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Graphical Abstract

Exploiting the Divalent Nature of Isonitriles: a novel Pictet-Spengler Amidination process.

Federico Medda and Christopher Hulme*

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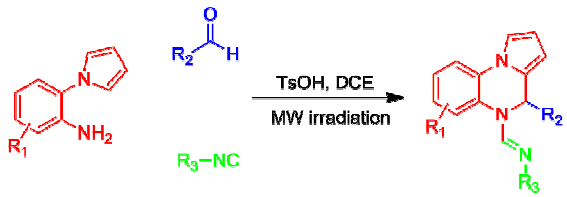

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Exploiting the Divalent Nature of Isonitriles: a novel Pictet–Spengler Amidination process

Federico Medda[a,b] and Christopher Hulme[a–c]*

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Abstract

An isocyanide-based multicomponent reaction (IMCR) utilized for the rapid assembly of novel, biologically relevant dihydropyrrolo[1,2-*a*]quinoxalines-amidines is herein presented. Starting from 1-(2-aminophenyl)pyrroles, aldehydes, and isonitriles, the target heterocyclic scaffold is assembled in a one-pot, operationally friendly process. With three points of diversity and formation of three chemical bonds in one step, this strategy proves to be very general. Novel, mild methodology for the generation of amidines from secondary amine anilines and isonitriles is also introduced.

Keywords

Isonitrile

Multicomponent reaction

Amidine

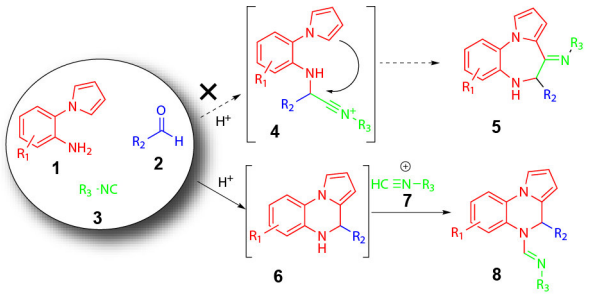
Pictet-Spengler

Multicomponent reactions (MCRs) are powerful transformations where three or more starting materials react in one pot, forming a final product incorporating all atoms of starting materials, with the exception of condensation byproducts, (i.e., H_2O, MeOH, or HCl).[1] The main advantage of MCRs thus resides in their capacity to generate complex chemotypes from simple starting materials, via atom-economic and convergent processes, with high bond-forming efficiency.[1] As such, the last two decades have witnessed renewed interest in MCRs as the need for facile access to libraries of pharmacologically relevant molecules has evolved.[1,2]

Within the MCR arena, isocyanide-based MCRs (IMCRs) are particularly attractive, due in large part to the chemical versatility of the isocyanide functional group, which is capable of behaving as both a nucleophile and, when converted into a nitrilium ion, as an electrophile. As such, isocyanides are divalent in nature, a property that can be exploited to give rise to a wide range of molecular scaffolds.[1–3] Traditionally involved in the generation of novel biologically appealing chemotypes via post-condensation modifications of IMCRs,[4] we recently turned our attention toward study of the Pictet–Spengler reaction, discovered in 1911, and classically defined as the condensation of a β-arylethylamine with a carbonyl compound in the presence of a protic or Lewis acid that gives rise to a substituted tetrahydroisoquinoline.[5] Subsequently, the scope and utility of this transformation was improved through the employment of novel aryl-amines linked to electron-rich aromatic heterocycles,[6] resulting in the synthesis of natural products and small molecules of biological interest.[7]

We were specifically drawn to the possibility of disrupting the Pictet–Spengler reaction of 1-(2-aminophenyl)pyrroles **1**, aldehydes **2**, and isonitriles **3** through enticing the pyrrole moiety to trap the intermediate nitrilium ion **4**, to afford heterocycles of structure **5**. However, studies

showed the predominant pathway proceeded through the Pictet–Spengler reaction via **6**, which intriguingly was highly susceptible to reaction with protonated isonitriles **7**, affording products of generic structure **8** in a single step. Enticingly, these new products contained three points of diversity, being derived from a novel, albeit unplanned, MCR containing an unexpected amidine

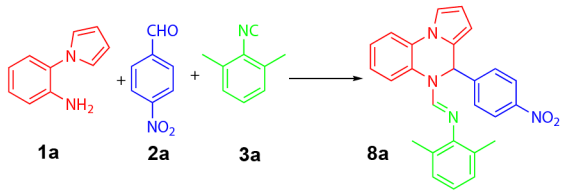


Scheme 1. Synthesis of N-((4-methylpyrrolo[1,2-a]quinoxalin-5(4H)-yl)methylene)methanamines **8** via a Pictet–Spengler amidination sequence.

functional group (**8**, Scheme 1). Interestingly, reactions of isonitriles with carboxylic acids have been recently reported by Danishefsky and others under mild conditions.[8] However, reactions of isonitriles with amines affording amidines are known to proceed only via relatively harsh metal catalysis,[9] and only one report from 1962[10] details a hydrochloric acid–mediated transformation of secondary anilinic amines with isonitriles to amidines which was not exemplified in any great detail. To the best of our knowledge, *para*-toluene sulfonic acid–promoted amidine formation of the intermediate aniline **6** represents a far milder example of this significantly under-utilized functional group transformation. Initial optimization of the IMCR focused on the one-pot reaction between amine **1a**, aldehyde **2a**, and isonitrile **3a** (Table 1) utilizing toluene as a solvent and *para*-toluenesulfonic acid as a catalyst, which resulted in acceptable yields of **8a**, as judged by LC/MS (entries 1–4). Conversely, use of protic solvents saw yields drop significantly (entries 5–6). A similar outcome was also seen using stronger acidic catalysis, including previously reported HCl[10] (entries 7–10), probably due to heightened instability of the isonitrile **3a** in these media, which is prone to formamide formation if adventitious water is present. Indeed, the latter

transformation is an excellent way of destroying low molecular weight pungent isonitriles during reaction work-up, again exploiting the inherent "divalent nature" of the isonitrile functional group.

Table 1. Optimization of the One-pot Model Reaction.[a]



1a 2a 3a 8a

entry	solvent	acid (eq.)	conditions	conversion[b]
1	toluene	TsOH (0.2)	rt, 18 h	56
2	toluene	TsOH (0.4)	rt. 18 h	70
3	toluene	TsOH (0.2)	reflux, 18 h	63
4	toluene	TsOH (0.4)	reflux, 18 h	45
5	MeOH	TsOH (0.4)	rt, 18 h	24
6	MeOH	TsOH (0.4)	reflux, 18 h	–
7	AcOH	cHCl[c]	rt, 18 h	21
8	AcOH	–	rt, 18 h	35
9	AcOH	cHCl[c]	reflux, 18 h	–
10	AcOH	–	reflux, 18 h	–
11	DCE	TsOH (0.4)	MW, 120 °C, 30'	97
12	DCE	TsOH (0.4)	MW, 120 °C, 60'	87
13	DCE	CF_3CH_2OH[d]	MW, 120 °C , 30'	65
14	DCE	AcOH (0.4)	MW, 120 °C , 30'	27
15	DCE	cHCl (0.4)	MW, 120 °C, 30'	53
16	DCE	TFA (0.4	MW, 120 °C , 30'	46
17	DCE	$HClO_4$ (0.4)	MW, 120 °C, 30'	29

[a]Starting materials used in a 1:1:1 molar ratio; [b]Conversion is expressed as % and was judged by means of LCMS analysis (see supplementary information); [c]One drop of 12N HCl used; [d]DCE:CF_3CH_2OH (2:1).

Upon silica-based purification of **8a**, pure product was recovered in only 10% yield (entry 2), suggesting a somewhat surprising instability on prolonged exposure to silica. Encouragingly, reverse-phase (C18) column chromatography enabled a satisfactory increase in yield (**8a**, 62%), and definitive structural confirmation was obtained with a small-molecule X-ray crystal structure (**8a**, Figure 1).

Isolated yields were further improved via microwave irradiation in DCE (Table 1), coupled with shorter reaction times (entries 11 and 12). Evaluation of various acid catalysts under these

improved conditions (entries 13–17) showed none to be as effective as *para*-toluene sulfonic

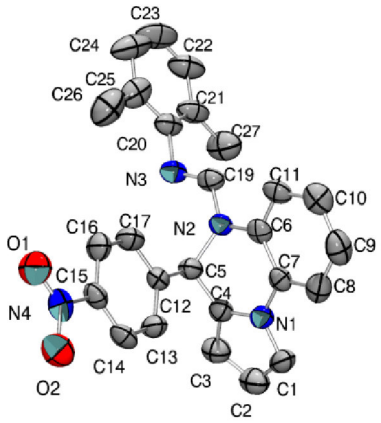
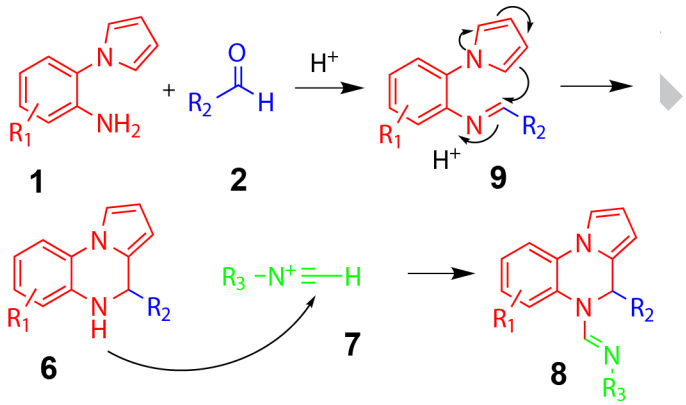


Figure 1. Crystal structure of compound **8a**.



Scheme 2. Proposed mechanism for the formation of **8**.

acid. Scheme 2 depicts a proposed mechanism where amine **1** and aldehyde **2** react to generate the expected Pictet–Spengler product **6** via iminium species **9**. Evidence for the intermediary formation of **6** was observed through LC/MS monitoring, and reaction with the protonated isonitrile **7** affords the final exocyclic amidine moiety **8**.

To the best of our knowledge, this is the first example of a Pictet–Spengler reaction embedded in a one-pot IMCR process that is capable of forming three new chemical bonds in one operation with the generation of an exocyclic amidine moiety. These novel scaffolds are likely to possess a range of biological activities.[11]

With an optimized procedure in hand, reaction scope was explored and twelve analogs (**8a**–**l**, Figure 2) prepared using three amines (**1a**–**c**), seven aldehydes (**2a**–**g**), and seven isonitriles (**3a**–**g**) as reagents [Note: only three 1-(2-aminophenyl)pyrroles were found to be commercially available]. To our delight, the one pot procedure proved to be general, tolerating the full range of starting materials in high yield (39%–87%). As noted, the Pictet–Spengler intermediate was observed during reaction monitoring, and therefore two Pictet–Spengler intermediates, **6a** and **6b**, were isolated and treated with an isonitrile in the presence of *para*-toluene sulfonic acid at

elevated temperatures in toluene. Final products **8a–b** were obtained in 52% and 61% isolated

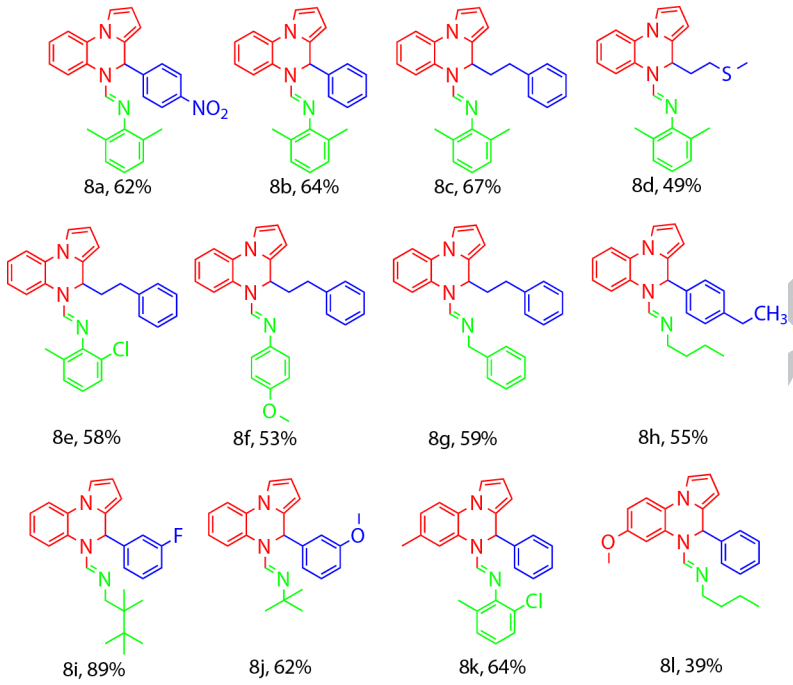
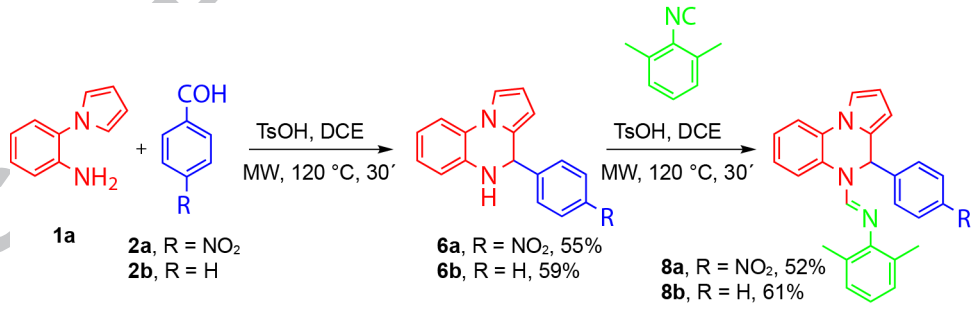


Figure 2. Structures of congeners **8a–l**.

yields respectively (Scheme 3). Moreover, in a preliminary scope study of the amidination process, the indoline **10a** and 1,2,3,4-tetrahydroquinoline **10b** both afforded amidine products **11a–b** in moderate to good yields (Scheme 4). However, non-anilinic amines (piperidine and pyrrolidine) failed to produce the desired amidine, presumably due to their inherent higher pKa

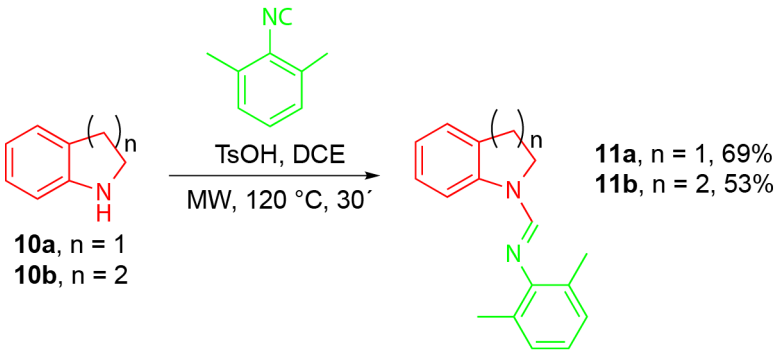


Scheme 3. Two-step preparation of dihydropyrrolo quinoxaline amidines **8a–b**.

values leading to competitive amine protonation and deactivation.

In summary, we have herein reported a novel, one-pot IMCR that enables the assembly of biologically relevant amidine-containing dihydropyrrolo[1,2-*a*]quinoxalines and additionally shown new utility and method improvement of a rarely used amidination reaction of anilines and

isonitriles. Due to the facile and practical production protocol of the IMCR, it is envisioned that access to larger libraries of diverse analogs will be feasible for further biological annotation.



Scheme 4. Reaction of isonitrile **3a** and indolines **10a–b** to afford corresponding amidines **11a–b**.

Acknowledgments. Financial support from the National Institutes of Health (Grant P41GM086190) is gratefully acknowledged. Dr. Sue A. Roberts and Mr. Gabriel B. Hall are thanked for small molecule crystal structure determination.

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Table 1. Optimization of the One-pot Model Reaction.[a]

entry	solvent	acid (eq.)	conditions	conversion[b]
1	toluene	TsOH (0.2)	rt, 18 h	56
2	toluene	TsOH (0.4)	rt. 18 h	70
3	toluene	TsOH (0.2)	reflux, 18 h	63
4	toluene	TsOH (0.4)	reflux, 18 h	45
5	MeOH	TsOH (0.4)	rt, 18 h	24
6	MeOH	TsOH (0.4)	reflux, 18 h	–
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8	AcOH	–	rt, 18 h	35
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10	AcOH	–	reflux, 18 h	–
11	DCE	TsOH (0.4)	MW, 120 °C, 30'	97
12	DCE	TsOH (0.4)	MW, 120 °C, 60'	87
13	DCE	CF_3CH_2OH[d]	MW, 120 °C , 30'	65
14	DCE	AcOH (0.4)	MW, 120 °C , 30'	27
15	DCE	cHCl (0.4)	MW, 120 °C, 30'	53
16	DCE	TFA (0.4	MW, 120 °C , 30'	46
17	DCE	$HClO_4$ (0.4)	MW, 120 °C, 30'	29

[a]Starting materials used in a 1:1:1 molar ratio; [b]Conversion is expressed as % and was judged by means of LCMS analysis (see supplementary information); [c]One drop of 12N HCl used; [d]DCE:CF_3CH_2OH (2:1).

Legends

Figure 1. Crystal structure of compound **8a**.

Figure 2. Structures of congeners **8a–l**.

Scheme 1. Synthesis of *N*-((4-methylpyrrolo[1,2-a]quinoxalin-5(4H)-yl)methylene)methanamines **8** via a Pictet–Spengler amidination sequence.

Scheme 2. Proposed mechanism for the formation of **8**.

Scheme 3. Two-step preparation of dihydropyrrolo quinoxaline amidines **8a–b**.

Scheme 4. Reaction of isonitrile **3a** and indolines **10a–b** to afford corresponding amidines **11a–b**.

Figure 1

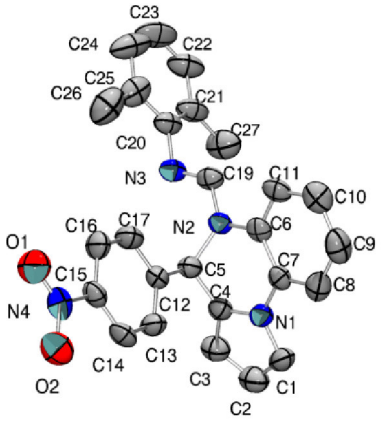
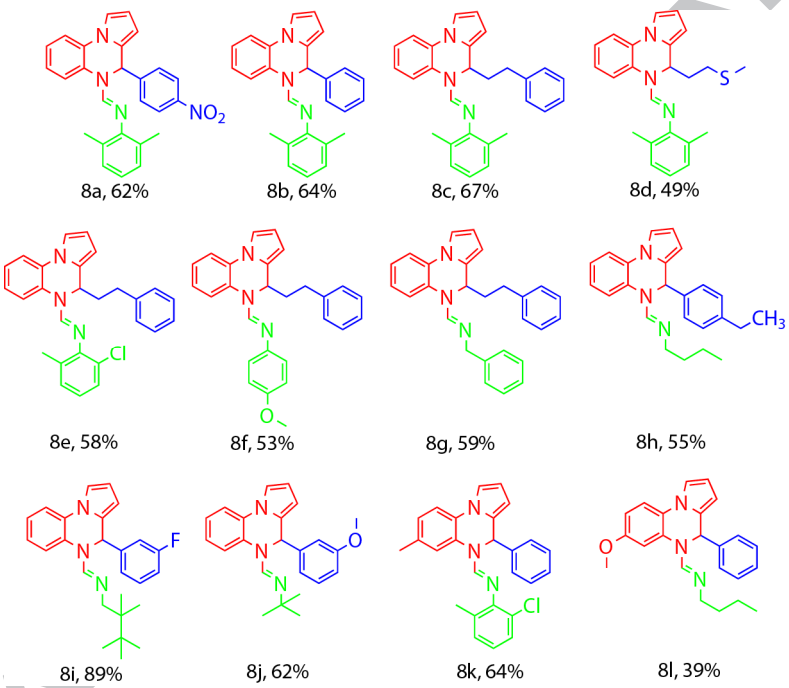
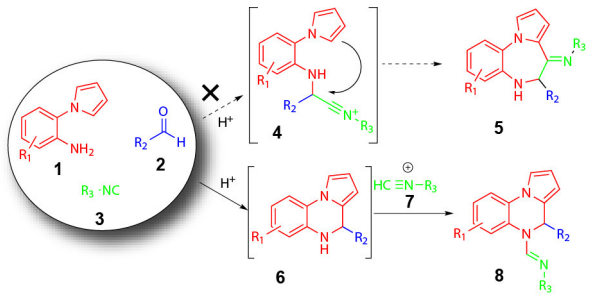


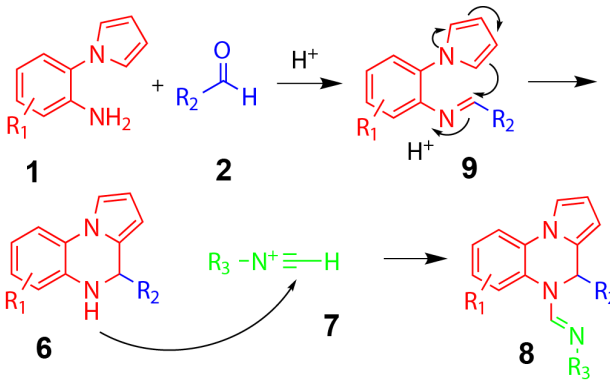
Figure 2



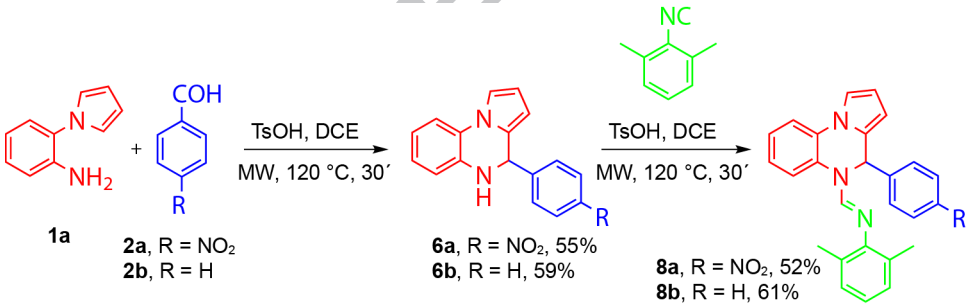
Scheme 1



Scheme 2



Scheme 3



Scheme 4