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Synthesis of novel annulated uracils via domino Knoevenagel-hetero-Diels–Alder reaction in aqueous media

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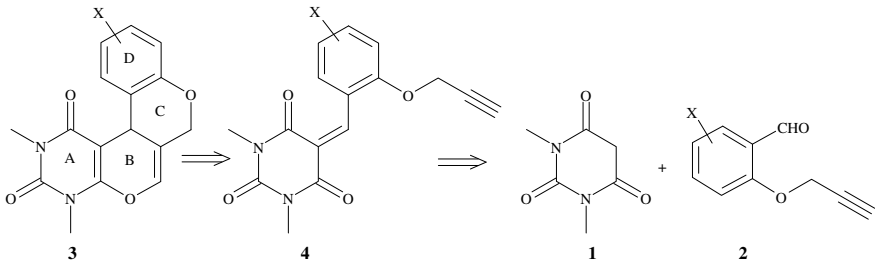
ABSTRACT

An efficient synthesis of tetracyclic uracil derivatives (polycyclic pyrans) is achieved via domino Knoevenagel-hetero-Diels–Alder reactions of O-propargylated salicylaldehyde derivatives with 1,3-dimethylbarbituric acid in water as solvent in the presence of CuI. The products are formed in good yields.

Modern research in organic chemistry requires the synthesis of complex organic molecules and emphasis on methods that provide maximum synthetic efficiency. Combinatorial chemistry has emerged as a powerful synthetic procedure in this area. Domino reactions which result from the combination of multiple transformations in a single pot are highly efficient means for the improvement of reaction efficiency.[1] Among these reactions, the domino Knoevenagel-hetero-Diels–Alder reaction, which was developed widely by Tietze and Rackelman[2] is a very efficient process in organic synthesis, especially in the area of heterocycles and natural products.

For a long time, the use of alkynes in hetero-Diels–Alder reactions was limited, because of the lower reactivity of unactivated alkynes compared to the corresponding alkenes. The use of different Lewis acids[3] provides new opportunities for various catalytic alkyne reactions. The development of copper catalysis for synthetic



Scheme 1. Retrosynthetic analysis.

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Table 1
Effect of catalyst and solvent on the domino Knoevenagel-hetero-Diels–Alder reactions[a] of **1** and **2a**

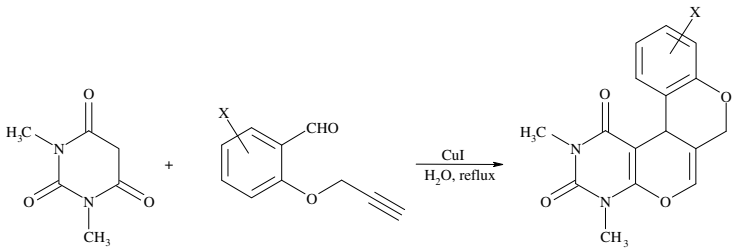
Lewis acid	Solvent	Yield (%)
–	Acetonitrile	–
AgOAc (20%)	Acetonitrile	–
AgOTf (20%)	Acetonitrile	–
$AuCl_3$ (20%)	Acetonitrile	–
CuI (20%)	Acetonitrile	10
CuI (20%)	Water	50
CuI (30%)	Water	67
CuI (40%)	Water	75

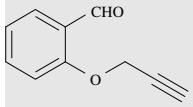
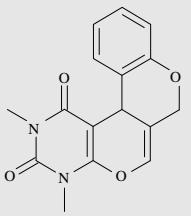
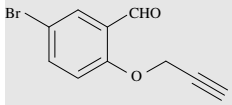
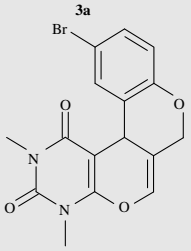
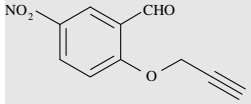
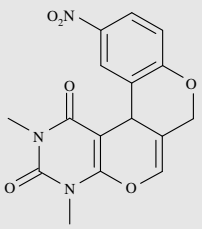
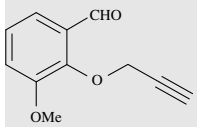
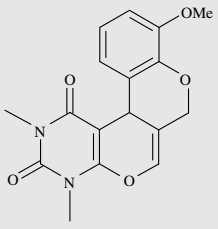
[a] Reaction time was 24 h.

reactions, particularly for alkyne transformations, has gained increasing attention. Copper(I) compounds are powerful catalysts that promote a wide variety of organic transformations such as intramolecular cyclization,[4] halogen exchange,[5] [3+2] cycloaddition,[6] and coupling reactions.[7]

Our goal was to design an efficient method to prepare the tetracyclic systems **3**, which consist of a uracil ring (A) annulated to a dihydropyran ring (B) (Scheme 1). It is highly desirable to develop environmentally benign processes that can be conducted in aqueous media. Furthermore, using water as a solvent has advantages, such as low cost, safety, and it is environmentally friendly.[8] Tetracyclic uracil derivatives have various biological activities. Herein,

Table 2
CuI-catalyzed domino Knoevenagel-hetero-Diels–Alder reaction of **2a–d** and **1**[a]



Aldehyde	Product	Time (h)	Yield[b] (%)
 **2a**	 **3a**	24	75
 **2b**	 **3b**	25	73
 **2c**	 **3c**	6	85
 **2d**	 **3d**	10	80

[a] Reactions were performed with aldehydes **2a–d** (1 mmol), 1,3-dimethylbarbituric acid (1.2 mmol), and CuI (40 mol %) in water (25 ml) under reflux conditions.
[b] Yield of isolated product.

we report the first domino intramolecular Knoevenagel-hetero-Diels–Alder reaction of O-propargylated salicylaldehydes with terminal unactivated acetylenes in the presence of CuI in aqueous media. A retrosynthetic analysis of **3** (Scheme 1) led to alkyne **4**, which is easily accessible via a Knoevenagel reaction of propargylated salicylaldehyde derivatives **2** with 1,3-dimethylbarbituric acid.

The O-propargylated salicylaldehyde derivatives **2a–d** were prepared in high yields and excellent purity from the reaction of substituted salicylaldehydes and propargyl bromide using potassium carbonate in DMF.[9]

Compound **2a** was used as a model system to achieve and optimize the desired domino intramolecular Knoevenagel-hetero-Diels–Alder reaction to give **3a**. Heating **2a** in acetonitrile under reflux conditions for 24 h did not lead to the anticipated product. Thus, the effect of various Lewis acids was studied. Using AgOTf, AgOAc, $AuCl_3$, and CuOTf as catalysts did not give the desired product. When CuI was employed as the catalyst, the desired product **3a** was formed in 10% yield. After investigation of the amount of catalyst and solvent, CuI (40%) and water as solvent gave the best results (Table 1).

Using these optimized conditions, the annulated uracils **3a–d** were synthesized in yields ranging between 73% and 85% (Table 2).

The structures of the products were deduced from their elemental analyses and spectroscopic data.[10] Characteristic signals for uracils **3a–d** in the ^{1}H NMR spectra are an AB quartet for the $-OCH_2$ group between 4.60 and 4.90 ppm and a singlet due to the O–CH= group at 6.65–7.18 ppm. The corresponding signals of the $O-CH_2$ and O–CH= groups in the ^{13}C NMR spectra appear at 65.3–67.6 ppm and 84.5–85.7 ppm, respectively. X-ray crystallography data also confirmed the structure of **3d**[11] (Fig. 1).

The shape of **3d** was confirmed by X-ray crystallography. The angle between the two planes is 60.7° (i.e., the angle between the planes C(8)–N(7)–C(6)–C(5)–C(10)–N(9) and C(3)–C(18)–C(17)–C(16)–C(15)–C(2)).

A possible mechanism for the domino intramolecular Knoevenagel-hetero-Diels–Alder reaction is shown in Scheme 2. The initial step is a Knoevenagel condensation between 1,3-dimethylbarbituric acid and the aldehyde **2a–d**. Next, the triple bond is activated with CuI through formation of a π-complex or a copper acetylide, which reduces the electron density of the alkyne[12] and provides the necessary conditions for the hetero-Diels–Alder reaction.

Copper acetylide is usually formed in the presence of a strong base. The product of the Knoevenagel condensation of **2a** with 1,3-dimethylbarbituric acid could be isolated. The hetero-Diels–Alder reaction of this product was performed under reflux conditions in the presence of CuI (20%) in acetonitrile as solvent without additional base. The desired product **3a** was formed in 45% yield under these conditions, therefore, the formation of a copper acetylide is possible.

In conclusion, we have developed a CuI-catalyzed domino intramolecular Knoevenagel-hetero-Diels–Alder reaction, which provided an efficient route for the formation of tetracyclic uracil derivatives. Further studies to extend the scope and synthetic utility of this Cu-catalyzed domino intramolecular Knoevenagel-hetero-Diels–Alder reaction with inactivated terminal acetylenes are in progress in our laboratory.

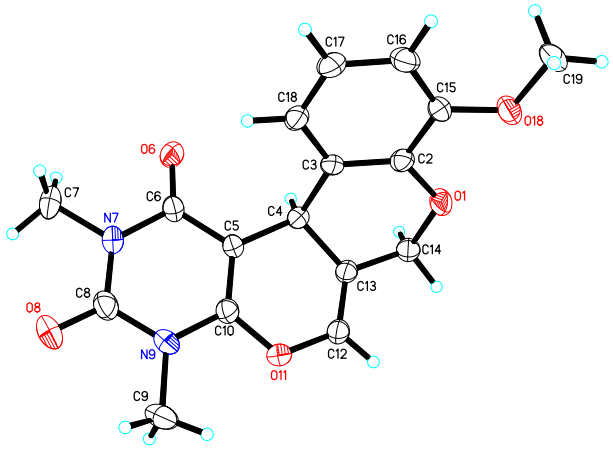
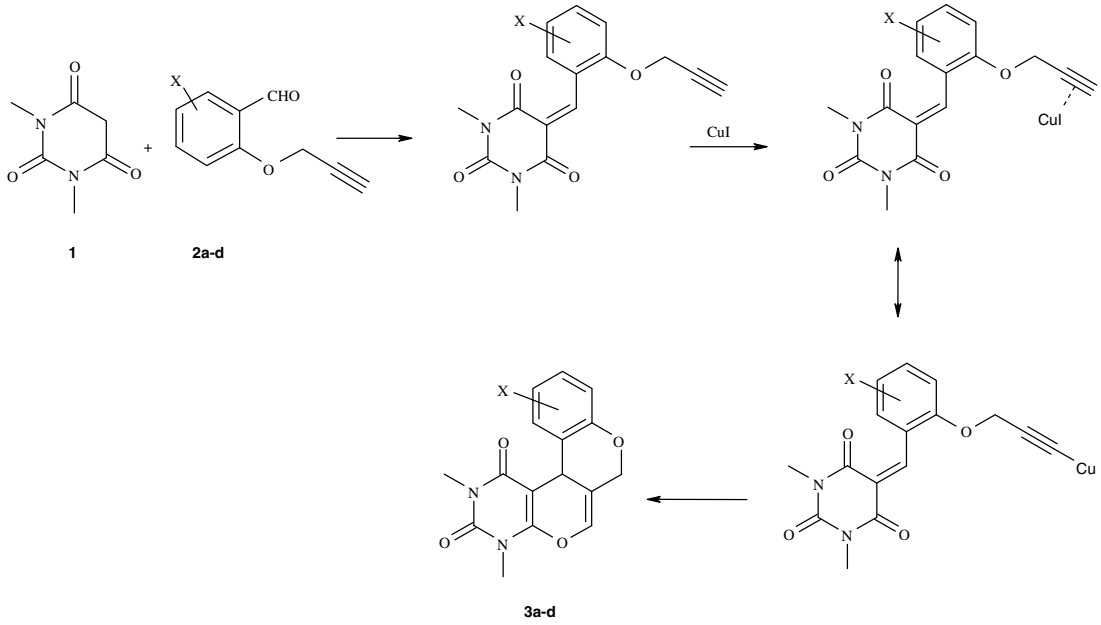


Figure 1. ORTEP representation of the structure of **3d**.



Scheme 2. A plausible mechanism for the formation of tetracyclic annulated uracils **3a–d**.

Acknowledgments

Saeed Balalaie is grateful to the Alexander von Humboldt foundation for a research fellowship and donation of equipment. We are thankful to Prof. Rolf Gleiter for his hospitality and useful discussions. Partial support of this work by the K.N. Toosi University of Technology Research Council is gratefully acknowledged.

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10. *General procedure for the synthesis of tetracyclic uracils*: A solution of O-propargylated salicylaldehyde **2a–d** (1 mmol), 1,3-dimethylbarbituric acid (1.2 mmol, mg), and CuI (0.4 equiv, 76 mg) in water was heated at reflux. The progress of the reaction was monitored by TLC. The resulting precipitated dark yellow solid was filtered and recrystallized from ethyl acetate.
2,4-Dimethyl-4,12b-dihydro-1H,7H-chromeno[4′,3′:4,5]pyrano[2,3-d]pyrimidine-1,3(2H)-dione **(3a)**. mp = 222.5–224 °C; IR (KBr, cm^{-1}) ν = 1704, 1632; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.40 (s, 3H, –NMe), 3.47 (s, 3H, –NMe), 4.63 (d, 1H, J = 11.8 Hz, CH), 4.74 (s, 1H, CH), 4.81 (d, 1H, J = 11.8 Hz, CH), 6.65 (s, 1H, =CH), 6.80 (d, J = 8.1 Hz, 1H, H_{Ar}), 6.87 (t, J = 7.5 Hz, 1H, H_{Ar}), 7.10 (d, J = 7.5 Hz, 1H, H_{Ar}), 7.14 (d, J = 7.5 Hz, 1H, H_{Ar}); ^{13}C NMR (75 MHz, $CDCl_3$) δ 27.7, 28.3, 29.4, 65.8, 85.7, 113, 116, 120, 125.6, 126.1, 127.3, 132.8, 149.7, 152.5, 152.8, 162.6. HR-MS (70 eV, EI) $C_{16}H_{14}N_2O_4$ $[M]^{+\cdot}$ found 298.0926, calcd 298.0953. Elemental Anal. Calcd for ($C_{16}H_{14}N_2O_4$): C 64.42, H: 4.73, N 9.39. Found: C 64.25, H 4.60, N 9.28.
11-Bromo-2,4-dimethyl-4,12b-dihydro-1H,7H-chromeno[4′,3′:4,5]pyrano [2,3-d]-pyrimidine-1,3(2H)-dione (**3b**): mp = 240.5–242 °C; IR (KBr, cm^{-1}): ν = 1709, 1642; ^{1}H NMR(500 MHz, DMSO-d_6) δ 3.26 (s, 3H, –NMe), 3.27 (s, 3H, –NMe), 4.63 (s, 1H, CH), 4.71 (d, J = 11.6 Hz, 1H, –CH), 4.84 (d, J = 11.6 Hz, 1H, –CH), 6.72 (d, J = 8.5 Hz, 1H, H_{Ar}), 7.12 (s, 2 H, H_{Ar} and =CH), 7.25 (d, J = 8.5 Hz, 1H, H_{Ar}); ^{13}C NMR (75 MHz, $CDCl_3$) δ 29.0, 29.8, 30.4, 67.1, 85.7, 112.3, 112.8, 119.7, 130.1, 130.4, 131.4, 136.0, 150.9, 153.6, 154.7, 163.9; HR-MS (70 eV, EI): $C_{16}H_{13}N_2O_4{}^{79}Br$: $[M]^{+\cdot}$ found 376.0064, calcd 376.0059; $C_{16}H_{13}N_2O_4{}^{81}Br$ $[M+2]^{+\cdot}$ found 378.0030, Calcd 378.0039. Elemental Anal. Calcd for ($C_{16}H_{13}N_2O_4Br$): C, 50.95; H, 3.47; N, 7.43. Found: C, 50.75; H, 3.38; N, 7.18.
2,4-Dimethyl-11-nitro-4,12b-dihydro-1H,7H-chromeno[4′,3′:4,5]pyrano[2,3-d]pyrimidine-1,3(2H)-dione **(3c):** mp = 254–255 °C, IR (KBr, cm^{-1}): ν = 1704, 1638, 1521, 1340; ^{1}H NMR(300 MHz, DMSO-d_6) δ 3.27 (s, 3H, –NMe), 3.30 (s, 3H, –NMe), 4.77 (s, 1H, –CH), 4.86 (d, J = 11.6 Hz, 1H, OCH), 4.98 (d, J = 11.6 Hz, 1H, OCH), 6.95 (d, J = 9.0 Hz, 1H, H_{Ar}), 7.18 (s, 1H, =CH), 7.97 (br s, 1H, H_{Ar}), 8.0 (d, J = 8.0 Hz, 1H, H_{Ar}); ^{13}C NMR (75 MHz, DMSO-d_6) δ 28.6, 29.5, 30.0, 67.6, 85.2, 111.0, 118.1, 124, 124.5, 128.0, 136.4, 140.8, 150.5, 154.4, 159.8, 163; HR-MS (70 eV, EI): $C_{16}H_{13}N_3O_6$ $[M]^{+\cdot}$ found 343.0805, calcd 343.0804. Elemental Anal. Calcd for ($C_{16}H_{13}N_3O_6$): C, 55.98; H, 3.79; N, 12.24. Found: C, 55.75; H, 3.69; N, 12.08.
2,4-Dimethyl-9-methoxy-4,12b-dihydro-1H,7H-chromeno[4′,3′:4,5]pyrano[2,3-d] pyrimidine-1,3(2H)-dione **(3d).** mp = 228.5–229.5 °C; IR (KBr, cm^{-1}): ν = 1707, 1639; ^{1}H NMR (500 MHz, DMSO-d_6) δ 3.25 (s, 3H, –NMe), 3.29 (s, 3H, –NMe), 3.70 (s, 3H, –OMe), 4.55 (s, 1H, –CH), 4.69 (d, J = 11.7 Hz, 1H, OCH), 4.81 (d, 1H, J = 11.7 Hz, 1H, OCH), 6.54 (d, J = 7.9 Hz, 1H, H_{Ar}), 6.70 (t, J = 7.9 Hz, 1H, H_{Ar}), 6.79 (d, J = 7.9 Hz, 1H, H_{Ar}), 7.0 (s, 1 H, =CH); ^{13}C NMR (125 MHz, DMSO-d_6) δ 27.3, 28.1, 28.7, 54.9, 65.3, 84.5, 110.0, 112.4, 117.4, 118.9, 127.4, 133.4, 141.9, 147.4, 149.3, 152.8, 162.0; HR-MS (70 eV, EI): $C_{17}H_{16}N_2O_5$ $[M]^{+\cdot}$ found 328.1057, calcd 328.1059. Elemental Anal. Calcd for ($C_{17}H_{16}N_2O_5$): C, 62.23; H, 4.90; N, 8.57. Found: C, 62.10; H, 4.86; N, 8.48.
11. $C_{17}H_{16}N_2O_5$, colorless crystal (polyhedron), dimensions $0.23 \times 0.22 \times 0.15$ mm^3, crystal system monoclinic, space group $P2_1/n$, Z = 4, a = 4.1440(1) Å, b = 23.7340(1) Å, c = 14.9220(1) Å, α = 90°, β = 93.8200(10)°, γ = 90°, V = 1464.37(4) $Å^3$, ρ = 1.489 g/cm^3, T = 200(2) K, θ_{max} = 24.11°, radiation Mo Kα, λ = 0.71073 Å, 0.3° ω-scans with CCD area detector, covering a whole sphere in reciprocal space, 3471 unique reflections (R(int) = 0.0725), 2618 observed ($I > 2\sigma(I)$), intensities were corrected for Lorentz and polarization effects, empirical absorption correction was applied using SADABS based on the Laue symmetry of the reciprocal space, μ = 0.11 mm^{-1}, T_{min} = 0.97, T_{max} = 0.98, structure solved by direct methods and refined against F^2 with a Full-matrix least-squares algorithm using the SHELXTL-PLUS (6.10) software package, 221 parameters refined, hydrogen atoms were treated using appropriate riding models, goodness of fit 1.08 for observed reflections, final residual values $R_1(F)$ = 0.057, $wR(F^2)$ = 0.129 for observed reflections, residual electron density −0.30 to 0.27 e$Å^{-3}$. CCDC 687800 contains supplementary crystallographic data for this Letter. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
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