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Streamlined access to 2,3-dihydropyrazino[1,2-*a*]indole-1,4-diones via Ugi reaction followed by microwave-assisted cyclization

Sergey Tsirulnikov [a], Mikhail Nikulnikov [a], Volodymyr Kysil [b], Alexandre Ivachtchenko [b], Mikhail Krasavin [a,*]

[a] *Chemical Diversity Research Institute, 2a Rabochaya St., Khimki, Moscow Reg. 141400, Russia*
[b] *ChemDiv, Inc., 6605 Nancy Ridge Dr., San Diego, CA 92121, USA*

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ABSTRACT

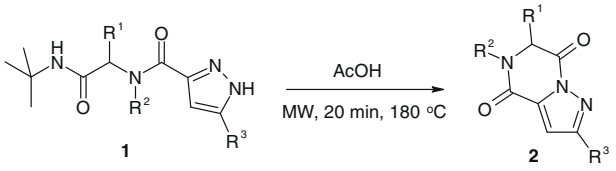
An efficient method is developed to construct drug-like 2,3-dihydropyrazino[1,2-*a*]indole-1,4-diones from 1*H*-indole-2-carboxylic acids, ethyl pyruvate, isocyanides, and primary amines via a one-pot, two-step procedure involving Ugi reaction and microwave-assisted cyclization.

The Ugi multi-component reaction (U-MCR)[1] is an efficient procedure for coupling reaction components from four different functional classes in a single condensation product. While it may have initially seemed that such striking atom economy would be tarnished by the redundancy of dipeptoid motifs present in the products of the U-MCR, the potential of the latter as a source of almost infinite scaffold diversity is uncovered by intelligent design of post-Ugi events. From the earlier work of Hulme on the 'Ugi-deprotect-cyclize' (UDC) strategy[2] to skillful functionalization of the U-MCR product with appendages capable of reacting in a second, orthogonal event (such as Mitsbunobu,[3] Heck,[4] Diels–Alder,[5] or photocycloaddition[6] processes)—it has become clear that U-MCR can be utilized for the formation of a wide range of heterocyclic molecular frameworks. Numerous reports on post-Ugi chemistry in the last decade (thoroughly reviewed by Akritopoulou-Zanze[7]) have promoted further activity in this area as witnessed in the recent literature.[8]

We recently reported that the products **1** of U-MCR of 1*H*-pyrazole-3-carboxylic acids in combination with *tert*-butyl isocyanide undergo microwave-assisted cyclization giving rise to medicinally important 5,6-dihydropyrazolo[1,5-*a*]pyrazine-4,7-diones **2** (Scheme 1).[9] In this cyclization process, the unsubstituted pyrazole nitrogen acts as an internal nucleophile to displace *tert*-butylamine from the terminal amide functionality. This view was supported by our later finding that other isocyanide-derived amide termini in scaffolds such as **1** can also cyclize onto the pyrazole moiety (albeit less effectively) and that replacement of the pyrazole with less reactive indole leads to significantly diminished yields.[10]

Herein we report that the products **3** of U-MCR of 1*H*-indole-2-carboxylic acids and ethyl pyruvate with various amines and isocyanides undergo high yielding microwave-assisted cyclization into 2,3-dihydropyrazino[1,2-*a*]indole-1,4-diones **4** (Scheme 2). Compounds containing such motifs have been reported to possess cytotoxic,[11] melatoninergic,[12] antiviral[13], and antifungal[14] activities. This broad medicinal relevance and the constrained peptidomimetic character of **4** make these new compounds attractive additions to any diversity set for biological screening.

The cyclization precursors **3** were prepared on 3 mmol scale as follows: Equimolar amounts of the amine and ethyl pyruvate were dissolved in methanol (10 mL) in a microwave reactor tube and heated at 50 °C for one hour to ensure complete imine formation.



Scheme 1. Cyclization of Ugi reaction products **1** derived from *t*-BuNC and 5-substituted-1*H*-pyrazole-3-carboxylic acids.[9]

* Corresponding author. Tel.: +7 495 995 4944; fax: +7 495 626 9780.
E-mail address: myk@chemdiv.com (M. Krasavin).

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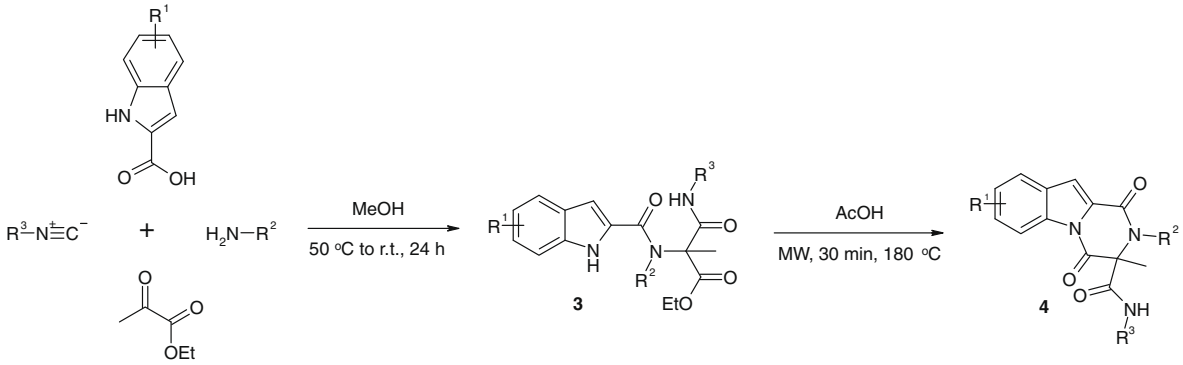
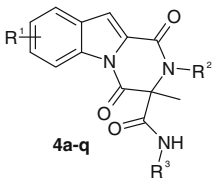


Scheme 2. Products of the Ugi reaction of 1*H*-indole-2-carboxylic acids, ethyl pyruvate, isocyanides, and primary amines and their microwave-assisted cyclization.

Next, a solution of the 1*H*-indole-2-carboxylic acid (1 equiv) in a minimum amount of methanol was added followed by a solution of the isocyanide (1 equiv) in methanol (1 mL). The mixture was stirred at room temperature for 24 h, at which point the reaction was complete by LC–MS analysis. The solvent was removed in vacuo[15] and the resulting solid was re-dissolved in glacial acetic acid (3 mL) and the reaction vessel sealed.

Microwave-assisted cyclization was achieved on heating the above solution at 180 °C for 30 min using a Biotage Initiator™ microwave synthesizer operating at 100 W. Notably, incomplete conversion was achieved in short reaction times or at lower temperatures. However, only products corresponding to the loss of an ethanol molecule were observed in the crude mixtures, with complete absence of the products similar to **2** resulting from cyclization onto the amide function. On cooling, the contents of the tube were poured into water (25 mL), and the resulting dense precipitate was collected by filtration. For all 17 examples studied, this procedure led to crude products of at least 85% purity (as determined by LC–MS). The products were obtained in good yields and analytically pure form by column chromatography on silica gel using an appropriate gradient of methanol in dichloromethane (Table 1). The identities and purities of products **4a–q** were confirmed by ^{1}H and ^{13}C NMR spectroscopy and by elemental analyses.[16]

Table 1
2,3-Dihydropyrazino[1,2-*a*]indole-1,4-diones **4** prepared in this work



4a-q

Entry	Product	R^1	R^2	R^3	Yield (%)
1	**4a**	6-MeO	Bn	Cyclohexyl	45
2	**4b**	5-Cl	Ph	Cyclopentyl	54
3	**4c**	6-MeO	4-$MeC_6H_4CH_2$	4-$MeC_6H_4CH_2$	72
4	**4d**	5-Cl	4-*i*PrC_6H_4	4-$FC_6H_4CH_2$	68
5	**4e**	5-Cl	4-*i*PrC_6H_4	3-$FC_6H_4CH_2$	62
6	**4f**	5-Cl	4-*i*PrC_6H_4	Cycloheptyl	47
7	**4g**	5-Cl	Bn	Cyclopentyl	73
8	**4h**	5-Cl	2,3-$Me_2C_6H_4$	Bn	38
9	**4i**	5-Cl	Ph	Bn	68
10	**4j**	5-Cl	2,5-$Me_2C_6H_4$	Bn	41
11	**4k**	5-Cl	2,4-$Me_2C_6H_4$	Cyclopentyl	44
12	**4l**	5-Cl	3,4-$Me_2C_6H_4$	Bn	58
13	**4m**	5-Cl	3-$MeSC_6H_4$	Cyclopentyl	67
14	**4n**	5-Cl	4-*i*PrC_6H_4	$MeOCH_2CH_2$	36
15	**4o**	5-Cl	4-*i*PrC_6H_4	Cyclopentyl	43
16	**4p**	5-Cl	2-$MeC_6H_4CH_2$	Cyclopentyl	48
17	**4q**	H	Bn	Cyclohexyl	55

In conclusion, we have developed an efficient method to construct drug-like 2,3-dihydropyrazino[1,2-*a*]indole-1,4-diones from 1*H*-indole-2-carboxylic acids, ethyl pyruvate, isocyanides, and primary amines via a one-pot, two-step procedure involving Ugi reaction and post-Ugi microwave-assisted cyclization. This procedure is amenable to parallel synthesis due to its simplicity and easy purification of the products.

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15. Parallel evaporation of volatiles from the microwave reactor tube was carried out using GeneVac® equipment.
16. Characterization data for selected compounds: compound **4a**—white solid, mp = 164–166 °C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.05 (d, J = 7.6 Hz, 1H), 7.85 (d, J = 2.2 Hz, 1H), 7.73 (d, J = 8.8 Hz, 1H), 7.44 (s, 1H), 7.18–7.35 (m, 5H), 7.08 (dd, J = 8.8, 2.5 Hz, 1H), 4.81 and 4.32 (ABq, J = 16.2 Hz, 2H), 3.86 (s, 3H), 3.40 (m, 1H), 1.73 (s, 3H), 1.36–1.70 (m, 5H), 0.97–1.21 (m, 5H); ^{13}C NMR (DMSO-d_6, 75 Hz) δ 165.2, 164.6, 159.8, 156.9, 137.9, 135.7, 128.1, 127.9, 127.1, 126.7, 123.5, 122.7, 114.7, 113.3, 99.6, 71.6, 55.7, 49.4, 46.6, 31.6, 31.4, 25.2, 24.7, 22.5; LC–MS (M+H$^+$) 460; calcd for $C_{27}H_{29}N_3O_4$: C, 70.57; H, 6.36; N, 9.14; found: C, 70.63; H, 6.42; N, 9.16. Compound **4d**—beige solid, mp = 176 °C (decomp.); ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.68 (m, 1H), 8.32 (d, J = 8.9 Hz, 1H), 7.91 (m, 1H), 7.58 (dd, J = 8.6, 1.9 Hz, 1H), 7.45 (s, 1H), 7.21 (m, 4H), 7.05 (m, 4H), 4.27 (m, 2H), 2.95 (m, 1H), 1.76 (s, 3H), 1.25 (d, J = 6.9 Hz, 6H); ^{13}C (DMSO-d_6, 75 Hz) δ 167.1, 163.9, 161.4 (d, J_{C-F} = 2.9 Hz), 156.6, 148.7, 135.0, 134.7,

133.0, 131.2, 130.6, 129.9, 129.5 (d, J_{C-F} = 7.9 Hz), 129.4, 127.6, 126.7, 122.2, 117.3, 114.8 (d, J_{C-F} = 21.1 Hz), 112.3, 72.2, 42.9, 33.0, 23.6, 21.1; LC–MS ($M+H^+$) 518; calcd for $C_{29}H_{25}ClFN_3O_3$: C, 67.24; H, 4.86; N, 8.11; found: C, 67.23; H, 4.91; N, 8.16. Compound **4n**—white solid, mp = 148–150 °C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.49 (t, J = 5.5 Hz, 1H), 8.32 (d, J = 8.9 Hz, 1H), 7.94 (d, J = 2.0 Hz, 1H), 7.60 (dd, J = 8.9, 2.0 Hz, 1H), 7.46 (s, 1H), 7.32 (d, J = 8.2 Hz, 2H), 7.14 (d, J = 8.2 Hz, 2H), 3.22 (s, 3H), 3.20–3.33 (m, 4H), 2.94 (m, 1H), 1.69 (s, 3H), 1.24 (d, J = 7.0 Hz, 6H); ^{13}C (DMSO-d_6, 75 Hz) δ 167.0, 163.9, 156.6, 148.6, 134.9, 132.9, 131.1, 130.5, 129.7, 129.4, 127.6, 126.9, 122.2, 117.4, 112.3, 71.9, 69.8, 58.0, 33.1, 23.8, 21.2; LC–MS ($M+H^+$) 468; calcd for $C_{25}H_{26}ClN_3O_4$: C, 64.17; H, 5.60; N, 8.98; found: C, 64.22; H, 5.66; N, 9.04.