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Communication

An efficient transformation of furano-hydroxychalcones to furanoflavones via base mediated intramolecular tandem *O*-arylation and C-O bond cleavage: A new approach for synthesis of furanoflavones†‡

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A new and efficient potassium carbonate mediated intramolecular tandem *O*-arylation followed by C-O bond cleavage of furano-hydroxychalcones has been described. The treatment of furano-hydroxychalcones pongamol (1a) and ovalitenone (2a) with potassium carbonate in DMF led to the direct formation of furanoflavones lanceolatin B (3ab) and pongaglabrone (4ab) in excellent yields. This is the first report on cyclization of furano-hydroxychalcones *via* C-O bond cleavage (demethoxylation) to produce furanoflavonoids.

Introduction

Pongamia pinnata is Indian medicinal plant widely distributed in forests,[1, 2] and is traditionally being used for the treatment of piles, skin diseases, tumors and ulcers.[3, 4] Seed oil of the plant is used as biodiesel[5] and also in the treatment of skin diseases,[6] rheumatism, ulcers, whooping cough,[6] bronchitis, and diabetes.[7] Roots of the plant are used in the treatment of gonorrhoea, cleaning teeth and gums;[8] and fruits as anti-dyslipidemic and antioxidant.[9] This plant is a rich source of bioactive flavonoids (flavones, flavans) and chalcones.[10, 11] Pongamol (**1a**) is a furano-hydroxychalcone, isolated from this plant in 1942 as one of the major constituents.[12] Its structural analog ovalitenone (**2a**) was isolated from the same plant in 1991.[13] Both these chalcones are reported to possess anti-diabetic activity.[14]

Furanoflavonoids lanceolatin B (**3ab**)[15] and pongaglabrone (**4ab**)[16] have been reported as potent anti-neuroinflammatory agents[17] and as inhibitors of IL-1β, IL-6, TNF-α, COX-2, iNOS, NFκB, and p-IκBα.[18] The previous reports on their synthesis involve multiple steps producing lower yields.[19-21] In this regard, the transformation of one natural product to other is of great importance, and it has been used historically as one of the most efficient way to large scale synthesis of medicinally important natural products (e.g. paclitaxel starting from 10-deacetylbaccatin III). Herein, we have accomplished an efficient one-pot transformation of 1,3-diketone (hydroxy-chalcones) class of natural products to naturally occurring flavones under mild basic conditions.

For synthesis of flavones from 1,3-diketones, four key approaches are known in the literature (shown in Figure 1A) *viz.* (a-b). dehydrative cyclization of 1-(2-hydroxyphenyl)-3-phenylpropane-1,3-diones,[22-24] (c) cyclocondensation of phloroglucinol with *β*-ketoesters,[25] (d) photocyclization of 2-chloro-substituted 1,3-diarylpropan-1,3-diones,[26] (e) base mediated cyclization of 1-(2-halophenyl)-3-phenylpropane-1,3-diones, wherein the *ortho*-substituted halogen is a leaving group (Ullmann-type *O*-arylation).[27]

The transformation of 1-(2-methoxyphenyl)-3-phenylpropane-1,3-diones to flavones described in this work, involves tandem *O*-arylation/ C-O bond cleavage (demethoxylation) (Figure 1B). Literature search indicated that metal-free demethoxylation under mild reaction conditions has never been reported, except a recent report[28] on $LiAlH_4$ with KOtBu catalyzed *O*-demethoxylation of aromatic ethers. The present paper reports K_2CO_3 catalyzed tandem *O*-arylation/ C-O bond cleavage (demethoxylation) of furano-hydroxychalcones for synthesis of furanoflavones (Figure 1B).

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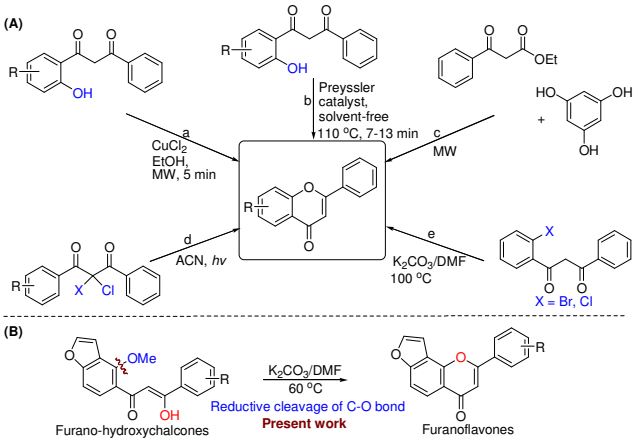
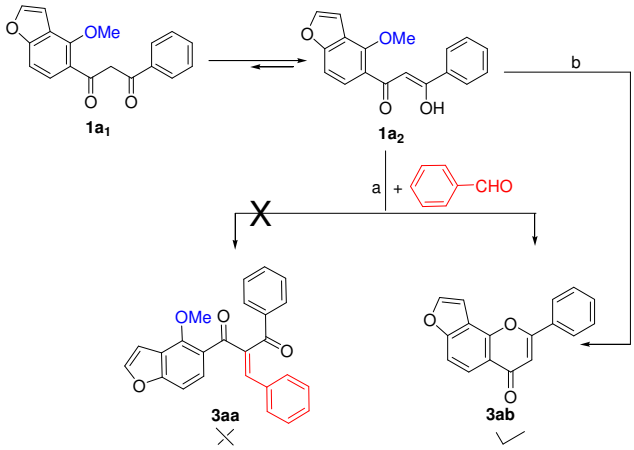


Figure 1. Synthesis of flavones from 1,3-diketones. (A) Literature reports; (B) present work on base-mediated tandem *O*-arylation *via* reductive cleavage of C-O bond.



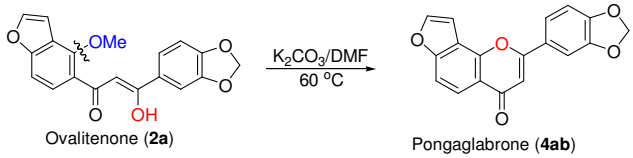
Scheme 1. Unexpected conversion of furanochalcone pongamol (**1a$_1$**) to furanoflavone lanceolatin B (**3ab**). Reagents and conditions: (a) benzaldehyde (1 equiv.), K_2CO_3 (2 equiv.), DMF, 60 °C, 12 h, 85%; (b). K_2CO_3 (2 equiv.), DMF, 60 °C, 12 h, 84%.

Results and discussion

The phytochemical investigations on seeds of *Pongamia pinnata* led to isolation of pongamol (**1a**) and ovalitenone (**2a**), which were characterized by comparison of their spectral data with literature values.[12, 29] Pongamol (**1a**) exists in keto-enol tautomeric forms (*β*-keto dihydrochalcone **1a$_1$** and *β*-hydroxychalcone **1a$_2$** – shown in Scheme 1),[30,31] which was also revealed from the ^{1}H and ^{13}C NMR of pongamol (**1a**) recorded by us. During our efforts on the synthetic modifications on pongamol (**1a**), the condensation of aryl aldehydes with active methylene group of 1,3-diketo functionality of pongamol was planned. The reaction of pongamol (**1a**) with benzaldehyde in presence of K_2CO_3 in DMF at 60 °C, resulted in the formation of a new product **3ab** (in 85% yield), and not a desired aldehyde-condensed product **3aa** (Scheme 1). The ^{1}H NMR of obtained product showed two important changes from the parent natural product *viz*. (a) disappearance of OMe signal (δ 4.14 ppm); and (b) disappearance of *H*-bonded OH signal (δ 16.91 ppm), however the number of olefinic/Ar-H protons remained same. This clearly indicated that **3aa** has not been formed, and the reaction has occurred on the OMe group. HR-ESIMS analysis revealed the molecular formula of obtained product as $C_{17}H_{10}O_3$ with molecular weight of *m/z* 263.0694 $[M+H]^+$. Further analysis of ^{13}C NMR and DEPT135 NMR spectra and comparison of spectral data and melting point with literature values indicated that **3ab** is a furanoflavone lanceolatin B.

Next, we performed a control experiment in the absence of benzaldehyde, which now as expected led to the formation of lanceolatin B (**3ab**) as the only product (in 84% yield). This observation indicated that the conversion of pongamol (**1a**) to lanceolatin B (**3ab**) must be involving reductive cleavage of C-O ether bond along with a cyclization (intramolecular *O*-arylation).

Further, we investigated this reaction on another structurally similar furano-hydroxychalcone ovalitenone (**2a**) under similar reaction conditions (K_2CO_3 in DMF at 60 °C for 12 h) (shown in Scheme 2). Like pongamol (**1a**), here as well a similar product **4ab** was obtained (87% yield) *via* tandem cyclization (intramolecular *O*-arylation) - demethoxylation. The product **4ab** is also a naturally occurring furanoflavone pongaglabrone (Scheme 2).



Scheme 2. Base-mediated transformation of ovalitenone (**2a**) to pongaglabrone (**4ab**). Reagents and conditions: (a) K_2CO_3 (2 equiv.), DMF, 60 °C, 12 h, 87%.

Next, in order to get mechanistic insights on this reaction, a few control reactions were carried out (Figure 2). To know whether this protocol can be utilized as a demethoxylation method, we performed a reaction on chalcone **5**[32] containing OMe group located at structurally similar position to that of pongamol (**1a**); however, there was no demethoxylation (entry a in Figure 2). The reaction on structurally similar furano-chalcone **6**,[32] devoid of enolic-OH also does not led to the formation of corresponding flavone or a demethoxylated product (entry b). Finally, the treatment of anisole with K_2CO_3 in DMF also not produced demethoxy product (entry c). These observations (Figure 2) clearly indicated that during the conversion of pongamol to lanceolatin B, demethoxylation occurs as a part of tandem-reaction process involving cyclization (intramolecular *O*-arylation) followed by demethoxylation (C-O bond cleavage) of furano-hydroxychalcones; and the present reaction conditions could not be used for individual reactions.

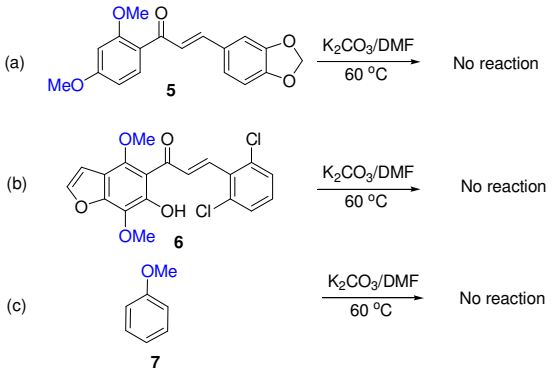


Figure 2. Control experiments.

As it is reported that pongamol and ovalitenone exists in keto-enol tautomerism (as shown in Scheme 1); thus in the presence of a base, the enolic OH undergoes *O*-arylation followed by the release of OMe group (C-O bond cleavage) leading to the formation of flavone **3ab** as depicted in Figure 3.

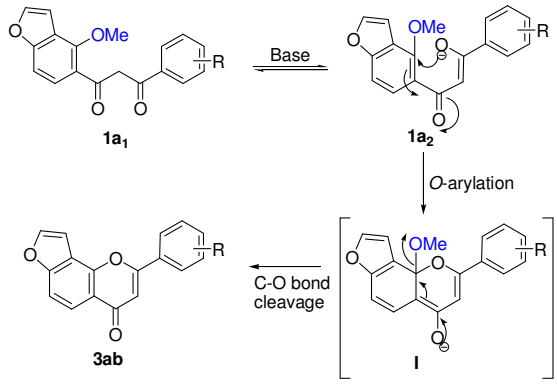


Figure 3. Proposed reaction mechanism for base-mediated conversion of pongamol (**1a**$_1$) to lanceolatin B (**3ab**).

Conclusion

In conclusion, we have described a new approach for synthesis of furanoflavone class of natural products lanceolatin B and pongaglabrone from furano-hydroxychalcones *via* tandem *O*-arylation followed by C-O bond cleavage under mild metal-free reaction conditions.

Experimental section

General. All chemicals were obtained from Sigma-Aldrich Company and used as received. ^{1}H, ^{13}C and DEPT NMR spectra were recorded on Bruker-Avance DPX FT-NMR 500 and 400 MHz instruments. Chemical data for protons are reported in parts per million (ppm) downfield from tetramethylsilane and are referenced to the residual proton in the NMR solvent ($CDCl_3$, 7.26 ppm). Carbon nuclear magnetic resonance spectra (^{13}C NMR) were recorded at 125 MHz or 100 MHz: chemical data for carbons are reported in parts per million (ppm, δ scale) downfield from tetramethylsilane and are referenced to the carbon resonance of the solvents ($CDCl_3$: 77.36 ppm). ESI-MS and HRMS spectra were recorded on Agilent 1100 LC-Q-TOF and HRMS-6540-UHD machines. IR spectra were recorded on Perkin-Elmer IR spectrophotometer. Melting points were recorded on digital melting point apparatus.

Plant material. The authentic plant material *Pongamia pinnata* was provided by the Biodiversity and Applied Botany Division of Indian Institute of Integrative Medicine (CSIR), Jammu, from the plain area of the Jammu region of India. The plant material was identified by Dr. Sumeet Gairola. A specimen sample (accession number: 22898) was preserved in Janaki Ammal Herbarium at the IIIM (CSIR), Jammu, India.

Extraction and isolation. The dried and powdered seeds (2.5 kg) of *Pongamia pinnata* were extracted by cold percolation with methanol (3 × 2 L) and combined filtrate was concentrated to afford 700 g of extract. This extract was suspended in water and sequentially fractionated with different solvents including hexane, EtOAc, $CHCl_3$, and *n*-BuOH yielding 200, 100, 90 and 120 g extracts, respectively. The EtOAc fraction (100 g) was subjected to column chromatography using step-gradient system of hexane and EtOAc in the range of 3 to 30%, which yielded ten major fractions. The 3rd and 4th fraction contained oily compound, which was subjected to crystallization in methanol to get pongamol (**1a**, 500 mg). The 4th, 5th and 6th fraction on crystallization in methanol gave ovalitenone (**2a**, 400 mg). The structures of these compounds were confirmed by comparison of their spectral data with literature values.[12, 29]

*Pongamol (**1a**).*Yellowish white needles; m.p. 137-138 °C; IR ($CHCl_3$): ν_{max} 3585, 3456, 3152, 2925, 2851, 2679, 1895, 1846, 1736, 1688, 1599, 1556, 1472, 1353, 1330, 1259 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 16.91 (s, 1H, OH), 7.99-7.97 (d, *J* = 8 Hz, 2H, CH), 7.89 (d, *J* = 8 Hz, 1H, CH), 7.63 (d, 1H, CH), 7.54-7.47 (m, 3H, CH), 7.31 (d, *J* = 8 Hz, 1H, CH), 7.17 (s, 1H,COC<u>H</u>=CH), 7.00 (d, 1H, CH), 4.15 (s, 3H, OMe); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 186.1 (C=O), 184.3(C=<u>C</u>-OH), 158.7 (C-7a), 153.7 (C-4), 144.8 (OC<u>H</u>=CH), 135.6 (C-1´), 132.2 (C-4'), 128.6 (C-3´,C-5´), 127.1 (C-2´, C-6´), 126.5 (C-8), 122.1 (C-5), 119.6 (C-3a), 107 (C-7), 105.3 (OCH=<u>C</u>H), 97.9 (C-2), 61.2 (OMe); HR-ESIMS: *m/z* 295.0955 $[M+H]^+$ calcd for $C_{18}H_{14}O_4$+ H^+ (295.0965) and *m/z* 317.0790 $[M+Na]^+$ calcd for $C_{18}H_{14}O_4$+ Na^+ (317.0784).

*Ovalitenone (**2a**).* Yellow powder; m.p. 117-118 °C; IR ($CHCl_3$): ν_{max} 3564, 3418, 3125, 2994, 2957, 2916, 2789, 2065, 1845, 1590, 1539, 1504, 1471, 1439, 1296, 1260, 1233, 1194, 1165 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 17.01 (s, 1H, OH), 7.86 (d, *J* = 8 Hz, 1H, CH), 7.62 (m, 2H, CH), 7.45 (d, 1H, OC<u>H</u>=CH), 7.30 (dd, 1H, CH), 7.06 (s, 1H, COC<u>H</u>=COH), 6.99 (d, 1H, OCH=C<u>H</u>), 6.89 (d, *J* = 8 Hz, 1H, CH), 6.06 (s, 2H, OCH_2), 4.13 (s, 3H, OMe); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 184.9 (C=O), 183.9 (C=<u>C</u>-OH), 158.5 (C-7a), 153.6 (C-4), 151.2, 148.1, 144.8 (OC<u>H</u>=CH), 130.2, 126.3, 122.8, 121.6, 119.5, 108.2, 107.2, 107.0, 105.2 (OCH=<u>C</u>H), 101.8 (CH_2), 97.9, 61.2 (OMe); HR-ESIMS: *m/z* 339.0872 $[M+H]^+$ calcd for $C_{19}H_{14}O_6$+ H^+ (339.0863).

Transformation of pongamol (1a) and ovalitenone (2a) to lanceolatin B (3ab) and pongaglabrone (4ab). To the solution

of pongamol (**1a**, 100 mg, 1 equiv.) in DMF was added K_2CO_3 (94 mg, 2 equiv.) and reaction mixture was stirred at 60 °C for 12 h. After completion of the reaction, reaction mixture was partitioned between water and dichloromethane. The organic layer was collected, evaporated *in vacuo* and the crude product was purified using silica gel column chromatography to get lanceolatin (**3ab**, 85%). Ovalitenone (**2a**) was converted to pongaglabrone (**4ab**) using similar method.

*Lanceolatin B (**3ab**)*. Yellowish white solid; 60 mg; yield: 85%; m.p. 126-128 °C; IR ($CHCl_3$): ν_{max} 3418, 2922, 2851, 2080, 1650, 1605,1530, 1494, 1458, 1449, 1404, 1360, 1282, 1216 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.19 (d, J = 8 Hz , 1H, CH-5), 7.98 (m, 2H, Ar-2'- 6'), 7.79 (d, J = 4 Hz 1H, OCH=CH), 7.56-7.56 (m, 4H, Ar-3',4',5', CH-6), 7.22 (d, J = 4Hz, 1H, OCH=CH), 6.90 (s, 1H,COCH=CPh); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 178.3 (C=O), 162.6, 158.3, 150.8, 145.8 (OCH=CH), 131.7, 131.6, 129.6, 126.2, 121.7, 119.3, 117.1, 110.2, 108.0 (OCH=CH), 104.2 (COCH=CPh); HR-ESIMS: *m/z* 263.0694 $[M+H]^+$ calcd for $C_{17}H_{10}O_3$+ H^+ (263.0703).

*Pongaglabrone (**4ab**)*. White brown cystals; 65 mg; m.p. 132-134 °C; IR ($CHCl_3$): ν_{max} 3584, 3356, 2993, 2920, 2852, 1642, 1607, 1584, 1528, 1504, 1482, 1404, 1374, 1331, 1295, 1239, 1211 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.18 (d, J = 8 Hz, 1H, CH-5), 7.78 (d, 1H, OCH=CH), 7.56 (m, 2H, CH), 7.41 (d, J = 4 Hz, 1H), 7.21 (d, 1H, OCH=CH), 6.97 (d, 1H, CH), 6.78 (s, 1H, COCH=CPh), 6.11 (s, 2H, OCH_2O); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 178.2 (C=O), 162.3, 158.3, 150.7, 150.6, 148.5, 145.8 (OCH=CH), 125.7, 121.7, 121.3, 119.2, 117.0, 110.1, 108.0, 107.0, 106.2 (OCH=CH), 104.2 (COCH=CPh), 101.9; HR-ESIMS: *m/z* 307.0596 $[M+H]^+$ calcd for $C_{18}H_{10}O_5$+ H^+ (307.0601).

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32. Compounds **5** and **6** are synthetic chalcones prepared via reaction of corresponding acetophenones with aryl aldehydes using a routine base-mediated chalcone synthesis procedure.