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A general and efficient route to 3-amino-4-sulfanylcoumarins via substitution and palladium-catalyzed amination of 3-bromo-4-tosyloxycoumarins

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Abstract—A highly efficient and practical route to 3-amino-4-sulfanylcoumarins from 3-bromo-4-tosyloxy-coumarins via substitution and palladium catalyzed amination reactions is described.

As a privileged fragment, the 3-aminocoumarin core is a ubiquitous subunit in many natural products with remarkable biological activities. Members of this family have wide applications in medicinal chemistry as antibiotic and antiviral agents.[1,2] For example, Novobiocin is a 3-aminocoumarin-derived antibiotics, an ATP competitive inhibitor of gyrase B subunit, blocking the negative supercoiling of relaxed DNA.[1d,2] Lamellarin is utilized as a selective inhibitor of HIV-1 integrase.[1c] On the other hand, the introduction of sulfur as a heteroatom in many molecules was shown to be an effective method for imparting significant biological activity.[3] For instance, benzo[*b*]thiophenes and 1,2-benzisothiazoles are often structural moieties of potential drug candidates,[4] and a number of sulfur containing deoxyribonucleosides based enzyme inhibitors have been reported to have antibacterial, antineoplastic, and antiviral activities.[5] We also discovered that 4-sulfanylcoumarins showed excellent anti-HCV activity.[6b] In light of our interest in coumarin chemistry,[7] we need an efficient method to generate a 3-amino-4-sulfanylcoumarin based focused library, with a hope to find more potent hits or leads for our particular biological assays.

Recently, we and others have identified 4-tosyloxycoumarin, which derived from 4-hydroxycoumarin, as an ideal electrophile (in terms of its stability, as well as cost and commercial availability of reagents for its synthesis) in palladium-catalyzed cross-coupling reactions to generate 4-substituted coumarins.[7,8] Since the 4-tosyloxy group attached to the electron-withdrawing α,β-unsaturated double bond, we also found that this substrate may be under 1,4-addition, followed by elimination when reacted with nucleophiles.[6a] Moreover, Yang et al.[9] reported Lewis acid $Mg(ClO_4)_2$, combined with NBS, in CH_3CN or EtOAc provided mild and fast bromination of 1,3-dicarbonyl compounds. In particular, this protocol could be applied to the α-monobromination of α-unsubstituted β-keto esters. Prompted by these results, we envisaged that 3-bromo-4-tosyloxy-coumarin **1** could be generated by treating 4-hydroxycoumarin with NBS[9] and *p*-toluenesulfonyl chloride subsequently, which could be then transferred to 3-amino-4-sulfanylcoumarins via substitution and palladium-catalyzed amination reactions.[10] The difficulty and challenge we conceived should be the amination step, since the existed sulfur atom may deactivate the transition metal catalyst. Herein, we would like to report our recent efforts for the synthesis of 3-amino-4-sulfanylcoumarins (Scheme 1).

The starting material 3-bromo-4-tosyloxy-coumarin **1a** was synthesized easily from 4-hydroxycoumarin as mentioned above.[7–9] After reaction with 2-bromobenzenethiol in the presence of triethylamine, 3-bromo-4-phenylsulfanyl-coumarin **2a** was afforded in almost quantitative yield (Scheme 2). We, therefore, started to

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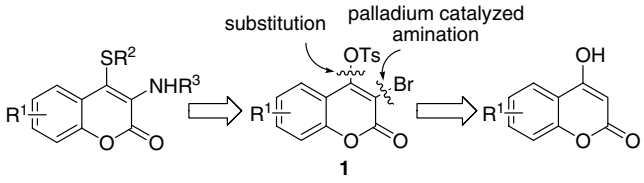
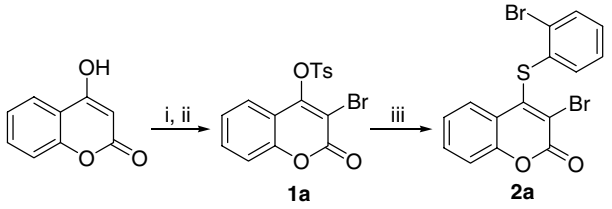


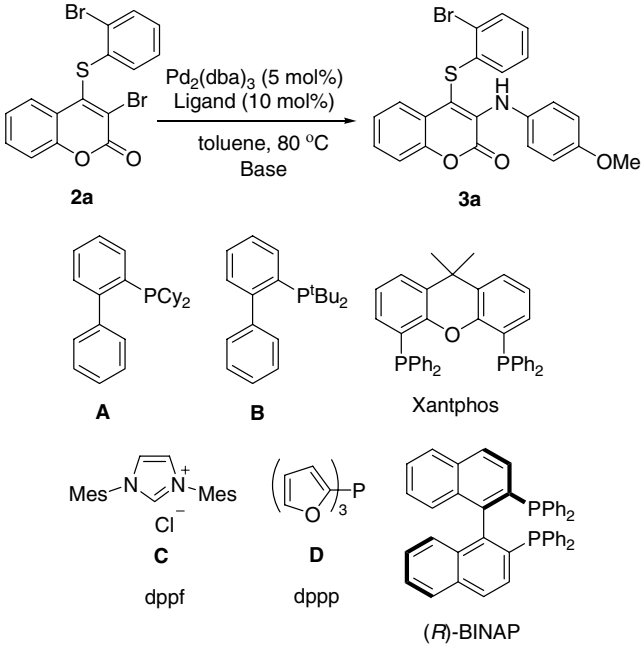
Scheme 1.

explore the possibility of introducing 3-amino group in the coumarin scaffold by using compound **2a** as an electrophile for the palladium-catalyzed amination reaction.[10]

Initial studies were aimed at finding the optimal reaction conditions for this amination reaction. Our investigation began with the reactions of 3-bromo-4-(2-bromophenyl)-sulfanylcoumarin **2a** with *p*-anisidine in toluene catalyzed by $Pd_2(dba)_3$ (5 mol %) in the presence of various ligands (such as phosphines, diphosphines, and *N*-heterocyclic carbene) and base (K_2CO_3, K_3PO_4, Cs_2CO_3, ^{t}BuOK, DIPEA, Et_3N) (Scheme 3). To our delight, expected product **3a** was generated in 55% yield when the reaction was performed in the presence of



Scheme 2. Reagents and conditions: (i) $Mg(ClO_4)_2$, NBS, Ref. 9, 85% yield, (ii) TsCl, Et_3N, 90% yield, (iii) 2-bromobenzenethiol, Et_3N, 99% yield.

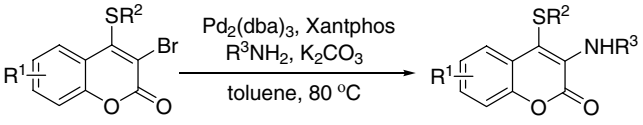


Scheme 3.

Xantphos and K_3PO_4 in toluene at 80 °C. Changing the base to K_2CO_3 improved the result (74% yield). This reaction went to completion within 24 h. The reaction of **2a** with *p*-anisidine furnished the desired product **3a** in 73% yield when (*R*)-BINAP was employed as the ligand, although prolonged reaction time (4 days) was necessary in order to obtain the respectable yield. No reaction occurred in the absence of any ligands. However, reduced reactivity and inferior results were displayed when NHC **C**, phosphine **D**, dppf and dppp were used in the reaction. No reaction occurred when ligand **A** and **B** were utilized. Potassium carbonate was the best choice of the base among all that tested. Only trace amount of product was detected when the reaction was carried out in the presence of organic base, such as DIPEA or Et_3N. Decreasing temperature or amount of catalyst retarded the reaction. For instance, prolonged reaction time (96 h) was needed when the reaction was carried out at room temperature. We also screened other solvents, such as DMF, DMSO, dioxane, and THF. Only dioxane was effective and gave similar result (70% yield).

With this promising result in hand, we investigated the cross-coupling reactions between 3-bromo-4-sulfanylcoumarin **2** and various amines under optimized reaction conditions [$Pd_2(dba)_3$ (5 mol %), Xantphos (10 mol %), K_2CO_3 (2.0 equiv), toluene, 80 °C] and the results are shown in Table 1. The substrate **2** was synthesized simply from 3-bromo-4-tosyloxycoumarin **1** with thiols in CH_2Cl_2 at room temperature in the presence of triethylamine.[11] As shown in Table 1, we found that the optimized conditions allowed us to perform a broad range of amination reactions of 3-bromo-4-sulfanylcoumarin **2** with amines. The reaction was found to be well-tolerated to a range of different groups with differ-

Table 1. Synthesis of 3-amino-4-sulfanylcoumarins via substitution and palladium-catalyzed amination reaction[11]



Entry	R^1	R^2	R^3	Product	Yield[a] (%)
1	H	2-BrC_6H_4 (**2a**)	4-$MeOC_6H_4$	**3a**	74
2	H	2-BrC_6H_4 (**2a**)	4-FC_6H_4	**3b**	65
3	H	2-BrC_6H_4 (**2a**)	C_6H_5	**3c**	66
4	H	C_6H_5 (**2b**)	4-$MeOC_6H_4$	**3d**	96
5	H	C_6H_5 (**2b**)	C_6H_5	**3e**	80
6	H	C_6H_5 (**2b**)	4-FC_6H_4	**3f**	77
7	H	4-ClC_6H_4 (**2c**)	4-$MeOC_6H_4$	**3g**	80
8	H	4-ClC_6H_4 (**2c**)	C_6H_5	**3h**	85
9	H	4-ClC_6H_4 (**2c**)	4-FC_6H_4	**3i**	83
10	H	4-ClC_6H_4 (**2c**)	$C_6H_5CH_2$	**3j**	62
11	6-F	4-ClC_6H_4 (**2d**)	4-$MeOC_6H_4$	**3k**	90
12	6-F	4-ClC_6H_4 (**2d**)	C_6H_5	**3l**	70
13	6-F	4-ClC_6H_4 (**2d**)	4-FC_6H_4	**3m**	67
14	6-F	4-$MeOC_6H_4$ (**2e**)	4-$MeOC_6H_4$	**3n**	94
15	6-F	4-$MeOC_6H_4$ (**2e**)	4-FC_6H_4	**3o**	74

[a] Isolated yield based on 3-bromo-4-sulfanylcoumarin **2**.

ent electronic demands on aromatic rings involving electron-donating and electron-withdrawing groups. Synthetically, all these amination reactions illustrated in Table 1 went to completion at 80 °C within 24 h, and the desired products were afforded in good to excellent yields. Better results were generated when anilines with electron-donating group attached on the aromatic ring were employed as substrates. For example, compound **2b** reacted with *p*-anisidine leading to the corresponding product **3d** in 96% yield, while only 77% yield of product **3f** was obtained when 4-fluoroaniline was utilized in the reaction (Table 1, entries 4 and 6). Benzylamine was also a suitable partner in this transformation. For instance, the reaction of compound **2c** with benzylamine furnished the desired product in 62% yield (entry 10).

In summary, the reaction described here represents a highly efficient and practical route to 3-amino-4-sulfanyl-coumarins. The synthesis of the focused library of this type biological activity screening of these small molecules are under investigation in our laboratory.

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11. General procedure for the synthesis of 3-amino-4-sulfanylcoumarins via substitution and palladium-catalyzed amination reaction. *Reaction of 3-bromo-4-tosyloxy-coumarin* **1** *with thiols*: Triethylamine (1.1 mmol) was added to a solution of 3-bromo-4-tosyloxy-coumarin **1** (1.0 mmol) and thiol (1.0 mmol) in dichloromethane (2.0 mL) at room temperature. After the reaction was complete monitored by TLC, the mixture was directly purified by flash column chromatography on silica gel to afford the desired 3-bromo-4-sulfanylcoumarin **2**. *Palladium-catalyzed reaction of 3-bromo-4-sulfanyl-coumarin* **2** *with amine*: A mixture of 3-bromo-4-sulfanyl-coumarin **2** (0.25 mmol), potassium carbonate (2.0 equiv), $Pd_2(dba)_3$ (5 mol %), and Xantphos (10 mol %) was added into a reaction tube under nitrogen atmosphere. Then toluene (2.0 mL) and amine (1.2 equiv) was added subsequently. The reaction mixture was stirred at 80 °C overnight. Following completion of the reaction as monitored by TLC, the reaction mixture was cooled, diluted with ethyl acetate (10 mL), washed with water (3.0 mL), brine (3.0 mL) and dried over Na_2SO_4. The solvent was removed under vacuum and the residue was purified by flash chromatography to give the corresponding 3-amino-4-sulfanylcoumarin **3**.