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Synthesis of N-((cyclohexylcarbamoyl)(aryl)methyl)-N-(4-(4-aminophenyl sulfonyl)phenyl)-2-oxo-2H-chromene-3-carboxamide derivatives via Ugi-four component reaction

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Abstract: A series of novel sulfonated-midated coumarins were synthesized by the Ugi-4CR of benzaldehyde derivatives, 4-(4-aminophenylsulfonyl)benzenamine as diamine, coumarin-3-carboxylic acid and cyclohexyl isocyanide with high yields and high bond-forming efficiency.

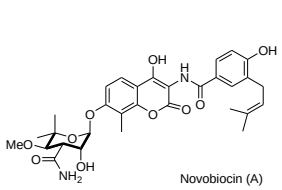
Keywords: Bond-forming efficiency, Isocyanid, Multi component reaction, Sulfonated-coumarincarboxamide, Ugi-4CR.

Introduction

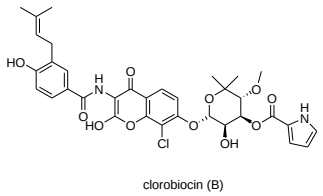
Isocyanide-based multicomponent reactions (IMCRs) which can be simply done by readily accessible starting materials tolerate a variety of functional groups. A wide variety of variations and subsequent transformations make a fairly large number of unique structures available, which would otherwise require lengthy preparations. Over the past two decades, field of IMCR research has had tremendous growth as a result of discovery and development of new variations of classical Passerini and Ugi IMCRs and has obtained significant interest in the scientific community as an efficient, convenient, time-saving and atom-economical approach toward different kinds of drug-like small heterocyclic molecules [1-6].

Coumarin structure and its derivatives which have received great attention in organic and medicinal chemistry [7] have numerous biological activities including antitumor [8], antimicrobial [9], anti-HIV [10] and antiviral ones [11]. Some coumarins demonstrate an inhibitory activity against some serine proteases, virus integrase, lipoxygenase (LOX), cyclooxygenase (COX) and matrix metalloproteases MMPs) [12, 13]. Moreover, they are largely applied as additives in food, cosmetics, perfumes, pharmaceutical, dispersed fluorescent, optical brighteners and laser dyes [14-17].

Also, it has been shown that some 3-substituted coumarin skeletons which contain amide functional group experience extended biological activities. Coumarin group antibiotics [18, 19] including novobiocin (A) and clorobiocin (B) are potent inhibitors of DNA gyrase and some of them have antiproliferative activities [20, 21].



Novobiocin (A)



clorobiocin (B)

To continue the present work on designing novel Isocyanide-based multicomponent reactions [22-24] and based on the diverse biological activities of coumarins and their derivatives, designing new reactions for creating an amide bond is more interesting.

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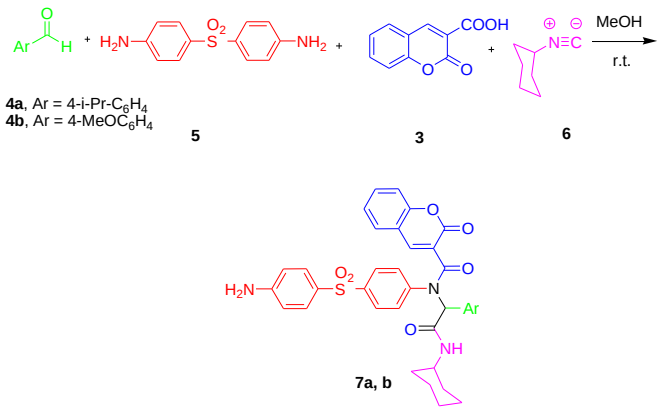
Due to the importance of coumarin skeleton, and the number of amid bonds, type of non-polar substituent as a spacer and in continuation of our research work [22] to design on novel one-pot reactions, herein, we wish to report designing an approach to synthesis of some novel amidated coumarins which contained lipophile moiety and more amide bonds via Ugi-4CR.

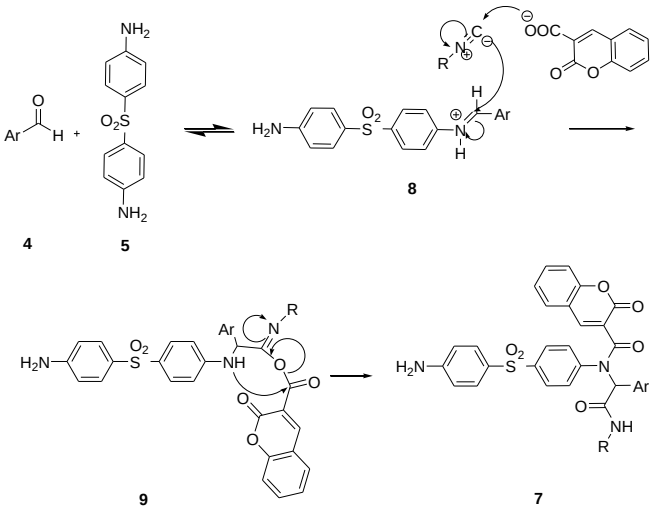
Results and discussion

Initially, Coumarin -3-carboxylic acid **3** was obtained from the reaction of salicyclaldehyde and Meldrum's acid in water with high yield [25]. Then four-component reaction of aromatic aldehyde **4**, 4-(4-aminophenylsulfonyl)benzenamine **5**, coumarin-3-carboxylic acid **3** and cylohexyl isocyanides **6** leads to sulfonated-midated coumarins **7a, b** in good yields and high bond forming efficiency (Scheme **1**).



Scheme 1: Synthesis of amidated coumarins (**7a, b**) through Ugi-4CR.

The structures of products were deduced from their spectroscopic data and also high-resolution mass spectrometry data (HR-ESI-MS). The IR spectrum of **7a** shows tree bands at 3463, 3365, 3242 (NH_2, NH) and two bands at 1721 and 1653 (C=O) cm^{-1}. The ^1H NMR spectrum of **7a** exhibited four doublet for methyl groups (δ = 1.08 ppm), NH (δ = 6.65 ppm) and aromatic protons (δ = 6.42 and 6.60 ppm); complex signals (δ = 1.13-2.00 ppm for the cyclohexyl protons, δ = 2.76 and 3.85 ppm for methyn protons and δ = 6.90-7.51 for aromatic protons); two singlet (δ = 6.10 for CH-N and 7.81 ppm for vinyl proton) along with a broad signal (δ = 4.27 ppm) due to the NH_2 protons. The ^{13}C-NMR spectrum revealed two distinct peaks at δ = 157-165 ppm for the amide C=O groups, and 167-168 ppm for the carbonyl of lactone in coumarin skeletone. Partial assignments of these resonances are given in the experimental section. We believe that this new functionality based multicomponent reactions have a huge potential in creating new molecules or simplifying the synthesis of existing compounds and the synthesized products have good potential for further reactions. According to the commonly accepted Ugi-4CR proposed mechanism, it seems that amine, the carbonyl compound and the acid are in equilibrium with the iminium carboxylate **8** in the reaction medium. The α-addition of the iminium carboxylate onto the carbenoid carbon of the isocyanide leads to the formation of the primary four-component adduct **9**, which undergoes an intramolecular acylation known as Mumm rearrangement to give the stable Ugi adduct **7** (Scheme **2**).



Scheme 2: Proposed mechanism for the synthesis of amidated coumarins (**7a, b**) through Ugi-4CR.

Conclusion

In conclusion, we have synthesized sulfonated 3-substituted coumarin carboxamides by using Ugi-4CR of coumarin-3-carboxylic acid, benzaldehydes, 4-(4-aminophenylsulfonyl)benzenamine and cyclohexyl isocyanides. The simplicity of the synthetic protocol and availability of diverse starting materials make this an attractive strategy for obtaining functionalized coumarins.

Experimental

Commercially available materials were used without further purification. Melting points were determined on an *Electrothermal 9100* apparatus and were uncorrected. IR spectra were obtained on an ABB FT-IR FTLA 2000 spectrometer. ^{1}HNMR and ^{13}CNMR spectra were run on Bruker DRX-500 AVANCE

spectrometer at 300 MHz for ^{1}HNMR, and 75 MHz for ^{13}CNMR. $CDCl_3$ was used as solvent. HRMS was recorded on Mass-ESI-POS (Apex Qe-FT-ICR instrument) spectrometer. Elemental analyses were performed using a Heraeus CHN-S-O-Rapid analyzer.

Synthesis of coumarin-3-carboxylic acid:

In a round-bottomed flask, salicylaldehyde (8 mmol) and Meldrum's acid (10 mmol) in water (15 ml) were heated at reflux under stirring for 9 h. The reaction mixture was cooled and filtered on Büchner funnel. Further purification was done using crystallization in methanol (Yield = 90%).

*2-Oxo-2H-chromene-3-carboxylic acid (**3**):*

Yield: 1.292 g (85%). M.p: 188-190 °C. IR (KBr): 3420, 1747, 1687, 1574 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.50 (d, 2H, *J* = 7.9 Hz, 2CH), 7.80 (d, 2H, *J* = 7.9 Hz, 2CH), 8.96 (s, 1H, CH), 12.27 (bs, 1H, COOH). ^{13}C NMR ($CDCl_3$) δ: 114.8, 117.2, 118.4, 126.2, 130.5, 135.8, 151.5, 154.5, 162.4, 164.1.

*General procedure for the synthesis of chromene-3-carboxamide derivatives **(7a, b)**:*

4-(4-aminophenylsulfonyl)benzenamine **5** (1 mmol) was added to a solution of aldehyde **4** (1 mmol) in methanol (5 mL) and the reaction mixture was stirred at room temperature for 1.5 h. Coumarin-3-carboxylic acid **3** (1 mmol) was added and stirring was continued for 15 min followed by addition of cylohexyl isocyanide **6** (1 mmol). The resulting solution was stirred at room temperature and complete after 16-20h (monitored by TLC). The solvent was removed under reduced pressure and the product was precipitated by addition of water. Further purification was done using column chromatography (eluent ethylacetate/petroleum ether 1:1).

*N-((cyclohexylcarbamoyl)(4-isopropylphenyl) methyl)-N-(4-(4-aminophenylsulfonyl)phenyl)-2-oxo-2H-chromene-3-carboxamide (**7a**)*:

Yield: 0.480 g (71%). M.p: 233-237 ºC. IR (KBr): 3463, 3365, 3242, 1723, 1656. 1303, 1148 Cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): 1.08, (d, 6H, *J* = 6.91 Hz, 2Me), 1.13-2.00 (m, 10H, $5CH_2$), 2.76 (m, 1H, CH), 3.85 (m, 1H, CH), 4.27 (bs, 2H, NH_2), 6.10 (s, 1H, CH), 6.42 (d, 1H, *J* = 6.65 Hz, NH), 6.60 (d , 2H, *J* = 8.7 Hz, 2CH), 6.90-7.01 (m, 4H, 4CH), 7.15-7.23 (m, 4H, 4CH), 7.33-7.51 (m, 6H, 6CH), 7.81 (s, 1H, CH). ^{13}C NMR (75 MHz, $CDCl_3$): 23.7, 24.8, 24.9, 25.3, 32.6, 32.8, 33.6, 49.1, 65.5, 113.9, 116.7, 117.7, 124.9, 126.5, 127.1, 128.2, 128.5, 129.5, 130.1, 130.7, 131.0, 132.9, 141.9, 142.8, 143.2, 149.4, 151.2, 153.6, 158.0, 165.0, 167.8. Anal. For $C_{39}H_{39}N_3O_6S$ (677.26): calcd. C 69.11, H 5.80, N 6.20; found C 68.57, H 6.03, N 6.02 %.

*N-((cyclohexylcarbamoyl)(4-methoxyphenyl)methyl)-N-(4-(4-aminophenylsulfonyl)phenyl)-2-oxo-2H-chromene -3-carboxamide (**7b**):*

Yield: 0.465 g (70%). M.p: 120-124 ºC. IR (KBr): 3456, 3324, 3214, 1718, 1660. 1305, 1145 Cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): 1.09-2.03 (m, 10H, $5CH_2$), 3.67 (s, 3H, OMe), 3.84 (m, 1H, CH), 4.25 (s, 2H, NH_2), 6.19 (s, 1H, CH), 6.37 (d, 1H, *J* = 6.58 Hz, NH), 6.54 (d, 2H, *J* = 8.5 Hz, 2CH), 6.57-6.65 (m, 2H, 2CH), 6.98 (d, 2H, *J* = 8.5 Hz, 2CH), 7.15-7.26 (m, 4H, 4CH), 7.34-7.64 (m, 6H, 6CH), 7.82 (s, 1H, CH). ^{13}C NMR (75 MHz, $CDCl_3$): 24.8, 25.3, 32.6, 32.8, 49.1, 55.1, 65.1, 113.8, 113.9, 116.7, 117.7, 124.9, 251.0, 125.2, 127.3, 128.6, 129.6, 130.9, 131.6, 132.9, 141.9, 142.7, 143.2, 143.5, 151.2, 153.7, 159.5, 165.0, 168.0. Anal. For $C_{37}H_{35}N_3O_7S$ (665.22): calcd. C 66.75, H 5.30, N 6.31; found C 66.26, H 5.56, N 5.93 %. HR-ESI-MS: 688.21013 ($[M+Na]^+$, $C_{37}H_{35}NaN_3O_7S^+$; calc. 688.20879).

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