Published in final edited form as:

Org Lett. 2012 March 2; 14(5): 1354–1357. doi:10.1021/ol3003282.

Straightforward Assembly of Phenylimidazoquinoxalines *via* a One-Pot Two Step MCR Process

Fabio De Moliner^a and Christopher Hulme^{a,b}

Christopher Hulme: hulme@pharmacy.arizona.edu

^aCollege of Pharmacy, BIO5 Oro Valley, 1580 E. Hanley Blvd, The University of Arizona, Tucson, AZ 85737, USA

^bDepartment of Chemistry and Biochemistry, The University of Arizona, Tucson, AZ 85721, USA

Abstract

An efficient multicomponent-based methodology providing a new entry into a medically important complex heterocyclic core is presented. The strategy is very general and able to endow target compounds with the highest possible number of diversity points. Notably, four new chemical bonds and two aromatic rings are formed in a one-pot fashion.

Multicomponent reactions (MCRs) are defined as condensations of three or more reagents (building blocks) reacting in a one-pot process, affording in a single step a final product containing atoms derived from all the reacting molecules.¹ As they allow for the assembly of very complex chemotypes from simple starting materials by means of easy and straightforward experimental operations, they are particularly suitable for diversity oriented synthesis.²

Historically, MCRs such as the Biginelli,³ Hantzsch⁴ and Strecker⁵ reactions date back to the 19th century. However, with an increasing need to explore new regions of the chemical space in a high-throughput fashion, there has been an exponential growth in the emergence of operationally friendly MCR methodology producing pharmacologically relevant molecules for biological evaluation.⁶

In this context, isocyanide-based multicomponent reactions (IMCRs) have blossomed in an unprecedented way, thanks to the versatility of isocyanide chemistry. In fact, owing to the divalent nature of the NC moiety, such species are able to simultaneously react as nucleophiles and as electrophiles, giving rise to a manifold of molecular frameworks suitable for further elaborations.⁷

Beyond the well-mined Ugi and Passerini reactions that furnish a plethora of new scaffolds *via* post-condensation modifications,⁸ other MCRs are underexploited and have vast

Correspondence to: Christopher Hulme, hulme@pharmacy.arizona.edu.

Supporting Information Available. Experimental procedures, characterization data, and ¹H and ¹³C NMR spectra for compounds **9a–p** and **9r**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

untapped potential.⁹ The Van Leusen imidazole synthesis, for instance, has been underused to date with only a few reports describing ‘Diversity Oriented Synthesis’ approaches available in the literature.¹⁰ This peculiar reaction, involving preliminary formation of a Schiff base **1** between an amine and an aldehyde followed by insertion of tosylmethylisocyanide **2** triggering cyclization, (Scheme 1)¹¹ displays the attractive feature of producing a medicinally relevant imidazole nucleus **3**.¹²

Thus, we were enticed to investigate possible applications of this protocol that afford drug-like scaffolds in a concise manner, specifically to generate imidazole-containing compounds of increased complexity and value. Hence, we decided to place a masked amino nucleophile on an aromatic amine input and to exploit arylglyoxaldehydes as the carbonyl components of the Van Leusen. By doing so, we purposefully choose widely commercially available building blocks and thus paved the way to the introduction of a high diversity level through the use of common starting materials. Design of an efficient and straightforward pathway started with optimization (Table 1), of the Van Leusen three-component reaction (V-3CR), which sometimes suffers from poor yields. Potassium carbonate (2 eq) was always used as the base, while both methanol and DMF, reportedly the best solvents for the V-3CR, were evaluated.¹³ In this respect, use of methanol (Entries 1, 3 and 5) proved to be detrimental, while DMF never failed to give satisfactory outcomes. Moreover, a panel of different conditions, ranging from stirring at room temperature to conventional heating and microwave irradiation, were explored both in regards to the preliminary imine preparation (Step A) and the TOSMIC addition (Step B). Gratifyingly, the pivotal condensation between *ortho*-*N*-Boc-phenylenediamine **4**, phenylglyoxaldehyde **5** and unsubstituted TOSMIC **7** always exhibited yields above 50% when performed in DMF, and the ideal conditions were identified as the combination of a short microwave-promoted heating cycle with overnight stirring at ambient temperature (Entry 4).

After gaining efficient access to compound **8a**, it was subjected to 10% TFA/DCE at varying temperatures (Table 2). Interestingly, when mild conditions were employed (Entries 1, 2 and 3) yields not only turned out to be improved, but the title compound **9a** was recovered in extremely pure (100%, NMR and LC-MS) form with no need for purification.

Noteworthy, this two step process afforded **9a** in a nice 65% overall yield by means of a simple and operationally friendly strategy requiring only one chromatography step. Nevertheless, further improvement was possible. Indeed, when step B of the Van Leusen condensation was conducted at 120°C (Table 1, Entry 8), 13% of cyclized compound **9a** was isolated. Intrigued by this finding, we were prompted to attempt harsher conditions in step B to promote the MCR and direct conversion of imidazole **8a** into final product **9a** in one-pot. After careful screening (Table 3), we found microwave induced heating at 180°C (Entry 4) represented a viable way to directly afford **9a** without isolation of its monocyclic precursor. As a matter of fact, lower temperatures proved to be sufficient to drive Boc deprotection and cyclization completely, although slightly poorer yields were obtained. Conversely, further increments up to 200°C (Entry 5) or longer reaction time (Entry 6) led to more side product formation.

To our delight, this resulted in the development of an efficient one-pot two step entry into a medicinally relevant family of imidazo[1,5-*a*]quinoxalines. Such a moiety is in fact the key motif of anticancer¹⁴ and anti-arthritis¹⁵ agents, showing remarkable activity in the inhibition of tyrosin-kinases¹⁶ and phosphodiesterases.¹⁷ From a synthetic point of view, the value of this methodology lies in its high simplicity and powerful capability to form two aromatic rings and four new chemical bonds in a one-pot fashion, with the possibility of simultaneous introduction of diversity inputs in almost every position of the resulting scaffold. Consequently, it is thus definitely superior to already reported lengthy multistep

routes¹⁸ for the preparation of the imidazo[1,5-a]quinoxaline core, often necessitating exotic and not easily available starting materials which make a diversity-oriented approach difficult. It is interesting to note that the Boc deprotection/cyclization strategy has therefore been extended to one more MCR, in addition to the “evergreen” Ugi¹⁹ and the more recently investigated Passerini²⁰ and Petasis²¹ condensations.

Having this optimized methodology in hand, we next explored the scope of the process and evaluated our modified V-3CR with different *ortho*-*N*-Boc-phenylenediamines, phenylglyoxaldehydes, and TOSMICs, our goal being to both determine route generality and to prepare a small collection of compounds **9**. (Table 4)

The method proved to have a broad applicability and tolerated a wide range of substituents regardless of their electron-donating or electron-withdrawing nature. The only limitation found was with the use of 2-substituted phenylglyoxaldehydes, which caused either a dramatic drop in the yield (**9r**) or even complete failure (**9q**). This phenomenon was ascribed to extreme sensitivity of the pathway toward steric hindrance. The isocyanide inputs showed quite different reactivity profiles. Indeed, we observed that phenylsubstituted TOSMICs were generally beneficial, exemplified by high yields of **9g**, **9k**, **9o**. This finding was unsurprising, since the presence of an extra aromatic ring enables further activation of the alpha position of these molecules (Scheme 1). Conversely, 2-ethyl-TOSMIC (**9h**, **9i**, **9j**) proved detrimental on overall yields.

In summary, we have described herein a facile and straightforward one-pot two step multicomponent-based strategy for the assembly of biologically appealing imidazo[1,5-a]quinoxalines. Of note, this approach allows for ready functionalization of the target heterocycle with a broad scope and is able to generate two aromatic rings and four new chemical bonds by means of two simple synthetic operations from commercially available building blocks. Due to its ease and wide applicability, which has been demonstrated through the preparation of a small collection of compounds, the protocol is perfectly suitable for parallel synthesis applications. It is hoped that this methodology will be embraced by the file enhancement community at large.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Financial support from the National Institutes of Health (Grant P41GM086190) is gratefully acknowledged.

References

1. (a) Zhu, J.; Bienaymè, H., editors. Multicomponent Reactions. Weinheim, Germany: Wiley-VCH; 2005. (b) Dömling A. Chem. Rev. 2006; 106:17. [PubMed: 16402771]
2. (a) Armstrong, WA.; Brown, SD.; Keating, TA.; Tempest, PA. Combinatorial Chemistry. Wilson, SR.; Czarnik, AW., editors. Weinheim, Germany: Wiley-VCH; 1997. (b) Burke MD, Schreiber SL. Angew. Chem. Int. Ed. 2004; 43:46. (c) Schreiber SL. Science. 2000; 287:1964. [PubMed: 10720315]
3. Biginelli P. Gazz. Chim. Ital. 1893; 23:360.
4. Hantzsch A. Justus Liebigs Ann. Chem. 1882; 215:1.
5. Strecker S. Ann. Chem. Pharm. 1850; 75:27.
6. (a) Bienaymè H, Hulme C, Oddon G, Schmitt P. Chem. Eur. J. 2000; 6:3321. [PubMed: 11039522] (b) Hulme C, Gore V. Curr. Med. Chem. 2003; 10:51. [PubMed: 12570721] (c) Akritopoulou-Zanze I. Curr. Op. Chem. Biol. 2008; 12:324.

7. (a) Ugi I, Werner B, Dömling A. *Molecules*. 2003; 8:53.(b) Doemling A, Ugi I. *Angew. Chem. Int. Ed.* 2000; 39:3168.
8. (a) Sunderhaus JD, Martin SE. *Chem. Eur. J.* 2009; 15:1300. [PubMed: 19132705] (b) Hulme C, Dietrich J. *Mol. Divers.* 2009; 13:195. [PubMed: 19205916] (c) Akritopoulou-Zanze I, Djuric SW. *Heterocycles*. 2007; 73:125.(d) Marcaccini S, Torroba T. *Nature Protoc.* 2007; 2:632. [PubMed: 17406624] (e) Banfi L, Riva R. *Org. React.* 2005; 65:1.(f) Banfi L, Riva R, Basso A. *Synlett*. 2010:23.(g) Basso A, Banfi L, Riva R. *Eur. J. Org. Chem.* 2010:1831.(h) Ayaz, M.; De Moliner, F.; Dietrich, J.; Hulme, C. *Evolution of Isocyanide Chemistry*. Nenajdenko, V., editor. Weinheim, Germany: Wiley-VCH; in press.
9. For recent reviews discussing less commonly used MCRs see: (a) Ruijter E, Scheffelaar R, Orru RVA. *Angew. Chem. Int. Ed.* 2011; 50:6234. (b) De Moliner F, Banfi L, Riva R, Basso A. *Comb. Chem. High Throughput Screening*. 2011; 14:782.
10. (a) Gracias V, Gasiiecki AF, Djuric SW. *Tetrahedron Lett.* 2005; 46:9049.(b) Gracias V, Darczak D, Gasiiecki AF, Djuric SW. *Tetrahedron Lett.* 2005; 46:9053.(c) Gracias V, Gasiiecki AF, Pagano TG, Djuric SW. *Tetrahedron Lett.* 2006; 47:8873.(d) Beebe X, Gracias V, Djuric SW. *Tetrahedron Lett.* 2006; 47:3225.(e) Wang L, Woods KW, Li Q, Barr KJ, McCroskey RW, Hannick SM, Gherke L, Credo RB, Hui Y-H, Marsh K, Warner R, Lee JY, Zielinski-Mozng N, Frost D, Rosenberg SH, Sham HL. *J. Med. Chem.* 2002; 45:1697. [PubMed: 11931625]
11. Van Leusen AM, Wildeman J, Oldenziel OH. *J. Org. Chem.* 1977; 42:1153.
12. For reviews providing an overlook on applications of imidazoles in medicinal chemistry see: (a) Bhatnagar A, Sharma PK, Kumar N. *Int. J. PharmTech Res.* 2011; 3:268. (b) De Luca L. *Curr. Med. Chem.* 2006; 13:1. [PubMed: 16457636] (c) Boiani M, Gonzalez M. *Mini-Rev. Med. Chem.* 2005; 5:68.
13. For practical details about the V-3CR standard processes see refs 10a–d
14. Moarboss G, Deleuze–Masquefa C, Bonnard V, Gayraud–Paniagua S, Vidal J–R, Bressolle F, Pinguet F, Bonnet P–A. *Bioorg. Med. Chem.* 2008; 16:6601. [PubMed: 18513976]
15. Kim K–H, Maderna A, Schnute ME, Hegen M, Mohan S, Miyashiro J, Lin L, Li E, Keegan S, Lussier J, Wrocklage C, Nickerson–Nutter CL, Wittwer AJ, Soutter H, Caspers N, Han S, Kurumbail R, Dunussi–Joannopoulos K, Douhan J III, Wissner A. *Bioorg. Med. Chem. Lett.* 2011; 21:6258. [PubMed: 21958547]
16. (a) Chen P, Norris D, Iwanovicz EJ, Spergel SH, Lin J, Gu HH, Shen Z, Witjak J, Lin T–A, Pang S, De Fex HF, Pitt S, Shen DR, Doweiko AM, Bassolino DA, Roberge JY, Poss MA, Chen B–C, Schieven GL, Barrish JC. *Bioorg. Med. Chem. Lett.* 2002; 12:1361. [PubMed: 11992777] (b) Barrish JC, Spergel SH. WO 99/10341. 1999
17. Hofgen, N.; Stange, H.; Langen, B.; Egerland, U.; Schindler, R. U. S. Patent. 0143391. 2009.
18. (a) Chen B–C, Zhao R, Bednarz MS, Wang B, Sundeen JE, Barrish JC. *J. Org. Chem.* 2004; 69:977. [PubMed: 14750833] (b) Sundaram GSM, Singh B, Venkatesh C, Ila H, Junjappa H. *J. Org. Chem.* 2007; 72:5020. [PubMed: 17539688] (c) Sharma S, Kundu B. *J. Comb. Chem.* 2009; 11:720. [PubMed: 19435370]
19. (a) Dietrich J, Kaiser C, Meurice N, Hulme C. *Tetrahedron Lett.* 2010; 51:3951. [PubMed: 20625451] (b) Xu Z, Dietrich J, Shaw AY, Hulme C. *Tetrahedron Lett.* 2010; 51:4566. [PubMed: 20706616]
20. Shaw AY, Medda F, Hulme C. *Tetrahedron Lett.* 2012; 53:1313. [PubMed: 22368307]
21. Ayaz M, Dietrich J, Hulme C. *Tetrahedron Lett.* 2011; 52:4821. [PubMed: 21987596]

Scheme 1.
Mechanism of the Van Leusen imidazole synthesis.

Table 1

Optimization of the Van Leusen imidazole synthesis.

entry	solvent	step A	step B	yield
1	MeOH	overnight, rt	overnight, rt	20%
2	DMF	overnight, rt	overnight, rt	60%
3	MeOH	MW (5', 100 °C)	overnight, rt	20%
4	DMF	MW (5', 100 °C)	overnight, rt	74%
5	MeOH	1hr, reflux	overnight, reflux	23%
6	DMF	1hr, 80 °C	overnight, 80 °C	71%
7	DMF	MW (5', 100 °C)	MW (10', 100 °C)	66%
8	DMF	MW (5', 100 °C)	MW (10', 120 °C)	57%

Table 2

Optimization of the deprotection-cyclization step.

entry	time	temperature	yield
1	overnight	rt	85%
2	10'	60 °C (MW)	88%
3	5'	80 °C (MW)	87%
4	10'	80 °C (MW)	78%
5	10'	100 °C (MW)	68%
6	10'	120 °C (MW)	68%

Table 3

Development of the two-step one pot process.

entry	solvent	time	temperature	yield
1	DMF	10'	140 °C	58%
2	DMF	10'	150 °C	52%
3	DMF	10'	160 °C	64%
4	DMF	10'	180 °C	67%
5	DMF	10'	200 °C	52%
6	DMF	20'	180 °C	55%

Note: conditions are referred to step B (TOSMIC and base addition). Imine formation was always conducted with MW (5', 100 °C).

Table 4

Scope of the Van Leusen 3-CR deprotection-cyclization one-pot route.

compound	R ₁	R ₂	R ₃	yield
9a	H	H	H	67%
9b	H	4-CF ₃	H	61%
9c	H	4-OMe	H	52%
9d	H	3-NO ₂	H	53%
9e	5-OMe	H	H	58%
9f	4-Br	H	H	66%
9g	H	H	Ph	74%
9h	H	H	Et	33%
9i	5-F	4-OMe	Et	40%
9j	4,5-di-Me	3,4,5-tri-OMe	Et	39%
9k	5-OMe	4-OMe	Ph	71%
9l	5-OMe	4-CF ₃	Ph	66%
9m	4-Br	3,4,5-tri-OMe	Ph	59%
9n	4-Br	4-F	4-Br-Ph	65%
9o	4,5-di-Me	3,4,5-tri-OMe	4-Br-Ph	70%
9p	4,5-di-Me	3-NO ₂	4-Br-Ph	55%
9q	H	2-OMe	H	/
9r	5-OMe	2-F	4-Br-Ph	13%