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A Van Leusen deprotection-cyclization strategy as a fast entry into two imidazoquinoxaline families

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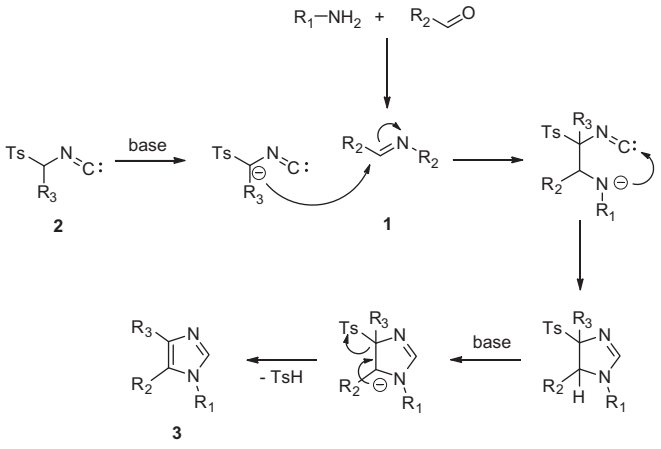
ABSTRACT

A concise synthesis of two pharmacologically relevant classes of molecules possessing the imidazoquinoxaline core is reported. The protocol involves use of 1,2-phenylenediamines and glyoxylic acid derivatives, namely ethyl glyoxylate or benzylglyoxamide, along with tosylmethylisocyanides in a microwave-assisted Van Leusen three-component condensation. Subsequent unmasking (Boc removal) of an internal amino-nucleophile promotes deprotection and cyclization that take place either spontaneously in a one-pot fashion to give **8** or upon acidic treatment under microwave irradiation after isolation of the imidazole intermediate to give **11**. Of note, a tricyclic framework is hence assembled by means of a rapid and straightforward method with a high bond-forming efficiency.

Tosylmethylisocyanides (TOSMICs) are a valuable and versatile class of synthons that are growing increasingly popular in the organic chemistry community. In addition to the isonitrile functional group, a well-known multi-purpose synthetic tool, TOSMICs also display two more reactive features:[1] namely, these molecules are endowed with a tosyl residue that can easily act as a leaving group,[2] and with an activated methylene they are prone to attack electrophiles upon deprotonation. Thanks to their peculiar nature, TOSMICs have been fruitfully employed in the preparation of several families of heterocycles, such as oxazoles,[3] pyrroles,[4] imidazoles,[5] benzofuranes,[6] quinoxalines,[7] and pyrrolopyrimidines.[8] Unsurprisingly, within this diversified panel of synthetic strategies multicomponent-based approaches stand out as a recurrent theme. In fact, multicomponent reactions (MCRs) represent an extremely powerful tool for the generation of a high level of molecular diversity and for the expeditious assembly of complex molecular frameworks in an efficient, straightforward, and facile manner.[9] In this context, the Van Leusen three-component reaction (V-3CR)[2] exemplifies a perfect combination between the operational ease and exploratory power of MCRs and the multiple reactivities of TOSMICs, resulting in a process that generates a medicinally relevant imidazole nucleus[10] upon a cascade mechanism triggered by nucleophilic attack onto a preformed Schiff base (Scheme 1). As proof of its importance, numerous reports describing its use to prepare biologically active compounds are available in the literature,[11] and extensive studies have been dedicated to further elaboration of its products[12] by means of post-condensation modifications, according to a *modus operandi* that is quite common in the MCR field.[13] Furthermore, a highly elegant MCR for the synthesis of imidazolines[14] has been developed from the V-3CR by Orru via the replacement of the TOSMICs with different α-acidic isocyanides. This merely reflects that this transformation constitutes a very fertile background for the development of more enabling novel chemical methodologies.



Scheme 1. Mechanism of the Van Leusen three-component reaction (V-3CR).

As a part of our endeavor to design novel general and succinct multicomponent-based routes that enable fast access to drug-like chemotypes in an operationally-friendly way,[15] we recently turned

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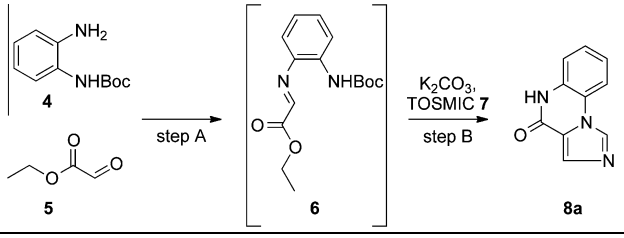
Table 1
Optimization of the one-pot Van Leusen cyclization protocol involving ethyl glyoxylate



Entry	Solvent	Conditions (Step A)	Conditions (Step B)	Yield (%)
1	DMF	MW (5 min, 100 °C)	MW (10 min, 140 °C)	30
2	DMF	MW (5 min, 100 °C)	MW (10 min, 160 °C)	35
3	DMF	MW (5 min, 100 °C)	MW (10 min, 180 °C)	41
4	DMF	MW (10 min, 100 °C)	MW (10 min, 180 °C)	47
5	DMF	MW (20 min, 120 °C)	MW (10 min, 180 °C)	38
6	DMF	MW (10 min, 100 °C)	MW (20 min, 180 °C)	45
7	DMF	MW (10 min, 100 °C)	MW (10 min, 200 °C)	39

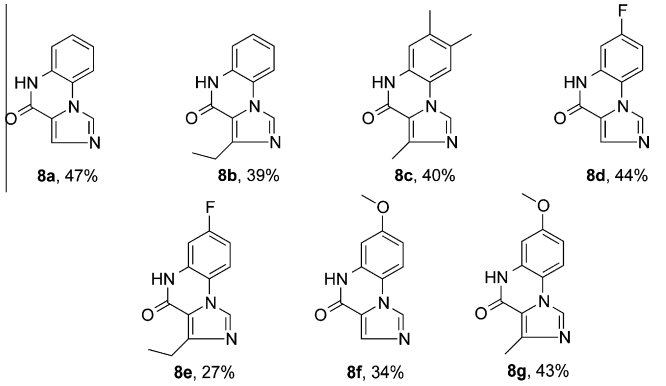


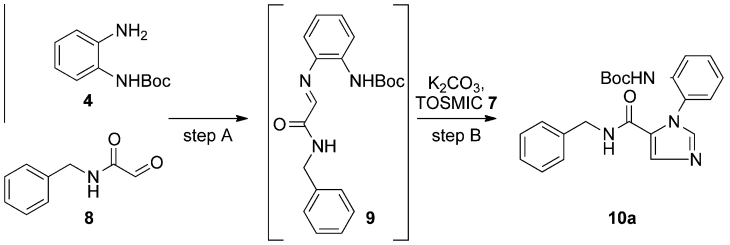
Figure 1. Compounds **8a**–**8g** synthesized from ethyl glyoxylate, *N*-Boc 1,2-phenylenediamines, and TOSMICs.

our attention to the enticing scenarios unveiled by coupling the Van Leusen imidazole synthesis with a post-condensation modification triggered by the unmasking of an internal nucleophile.[16] By choosing ethyl glyoxylate and benzyl glyoxamide as the carbonyl inputs and *N*-Boc 1,2-phenylenediamines as the amine building blocks, two diverse imidazoquinoline-based scaffolds were readily synthesized. The new methodologies represent enticing enhancements to the V-3CR reactivity domain, delivering tricyclic chemotypes that will be of high interest in the drug discovery arena.

Initially, ethyl glyoxylate was examined as a partner in the MCR pathway (Table 1). Based on our previous experience in this field,[16] DMF was evaluated as the solvent for both the Schiff base preformation, which is required for the Van Leusen reaction,[9] and the second, base-promoted step under microwave irradiation conditions. Gratifyingly, short cycle times turned out to be optimal for both steps, and when intermediate **6** was combined with TOSMIC **7** and potassium carbonate and subjected to elevated temperatures, a one-pot multi-component condensation, Boc-deprotection, and cyclization rendered **8a**. Optimal conditions were found to be microwave irradiation at 100 °C for 10 min for step A, followed by further irradiation at 180 °C for 10 min, which pushed the process to completion after the addition of isonitrile and base (entry 4).[17] A good overall yield (47% isolated in **8a**) was observed under these conditions.

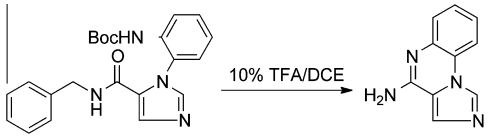
Encouraged by this result, a small collection of seven imidazo[1,5-*a*]quinoxalinones (Fig. 1) were thus prepared by means of the optimized methodology employing a diversity-enhancing set of four *N*-Boc 1,2-phenylenediamines and three TOSMICs. All proceeded smoothly, affording the expected products in yields ranging from 27% to 47%, representing a good level of efficiency

Table 2
Optimization of the Van Leusen reaction involving benzylglyoxamide



Entry	Solvent	Conditions (Step A)	Conditions (Step B)	Yield (%)
1	DMF	MW (10 min, 100 °C)	MW (10 min, 180 °C)	—
2	DMF	MW (10 min, 100 °C)	MW (10 min, 160 °C)	—
3	DMF	MW (10 min, 100 °C)	MW (10 min, 140 °C)	63
4	DMF	MW (10 min, 100 °C)	MW (10 min, 120 °C)	63
5	DMF	MW (10 min, 100 °C)	MW (10 min, 100 °C)	62
6	DMF	MW (10 min, 100 °C)	MW (10 min, 80 °C)	73
7	DMF	MW (10 min, 100 °C)	rt, overnight	83
8	DMF	MW (5 min, 100 °C)	rt, overnight	75
9	DMF	MW (20 min, 120 °C)	rt, overnight	60

Table 3
Optimization of the double deprotection-cyclization step



10a **11a**

Entry	Time	Temperature	Yield (%)
1	Overnight	rt	87
2	10 min	60 °C (MW)	80
3	10 min	80 °C (MW)	85
4	10 min	100 °C (MW)	85
5	10 min	120 °C (MW)	88
6	10 min	140 °C (MW)	74

in light of the number of transformations embedded in this pathway. As regards to the scope, it turned out to be quite general for the amine input, while TOSMICs with R_3 = Aryl were found to be incompatible where only complex mixtures of side products being observed.

Having developed a new expeditious route into a medicinally relevant tricyclic scaffold, which has been reported to be the key feature in molecules active against a number of pathologies such as cancer, arthritis, and erectile disfunction,[18] we envisaged that introduction of an exocyclic amino group would be pivotal in generating one more pharmacologically active chemotype. In fact, imidazo[1,5-*a*]quinoxalines displaying such a substituent are known to exert inhibition of important members of the tyrosine kinase family.[19] Additionally, the required use of glyoxamides in this strategy represents employment of a novel reagent in the V-3CR. Although scarce commercial availability and synthetic accessibility impeded evaluation of different amide inputs, benzylglyoxamide could be readily obtained from the corresponding tartaric acid amide by means of treatment with periodic acid according to a reported procedure.[20] However, in this case, (Table 2) irradiating at temperatures above 140 °C (entries 1 and 2, step B) afforded no observable product, while milder conditions proved beneficial (entry 7) even though only imidazole intermediate **10a** was recovered and tricyclic product could not be formed in a one-pot fashion. In regards to Schiff base formation (step A), heating at 100 °C for 10 min again proved optimal.

With a proficient route[21] to **10a** in hand, simple dissolution in a 10% TFA solution in DCE at room temperature promoted cyclization, and unexpectedly debenzylation in one pot afforded **11a**. Upon further screening (Table 3) this behavior was found to be reproducible under microwave irradiation, and **11a** was constantly recovered in high yield, with optimal conditions shown in entry 5.[22]

To the best of our knowledge, removal of a benzyl residue in acidic conditions is unprecedented in the primary literature. From a biological perspective, this deprotection was highly encouraging, as imidazoquinoxalines bearing a primary amino group have been shown to target phosphodiesterases and adenosine receptors.[23]

The two-step pathway was subsequently used to synthesize seven examples. Four 1,2-phenylenediamines and six TOSMICs were successfully explored in the Van Leusen reaction along with benzylglyoxamide, giving desired products in good yields ranging from 52% to 83% (Fig. 2). Subsequent acid-induced deprotection–cyclization proceeded smoothly, and **11a**–**11g** were obtained in excellent 84–99% yields in a very clean manner that required no purification, with the only loss of material due to the aqueous work-up. Of note, when heterocyclic diamines having a pyridine or pyrimidine core were evaluated, the Van Leusen reaction performed poorly (<15% yield) and no tricyclic products **11** were observed, even under prolonged irradiation.

In conclusion, we have herein reported a straightforward MCR-based methodology exploiting the Van Leusen three-component reaction (V-3CR) followed by a deprotection–cyclization step to provide fast entry into two biologically enticing imidazoquinoxaline families. For the first time ethyl glyoxylate and benzyl glyoxamide were employed in the V-3CR, resulting in an extension of the scope of this condensation. With high operational ease and the capability of furnishing target structures **8** and **11** with two diversity points, this route appears superior to the existing lengthy multistep pathways toward such chemotypes. Thanks to the advantages outlined above, our strategy is highly amenable for high-throughput applications and will hopefully represent a valuable new tool available for the lead generation community.

Acknowledgements

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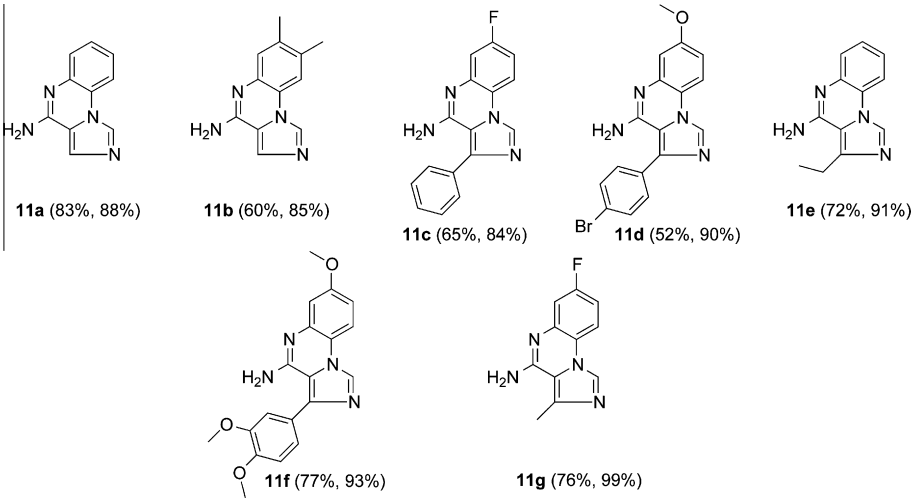

Figure 2. Compounds **11a**–**11g** synthesized from ethyl glyoxylate, *N*-Boc 1,2-phenylenediamines, and TOSMICs (X%, X% = Van Leusen yield, deprotection-cyclization yield).

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17. *General procedure exemplified for the preparation of* ***8c***: Ethyl glyoxylate (1.5 equiv, 0.72 mmol, 173 μL of a 50% soln. in toluene) and *tert*-butyl (2-amino-4,5-dimethylphenyl)carbamate (1 equiv, 0.48 mmol, 113 mg) were dissolved in DMF (2 mL) and heated at 100 °C for 10 min by means of microwave irradiation. Potassium carbonate (2 equiv, 0.96 mmol, 132 mg) and methyl-TOSMIC (1 equiv, 0.48 mmol, 100 mg) were then added, and the reaction mixture was heated at 180 °C for 10 min. After cooling to room temperature, water (20 mL) was added and extraction with EtOAc (3 × 20 mL) was performed. The organic phase was dried over $MgSO_4$ and concentrated under reduced pressure, and the crude was purified by flash chromatography (EtOAc/Hexane 50–100%) using an ISCO™ purification system to afford 3,7,8-trimethylimidazo[1,5-*a*]quinoxalin-4(5*H*)-one **8c** as a yellow solid (44 mg, 40% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.02 s, 1H), 8.75 (s, 1H), 7.87 (s, 1H), 6.98 (s, 1H), 2.52 (s, 3H), 2.23 (s, 3H), 2.20 (s, 3H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6) δ: 156.2, 142.2, 135.6, 131.4, 128.2, 127.2, 118.8, 117.3, 116.3, 109.9, 19.7, 19.5, 14.5 ppm.
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21. *General procedure exemplified for the preparation of* ***10e***. Benzylglyoxamide (1 equiv, 0.48 mmol, 78 mg) and *tert*-butyl (2-aminophenyl)carbamate (1 equiv, 0.48 mmol, 100 mg) were dissolved in DMF (2 mL) and heated at 100 °C for 10 min by means of microwave irradiation. Potassium carbonate (2 equiv, 0.96 mmol, 132 mg) and ethyl–TOSMIC (1 equiv, 0.48 mmol, 107 mg) were then added, and the reaction mixture was stirred overnight at room temperature. Water (20 mL) was added and extraction with EtOAc (3 × 20 mL) was performed. The organic phase was dried over $MgSO_4$ and concentrated under reduced pressure, and the crude was purified by flash chromatography (EtOAc/hexane 50–100%) using an ISCO™ purification system to afford *tert*-butyl (2-(5-(benzylcarbamoyl)-4-ethyl-1*H*-imidazol-1-yl)phenyl)carbamate **10e** as an orange oil (138 mg, 69% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.85–7.80 (m, 1H), 7.45 (s, 1H), 7.43–7.37 (m, 1H), 7.28–7.21 (m, 3H), 7.15–7.11 (m, 2H), 7.09–7.03 (m, 2H), 6.53 (s, 1H), 6.30 (s, 1H), 4.47–4.35 (m, 2H), 2.88 (q, J = 7.5 Hz, 2H), 1.41 (s, 9H), 1.33 (t, J = 7.6 Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ: 160.2, 152.9, 148.2, 139.0, 137.6, 134.4, 130.1, 128.6, 128.5, 127.9, 127.5, 127.4, 125.0, 124.9, 123.9, 123.7, 123.2, 81.4, 43.5, 28.1, 21.7, 13.8 ppm.
22. *General procedure exemplified for the preparation of* ***11e***. *tert*-Butyl (2-(5-(benzylcarbamoyl)-4-ethyl-1*H*-imidazol-1-yl)phenyl)carbamate **10e** (1 equiv, 0.29 mmol, 120 mg) was dissolved in 3 mL of a 10% TFA/DCE solution and heated at 120 °C for 10 min by means of microwave irradiation. After cooling to room temperature, the reaction mixture was diluted with $NaHCO_3$ sat. solution (20 mL) and extraction with EtOAc (3 × 20 mL) was performed. The organic phase was dried over $MgSO_4$ and concentrated under reduced pressure to afford **11e** as a pink powder (55 mg, 91% yield) with no need of purification. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.13 (br s, 2H), 8.87 (s, 1H), 8.09 (dd, J = 8.2, 1.1 Hz, 1H), 7.33–7.23 (m, 2H), 7.21–7.14 (m, 1H), 2.97 (q, J = 7.5 Hz, 2H), 1.21 (t, J = 7.5 Hz, 3H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6) δ: 156.0, 148.2, 131.8, 129.4, 129.0, 127.3, 123.1, 120.9, 116.9, 115.9, 21.4, 14.4 ppm.
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