allyloxychalcones.



Entry	Substrate	Product	Yield (%)
1	 1a	 2a	92

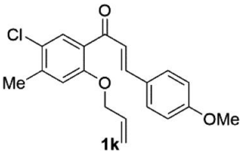
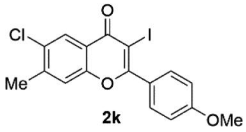
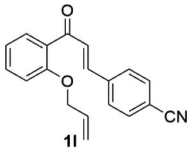
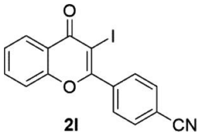
(Continued)

Table 2. Continued.

Entry	Substrate	Product	Yield (%)
2	 **1b**	 **2b**	88
3	 **1c**	 **2c**	85
4	 **1d**	 **2d**	87
5	 **1e**	 **2e**	88
6	 **1f**	 **2f**	91
7	 **1g**	 **2g**	87
8	 **1h**	 **2h**	88
9	 **1i**	 **2i**	89
10	 **1j**	 **2j**	85

(*Continued*)

Table 2. Continued.

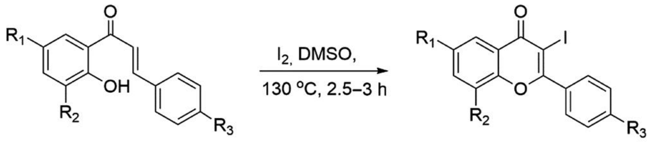
Entry	Substrate	Product	Yield (%)
11	 **1k**	 **2k**	91
12	 **1l**	 **2l**	85

DMSO, dimethyl sulfoxide.

with respect to yield, in case of activating or deactivating substituents on ring B of the substrates. The substrate bearing strong electron-withdrawing group like nitrile (–CN) also offered better yield (85%) of the corresponding iodoflavone. When 2′-allyloxychalcone bearing allyloxy group on ring B was stirred under the optimal reaction condition, offered the corresponding flavone (monitored using TLC) within 30 min. Continuation of the same reaction for 6–7 h resulted in the inseparable mixture of compounds. Further increase in I_2 equivalence or reaction hours resulted in more complex products.

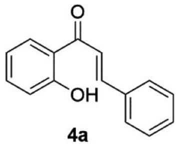
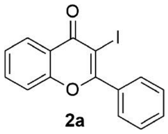
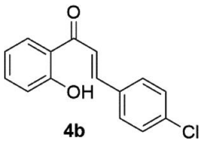
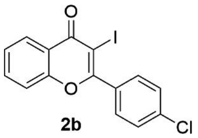
With the successful conversion of all the 2′-allyloxychalcones to the corresponding 3-iodoflavones, we got curious to check the response of 2′-hydroxychalcones under the same reaction condition. Consequently, usage of unsubstituted 2′-hydroxychalcone **4a** produced 3-iodoflavone **2a** in 94% yield with a greater ease. But a 10 °C increase in the reaction temp reduced the reaction time to 2.5–3 h. Therefore, various activated and deactivated 2′-hydroxychalcones **4a–e, m** were converted efficiently to obtain the corresponding 3-iodoflavones **2a–e, m** in better yields (Table 3).

Table 3. Synthesis of 3-iodoflavones from 2′-hydroxychalcones.



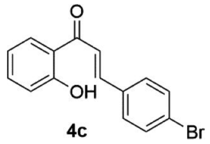
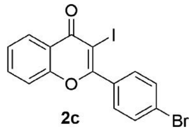
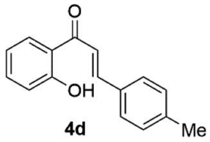
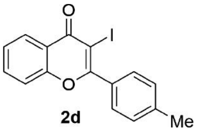
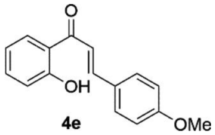
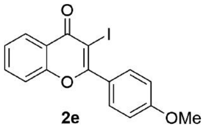
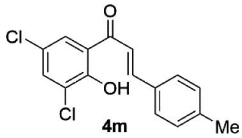
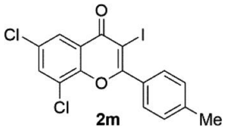
4a-e, m

2a-e, m; Yield: 86–94%
R_1, R_2 = H, Cl, R_3 = H,
Me, OMe,halogen

Entry	Substrate	Product	Yield (%)
1	 **4a**	 **2a**	94
2	 **4b**	 **2b**	86

(*Continued*)

Table 3. Continued.

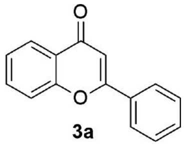
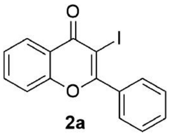
Entry	Substrate	Product	Yield (%)
3	 **4c**	 **2c**	87
4	 **4d**	 **2d**	89
5	 **4e**	 **2e**	91
6	 **4m**	 **2m**	89

DMSO, dimethyl sulfoxide.

However, the yield obtained in case of unsubstituted 3-iodoflavones was little higher compared to substituted 3-iodoflavones. The required 2–3 alkene in 3-iodoflavone already exists in the acyclic substrates where, aromatic alkynones are used as the starting material[5] (Fig. 1). But here, in case of 2′-allyloxy and 2′-hydroxychalcones double bond is generated after the cyclization step where molecular iodine acts as dehydrogenating reagent.

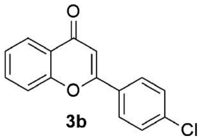
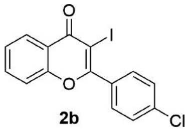
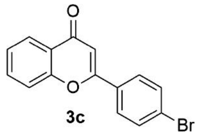
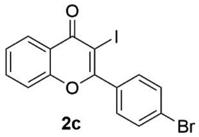
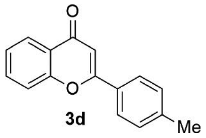
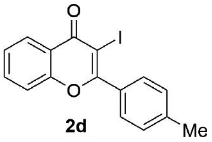
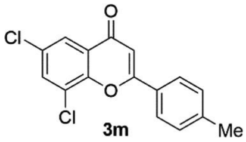
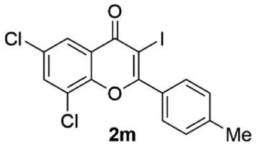
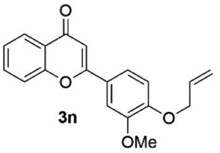
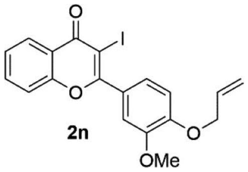
Although there are a few reports about the preparation of 3-iodoflavones from the corresponding flavones which use Li, Zn, and cerium metal containing activators, still there is scope for the use of ecofriendly reagent like molecular I_2. As a trial when we examined flavone **3a** under optimized reaction condition, to our delight we got the corresponding 3-iodoflavone **2a** with better yield (Table 4, entries 1–6). The reaction time was successfully

Table 4. Synthesis of 3-iodoflavones from flavones.

Entry	Substrate	Product	Yield (%)
1	 **3a**	 **2a**	92

(*Continued*)

Table 4. Continued.

Entry	Substrate	Product	Yield (%)
2	 **3b**	 **2b**	89
3	 **3c**	 **2c**	88
4	 **3d**	 **2d**	90
5	 **3m**	 **2m**	87
6	 **3n**	 **2n**	89

DMSO, dimethyl sulfoxide.

reduced to 2–2.5 h just by a 10 °C increase in the temperature and various substrates (**3a–d, m, n**) were converted to the corresponding 3-iodoflavones (**2a–d, m, n**). Various substitution on ring B could not affect the yields significantly.

Flavone **3n** bearing 4′-allyloxy group was smoothly converted to 3-iodoflavone **2n** (yield 89%) keeping the allyloxy group unaffected on the ring B. Probably, addition of iodine to activated alkene followed by oxidative cyclization is a preferred process, and the generated iodine may be interacted with the new alkene bond. Thus, iodine may not be available for deallylation in B-ring. This selective deallylation reaction could find an application in the synthesis of some natural products.[18]

All the chalcones were easily prepared by the well-known Claisen–Smidth condensation of the commercially available 2′-hydroxyacetophenones and different substituted benzaldehydes.[19] 2′-allyloxychalcones were prepared by the treatment of allyl bromide with the 2′-hydroxychalcones in K_2CO_3/DMF condition.[20] Flavones **3a–d, m, n** were prepared by the treatment of corresponding 2′-hydroxychalcones with 0.6 equiv. of molecular iodine in DMSO solvent at 130 °C.[21]

Stirring of 2′-allyloxychalcones and 2′-hydroxychalcones separately under the I_2-DMSO condition for 0.5 h resulted in the formation of flavones (Table 1, entry a). Whereas various flavones have been converted in to the corresponding 3-iodoflavones (Table 4). This observed experimental outcome suggests that this iodination reaction

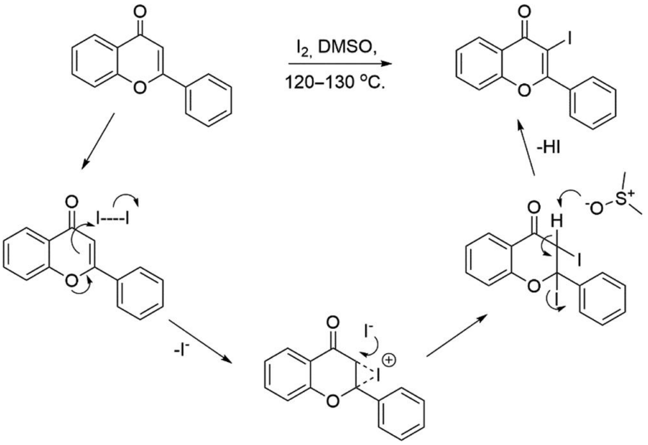


Figure 2. Probable mechanism for the regioselective iodination of flavones. *Note*: DMSO, dimethyl sulfoxide.

proceeds *via* flavone intermediate. DMSO solvent might be helping in dehydro-iodination process. The phenolic oxygen facilitates the iodination at 3-position, as depicted in Fig. 2.

Conclusion

In conclusion, we have developed an iodine mediated direct one pot procedure for the exclusive synthesis of 3-iodoflavones from 2′-allyloxychalcones, 2′-hydroxychalcones and flavones in high yields. Deallylation, cyclization, dehydrogenation, and iodination reactions occur in one-pot, avoiding the isolation of flavanone and flavone intermediate. Nonindulgence of ring “A” in the iodination process proves the regioselectivity of this method. Easy preparation of all the substrates renders this method more practical. 2′-hydroxychalcones are useful where protection is not needed and 2′-allyloxychalcones are useful where protection is needed for the synthesis of 3-iodo-flavones. 3-Iodoflavones are potential candidates to be used for different couplings and functional transformations.

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