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ORIGINAL PAPER

Formation of epoxychromeno[4,3-*c*]isoquinolines through diastereoselective one-pot IMDA reaction of 4-chloro-3-[(1*E*)-3-oxo-3-phenyl-1-propen-1-yl]-2*H*-chromen-2-one and furfurylamine

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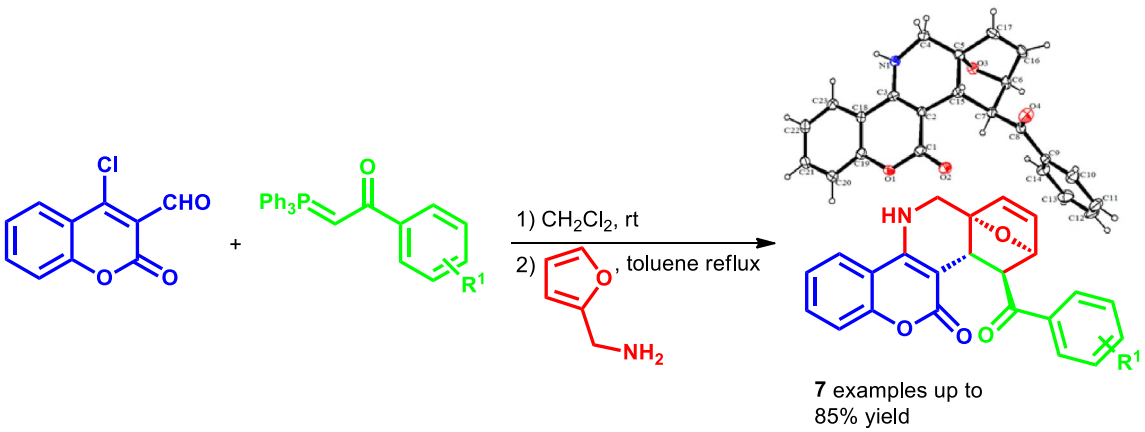
Abstract
An intramolecular Diels–Alder mediated reaction of (2*E*)-3-(4-chloro-2-methylene-2*H*-chromen-3-yl)-1-phenyl-2-propen-1-one, which was obtained in situ from the reaction of 4-chloro-2-oxo-2*H*-chromene-3-carbaldehyde and Wittig reagent, with furfurylamine leads to fused epoxychromeno[4,3-*c*]isoquinolines. Reaction performed in one-pot condition and only one diastereomer was obtained. In this method, the key step for the formation of the final product is IMDA reaction.

Graphic abstract
A series of fused epoxychromeno[4,3-*c*]isoquinoline compounds containing chromene skeleton have been synthesized through the cyclization strategy, from 4-chloro-2-oxo-2*H*-chromene-3-carbaldehyde, Wittig reagent, and furfurylamine. The reactions were carried out under reflux condition in DCM/toluene.



Keywords 4-Chloro-2-oxo-2*H*-chromene-3-carbaldehyde · Wittig reagent · (2*E*)-3-(4-chloro-2-methylene-2*H*-chromen-3-yl)-1-phenyl-2-propen-1-one · Furfurylamine · IMDA reaction · Coumarin-based heterocycles · One-pot process · Diastereoselective

Introduction

Coumarins are one of the most common and valuable naturally occurring structures in chemistry and biological chemistry [1–3]. These structures are widely found in plants and many of them extracted successfully and applied

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in biological and pharmaceutical purposes [4]. Investigations showed that coumarin-based heterocycles exhibit different biological activities compared to simple coumarin derivatives so adding a heterocycle moiety to coumarin structure either as linking group or as a fused part of whole structure could be a powerful and general tool to synthesize new range of coumarins for evaluation of their biological activities [5, 6]. A survey in the literature revealed that scientists tried different methods to synthesize new coumarin heterocyclic derivatives. For instance, Yang and co-workers applied a four-component Ugi reaction to achieve this goal. They used coumarin-3-carboxylic, isocyanides, anilines, and different aldehydes to obtain chromeno[3,4-*c*]pyrrole-3,4-diones [7]. Another application of multicomponent reaction in the synthesis of coumarin-based heterocycles was reported by Shi et al. [8]. The final 3-pyrrolyl coumarin was obtained through the four-component reaction between arylglyoxal, dialkyl acetylenedicarboxylates, amines, and 4-hydroxycoumarin. Besides multicomponent reaction, some scientists used the metal catalyst for the synthesis of fused coumarins. For example, the Snieckus group reported the synthesis of coumestan derivatives using a Suzuki–Miyaura cross-coupling strategy followed by cyclization with acid catalysis [9]. Another application of metal catalysts in this way is reported by Xu et al. [10]. This cascade reaction includes the addition of the broad range of prepared dialkynyl zincs to 3-bromo-4-acetoxycoumarins in the presence of palladium/copper catalyst. With this method, furocoumarins could be obtained in good-to-high yields.

In addition of heterocyclic coumarins, many methods have been developed for synthesis of fused chromene, especially fused chromenones. Reddy and co-workers used $Rh_2(OAc)_4$ for catalysis formation of fused furochromenone structures [11]. Another multicomponent reaction has been developed for synthesis of pyrrole-fused chromanones by Ghandi et al. [10, 12]. Among all these methods, few reports have been addressed about epoxychromenes due to their complex structure. Mikhalchenko group studied new bicyclic chromenes and investigated their analgesic activity [13].

Among various methods and approaches, intramolecular Diels–Alder reaction has found a notable place in organic chemistry and displayed multiple applications in organic syntheses such as macrocyclization, natural product synthesis, and formation of molecular complexity [14–17]. Also, multiple carbon–carbon or carbon–heteroatom bond formation, high atom economy, and stereoselective product have made this reaction to one of the main topics in organic synthesis. Samant and co-workers employed IMDA to synthesize a new class of fluorescent coumarin-based heterocycles [18].

Based on the significant role of coumarin-based heterocyclic compounds in different aspects of chemistry and biological chemistry, we focused our attempts on the synthesis of novel classes of coumarin-based bicyclic compounds starting from coumarin core and utilizing IMDA as a key reaction in the synthesis of epoxychromeno[4,3-*c*]isoquinolines.

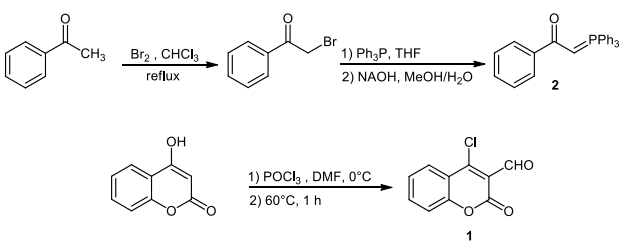
First, we initiate to prepare starting materials. Wittig reagent **2** was prepared based on the reported procedures starting from acetophenone [19]. 4-Chloro-2-oxo-2*H*-chromene-3-carbaldehyde **1** also synthesized through the procedure reported by China Raju [20] (Scheme 1).

Experimental section

Melting points were measured on an Electrothermal 9100 apparatus. IR spectra were recorded as KBr pellets on a NICOLET FT-IR 100 spectrometer. ^{1}H NMR (500 and 300 MHz) and ^{13}C NMR (125 and 75 MHz) spectra were obtained using Bruker DRX-500 AVANCE and Bruker DRX-300 AVANCE spectrometers. NMR spectra at room temperature were recorded in DMSO-d_6. Chemical shifts are reported in parts per million (δ) downfield from an internal tetramethylsilane reference. Coupling constants (J values) are reported in Hertz (Hz), and spin multiplicities are indicated by the following symbols: bs (broad singlet), s (singlet), d (doublet), t (triplet), m (multiplet). Elemental analyses for C, H, and N were performed using a Heraeus CHN–O–Rapid analyzer. All the products were recrystallized from CH_3CN for CHN analysis. Mass spectra were recorded on a FINNIGAN-MATT 8430 mass spectrometer operating at an ionization potential of 20 or 70 eV. All the reagents and solvents were purchased from Merck or Aldrich without any purification.

General procedure for preparation of phenacyl bromide derivatives

This compound was prepared based on reported procedures in the literature [21, 22]. A solution of acetophenone (50 mmol, 6 g) in 30 ml $CHCl_3$ was introduced to a 100-ml three-neck round-bottom flask. The flask was equipped with a pressure-equalizing dropping funnel, which charged with the solution of bromine (52.5 mmol, 8.4 g) in 5 ml $CHCl_3$. The apparatus was placed in a 60 °C oil bath on a magnetic



Scheme 1 Synthetic route for the preparation of starting materials

stirrer, and bromine was added dropwise over 30 min. The reaction was carried out in an open vessel condition, so that the produced HBr could leave the flask. After the addition of bromine, the reaction was refluxed for another 2 h. Then, the reaction mixture was cooled to room temperature and the solvent was removed under vacuum and 15 ml hexane was added to the residue. The mixture was placed in the refrigerator for a day. The resulting solid was filtered and washed with water.

General procedure for preparation of Wittig reagent (1-phenyl-2-(triphenyl-λ^5-phosphanylidene) ethan-1-one)

This compound was prepared based on reported procedures in the literature [19].

General procedure for synthesis of 4-chloro-3-formylcoumarin

This is a known compound, and it was prepared according to procedures reported in the literature [20, 23].

General procedure for one-pot synthesis of compounds 5a–g

4-Chloro-3-formylcoumarin (1 mmol, 208 mg) and Wittig reagent (1 mmol, 380 mg) were introduced to a 25-ml round-bottom flask. Then, CH_2Cl_2 (10 ml) was added to flask and reaction mixture was stirred at room temperature for about a day. Afterward, furfurylamine (2 mmol, 194 mg) was added to flask following by addition of 10 ml toluene as a co-solvent and the mixture was refluxed for 4–5 h until consumption of starting materials. The resulting solid was filtered and washed with ethyl acetate.

(6aR,9S,10S,10aR)-10-Benzoyl-5,9,10,10a-tetrahydro-6*H*,11*H*-6a,9-epoxychromeno[4,3-*c*]isoquinolin-11-one (5a) White powder, mp = 205–206 °C, 0.302 g, yield: 82%. IR (KBr) (ν_{max}, cm^{-1}): 3340 (NH), 1653 (C=O), 1608 (C=C), 1547 and 1448 (Ar), 1217 (C–O of lactone), 1062 (C–O of ether). Anal. Calcd for $C_{23}H_{17}NO_4$ (371.39): C, 74.38; H, 4.61; N, 3.77%. Found: C, 74.42; H, 4.59; N, 3.78%. MS (EI, 70 eV): *m*/*z* (%) = 371 (M^+, 8), 342 (10), 274 (8), 273 (34), 267 (14), 266 (71), 252 (20), 251 (37), 249 (9), 248 (30), 238 (15), 236 (8), 115 (8), 105 (41), 81 (100), 77 (24), 53 (17). ^{1}H NMR (300 MHz, DMSO-d_6): δ_H 3.01 (1H, d, $^3J_{HH}$ = 3.6 Hz, CH^{10a}), 3.77 (1H, dd, $^3J_{HH}$ = 14.0 Hz, $^3J_{HH}$ = 3.7 Hz, CH_2^6), 3.90 (1H, d, $^3J_{HH}$ = 4.1 Hz, CH^{10}), 3.97 (1H, d, $^3J_{HH}$ = 14.0 Hz, CH_2^6), 4.04 (2H, s, CH_2NH_3), 5.21 (1H, d, $^3J_{HH}$ = 4.6 Hz, CH^9), 6.12 (1H, d, $^3J_{HH}$ = 5.7 Hz, CH^8), 6.48 (1H, d, $^3J_{HH}$ = 2.8 Hz, CH^4 of furan), 6.51 (1H, d, $^3J_{HH}$ = 2.8 Hz, CH^3 of furan), 6.54 (1H, d, $^3J_{HH}$ = 5.8 Hz, CH^7), 7.27 (1H, d, $^3J_{HH}$ = 8.2 Hz, CH^1), 7.31 (1H, t, $^3J_{HH}$ = 7.6 Hz, CH^3), 7.53 (1H, d, $^3J_{HH}$ = 7.7 Hz, CH^2), 7.61 (2H, d, $^3J_{HH}$ = 8.3 Hz, $2CH_{meta}$ of Ph), 7.71 (1H, t, $^3J_{HH}$ = 8.3 Hz, CH_{para} of Ph) 7.71 (1H, s, CH^5 of furan), 8.03 (1H, d, $^3J_{HH}$ = 7.9 Hz, CH^4), 8.05 (2H, d, $^3J_{HH}$ = 8.3 Hz, $2CH_{ortho}$ of Ph), 8.12 (1H, s, NH), 8.56 (3H, s, NH_3). ^{13}C NMR (75.46 MHz, DMSO-d_6): δ_C 34.91 (CH^{10a}), 37.56 (CH^{10}), 40.86 (CH_2NH_3), 57.14 (CH_2^6), 79.97 (CH^9), 85.13 (C^{6a}), 94.86 (C^{10b}), 110.27 (CH^3 of furan), 110.90 (CH^4 of furan), 114.22 (C^{4a}), 116.64 (CH^1), 122.37 (CH^3), 123.40 (CH^4), 128.73 ($2CH_{ortho}$ of Ph), 128.74 ($2CH_{meta}$ of Ph), 131.20 (CH^2), 132.97 (CH_{para} of Ph), 133.54 (CH^7), 136.50 (C_{ipso} of Ph), 136.77 (CH^8), 143.54 (CH^5 of furan), 147.27 (C^2 of furan), 147.62 (C^{4b}), 152.01 (C^{12a}), 161.25 (COO of chromene), 195.60 (C=O). Crystal data for **5a** $C_{23}H_{17}NO_4$ (CCDC 1903316): M_W = 415.56, Monoclinic, C 2/c, *a* = 14.262(3) Å, *b* = 17.824(4) Å, *c* = 14.919(3) Å, α = 90.00, β = 107.15 (3), γ = 90.00, *V* = 3623.9(14) $Å^3$, Z = 8, Dc = 1.361 mg/m^3, F (000) = 1552, radiation, Mo Kα (λ = 0.71073 Å), $1.881 \le 2\theta \le 26.899$, intensity data were collected at 293(2) K with a STOE IPDS-2T diffractometer, and employing $\omega/2\theta$ scanning technique, in the range of $-18 \le h \le 18$, $-22 \le k \le 22$, $-18 \le l \le 18$; the structure was solved by a direct method, all non-hydrogen atoms were positioned and anisotropic thermal parameters refined from 2614 independent reflections with R (into) = 0. 1813 by a full-matrix least-squares technique converged to $R1 = 0.0428$, $wR2 = 0.0623$ [$I > 2\text{sigma}(I)$].

(6aR,9S,10S,10aR)-10-(4-Bromobenzoyl)-5,9,10,10a-tetrahydro-6*H*,11*H*-6a,9-epoxychromeno[4,3-*c*]isoquinolin-11-one (5b) White powder, mp = 190–191 °C, 0.315 g, yield: 70%. IR (KBr) (ν_{max}, cm^{-1}): 3324 (NH), 1671 (C=O), 1611 (C=C), 1550 and 1492 (Ar), 1218 (C–O of lactone), 1066 (C–O of ether). Anal. Calcd for $C_{23}H_{16}BrNO_4$ (450.28): C, 61.35; H, 3.58; N, 3.11%. Found: C, 61.36; H, 3.55; N, 3.12%. MS (EI, 70 eV): *m*/*z* (%) = 451 (M^++2, 1), 450 (M^++1, 1), 449 (M^+, 1), 353 (14), 266 (48), 252 (11), 251 (28), 248 (11), 185 (16), 183 (16), 97 (21), 81 (100), 53 (20). ^{1}H NMR (500 MHz, DMSO-d_6): δ_H 2.97 (1H, d, $^3J_{HH}$ = 3.6 Hz, CH^{10a}), 3.81 (1H, dd, $^3J_{HH}$ = 14.0 Hz, $^3J_{HH}$ = 3.7 Hz, CH_2^6), 3.86 (1H, t, $^3J_{HH}$ = 4.1 Hz, CH^{10}), 3.93 (1H, d, $^3J_{HH}$ = 14.0 Hz, CH_2^6), 4.04 (2H, s, CH_2NH_3), 5.21 (1H, d, $^3J_{HH}$ = 4.6 Hz, CH^9), 6.14 (1H, d, $^3J_{HH}$ = 5.7 Hz, CH^8), 6.49 (1H, d, $^3J_{HH}$ = 2.8 Hz, CH^4 of furan), 6.53 (1H, d, $^3J_{HH}$ = 5.7 Hz, CH^7), 6.54 (1H, d, $^3J_{HH}$ = 2.8 Hz, CH^3 of furan), 7.25 (1H, d, $^3J_{HH}$ = 8.2 Hz, CH^1), 7.31 (1H, d, $^3J_{HH}$ = 7.6 Hz, CH^3), 7.54 (1H, d, $^3J_{HH}$ = 7.7 Hz, CH^2), 7.70 (2H, d, $^3J_{HH}$ = 8.3 Hz, 2CH of Ar), 7.72 (1H, s, CH^5 of furan), 7.98 (2H, d, $^3J_{HH}$ = 8.3 Hz, 2CH of Ar), 8.05 (1H, d, $^3J_{HH}$ = 7.6 Hz, CH^4), 8.16 (1H, s, NH), 8.58 (3H, s, NH_3). ^{13}C NMR (125 MHz, DMSO-d_6): δ_C 35.39 (C^{10a}), 38.34 (C^{10}), 41.28 (CH_2NH_3), 57.53 (CH_2^6), 80.36 (C^9), 85.60

(C^{6a}), 95.21 (C^{10b}), 110.71 (CH^3 of furan), 111.35 (CH^4 of furan), 114.66 (C^{4a}), 117.10 (CH^1), 122.87 (CH^3), 123.86 (CH^4), 127.54 (C_{ipso}-Br), 130.75 (2CH of Ar), 131.67 (CH^2), 132.22 (2CH of Ar), 133.93 (CH^7), 136.31 (CH^8), 137.05 (C_{ipso}-C=O), 143.99 (CH^5 of furan), 147.73 (C^2 of furan), 148.09 (C^{4b}), 152.46 (C^{12a}), 161.75 (COO of chromene), 195.51 (COPh).

(6aR,9S,10S,10aR)-10-(2-Chlorobenzoyl)-5,9,10,10a-tetrahydro-6*H*,11*H*-6a,9-epoxychromeno[4,3-*c*]isoquinolin-11-one (5c) White powder, mp = 193–194 °C, 0.287 g, yield: 71%. IR (KBr) (ν_{max}, cm^{-1}): 3281 (NH), 1652 (C=O), 1610 (C=C), 1550 and 1494 (Ar), 1214 (C–O of lactone), 1058 (C–O of ether). Anal. Calcd for $C_{23}H_{16}ClNO_4$ (405.83): 68.07; H, 3.97; N, 3.45%. Found: C, 68.09; H, 3.96; N, 3.45%. MS (EI, 70 eV): *m/z* (%) = 407 (M^++2, 2), 406 (M^++1, 2), 405 (M^+, 6), 377 (8), 376 (7), 307 (7), 267 (25), 266 (100), 252 (30), 251 (56), 248 (37), 238 (17), 141 (15), 139 (42), 111 (18), 81 (94), 53 (22). ^{1}H NMR (500 MHz, DMSO-d_6): δ_H 2.93 (1H, d, $^3J_{HH}$ = 3.7 Hz, CH^{10a}), 3.63 (1H, t, $^3J_{HH}$ = 4.0 Hz, CH^{10}), 3.79 (1H, dd, $^2J_{HH}$ = 14 Hz, $^4J_{HH}$ = 3.5 Hz, CH_2^6), 3.94 (1H, d, $^2J_{HH}$ = 14 Hz, CH_2^6), 4.05 (2H, s, C$H_2$$NH_3$), 5.11 (1H, d, $^3J_{HH}$ = 4.1 Hz, CH^9), 6.30 (1H, d, $^3J_{HH}$ = 5.6 Hz, CH^8), 6.49 (1H, s, CH^4 of furan), 6.54 (1H, d, $^3J_{HH}$ = 2.6 Hz, CH^3 of furan), 6.57 (1H, d, $^3J_{HH}$ = 5.6 Hz, CH^7), 7.30 (1H, d, $^3J_{HH}$ = 8.6 Hz, CH^1), 7.33 (1H, t, $^3J_{HH}$ = 7.5 Hz, CH^3), 7.44 (1H, t, $^3J_{HH}$ = 7.2 Hz, CH of Ar), 7.49 (1H, t, $^3J_{HH}$ = 7.2 Hz, CH of Ar), 7.52 (1H, d, $^3J_{HH}$ = 7.6 Hz, CH of Ar), 7.56 (1H, t, $^3J_{HH}$ = 7.5 Hz, CH^2), 7.72 (1H, s, CH^5 of furan), 7.83 (1H, d, $^3J_{HH}$ = 7.6 Hz, CH of Ar), 8.02 (1H, d, $^3J_{HH}$ = 7.9 Hz, CH^4), 8.12 (1H, s, NH), 8.50 (3H, s, NH_3). ^{13}C NMR (125 MHz, DMSO-d_6): δ_C 34.93 (CH^{10a}), 38.30 (C^{10}), 40.80 (CH_2NH_3), 61.36 (CH_2^6), 79.37 (CH^9), 85.30 (C^{6a}), 94.40 (C^{10b}), 110.25 (CH^4 of furan), 110.89 (CH^3 of furan), 114.16 (C^{4a}), 116.69 (CH^1), 122.50 (CH^3), 123.45 (CH^4), 127.64 (CH of Ar), 129.24 (CH of Ar), 129.50 (CH of Ar), 130.23 (CH of Ar), 131.29 (CH^2), 131.83 (C_{ipso}-Cl), 133.66 (CH^7), 136.70 (CH^8), 139.49 (C_{ipso}-C=O), 143.52 (CH^5 of furan), 147.43 (C^2 of furan), 147.64 (C^{4b}), 152.00 (C^{12a}), 161.61 (COO of chromene), 198.44 (C=O).

(6aR,9S,10S,10aR)-10-(4-Chlorobenzoyl)-5,9,10,10a-tetrahydro-6*H*,11*H*-6a,9-epoxychromeno[4,3-*c*]isoquinolin-11-one (5d) Pale yellow powder, mp = 186–187 °C, 0.299 g, yield: 74%. IR (KBr) (ν_{max}, cm^{-1}): 3329 (NH), 1672 (C=O), 1611 (C=C), 1550 and 1439 (Ar), 1218 (C–O of lactone), 1091 and 1051 (C–O of ether). Anal. Calcd for $C_{23}H_{16}ClNO_4$ (405.83): C, 68.07; H, 3.97; N, 3.45%. Found: C, 68.09; H, 3.94; N, 3.44%. MS (EI, 70 eV): *m/z* (%) = 407 (M^++2, 2), 406 (M^++1, 2), 405 (M^+, 7), 377 (8), 307 (19), 267 (24), 266 (98), 252 (27), 251 (62), 249 (9), 248 (29), 238 (17), 141 (16), 139 (44), 111 (24), 81 (100), 53 (21). ^{1}H NMR (500 MHz, DMSO-d_6): δ_H 2.99 (1H, d, $^3J_{HH}$ = 3.6 Hz, CH^{10a}), 3.80 (1H, dd, $^2J_{HH}$ = 14 Hz, $^4J_{HH}$ = 3.7 Hz, CH_2^6), 3.88 (1H, t, $^3J_{HH}$ = 4.1 Hz, CH^{10}), 3.96 (1H, d, $^2J_{HH}$ = 14 Hz, CH_2^6), 4.06 (2H, s, C$H_2$$NH_3$), 5.22 (1H, d, $^3J_{HH}$ = 4.6 Hz, CH^9), 6.15 (1H, d, $^3J_{HH}$ = 5.7 Hz, CH^8), 6.50 (1H, t, $^3J_{HH}$ = 2.8 Hz, CH^4 of furan), 6.53 (1H, d, $^3J_{HH}$ = 5.8 Hz, CH^7), 6.54 (1H, d, $^3J_{HH}$ = 2.8 Hz, CH^3 of furan), 7.28 (1H, d, $^3J_{HH}$ = 8.2 Hz, CH^1), 7.33 (1H, t, $^3J_{HH}$ = 7.6 Hz, CH^3), 7.55 (1H, t, $^3J_{HH}$ = 7.7 Hz, CH^2), 7.58 (2H, d, $^3J_{HH}$ = 8.3 Hz, 2CH of Ar), 7.73 (1H, s, CH^5 of furan), 8.00 (1H, d, $^3J_{HH}$ = 7.9 Hz, CH^4), 8.06 (1H, s, NH), 8.07 (2H, d, $^3J_{HH}$ = 8.3 Hz, 2CH of Ar), 8.45 (3H, s, NH_3). ^{13}C NMR (125 MHz, DMSO-d_6): δ_C 34.94 (CH^{10a}), 37.88 (CH^{10}), 40.84 (CH_2NH_3), 57.11 (CH_2^6), 79.93 (CH^9), 85.17 (C^{6a}), 94.76 (C^{10b}), 110.26 (CH^3 of furan), 110.91 (CH^4 of furan), 114.22 (C^{4a}), 116.66 (CH^1), 122.43 (CH^3), 123.41 (CH^4), 128.82 (2CH of Ar), 130.20 (2CH of Ar), 131.23 (CH^2), 133.50 (CH^7), 135.53 (C_{ipso}-C=O), 136.61 (CH^8), 137.93 (C_{ipso}-Cl), 143.55 (CH^5 of furan), 147.30 (C^2 of furan), 147.67 (C^{4b}), 152.03 (C^{12a}), 161.31 (COO of chromene), 194.86 (C=O).

(6aR,9S,10S,10aR)-10-(4-Methoxybenzoyl)-5,9,10,10a-tetrahydro-6*H*,11*H*-6a,9-epoxychromeno[4,3-*c*]isoquinolin-11-one (5e) White powder, mp = 207–208 °C, 0.276 g, yield: 69%. IR (KBr) (ν_{max}, cm^{-1}): 3288 (NH), 1661 (C=O), 1607 (C=CC=C), 1550 and 1495 (Ar), 1255, 1222, 1170 and 1028 (C–O). Anal. Calcd for $C_{24}H_{19}NO_5$ (401.41): C, 71.81; H, 4.77; N, 3.49%. Found: C, 71.8; H, 4.76; N, 3.46%. MS (EI, 70 eV): *m/z* (%) = 401 (M^+, 4), 305 (7), 303 (14), 267 (17), 266 (81), 252 (12), 251 (36), 248 (12), 238 (9), 236 (14), 136 (11), 135 (100), 81 (75), 53 (6). ^{1}H NMR (500 MHz, DMSO-d_6): δ_H 3.01 (1H, s, CH^{10a}), 3.82 (3H, s, OMe), 3.83 (1H, b, CH_2^6), 3.90 (1H, b, CH^{10}), 3.94 (1H, b, CH_2^6), 4.03 (2H, s, C$H_2$$NH_3$), 5.18 (1H, s, CH^9), 6.10 (1H, s, CH^8), 6.48 (1H, s, CH^4 of furan), 6.53 (1H, s, ^{7}CH), 6.55 (1H, s, CH^3 of furan), 7.02 (2H, s, 2CH of Ar), 7.26 (1H, s, CH^1), 7.30 (1H, s, CH^3), 7.53 (1H, s, CH^2), 7.71 (1H, s, CH^5 of furan), 8.02 (1H, s, CH^4), 8.03 (2H, s, 2CH of Ar), 8.15 (1H, s, NH), 8.57 (3H, s, NH_3). ^{13}C NMR (125 MHz, DMSO-d_6): δ_C 35.43 (CH^{10a}), 37.74 (CH^{10}), 41.33 (CH_2NH_3), 55.97 (OMe), 57.28 (CH_2^6), 80.43 (CH^9), 85.56 (C^{6a}), 95.41 (C^{10b}), 110.64 (CH^3 of furan), 111.34 (CH^4 of furan), 114.43 (2CH of Ar), 114.71 (C^{4a}), 117.04 (CH^1), 122.87 (CH^3), 123.80 (CH^4), 130.18 (C_{ipso}-C=O), 130.99 (2CH of Ar), 131.59 (CH^2), 134.07 (CH^7), 136.81 (CH^8), 143.94 (CH^5 of furan), 147.70 (C^2 of furan), 148.22 (C^{4b}), 152.47 (C^{12a}), 161.65 (COO of chromene), 163.42 (C_{ipso}-OMe), 194.32 (C=O).

(6aR,9S,10S,10aR)-10-(4-Methylbenzoyl)-5,9,10,10a-tetrahydro-6*H*,11*H*-6a,9-epoxychromeno[4,3-*c*]isoquinolin-11-one (5f) White powder, mp = 201–202 °C, 0.3 g, yield: 78%. IR (KBr) (ν_{max}, cm^{-1}): 3374 (NH), 1669 (C=O), 1611 (C=C),

1550 and 1495 (Ar), 1220 (C–O of lactone), 1053 (C–O of ether). Anal. Calcd for $C_{24}H_{19}NO_4$ (385.41): C, 74.79; H, 4.97; N, 3.63%. Found: C, 74.76; H, 4.98; N, 3.60%. MS (EI, 70 eV): *m/z* (%) = 385 (M^+, 6), 288 (7), 287 (25), 267 (24), 266 (100), 252 (24), 251 (53), 248 (29), 238 (15), 139 (22), 119 (28) 91 (14), 81 (78), 53 (17). ^{1}H NMR (500 MHz, DMSO-d_6): δ_H 2.37 (3H, s, Me), 3.01 (1H, d, $^3J_{HH}$ = 3.8 Hz, CH^{10a}), 3.80 (1H, dd, $^3J_{HH}$ = 14 Hz, $^3J_{HH}$ = 4.0 Hz, CH_2^6), 3.87 (1H, t, $^3J_{HH}$ = 4.3 Hz, CH^{10}), 3.93 (1H, d, $^2J_{HH}$ = 14 Hz, CH_2^6), 4.05 (2H, s, CH_2NH_3), 5.19 (1H, d, $^3J_{HH}$ = 4.8 Hz, CH^9), 6.11 (1H, dd, $^3J_{HH}$ = 5.7 Hz, $^3J_{HH}$ = 1.5 Hz, CH^8), 6.48 (1H, dd, $^3J_{HH}$ = 3.1 Hz, $^3J_{HH}$ = 1.7 Hz, CH^4 of furan), 6.51 (1H, d, $^3J_{HH}$ = 5.7 Hz, CH^7), 6.56 (1H, d, $^3J_{HH}$ = 3.1 Hz, CH^3 of furan), 7.26 (1H, d, $^3J_{HH}$ = 8.3 Hz, CH^1), 7.32 (2H, d, $^3J_{HH}$ = 8.0 Hz, 2CH of Ar), 7.33 (1H, t, $^3J_{HH}$ = 7.0 Hz, CH^3), 7.54 (1H, t, $^3J_{HH}$ = 7.3 Hz, CH^2), 7.72 (1H, dd, $^3J_{HH}$ = 1.7 Hz, $^3J_{HH}$ = 0.8 Hz, CH^5 of furan), 7.94 (2H, d, $^3J_{HH}$ = 8.0 Hz, 2CH of Ar), 8.04 (1H, d, $^3J_{HH}$ = 7.6 Hz, CH^4), 8.12 (1H, s, NH), 8.57 (3H, s, NH_3). ^{13}C NMR (125 MHz, DMSO-d_6): δ_C 21.58 (Me), 34.95 (CH^{10a}), 37.37 (CH^{10}), 40.88 (CH_2NH_3), 57.10 (CH_2^6), 79.99 (CH^9), 85.14 (C^{6a}), 94.93 (C^{10b}), 110.28 (CH^3 of furan), 110.92 (CH^4 of furan), 114.25 (C^{4a}), 116.64 (CH^1), 122.37 (CH^3), 123.40 (CH^4), 128.37 (2CH of Ar), 129.27 (2CH of Ar), 131.19 (CH^2), 133.58 (CH^7), 134.32 (C_{ipso}-C=O), 136.45 (CH^8), 143.28 (C_{ipso}-Me), 143.56 (CH^5 of furan), 147.26 (C^2 of furan), 147.63 (C^{4b}), 152.03 (C^{12a}), 161.23 (COO of chromene), 195.06 (C=O).

(6aR,9S,10S,10aR)-10-(4-Nitrobenzoyl)-5,9,10,10a-tetrahydro-6*H*,11*H*-6a,9-epoxychromeno[4,3-*c*]isoquinolin-11-one (5g) Yellow powder, mp = 209–210 °C, 0.348 g, yield: 84%. IR (KBr) (ν_{max}, cm^{-1}): 3350 (NH), 1664 (C=O), 1608 (C=C), 1534 and 1350 (NO_2), 1213 (C–O of lactone), 1046 (C–O of ether). Anal. Calcd for $C_{23}H_{16}N_2O_6$ (416.38): C, 66.34; H, 3.87; N, 6.73%. Found: C, 66.35; H, 3.85; N, 6.74%. MS (EI, 70 eV): *m/z* (%) = 416 (M^+, 5), 318 (15), 267 (10), 266 (52), 251 (33), 248 (11), 150 (10), 81 (100), 53 (4). ^{1}H NMR (500 MHz, DMSO-d_6): δ_H 2.96 (1H, d, $^3J_{HH}$ = 3.6 Hz, CH^{10a}), 3.83 (1H, dd, $^3J_{HH}$ = 14.0 Hz, $^3J_{HH}$ = 3.7 Hz, CH_2^6), 3.86 (1H, d, $^3J_{HH}$ = 4.1 Hz, CH^{10}), 3.94 (1H, d, $^3J_{HH}$ = 14.0 Hz, CH_2^6), 4.04 (2H, s, CH_2NH_3), 5.26 (1H, d, $^3J_{HH}$ = 4.6 Hz, CH^9), 6.18 (1H, d, $^3J_{HH}$ = 5.7 Hz, CH^8), 6.48 (1H, d, $^3J_{HH}$ = 5.8 Hz, CH^7), 6.55 (1H, s, CH^4 of furan), 6.56 (1H, s, CH^3 of furan), 7.26 (1H, d, $^3J_{HH}$ = 8.2 Hz CH^1), 7.32 (1H, d, $^3J_{HH}$ = 7.6 Hz CH^3), 7.54 (1H, d, $^3J_{HH}$ = 7.7 Hz CH^2), 7.72 (1H, s, CH^5 of furan), 8.05 (1H, d, $^3J_{HH}$ = 7.9 Hz, CH^4), 8.12 (1H, s, NH), 8.19 (2H, d, $^3J_{HH}$ = 8.3 Hz, 2CH of Ar), 8.29 (2H, d, $^3J_{HH}$ = 8.3 Hz, 2CH of Ar), 8.50 (3H, s, NH_3). ^{13}C NMR (125 MHz, DMSO-d_6): δ_C 35.44 (CH^{10a}), 38.96 (CH^{10}), 41.26 (CH_2NH_3), 58.02 (CH_2^6), 80.37 (CH^9), 85.66 (C^{6a}), 95.06 (C^{10b}), 110.63 (CH^4 of furan), 111.33 (CH^3 of furan), 114.61 (C^{4a}), 117.15 (CH^1), 122.89 (CH^3), 123.89 (CH^4), 124.27 (2CH of Ar), 130.08 (2CH of Ar), 131.74 (CH^2), 133.83 (CH^7), 137.27 (CH^8), 142.06 (C_{ipso}-C=O), 143.97 (CH^5 of furan), 147.78 (C^{4b}), 148.23 (C^2 of furan), 150.25 (C_{ipso}-NO_2), 152.45 (C^{12a}), 161.84 (COO of chromene), 195.85 (C=O).

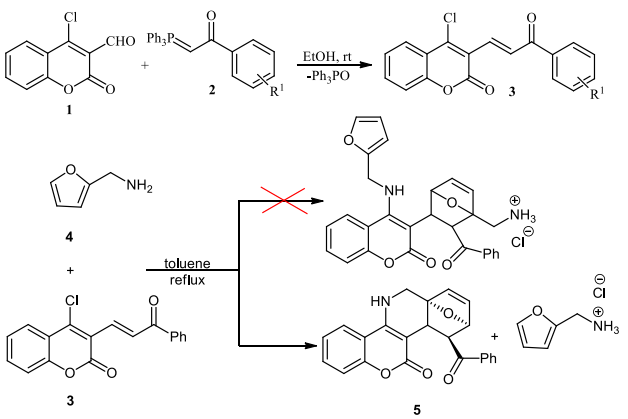
Results and discussion

After preparation of starting materials, we interested in the reaction of furfurylamine **3**, Wittig reagent **2**, and 4-chloro-2-oxo-2*H*-chromene-3-carbaldehyde **1**, so at the beginning, we reacted 3-formylcoumarin **1** with Wittig reagent **2** in EtOH and the product **3** was isolated. Then, this product **3** was reacted with furfurylamine **4** in toluene and the product **5** was isolated and characterized using IR, mass spectroscopy, ^{1}H NMR, ^{13}C NMR, and single-crystal X-ray analysis.

When the reaction was performed, we realized that two equivalents of furfurylamine consumed in the reaction. Analysis of mass spectroscopy, ^{1}H NMR, and ^{13}C NMR confirmed this suggestion, so we assumed a proposed structure, but when the single-crystal analysis was done, we found that one equivalent of furfurylamine appeared in the final product and another equivalent of that emerged as the salt of furfurylamine in NMR spectra (Scheme 2).

After confirmation of the structure by X-ray analysis, we decided to perform the reaction in one-pot condition. Many solvents were employed for this goal, and the mixture of DCM and toluene affords the best result (Table 1).

In the first step, Wittig reagent and 3-formylcoumarin reacted in room temperature, and then, furfurylamine was added to reaction pot following by the addition of toluene as co-solvent and the reaction heated up to 80 °C. With optimized conditions in hand, the scope of reaction investigated with different starting acetophenones and the results are shown in Table 2. An exploration in the ^{1}H NMR and ^{13}C NMR showed that only one diastereomer formed during the



Scheme 2 Proposed structure of the reaction products

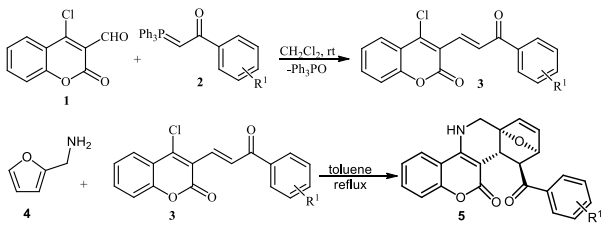
Table 1 Optimization of solvents for one-pot condition

Entry	Solvent	Temperature (°C)	Yield (%)[a]
1	EtOH	80	45
2	CH_3CN	80	55
3	THF	70	30
4	MeOH	70	25
5	CH_2Cl_2	25	45
6	DCM/toluene	80	82
7	Toluene	80	20
8	Toluene	100	35

All runs were performed on a 1-mmol scale (**1**: 1 mmol, **2a**: 1 mmol, **3**: 1 mmol), and the reaction was run at reflux temperature

[a]Isolated yield

Table 2 Two-step and one-pot synthetic pathway to epoxychromeno[4,3-*c*]isoquinolines **5**



Entry	R^1	Product **5**	Yield (%)[a]
1	H	**5a**	82
2	4-Br	**5b**	78
3	2-Cl	**5c**	74
4	4-Cl	**5d**	71
5	4-MeO	**5e**	69
6	4-Me	**5f**	84
7	4-NO_2	**5g**	69

All runs were performed on a 1-mmol scale (**1**, 1 mmol; **2**, 1 mmol; **4**, 1 mmol), and the reaction was run at two steps in one pot; in first step, **1** and **2** was mixed in DCM and and the reaction mixture was stirred at room temperature for about a day; in the second step, furfurylamine (2 mmol, 194 mg) was added to flask following by addition of 10 ml toluene as a co-solvent and the mixture was refluxed for 4–5 h

[a]Isolated yield

reaction. With the optimal condition in hand, we started to develop the scope of the reaction.

All the characteristic data of all products were gathered. The molecular ion peak of **5a** appeared at 371 *m/z* value in mass spectroscopy, which confirmed the proposed structure. The IR spectrum showed a band at 3340 cm^{-1} which is related to NH absorption bands. The carbonyl absorption

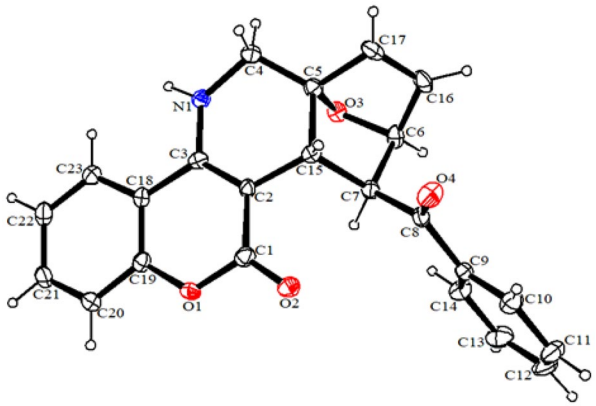
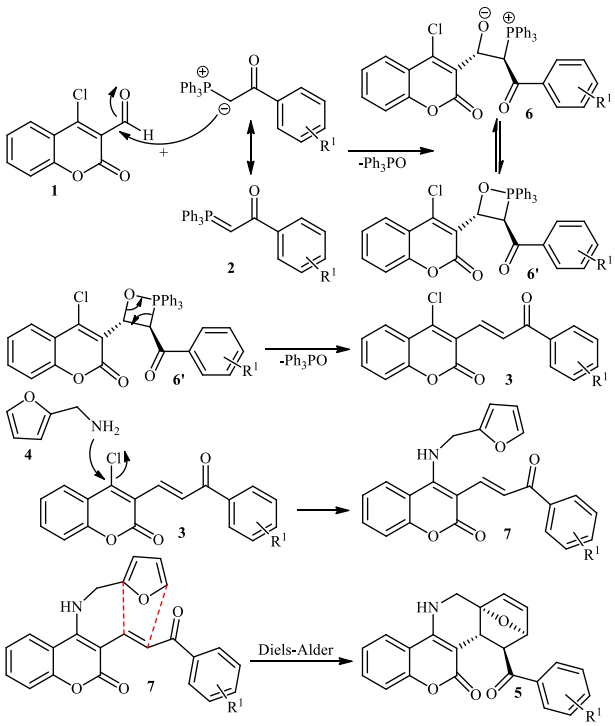


Fig. 1 ORTEP diagram of compound **5a**



Scheme 3 A plausible mechanism for the formation of **5**

band also appeared at 1653 cm^{-1}. The ^1H NMR and ^{13}C NMR spectra confirmed the proposed mechanism, but the furfurylamine salt is also seen in the spectrum (See ESI). The final validation of the structure came from X-ray analysis (Fig. 1).

Based on afforded product, a proposed mechanism for this transformation is shown in Scheme 3.

Apparently, the addition of Wittig reagent **2** to 4-chloro-3-formylcoumarin **1** affords Wittig coumarin **3**. In the following, the nucleophilic addition of furfurylamine **4** to this coumarin leads to intermediate **7**. This intermediate

performs an intramolecular Diels–Alder reaction to afford the final epoxychromeno[4,3-*c*]isoquinoline **5**.

Conclusions

Briefly, we developed a one-pot diastereoselective strategy to obtain a valuable new class of bicyclic-fused coumarins from the available starting materials. The key reaction in this strategy is an intramolecular Diels–Alder reaction. Good-to-high yields, stereoselectivity, metal-free and one-pot condition are some of the advantages of this reaction.

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