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# Unexpected one-pot synthesis of new polycyclic coumarin[4,3-*c*]pyridine derivatives via a tandem hetero-Diels–Alder and 1,3-dipolar cycloaddition reaction

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ABSTRACT

*O*-Methyl-4-coumarincarbaldehyde oxime reacted as an azadiene with electron-deficient and electron-rich dienophiles to give, via one-step hetero-Diels–Alder cycloaddition reactions, the corresponding 5*H*-coumarin[4,3-*c*]pyridin-5-ones. When excess of the dienophile was used, fused azatetracyclo derivatives were also formed via a tandem Diels–Alder and 1,3-dipolar cycloaddition reaction of the dienophile to an azomethine ylide formed by the intermediate 2,3-dihydro-5*H*-coumarin[4,3-*c*]pyridine-5-one. The regio- and stereoselectivities of the new compounds correspond well with spectroscopic (2D NMR) and theoretical data. A possible mechanistic scheme is provided.



Coumarins represent a class of naturally and synthetically obtained compounds that possess a wide variety of biological activities,[1,2] often depending on the substituent they bear on their main benzopyran skeleton. Introduction of an oxy-imino type linkage at the allylic position with respect to the biogenetic C3=C4 double bond in the form of oximes, amidoximes, oxadiazoles, isoxazolines, etc. has resulted in compounds with promising antiproteolytic, antioxidant, and antiinflammatory properties.[3] Fused 3,4-heterocyclic coumarin derivatives[2,4] also exhibit a wide range of biological activities. Specifically, those bearing a benzopyranone–pyridine or piperidine skeleton (Fig. 1) were found to interact with DNA,[5] to transfer energy in photophysical processes,[6] to be potential platelet activating factor antagonists,[7] depressant or hypotensive activators[8] and potent antipsychotic agents,[9] whereas others exhibited antibacterial,[10] antitumor,[11] anticholinergic,[12] and antimicrobial[13] activities. Finally, some naturally occurring fused heterocyclic chromone alkaloids, such as shumanniophytine and isoshumanniophytine, were found to possess antiviral activity.[14]

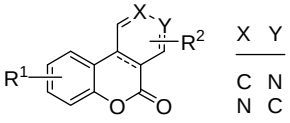


**Figure 1.** Coumarin[3,4-*c*] or [4,3-*c*]pyridine derivatives.

The preparation of polyheterocyclic nitrogen-containing compounds, which are found in nature or of synthetic origin, via hetero-Diels–Alder (HDA) reactions is well documented in the literature.[15–17]

1-Azadienes have been reported to undergo HDA reactions, but with poor conversions of the starting materials.[16] Introduction of a nitrogen atom at position 1 of the diene creates a π electron-deficient system, and thus lowering its reactivity in the normal $HOMO_{diene}$-controlled [4+2] HDA cycloaddition reactions with electron-poor dienophiles. Electronic effects on both the diene and the dienophile seem to affect the formation of the cycloadduct, whereas catalysis or variation in the reaction conditions has been shown to improve the reaction efficiency to only a limited extent.[16]

Our interest in coumarins as pharmacophores and synthetic intermediates[2,3,18] prompted us to investigate the synthesis of coumarin[4,3-*c*]pyridine derivatives in an effort to provide a convenient and convergent approach for their preparation. Until

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now, the synthesis of these compounds[19] had been realized via procedures, often multistep, utilizing as precursors, substituted four-membered 2-aryl-cyclic nitrones,[20] *o*-cyanocarbonyl-coumarin derivatives,[21] and suitably substituted oxopiperidinecarboxylates,[8] aryl-4-picolines,[22] quinolinones,[23] and quinolines.[24] To the best of our knowledge, the application of HDA reactions on the coumarin nucleus is limited.[25] The expected coumarin derivatives, besides their presumable biological activity, are anticipated to be useful as synthons for the construction of other heterocyclic scaffolds, due to the fertile chemistry of the lactone ring,[23,24] and the variation of the substituents on both the coumarin and pyridine rings.

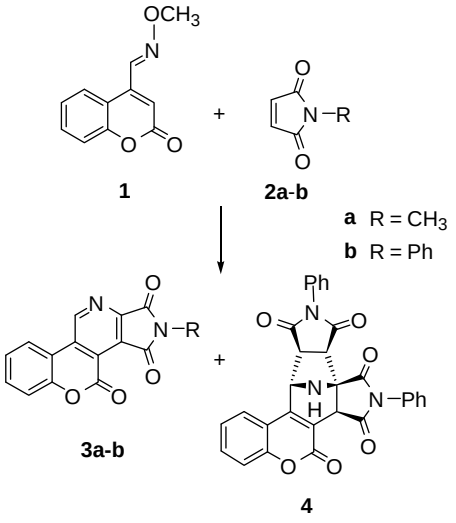
Treatment of *O*-methyl-4-coumarincarbaldehyde oxime[3c] (**1**) with equimolar amounts of the electron-deficient *N*-methyl- or *N*-phenylmaleimides **2a**–**b** in refluxing xylene for 24 h afforded coumarin[4,3-*c*]pyridines **3a** (46%) and **3b** (38%), respectively (Scheme 1). When the reaction of **1** was performed in the presence of 3 equiv of maleimide **2b** in refluxing xylene for 24 h, the unexpected bis-cycloadduct **4** (24%) was formed along with **3b** (50%).

MS spectrometry and extensive 2D NMR studies allowed us to assign structure **4**.

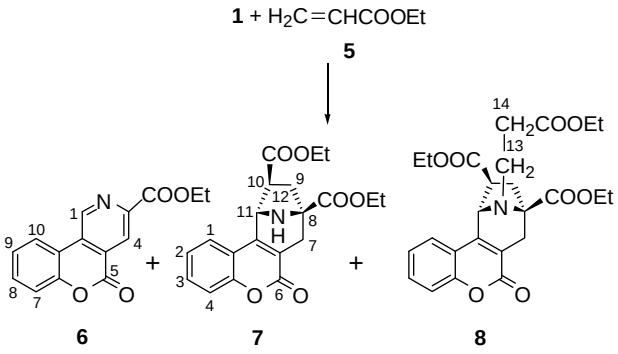
The reaction of **1** with ethyl acrylate, used in excess as solvent (**5**, bp 99 °C), at reflux for 6 days, resulted after separation, in a complex mixture of the 3-ethoxycarbonyl-coumarin[4,3-*c*]pyridine (**6**, 35%), the bis-cycloadduct **7** (24%) analogous to **4**, and another unexpected product[26] **8** (9%), formed after Michael addition of **7** to another molecule of ethyl acrylate. Some starting material was also recovered (15%). Extensive 2D NMR studies allowed us to assign structures **7** and **8** (Scheme 2).

Next, we tested the reactivity of diene **1** with electron-rich dienophiles. Therefore, **1** was treated with butyl vinyl ether (**9**, bp 94 °C), used in excess as a solvent, under reflux for 8 days to afford the known[22] coumarin[4,3-*c*]pyridine (**10**) in 36% yield, while a significant amount of the starting material (59%) remained unchanged (Scheme 3).

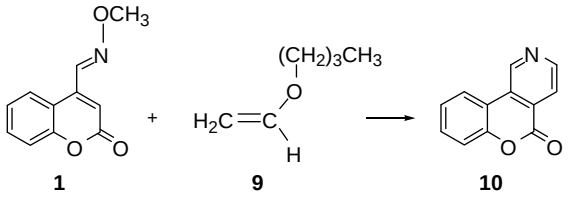
A combination of the mechanistic pathways depicted in Scheme 4 is used to explain the experimental results. Elimination of methanol from the initially formed cycloadduct **12** yields the unstable intermediate **13**. The latter is able to undergo air oxidation (path a) to give the fully aromatized derivative **14**. However, it is known that thermally induced 1,2-prototropic rearrangement of α-amino acid imines leads to the formation of azomethine ylides.[27]



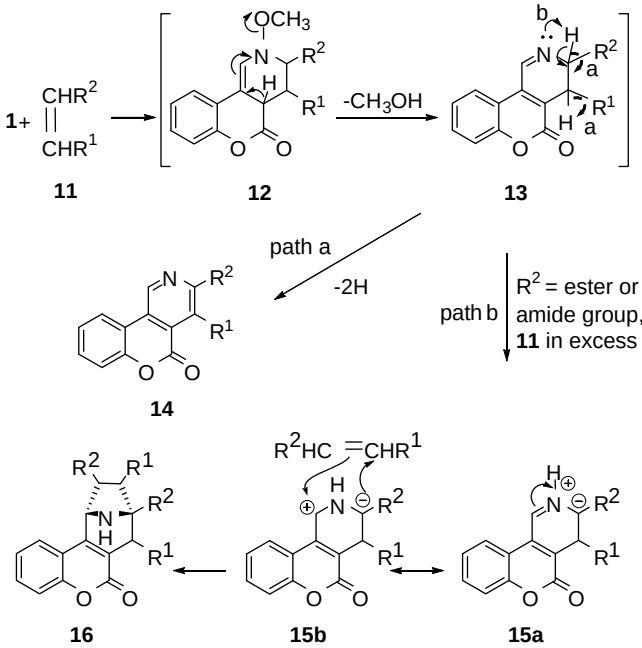

**Scheme 1.** HDA reactions of **1** with maleimides **2a**–**b**.




**Scheme 2.** HDA reaction of **1** with ethyl acrylate in excess as solvent.



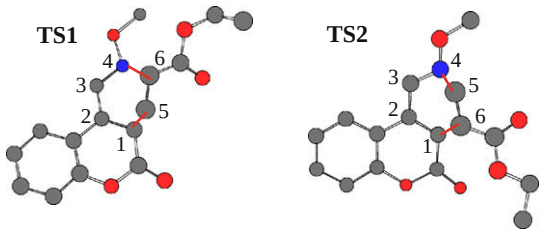

**Scheme 3.** HDA reaction of **1** with butyl vinyl ether in excess as solvent.




**Scheme 4.** Proposed mechanistic pathways.

Analogously, when $R^2$ is an ester or amide group, intermediate **13** most probably gives in our case ylide **15** (path b), which in the presence of excess dienophile undergoes a subsequent 1,3-dipolar cycloaddition reaction to afford the tetracyclic derivative **16**.

The regioselectivities of the HDA and 1,3-dipolar cycloaddition reactions were confirmed by NMR analysis of the products. Regarding the HDA reaction, a theoretical study involving calculations of both $HOMO_{diene}$ and $LUMO_{dienophile}$ energies (AM1)[28,29] led to the same preferred structures for the intermediate **12** being fully in accordance with the experimental results. In Figure 2, the




| Favored TS[a] | Not Favored TS[b] |
|---|---|
| C1–C2 = 1.425[c] | C1–C2 = 1.371 |
| C2–C3 = 1.426 | C2–C3 = 1.438 |
| C3–N4 = 1.332 | C3–N4 = 1.341 |
| C5–C6 = 1.405 | C5–C6 = 1.406 |
| C1–C5 = 1.738 | C1–C6 = 2.512 |
| N4–C6 = 2.577 | N4–C5 = 1.618 |
| $\Delta G^{\#}_{TS}$ = 36.81[d] | $\Delta G^{\#}_{TS}$ = 41.87 |
| $\tilde{\nu}$ = –591[e] | $\tilde{\nu}$ = –517 |

$\Delta\Delta G^{\#}_{TS}$ = 5.06 kcal/mol[f]

**Figure 2.** Transition structures optimized at the AM1 level for the interaction of **1** with acrylate **5**. (a) **TS1**: Favored approach of reactants leading to product **6**. (b) **TS2**: Approach of reactants not leading to products. (c) Bond lengths in Angstroms (Å). (d) $\Delta G^{\#}_{TS}$ for the transition state in kcal/mol. (e) The imaginary IR frequency for the newly formed bond. (f) The energy preference of **TS1** versus **TS2**. The numbering of atoms is arbitrary; only the reacting atoms are indicated.

transition structures **TS1** and **TS2** optimized at AM1 level for the interaction of **1** with acrylate **5** are depicted. The bond lengths involved in the new cyclohexene ring and the free energy of activation $\Delta G^{\#}$ of the activated complex along with the vibrating frequency of the shorter newly formed bond at 372 K are given. From both methods, the methylene carbon is predicted to react first with the diene moiety, since the newly formed bonds (in red color) of the methylene carbon are shorter in both **TS1** and **TS2**. On the other hand, the regioselectivity of azomethine imines in 1,3-dipolar cycloaddition reactions with monosubstituted dipolarophiles, as in the case of **5**, is general well predicted[30] and again in agreement with the obtained results.

In conclusion, we have demonstrated a one-step method for the construction of complex coumarin[4,3-*c*]pyridine or piperidin-5-one polycyclic derivatives in a complete regio- and stereoselective manner, in moderate overall yields. The direct formation of bis-cycloadducts **4**, **7,** and **8** via a unique and novel HDA/1,3-dipolar cycloaddition pathway opens a new approach toward the facile one-pot synthesis of complicated heterocyclic scaffolds. Exploitation of these results and further optimization regarding the reaction conditions will be our next goal.

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26. A solution of oxime ether **1** (0.250 g, 1.23 mmol) in ethyl acrylate (5 mL) was heated at reflux (100 °C) for 6 days. The reaction mixture was concentrated on a rotary evaporator, and the residue was purified by chromatography on silica gel (hexane/EtOAc, 4:1 up to 3:1) to afford in order of elution: unreacted oxime **1** (0.038 g, 15%). Compound **8** (0.045 g, 9%); mp 109–110 °C (ethanol–ether). IR (Nujol) $\nu_{max}$ 1742, 1730, 1720, 1605 $cm^{-1}$. $^1H$ NMR ($CDCl_3$, 300 MHz): 1.21 (t, $J$ = 7.2 Hz, 3H, 14-$CH_2CH_3$), 1.33 (t, $J$ = 7.2 Hz, 3H, 10-$CH_2CH_3$), 1.37 (t, $J$ = 7.2 Hz, 3H, 8-$CH_2CH_3$), 2.11 (dt, $J$ = 11.0, 4.2 Hz, 1H, 9-$H_a$), 2.53 (dd, $J$ = 7.1, 2.2 Hz, 2H, 14-H), 2.60 (m, 1H, 13-H), 2.69 (d, $J$ = 19.2 Hz, 1H, 7-$H_a$), 2.94 (dt, $J$ = 11.0, 2.7 Hz, 1H, 9-$H_b$), 2.96 (dd, $J$ = 4.2, 2.7 Hz, 1H, 10-H), 3.00 (m, 1H, 13-H), 3.03 (dd, $J$ = 19.2, 1.5 Hz, 1H, 7-$H_b$), 4.053/4.066 (q, $J$ = 7.2 Hz, 2H, 14-$OCH_2$), 4.269/4.272 (q, $J$ = 7.2 Hz, 2H, 10-$OCH_2$), 4.279/4.290 (q, $J$ = 7.2 Hz, 2H, 8-$OCH_2$), 5.05 (s, 1H, 11-H), 7.37 (ddd, $J$ = 8.1, 7.2, 1.2 Hz, 1H, 2-H), 7.39 (dd, $J$ = 8.5, 1.2 Hz, 1H, 4-H), 7.56 (ddd, $J$ = 8.5, 7.2, 1.4 Hz, 1H, 3-H), 7.72 (dd, $J$ = 8.1, 1.4 Hz, 1H, 1-H). $^{13}C$ NMR ($CDCl_3$, 75 MHz) $\delta$ 14.06 (14-$OCH_2CH_3$), 14.10 (10-$OCH_2CH_3$), 14.2 (8-$OCH_2CH_3$), 28.5 (C-7), 34.5 (C-14), 38.2 (C-9), 40.9 (C-13), 49.5 (C-10), 59.1 (C-11), 60.4 (14-$OCH_2$), 61.2 (10-$OCH_2$), 61.5 (8-$OCH_2$), 65.3 (C-8), 117.3 (C-4), 117.7 (C-11b), 119.2 (C-6a), 122.7 (C-1), 124.6 (C-2), 131.4 (C-3), 147.4 (C-11a), 152.7 (C-4a), 160.5 (C-6), 171.6 (10-CO), 172.02 (14-CO), 172.09 (8-CO). MS (ESI) 472 $[M+H]^+$, 494 $[M+Na]^+$. HRMS calcd for $C_{25}H_{29}LiNO_8$ $[M+Li]^+$: 478.2048, found: 478.1997.
Compound **6** (0.099 g, 35%); mp 236–237 °C (hexane–EtOAc). IR (Nujol) $\nu_{max}$ 1730, 1710, 1610 $cm^{-1}$. $^1H$ NMR ($CDCl_3$, 300 MHz) $\delta$ 1.49 (t, $J$ = 7.3 Hz, 3H, 3-$OCH_2CH_3$), 4.55 (q, $J$ = 7.3 Hz, 2H, 3-$OCH_2$), 7.43–7.49 (m, 2H, 7-H, 9-H), 7.64 (dd, $J$ = 7.8, 7.3 Hz, 1H, 8-H), 8.25 (d, $J$ = 7.5 Hz, 1H, 10-H), 8.95 (s, 1H, H-4),

9.66 (s, 1H, 1-H). $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ 14.3 ($CH_3$), 62.4 ($CH_2$), 115.1 (C-10a), 118.3 (C-7), 123.2 (C-10), 124.2 (C-9), 125.5 (C-4), 127.6 (C-4a), 131.3 (C-10b), 132.6 (C-8), 145.7 (C-1), 147.9 (C-3), 152.3 (C-6a), 163.9 (C-5), 168.1 (3-C=O). MS (ESI) 270 $(M+H)^+$. Anal. Calcd for $C_{15}H_{11}NO_4$: C, 66.91; H, 4.12; N, 5.20. Found: C, 66.75; H, 4.10; N, 5.09.

Compound **7** (0.092 g, 24%); mp 151–153 °C (hexane–EtOAc). IR (Nujol) $\nu_{max}$ 3400, 1735, 1715, 1605 $cm^{-1}$. $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 1.347 (t, $J$ = 7.1 Hz, 3H, $CH_3$), 1.349 (t, $J$ = 7.2 Hz, 3H, $CH_3$), 2.26 (dd, $J$ = 13.7, 9.0 Hz, 1H, 9-$H_a$), 2.53 (ddd, $J$ = 13.7, 3.1, 1.7 Hz, 1H, 9-$H_b$), 2.89 (d, $J$ = 18.4 Hz, 1H, 7-$H_a$), 2.99 (br s, 1H, NH), 3.03 (dd, $J$ = 18.4, 1.7 Hz, 1H, 7-$H_b$), 3.19 (dd, $J$ = 9.0, 3.1 Hz, 1H, 10-$H_a$), 4.27 (q, $J$ = 7.1 Hz, 2H, $OCH_2$), 4.32 (dq, $J$ = 7.2, 2.6 Hz, 2H, $OCH_2$), 5.01 (br s, 1H, 11-H), 7.35 (ddd, $J$ = 8.2, 7.0, 1.2 Hz, 1H, 2-H), 7.37 (dd, $J$ = 8.5, 1.2 Hz, 1H, 4-H), 7.55 (ddd, $J$ = 8.5, 7.0, 1.4 Hz, 1H, 3-H), 7.65 (dd, $J$ = 8.2, 1.4 Hz, 1H, 1-H). $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ 14.19 (10-$OCH_2CH_3$), 14.23 (8-$OCH_2CH_3$), 35.8 (C-7), 38.8 (C-9), 52.8 (C-10), 58.1 (C-11), 61.68 (10-$OCH_2$), 61.76 (8-$OCH_2$), 65.2 (C-8), 116.8 (C-11b), 117.4 (C-4), 119.1 (C-6a), 122.7 (C-1), 124.7 (C-2), 131.4 (C-3), 150.0 (C-11a), 153.0 (C-4a), 161.2 (C-6), 172.76 (10-CO), 172.84 (8-CO). MS (ESI) 372 $[M+H]^+$. HRMS calcd for $C_{20}H_{21}LiNO_6$ $[M+Li]^+$: 378.1523, found: 378.1496.


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