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A convenient and expeditious synthesis of 3-(N-substituted) aminocoumarins via palladium-catalyzed Buchwald–Hartwig coupling reaction

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Abstract—A convenient protocol for the rapid and efficient synthesis of 3-(N-substituted) aminocoumarins is described. The synthetic route developed involves the Pd-catalyzed C–N coupling reaction from readily available 3-bromocoumarin derivatives in the presence of the catalytic system $Pd(OAc)_2$/Xantphos. Under these conditions, a series of nucleophiles including amides, sulfonamides, carbamates and functionalized amines, have been successfully reacted to afford the coupling products in fair to good yields.

The diverse biological activities of natural and synthetic coumarins as anticoagulants and antithrombotics are well known.[1] Some of the coumarin derivatives are reported as anti-HIV agents[2] and antioxidants.[3] They have also been found to possess vasorelaxant,[4] anti-inflammatory[5] antitumoral activity[6] and many coumarin derivatives are known as free radical scavengers.[7] Recent works demonstrated that novobiocin, a 3-amidocoumarin-containing DNA gyrase inhibitor, binds to the C-terminal nucleotide-binding region[8] of heat shock protein 90, an exciting new target in cancer drug discovery,[9] leading to decrease in hsp90 client proteins in various cancer cell lines.[10]

Unfortunately, the ability of novobiocin to induce degradation of hsp90 client proteins (e.g., ErbB2 in SkBr3 breast cancer cells)[6] is relatively weak (~700 μM) and requires further investigation. In an effort to identify more potent inhibitors of hsp90, we became interested in the synthesis of a combinatorial library based on the scaffold of 3-(N-substituted) aminocoumarin of type **A**, which includes two centres for introduction of diversity into coumarin molecule (Scheme 1).

The literature reports a short number of synthetic routes to these compounds and the most common route is undoubtedly the reduction of 3-nitrocoumarins into 3-aminocoumarins followed by N-functionalization.[11] While this multi-step procedure is a suitable method the variety of substrates, however, is very limited. Therefore, our approach to the synthesis of 3-(*N*-acyl)- or 3-(*N*-sulfonamyl) coumarins and related compounds focused on the well-documented palladium-catalyzed C–N bond coupling reaction starting from 3-halocoumarins. The latter are of particular interest, in that the coupling would offer a convergent and straightforward approach to various 3-(N-substituted) aminocoumarins.

Although, significant advances have occurred in the metal-catalyzed[12] amination or amidation of aryl halides during the last decade, application of this coupling to various heterocyclic structures is still a relatively unexplored process.[13] Very recently, Wu and co-workers[14] reported the synthesis of 3-amino-4-sulfanyl-coumarins starting from 3-bromo-4-sulfanyl-coumarin compounds. In Wu study, the C–N bond coupling reaction was only described with aniline derivatives. These results prompted us to report our general approach to provide a variety of 3-(N-substituted)-coumarins from various low-nitrogen nucleophiles including amides, sulfonamides, carbamates and functionalized alkylamines. We found that the use of $Pd(OAc)_2$/Xantphos couple in

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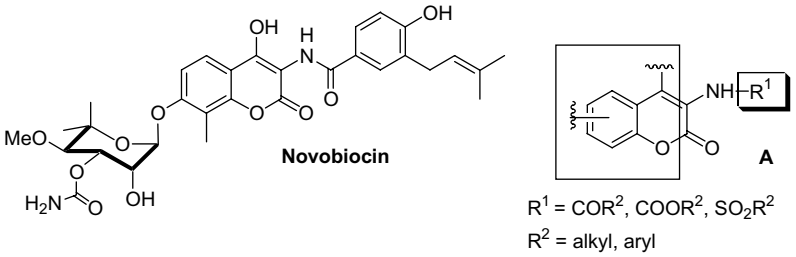


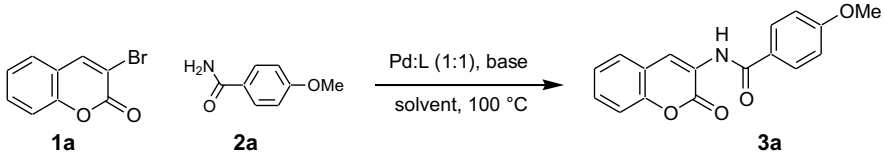
Scheme 1.

the presence of Cs_2CO_3 in dioxane is an efficient catalytic system to provide a general route to a range of unkown 3-(*N*-acyl)-, 3-(*N*-sulfonamyl)-coumarins and related compounds.

In our initial screening experiments, 3-bromocoumarin **1a** and 4-methoxyphenyl-acetamide **2a** were used as the model substrates for investigating the effects of various ligands, palladium sources, solvents and bases. Because coumarins are sensitive substrates in alkaline media and may result in the cleavage of the lactone ring, we carefully examined the alkaline conditions for the coupling of **1a** with **2a**. In fact, 3-bromocoumarin **1a** completely disappeared within a few hours when heated with 4-methoxyphenyl-acetamide **2a** in the presence of NaO*t*Bu or K_2CO_3. In spite of this difficulty, the amidation proceeded reasonably well, as can be seen in Table 1.

To check the validity of the coupling reaction of **1a** with **2a**, we set up a test under the Buchwald conditions[15] for the amidation of aryl halides ($Pd(OAc)_2$, Xantphos,[16] Cs_2CO_3 in 1,4-dioxane at 100°C). We were delighted to observe complete conversion of **1a** after only 30 min using a 1:1 ratio of Pd:L (2 mol %) and the expected coupling product **3a** was formed in 87% yield (Table 1, entry 1). As the ligand nature has been previously shown to affect the C–N bond coupling reactions, we examined the process in the presence others phosphine ligands. As expected, no reaction occurred in the absence of any

Table 1. Coupling reaction of **1a** with amide **2a** under various conditions:[a] synthesis of 3-amidocoumarin **3a**



1a **2a** **3a**

Entry	[Pd]	Ligand	Base	Solvent	Conv[b] (%)	Yield[c] (%)
1	$Pd(OAc)_2$	Xantphos	Cs_2CO_3	Dioxane	100	87[d]
2	$Pd(OAc)_2$	—	Cs_2CO_3	Dioxane	0	0
3	$Pd(OAc)_2$	Xphos	Cs_2CO_3	Dioxane	100	85
4	$Pd(OAc)_2$	DPEphos	Cs_2CO_3	Dioxane	7	nd[f]
5	$Pd(OAc)_2$	BINAP	Cs_2CO_3	Dioxane	<5	nd[f]
6	$Pd(OAc)_2$	dppf[e]	Cs_2CO_3	Dioxane	0	0
7	$Pd(OAc)_2$	dipf[e]	Cs_2CO_3	Dioxane	0	0
8	$Pd_2(dba)_3$[h]	Xantphos	Cs_2CO_3	Dioxane	13	8
9	$Pd(OAc)_2$	Xantphos	K_2CO_3	Dioxane	45	36
10	$Pd(OAc)_2$	Xantphos	NaO*t*Bu	Dioxane	0	0[g]
11	$Pd(OAc)_2$	Xantphos	KO*t*Bu	Dioxane	0	0[g]
12	$Pd(OAc)_2$	Xantphos	Na_2CO_3	Dioxane	0	0
13	$Pd(OAc)_2$	Xantphos	K_3PO_4	Dioxane	0	0
14	$Pd(OAc)_2$	Xantphos	Cs_2CO_3	Toluene	83	65
15	$Pd(OAc)_2$	Xantphos	Cs_2CO_3	THF	100	76
16	$Pd(OAc)_2$	Xantphos	Cs_2CO_3	*t*AmOH	33	nd[f]
17	$Pd(OAc)_2$	Xantphos	Cs_2CO_3	*t*BuOH	30	nd[f]

[a] All reactions of **1a** (1.0 mmol) with **2a** (1.2 mmol) were performed at 100 °C for 30 min in 3 mL of solvent by using a 1:1 ratio of Pd:L (2 mol %), and base (1.5 equiv).

[b] Conversion was determined by ^1H NMR in the crude reaction mixture and is based on remaining **1a**.

[c] Isolated yields.

[d] No reaction occurred at room temperature and only 42% conversion was observed when performing the reaction at 80 °C for 30 min.

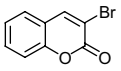
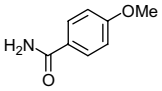
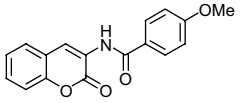
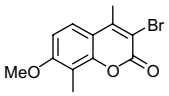
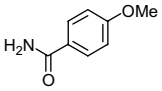
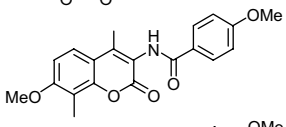
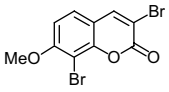
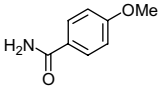
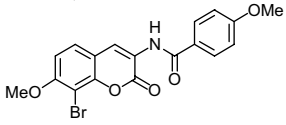
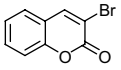
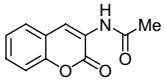
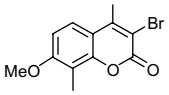
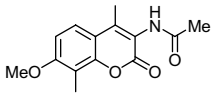
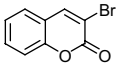
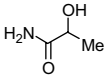
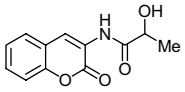
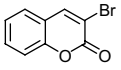
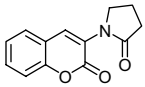
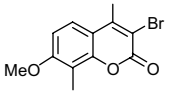
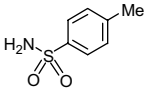
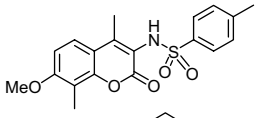
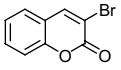
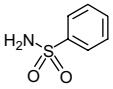
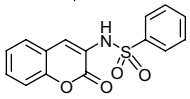
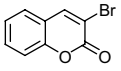
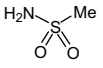
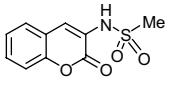
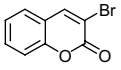
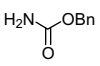
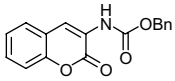
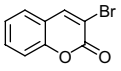
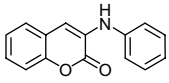
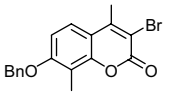
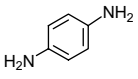
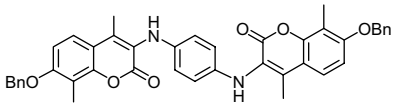
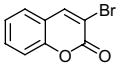
[e] dppf: diphenylphosphinoferrocene. dipf: 1,1-bis(di-*iso*propylphosphino)ferrocene.

[f] Yield not determined.

[g] No starting material was recovered.

[h] Performing the coupling reaction of **1a** with **2a** under Wu conditions[14] (5 mol % $Pd_2(dba)_3$, 10 mol % Xantphos and 2 equiv of K_2CO_3 in toluene at 80 °C for 30 min) resulted in incomplete conversion (<10%) even after extended heating (12 h).

Table 2. Synthesis of functionalized 3-(N-substitued) aminocoumarins **3**[a]

Entry	Bromocoumarin **1**		Nucleophile	Time (h)	Product **3**		Yields[b] (%)
1		**1a**		0.5		**3a**	87
2		**1b**		6		**3b**	76
3		**1c**		0.5		**3c**	51
4		**1a**		4		**3d**	60
5		**1b**		12		**3e**	45
6		**1a**		30		**3f**	60
7		**1a**		12		**3g**	0
8		**1b**		12		**3h**	53
9		**1a**		12		**3i**	42
10		**1a**		12		**3j**	12[c]
11		**1a**		12		**3k**	26[d]
12		**1a**		2		**3l**	78
13		**1d**		2		**3m**	60[e]
14		**1a**		2		**3n**	65
15		**1c**		2		**3o**	59
16		**1d**		12		**3p**	57

[a] Unless otherwise stated, all coupling reactions of **1** (1.0 mmol) with nucleophile (1.2 mmol) were performed at 100 °C for 30 min in 3 mL of 1,4-dioxane by using a 1:1 ratio of Pd:L (2 mol %), and Cs_2CO_3 (1.5 equiv). For a general procedure; see Ref. 18.

[b] Isolated yields.

[c] Starting material was recovered.

[d] 40% of the reduced coumarin was obtained.

[e] 15% of monocoupling product was obtained.

ligands (entry 2). Changing the bidentate ligand phopshine Xantphos to sterically hindered monodentate ligand Xphos also led to total conversion of **1a** after 1 h (entry 3). The use of other bidentate phosphine ligands such as DPEphos, BINAP, dppf or dipf however, did not promote the C–N bond coupling reaction (entries 4–7).

The palladium source was also examined and in the present reaction, in contrast to Wu conditions,[13] the catalytic activity of $Pd(OAc)_2$ proved to be superior to $Pd_2(dba)_3$ as the use of $Pd_2(dba)_3$ in combination with Xantphos ligand induced a lowering of the conversion rate and gave **3a** in only 8% yield (entry 8). The effect of bases and solvents were then explored. Of the bases screened, the highest yield was achieved by using Cs_2CO_3 (entries 1 and 3). In contrast to Wu conditions,[13] replacing Cs_2CO_3 by K_2CO_3 was found less effective and gave much lower yield of **3a** (entry 9). NaO*t*Bu and KO*t*Bu cleaved the lactone ring and were thus ineffective (entries 10 and 11) whereas, the use of other bases including, Na_2CO_3 and K_3PO_4 did not promote any coupling reaction and starting material was recovered unchanged (entries 12 and 13). Finally, in the presence of other solvents such as THF and toluene, two common solvents used for the aryl amination, the C–N bond coupling reaction proved also to be effective providing **3a** but in slightly lower yields (entries 14 and 15). Use of *tert*-butyl or *tert*-amyl alcohol as previously was reported[17] induced a lowering of the conversion rate (entries 16 and 17).

With optimized conditions in hand, we subsequently explored the substrate scope of the reaction with a series of 3-bromocoumarin derivatives and various nucleophiles including amides, sulfonamides as well as functionalized alkylamines. Considering its high activity in all cases, ligand Xantphos was our choice for further experimentation. As summarized in Table 2, various 3-bromocoumarins undergo smoothly the C–N coupling reaction with amides over the catalytic system $Pd(OAc)_2$/Xantphos. The representative examples in Table 2 illustrate the generality of this reaction. As shown, various types of amides underwent coupling reactions efficiently under the optimized conditions. Both primary aromatic and aliphatic amides reacted to provide 3-amidocoumarin derivatives **3a**–**f** in fair to good isolated yields (Table 2, entries 1–6). It is worthy to note that the chemoselectivity of the reaction must be especially underlined as the amidation of substrate **1c** containing two carbon–bromine atoms provide exclusively the coupling product at the more activated C-3 position (entry 3). The reaction was also effective with functionalized primary amides (entry 6) whereas, with cyclic amides, the reaction turned out to be less effective even if other ligands and palladium sources were used (entry 7). Unlike the amidations with primary aromatic amides, however, the catalytic system $Pd(OAc)_2$/xantphos was less effective in the couplings with the less nucleophilic primary arylsulfonamides, providing only a moderate yield of the desired products (entries 8 and 9). Primary aliphatic sulfonamides were more sluggish to react (entry 10), with incomplete conversion even after extended heating or if other ligands and palladium sources were used. In this case, the majority of the mass balance is made up of unreacted starting material. Finally, primary benzyl carbamate, also reacted slowly to give only 26% yield of the desired product **3k** (entry 11) together with a notable amount (40%) of a side coumarin compound formed from a carbon–bromine bond reduction.

Under the optimized conditions, we then explored the coupling of 3-bromocoumarin derivatives with amines as nucleophiles. The results outlined in Table 2 show that the reactions performed with aniline and benzylamine derivatives (entries 12–15) were generally complete within 2 h, with fair to good yields. For substrate **1c** containing two C–Br substituents, the reaction selectivity was examined with *R*(+)-1-(1-naphtyl)ethylamine. A 1:1.2 ratio of **1c**:amine gave selectively the mono-coupling product **3o** in 59% yield (entry 15). Performing the C–N bond forming reactions with *para*-phenylenediamine (ratio **1d**:diamine = 2:1) provides the bis-coupling compound **3m** in 60% yield together with a small amount (15%) of mono-coupling product (entry 13). Amination of 3-bromocoumarins using chlorohydrate of ethyl ester glycine expectedly turned out to be a slow reaction (12 h); giving **3p** in 57% yield (entry 16). Under these conditions, we were pleased to observe that the ethoxycarbonyl group was tolerated in the presence of our catalytic system.

In conclusion, we have succeeded in developing an efficient and selective Pd-mediated C–N coupling reactions of 3-bromocoumarins with various nucleophiles including amides, sulfonamides and amines using palladium acetate as a catalyst, Xantphos as a ligand and Cs_2CO_3 as a base. Under this synthetic way, a series of 3-(N-substituted) aminocoumarin derivatives was obtained in sufficiently good yields and isolation of the products is easily achieved by column chromatography. The application of this C–N coupling methodology to synthesize a small 3-aminocoumarin library related to novobiocin is currently under investigation in our laboratory.

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18. *General procedure for Pd-catalyzed couplings of 3-bromocoumarins with various nucleophiles (amines, amides, sulfonamides and carbamates)*: A flame-dried resealable Schlenk tube was charged with $Pd(OAc)_2$ (0.025 mmol, 2.0 mol %), Xantphos (0.025 mmol, 2.0 mol %), the solid reactant(s) (1.0 mmol of the bromocoumarin, 1.2 mmol of the amide/amine/carbamate/sulfonamide) and Cs_2CO_3 (1.5 mmol). The Schlenk tube was capped with a rubber septum, evacuated and backfilled with argon; this evacuation/backfill sequence was repeated one additional time. The liquid reactant(s) and 1,4-dioxane (2 mL per mmol) were added through the septum. The septum was replaced with a teflon screwcap. The Schlenk tube was sealed, and the mixture was stirred at 100 °C (reaction time, see Table 2). The resulting suspension was cooled to room temperature and filtered through a pad of Celite eluting with ethyl acetate, and the inorganic salts were removed. The filtrate was concentrated and purification of the residue by silica gel column chromatography gave the desired product. Compound **3a**: Yield: 87%; TLC: R_f 0.48 (CH_2Cl_2). mp = 177–179 °C; IR (neat): 3401, 1712, 1667, 1604, 1578, 1507, 1446, 1359, 1296, 1246, 1190, 1112, 1063, 925, 910, 859, 842, 754, 691, 643, 606, 568 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 8.77 (s, 1H), 8.69 (br s, 1H), 7.82 (d, 2H, $J = 8.8$ Hz), 7.47 (dd, 1H, $J = 7.7$ Hz, $J = 1.3$ Hz), 7.38 (td, 1H, $J = 8.4$ Hz, $J = 1.5$ Hz), 7.30–7.18 (m, 2H), 6.92 (d, 2H, $J = 8.8$ Hz), 3.81 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 165.6, 163.1, 159.1, 149.8, 129.6, 129.2(2C), 127.9, 125.7, 125.2, 124.3, 123.0, 120.0, 116.4, 114.2 (2C), 55.5. *m/z* MS (ES+) 318.0 ($M+Na^+$). Compound **3e**: Yield: 45%; TLC: R_f 0.16 (Cyclo/AcOEt 4:6); mp = 220–222 °C; IR (neat): 3255, 1706, 1655, 1605, 1519, 1439, 1401, 1367, 1351, 1285, 1260, 1201, 1119, 1039, 988, 944, 814, 779, 766, 705, 601, 581, 561 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz): δ 9.45 (br s, 1H), 7.65 (d, 1H, $J = 8.9$), 7.10 (d, 1H, $J = 8.9$), 3.93 (s, 3H), 2.26 (s, 3H), 2.21 (s, 3H), 2.06 (s, 3H); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 168.7, 159.4, 158.5, 150.0, 146.4, 123.9, 118.2, 113.2, 112.1, 107.7, 56.1, 22.6, 14.4, 7.9; *m/z* MS (ES+) 284.0 ($M+Na^+$). Compound **3i**: Yield: 42%; TLC: R_f 0.50 (CH_2Cl_2); mp = 141–143 °C; IR (neat): 3328, 3056, 1703, 1627, 1589, 1531, 1493, 1444, 1362, 1321, 1280, 1243, 1189, 1139, 1109, 1027, 925, 872, 751, 707, 687, 635, 590,573 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.85–7.81 (m, 2H), 7.72 (s, 1H), 7.54 (m, 1H), 7.46–7.30 (m, 5H), 7.26–7.18 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 158.3, 150.3, 138.7, 133.8, 130.2, 129.4 (2C), 127.6, 127.2 (2C), 125.3, 123.2, 123.0, 119.0, 116.5; *m/z* MS (ES+) 324.0 ($M+Na^+$). Compound **3l**: Yield: 78%; TLC: R_f 0.76 (CH_2Cl_2); mp = 108–110 °C; IR (neat): 3328, 3054, 1702, 1626, 1589, 1572, 1531, 1494, 1456, 1444, 1362, 1322, 1281, 1243, 1215, 1139, 1114, 1027, 926, 867, 837, 750, 740, 705, 656, 639, 592 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.22 (d, 1H, $J = 7.5$ Hz), 7.19 (d, 1H, $J = 7.5$), 7.14–7.00 (m, 8H), 6.95 (s, 1H), 6.89 (t, 1H, $J = 7.4$), 6.63 (br s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 159.8, 148.5, 139.8, 129.6 (2C), 129.3, 126.8, 125.6, 124.8, 123.5, 121.0, 120.6 (2C), 116.1, 108.5; *m/z* MS (ES+) 260.0 ($M+Na^+$). Compound **3p**: Yield: 57%; TLC: R_f 0.44 (CH_2Cl_2); mp = 105–107 °C; IR (neat): 3402, 2923, 1730, 1698, 1610, 1500, 1453, 1372, 1334, 1275, 1209, 1167, 1122, 1018, 860, 801, 767, 732, 696, 591 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.38–7.26 (m, 5H), 6.79 (d, 1H, $J = 9.0$ Hz), 5.06 (s, 2H), 4.10 (q, 2H, $J = 14.3$ Hz), 3.88 (s, 2H), 2.28 (s, 3H), 2.25 (s, 3H), 1.17 (t, 3H, $J = 7.1$ Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 170.4, 159.1, 158.4, 155.9, 150.5, 147.8, 135.5, 128.2, 127.6 (2C), 127.0, 126.0 (2C), 120.0, 113.2, 107.5, 69.5, 60.2, 48.3, 15.3, 12.4, 7.4; *m/z* MS (ES+) 408.0 ($M+Na^+$).