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# One-Pot Syntheses of Chromeno[3,4-*c*]pyrrole-3,4-diones via Ugi-4CR and Intramolecular Michael Addition

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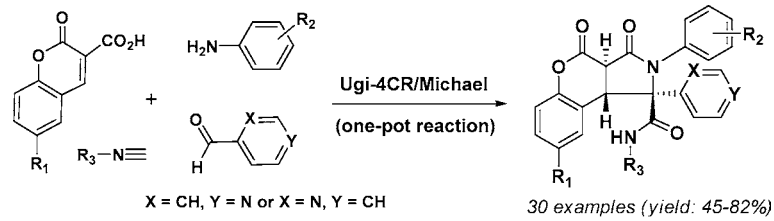
## ABSTRACT




**One-pot and diastereoselective syntheses of diverse chromeno[3,4-*c*]pyrrole-3,4-diones from readily available starting materials were achieved via sequential Ugi-4CR and intramolecular Michael addition.**

Multicomponent reactions (MCRs)[1] can efficiently generate collections of functionally and stereochemically diverse small molecules, which possess skeletons found in natural products.[2] The use of MCRs has therefore been frequently adopted by biomedical research for the development of chemical libraries and the identification of chemical probes.[3]

Coumarins have been reported to possess multiple biological activities[4] and have been widely used to treat various diseases, including cancer, cardiovascular, and rheumatic diseases.[5] Furthermore, pyrrolidin-2-ones and their *N*-substituted derivatives frequently occurred as a substructure in medicines and natural products.[6]

Our laboratories have for years been involved in developing a chemical genetic approach to analyze biological systems by way of interfacing libraries of small molecules

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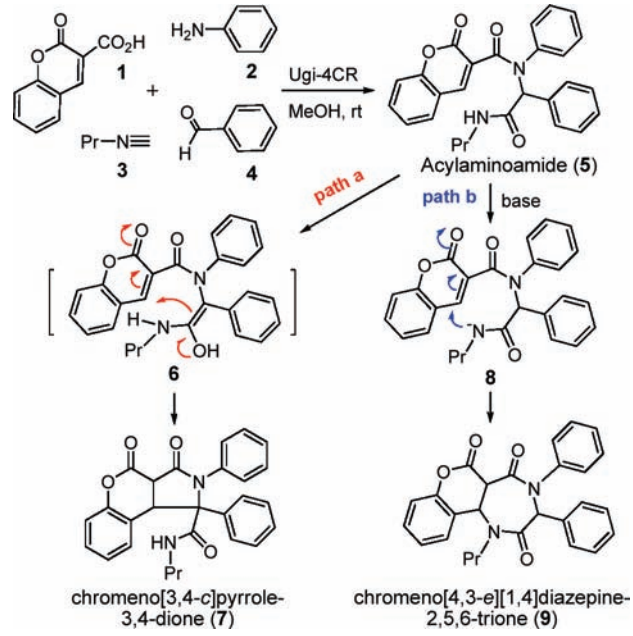
with creative biological assays.[7] As part of this research objective, we became interested in establishing a novel synthetic strategy to construct diverse coumarin-based heterocycles. We believed that the construction of coumarin-fused heterocycles is a meaningful endeavor in organic chemistry because a large number of naturally occurring products that are endowed with a wide array of biological properties have this type of scaffold.[8] Herein we report our recent efforts to develop a novel strategy for diastereoselective and one-pot syntheses of diverse chromeno[3,4-*c*]pyrrole-3,4-diones.

In the design of coumarin-based heterocycles, we envisioned that coumarin-3-carboxylic acid could be utilized as a component in Ugi-4CR and that the formed acyaminoamide **5** containing a pendant α,β-unsaturated double bond in the coumarin unit could offer a straightforward and atom-economical access to chromeno[3,4-*c*]pyrrole-3,4-dione **7** and chromeno[4,3-*e*][1,4]diazepine-2,5,6-trione **9**. These reactions generally require acid and base catalysis and may be viewed as proceeding through an intramolecular 5-*endo*-*trig*[9] (Path a) and 7-*endo*-*trig*[10] (Path b) attack of the nucleophiles onto the Michael acceptors of coumarins.

For the initial study of the proposed tandem reactions, the coumarin-based Ugi-product **5** was prepared by the condensation of substrates **1**−**4** (Scheme 1) in methanol at room temperature, and the expected α-acylaminoamide **5** was indeed obtained in high yield. However, several attempts to cyclize acyaminoamide **5** to its corresponding products **7** and **9** under either basic conditions or acid conditions failed.

**Scheme 1.** Retrosynthetic Analysis




The use of isonicotinaldehyde **10a**, which is another class of electron-deficient pyridine-based aryl aldehyde, was then investigated. **10a** was reacted with three other components, **1**−**3**, to afford an acylaminoamide intermediate, which was continuously stirred at room temperature for 12 h. The annulated product **12a** was obtained in 82% yield as a single diastereoisomer (Scheme 2). Hence it seems that in order to proceed with the annulation, electron-deficient aryl aldehyde is required. We then tested another two commercially available compounds, picolinaldehyde **10b** and nicotinaldehyde **10c** (Scheme 2), to carry out the annulation reaction under similar conditions. Interestingly, only **10b** gave desired annulated product **12b** in 65% yield. For substrate **10c**, only Ugi-4CR product **11c** was formed in 76% yield.

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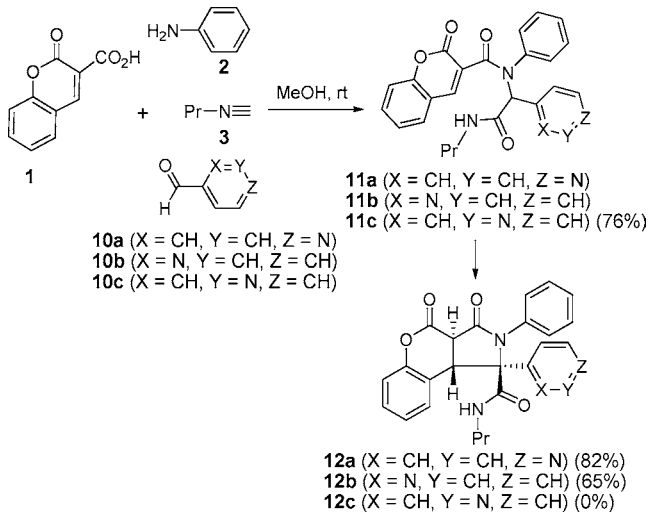
**Scheme 2.** One-Pot Syntheses of Chromeno[3,4-*c*]pyrrole-3,4-diones **12a** and **12b**

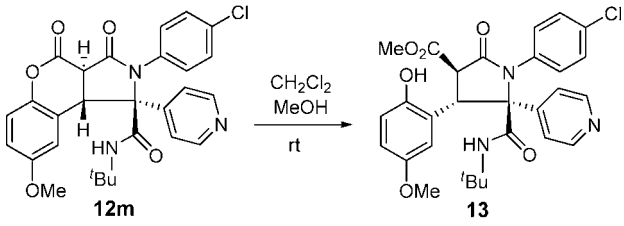


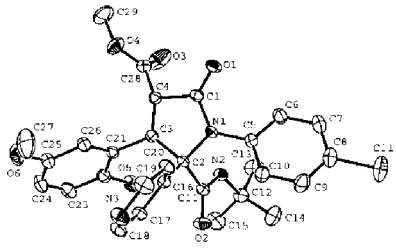

Initially, we attributed this observation to the *ortho*- and *para*-substitutional effect of nitrogen on the aryl aldehyde. We proposed that the intermediates **11a** and **11b**, derived from **10a** and **10b**, had a strong tendency to form their corresponding enolates (such as **5** to **6** in Scheme 1) and, as a result, products **12a** and **12b** could be generated easily.

To validate our rationale, we replaced **10a** and **10b** with 2-nitrophenyl aldehyde and 4-nitrophenyl aldehyde to undertake the same annulation reactions. To our surprise, no desired product was observed under various reaction conditions. These results suggest that our proposed electron-withdrawing effect of aryl aldehyde on the outcome of annulations might not be the sole factor contributing to the observed annulation.

On the basis of this information, we started to profile the reaction scope by using **10a** and **10b** as substrates to perform

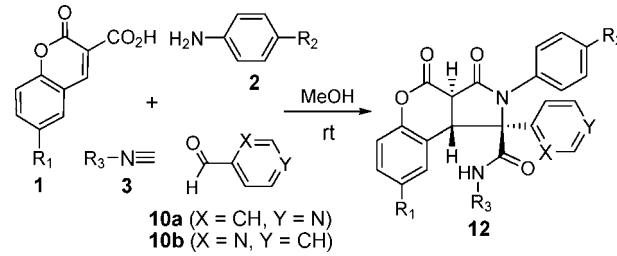
**Scheme 3.** Synthesis of Compound **13**



X-ray structure of compound **13**

**Table 1.** Syntheses of Substituted Chromeno[3,4-*c*]pyrrole-3,4-diones




| entry | $R_1$ | $R_2$ | $R_3$ | aldehyde | product | yield (%) |
|---|---|---|---|---|---|---|
| 1 | Me | H | *n*-Pr | **10a** | **12d** | 71 |
| 2 | OMe | H | *n*-Pr | **10a** | **12e** | 68 |
| 3 | H | OMe | *n*-Pr | **10a** | **12f** | 76 |
| 4 | H | Cl | *n*-Pr | **10a** | **12g** | 77 |
| 5 | OMe | OMe | *n*-Pr | **10a** | **12h** | 66 |
| 6 | Me | Cl | *n*-Pr | **10a** | **12i** | 70 |
| 7 | H | Cl | *t*-Bu | **10a** | **12j** | 67 |
| 8 | Me | Cl | *t*-Bu | **10a** | **12k** | 51 |
| 9 | Me | Me | *t*-Bu | **10a** | **12l** | 55 |
| 10 | OMe | Cl | *t*-Bu | **10a** | **12m** | 65 |
| 11 | OMe | Me | *t*-Bu | **10a** | **12n** | 67 |
| 12 | Cl | H | *t*-Bu | **10a** | **12o** | 68 |
| 13 | Cl | Cl | *t*-Bu | **10a** | **12p** | 72 |
| 14 | Cl | Me | *t*-Bu | **10a** | **12q** | 66 |
| 15 | OMe | H | Cy | **10a** | **12r** | 74 |
| 16 | OMe | Cl | Cy | **10a** | **12s** | 68 |
| 17 | OMe | Me | Cy | **10a** | **12t** | 66 |
| 18 | Cl | Cl | Cy | **10a** | **12u** | 56 |
| 19 | Cl | Me | Cy | **10a** | **12v** | 64 |
| 20 | H | H | *t*-Bu | **10b** | **12w** | 70 |
| 21 | H | Cl | *t*-Bu | **10b** | **12x** | 67 |
| 22 | H | Cl | *n*-Pr | **10b** | **12y** | 50 |
| 23 | H | Me | *t*-Bu | **10b** | **12z** | 45 |
| 24 | H | OMe | *t*-Bu | **10b** | **12aa** | 55 |
| 25 | Cl | H | *t*-Bu | **10b** | **12ab** | 47 |
| 26 | Cl | Cl | *t*-Bu | **10b** | **12ac** | 65 |
| 27 | Cl | Me | *t*-Bu | **10b** | **12ad** | 57 |
| 28 | Cl | OMe | *t*-Bu | **10b** | **12ae** | 62 |

[a] Reagents and conditions for the annulations: acid (0.5 mmol), aldehyde (0.5 mmol), isonitrile (0.55 mmol), and aryl amine (0.5 mmol) in MeOH (5 mL) at room temperature for 12−24 h. [b] Isolated yields.

the one-pot annulation reactions for the synthesis of structurally diverse **12**. Some of the selected examples are listed in Table 1. The structures of the compounds listed in Table 1 were originally assigned on the basis of the $^1$H NMR, $^{13}$C NMR and high resolution MS, and subsequently unambiguously confirmed by the X-ray diffraction analysis of compound **13** (Scheme 3), which was derived from its methanolysis of **12m** during the time of preparing its single crystals.

In conclusion, we have developed a novel and efficient approach to diastereoselectively synthesize chromeno[3,4-*c*]pyrrole-3,4-diones by using a sequential Ugi reaction and intramolecular Micheal addition reaction from simple and commercially available materials. The synthetic protocol embodies a domino process and is accomplished in a one-pot process according to the chemical efficiency paradigm. We anticipate that this method could have interesting implications in the construction of diversified heterocyclic molecules. Moreover, the observed substitutional effect on

the outcome of annulation is worth noting. Further research aimed to address this interesting observation is currently underway in our laboratories, and will be reported in due course.

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**Supporting Information Available:** Experimental procedures and NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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