Tetrahedron Letters 51 (2010) 1099–1102

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

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

Asish R. Das *, Arunima Medda, Raghunath Singha

*Department of Chemistry, University of Calcutta, Kolkata 700009, India*

ARTICLE INFO

*Article history:*
Received 5 November 2009
Revised 12 December 2009
Accepted 17 December 2009
Available online 23 December 2009

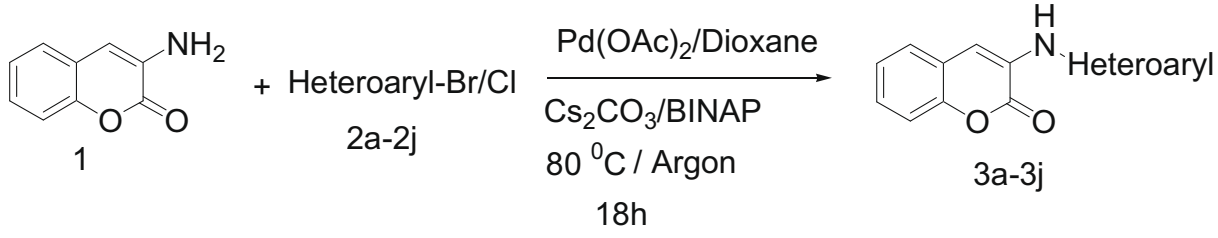
*Keywords:*
3-Aminocoumarin
Heteroarylhalides
Palladium acetate
C–N bond coupling reaction
BINAP
Cesium carbonate

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.**

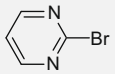
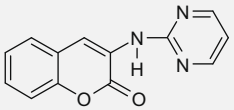
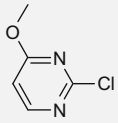
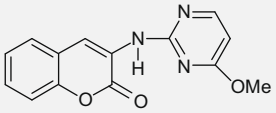
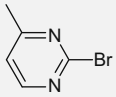
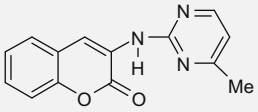
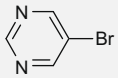
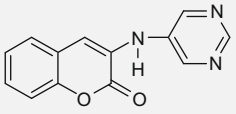
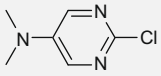
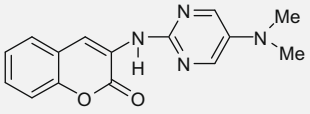
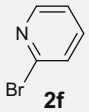
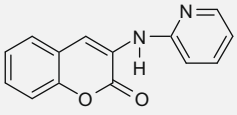
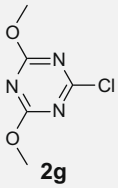
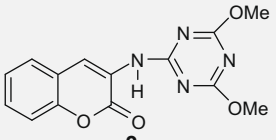
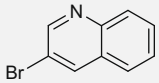
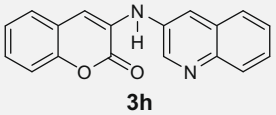
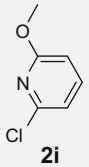
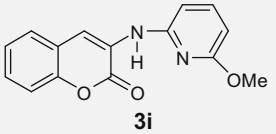
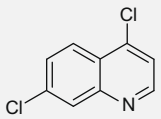
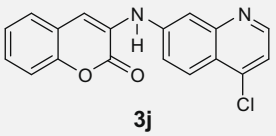
* Corresponding author. Tel.: +91 3323501014/9433120265; fax: +91 33235 19754.
*E-mail address:* ardchem@caluniv.ac.in (A.R. Das).

0040-4039/$ - see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2009.12.089

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.