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Ligand-free palladium-catalyzed intramolecular arylation of chromones: an expedient synthesis of 1-benzopyrano[3,2-*c*]quinolines

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ABSTRACT

Synthesis of hitherto unreported 1-benzopyrano[3,2-*c*]quinolin-12-ones has been accomplished by a ligand-free Pd-catalyzed intramolecular C–H arylation protocol at the C-2 position of a chromone moiety in an Ugi product.

Chromones, flavones, isoflavones, and the heterocycles derived from them are widely distributed in nature[1] and possess a broad range of activities of pharmaceutical importance.[2] Arylation of chromone at the C-2 or C-3 position generates flavones or isoflavones, respectively. Arylation at the C-3 position has been accomplished using 3-halochromone and arylboronic acid or triarylbismuth in the presence of a palladium catalyst.[3] Alkenylation or alkynylation has also been accomplished using 3-halochromone.[4] Recently 3-alkynylation has been achieved by C–H activation at the 3-position of the chromone ring.[5] Although C-3 arylation or olefination has been well-studied, direct C-2 arylation on the chromone ring is scarce in the literature.[6] Pd-catalyzed 1,4-addition of arylboronic acid has been achieved using $Fe(OTf)_3$ as Lewis acid. The addition product on subsequent oxidation by DDQ and KNO_2 led to the formation of 2-arylchromone.[7]

1-Benzopyranoquinolines possess versatile biological activities depending on the nature of fusion between the chromone and quinoline rings. 1-Benzopyrano[4,3-*b*]quinolines are antispasmodic and antihistaminic,[8] whereas 1-benzopyrano[3,4-*f*]quinoline acts as a nonsteriodal human progesterone receptor (HPR) agonist.[9] Recently, a naphthopyrano[4,3-*b*]quinoline-based fluorescent off–on probe has been established for bioimaging.[10] Earlier we have reported the synthesis of 1-benzopyrano[4,3-*b*]quinolines[11] and 1-benzopyrano[2,3-*b*]quinolines[12] and herein we report a ligand-free Pd-catalyzed intramolecular C–H arylation at the C-2 position of the chromone moiety for the synthesis of hitherto unreported 1-benzopyrano[3,2-*c*]quinolines of biological interest.

The Ugi product (**5**)[13] derived from a 3-formylchromone (**1**), a 2-haloaniline (**2**), an isocyanide (**3**), and a carboxylic acid (**4**) provides a privileged structure for the synthesis of polycyclic heterocycles (Scheme 1). A close look at the α-arylaminoamides (**5**) bearing a chromone and α-halophenyl moiety reveals that there are two possible modes for Pd-catalyzed cyclization: (i) C–N coupling between the *o*-halophenyl and the amide NH group[14] to form the ketopiperazine **7** or (ii) C–C coupling between the C-2 or C-3 position of the chromone ring and the *o*-halophenyl group. Considering all these possibilities a mixture of **5b** (0.2 mmol), $Pd(OAc)_2$ (10 mol %), K_2CO_3 (0.4 mmol), and Ph_3P (20 mol %) was heated in DMF (10 mL) at 100–110 °C under argon atmosphere for 2 h (Scheme 1). After the usual work-up the reaction mixture produced **6b** in 24% yield (Scheme 1) (Table 1, entry 1).

Enlightened by this selective cyclization, attempts were made to improve the yield of **6**. The intramolecular Heck reaction was standardized using **5b** as the substrate and varying the source of palladium, base, and solvent. The effect of the ligand was also tested (Table 1). $PdCl_2$ was found to be a more effective catalyst

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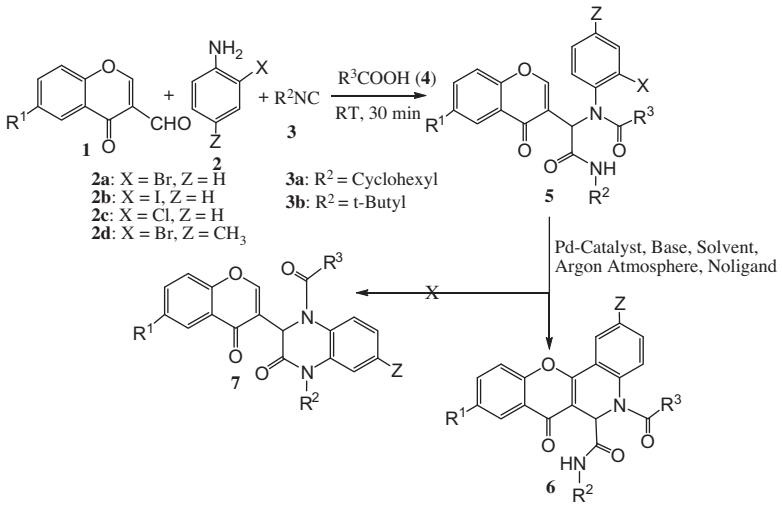
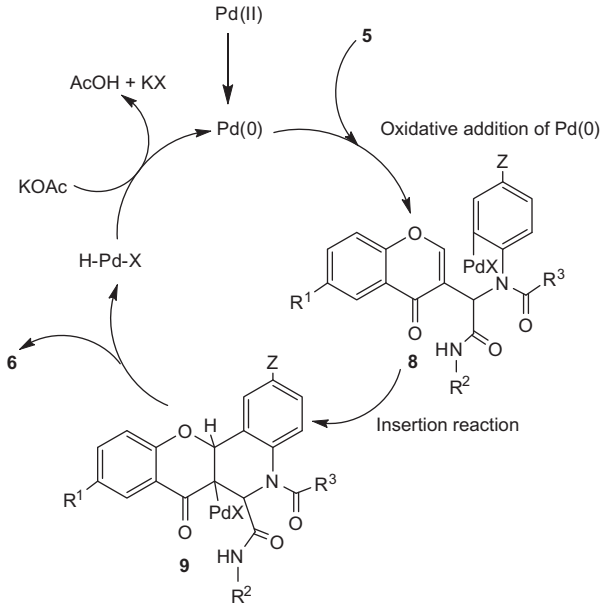


Scheme 1. Synthesis of **6**.

Table 1
Optimization of reaction conditions for the synthesis of **6b** from **5b**

Entry	Catalyst	Base	Solvent	Ligand	Additives	**6b** (%)
1	10% $Pd(OAc)_2$	K_2CO_3	DMF	Ph_3P	—	24
2	10% $PdCl_2$	K_2CO_3	DMF	Ph_3P	—	30
3	10% $Pd(OAc)_2$	Cs_2CO_3	DMF	Ph_3P	—	10
4	10% $PdCl_2$	Cs_2CO_3	DMF	Ph_3P	—	15
5	10% $PdCl_2$	Et_3N	DMF	Ph_3P	—	5
6	10% $PdCl_2$	NaOAc	DMF	Ph_3P	—	14
7	10% $PdCl_2$	KOAc	DMF	Ph_3P	—	40
8	10% $PdCl_2$	KOAc	CH_3CN	Ph_3P	—	20
9	10% $PdCl_2$	KOAc	Dioxan	Ph_3P	—	15
10	10% $PdCl_2$	KOAc	$PhCH_3$	Ph_3P	—	15
11	10% $PdCl_2$	KOAc	DMF	dba	—	—
12	10% $PdCl_2$	KOAc	DMF	Phen	—	7
13	10% $PdCl_2$	KOAc	DMF		—	54
14	15% $PdCl_2$	KOAc	DMF		—	52
15	5% $PdCl_2$	KOAc	DMF		—	25
16	10% $PdCl_2$	KOAc	DMF		TBAB	35
17	10% $PdCl_2$	KOAc	DMF		PA	30
18	10% $Pd(OAc)_2$	KOAc	DMF		—	26

'Phen' stands for 9,10-phenanthroline; 'dba' for dibenzylideneacetone; 'TBAB' for $(^nBu_4N)Br$; 'PA' for Pivalic acid.



Scheme 2. Mechanism for the formation of **6** from **5**.

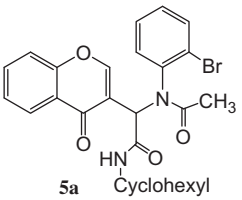
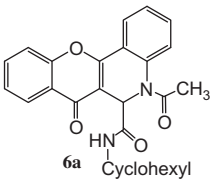
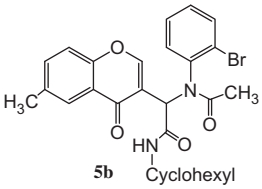
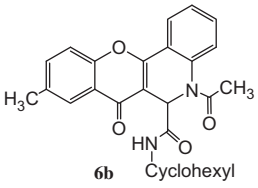
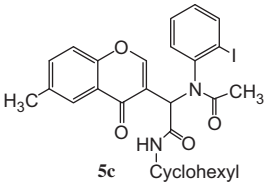
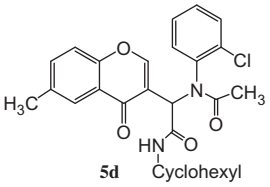
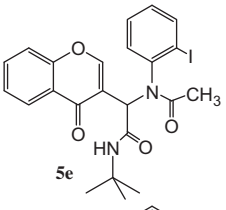
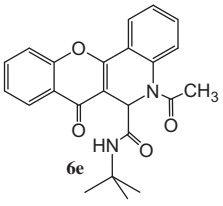
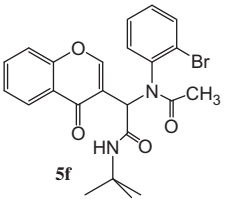
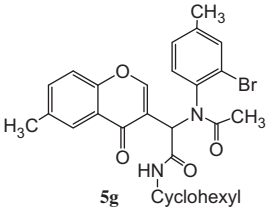
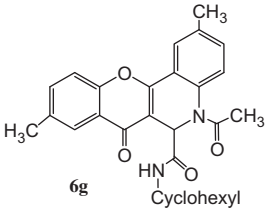
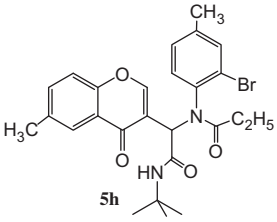
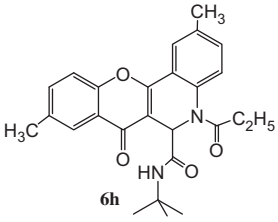
than $Pd(OAc)_2$ (entries 1–4). Different bases such as K_2CO_3, Cs_2CO_3, Et_3N, NaOAc, and KOAc were tested and KOAc was found to be the base of choice (entries 1–7). Among the solvents DMF, CH_3CN, dioxane, and toluene, DMF was the best solvent (entries 7–10). Use of ligands showed a detrimental effect. A much better yield was obtained without adding any ligand (entries 7 and 11–13). Regarding catalyst loading, 10% $PdCl_2$ was found to be the optimal (entries 13–15). Additives like TBAB or pivalic acid lowered the yield (entries 16 and 17). Use of $Pd(OAc)_2$ in place of $PdCl_2$ in the absence of ligand lowered the yield of **6** markedly (entries 13 and 18). The detrimental effects of ligands, additive (pivalic acid), or of using $Pd(OAc)_2$ instead of $PdCl_2$ may be due to steric crowding across the palladium center in the intermediate **8** (Scheme 2). Bulky groups attached to palladium hinder the achievement of the required conformation for cyclization as shown in **8**.

After finding the optimized reaction conditions[15] (entry 13), the scope of the reaction was explored using various substrates. The versatility of substrate **5** arises from the four components utilized in the Ugi reaction. Different *o*-haloanilines (**2**, Z = H, X = Cl, Br and I) were used for the formation of **5**, which was then employed for the synthesis of **6**. During the synthesis of **5a**–**j** (Table 2), it was observed that the yield of **5** was much better (94–99%) (entries 1, 2, 6, and 9) using **2a** as the amine component compared to that when **2b** or **2c** was used (entries 3–5), whereas changing the acid component from acetic acid to propanoic acid, was found to decrease the

Table 2
Synthesis of Ugi product **5**

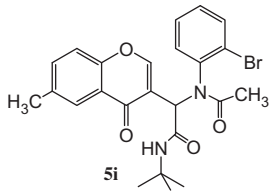
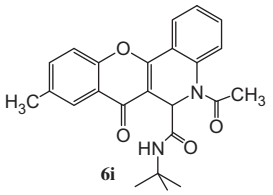
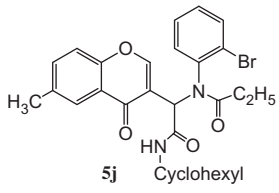
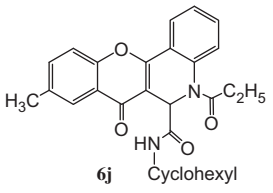
Entry	R^1 in **1**	**2**	**3**	R^3 in **4**	Product	mp (°C)	Yield (%)
1	H	**2a**	**3a**	CH_3	**5a**	188–190	98
2	CH_3	**2a**	**3a**	CH_3	**5b**	232–234	94
3	CH_3	**2b**	**3a**	CH_3	**5c**	212–214	80
4	CH_3	**2c**	**3a**	CH_3	**5d**	224–226	79
5	H	**2b**	**3b**	CH_3	**5e**	212–214	75
6	H	**2a**	**3b**	CH_3	**5f**	206–208	94
7	CH_3	**2d**	**3a**	CH_3	**5g**	176–178	90
8	CH_3	**2d**	**3b**	C_2H_5	**5h**	218–220	82
9	CH_3	**2a**	**3b**	CH_3	**5i**	162–164	99
10	CH_3	**2a**	**3a**	C_2H_5	**5j**	224–226	71

Table 3
Synthesis of 1-benzopyrano[3,2-*c*]quinolines **6** from **5**

Entry	Substrate	Product	mp (°C)	Yield (%)
1	 **5a**	 **6a**	242–243	50
2	 **5b**	 **6b**	182–184	54
3	 **5c**	**6b**	182–184	59
4	 **5d**	**6b**	182–184	25
5	 **5e**	 **6e**	248–250	70
6	 **5f**	**6e**	248–250	58
7	 **5g**	 **6g**	216–218	59
8	 **5h**	 **6h**	220–222	66

(*continued on next page*)

Table 3 (*continued*)

Entry	Substrate	Product	mp (°C)	Yield (%)
9	 **5i**	 **6i**	246–248	56
10	 **5j** Cyclohexyl	 **6j** Cyclohexyl	168–170	48

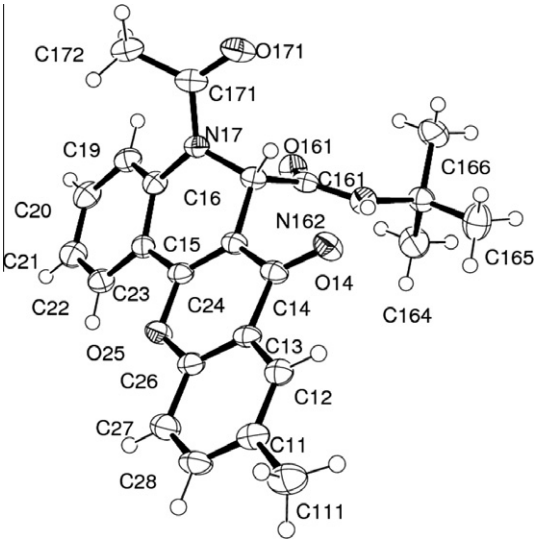


Figure 1. ORTEP diagram of **6i**.

yield of **5** (entries 7–10) and when pivalic acid (**4**, $R^3 = CMe_3$) was used as the acid component, **5** ($R^3 = CMe_3$) could not be isolated.

Transformation of **5a–j** to the corresponding compounds **6a–j** was successfully accomplished. It was observed that the arylation reactions using iodo-compounds gave better yields than those using the corresponding bromo or chloro compounds (Table 3, entries 2–4). Ugi products (**5**) having the *N*-*tert*-butylamide group produced **6** in slightly better yields than those with the *N*-cyclohexylamide group (entries 1, 6, 2, and 9). It has been reported earlier that in a Pd-catalyzed isocyanide-insertion reaction *tert*-butyl isocyanide acted more efficiently than cyclohexyl isocyanide.[16] Use of **5e** having both *N*-*tert*-butylamide and iodoaryl moieties yielded **6e** in 70% yield (entry 5). The small effect of an extra methyl group was reflected in the yields of **6g** (entries 2 and 7) and **6j** (entries 2 and 10).

The structure of **6** was determined on the basis of ^1H, ^{13}C NMR, IR, and mass spectral analyses.[17] In the ^1H NMR spectrum of **6**, the disappearance of the singlet peak for H-2 of the chromone moiety in **5** and the presence of a broad doublet signal for the cyclohexyl NH or the broad singlet of the ^{t}butyl NH rule out the possibility of the formation of **7**. One observation in support of structure **6** ($R^3 = CH_3$) is that after cyclization the CH_3 protons of the $NCOCH_3$ group are highly deshielded [$\sim\delta$ 1.86 in **5** ($R^3 = CH_3$) to $\sim\delta$ 2.36 in **6**]. This may be explained by considering the extended conjugation of the ring nitrogen with the carbonyl functionality of the chromone ring in **6**. Finally the structure of **6i** was confirmed by single crystal X-ray diffraction analysis (Fig 1).[18]

Formation of **6** from **5** may be rationalized by considering the oxidative addition of Pd(0) to the aryl halide moiety of **5** to form **8**, which undergoes intramolecular palladation at the C2–C3 double bond of the chromone moiety (→**9**). Compound **6** is produced from **9** by the elimination of HPdX, which regenerates Pd(0) by the action of base (Scheme 2).

In conclusion, we have achieved the synthesis of hitherto unreported 1-benzopyrano[3,2-*c*]quinolin-12-ones by an intramolecular C–H arylation at the C-2 position of the chromone moiety in the Ugi product derived from 3-formylchromone (**1**), *o*-haloanilines (**2**), isocyanides (**3**), and carboxylic acids (**4**).

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13. *General synthesis of **5**:* A mixture of chromone-3-carboxaldehyde (**1**, 0.5 mmol), *o*-haloaniline (**2**, 0.5 mmol) and isocyanide (**3**, 0.6 mmol) in acetic acid (5 mL) was stirred at room temperature for 30 min. The reaction mixture was poured into ice-water (50 g) to get a faint yellow solid, which was filtered, washed with water, dried in air and crystallized from toluene–light petroleum to produce a white crystalline solid **5**. Although compound **5** developed a single spot in TLC, its NMR spectrum showed a mixture of diastereomers. Earlier reports[19] also mentioned the presence of a mixture of diastereomers in the Ugi product when *o*-substituted anilines were used as the amine component.
*Characterisation data of **5i** (mixture of diastereomers D_1:D_2::4:1).* White crystalline compound, mp 162–164 °C; yield 99%; IR (KBr): 3310, 2932, 2852, 1655, 1642, 1542 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.53 (1H, s, H-2, D_2), 7.98 (1H, br s, H-5, D_1+D_2), 7.66 (1H, br d, J = 7.8 Hz, ArH, D_1+D_2), 7.62 (1H, s, H-2, D_1), 7.51 (1H, br d, J = 7.8 Hz, ArH, D_1+D_2), 7.45–7.40 (2H, m, ArH, D_1+D_2), 7.29–7.17 (2H, m, ArH, D_1+D_2), 6.66 (1H, br s, exchangeable, NH, D_1), 6.64 (1 H, s, methine H, D_1), 6.36 (1H, br s, exchangeable, NH, D_2), 5.93 (1H, s, methine H, D_2), 2.45 (3H, s, $ArCH_3$, D_2), 2.44 (3H, s, $ArCH_3$, D_1), 1.88 (3H, s, $COCH_3$, D_2), 1.86 (3H, s, $COCH_3$, D_1), 1.34 (9H, s, CMe_3, D_1), 1.27 (9H, s, CMe_3, D_2); ^{13}C NMR ($CDCl_3$). δ 176.4 (D_2), 176.0 (D_1), 171.6 (D_2), 171.3 (D_1), 168.7 (D_1), 165.8 (D_2), 158.5 (D_2), 157.9 (D_1), 154.0 (D_2), 153.8 (D_1), 141.3 (D_2), 138.7 (D_2), 135.5 (D_2), 135.3 (D_1), 135.2 (D_2), 134.9 (D_1), 133.5 (D_2), 133.4 (D_1), 132.2 (D_1), 131.5 (D_2), 130.4 (D_1), 129.9 (D_2), 128.8 (D_1), 128.7 (D_2), 128.3 (D_1), 126.7 (D_1), 125.5 (D_1), 125.3 (D_2), 123.2 (D_1), 119.2 (D_2), 117.9 (D_2), 117.7 (D_1), 116.5 (D_1), 57.9 (D_2), 53.1 (D_1), 51.4 (D_1), 31.6 (D_2), 28.6 (3C, D_1+D_2), 23.2 (D_1), 23.1 (D_2), 22.6 (D_2), 20.9 (D_1), 14.1 (D_2); MS: *m*/*z* 509 ($M+2+Na^+$), 507 ($M+Na^+$), 487 ($M+2+H^+$), 485 ($M+H^+$); Anal. Calcd for $C_{24}H_{25}BrN_2O_4$: C, 59.39; H, 5.19; N, 5.77. Found: C, 59.48; H, 5.09; N, 5.66.
14. Kalinski, C.; Umkehrer, M.; Ross, G.; Kolb, J.; Burdack, C.; Hiller, W. *Tetrahedron Lett.* **2006**, *47*, 3423–3426.
15. *General Procedure for the synthesis of 2-acyl-1-N-substitutedcarbamoyl-1,2-dihydro-12H-1-benzopyrano[3,2-c]quinolin-12-one (**6**):* A mixture of **5** (0.2 mmol), $PdCl_2$ (10 mol %) and KOAc (0.4 mmol) was heated in DMF (10 mL) at 100–110 °C for 2 h. The resultant reaction mixture was cooled and poured into ice-water (300 g) with stirring. Saturated brine solution (20 mL) was added and stirred vigourously for 1 h when a grey solid separated out. The separated solid was filtered and dissolved in $CHCl_3$. The $CHCl_3$ solution was washed with water, dried over Na_2SO_4 and chromatographed over silica gel to yield **6** when eluted with 40% ethyl acetate in light petroleum.
16. Wang, Y.; Wang, H.; Peng, J.; Zhu, Q. *Org. Lett.* **2011**, *13*, 4604–4607.
17. *Characterisation data of **6i**.* White crystalline compound, mp 246–248 °C; yield 56%; IR (KBr): 3305, 2914, 1687, 1673, 1635, 1603 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.07 (1H, br s, H-11), 7.95 (1H, br d, J = 7.8 Hz, ArH), 7.58–7.49 (4H, m, ArH), 7.33–7.28 (1H, m, ArH), 7.03 (1H, br s, NH), 6.59 (1H, br s, H-1), 2.50 (3H, s, $ArCH_3$), 2.36 (3H, s, $COCH_3$), 1.24 (9H, s, CMe_3); ^{13}C NMR ($CDCl_3$) δ 175.9, 169.8, 167.3, 153.8, 139.6, 135.7(2C), 135.4 (2C), 132.2, 125.2 (2C), 125.1, 124.5, 124.3, 122.9, 117.8, 77.2, 51.2, 28.7 (3C), 22.8, 20.9; MS: *m*/*z* 427 ($M+Na^+$), 405 ($M+H^+$); Anal. Calcd for $C_{24}H_{24}N_2O_4$: C, 71.27; H, 5.98; N, 6.93. Found: C, 71.15; H, 6.04; N, 6.87.
18. CCDC 917221 contains the supplementary crystallographic data for this Letter. This data can be obtained free of charge via http://www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk).
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