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Regio- and Stereospecific Synthesis of Novel 3-Enynyl-Substituted Thioflavones/Flavones Using a Copper-Free Palladium-Catalyzed Reaction†

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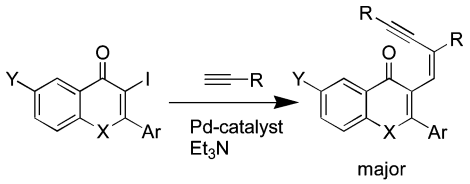

R ≠ Aryl; X = O, S; Y = H, Cl

A variety of 3-enynyl substituted flavones/thioflavones were synthesized via a sequential one-pot procedure using copper-free palladium-catalyzed cross coupling in a simple synthetic operation. The cross coupling between 3-iodo(thio)flavone and a broad range of terminal alkynes was carried out in the presence of $Pd(PPh_3)_2Cl_2$ and triethylamine to afford the corresponding 3-enynyl derivatives in a regio- and stereoselective fashion. The best results are obtained by employing 3 equiv of the terminal alkynes. The process worked well irrespective of the substituents present on the (thio)flavone ring as well as in the terminal alkynes except arylalkynes. The reaction is quite regioselective, placing the substituent of the terminal alkyne at the far end of the double bond attached with the (thio)flavone ring. The orientation of the (thio)flavonyl and acetylenic moieties across the double bond was found to be syn in the products isolated. A tandem C−C bond-forming reaction in the presence of palladium catalyst rationalized the formation of coupled product. The catalytic process apparently involves heteroarylpalladium formation, regioselective addition to the C−C triple bond of the terminal alkyne, and subsequent displacement of palladium by another mole of alkyne. The present methodology is useful for the introduction of an enynyl moiety at the C-3 position of flavones and thioflavone rings to afford novel compounds of potential biological interest. In the presence of CuI the process afforded 3-alkynyl (thio)flavones in good yields.

Introduction

3-Substituted (thio)flavones have drawn considerable interest because of their occurrence in nature[1] and their profound biological activities.[2,3] For example, 3-substituted flavones are useful as antianaphylactic agents[3b] for the treatment of asthma, as potential cardio protective agents in doxorubicin antitumor therapy,[3c] or as STS (steroid sulfatase) inhibitors for the possible treatment of a number of diseases including breast cancer.[3d] On the other hand, enynes play an important role in medicinal chemistry, not only as valuable precursors to a variety of functionalized compounds, but as key structural units

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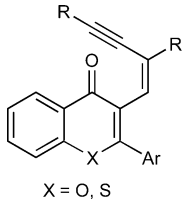

A

FIGURE 1. 3-Enynyl-substituted flavones/thioflavones.

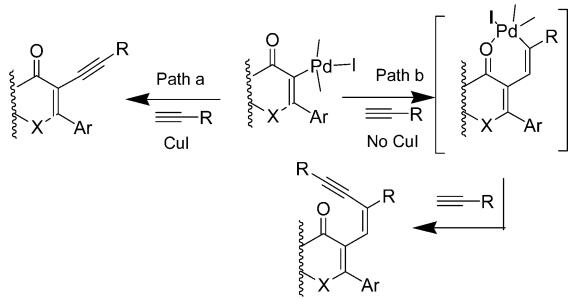

FIGURE 2. Strategy for the synthesis of 3-enynyl(thio)-flavones.

in highly potent antitumor[4a] as well as strong antifungal agents.[4b] For these reasons, the design and synthesis of flavones and thioflavones attached with an enyne moiety is attractive in the field of new drug discovery as that may give rise to compounds of potential pharmacological interest. We felt that due to the common structural features a (thio)flavone ring possessing an enyne moiety at the C-3 position (**A**, Figure 1) might exhibit pharmacological properties similar to 5-vinyl/alkynyl uracil derivatives especially in terms of inhibition of Thymidylate Synthase (TS)—an essential enzyme required for the growth of cells.[5]

On the grounds of above considerations and our interest in the medicinal chemistry of oxygen-containing heterocycles[6,7] we became interested in the synthesis[8] of 3-alkenyl/alkynyl-substituted (thio)flavones.[9] Despite their biological significance, only a few methods (including Suzuki coupling of 3-haloflavones)[2c] have been reported for the synthesis of 3-substituted (thio)flavones[3d,10] whereas a number of methods are available for the synthesis of enynes[11] including transition metal catalyzed reactions. Over the last 25 years, palladium-catalyzed vinylation (the Heck reaction)[12a] and alkynylation (the Sonogashira coupling)[12b] of (hetero)arenes have become attractive and powerful tools for C−C bond-forming reactions. These approaches have been shown to be superior to many tedious classical methods and therefore have been used extensively for the rapid assemblage of natural and unnatural products.[12c,d] Typically, these reactions are carried out in the presence or absence of a copper(I) salt. We envisioned that palladium-mediated alkynylation of an enone moiety in the absence of a copper salt might suppress the normal Sonogashira coupling (path a, Figure 2) and participate in the palladium-catalyzed reaction cascades where several C−C bonds are formed in a single synthetic operation (path b, Figure 2). This palladium-catalyzed transformation is particularly interesting, because it should afford a functionalized enynone system [−COC(=C−)C=C−C≡C−] via a sequential coupling carbopalladation process. While the generation of an enyne system (−C=C−C≡C−) using a similar type of palladium chemistry has been explored earlier, the related studies were only confined to the naphthalene and benzene rings.[13] Moreover, only a

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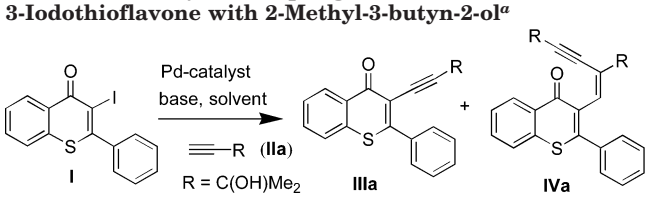
limited number of terminal alkynes (e.g., HC≡CR, when R = CMe_2OH, TMS, CH_2OH, or C_6H_4Me-*p*) were examined in these cases. Nevertheless, the use of a halogenated enone of type −C═C(X)CO− (when X = I or Br) in place of arylhalide to afford π-conjugated acyclic compounds has not been investigated. Herein, we report our detailed study on the new and one-step synthesis of 3-enynyl(thio)flavones (along with their 3-alkynyl analogues) using a copper-free palladium-catalyzed coupling of 3-iodo(thio)flavone with terminal alkynes. A copper-free coupling is beneficial, because it omits the possibility of oxidative homocoupling of terminal alkynes (Glaser-type coupling)[14a] as well as cumbersome purification procedures and therefore may improve the product yields.[14b−d]

Results and Discussion

During our studies on the palladium -catalyzed reaction of 3-iodothioflavone (**Ia**) with a terminal alkyne (**IIa**, R = CMe_2OH) we noted that in addition to the expected 3-alkynylthioflavone (**IIIa**), an unusual product 3-[5-hydroxy-2-(1-hydroxy-1-methylethyl)-5-methyl-1-hexen-3-ynyl]-2-phenylthiochromen-4-one (**IVa**, R = CMe_2OH) was formed in 42% purified isolated yield (Table 1). The compound **IVa** was characterized by ^1H and ^{13}C NMR and other spectroscopic methods. The mass spectra showed an intense molecular ion peak at *m/z* 405.5 ($M^+ + 1$) that was higher than *m/z* of **IIIa** [321 (M^+)]. In the ^1H NMR spectra compound **IVa** gave a signal at δ 6.83 due to the vinylic proton that was not observed in the case of **IIIa**. Moreover, **IVa** gave an additional signal at δ 1.15 accounting for two extra methyl groups. The spectral data thus identified **IVa** as an enyne possessing the thioflavone moiety attached to the vinylic group.[14e] The unexpected formation of this product prompted us to investigate this reaction in a more systematic way.

The reaction was originally carried out in dry DMF in the presence of $PdCl_2(PPh_3)_2$ (0.04 equiv) and triethylamine (8 equiv) under a nitrogen atmosphere using 1.5 equiv of a terminal alkyne (**II**) followed by the addition of CuI (0.05 equiv) and one further equivalent of alkyne after 2−3 h. We were surprised to detect and isolate **IVa**[14f] in addition to **IIIa** from the reaction mixture

TABLE 1. Effect of Reaction Conditions on the Palladium-Catalyzed Coupling Reaction of 3-Iodothioflavone with 2-Methyl-3-butyn-2-ol[a]



entry	Pd catalyst	base; solvent	yield (%)[b] IIIa	yield (%)[b] IVa
1[c]	$PdCl_2(PPh_3)_2$	Et_3N; DMF	18	42
2	$PdCl_2(PPh_3)_2$	Et_3N; DMF	10	55
3[d]	$PdCl_2(PPh_3)_2$	Et_3N; DMF	23	25
4	$Pd(PPh_3)_4$	Et_3N; DMF	20	43
5	$Pd(OAc)_2-PPh_3$	Et_3N; DMF	20	45
6	10% Pd/C−PPh_3	Et_3N; DMF	15	12
7	$Pd(PPh_3)_2Cl_2$	no base; DMF		
8	$Pd(PPh_3)_2Cl_2$	(*i*-Pr)$_2$NEt; DMF	28	9

[a] Reaction conditions: **Ia** (1.0 equiv), **IIa** (2.5−3.0 equiv), Pd catalyst (0.04−0.05 equiv), Et_3N (8 equiv) in a solvent at 80 °C for 12 h under N_2. [b] Isolated overall yields. [c] CuI (0.05 equiv) was used. [d] 1.5 equiv of **IIa** was used.

(Entry 1, Table 1), and therefore we decided to explore the conditions to improve the selectivity. Initially we felt that the delayed use of copper salt was probably responsible for the formation of **IVa**.[8a] However, to understand the nature of the catalytic reaction that might take place before the addition of CuI, we examined the reaction mixture carefully in the absence of CuI. Remarkably, we observed that formation of **IVa** (but not **IIIa**) starts even before the addition of CuI and the normal Sonogashira coupled product **IIIa** was observed to form after the addition of CuI. It is well-known that copper salts activate terminal alkynes by generating a copper acetylide, which then undergoes transmetalation with the arylpalladium halide to form the alkynylpalladium species and upon reductive elimination gives the final alkyne **IIIa**. Thus the complete omission of CuI from the reaction mixture where coupling of **Ia** with **IIa** was carried out for 12 h increased the isolated yield of **IVa** from 42% to 55% (Entry 2, Table 1). In a separate study we carried out this reaction using a lesser amount of terminal alkyne **IIa**, which, however, did not prevent the formation of **IVa** and the reaction did not reach completion (Entry 3, Table 1). These observations clearly indicated that the formation of enyne **IV** was not dependent on the quantity of terminal alkyne used but could be affected by the use of copper salt. In an earlier study Echavarren and co-workers reported that the reactions of aryl halides possessing a bulky peri or ortho group with terminal alkynes afforded the corresponding arylenynes along with arylalkynes.[13a] The use of Ag_2O in place of CuI improved the selectivity for arylenynes in their study. However, we did not observe any improvement in the yield of **IVa** when Ag_2O was used as a cocatalyst under the condition employed. Recently, Yeh and co-workers also noted a similar observation during their study on the synthesis of porphyrinic enynes.[13c] Notably, the use of other palladium catalysts, e.g., $(PPh_3)_4Pd$ and $Pd(OAc)_2/PPh_3$, gave a significant amount of Sonogashira product **IIIa** along with **IVa** (Entries 4 and 5, Table 1) whereas Pd/C−PPh_3 afforded **IVa** in low yield (Entry 6, Table 1). No reaction occurred in the absence of palladium catalyst. Originally,

(14) (a) Dimerization of terminal alkynes to the corresponding diyne is often a side reaction under the Sonogashira coupling conditions and this oxidative homocoupling (Glaser coupling) predominates in the presence of oxygen or other reagents, see for example: Kundu, N. G.; Pal, M.; Chowdhury, C. *J. Chem. Res., Synop.* **1993**, 432. See also: Lei, A.; Srivastava, M.; Zhang, X. *J. Org. Chem.* **2002**, *67*, 1969. Batsanov, A. S.; Collings, J. C.; Fairlamb, I. J. S.; Holland, J. P.; Howard, J. A. K.; Lin, Z.; Marder, T. B.; Parsons, A. C.; Ward, R. M.; Zhu, J. *J. Org. Chem.* **2005**, *70*, 703 and references therein. CuI in the presence of amine base seemed to have a significant role in such oxidative homocoupling of terminal acetylenes. (b) For a discussion, see: Pal, M.; Parasuraman, K.; Gupta, S.; Yeleswarapu, K. R. *Synlett* **2002**, 1976. See also: (c) Urgaonkar, S.; Verkade, J. G. *J. Org. Chem.* **2004**, *69*, 5752. (d) Park, S. B.; Alper, H. *Chem. Commun.* **2004**, 1306. (e) Spectral data for **IVa**: brown solid; DSC 180.8 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.49 (d, J = 8.2 Hz, 1H), 7.63−7.59 (m, 2H), 7.58−7.48 (m, 3H), 7.39−7.36 (m, 3H), 6.83 (s, 1H), 3.11 (br s, D_2O exchangeable, 1H), 3.02 (br s, D_2O exchangeable, 1H), 1.36 (s, 6H), 1.15 (s, 6H); IR (KBr, cm^{-1}) 3384 (br s, OH), 3301, 2926, 1605 (C═O), 1580, 1526; MS (CI, isobutane) 405.5 ($M^+ + 1$, 100%); ^{13}C NMR (50 MHz, DMSO-d_6) δ 179.1, 149.6, 136.9 (2C), 135.3, 132.0, 131.8, 130.2, 129.4 (2C), 128.3 (2C), 128.1 (2C), 128.0, 126.8, 126.6, 101.7, 78.7, 71.9, 63.6, 31.5 (2C), 29.1 (2C). (f) This product was detected while monitoring the reaction using TLC where it appeared below the desired product **IIIa** when visualized under UV light.

we speculated that the formation of **IVa** might first involve the formation of **IIIa** and subsequent reaction of **IIIa** with another mole of terminal alkyne in the presence of palladium catalyst yielded enyne **IVa**. Accordingly, we examined the coupling between the alkyne **IIIa** and the terminal alkyne **IIa** under the optimized condition as described above (cf. Entry 2, Table 1). However, the reaction did not yield **IVa** even in trace amount, which clearly ruled out the possibility of formation of **IVa** via **IIIa**. This also deviates from the observation noted by Echavarren and co-workers where further treatment of the 8-iodonaphthyl alkyne (generated from 1,8-diiodonaphthelene) with a second terminal alkyne in the presence of palladium catalyst afforded corresponding arylenyne.[13a] Triethylamine was used as the base in the present reaction, the omission of which resulted in no reaction as well as recovery of the starting material **Ia** (Entry 7, Table 1). The use of a sterically hindered amine base, i.e., diisopropylethylamine, favored Sonogashira product albeit in low yield (Entry 8, Table 1).

Originally, the reaction was carried out with 2.5−3.0 equiv of terminal alkyne with respect to the halide **I**. However, the stoichiometry of the reaction was evaluated further by conducting a number of experiments. Lower conversion of **I** to **IVa** was observed when a lesser equivalent of terminal alkyne was used. On the other hand use of excess terminal alkyne (more than 3 equiv) did not improve the yield of **IVa** but afforded polymeric products. With the optimized condition in hand we then wanted to assess the limitations and scope of this copper-free palladium-catalyzed transformation and therefore tested the reaction conditions with a variety of terminal alkynes. Thus, when 3-iodo(thio)flavone (**I**, X = O, S)[15a] was treated with a overall 3.0 equiv of a terminal alkyne (**II**, R = alkyl, hydroxyalkyl, etc.)[15b] in dimethylformamide (DMF) in the presence of $PdCl_2(PPh_3)_2$ (0.04−0.05 equiv) and triethylamine (8 equiv) under a nitrogen atmosphere, 3-enynyl-substituted (thio)flavone (**IV**) was obtained (Scheme 1). The results of this study are summarized in Table 2. A number of novel 3-enynyl-substituted thioflavones (entries 1−15, Table 2) have been prepared in fair to moderate yields (42−57%) by using this copper-free palladium-catalyzed reaction. Terminal alkynes containing a variety of functional groups, i.e., alkyl, hydroxyalkyl, and ether, were employed and tolerated during the course of the reaction. Yields of enynes **IV** were not affected significantly by the nature of the R group attached to the C≡C of the alkyne **II**. However, the use of arylacetylenes (e.g., R = C_6H_5, or $C_6H_4CH_3$-*p*) afforded only Sonogashira products **III** in 55−75% yield but no 3-enynyl analogues (**IV**) indicating that the reaction is perhaps sensitive to the reactivity of the terminal alkyne used (see later for a mechanistic discussion). Thioflavone bearing a substituent at the C-6 position (**Ib**) was used successfully (entries 13−15, Table 2). The use of 3-iodoflavone (**Ic**,**d**) also afforded corresponding 3-enynyl derivatives (entries 16−19, Table 2). It is noteworthy that the coupling of **Id** with terminal alkyne (**IIq**) in the presence of $PdCl_2(PPh_3)_2$ and CuI afforded 3-alkynylflavone as a major product in 56% yield along with the 3-enynyl analogue in 10% yield.[8a] However, under the copper-free condition we were able to isolate the 3-enynyl analogue (**IVq**) in 45% yield (entry 18, Table 2). In general, 10−35% improvement in yield of **IV** was observed using the present procedure when compared with the Pd−Cu-based methodology developed by us earlier.[8a]

Typically the present reaction where two C−C bonds were generated in a single synthetic operation was carried out by heating a mixture of 3-idod(thio)flavone, $PdCl_2(PPh_3)_2$, and triethylamine at 80 °C for 1 h followed by addition of a solution of terminal alkyne (2.0 equiv) in DMF at 25 °C. After the mixture was stirred for 2 h at 25 °C one more equivalent of terminal alkyne in DMF was added and the mixture was then stirred at 80 °C for 12−15 h (see the Experimental Section for details). It is noteworthy that the initial heating (80 °C for 1 h) of the mixture of iodo compound, palladium catalyst, and triethylamine in DMF was required to initiate the coupling reaction. Presumably Pd(II) was reduced to Pd(0) during this period. Although 3-alkynyl analogues **III** (Sonogashira product) were isolated as minor products (10−15%) in this present coupling reaction, 3-alkynyl thioflavones (**IIIa**−**j**), however, could be prepared in good to excellent yields by treating **Ia** or **Ib** with 1.5−2.0 equiv of a terminal alkyne (**II**) in DMF in the presence of $PdCl_2(PPh_3)_2$ (0.04 equiv), CuI (0.05 equiv), and triethylamine (8 equiv) under a nitrogen atmosphere (Scheme 2). 3-Alkynyl flavones[15c] on the other hand have been prepared in good yields using (*S*)-prolinol as a base in DMF−H_2O[8b] and the chemistry has subsequently been employed by others for the synthesis of paramagnetic and diamagnetic flavones.[15d] Interestingly, the palladium-mediated coupling of 3-iodoflavone with internal alkynes[16a] (due to the participation of the neighboring aryl group in reaction cascades)[16b] resulted in the formation of annulated products. The present copper-free palladium-catalyzed cross-coupling reaction leading to **IV** was found to be highly stereospecific as only a single isomer of **IV** was isolated from the reaction mixture. The stereochemistry (*E* or *Z*) of the double bond in products (**IV**) was assigned based on their 1D NOESY spectral data. In the case of **IVa** (Figure 3), a clear NOESY correlation was found between H-1 (δ 6.82) and methyls (δ 1.15) of the $C(OH)Me_2$ group at C-2, but none between H-1 and the Me (δ 1.36) at C-5 indicating the syn orientation of the thioflavonyl and acetylenic moieties across the double bond. Similarly, NOESY correlation was also observed between H-1 (δ 7.0) and CH_2 (δ 4.68) at C-2 in the case of **IVi** (Figure 3).[17] Thus we have demonstrated that the

(15) (a) 3-Iodothioflavone and 3-iodoflavone were prepared according to a known procedure, see: Zhang, F. J.; Li, Y. L. *Synthesis* **1993**, 565. (b) All the terminal alkynes used are commercially available. (c) For the synthesis of simple 3-alkynyl flavones from 3-iodoflavone having no substituent at the 2-position under Sonogashira condition, see: Yao, T.; Zhang, X.; Larock, R. C. *J. Am. Chem. Soc.* **2004**, *126*, 11164. (d) Kálai, T.; Kulcsár, G.; Ösz, E.; Jekö, J.; Sümegi, B.; Hideg, K. *ARKIVOC* **2004**, *Part vii*, 266.

(16) (a) Larock, R. C.; Tian, Q *J. Org. Chem.* **1998**, *63*, 2002. (b) A similar observation was noted during the Pd-catalyzed coupling reaction of 9-bromoanthracene with terminal alkynes in the presence of alumina-supported $CuSO_4$, see: Dang, H.; Garcia-Garibay, M. A. *J. Am. Chem. Soc.* **2001**, *123*, 355.

(17) Compound **IVi** was isolated as yellow solid: DSC 125.45 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.26 (d, J = 7.5 Hz, 1H,), 8.14−8.11 (m, 2H), 7.86−7.84 (m, 2H), 7.77−7.58 (m, 2H), 7.62−7.58 (m, 2H), 7.45−7.36 (m, 6H), 7.02 (t, J = 9.2 Hz, 1H), 7.0 (s, 1H), 6.95 (d, J = 9.4 Hz, 1H), 4.99 (s, 2H), 4.68 (s, 2H); IR (KBr, cm^{-1}) 1606 (C=O), 1585; *m/z* (CI, isobutane) 591 (M + 1, 100%); ^{13}C NMR (50 MHz, $CDCl_3$) δ 178.8, 162.9, 162.0, 151.9, 141.7, 141.6, 136.9, 136.3, 134.7, 131.7 (2C), 130.1 (2C), 129.8, 129.4, 128.9, 128.7, 128.3 (2C), 127.8, 125.7, 125.6 (2C), 125.3, 121.5, 114.8 (2C), 114.5 (2C), 89.0, 84.7, 69.9, 56.7.

TABLE 2. Synthesis of 3-Enynyl-Substituted Flavones/Thioflavones via a Copper-Free Palladium-Catalyzed Sequential Coupling Reaction[a]

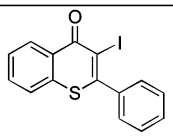
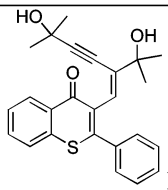
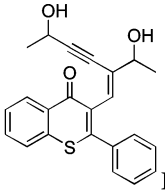
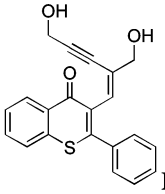
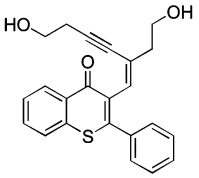
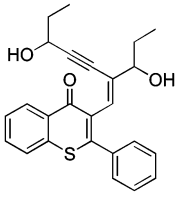
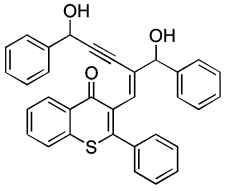
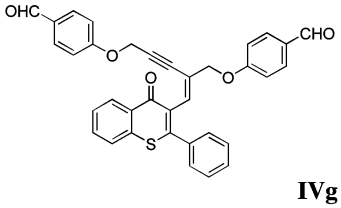
Entry	(Thio)flavones (**I**)	Alkynes (**II**) R =	Conditions	Products[b] (**IV**)	Isolated yield (%) **IV**
1	 **Ia**	$C(OH)Me_2$ **IIa**	12	 **IVa**	55
2	**Ia**	$CH(OH)CH_3$ **IIb**	12	 **IVb**	50
3	**Ia**	CH_2OH **IIc**	12	 **IVc**	52
4	**Ia**	CH_2CH_2OH **IId**	12	 **IVd**	47
5	**Ia**	$CH(OH)C_2H_5$ **IIe**	12	 **IVe**	55
6	**Ia**	$CH(OH)C_6H_5$ **IIf**	12	 **IVf**	58
7	**Ia**	$CH_2OC_6H_4CHO$-*p* **IIg**	12	 **IVg**	48

Table 2 (Continued)

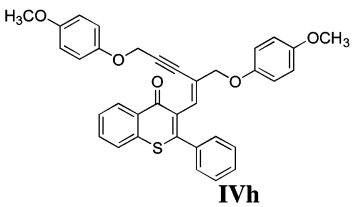
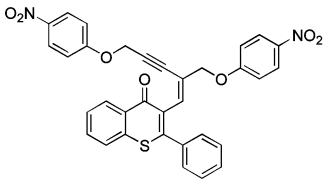
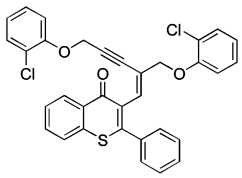
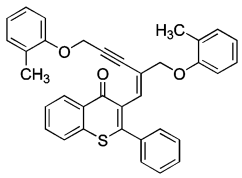
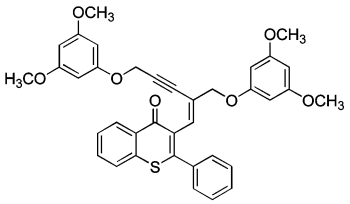
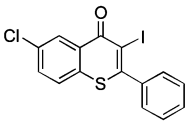
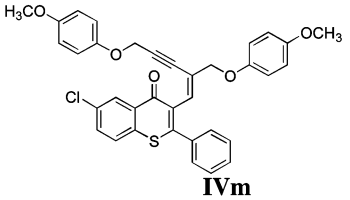
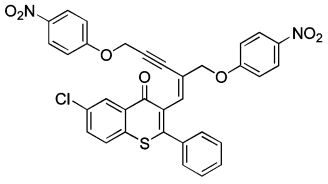
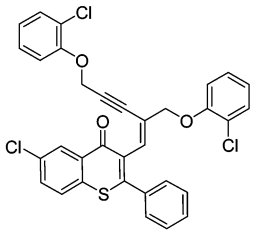
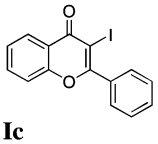
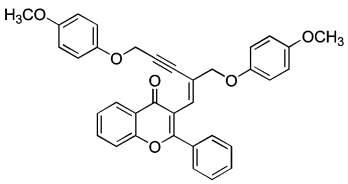
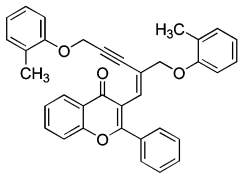
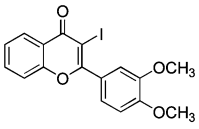
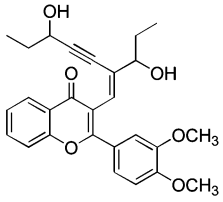
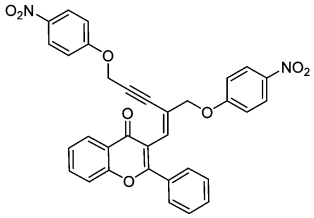
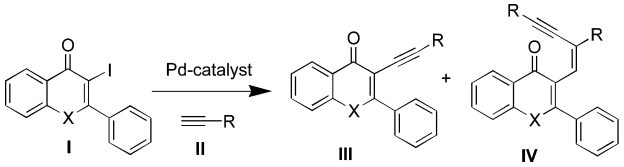
Entry	(Thio)flavones (**I**)	Alkynes (**II**) R =	Conditions	Products[b] (**IV**)	Isolated yield (%) **IV**
8	**Ia**	$CH_2OC_6H_4OCH_3$-*p* **IIh**	12	 **IVh**	42
9	**Ia**	$CH_2OC_6H_4NO_2$-*p* **IIi**	12	 **IVi**	45
10	**Ia**	$CH_2OC_6H_4Cl$-*o* **IIj**	12	 **IVj**	53
11	**Ia**	$CH_2OC_6H_4CH_3$-*o* **IIk**	12	 **IVk**	55
12	**Ia**	$CH_2OC_6H_3(OCH_3$-*m*$)_2$ **IIl**	16	 **IVl**	53
13	 **Ib**	$CH_2OC_6H_4OCH_3$-*p* **IIm**	15	 **IVm**	51
14	**Ib**	$CH_2OC_6H_4NO_2$-*p* **IIn**	15	 **IVn**	40

Table 2. (Continued)

Entry	(Thio)flavones (**I**)	Alkynes (**II**) R =	Conditions	Products[b] (**IV**)	Isolated yield (%) **IV**
15	**Ib**	$CH_2OC_6H_4Cl$-*o* **IIj**	16	 **IVo**	47
16	 **Ic**	$CH_2OC_6H_4OCH_3$-*p* **IIo**	15	 **IVp**	44
17	**Ic**	$CH_2OC_6H_4CH_3$-*o* **IIp**	15	 **IVq**	57
18	 **Id**	$CH(OH)CH_2CH_3$ **IIq**	15	 **IVr**	45
19	**Ic**	$CH_2OC_6H_4NO_2$-*p* **IIi**	16	 **IVs**	51

[a] All reactions were carried out using **I** (1.0 equiv), **II** (2.0 + 1.0 equiv), $PdCl_2(PPh_3)_2$ (0.04−0.05 equiv), and Et_3N (8 equiv) in DMF. [b] Identified by ^1H NMR, ^{13}C NMR, IR, and mass spectroscopy.

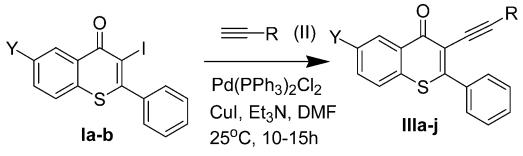
SCHEME 1. Palladium-Catalyzed Coupling of 3-Iodoflavone/Thioflavone with Terminal Alkynes



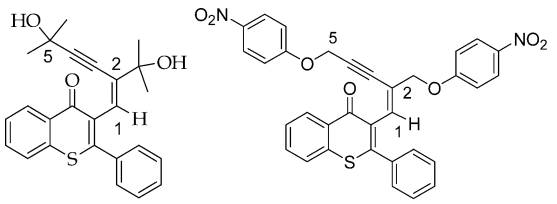
procedure is regio- and stereoselective regardless of the nature of terminal alkyne **II** used.

To account for the present regio- and stereoselectivity, a plausible mechanism for this palladium-mediated tandem reaction leading to the formation of enynyl derivative **IV** is presented in Scheme 3 (ligands are not shown). In the precursor of catalytic species, palladium(II) is first reduced to palladium(0) in the presence of

SCHEME 2. Synthesis of 3-alkynyl Thioflavones under Pd−Cu Catalysis[a]



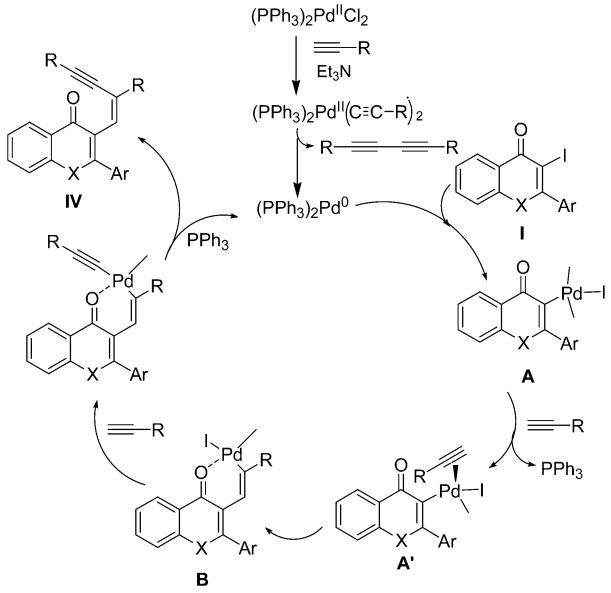
[a] **IIIa−h** (yield %): Y = H, R = $C(OH)Me_2$ (75%), $CH(OH)CH_3$ (78%), CH_2OH (59%), CH_2CH_2OH (81%), $CH(OH)C_2H_5$ (79%), $CH(OH)C_6H_5$ (82%), $CH_2OC_6H_4CHO$-*p* (72%), $CH_2OC_6H_4OCH_3$-*p* (62%). **IIIi,j** (yield%): Y = Cl, R = $CH_2OC_6H_4NO_2$-*p* (65%), $CH_2OC_6H_4Cl$-*o* (70%).



IVa **IVi**

FIGURE 3. Structures of **IVa** and **IVi** are shown for NOESY correlation.

SCHEME 3. Proposed Mechanism for the Copper-Free Palladium-Catalyzed Coupling Reaction of 3-Iodo(thio)flavones with Terminal Alkynes



terminal alkynes and Et_3N.[18a] A arylpalladium species **A** is subsequently generated by the oxidative addition of active Pd(0) species with 3-iodo(thio)flavone. Complexation of the reactant alkyne with this arylpalladium species **A** then initiates the process to produce a transient π-complex **A′**. This complex then undergoes syn addition of the arylpalladium species to the precoordinated triple bond to provide the crucial Pd−C σ-bonded vinylpalladium species (**B**) (Scheme 3).[18b] Due to the required stability imparted by the adjacent carbonyl oxygen of the flavone moiety[18c] this long-lived key intermediate (**B**) then undergoes further reaction with the terminal alkyne to give the enynyl derivative **IV**. Precomplexation of alkyne with the reactive Pd(0) species followed by the interaction with the 3-iodo(thio)flavone could be the alternative pathway to provide the intermediate **B**. Though the directing effect of alkyne as a ligand in the oxidative addition of Pd(0) with iodoolefine has been reported by Nuss and co-workers,[18d] precomplexation of the Pd(0) species was aided by the lack of reactivity of 1,1-diiodoolefine toward palladium catalysts before complexation. 3-Iodo(thio)flavone being a reactive halide toward the palladium catalyst is expected to participate preferentially in the oxidative addition process to give **A**. To gain further evidence on its reactivity, 3-iodothioflavone (**Ia**) was treated with $PdCl_2(PPh_3)_2$ in DMF in the presence of Et_3N at 80 °C. Isolation of a substantial

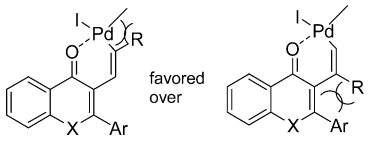
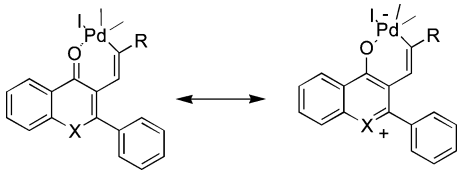


FIGURE 4. Steric factor governing the regiochemistry of alkyne insertion.

quantity of de-iodinated product clearly indicates that **Ia** interacts with Pd(0) generated in situ.

According to the mechanism proposed in Scheme 3 it is now evident that the stereochemistry of the product formed is guided by the orientation of groups attached to the palladium center within the complex **B**. The insertion of unsymmetrical alkynes into an arylpalladium bond is known to proceed via placing the less hindered group next to palladium.[19a] This, however, has not been our observation or that of Larock[19b] as well as Cacchi.[19c] The controlling factor in this insertion process could be the steric hindrance present in the developing carbon−carbon bond as well as the orientation of the alkyne immediately prior to syn-insertion of the alkyne into the aryl palladium bond. Alkyne insertion is likely to occur via generation of least steric crowding in the vicinity of the shorter, developing carbon−carbon palladium bond rather than the long carbon−palladium bond (Figure 4). However, the orientation adopted by the alkyne in the transient π-complex **A′** as shown in Scheme 3 may also be important. The alkyne and arylpalladium bond should be parallel and cis-coordinated in order to cause the syn-addition. The alkyne may adopt an orientation in which the larger group R remains away from the bulky (thio)-flavone moiety. However, this would afford the other isomer that was not isolated. Thus the alternative orientation where R remains nearer to the (thio)flavone moiety is more likely in the present case. This is favored because it leads to the stable complex **B** where the palladium is ligated with the nearby carbonyl oxygen of

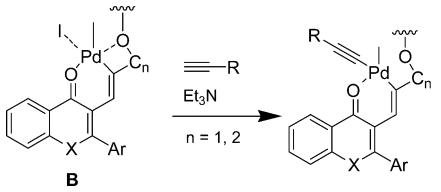
(18) (a) For a discussion on the generation of Pd(0) species from Pd(II) complexes see; Hegedus, L. S. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1113 and references therein. However, recent work by Amatore and Jutand have shown that under typical conditions, the palladium(0) generated by $Pd(PPh_3)_2Cl_2$ reduction is an anionic complex $Pd^0(PPh_3)_2Cl^-$. For a review see: Amatore, C.; Jutand, A. *Acc. Chem. Res.* **2000**, *33*, 314. (b) Wu, M.-J.; Wei, L.-M.; Lin, C.-F.; Leou, S.-P.; Wei, L.-L.; *Tetrahedron* **2001**, *57*, 7839. See also ref 8b. (c) The stability of **A** may be accounted for by the contribution from the following resonating structures.



(d) Nuss, J. M.; Rennels, R. A.; Levine, B. H. *J. Am. Chem. Soc.* **1993**, *115*, 6991.

(19) (a) Pfeffer, M. *Recl. Trav. Chim. Pays-Bas* **1990**, *109*, 567. (b) Larock, R. C.; Yum, E. K.; Refvik, M. D. *J. Org. Chem.* **1998**, *63*, 7652. (c) Cacchi, S. *Pure Appl. Chem.* **1990**, *62*, 713. (d) A similar effect imparted by hydroxyl groups of acetylenic alcohols was observed during palladium-catalyzed hydroarylation of propargylic alcohols, see: Arcadi, A.; Bernocchi, E.; Burini, A.; Cacchi, S.; Marinelli, F.; Pietroni, B. *Tetrahedron* **1988**, *44*, 481 and references therein. (e) Presumably the milder nature of the reaction conditions as well as the stability of the C−S bond could be other reasons for not observing the cleavage of the heterocyclic ring in the present case as noted by Larock and Tian[16a] in their study.

SCHEME 4. Effect of Neighboring Group on the Coupling of B with the Second Alkyne



the (thio)flavone ring. Thus intramolecular interaction of the C-bonded palladium center with the carbonyl oxygen of the flavone moiety clearly favors the formation of that isomer where orientation of the thioflavonyl and acetylenic moieties across the double bond remain as syn. Notably addition of arylpalladium species **A** to the internal alkynes generated vinylpalladium complex where the neighboring aryl group participated in the intramolecular interaction rather than carbonyl oxygen.[16a]

As shown in Scheme 3, the present copper-free process can be envisioned as a three-component procedure that can be changed significantly to a two-component procedure (i.e., Sonogashira coupling) in the presence of CuI. Thus copper-free coupling of **I** with terminal alkynes was expected to afford a better yield of **IV**, which was clearly supported by the experimental results. Arylalkynes, however, participated in the normal Sonogashira coupling even in the absence of copper salt presumably due to the more acidic nature of the acetylenic hydrogen, thereby facile generation of acetylide anion in the presence of Et_3N is compared to the other terminal alkynes used in the present study. Steric crowding created by the aryl group attached directly to the C−C triple bond could be the other reason for preventing arylalkynes to participate in the alkyne insertion process via **A′** (Scheme 3). Notably, the terminal alkyne that usually did not participate in the normal Sonogashira coupling in the absence of copper salt in the initial step displaces iodode from Pd−I of **B** (Scheme 3) following a path similar to the Sonogashira-type coupling. This appeared to be the result of intramolecular coordination of the neighboring alcohol or ether moiety to the palladium[19d] during the iodide displacement step (Scheme 4). Nonetheless, perhaps it is the reactivity of the terminal alkyne in the absence or presence of copper salt (i.e., delayed use of CuI)[8a] in addition to its orientation adopted during the insertion process that did not allow the palladium complex **B** to undergo intramolecular interaction involving the neighboring aryl group leading to the formation of the annulated product or ring-opening of the pyrone ring.[16a,19e]

In conclusion, we have described a facile and mild procedure for the synthesis of novel 3-enynyl(thio)-flavones via a copper-free palladium-catalyzed sequential coupling of 3-iodo(thio)flavone with terminal alkynes. The scope and limitations of this process and the mechanism of the reaction have been discussed. This sequence provides a convenient one-pot procedure to obtain enyne derivatives regio- and stereoselectively having a (thio)-flavone moiety attached to the vinylic group. Factors governing the regio- and stereoselectivity have also been discussed. This novel class of compounds that perhaps could not be prepared by alternative routes is amenable to further functional group transformation.[20] Thus the described methodology is useful for the introduction of an enynyl moiety at the C-3 position of flavone or thioflavone ring via the C−C bond forming reaction. Some of the compounds synthesized were tested for their pharmacological properties and few of them showed interesting biological activities in vitro.[21] Because metal-mediated cascade reactions are useful tools for the short synthesis of complex organic molecules, further exploration of this chemistry is under investigation.

Experimental Section

General Procedure for the Preparation of IV. A mixture of **I** (2 mmol), $(PPh_3)_2PdCl_2$ (0.08−0.10 mmol), and triethylamine (16 mmol) in DMF (4 mL) was stirred at 80 °C for 1 h under a nitrogen atmosphere. The mixture was then cooled to room temperature and acetylenic compound **II** (4 mmol) dissolved in DMF (1.0 mL) was added slowly with stirring. The reaction mixture was stirred at 25 °C for 2 h and then an additional quantity of acetylenic compound **II** (2 mmol) dissolved in DMF (1.0 mL) was added with stirring. Stirring was continued for 12−15 h under a nitrogen atmosphere and the mixture was poured into cold 2 N HCl solution with stirring. The mixture was then extracted with EtOAc (3 × 200 mL), and the combined organic layers were washed with cold water (2 × 100 mL), then dried over Na_2SO_4, filtered, and concentrated under vacuum. The residue was purified by column chromatography (petroleum ether−EtOAc) to afford the desired product.

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Supporting Information Available: Characterization for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(20) See for example: (a) Ghosh, C. K.; Bandyopadhyay, C.; Biswas, S.; Chakravarty, A. K. *Indian J. Chem. Sect. B* **1990**, *29*, 814. (b) Yao, T.; Zhang, X.; Larock, R. C. *J. Am. Chem. Soc.* **2004**, *126*, 11164.

(21) Compounds **IVa** and **IVc** showed anticancer activity with an average GI_{50} of 32 and 33 μM respectively on a tested panel of cancer cell lines [e.g. HT29 (colon), H460 (lung), LoVo (colon), etc.].