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Synthesis of biologically potent new 3-(heteroaryl)aminocoumarin derivatives via Buchwald–Hartwig C–N coupling

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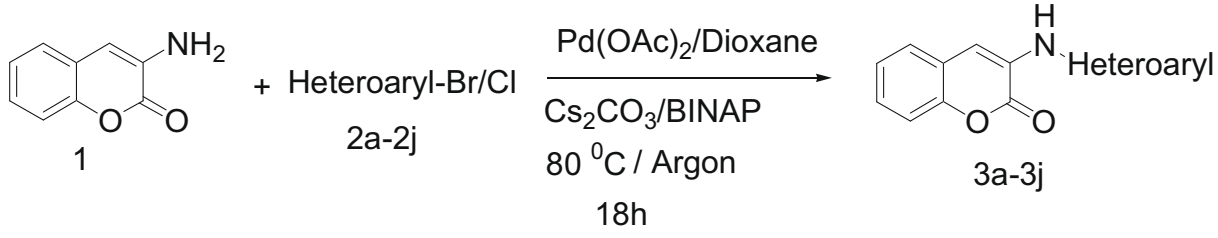
ABSTRACT

New 3-(heteroaryl)aminocoumarin derivatives were synthesized from 3-aminocoumarin, applying optimized Buchwald–Hartwig amination conditions using Palladium acetate, Cesium carbonate, and BINAP in 1,4-dioxane employing elevated temperature conditions and under an argon atmosphere. The target heteroarylaminocoumarin derivatives were obtained in moderate to good yields ranging from 56% to 98%. The procedure described could be widely employed for the preparation of new heterocyclic compounds when one of the core moieties is coumarin and has the potential to be active drug candidates.

Coumarin and its derivatives represent one of the most active classes of compounds possessing a wide spectrum of biological activity.[1] Many of these compounds have proved to be active as antitumor,[2] antibacterial,[3] antifungal,[4] anticoagulant,[5] anti-inflammatory,[6] and antiviral[7] agents. In addition, these compounds are used as additives to food and cosmetics,[8] dispersed fluorescent, and laser.[9] Various analogues of 3-substituted coumarins such as 3-aminocoumarins exhibit antimicrobial activity.[10] Novobiocin is 3-aminocoumarin-derived antibiotics, an ATP competitive inhibitor of gyrase B subunit, blocking the negative super coiling of relaxed DNA.[11] On the other hand, aminopyrimidine, pyridine, and triazine moieties are a common structural subunit in a large number of both natural products and synthetic compounds with important biological activities.[12] These activities include antifungal, pesticidal, and enzyme inhibitory activity against a number of kinases. A representative example of such substituted 2-aminopyrimidines is imatinib, a highly selective B or Abl kinase treatment of chronic myeloid leukemia.[13] There is considerable evidence that coumarins are important lead compounds for the development of antiviral and/or virucidal drugs against HIV.[14] During the last 20 years,[15] the study of the biological activities of coumarin derivatives has been the aim of many researchers. Also, the structure activity relationships of



Scheme 1.

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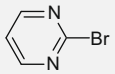
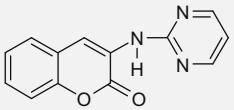
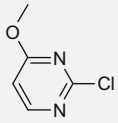
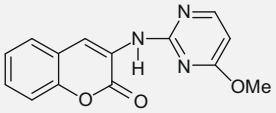
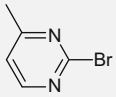
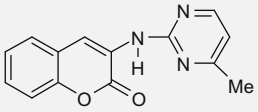
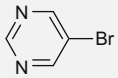
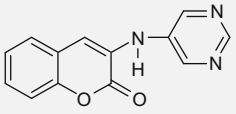
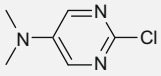
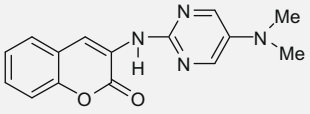
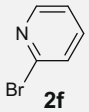
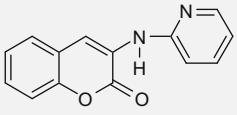
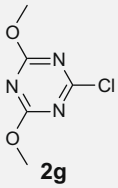
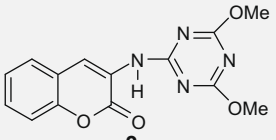
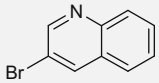
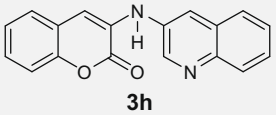
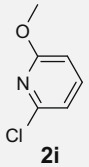
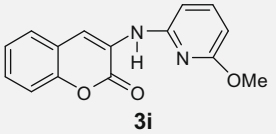
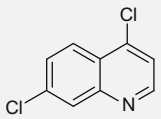
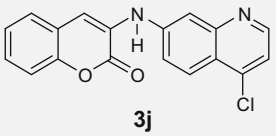
heteroaryl-coumarins have revealed that the presence of substituted heteroaryl derivatives is an essential feature of their pharmacological action. Based on these findings, we herein describe the synthesis of some compounds featuring different heterocyclic rings fused onto the coumarin moiety with the aim of obtaining more potent pharmacologically active compounds.

To the best of our knowledge, hybridized molecules containing coumarin with pyrimidines or pyridines or triazines, or pyrazines

Table 1
Synthesis of functionalized 3-(heteroaryl)aminocoumarins (**3**) from 3-aminocoumarin (**1**)

Entry	Electrophile	Time (h)	Product	Isolated yield[a] (%)
1	 **2a**	18	 **3a**	77
2	 **2b**	18	 **3b**	88
3	 **2c**	18	 **3c**	80
4	 **2d**	18	 **3d**	86
5	 **2e**	18	 **3e**	90
6	 **2f**	18	 **3f**	98
7	 **2g**	18	 **3g**	83
8	 **2h**	18	 **3h**	56
9	 **2i**	18	 **3i**	60
10	 **2j**	18	 **3j**	68

[a] Yield of the purified product.

with an amino linker have never been reported. In light of our interest in coumarin chemistry, we needed an efficient method to generate a 3-(heteroaryl)aminocoumarin-based focused library, with a hope to find more potent hits or leads for our particular biological assays.

Although significant advances[16] have occurred in the metal-catalyzed amination or amidation of aryl halides during the last decade, application of this coupling to various heterocyclic structures is still a relatively unexplored process. Very recently, Wu and coworkers[17] studied the C–N bond coupling reaction with only aniline derivatives. These results prompted us to report our general approach to provide a variety of 3-(heteroaryl)aminocoumarins from various heteroarylhalides and 3-aminocoumarin. We found that the use of $Pd(OAc)_2$/BINAP couple in the presence of Cs_2CO_3 in dioxane is an efficient catalytic system to provide a general route (Scheme 1) to a range of unknown 3-(heteroaryl)aminocoumarins.

The starting material 3-aminocoumarin (**1**) was synthesized easily from salicylaldehyde and *N*-acetylglycine.[18] We therefore started to explore the possibility of introducing heteroaryl moiety in coumarin scaffold by using various heteroarylhalides as electrophile for the palladium-catalyzed amination reaction. We found that the use of $Pd(OAc)_2$/BINAP couple in the presence of Cs_2CO_3 in dioxane is an efficient route to unknown 3-(heteroaryl)aminocoumarins.[19] In our first phase of screening experiment, 2-bromopyrimidine (**2a**) and 3-aminocoumarin (**1**) were used as model substrates for investigating the effects of various solvents, bases, ligands, and palladium sources. Because coumarins are sensitive substrates in basic conditions and may result in the opening of the lactone ring, we carefully examined the basic conditions for the coupling between **1** and **2a**. In fact 3-aminocoumarin (**1**) completely disappeared within a few hours when heated with 2-bromopyrimidine (**2a**) in the presence of NaO^tBu or K_2CO_3 or K_3PO_4, however, no desired product (**3a**) was obtained. In spite of this difficulty, the amination proceeded reasonably well as can be seen in Table 1. To our delight, expected product **3a** was generated in 77% yield when the reaction was performed in the presence of catalyst $Pd(OAc)_2$, ligand BINAP, and the base Cs_2CO_3 in dioxane at 80 °C. The reaction went to completion within 18 h. No amination occurred in the absence of any ligand. The use of Pd/Xanthaphos in lieu of Pd/BINAP, the expected product **3a** was obtained in only 55% yield compared to 77% while using BINAP as a bidentate ligand. The amination remained unsuccessful between **2a** and 3-aminoaoumarin (**1**) in toluene when catalyzed by $Pd_2(dba)_3$. The use of organic bases such as DIPEA or Et_3N also failed to give any desired product. Decreasing the temperature (<80 °C) or amount of catalyst retarded the reaction. We also attempted with other solvents, such as DMF, DMSO, toluene, THF, and EtOAc; only dioxane appeared to be effective and provided a target amine compound with fair to good yield. We also employed the same amination condition in case of 3-iodo-pyridine or 5-iodo-1-methyl-1*H*-imidazole for coupling with 3-aminocoumarin (**1**), but surprisingly no desired aminated product was isolated in either case.

With this promising result in hand, we then investigated the cross-coupling reactions between 3-aminocoumarin (**1**) and various heteroaryl bromides or chlorides (**2**) under optimized reaction conditions. [$Pd(OAc)_2$ (5 mol %), BINAP (7.5 mol %), Cs_2CO_3 (1.5 equiv), dioxane, 80 °C]. The amination was found to be well tolerated to a range of different groups with different electronic demands on heteroaromatic rings involving electron-donating and electron-withdrawing groups. We have successfully prepared (Scheme 1) different substituted 3-(heteroaryl) aminocoumarins **3a–j**. The chemoselective reaction of 4,7-dichloroquinoline (**2j**) with 3-aminocoumarin via optimized Buchwald–Hartwig amination conditions afforded exclusive formation of 3-(4-chloro-quinolin-7-ylamino)coumarin (**3j**). For the structural identification of compounds **3a–j**, our assignment is based on their spectroscopic data (^1H NMR, ^{13}C NMR, and mass spectra). For example, the molecular weight for 3-(pyrimidine-2-ylamino)coumarin (**3a**, $C_{13}H_9N_3O_2$) was determined as 240.1 (M+1) by LC–MS–MS. Its IR spectrum shows an absorption at 1718 cm^{-1}, which came from the lactone and 3387 cm^{-1} for NH group. Its ^1H NMR spectrum exhibited a singlet at δ 8.77 ppm, which is attributed to the C-4 proton of coumarin moiety. A resonance centered around δ 8.54 ppm came from two aromatic protons of pyrimidine moiety of adjacent *N*-atoms and at δ 8.14 ppm as a broad singlet came from NH group. For its ^{13}C NMR spectrum, peaks showed up between 113.81 and 130.83 ppm, which belong to sp^2 carbons in **3a**. The lactone carbon resonated at 159.47 ppm was also detected clearly.

Furthermore, 10 synthesized 3-(heteroaryl)aminocoumarins were assessed to evaluate their bioactivities involving 3D-QSAR techniques. The result showed that compound (**3g**) may prevent cell proliferation by inhibiting transmembrane transduction cell pathways while compound (**3i**) may be a promise against endocrine dependent cancer. In addition compound (**3b**) and (**3c**) have aromatase inhibitory activities and HIV-1 inhibitory activities with high cytotoxicity to MT-2 cell lines.

In conclusion, we have succeeded in developing a Pd-mediated efficient and simple procedure for the aminolysis of heteroarylhalides (**2**) using coumarin as a core moiety which offered significant preparative advantages over the existing methods. Under this pathway, a series of 3-(heteroaryl)aminocoumarin derivatives were obtained in sufficiently good yields and isolation of the products was easily achieved by column chromatography which has sufficient promise as active drug candidates or most likely candidates for further evaluation. This work now opened the door for numerous synthetic applications to diversified coumarins. Efforts toward this goal and screening for biological activity of these small molecules are being undertaken in our laboratory and will be communicated shortly.

Acknowledgements

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.12.089.

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19. General procedure for Pd-catalyzed couplings of 3-aminocoumarin with various electrophiles (heteroarylhalides): An oven dried round-bottomed flask was charged sequentially with 3-aminocoumarin (1 mmol), Cs_2CO_3 (1.5 mmol), BINAP (7.5 mol %), $Pd(OAc)_2$ (5 mol %) and the corresponding solid heteroarylhalides (1 mmol). The reaction flask was capped with rubber septum, evacuated, and backfilled with argon (repeated four times). The heteroarylhalide(s) and 1,4-dioxane (5 mL per mmol) were added through the septum. Finally, the total reaction mixture was evacuated and purged with argon. The reaction mixture was placed in a preheated oil bath (80 °C) and heating was continued with gentle stirring for 18 h. The reaction mixture 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 **3a**–**j**. Yield: 56–98%.