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Two-step solution-phase synthesis of novel quinoxalinones utilizing a UDC (Ugi/de-Boc/cyclize) strategy

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Abstract—The novel solution-phase synthesis of an array of biologically relevant quinoxalinones in a simple two-step procedure is revealed. Transformations are carried out in excellent yield by condensation of mono-Boc protected *ortho*-phenylene di-amine, glyoxylic acids and supporting Ugi reagents. Subsequent acid treatment and evaporation affords quinoxalinones in good to excellent yields. © 2002 Elsevier Science Ltd. All rights reserved.

The year 1959 witnessed the discovery of a remarkable four-component reaction by Professor Ivar Ugi.[1] A short time later the first medicinal-chemistry-related application of the U-4CR (Ugi four-component reaction) was realized, with the one-step preparation of the local anaesthetic Xylocain.[2] With tremendous foresight, Ugi also recognized that the reaction was ideally suited to probe structure–activity relationships via the synthesis of 'large collections of compounds', now referred to as libraries.[3] Today, with the emergence of combinatorial chemistry and high-speed parallel synthesis, the multi-component reaction (MCR) is widely employed for the rapid assembly of arrays with high molecular diversity.[4] Coupled with a post-condensation modification, the power of these reactions is increased even further, giving rise to a plethora of complex, pharmacologically relevant templates for screening purposes. Several novel intra-molecular variations on the reaction have been reported, producing constrained products that result from interception of the intermediate nitrilium ion.[5] Post-condensation modifications with an appropriately protected internal nucleophile have also been extensively reported.[6] Following the latter theme, this letter describes a novel two-step procedure for producing quinoxalinones **1** in two simple, easily automated steps (Fig. 1).

Quinoxalinones have been shown to exhibit a wide range of biological functions, including utility as kinase inhibitors, **2**, and benzodiazepine receptor agonists, **3**.[7] Simply mixing an *ortho*-*N*-Boc protected phenylene diamine **4**, glyoxylic acid, isonitrile and primary amine, in methanol, gives the Ugi product **5** [60–80 area% (A%) purity as judged by LC/MS at UV 215 nm]. TFA promoted Boc removal and cyclization, with a concomitant loss of water, affords the desired quinoxalinone, with four potential points of diversity and general structure, **1** (Scheme 1). As such, this transformation represents a novel extension of UDC (Ugi/de-Boc/cyclize) methodology, initially reported in 1998.[6a] Note that benzimidazole formation, via cyclization onto the carboxylic acid derived carbonyl, was not observed. These reaction products result from the use of standard carboxylic acids and have recently been reported.[8]

Area % purities of 12 examples are reported in Table 1 and the procedure is general for a range of commer-

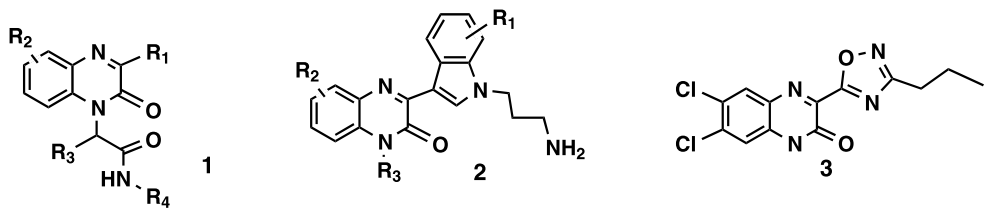

Figure 1.

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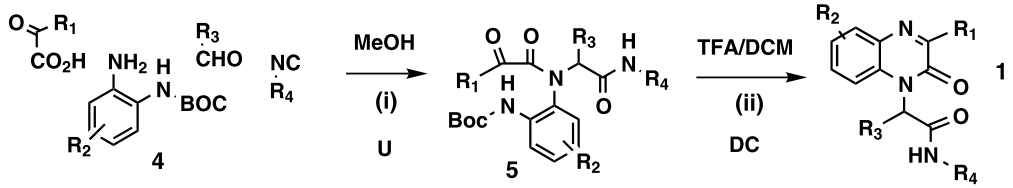

Scheme 1. *Reagents and conditions*: (i) aldehyde, glyoxylic acid, isonitrile, **4**, rt, 36 h; (ii) PS-tosylhydrazine (3 equiv.), THF:CH_2Cl_2, 1:1, 24 h; (iii) 10% TFA/CH_2Cl_2, 18 h.

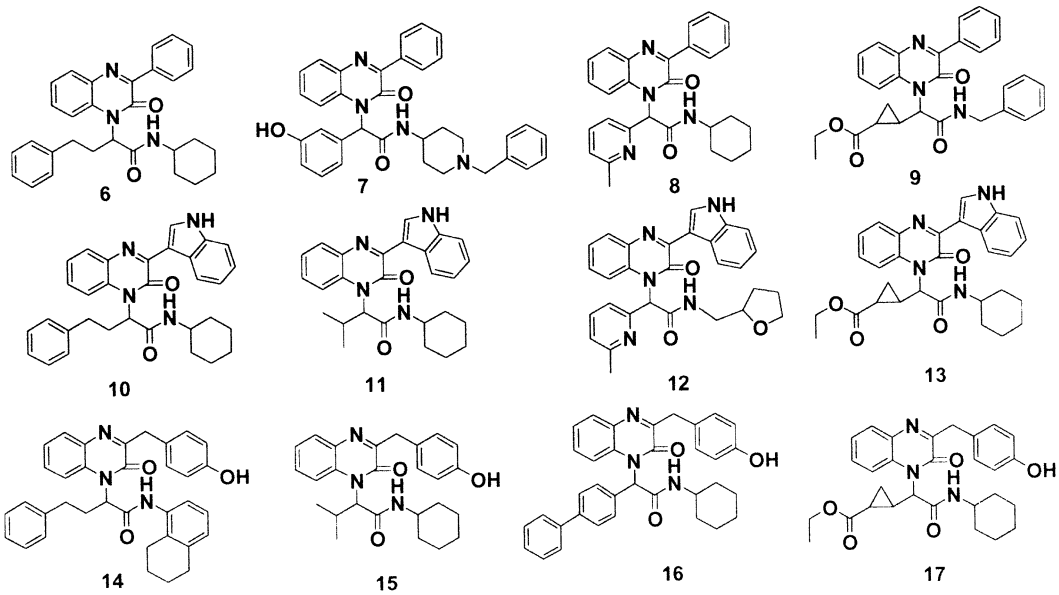

Table 1.

Cpd #	*A* (%)[a]	*A* (%)[b]	MH$^+$	Cpd #	*A* (%)[a]	*A* (%)[b]	MH$^+$	Cpd #	*A* (%)[a]	*A* (%)[b]	MH$^+$
6	100	91	465	**10**[d]	100	81	504	**14**	57	42	495
7	53	45	403	**11**	97	90	442	**15**	92	81	433
8[c]	100	83	452	**12**	78	64	493	**16**	77	71	482
9	72	67	473	**13**	100	87	512	**17**	100	92	503

[a] Area % purities by LC/MS with ELS detection.
[b] Area % purities by LC/MS with UV215 detection. LC/MS-HP1100 LC with LCQ, YMC-AM 4.6×150 mm column, ESI source.[9]
[c] Isolated yield, **8**, >95%.
[d] Isolated yield, **10**, >95%.

cially available glyoxylic acids, isonitriles and aldehydes. Unfortunately, *ortho-N*-Boc phenylene diamines **4** are not commercially available, and this proves to be a limiting factor in array synthesis.

Encouraged with the results shown in Table 1, the protocol was adapted to high-throughput synthesis in a 96 well plate format. An array of 80 compounds was thus prepared using 1(mono-Boc phenylene diamine)× 8(isonitriles)×10(aldehydes)×1(glyoxylic acid). The general procedure for plate level production of quinoxalinones is as follows. Methanol solutions (200 μl) of the four inputs (0.1 M for amines, acids and isonitriles, 0.15 M for aldehydes) were added in order of their participation in the Ugi condensation yielding 20 μmol of final, theoretical product. Excess aldehyde was employed to increase the yields of the initial Ugi condensation. Reagents were transferred into 2 ml square 96 well plates using a Quadra 96 (Tomtec), and the reaction proceeded at room temperature over 36 h. The methanol was evaporated in vacuo at 65°C[10] for 2 h, which was followed by a one-pot double scavenging step of unreacted aldehyde and acid with immobilized tosylhydrazine and *N*-methylmorpholine respectively.[11] After resin filtering and evaporation, treatment with a 10% TFA/DCM solution over 24 h at room temperature and evaporation, afforded the array of 80 quinoxalinones. The purity distribution of the library is shown in Fig. 2. Area% purities of individual library members are comparable to isolated yields from scaled up procedures. For example, quinoxalinone **10**, was produced on a milli-molar scale with an isolated yield of >95%.[12]

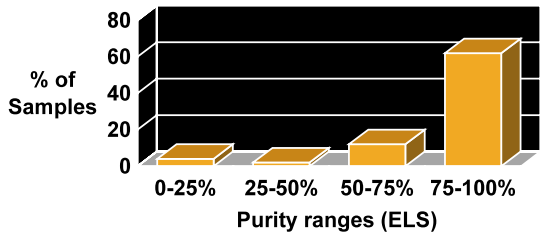

Figure 2. Purity distribution for quinoxalinones.

In summary, a novel two-step procedure for the solution-phase synthesis of quinoxalinones has been reported. With final products containing four potential points of diversity and a facile and rapid protocol, access to thousands of diverse analogs of this medicinally important core is feasible. Current efforts are now focusing on development of potential solid-phase approaches.

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9. LC/MS analysis was performed using a C18 Hypersil BDS 3μ 2.1×50 mm column with a mobile phase of 0.1% TFA in CH_3CN/H_2O, gradient from 10% CH_3CN to 100% over 10 min HPLC was interfaced with APCI techniques.
10. Performed in a SAVANT® evaporator.
11. Tosylhydrazine resin purchased from Argonaut® technologies.
12. The following procedure was followed for the large scale preparation of **10**: Solutions of 3-phenylpropionaldehyde (0.1 M, 10 ml in MeOH), 2-*N*-(*tert*-butoxycarbonyl)-aniline (0.1 M, 10 ml in MeOH), cyclohexylisocyanide (0.1 M, 10 ml in MeOH) and indole-3-glyoxylic acid (0.1 M, 10 ml in MeOH) were added to a round bottom flask and stirred at room temperature for 24 h. The solution was concentrated and the resulting oil was dissolved in 10% TFA/DCM. After 18 h the solution was concentrated and fractionated by FCC to yield a yellow solid (498 mg, 99%). 1H (400 MHz, $CDCl_3$) 11.79 (s, 1H), 9.01 (m, 1H), 8.91 (s, 1H), 8.02 (m, 1H), 7.44 (m, 1H), 7.38 (m, 5H), 7.09 (m, 4H), 7.02 (m, 1H), 6.23 (m, 1H), 6.61 (m, 1H), 3.76 (m, 1H), 2.85 (m, 1H), 2.69 (m, 1H), 2.47 (m, 2H), 1.84 (m, 1H), 1.68 (m, 2H), 1.51 (m, 2H), 1.25 (m, 2H), 1.00 (m, 2H), 0.76 (m, 1H); ^{13}C (100 MHz, $CDCl_3$) 170.3, 156.9, 152.2, 141.9, 138.0, 137.9, 136.0, 134.5, 131.3, 129.9, 129.5, 128.2, 127.7, 125.7, 124.9, 124.8, 123.3, 116.9, 113.9, 113.2, 56.9, 50.5, 34.3, 34.1, 31.2, 26.8, 26.4, 26.2. FTIR: 3272, 1645, 1146, 748 cm^{-1}. HRMS: MH^+ theoretical value: 505.2604. Actual value: 505.2621. dM/M = 3.4 ppm. At the same scale, **8**, was also produced and fully characterized. After 18 h of reaction time the solution was concentrated and fractionated by FCC to yield a white solid, **8**, (256 mg, 96%). ^1H (400 MHz, $CDCl_3$) 9.54 (s, 1H), 8.31 (m, 2H), 7.98 (m, 1H) 7.61 (dd, 1H, J = 8, 8 Hz), 7.46 (m, 3H), 7.35 (m, 2H), 7.21 (d, 1H, J = 8 Hz), 7.00 (d, 1H, J = 8 Hz), 6.89 (d, 1H, J = 8 Hz), 3.74 (s, 1H), 2.72 (s, 3H), 1.95 (m, 2H), 1.72 (m, 2H), 1.59 (m, 1H), 1.21–1.44 (m, 6H); ^{13}C (100 MHz, $CDCl_3$) 164.5, 156.7, 155.0, 153.9, 153.1, 139.6, 135.7, 133.6, 132.0, 130.8, 130.5, 129.9, 129.7, 128.1, 124.1, 123.2, 119.8, 115.3, 58.0, 48.8, 32.6, 32.4, 25.6, 24.4, 23.3. FTIR: 3390, 1651, 1149, 637 cm^{-1}. HRMS: MH^+ theoretical value: 453.2291. Actual value: 453.2312. dM/M = 4.6 ppm.