chemistry proceedings

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Proceeding Paper

Regioselective Synthesis of Coumarin-Annulated Polycyclic Heterocycles via Sequential Claisen Rearrangement and Radical Cyclization Reaction †

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† Presented at the 28th International Electronic Conference on Synthetic Organic Chemistry (ECSOC 2024), 15-30 November 2024; Available online: https://sciforum.net/event/ecsoc-28.

Abstract: Coumarin and its annulated heterocycles are mainly found in natural products, many of that showed significant biological activities and extensively used for the preparation of pharmaceutical products. Investigation revealed that many heterocyclic compounds fused with coumarin moiety exhibited antihelmentic, hypnotic, insecticidal, antifungal and anti-coagulant properties. In industry, coumarin scaffolds are widely used for the preparation of drugs, agrochemicals, pesticides and dyes. In recent studies, several coumarin derivatives have been used in the material science for the preparation of organic cell imaging materials, fluorescent biological probes etc. Due to the immense applications in biological science and material chemistry field, much attention has been paid by the researchers towards the synthesis of new class of coumarin annulated heterocycles. In this paper, the synthesis of coumarin-annulated polycyclic heterocycles *via* sequential Claisen rearrangement and tin-hydride mediated radical cyclization has been reported. The requisite starting materials 3-((4-chlorobut-2-yn-1-yl)oxy)-2*H*-chromen-2-one (**1**) was prepared from 3-hydroxycoumarin and 1,4-dichlorobut-2-yne. The Claisen rearrangement of **1** in refluxing chlorobenzene afforded 1-(chloromethyl)pyrano[2,3-*c*]chromen-5(3*H*)-one (**2**). Finally, radical cyclization reactions were carried out smoothly using $^{n}Bu_3SnH$ and AIBN in toluene at 110 °C, leading to the coumarin-annulated polycyclic heterocycles in high yields. The process is operationally simple and easy to work-up that makes it more convenient for the preparation of coumarin annulated heterocycles.

Keywords: coumarin; polycyclic heterocycles; Claisen rearrangement; radical cyclization

Citation: Debnath, P. Regioselective Synthesis of Coumarin-Annulated Polycyclic Heterocycles via Sequential Claisen Rearrangement and Radical Cyclization Reaction. *Chem. Proc.* **2024**, *6*, x. https://doi.org/10.3390/xxxxx

Academic Editor(s): Name

Published: 15 November 2024

1. Introduction

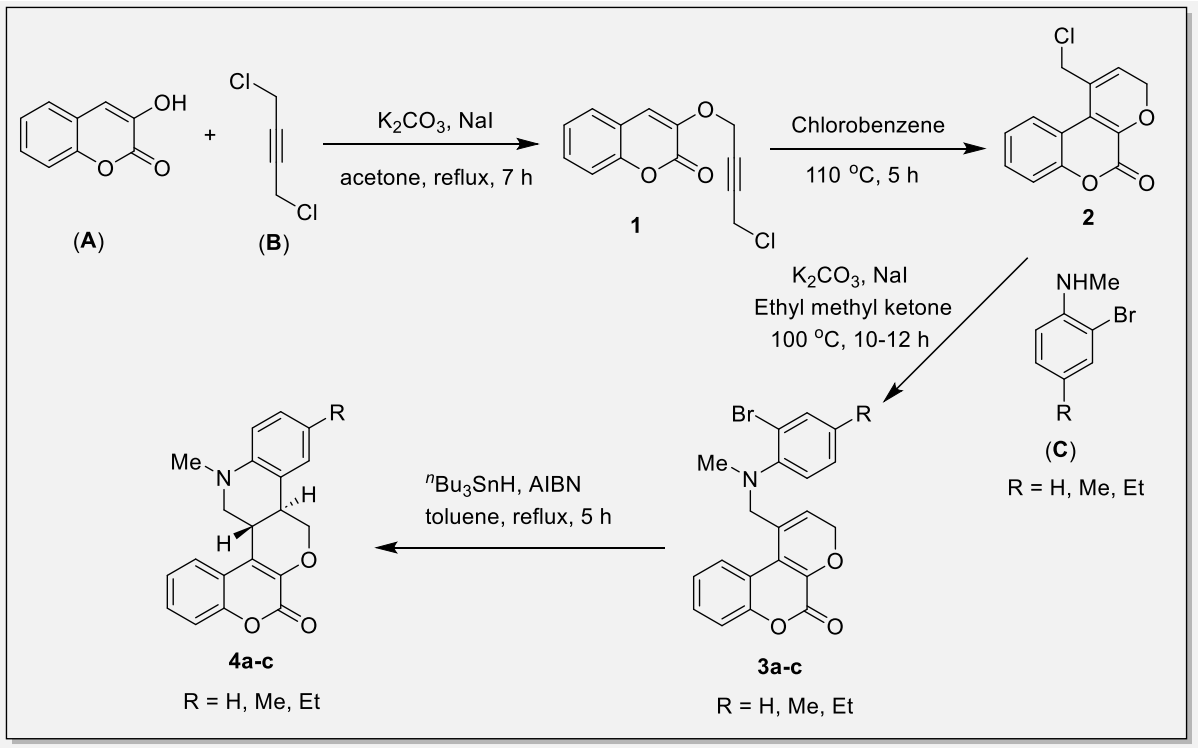
Coumarin and its annulated molecules are largely found in natural products many of that showed significant physiological activities and used for the preparation of drug molecules [1]. According to the literature reports, several coumarin derivatives have potential biological activities [2] including antihelmentic, hypnotic, insecticidal, antidiabetic, antifungal, antiviral, anti-HIV, antibacterial and anti-coagulant properties [3]. Coumarin-annulated molecules are extensively used in the industry for the preparation of various pesticides, agrochemicals, and dye molecules [4]. Due to its fluorescence properties, several coumarin derivatives have been used in the material science for the preparation of organic cell imaging materials and fluorescent biological probes [5]. Owning to their diverse applications, the synthesis of this class of compounds is still a hot topic in modern research [6]. As a result, several methods have unceasingly developed for the synthesis of coumarin-annulated heterocycles.

Claisen rearrangement is a classical method applied for the construction of C-C bond in organic synthesis with high degree of regio-selectivity [7]. In our previous reports, we

have synthesized a numbers of polycyclic heterocycles of biological interest using Claisen rearrangement [8]. On the other hand, radical-mediated cyclization has been considered as important tools for the synthesis of carbo- and heterocycles via carbon-carbon and carbon-heteroatom bond forming reactions [9]. Particularly, intramolecular addition of carbon centred-radical intermediate to aromatic heterocycles has gained an efficient method for the construction carbocycles, heterocycles as well as spirocyclic compounds. This protocol has also been applied as an intermediate step in total synthesis of natural products [10]. In this paper, the synthesis of coumarin-annulated polycyclic heterocycles *via* sequential Claisen rearrangement and tin-hydride mediated radical cyclization has been discussed starting from 3-hydroxycoumarin and 1,4-dichlorobut-2-yne as starting materials. The development protocol is operationally simple, easy work-up procedure, leading to high yield of the coumarin-fused polycyclic heterocycles.

2. Results and Discussion:

The requisite starting materials 3-((4-chlorobut-2-yn-1-yl)oxy)-2*H*-chromen-2-one (**1**) was prepared from 3-hydroxycoumarin (**A**) and 1,4-dichlorobut-2-yne (**B**) in refluxing acetone for 7 h. The Claisen rearrangement of **1** in refluxing chlorobenzene for 5 h provided 1-(chloromethyl)pyrano[2,3-*c*]chromen-5(3*H*)-one (**2**). The radical precursors **3** were prepared by the nucleophile substitution reaction between compound **2** and 2-bromo anilines (**C**) in refluxing ethyl methyl ketone in the presence of K_2CO_3 and catalytic amount of NaI. The treatment of radical precursors (**3**) with ^{n}BuSnH (1.0 eq) and AIBN (0.5 eq.) in toluene at 110 °C, leading to the formation of polyheterocyclic compounds **4** in 75–82% yields (Scheme 1).

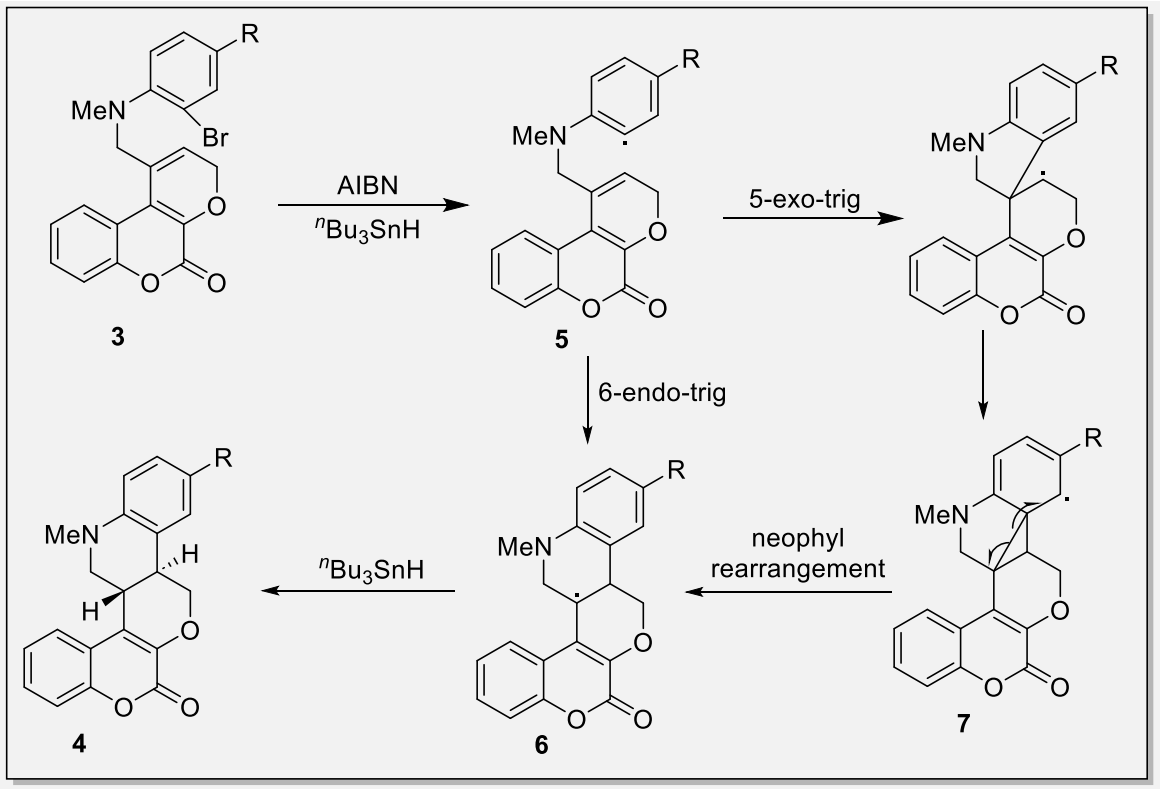


Scheme 1. Preparation of starting materials (**1**) and its conversion to the coumarin-annulated polycyclic heterocycles (**4**).

In initial attempt to effect the radical cyclization, the substrate **3a** was taken as radical precursor. The treatment of compound **3a** with ^{n}Bu$_3$SnH (1.0 eq) and 0.5 eq. of azobisisobutyronitrile (AIBN) in dry toluene at 80 °C for 5 h under N_2 atmosphere afforded cyclized product tetrahydrochromeno[4′,3′:5,6]pyrano[4,3-*c*]quinolin-1(6c*H*)-one (**4a**) in 52% yield. However, the yield of the product was increased to 75% with increasing the temperature

at 110 °C (Scheme 1). By changing the solvent with benzene, xylene and tetrahydrofuran did not achieved any improvement in the yield. Under the same reaction conditions [^{n}Bu$_3$SnH (1.0 eq), AIBN (0.5 eq.), toluene, 110 °C, N_2 atm, 5 h), other substrates **3b** and **3c** were also gave the desired products **4b** and **4c** in 82% and 80% yields, respectively. The structure of the product **4** was explained from ^{1}H NMR spectroscopy. The ^{1}HNMR (400 MHz, $CDCl_3$) spectra of compound **4a** showed one proton of ring juncture showed double triplet (dt) at δ = 2.13 (*J* = 3.2 Hz and 14.4 Hz) and another one proton doublet triplet at δ = 2.34 (*J* = 2.9 Hz and 15.3 Hz). This indicates that radical cyclization proceeded with the formation of trans-ring juncture with coupling constant >14 Hz of the ring juncture protons. The mass spectrum of compound **4a** showed a molecular ion peak at *m*/*z* [M$^+$+H] = 320.1012.

The formation of the products **4** from the radical precursors **3** can be explained by the generation of aryl radical **5** which may undergo a 6-endo-trig radical cyclization with the nearest double bond of pyran ring to produce a resonance stabilized allyl radical (**6**) followed by the abstraction of hydrogen from ^{n}Bu$_3$SnH to afford the desired cyclic product **4**. An alternative route may also be possible, in which a 5-exo-trig cyclization may give a spiro-cyclic radical intermediate, followed by neophyl rearrangement and abstraction of hydrogen from tin-hydride to give [6,6]-fused cyclic product **4** (Scheme 2).



Scheme 2. Plausible reaction mechanism for the formation of coumarin-annulated polycyclic heterocycles.

3. Conclusions

In conclusion, we have successfully synthesized coumarin-annulated pentacyclic heterocycles *via* sequential Claisen rearrangement and tin-hydride mediated radical cyclization. The radical cyclization reaction proceeded smoothly in the presence of ^{n}Bu$_3$SnH and AIBN in toluene, leading to the regioselective synthesis of coumarin-annulated polycyclic heterocycles in high yields. The process is operationally simple and easy work-up procedure makes it more convenient for the preparation of coumarin annulated polyheterocycles.

4. Experimental

Open capillaries were used to determine the melting points and are uncorrected. TLC plates were purchased from Merck and used for thin-layer chromatography (TLC). Petroleum ether refers to the fraction boiling between 60 °C to 80 °C. ^{1}H NMR spectra were recorded on a Bruker Ascend 400 MHz spectrometer (Bruker, Germany) at 400 MHz using $CDCl_3$ solvents and TMS as internal standard. Chemical shifts values are given in parts per million (ppm, δ) with reference to as internal standard and coupling constants are reported in Hertz (Hz).

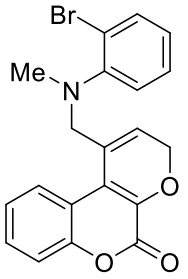
(a) General procedure for the radical cyclization of substrates 3 to cyclized product 4.

A suspension of compound **3** (0.5 mmol), ^{n}Bu$_3$SnH (0.5 mmol, 1.0 eq., 0.14 mL) and AIBN (40 mg, 0.25 eq) in dry toluene was refluxed at 110 °C under N_2 atmosphere for 5 h. After completion of the reaction, the solvent was removed under reduced pressure and residue was dissolved with DCM (15 mL), and washed with water (2 × 10 mL). Finally, DCM was washed with brine and dried over anhy Na_2SO_4. The solvent was removed and residual mass was purified with column chromatography over silica gel using petroleum/ethyl acetate as eluent.

(b) Spectral analysis:

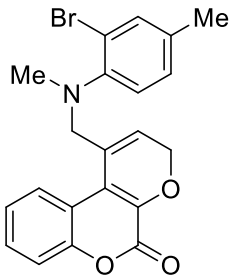
1-(((2-Bromophenyl)(methyl)amino)methyl)pyrano[2,3-*c*]chromen-5(3*H*)-one (3a)

White solid; R_f = 0.50 (SiO_2, petroleum ether/ethyl acetate = 50:50); Yield: 74% (147 mg, 0.37 mmol), mp 155–157 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 2.71 (s, 3H), 4.13 (s, 2H), 4.76 (d, *J* = 4.8 Hz, 2H), 6.41 (t, *J* = 4.7 Hz, 1H), 6.91 (t, *J* = 8.0 Hz, 1H), 7.08 (d, *J* = 8.0 Hz, 1H), 7.17 (d, *J* = 7.2 Hz, 1H) 7.23–7.38 (m, 3H), 7.51 (d, *J* = 7.6 Hz, 1H), 7.66 (d, *J* = 8.0 Hz, 1H). HRMS (ESI): *m*/*z* calcd for $C_{20}H_{17}BrNO_3$ [M$^+$+H]: 398.0314; found: 398.1202.



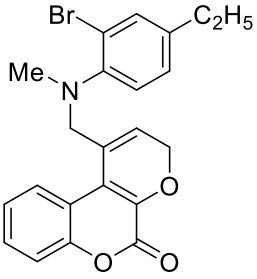
1-(((2-Bromo-4-methylphenyl)(methyl)amino)methyl)pyrano[2,3-*c*]chromen-5(3*H*)-one (3b)

White solid; R_f = 0.50 (SiO_2, petroleum ether:ethyl acetate = 50:50); Yield: 70% (144 mg, 0.35 mmol), mp 172–174 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 2.25 (s, 3H), 2.67 (s, 3H), 4.07 (s, 2H), 4.72 (d, *J* = 4.7 Hz, 2H), 6.34 (t, *J* = 4.7 Hz, 1H), 6.94 (d, *J* = 8.1 Hz, 1H), 7.01 (dd, *J* = 1.3 Hz, 8.1 Hz, 1H), 7.14–7.19 (m, 1H), 7.27–7.30 (m, 2H), 7.33–7.37 (m, 1H), 7.69 (dd, *J* = 1.2 Hz, and 8.1 Hz, 1H). HRMS (ESI): *m*/*z* calcd for $C_{21}H_{19}BrNO_3$ [M$^+$+H]: 412.0470; found: 412.0498.



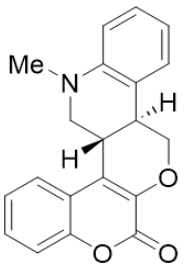
1-(((2-Bromo-4-ethylphenyl)(methyl)amino)methyl)pyrano[2,3-*c*]chromen-5(3*H*)-one (3c)

White solid; R_f = 0.45 (SiO_2, petroleum ether/ethyl acetate = 50:50); Yield: 82% (174 mg, 0.41 mmol), m.p.: 137–139 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.21 (t, *J* = 7.6 Hz, 3H), 2.56 (q, *J* = 7.2 Hz, 2H), 2.68 (s, 3H), 4.09 (s, 2H), 4.74 (d, *J* = 4.4 Hz, 2H), 6.38 (t, *J* = 4.6 Hz, 1H), 6.98 (d, *J* = 8.4 Hz, 1H), 7.06 (d, *J* = 8.0 Hz, 1H), 7.18 (d, *J* = 7.2 Hz, 1H) 7.27–7.38 (m, 3H), 7.67 (d, *J* = 8.0 Hz, 1H). HRMS (ESI): *m*/*z* calcd for $C_{22}H_{21}BrNO_3$ [M$^+$+H]: 426.0627 found: 426.0634.



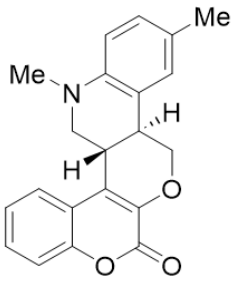
(6c*R*,12b*R*)-8-methyl-7,8,12b,13-tetrahydrochromeno[4′,3′:5,6]pyrano[4,3-*c*]quinolin-1(6c*H*)-one (**4a**)

Brown solid; R_f = 0.50 (SiO_2, petroleum ether/ethyl acetate = 65:35); Yield: 75% (120 mg, 0.375 mmol), m.p.: 182–183 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 2.13 (dt, *J* = 3.2 Hz, 14.4 Hz, 1H), 2.34 (dt, *J* = 2.9 Hz, 15.3 Hz, 1H), 2.92 (s, 3H), 3.46 (d, *J* = 9.7 Hz, 1H), 3.82 (d, *J* = 9.7 Hz, 1H), 4.26 (dt, *J* = 1.8 Hz, 11.4 Hz, 1H), 4.53 (dt, *J* = 3.5 Hz, 11.3 Hz, 1H), 6.58–6.62 (m, 2H), 6.69–6.70 (m, 2H), 6.90 (t, *J* = 7.1 Hz, 1H), 7.02 (d, *J* = 7.6 Hz, 1H), 7.15–7.28 (m, 2H). HRMS (ESI): *m*/*z* calcd for $C_{20}H_{18}NO_3$ [M$^+$+H]: 320.1208, found: 320.1012.



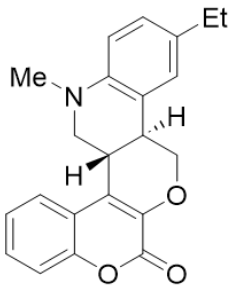
(6c*R*,12b*R*)-8,11-Dimethyl-7,8,12*b*,13-tetrahydrochromeno[4′,3′:5,6]pyrano[4,3-*c*]quinolin-1(6c*H*)-one (**4b**)

Brown solid; R_f = 0.48 (SiO_2, petroleum ether/ethyl acetate = 70:30); Yield: 82% (136 mg, 0.41 mmol), m.p. 162–164 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 2.11 (dt, *J* = 2.8 Hz, 14.9 Hz, 1H), 2.13 (s, 3H), 2.33 (dt, *J* = 2.8 Hz, 14.2 Hz, 1H), 2.90 (s, 3H), 3.45 (d, *J* = 9.7 Hz, 1H), 3.78 (d, *J* = 9.7 Hz, 1H), 4.26 (dt, *J* = 2.0 Hz, 11.3 Hz, 1H), 4.55 (dt, *J* = 3.7 Hz, 11.3 Hz, 1H), 6.53 (d, *J* = 7.6 Hz, 1H), 6.71 (s, 1H), 6.91–6.94 (m, 1H), 6.97 (d, *J* = 8.1 Hz, 1H), 7.07 (d, *J* = 8.1 Hz, 1H), 7.22–7.24 (m, 1H), 7.28 (dd, *J* = 1.1 Hz, 8.1 Hz, 1H). HRMS (ESI): *m*/*z* calcd for $C_{21}H_{20}NO_3$ [M$^+$+H]: 334.1365 found: 334.1134.



(6c*R*,12b*R*)-11-ethyl-8-methyl-7,8,12b,13-tetrahydrochromeno[4′,3′:5,6]pyrano[4,3-c]quinolin-1(6c*H*)-one (4c)

Brown solid; R_f = 0.48 (SiO_2, petroleum ether/ethyl acetate = 65:35); Yield: 80% (139 mg, 0.4 mmol), mp 155–157 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.02 (t, *J* = 7.7 Hz, 3H), 2.09 (dt, *J* = 2.8 Hz, 14.2 Hz, 1H), 2.34 (dt, *J* = 2.2 Hz, 14.2 Hz, 1H), 2.41 (q, *J* = 7.5 Hz, 2H), 2.89 (s, 3H), 3.43 (t, *J* = 9.7 Hz, 1H), 3.75 (d, *J* = 9.7 Hz, 1H), 4.25 (dt, *J* = 1.96 Hz, 12.3 Hz, 1H), 4.53 (dt, *J* = 3.6 Hz, 11.3 Hz, 1H), 6.56 (d, *J* = 8.04 Hz, 1H), 6.88–6.92 (m, 1H), 6.98–7.05 (m, 2H), 7.20–7.33 (m, 3H). HRMS (ESI): *m*/*z* calcd for $C_{22}H_{22}NO_3$ [M^++H]: 348.1521, found: 348.0986.



Funding:

Institutional Review Board Statement:

Informed Consent Statement:

Data Availability Statement:

Acknowledgments: The author acknowledges Maharaja Bir Bikram College, Agartala for providing infrastructural facilities to this work and Bose Institute, Kolkata for spectral analysis.

Conflicts of Interest: The author declares that there is no conflict of interest.

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