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Palladium mediated stereospecific synthesis of 3-enynyl substituted thioflavones/flavones ☆

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Abstract—The stereocontrolled synthesis of enynes has been accomplished via a sequential Heck–Sonogashira reaction in a simple synthetic operation. A variety of terminal alkynes were reacted with 3-iodo(thio)flavone in the presence of a palladium catalyst and a copper salt affording a mild and one-pot method for the first synthesis of the corresponding 3-enynyl and/or alkynyl derivatives. The mechanism and scope of the reaction are discussed.

Interest in 3-substituted (thio)flavones has been considerable because of their occurrence in nature[1] and their biological activities.[2,3] On the other hand, enynes are found to be integral parts of highly potent antitumor,[4] as well as strong antifungal, agents.[5] In connection with our studies on the development of various heterocyclic structures[6–8] we became interested in the synthesis[9a] of 3-alkenyl/alkynyl-substituted (thio)flavones.[9b] 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[10] whereas a number of methods are available for the synthesis of enynes[11] including transition metal catalyzed reactions. Synthesis of 3-enynyl/alkynyl substituted thioflavones, however, has not been reported in the literature. Over the last 25 years, palladium catalyzed alkenylation (the Heck reaction)[12a] and alkynylation (the Sonogashira coupling)[12b] have become attractive and powerful tools for C–C bond forming reactions.[12c] We have a long-term interest in palladium catalyzed reactions[13] and now wish to report a new synthesis of 3-enynyl (thio)flavones (along with their 3-alkynyl analogues) via palladium catalyzed reaction cascades where several C–C bonds are formed in a single synthetic operation.[12c]

During the course of our studies on the palladium catalyzed reaction of a variety of heteroaryl halides[9a,14a] with terminal alkynes, we noted that in addition to the expected product, an unusual product[14b] was formed depending on the delayed use of copper salts in certain cases, especially when 3-iodothioflavone was used as the heteroaryl halide. The spectral data identified it as an enyne possessing the thioflavone moiety attached to the vinylic group.[14c] The unexpected formation of this product prompted us to investigate this reaction in a more systematic way. Thus, when 3-iodo(thio)flavone (**I**, X = O, S)[15a] was treated with 2 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 equiv), CuI (0.05 equiv), and triethylamine (8 equiv) under a nitrogen atmosphere, 3-alkynyl (thio)flavone (**III**, method A, Scheme 1) was obtained as the only product in good to excellent yield (the Sonogashira reaction). However, 3-enynyl substituted analogues (**IV**) were isolated as the major products in most cases when the same reaction was performed with 1.5 equiv of alkyne at 25–30 °C in the absence of CuI, initially for 2–3 h (under Heck reaction conditions), followed by the subsequent addition of CuI (0.05 equiv) along with one further equivalent of alkyne (method B, Scheme 1).[15c] The results of this preliminary study are summarized in Table 1.

While the yields are not optimized, the enynylation of (thio)flavones (**I**) in a single synthetic operation afforded the desired products (**IV**) in satisfactory yields. By using this palladium catalyzed reaction a wide variety of

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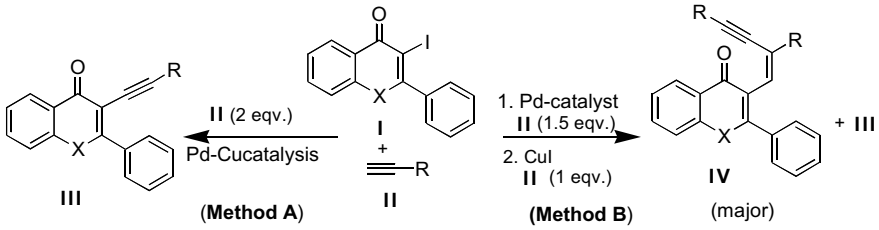


Scheme 1. Palladium catalyzed coupling of 3-iodoflavone/thioflavones with terminal alkynes.

Table 1. Synthesis of 3-enynyl substituted flavones/thioflavones via the sequential Heck–Sonogashira strategy (method B)[a]

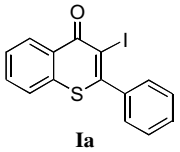
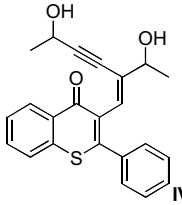
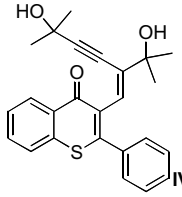
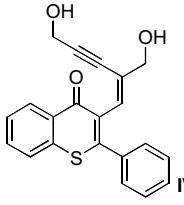
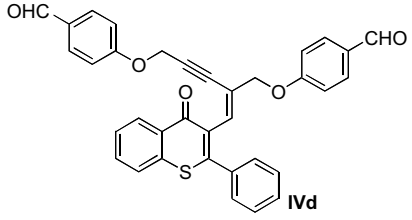
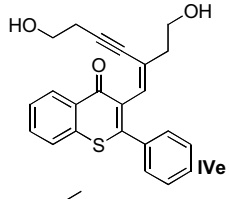
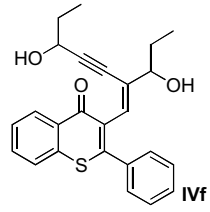
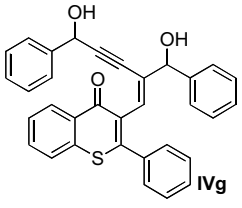
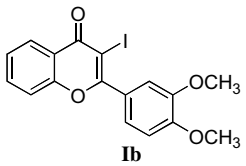
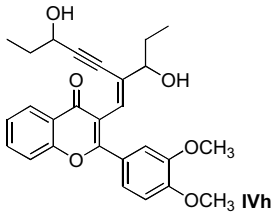
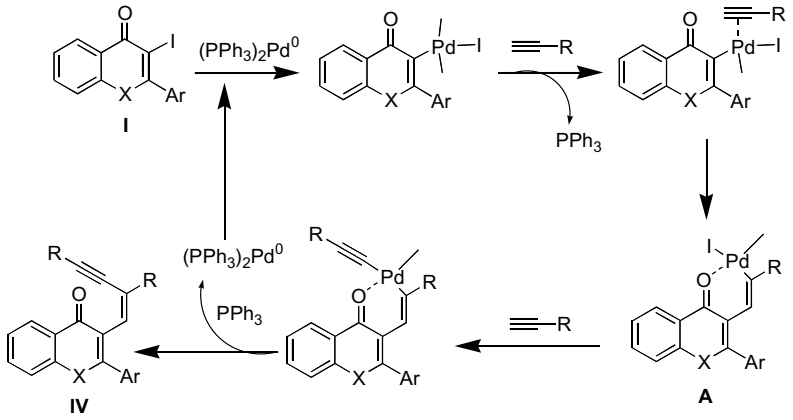
Entry	(Thio)flavones (**I**)	Alkynes (**II**) R =	Products[b] (**IV**)	Yield (%)[c] **IV**
1	 **Ia**	$CH(OH)CH_3$	 **IVa**	40
2	**Ia**	$C(OH)Me_2$	 **IVb**	42
3	**Ia**	CH_2OH	 **IVc**	40
4	**Ia**	$CH_2OC_6H_5CHO$-*p*	 **IVd**	30
5	**Ia**	CH_2CH_2OH	 **IVe**	43
6	**Ia**	$CH(OH)C_2H_5$	 **IVf**	45
7	**Ia**	$CH(OH)C_6H_5$	 **IVg**	45

Table 1 (*continued*)

Entry	(Thio)flavones (**I**)	Alkynes (**II**) R =	Products[b] (**IV**)	Yield (%)[c] **IV**
8	 **Ib**	$CH(OH)CH_2CH_3$	 **IVh**	10[d]

[a] All reactions were carried out using **I** (1.0 equiv), **II** (1.5 + 1.0 equiv), $PdCl_2(PPh_3)_2$ (0.04 equiv), CuI (0.05 equiv), Et_3N (8 equiv) in DMF.
[b] Identified by ^1H NMR, ^{13}C NMR, IR, and mass spectroscopy.
[c] Isolated yields.
[d] **IIIh** was isolated in 56% yield.



Scheme 2. Probable mechanism for the tandem Heck–Sonogashira coupling reaction.

terminal acetylenes were reacted with 3-iodothioflavone (**Ia**, Table 1). The use of 3-iodoflavone (**Ib**), however, led to the formation of the 3-alkynyl analogue as the major product rather than 3-enynyl derivative (entry 8, Table 1). The reaction was generally carried out at 25 °C in both cases (methods A and B), however, initial heating (80 °C) of the mixture of iodo compound, palladium catalyst, and triethylamine in DMF was required (1 h) for the initiation of Heck–Sonogashira coupling (method B).

Both the coupling reactions (methods A and B, Scheme 1) were usually carried out using $(PPh_3)_2PdCl_2$ as the palladium catalyst and CuI as a co-catalyst. Triethylamine was used as the base in both cases, the omission of which resulted in no reaction as well as recovery of the starting material **I**. Method A afforded normal coupling products (**III**) in good yields. The use of CuI was found to be critical in the tandem Heck–Sonogashira coupling reaction (method B) as the course of the reaction along with the nature of the product were changed depending on the subsequent addition (2 h after the addition of 1.5 equiv of **II**) of CuI to the reaction mixture. As indicated by the nature of products (**III** or **IV**) isolated in both cases, it is evident that the reaction followed the Sonogashira pathway in the first case and the Heck–Sonogashira sequence in the second case. Nevertheless, the isolation of 3-alkynyl thioflavone **III** (Sonogashira product) as a minor product (10–20% yield) in the second case indicated that the Sonogashira coupling was often a side reaction during the formation of the 3-enynyl thioflavone. Interestingly, the palladium mediated coupling of 3-iodoflavone with internal alkynes (due to the participation of the neighboring aryl group in reaction cascades) resulted in the formation of annulated products.[16] The Heck–Sonogashira reaction was found to be highly stereospecific as only a single isomer of **IV** was isolated from the reaction mixture.[17]

While the precise mechanism of the palladium mediated tandem reaction leading to the formation of enynyl derivative **IV** is not clear at this stage, presumably, the reaction proceeds via *syn* addition of the arylpalladium complex [generated by the interaction of the 3-iodo(thio)flavone and the active Pd(0) species][18a] to the triple bond of the reactant alkyne, which yields the reactive alkenyl palladium species (**A**) (Scheme 2).[18b] Due to the required stability imparted by the adjacent carbonyl oxygen of the flavone moiety[18c] this long-lived species (**A**) then undergoes further reaction with the terminal alkyne to give the enynyl derivative **IV**. It is well known that CuI activates terminal alkynes by generating copper acetylides in situ. Therefore CuI facilitates the Sonogashira reaction in method A as well as the reaction of terminal alkynes with palladium species **A** in method B. Further study is in progress to evaluate the specific role of CuI especially in method B. Nonetheless, perhaps it is the reactivity of the copper

acetylide, which does not allow the palladium complex **A** to undergo intramolecular interaction involving the neighboring aryl group leading to the formation of the annulated product or ring opening of the pyrone ring.[16,18d]

In summary, we have described a facile and mild procedure for the stereospecific synthesis of novel 3-enynyl (thio)flavones via a Heck–Sonogashira strategy. To the best of our knowledge this is the first example of the one-pot synthesis of enyne derivatives having a heteroaryl moiety attached to the vinylic group. Since, metal mediated cascade reactions are known to be useful tools for the short synthesis of complex organic molecules, the methodology described holds promise for modern organic synthesis.

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stirring. Stirring was continued for 8–11 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), 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. Compound **IVa** was isolated as pale yellow solid, yield 40%; DSC: 146.39 °C; ^{1}H NMR (400 MHz, $CDCl_3$): 8.53 (d, $J = 7.8$ Hz, 1H), 7.62–7.53 (m, 4H), 7.49–7.46 (m, 2H), 7.42–7.38 (m, 2H), 6.74 (s, 1H, –CH=C), 4.49–4.44 (m, 1H, –C≡C–C*H*(OH)Me), 4.30–4.26 (m, 1H, –C=C–C*H*(OH)Me), 1.78–1.58 (br s, D_2O exchangeable, 2H, OH), 1.30–1.26 (m, 3H, Me), 1.12–1.09 (m, 3H, Me); IR (KBr, cm^{-1}): 3432, 2927, 1578, 1529, 1441; MS (CI, *i*-butane): 377 (M^++1, 100%); ^{13}C NMR (50 MHz, DMSO-d_6): 178.9 (C=O), 149.8, 136.8, 136.7, 131.9, 131.9, 130.8, 129.8, 129.3, 129.1 (2C), 128.1, 128.0 (2C), 127.9, 127.6, 126.4, 99.1 (C≡C), 79.6 (C≡C), 68.6 (C(OH)Me), 56.6 (C(OH)Me), 24.4 (Me), 22.5 (Me). Spectral data for **IVb**: brown solid, yield 42%; DSC: 180.8 °C; ^{1}H NMR (400 MHz, $CDCl_3$): 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, –CH=C), 3.11 (br s, D_2O exchangeable, 1H, OH), 3.02 (br s, D_2O exchangeable, 1H, OH), 1.36 (s, 6H, Me), 1.15 (s, 6H, Me); IR (KBr, cm^{-1}): 3384, 3301, 2926, 1580, 1526; MS (CI, *i*-butane): 405.5 (M^++1, 100%); UV (MeOH, nm): 260, 206.5; ^{13}C NMR (50 MHz, DMSO-d_6): 179.1 (C=O), 149.6, 136.9, 136.9, 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 (C≡C), 78.7 (C≡C), 71.9 (–CMe_2OH), 63.6 (–CMe_2OH), 31.5 (2C, Me), 29.1 (2C, Me).

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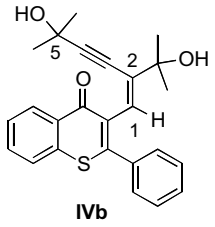
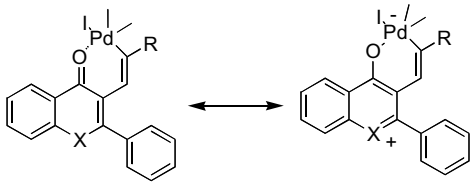


IVb

18. For a discussion on the generation of Pd(0) species from Pd(II) complexes, see: (a) Hegedus, L. S. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1113, and references cited 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. 17; (c) The stability of **A** may be accounted for by the contribution from the following resonance structures



(d) 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.