

One-Pot Syntheses of Isoquinolin-3-ones and Benzo-1,4-diazepin-2,5-diones Utilizing Ugi-4CR Post-Transformation Strategy[†]

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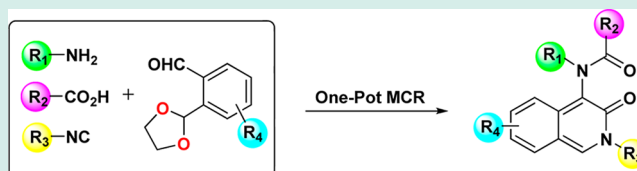
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Supporting Information

ABSTRACT: One-pot and efficient syntheses of structurally diverse isoquinolin-3-ones and isoquinolin-3-one-based benzo-1,4-diazepin-2,5-diones have been developed. The notable features of the process include the Ugi condensation of monomasked phthalaldehydes with amines, carboxylic acids, and isonitriles, followed by HClO₄-mediated intramolecular condensation of the carbonyl with amide.

KEYWORDS: isoquinolin-3-ones, benzo-1,4-diazepin-2,5-diones, multicomponent reaction, Ugi-4CR, one-pot synthesis, diversity-oriented synthesis



INTRODUCTION

Multicomponent reactions (MCRs)¹ serve as a powerful tool for the rapid and efficient assembly of complex structures from simple starting materials and with minimized production of wastes. These highly step-economic reactions are appealing in both combinatorial and diversity-oriented synthesis, and are particularly useful for the construction of diverse chemical libraries of “drug-like” molecules.²

The isoquinolinones constitute the scaffolds of great biological and pharmacological interest in medicinal chemistry and exhibit an array of promising biological properties, including antitumor,³ anti-inflammatory,⁴ antimalarial,⁵ antiarrhythmic,⁶ antithrombotics activities,⁷ and inhibition to NSSB polymerase of HCV,⁸ PDES,⁹ and PARP.¹⁰ These scaffolds are also widely found in many biologically active alkaloids, such as 2-hydroxyaccuminatine (I)¹¹ and oxyavicine (II) (Figure 1).¹² On the other hand, benzodiazepines and its analogues are recognized as privileged scaffolds in medicinal chemistry and exhibit a wide scope of biological activity, known as anxiolytic drugs,¹³ antitumor agents (III),¹⁴ antitubercular agents,¹⁵ and anti-HIV agents.¹⁶ Recently, these classes of compounds were found to hit various pharmacologically relevant targets, such as GABA_A receptor,¹⁷ histone deacetylases (HDAC),¹⁸ apoptotic protease-activating factor 1 (Apaf-1),¹⁹ and Hdm2 protein (IV).²⁰

For many years our laboratories have been involved in developing a chemical genetic approach to analyze biological systems by way of interfacing libraries of small molecules with

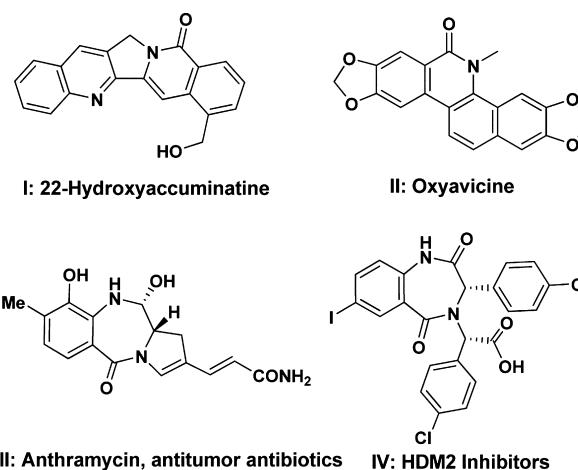


Figure 1. Medicinally important isoquinolinones and benzodiazepines.

creative biological assays.²¹ As part of this research objective, we became interested in establishing a novel synthetic strategy to construct diverse isoquinolinone and benzodiazepine-based heterocycles. In a previous paper, we have reported a diversity-

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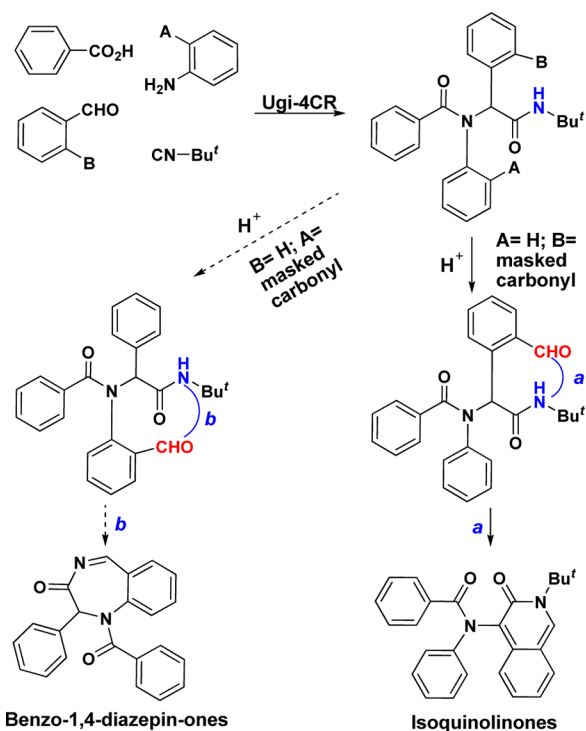
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based approach for the construction of isoquinoline scaffolds via Ugi-Heck reaction sequence.^{22,23} As a continuing effort, we herein report an alternative Ugi-based MCR approach to one-pot syntheses of diverse isoquinolinones and isoquinolinone-based benzo-1,4-diazepin-2,5-diones.

RESULTS AND DISCUSSION

The Ugi reaction, offering a large number of potential inputs, has gained popularity as a powerful tool for generating diverse compound libraries, and its union with other transformations can further expand the structural type of compound libraries. From a design perspective, it was envisioned that the isoquinolinones could be assembled through an intramolecular condensation of a carbonyl with the amide group in the α -acylaminoamide which was in turn produced by the Ugi-4CR of carboxylic acid, amine, isonitrile, and monomasked phthalaldehyde (Scheme 1, Path a), and the benzo-1,4-diazepinone could

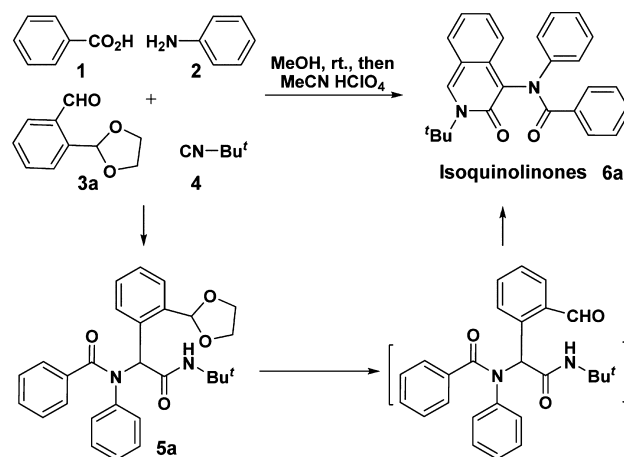
Scheme 1. Synthetic Analysis for Isoquinolinones and Benzo-1,4-diazepinones



be built up in a similar manner using the aniline bearing a masked carbonyl in *ortho* position (Scheme 1, Path b). The proposed strategy could provide rapid access to a variety of isoquinolinones and benzo-1,4-diazepinones from simple starting materials.

The proposed strategy was examined by the Ugi reaction of aldehyde 3a with benzoic acid, aniline, and *tert*-butyl isonitrile in MeOH at room temperature (Scheme 2), which was followed by the treatment with various Brønsted acids. We were pleased to find that a number of Brønsted acids including PTSA, H₂SO₄, HCl, and HClO₄ were able to facilitate the desired transformation. After a preliminary survey of reaction parameters, the use of HClO₄ in acetonitrile was found to be most effective to provide isoquinolinone 6a in 82% yield. During our further study of benzo-1,4-diazepinone construction, we encountered difficulties in the Ugi reaction, and the

Scheme 2. One-Pot Synthesis of Isoquinolinones



products were messy and often the Passerini product was obtained as the major product.

To profile the scope and potential of the present reaction, we next examined a series of commercially available carboxylic acids, amines, isonitriles with aldehyde 3a to form the structurally diversified isoquinolinones under the optimal reaction conditions, and their derived products are listed in Table 1. Pleasingly, all the selected substrates underwent Ugi-4CR/hydrolysis/intramolecular condensation transformations smoothly to give the corresponding isoquinolinones (6b–k) in good to excellent yields. With regard to carboxylic acid input, the performances of aromatic acids were slightly better than those of aliphatic acids, and aromatic or aliphatic amines appear to be comparable in this transformation. In addition, substituents on the amide nitrogen originating from isonitriles did not affect the annulations, since *tert*-butyl, cyclohexyl, and propyl isonitriles provided the similar results.

To further extend the reaction scope, four additional substituted 2-(1,3-dioxolan-2-yl)benzaldehyde 3b, 3c, 3d, and 3e were made (see Supporting Information for detail), and their annulated results are listed in Table 2. With regard to the substituent effect on the phenyl ring of 2-(1,3-dioxolan-2-yl)benzaldehyde, neither electron-donating groups (Table 2, entries 1 to 6) nor electron-withdrawing groups (Table 2, entries 7 to 10) on the phenyl ring affected the efficiency of the reaction. Once again, all the expected products were obtained in good to excellent yields.

As an expansion of this study, we decided to develop the post-transformation strategy for the developed Ugi-condensation synthetic protocol to further expand the compound library of biological interest. We envisioned that quinolin-3-one-based benzo-1,4-diazepin-2,5-diones 7a could be synthesized starting from nitro-substituted benzoic acid, glycine methyl ester, aldehyde, and isonitrile, as shown in the Scheme 3. The reaction sequence for the formation of 7a involved the Ugi-condensation reaction followed by the intramolecular lactamization which was achieved through the reduction of the nitro group under acidic conditions. In addition, this sequence could be achieved in one-pot fashion, which makes this process more practical and efficient. By varying of acid, aldehyde, and isonitrile components, a series of benzo-1,4-diazepin-2,5-diones were generated in moderate to good yields, as listed in the Table 3.

In summary, we have developed an efficient and one-pot synthesis of structurally diverse isoquinolinones and isoquino-

Table 1. Synthesis of Compounds 6b–6k

entry	Starting Materials	Product	Yield
1			76%
2			83%
3			80%
4			68%
5			70%
6			77%
7			89%
8			72%
9			62%
10			64%

linone-based benzo-1,4-diazepin-2,5-diones involving Ugi-4CR/condensation and Ugi-4CR/condensation/reduction/lactamization sequence. This developed synthetic protocol was anticipated to be applicable in the fields of combinatorial chemistry, diversity-oriented synthesis, and drug discovery. The biological evaluation of the synthesized compounds is currently underway in our lab, and the results will be reported in due course.

Table 2. Synthesis of Compounds 6l–6u

entry	Starting Materials	Product	Yield
1			72%
2			86%
3			72%
4			69%
5			75%
6			74%
7			66%
8			54%
9			89%
10			72%

EXPERIMENTAL PROCEDURES

General Experimental Details. Unless noted otherwise, all reactions were performed under a nitrogen atmosphere, and materials obtained from commercial suppliers were used without further purification. Purification of products was

Scheme 3. One-Pot Synthesis of Isoquinolinone-Based Benzo-1,4-diazepin-2,5-diones

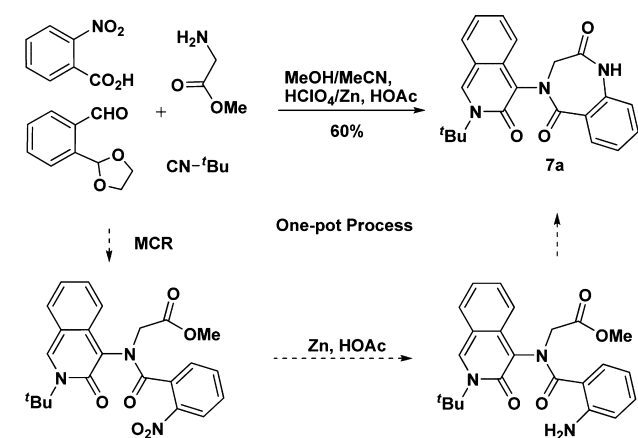


Table 3. Synthesis of Compounds 7b–7u

entry	R ₁	R ₂	R ₃	product	yield
1	H	H	Cy	7b	67%
2	H	H	<i>n</i> -Py	7c	62%
3	5-F	H	<i>n</i> -Py	7d	78%
4	4-Cl	H	<i>t</i> -Bu	7e	80%
5	4-Cl	H	Cy	7f	68%
6	5-MeO	H	<i>n</i> -Py	7g	54%
7	5-MeO	H	Cy	7h	50%
8	5-Cl	4,5-2MeO	Cy	7i	53%
9	4-Cl	4,5-2MeO	Cy	7j	63%
10	H	4,5-2MeO	<i>n</i> -Py	7k	56%
11	5-MeO	4,5-2MeO	Cy	7l	46%
12	H	5-MeO	<i>t</i> -Bu	7m	53%
13	5-F	5-MeO	Cy	7n	47%
14	4-Cl	5-MeO	<i>t</i> -Bu	7o	45%
15	5-MeO	5-CF ₃	<i>t</i> -Bu	7p	40%
16	5-F	5-CF ₃	<i>t</i> -Bu	7q	35%
17	H	5-CF ₃	Cy	7r	56%
18	H	5-Cl	<i>t</i> -Bu	7s	54%
19	5-Cl	5-Cl	<i>t</i> -Bu	7t	48%
20	5-MeO	5-Cl	Cy	7u	48%

conducted by flash column chromatography on silica gel (200–300 mesh) purchased from Qing Dao Hai Yang Chemical Industry Co. ¹H NMR spectra were recorded on a Bruker 300 or 500 MHz spectrometer using residual solvent (δ (CDCl₃) = 7.26) as internal standard. All the coupling constants are reported in hertz (Hz). ¹³C NMR spectra were recorded on the same instruments, and chemical shifts were measured relative to solvent resonances (δ (CDCl₃) = 77.0). High-resolution mass spectra were obtained on a quadrupole time-of-flight (QqTOF) mass spectrometer.

Typical Procedure for Four Component Reaction to Isoquinolinones 6. To a solution of 2-(1,3-dioxolan-2-yl)benzaldehyde (0.5 mmol) in MeOH (3 mL) were added amine (0.5 mmol), carboxylic acid (0.5 mmol), and isocyanide

(0.5 mmol). The reaction mixture was stirred at room temperature for 12 h, and the solvent was removed under vacuum. To the resulting residue in CH₃CN (4 mL) was added HClO₄ (70%, 6.1 μ L, 0.075 mmol), and the reaction mixture was stirred at room temperature for 8 h. The reaction mixture was worked up by the addition of NH₃·H₂O to pH = 8 and then extracted with CH₂Cl₂ (3 \times 10 mL), and the combined organic layers were dried over anhydrous Na₂SO₄. The solvent was removed under vacuum, and the residue was purified by a flash column chromatography on silica gel (CH₂Cl₂/CH₃OH = 50:1) to give the desired product. 6a, yellow solid; Mp 190 °C; IR ν 3063, 2976, 2898, 1664, 1637, 1564, 1531, 1483, 1396, 1371, 1319, 1286, 856, 775 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 8.30 (s, 1H), 7.54–7.49 (m, 3H), 7.41–7.26 (m, 6H), 7.18–7.08 (m, 4H), 6.92–6.87 (m, 1H), 1.71 (s, 9H); ¹³C NMR (75 MHz, CDCl₃) δ 158.6, 142.7, 138.0, 137.9, 137.0, 133.2, 129.6, 129.2, 128.7, 127.1, 125.6, 125.5, 123.6, 121.5, 119.3, 115.8, 64.3, 28.2; HRMS (*m/z*) calc. for C₂₆H₂₅N₂O₂ (+) 397.1916, found 397.1907.

Typical Procedure for MCR to Benzo-1,4-diazepin-2,5-diones 7. To a mixture of glycine methyl ester hydrochloride (0.56 mmol) and Na₂CO₃ (0.28 mmol) in MeOH (3 mL) prestirring for 15 min were added 2-(1,3-dioxolan-2-yl)benzaldehyde (0.56 mmol), 2-nitrobenzoic acid (0.56 mmol), and *tert*-butyl isocyanide (0.56 mmol). The reaction mixture was stirred at room temperature for 12 h, and the solvent was removed under vacuum. To the resulting residue in CH₃CN (4 mL) was added HClO₄ (70%, 6.1 μ L, 0.075 mmol), and the reaction mixture was stirred at room temperature for 8 h. The solvent was then removed under vacuum to give the yellow solid, to which was added AcOH (4 mL) and Zinc powder (364 mg), and the reaction mixture was stirred at 60 °C for 8 h. The reaction mixture was worked up by the addition of NH₃·H₂O to pH = 8 and then extracted with CH₂Cl₂ (3 \times 10 mL), and the combined organic layers were dried over anhydrous Na₂SO₄. The solvent was removed under vacuum, and the residue was purified by a flash column chromatography on silica gel (CH₂Cl₂/CH₃OH = 50:1) to give the desired product. 7a, yellow solid; Mp 165 °C; IR ν 3219, 3068, 2974, 2924, 1693, 1641, 1533, 1481, 1448, 1408, 1190, 758, 698 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 8.64 (s, 1H), 8.46 (s, 1H), 8.09 (*dd*, *J* = 0.9, 6.9 Hz, 1H), 7.51 (*m*, 2H), 7.32 (*m*, 3H), 7.18 (*d*, *J* = 8.1 Hz, 1H), 7.06 (*d*, *J* = 6.9 Hz, 1H), 6.96 (*m*, 1H), 4.51 (*d*, *J* = 15.3 Hz, 1H), 4.14 (*d*, *J* = 15.3 Hz, 1H), 1.86 (s, 9H); ¹³C NMR (75 MHz, CDCl₃) δ 172.2, 167.3, 158.0, 138.0, 137.8, 136.3, 133.4, 132.7, 132.2, 129.1, 126.1, 125.0, 122.2, 122.0, 120.9, 120.0, 116.4, 64.9, 52.3, 28.6; HRMS (*m/z*) calc. for C₂₂H₂₂N₃O₃ (+) 376.1661, found 376.1660.

■ ASSOCIATED CONTENT

Supporting Information

Detailed experimental procedures, compound characterization data, and ¹H, ¹³C NMR spectra for all products. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

DEDICATION

[†]This paper is dedicated to Professor Zhongning Zhang on the occasion of his 70th birthday.

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