Published in final edited form as:

Tetrahedron Lett. 2014 June 4; 55(23): 3406–3409. doi:10.1016/j.tetlet.2014.04.013.

Novel succinct routes to Quinoxalines and 2-Benzimidazolylquinoxalines via the Ugi reaction

Muhammad Ayaz, Zhigang Xu, and Christopher Hulme^{*,†}

^{*}College of Pharmacy, BIO5 Oro Valley, The University of Arizona, 1580 E. Hanley Blvd, Oro Valley, AZ 85737, USA.

[†]Department of Chemistry and Biochemistry, The University of Arizona, Tucson, AZ 85721, USA.

Abstract

This communication reveals a unique, user-friendly, concise two-step, one-pot protocol for the synthesis of highly substituted quinoxalines. Conducting the Ugi reaction with appropriately functionalized classical Ugi reagents with subsequent acid treatment of the Ugi adduct affords collections of diversified quinoxalines in good to excellent yields. The methodology exploits what may be viewed as a ‘convertible carboxylic acid’, which in addition may be captured in an intramolecular sense to generate structurally complex 2-benzimidazolylquinoxalines in a mere two steps.

Keywords

Ugi reaction; Post-condensation modifications; Quinoxaline; Benzimidazole; Acyl Transfer

Isocyanide based multi-component reactions (IMCRs) are viewed in many circles as a premier field of study for the generation of both new chemotype diversity and preferred methodologies to afford known heterocycles.¹ Specifically, the venerable Ugi reaction, Scheme 1, has proved extremely versatile in enabling access to libraries of small molecules through a variety of strategies that encompass post-condensation modifications of the Ugi adduct and exploitation of the ‘diversity of nucleophiles’ able to trap out the intermediate ‘nitrilium ion’ of the Ugi reaction in both intra- and intermolecular modalities. Indeed, the collection of reactions that emanate from the original version of the Ugi transformation have been exploited for the synthesis of chemical libraries since the early 1990s, in-line with the emergence of high-throughput screening.² Efforts by several groups have seen concise methodologies developed that enable access to diazepines,³ ketopiperazines,⁴ imidazolines,⁵ β -lactams⁶ and hydantoins to name but a few.⁷ As such, the synthetic routes fall into the realm of UDC methodology (Ugi/Deprotect/Cyclize) where the final ring closing event is

© 2014 Elsevier Ltd. All rights reserved.

hulme@pharmacy.arizona.edu.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

mediated through amide bond formation.^{1e,f} This article details studies directed toward the preparation of functionalized quinoxalines that constitute an important class of nitrogen containing heterocycles utilized in many sectors of the chemical industry.^{8,9} Unfortunately, reported methods to synthesize quinoxalines suffer from various drawbacks, most noticeably harsh reaction conditions and use of toxic metals.¹⁰ The most widely used protocol¹¹ for quinoxaline preparation is limited to the trivial condensation of 1,2-diamines with 1,2-dicarbonyl reagents or acyl halides; a strategy allowing only two points of diversity. Recently we have reported¹² the synthesis of tetrazole-embedded quinoxalinones using the TMS-azide version of the Ugi reaction, and herein, this communication reveals¹³ alternate user-friendly methodology comprised of concise two-step one-pot procedures for the synthesis of highly functionalized quinoxalines **6**, utilizing the classical Ugi reaction and an embedded amino-nucleophile to generate pre-requisite diversity elements.

Thus, a model reaction using benzoic acid **1**, 3-bromophenyl glyoxaldehyde **2**, *N*-Boc-(4,5-dimethyl)1,2-phenylenediamine **3** and commercially available *n*-butylisocyanide **4**, proceeded smoothly in methanol at ambient temperature giving the Ugi adduct **5** in 70% yield (Scheme 2). Intriguingly, simple TFA treatment of **5** delivers **6a** in good yield, representing the first reported synthesis of quinoxalines derived in one step from the Ugi reaction, postulated to proceed in unexpected fashion through intermediates **7** and **8** with loss of a benzoyl group.³ Interestingly, the final product is significantly different from its Ugi precursor and as such, the methodology provides a unique opportunity to rapidly access such diversity space. During our studies, it was found that the cyclization step required optimization and different concentrations of TFA were thus investigated. The optimal yield for quinoxaline **6a** was obtained using a 20% TFA/DCE solution in the presence of a catalytic amount of water, with microwave irradiation at 140 °C in 20 minutes (Scheme 2).

Interested by the final loss of the benzoyl moiety from intermediate **8** and in search of a potentially milder and more atom-economic transformation, a number of carboxylic acids of different strength and size were thus evaluated for effect on isolated yield of **6a** (Table 1).

Study of a limited set of aromatic acids (Entries 1 through 5) revealed 2-*N*-Boc-aminophenyl proved optimal (73%, **6a**) and one could rationalize this observation through carbonyl-activation via internal hydrogen bonding of the adjacent aniline. Entries 3 and 5 afforded more moderate yields of **6a**, whereas 2 and 4 were deemed incompatible with the initial condensation. In search for optimal atom-economy, formic acid was employed and encouragingly for uptake in the organic community, quinoxaline **6a** was isolated after acid treatment in 69% yield (Entry 6), proving to be our acid of choice. To further simplify the procedure, 20% TFA/DCE was added directly to the Ugi adduct in methanolic solution and the resulting mixture heated via microwave irradiation at 140 °C for 20 minutes (Entry 7, Table 1). To our delight, the one pot procedure translated into higher overall yield (43%) when compared to that of the two step process (34%, Entry 6).

Exploring the scope of the reaction, various aldehydes, diamines and isocyanides were used to furnish a set of diversified quinoxalines and gratifyingly, the transformation worked equally well for all inputs, (Scheme 4).

Seeking to expand accessible skeletal diversity using the same reaction conditions, it was envisioned that use of isonitrile **9** (*ortho*-*N*-Boc-phenylisonitrile)¹⁴ would facilitate access to 2-benzimidazolylquinoxalines, **11**. The Ugi reaction proceeded smoothly and upon microwave irradiation of Ugi products **10** with 20% TFA/DCE, 2-benzimidazolylquinoxalines **11a–11c** were obtained in good yield (Scheme 5). Considering the well documented medicinal utility of benzimidazoles and quinoxalines, these tethered combinations of the two scaffolds afford new opportunities to probe their biological activity.

During these studies an interesting series of 2-benzimidazolylquinoxaline products **12a–12f** were observed when utilizing bulky *ortho*-substituted aromatic acids which had retained the benzoyl group through an internal acyl-transfer from the nitrogen derived from the original Ugi amine input to the adjacent benzimidazole. To the best of our knowledge this *Nitrogen* to *Nitrogen* acyl transfer has no literature precedent. The closest correlation if any, would be the use of imidazole based catalysts that are used to expedite oxygen to oxygen or oxygen to nitrogen acyl transfer reactions.¹⁵ Interestingly this behavior was observed only when *ortho*-Br, *ortho*-I or *ortho*-NO₂-benzoic acid was employed (Scheme 5). This peculiar acyl transfer may be partially explained by the crystal structures of **12d** and **12f** respectively (Figure 1), where the *ortho*-substituted aryl group is seemingly positioned to enjoy a planar π - π interaction with the quinoxaline moiety.

In summary, we have devised a simple, mild, robust and high yielding one-pot protocol to produce quinoxalines and tethered quinoxaline-benzimidazoles. The products have the potential to be further decorated and constrained using additional functional groups. Moreover, the generic nature and simplicity of the protocol renders it highly attractive as a valuable addition to the repertoire of synthetic transformations used by the organic and medicinal chemist respectively.

Acknowledgments

The authors thank the NIH (P41GM08619001) for financial support and S. A. Roberts for X-ray analyses.

References and notes

- 1a). Dömling A. Chem. Rev. 2006; 106:17–89. [PubMed: 16402771] b) Hulme C, Dietrich J. Mol Divers. 2009; 13:195–207. [PubMed: 19205916] c) El Kaim L, Grimaud L. Tetrahedron. 2009; 65:2153–2171. d) Banfi L, Riva R, Basso A. Synlett. 2010; 1:23–41. e) Hulme C, Gore V. Curr. Med. Chem. 2003; 44:1947–1950. f) Xu Z, Ayaz M, Capelli A, Hulme C. ACS Comb. Sci. 2012; 14:460–464. [PubMed: 22746181] g) Xu Z, De Moliner F, Capelli AP, Hulme C. Ang. Chem. Int. Ed. 2012; 51:8037–8040.
2. Armstrong, RW. Regents of the University of California. USA: 1995. p. 91
- 3a). Hulme C, Peng J, Tang SY, Burns CJ, Morize I, Labaudiniere R. J. Org. Chem. 1998; 63:8021–8023. b) Huang Y, Khoury K, Chanas T, Doemling A. Org. Lett. 2012; 14:5916–5919. [PubMed: 23157402]
- 4a). Hulme C, Peng J, Louridas B, Menard P, Krolikowski P, Kumar NV. Tetrahedron Lett. 1998; 39:8047–8050. b) Hulme C, Peng J, Morton G, Salvino JM, Herpin T, Labaudiniere R. Tetrahedron Lett. 1998; 39:7227–7230.
5. Hulme C, Ma L, Romano J, Morrisette M. Tetrahedron Lett. 1999; 40:7925–7928.
6. Hulme C, Ma L, Cherrier MP, Romano JJ, Morton G, Duquenne C, Salvino J, Labaudiniere R. Tetrahedron Lett. 2000; 41:1883–1887.

- 7a). Hulme C, Ma L, Romano JJ, Morton G, Tang S-Y, Cherrier M-P, Choi S, Salvino J, Labaudiniere R. *Tetrahedron Lett.* 2000; 41:1889–1893.b) Pakornwit S, Krasivan M. *Tetrahedron Lett.* 2014; 55:2299–2303.
- 8a). Husain A, Madhesia D. *J. Pharm. Res.* 2011; 4:924–929.b) Noorulla S, Sreenivasulu N. *Int. J. Pharm. Sci. Res.* 2011; 2:2337–2342.c) Patidar AK, Jeyakandan M, Mobiya AK, Selvam G. *Int. J. Pharm. Tech. Res.* 2011; 3:386–392.d) Singh DP, Hashim SR, Singhal RG. *Int. J. Drug Dev. Res.* 2010; 2:810–815.e) Taher A, Khalil NA, Ahmed EM. *Bull. Fac. Pharm. (Cairo Univ.)*. 2009; 47:19–26.
9. Heravi MM. *ARKIVOC.* 2006; 16:16–22.
- 10a). Barluenga JA, Liz F, Cabal R, Maria-Paz. *Synthesis.* 1985:313–314.b) Petukhov PA, Tkachev AV. *Tetrahedron.* 1997; 53:9761–9768.c) Zhao Z, Wisnoski DD, Wolkenberg SE, Leister, Wang Y, Lindsley CW. *Tetrahedron Lett.* 2004; 45:4873–4876.
- 11a). Bachhav HM, Bhagat SB, Telvekar VN. *Tetrahedron Lett.* 2011; 52:5697–5701.b) Bendale AR, Kotak D, Damahe DP, Narkhede SP, Jadhav AG, Vidyasagar G. *Der Chemica Sinica.* 2011; 2:20–24.c) Cuenca A, Pérez S, Yépez A, Paredes L, Montecinos L, Llovera L, Rodríguez C. *J. Heterocycl. Chem.* 2008; 45:1199–1201.d) Hasaninejad A, Zare A, Mohammadzadeh MR, Karami Z. *J. Iran. Chem. Soc.* 2009; 6:153–158.e) Jafarpour M, Rezaeifard A, Daneshchin M. *Appl. Catal. A.* 2011; 394:48–51.f) Jafarpour M, Rezaeifard A, Heidari M. *Lett. Org. Chem.* 2011; 8:202–209.g) Remli M, Ayi AI, Guedj R. *J. Fluorine Chem.* 1989; 44:15–23.
12. Gunawan S, Nichol G, Hulme C. *Tetrahedron Lett.* 2012; 53:1664–1667. [PubMed: 22707799]
13. Ayaz, M.; Xu, Z.; Hulme, C. Abstracts of Papers, 241st National Meeting of the American Chemical Society; Anaheim, CA. March 27–31, 2011; ORGN 584These results were originally outlined in the following poster:
14. Gunawan S, Ayaz M, De Moliner F, Frett B, Kaiser C, Patrick N, Xu Z, Hulme C. *Tetrahedron.* 2012; 68:5606–5611. [PubMed: 22923851]
15. Alan SA, Spivey C. *Top. Curr. Chem.* 2010; 291:223–280.
16. CCDC 992230 (**12d**) and CCDC 992449 (**12f**) contain the supplementary crystallographic data for this paper. This data can be obtained free of charge from The Cambridge Crystallographic Data Center via www.ccdc.cam.ac.uk/data_request/cif
17. General one-pot procedure exemplified for the synthesis of **6a**: The Ugi reaction was carried out at 0.25 mmol scale. A 10 mL microwave vial, charged with a magnetic bar was loaded with equimolar amounts of 3-bromophenylglyoxaldehyde and *tert*-butyl (2-amino-4,5-dimethylphenyl)carbamate. Using ~0.5 mL of methanol as solvent, the reaction was stirred at room temperature for two minutes followed by the addition of formic acid (0.25 mmol) and *n*-butyl isocyanide (0.25 mmol) respectively. The progress of the reaction was monitored by TLC and LC/MS (UV 214 nm). After completion of the reaction (~18 hr), solvent was removed under reduced pressure and without any intermediary purification, 0.5 mL of 20% TFA/DCE solution was added to the crude Ugi product along with a single drop of water. The reaction was subsequently heated in a microwave at 140 °C for 20 minutes (Biotage Initiator60™). After cooling the reaction to room temperature, the solvent and excess TFA were evaporated *in vacuo*. The final product (**6a**) was purified with a CombiFlash® *R_f* using ethyl acetate/hexane as eluent (0% to 100% ethyl acetate over a period of 20 minutes). 3-(3-bromophenyl)-*N*-butyl-6,7-dimethylquinoxaline-2-carboxamide (**6a**). White solid, m.p. 136–138 °C. Yield 48% (46.1 mg). ¹H NMR (400 MHz, CDCl₃): δ 8.14 (dd, *J* = 16.8, 7.5 Hz, 2H), 7.91 – 7.78 (m, 3H), 7.59 (d, *J* = 6.3 Hz, 3H), 7.33 (t, *J* = 7.9 Hz, 1H), 3.47 (dd, *J* = 13.6, 6.7 Hz, 2H), 1.71 – 1.57 (m, 2H), 1.50 – 1.35 (m, 2H), 0.97 (t, *J* = 7.3 Hz, 3H). ¹³C NMR (100 MHz, CDCl₃): δ 164.31, 151.88, 144.59, 141.85, 140.40, 139.20, 131.98, 131.82, 131.64, 130.79, 129.43, 129.32, 129.10, 127.54, 122.20, 39.59, 31.55, 20.15, 13.79. HRMS (EI⁺) calculated for C₁₉H₁₉BrN₃O 384.0706 [M+H⁺]. Found 384.0702
18. General one-pot procedure for the synthesis of **11a** and **12a**: Equimolar amounts of phenylglyoxaldehyde, *tert*-butyl (2-amino-4,5-dimethylphenyl)carbamate, 2-nitrobenzoic acid and *tert*-butyl (2-isocyano-4,5-dimethylphenyl)carbamate were stirred at room temperature for 18 hours. The Ugi adduct **10a** was purified, treated with 20% TFA/DCE (0.5 ml) and allowed to stir at rt for 3 days. **12a** was subsequently purified using a CombiFlash® *R_f* with ethyl acetate/hexane as eluent (0% to 100% ethyl acetate over a period of 30 minutes). For the preparation of **11a**: the

Ugi product **10a** was treated with 20% TFA/DCE (0.5 ml) and irradiated at 140 °C for 20 minutes. Solvent was evaporated *in vacuo* and crude material purified using a CombiFlash® R_f with ethyl acetate/hexane as eluent (0% to 100% ethyl acetate over a period of 30 minutes). (2-(6,7-dimethyl-3-phenylquinoxalin-2-yl)-1*H*-benzo[*d*]imidazol-1-yl)(2-nitrophenyl)methanone (**12a**). Thick brown oil, Yield 37% (46.2 mg). **¹H NMR** (400 MHz, CDCl₃): δ 7.98 (d, *J* = 7.2 Hz, 1H), 7.93 – 7.86 (m, 3H), 7.60 (d, *J* = 8.3 Hz, 2H), 7.47 – 7.43 (m, 2H), 7.42 – 7.38 (m, 2H), 7.34 (t, *J* = 7.4 Hz, 2H), 7.22 (d, *J* = 7.8 Hz, 1H), 6.82 (s, 1H), 6.51 (s, 1H), 2.54 (s, 6H). **¹³C NMR** (100 MHz, CDCl₃): 165.06, 152.18, 151.29, 143.84, 143.06, 142.06, 140.95, 139.41, 137.97, 135.08, 133.47, 132.68, 132.32, 129.63, 129.42, 129.06, 128.73, 128.48, 128.28, 127.31, 125.83, 125.10, 121.43, 120.38, 113.36, 20.53. (EI⁺) calculated for C₃₀H₂₂N₅O₃ 500.1723 [M+H⁺] Found 500.17252-(1*H*-benzo[*d*]imidazol-2-yl)-3-phenylquinoxaline (**11a**). White solid, mp 281-283 °C. Yield 46% (37.0 mg). **¹H NMR** (400 MHz, CDCl₃): δ 10.23 (s, 1H), 8.21 – 8.16 (m, 2H), 7.85 – 7.80 (m, 2H), 7.74 – 7.68 (m, 3H), 7.49 (dt, *J* = 8.8, 4.8 Hz, 4H), 7.31 (s, 1H), 7.23 (d, *J* = 7.2 Hz, 1H). **¹³C NMR** (100 MHz, CDCl₃): δ 153.63, 149.01, 144.29, 141.73, 140.40, 138.59, 133.42, 131.09, 130.51, 129.69, 129.44, 129.30, 129.00, 128.16, 124.51, 122.61, 121.27, 110.94. HRMS (EI⁺) calculated for C₂₁H₁₅N₄ 323.1291 [M+H⁺] Found 323.1294

Figure 1.
Array of products derived from Scheme 4.

Figure 2.
X-ray crystal structures of compounds **12d** and **12f**¹⁴

Scheme 1.
Mechanism of the four-component Ugi reaction

Scheme 2.

Four component one-pot Ugi reaction.

Scheme 3.

Conversion of Ugi adduct into Quinoxaline **6a** via intermediates **7** and **8**.

Products 6a-6i:

Scheme 4.

Study of the reaction scope of optimized methodology

Scheme 5.
Synthesis of 2-benzimidazolylquinoxalines **11**.

Table 1

Effect of carboxylic acids on quinoxaline yield

Entry	R	Yields (5a-5f)	Yield (6a)
1	2- <i>N</i> -Boc aminophenyl	47% (5a)	73%
2 ^a	2-Methoxyphenyl	nd (5b)	nd
3	4-Trifluoromethylphenyl	47% (5c)	58%
4 ^a	2,4-Dimethylaminophenyl	nd (5d)	nd
5	2,6-Difluorophenyl	51% (5e)	57%
6	H	49% (5f)	69%
7	H	nd (5f)	43%

^a Complex mixture during initial MCR, yield not determined.