

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

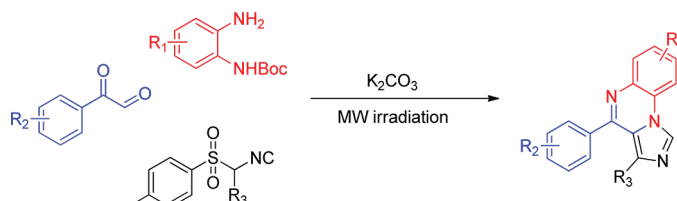
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ABSTRACT



An efficient multicomponent-based methodology providing a new entry into a medicinally 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 Hantzsch,⁴ 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, because of 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 postcondensation modifications,⁸ other MCRs are underexploited and have vast untapped potential.⁹ The Van Leusen imidazole

(1) (a) *Multicomponent Reactions*; Zhu, J., Bienaymé, H., Eds.; Wiley-VCH: Weinheim, Germany, 2005. (b) Dömling, A. *Chem. Rev.* **2006**, *106*, 17.

(2) (a) Armstrong, W. A.; Brown, S. D.; Keating, T. A.; Tempest, P. A. In *Combinatorial Chemistry*; Wilson, S. R., Czarnik, A. W., Eds.; Wiley-VCH: Weinheim, Germany, 1997. (b) Burke, M. D.; Schreiber, S. L. *Angew. Chem., Int. Ed.* **2004**, *43*, 46. (c) Schreiber, S. L. *Science* **2000**, *287*, 1964.

(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) Bienaymé, H.; Hulme, C.; Oodon, G.; Schmitt, P. *Chem.—Eur. J.* **2000**, *6*, 3321. (b) Hulme, C.; Gore, V. *Curr. Med. Chem.* **2003**, *10*, 51. (c) Akritopoulou-Zanze, I. *Curr. Opin. Chem. Biol.* **2008**, *12*, 324.

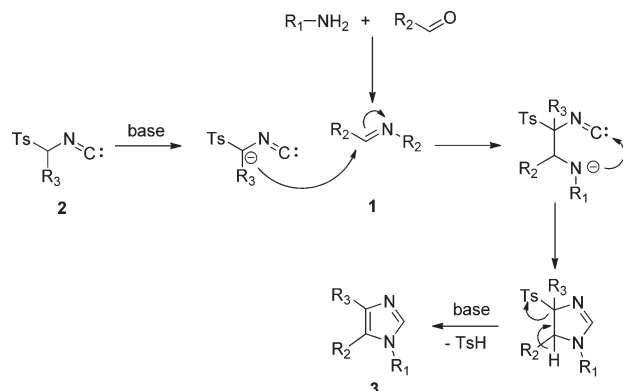
(7) (a) Ugi, I.; Werner, B.; Dömling, A. *Molecules* **2003**, *8*, 53. (b) Dömling, A.; Ugi, I. *Angew. Chem., Int. Ed.* **2000**, *39*, 3168.

(8) (a) Sunderhaus, J. D.; Martin, S. E. *Chem.—Eur. J.* **2009**, *15*, 1300. (b) Hulme, C.; Dietrich, J. *Mol. Diversity* **2009**, *13*, 195. (c) Akritopoulou-Zanze, I.; Djuric, S. W. *Heterocycles* **2007**, *73*, 125. (d) Marcaccini, S.; Torroba, T. *Nat. Protoc.* **2007**, *2*, 632. (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. In *Evolution of Isocyanide Chemistry*; Nenajdenko, V., Ed.; Wiley-VCH: Weinheim, Germany, in press.

(9) For recent reviews discussing less commonly used MCRs, see: (a) Ruijter, E.; Scheffelaar, R.; Orru, R. V. A. *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.

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

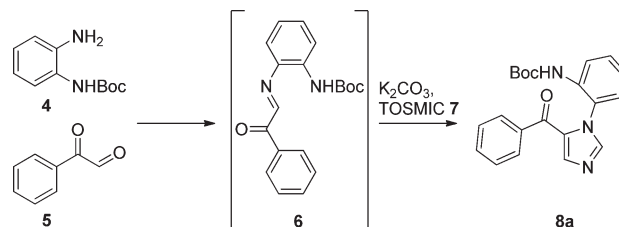
Scheme 1. Mechanism of the Van Leusen Imidazole Synthesis



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 chose 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 equiv) 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 (Table 1, 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 (Table 1, entry 4).

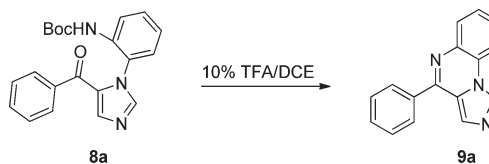
Table 1. Optimization of the Van Leusen Imidazole Synthesis



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	1 h, reflux	overnight, reflux	23
6	DMF	1 h, 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

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 (Table 2, entries 1, 2 and 3), not only did the yields turn out to be improved, but also the title compound **9a** was recovered in extremely pure (100%, NMR and LC–MS) form with no need for purification.

Table 2. Optimization of the Deprotection–Cyclization Step



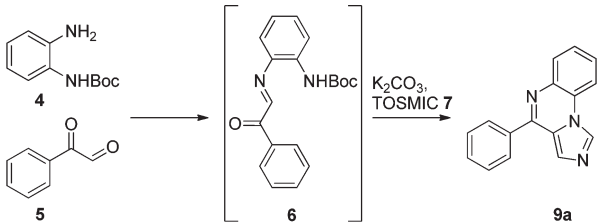
entry	time	temperature	yield (%)
1	overnight	rt	85
2	10'	60 °C (MW)	88
3	5'	80 °C (MW)	87
4	10'	80 °C (MW)	78
5	10'	100 °C (MW)	68
6	10'	120 °C (MW)	68

(10) (a) Gracias, V.; Gasielki, A. F.; Djuric, S. W. *Tetrahedron Lett.* **2005**, 46, 9049. (b) Gracias, V.; Darczak, D.; Gasielki, A. F.; Djuric, S. W. *Tetrahedron Lett.* **2005**, 46, 9053. (c) Gracias, V.; Gasielki, A. F.; Pagano, T. G.; Djuric, S. W. *Tetrahedron Lett.* **2006**, 47, 8873. (d) Beebe, X.; Gracias, V.; Djuric, S. W. *Tetrahedron Lett.* **2006**, 47, 3225. (e) Wang, L.; Woods, K. W.; Li, Q.; Barr, K. J.; McCroskey, R. W.; Hannick, S. M.; Gherke, L.; Credo, R. B.; Hui, Y.-H.; Marsh, K.; Warner, R.; Lee, J. Y.; Zielinski-Mozing, N.; Frost, D.; Rosenberg, S. H.; Sham, H. L. *J. Med. Chem.* **2002**, 45, 1697.

(11) Van Leusen, A. M.; Wildeman, J.; Oldenzil, O. H. *J. Org. Chem.* **1977**, 42, 1153.

(12) For reviews providing an overlook on applications of imidazoles in medicinal chemistry, see: (a) Bhatnagar, A.; Sharma, P. K.; Kumar, N. *Int. J. PharmTech Res.* **2011**, 3, 268. (b) De Luca, L. *Curr. Med. Chem.* **2006**, 13, 1. (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–10d.

Table 3. Development of the Two-Step One-Pot Process^a


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

^aNote: Conditions are referred to step B (TSMIC and base addition). Imine formation was always conducted with MW (5', 100 °C).

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 (Table 3, 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 (Table 3, entry 5) or longer reaction time (Table 3, 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 medically relevant family of imidazo[1,5-a]quinoxalines. Such a moiety is in fact the key motif of anticancer¹⁴ and antiarthritis¹⁵ agents, showing remarkable activity in the inhibition of tyrosin-kinases¹⁶ and phosphodiesterases.¹⁷ From a synthetic point of view, the

(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.

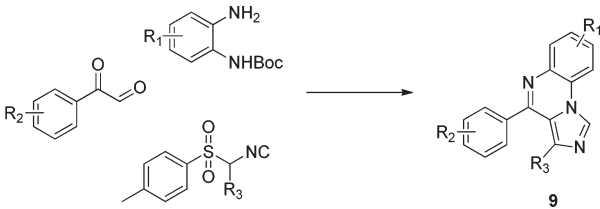
(15) Kim, K.-H.; Maderna, A.; Schnute, M. E.; Hegen, M.; Mohan, S.; Miyashiro, J.; Lin, L.; Li, E.; Keegan, S.; Lussier, J.; Wrocklage, C.; Nickerson-Nutter, C. L.; Wittwer, A. J.; Soutter, H.; Caspers, N.; Han, S.; Kurumbail, R.; Dunussi-Joannopoulos, K.; Douhan, J., III.; Wissner, A. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 6258.

(16) (a) Chen, P.; Norris, D.; Iwanovicz, E. J.; Spengel, S. H.; Lin, J.; Gu, H. H.; Shen, Z.; Witjak, J.; Lin, T.-A.; Pang, S.; De Fex, H. F.; Pitt, S.; Shen, D. R.; Doweiko, A. M.; Bassolino, D. A.; Roberge, J. Y.; Poss, M. A.; Chen, B.-C.; Schieven, G. L.; Barrish, J. C. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 1361. (b) Barrish, J. C.; Spengel, S. H. WO 99/10341, 1999.

(17) Hofgen, N.; Stange, H.; Langen, B.; Egerland, U.; Schindler, R. U. S. Patent 0143391, 2009.

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 TSMICs, our goal being to both determine route generality and to prepare a small collection of compounds **9**. (Table 4)

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

(18) (a) Chen, B.-C.; Zhao, R.; Bednarz, M. S.; Wang, B.; Sundeen, J. E.; Barrish, J. C. *J. Org. Chem.* **2004**, *69*, 977. (b) Sundaram, G. S. M.; Singh, B.; Venkatesh, C.; Ila, H.; Junjappa, H. *J. Org. Chem.* **2007**, *72*, 5020. (c) Sharma, S.; Kundu, B. *J. Comb. Chem.* **2009**, *11*, 720.

(19) (a) Dietrich, J.; Kaiser, C.; Meurice, N.; Hulme, C. *Tetrahedron Lett.* **2010**, *51*, 3951. (b) Xu, Z.; Dietrich, J.; Shaw, A. Y.; Hulme, C. *Tetrahedron Lett.* **2010**, *51*, 4566.

(20) Shaw, A. Y.; Medda, F.; Hulme, C. *Tetrahedron Lett.* **2012**, *53*, 1313.

(21) Ayaz, M.; Dietrich, J.; Hulme, C. *Tetrahedron Lett.* **2011**, *52*, 4821.

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**, and **9o**. This finding was unsurprising, since the presence of an extra aromatic ring enables further activation of the α -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. Because of 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 fine enhancement community at large.

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

The authors declare no competing financial interest.