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Synthesis of Rigid Analogues of Flavone by Intramolecular Heck Reaction

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A novel concise method to synthesize rigid analogues of flavone by an intramolecular Heck reaction with wide substrate scope was developed. The key intermediates 3-(2-bromo-

Introduction

Flavonoids are products with diverse biological activities such as antioxidant,^[1] anti-allergic,^[2] anticancer,^[3] anti-inflammatory,^[4] antimicrobial,^[5] anxiolytic,^[6] myorelaxant properties,^[7] and anti-osteoporosis in particular.^[8] Galangin is a natural flavonoid which is found in high concentrations in Alpinia officinarum and Helichrysum aureonitens. Galangin inhibits osteoclastogenic factors and increases osteoprotegerin (OPG) levels in osteoblasts.^[9] Glabridin was found to have anti-resorptive activity by the inhibition of RANKL-induced expression of c-Fos and NFATc1.^[10] Apibenzyl)-4H-chromen-4-ones were prepared easily in two steps. Most compounds were obtained with moderate to good yields (34-90 % yield, 19 examples).

genin was reported to inhibit the differentiation of RAW 264.7 cells into tartrate resistant acid phosphatase (TRAP) positive and multinucleated osteoclasts.[11] Another example is ipriflavone which has been used as a therapeutic agent in preventing and treating osteoporosis.^[11a] (Figure 1).

In recent years, a large amount of effort has been devoted to studying the chromone ring system,^[12] including rigid flavone derivatives. In 1992, a novel isoflavone wrightiadione, which showed cytotoxic activity, was isolated from the bark of Wrightia tomentosa (Figure 1).[13] Williams and co-workers prepared and studied benz[b]indeno[2,1-e]pyran-10,11-dione 5 and analogues for inducing endoge-



Figure 1. Structures of flavone and rigid analogues.

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nous erythropoietin (Epo), which is a hematopoietic growth factor stimulating the differentiation and supporting the survival of cells of erythroid lineage. They applied 2'hydroxy-2-(methysulfinyl)acetophenone and a symmetrical benzene-1,2-dicarboxaldehyde to obtain 5.[14] Valenti and co-workers synthesized a rigid analogue of flavone-8-acetic acid (6) displaying a remarkable indirect cytotoxity through a condensation of 2-hydroxy-3-allylacetophenone and phthalaldehyde followed by further manipulation.^[15] In addition, the hetero-Diels-Alder reaction of the ortho-quinone methide (o-QM) with indene has been used to construct the frame of substituted 4b,10,10a,11-tetrahydroindeno-[1,2-*b*]chromene (compounds 44–47).^[16] However, some of the steps in these synthetic methods mentioned above were low-yielding and the synthesis of some substituted rigid analogues of flavone through these protocols was limited by starting materials. With the consideration of these problems and the reported interesting biological activities, we decided to develop a novel concise method to prepare various substituted indeno[1,2-*b*]chromen-10(11*H*)-ones for further biological activity studies.

Results and Discussion

The Heck reaction is one of the powerful and widely used methods for the formation of C–C bonds.^[17] We envisaged that the title scaffold could be synthesized by an intramolecular Heck reaction from 3-(2-bromobenzyl)-4*H*-chromen-4-one, which was prepared in two steps (Scheme 1).

The synthesis of compounds 2a-2t proceeds through the migration of the double bond^[18] of compounds 1a-1t, which were prepared by an aldol condensation^[19] (Scheme 1). As indicated in Table 1, we started our studies by treating 3-(2-bromobenzyl)-4H-chromen-4-one (2a) with $Pd(OAc)_2$ (10 mol-%) in the presence of PPh_3 (20 mol-%), K₂CO₃ (3 equiv.) in PhMe at 110 °C. However, the desired product was not found (entry 1). Then the reaction was performed by taking KOAc (3 equiv.) as the base and Pd(OAc)₂ (10 mol-%) as the catalyst in DMF at 110 °C while no ligand added. Intriguingly, the title compound 3a was isolated in 13% yield (entry 2). A great improvement was achieved by applying JohnPhos (20 mol-%) as the ligand, which was considered to stabilize the Pd intermediate and the yield was raised to 54% (entry 3). With this pleasing result in hand, we turned to optimize the reaction further. A screen of the $Pd(OAc)_2$ loading showed that the



yield was improved as the loading of Pd(OAc)₂ increased (entries 3-5), whereas changing the catalyst from Pd(OAc)₂ to PdCl₂ decreased the yield of compound 3a and no reaction occurred with Pd(Ph₃P)₄ (entries 6 and 7). No transformation of 2a into 3a was observed when the ligand was changed to DPPF (20 mol-%) or (R)-BINAP (20 mol-%) (entries 8 and 9) and the yield decreased when TTBP (20 mol-%) was used (entry 10). Other solvents and bases were also investigated and they did not show any advantages compared with DMF and KOAc (entries 11–16). Attempts to reduce the loading of KOAc revealed that the use of 2 equiv. of KOAc was the best choice (entries 17 and 18) and a further decrease in the amount of ligand proved ineffective (entries 19 and 20). Moreover, investigation of the reaction temperature (entries 21 and 22) led us to establish the optimized reaction conditions as follows: Pd(OAc)₂ (20 mol-%), JohnPhos (20 mol-%), KOAc (2 equiv.), and DMF (4 mL) as the solvent at 110 °C for 40 min.

We next explored the scope and generality of this intramolecular Heck reaction with the optimized reaction conditions in hand. As shown in Table 2, the 3-(2-bromobenzyl)-4*H*-chromen-4-one **2a**–**2t** bearing either electron-donating or electron-withdrawing groups at different positions all underwent the reaction to give the products in moderate to good yields. Under the optimized conditions, a wide range of functional groups could be tolerated. To study the position effect of the substituent on the benzyl group of compounds 2, we applied compounds 2b, 2c, 2d, 2e with an electron-withdrawing fluorine substituent on different positions. When the 6'-fluoro-substituted substrate 2b was applied, the desired product was obtained in better yield than the 3'-fluoro- (3e), 4'-fluoro- (3c) or 5'-fluoro- (3d) substituted compound 2. From the above results we found that subtle change of electron density on the benzyl group of compounds 2 had a great impact on the yields. This phenomenon was also observed on 2g and 2i. The compound



R1 = H, i-Pr, OMe, Me; R2 = H, OMe; R3 = H, F; R4 = H, F, OMe, Me; R5 = H, F, OMe, CF3; R6 = H, F; X = Br, Cl.

Scheme 1. The synthesis of compounds 3a-3t. (a) TiCl₄, pyridine, THF; (b) K₂CO₃, DMF.

SHORT COMMUNICATION

Table 1. Reaction conditions screening.[a]



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Entry	Solvent	Base (equiv.)	Catalyst/Ligand (mol-%) ^[b]	Temp. [°C]	Yield ^[c] [%]
1	PhMe	K ₂ CO ₃ (3)	Pd(OAc) ₂ (10)/L ₀ (20)	110	n.r
2	DMF	KOAc(3)	$Pd(OAc)_2(10)$	110	13
3	DMF	KOAc(3)	$Pd(OAc)_2(10)/L_1(20)$	110	54
4	DMF	KOAc(3)	$Pd(OAc)_2(5)/L_1(20)$	110	24
5	DMF	KOAc(3)	$Pd(OAc)_2(20)/L_1(20)$	110	68
6	DMF	KOAc(3)	$PdCl_2(20)/L_1(20)$	110	57
7	DMF	KOAc(3)	$Pd(PPh_3)_4(20)$	110	n.r
8	DMF	KOAc(3)	$Pd(OAc)_2(20)/L_2(20)$	110	n.r
9	DMF	KOAc(3)	$Pd(OAc)_2(20)/L_3(20)$	110	n.r
10	DMF	KOAc(3)	$Pd(OAc)_2(20)/L_4(20)$	110	60
11	DMF ^[d]	KOAc(3)	$Pd(OAc)_2(20)/L_1(20)$	110	n.r
12	PhMe	KOAc(3)	$Pd(OAc)_2(20)/L_1(20)$	110	n.r
13	DMSO	KOAc(3)	$Pd(OAc)_2(20)/L_1(20)$	110	n.r
14	DMF	KF(3)	$Pd(OAc)_2(20)/L_1(20)$	110	14
15	DMF	$K_3PO_4(3)$	$Pd(OAc)_2(20)/L_1(20)$	110	n.r
16	DMF	CsOAc(3)	$Pd(OAc)_2(20)/L_1(20)$	110	n.r
17	DMF	KOAc(2)	Pd(OAc) ₂ (20)/L ₁ (20)	110	76
18	DMF	KOAc(1.5)	$Pd(OAc)_2(20)/L_1(20)$	110	43
19	DMF	KOAc(2)	$Pd(OAc)_2(20)/L_1(15)$	110	70
20	DMF	KOAc(2)	$Pd(OAc)_2(20)/L_1(10)$	110	68
21	DMF	KOAc(2)	Pd(OAc) ₂ (20)/L ₁ (20)	90	35
22	DMF	KOAc(2)	Pd(OAc) ₂ (20)/L ₁ (20)	130	54



[a] Reagents and conditions: **2a** (0.16 mmol), base, catalyst, ligand, solvent (4 mL), 40 min. [b] $L_0 = PPh_3$, $L_1 = JohnPhos$, $L_2 = DPPF$, $L_3 = (R)$ -BINAP, $L_4 = TTBP$. [c] Isolated yield. [d] One drop of water was added.

2g, bearing a methoxy group at the 4'-position, underwent coupling in 84% yield (3g) and the yield was better than that of 2f with a 5'-methoxy substituent. Alkyl groups were acceptable as substituents on the A ring or D ring (compounds 3i, 3p, 3r, 3s, 3t) whereas the results showed that the substrate with strong electron-withdrawing groups might give a decreased yield (compounds 3h, 3n). When there was a methoxy substituent at the 7-position, the yield was lower compared with 6-methoxy substituted product (compound 3k vs. 3j). However, the single methoxy-substituted compounds 2m and 2l lead to contradicting results (compound 3m vs. 3l). Compared with compounds 3j and 3s, the product 3q was obtained with a 34% yield when the group on the 6-position was isopropyl. However, the yield was raised to 74 and 84%, respectively, when the substituents were changed as for compounds 3p and 3r in comparison with compound 3q. It is hard to tell how the groups affect the yields according to the results. What is more, the chloro-substituted substrate 20 was also converted into the corresponding product though the yield was only 27%.

Table 2. Synthesis of compounds 3a-3t from compounds 2a-2t.



[a] Optimal conditions: for 2a-2t (0.4 mmol), Pd(OAc)₂ (20 mol-%), JohnPhos (20 mol-%), KOAc (2 equiv.), DMF (4 mL) as the solvent at 110 °C for 40 min.

Conclusions

In summary, we have developed a novel concise method to synthesize the rigid analogues of flavone by an intramolecular Heck reaction. This method offers several advantages, such as concise procedures, easily obtained starting materials and wide scope. The reaction could be a powerful tool to enlarge the chromone ring system and further biological activity studies are ongoing in our lab.

Experimental Section

The Synthesis of Substituted Indeno[1,2-*b*]chromen-10(11*H*)-one (3a–3t): General Procedure: A 25 mL two-necked round-bottomed flask equipped with magnetic stirrer was charged with 3-(2-bromobenzyl)-4*H*-chromen-4-one (0.4 mmol) followed by Pd(OAc)₂ (20 mmol-%), JohnPhos (20 mmol-%) and KOAc (0.8 mmol). The flask was evacuated and back-filled with N₂ (3 times, balloon). Afterwards, anhydrous DMF (5 mL) was added by syringe. After the reaction mixture was stirred at 110 °C for 40 min, it was cooled to room temperature. The reaction mixture was partitioned between EtOAc and brine. The separated organic layer was washed with brine (50 mL × 3), dried with anhydrous Na₂SO₄ and the solvents evaporated to dryness. The crude product was purified by silica gel chromatography eluted with petroleum ether/EtOAc = 5:1 to give the product (80 mg, 85%) as a yellow solid.

Supporting Information (see footnote on the first page of this article): NMR spectra of the obtained compounds.

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