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A simple one-pot 2-step *N*-1-alkylation of indoles with α-iminoketones toward the expeditious 3-step synthesis of *N*-1-quinoxaline-indoles.

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ABSTRACT

A straightforward procedure for the preparation of *N*-quinoxaline-indoles is presented. A base-catalyzed one-pot addition of indoles to a preformed α-iminoketone proceeds on the *N*-1 indole and the subsequent adduct undergoes an acid-mediated deprotection of an internal amino nucleophile, intramolecular cyclization and final oxidation generating *N*-1-quinoxaline-indoles in good yield.

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Over the last 20 years, attempts to marry chemical and relevant biological space has often been based on the premise of incorporation of 'privileged scaffolds' into small molecule targets, a term defined by Veber as 'molecular chemotypes capable of providing efficient ligands for different biological receptors'.[1] As such the development of facile synthetic protocols to incorporate privileged scaffolds in either individual small molecules or libraries will further enable these target-oriented efforts, increasing the tool-box of techniques available to the 'drug hunter' and consequently the probability of success in finding probes or hits that interact with biologically relevant targets of interest.[2] In particular, indoles and quinoxalines are heterocycles of significant importance in the drug development arena, being present in a diverse range of drugs and natural products with associated pharmacological activity.[3]

To cite just a few, the indole chemotype is present in Oxypertine® **1**, approved for the treatment of schizophrenia; Sumatripan® **2**, used to relieve migraine headaches; and Zafirlukast®, employed for the treatment of asthma.[4–6] Conversely, quinoxalines display a wealth of therapeutical applications, exemplified by Quinacillin®, used for the treatment of bacterial infections[7] and Varenicline® **3** which reduces anxiety incurred by smoking cessation.[8] More importantly, indolyl-quinoxalines also display a number of pharmacological activities, such as antibacterial[9] and Glucagon-like-peptide-1 (GLP1) modulation for the potential treatment of diabetes.[10] Interestingly, a recent report describes the synthesis of an indolyl-quinoxaline **4** ~~with the~~ two heterocycles connected through the indole *N*-1 nitrogen[11] - the topic of the methodology described herein - as opposed to the more familiar C-3 substitution pattern derived from acid-mediated aza-Friedel-Crafts alkylations of indoles.[12] The resulting chemotype **4**, possessed PAS kinase-inhibitory activity, yet was obtained in a lengthy multi-step sequence.[11] To enable further biological exploration via a more operationally friendly protocol, we herein describe novel methodology for the preparation of *N*-1-quinoxaline-indoles **10**, **Scheme 3**.

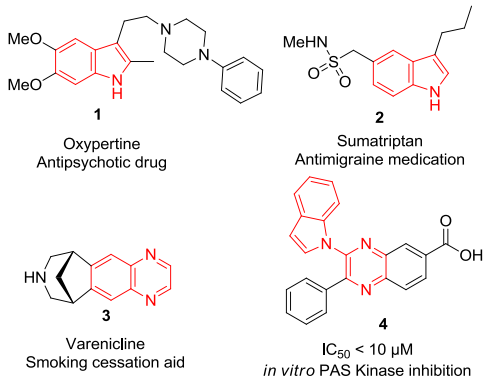


Figure 1. Medicinal relevance of indole-quinoxaline scaffolds.

Given our interest in the development of kinase inhibitors[13] and multi-component reactions (MCRs),[14] a new base-catalyzed MCR was envisioned that could introduce strategically placed functional groups and diversity elements to enable ready-access to the *N*-1-quinoxaline-indole scaffold in an efficient manner,

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Scheme 1. The strategy employs the base-catalyzed addition of indole **8a** onto a preformed α-iminoketone **7a** adorned with a masked amino nucleophile to afford the MCR adduct **9a Scheme 1**, which upon acid treatment undergoes Boc-deprotection, cyclization and oxidation to deliver the target hybrid heterocycle **10a Scheme 3**, in significantly fewer steps than reported methodology.[11]

Optimization studies were carried out with a model reaction comprised of reagents *mono-N*-Boc-4,5-dimethylphenylene diamine **5a**, phenylglyoxaldehyde **6a** and 4-bromoindole **8a**, **Scheme 1**, **Table 1**. Given the somewhat poor nucleophilicity of the anilinic amine **5a**, microwave irradiation was employed to enable formation of the α-iminoketone **7a** (100–120 °C, 10 min). The reaction mixture was cooled to room temperature with subsequent addition of 4-bromoindole and base (1.1 eq.). Entry 6, **Table 1**, proved optimal for **9a** formation (64% yield) using cesium carbonate as the base. The use of more polar solvents or alternate bases had a detrimental impact on isolated yield (Entries 1–3, Table 1). Similarly, conducting indole addition at an even slightly elevated temperature proved to be counterproductive (Entry 7, Table 1). *To the best of our knowledge, this is the first example of an indole N-1 alkylation process with α-iminoketones and is complementary to well-documented C-3 Friedel-Craft mediated functionalization with similar species*.[12]

Scheme 1. α-iminoketone formation/base-catalyzed *N*-1-indole addition.

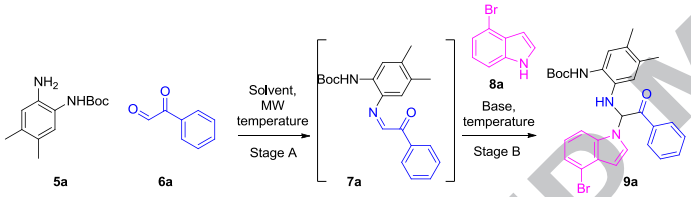


Table 1. Optimization of the one-pot MCR.[a]

Entry	Solvent	Conditions (Stage A)	Conditions (Stage B)[c]	Yield (%)
1[b]	MeCN	rt	Na_2CO_3, rt	traces
2	MeCN	100 °C	Na_2CO_3, rt	12
3	DMF	100 °C	K_2CO_3, rt	21
4	Toluene	100 °C	K_2CO_3, rt	34
5	DCE	100 °C	K_2CO_3, rt	46
6	DCE	120 °C	Cs_2CO_3, rt	64
7	DCE	100 °C	Cs_2CO_3, 60 °C	48

[a] All reactions were carried out at 0.25 mmol scale and the indicated yields are based on UV 254 nm-LC/MS analysis. [b] The imine formation was carried out by heating **5a** and **6a** via microwave irradiation for 10 minutes, except for entry one where the reaction mixture was stirred at rt for ~12 h. [c] Reaction mixtures were stirred at the indicated temperature for 16 h.

Compound **9a** was subsequently exposed to a 20% solution of TFA in DCE at various temperatures (Table 2). Heating the reaction mixture via microwave irradiation depressed the yield (Table 2 Entries 1, 2, 3), whilst simply stirring at room temperature for 1 h, afforded final product **10a** in an acceptable 92% conversion from **9a**, representative of a 3 step deprotection/cyclization/oxidation transformation. Note that the intermediate dihydroquinoxaline was not isolated under these conditions.

Scheme 2. *N*-1-quinoxaline-indole formation.

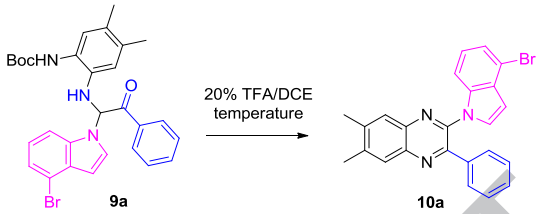


Table 2. Optimization: deprotection-cyclization-oxidation to **10a**.[a]

Entry	Time (h)	Temperature (°C)	Yield (%)
1	0.25	120, MW	66
2	0.25	100, MW	75
3	0.25	80, MW	83
4	1	rt	92
5	5	rt	88

[a] Yields are based on UV 254 nm-LC/MS analysis. MW = microwave irradiation

With the optimized conditions in hand, the scope of the two-step one-pot procedure was thus explored. Using various combinations of four amines, three glyoxaldehydes and two indoles, a small library of *N*-1-quinoxaline-indoles (**10a-g)** was prepared (**Table 3**, **Scheme 3**).[15, 16] It was observed that while the α-iminoketones **7** were formed quantitatively, base catalyzed *N*-1-indole addition to afford **9** proceeded in moderate isolated yields. Nevertheless, addition of indoles to render **9** appeared independent of the substitution patterns and/or the electronic nature of the reactants. The deprotection-cyclization step was straightforward with excellent yields for all examples (**10a-g**, 80-93%). Overall combined isolated yields for the two-step protocol were in the range of 36 to 58% (**Table 3**, Entries 3 and 1, respectively). *N*-1 indole connectivity to the quinoxaline was unequivocally confirmed by X-ray analysis of compound **10a**, **Figure 1**.

Scheme 3. *N*-1-quinoxaline-indole formation.

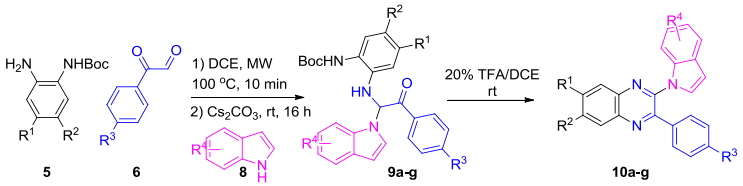


Table 3. Scope of the two-step protocol for the synthesis of *N*-1-quinoxaline-indoles.[a]

Entry	R^1	R^2	R^3	R^4	Yield [%] of **9**[a]	Yield[%] of **10**[a]
1	CH_3	CH_3	H	4-Br	63	92
2	H	OCH_3	H	4-Br	48	83
3	Methylenedioxy (R^1 & R^2)		H	6-Br	43	84
4	H	4-F	H	4-Br	51	93
5	H	H	H	4-Br	58	89
6	CH_3	CH_3	OCF_3	4-Br	47	88
7	CH_3	CH_3	OCH_3	4-Br	61	80

[a] Isolated yields.

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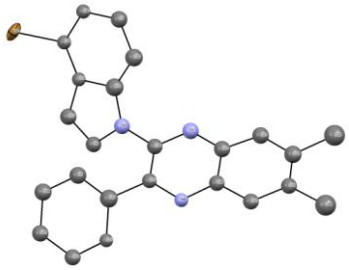


Figure 1. X-Ray structure of **10a**

In conclusion, an operationally friendly MCR to access *N*-1 derivatized indole analogs with α-iminoketones has been developed. With strategic reagent decoration this enabled access to *N*-1-quinazoline-indoles, containing two widely recognized privileged motifs in the medicinal chemistry community **10**. Good yields, three sources of reagent diversity, operational ease and the medicinal relevance of the heterocycles embedded in the overall generic scaffold make this protocol ideal for automated synthesis applications for further biological annotation. Biological evaluation of compounds **10a–g** as well as attempts to apply this protocol for generating higher order complexity are currently underway.

Acknowledgments

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15. *General procedure exemplified for the preparation of* ***9a.*** Arylglyoxaldehyde hydrate (1.1 eq., 0.55 mmol, 0.083 g) and *tert*-butyl (2-amino-4,5-dimethylphenyl)carbamate (1eq., 0.5 mmol, 0.118 g) were dissolved in DCE (2 mL) and heated at 100 °C for 10 minutes in a CEM 72 Explorer™. After confirming the exclusive formation of Schiff base (via TLC), the reaction was allowed to cool to rt. Cesium carbonate (1.1 eq., 0.55 mmol, 0.179 g) and 4-bromo-indole (1eq., 0.5 mmol, 0.098 g, 0.063 mL) were then added and the reaction mixture was stirred at room temperature for 16 h. After reaction completion (TLC and LC/MS), the crude mixture was directly purified by flash chromatography (EtOAc/Hexane 0-20%) using an ISCO ™ purification system to afford *tert*-butyl (2-((1-(4-bromo-1H-indol-1-yl)-2-oxo-2-phenylethyl)amino)-4,5-dimethylphenyl)carbamate **9a** as an orange oil (0.173 g, 63% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.51 (s, 9H), 1.98(s, 3H), 2.10 (s, 3H), 6.53 (s, 3H), 6.74 (d, 1H), 7.04 (s, 1H), 7.22 (m, 2H), 7.38(m, 2H), 7.48(d, 1H), 7.56 (m, 1H), 7.73 (s, 1H), 7.78 (d, 2H), 8.51 (d, 1H) ppm.^{13}C NMR (100 MHz, $CDCl_3$): δ 28.39, 80.33, 108.29, 108.33, 114.97, 115.22, 125.56, 126.30, 128.93, 129.00, 129.24, 130.35, 131.27, 133.86, 135.65, 150.71, 152.62 ppm. $[M+1]^+$= 549 m/z.
16. *General procedure exemplified for the preparation of* ***10a***. *tert*-butyl (2-((1-(4-bromo-1H-indol-1-yl)-2-oxo-2-phenylethyl)amino) -4,5-dimethylphenyl)carbamate **9a** (1eq., 0.305 mmol, 0.173 g) was dissolved in 3 mL of a 20% TFA/DCE solution and stirred at room temperature for 1h. The crude mixture was directly purified by flash chromatography (EtOAc/Hexane 0-20%) using an ISCO ™ purification system to afford 2-(4-bromo-1H-indol-1-yl)-6,7-dimethyl-3-phenylquinoxaline **10a** as a beige solid (0.131 g, 92% yield). Crystals suitable for X-ray crystal structure determination were obtained by means of slow evaporation from ethyl ether/Hexane. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.56 (s,6H), 6.60 (d,1H), 6.96(d,1H), 7.09(t, 1H), 7.40(m, 5H), 7.66 (d, 1H), 7.93 (s, 1H), 8.02(s,1H), ppm.^{13}C NMR (100 MHz, $CDCl_3$): δ 20.59, 105.81, 105.87,111.41, 114.83, 124.18, 124.67, 125.58, 125.63, 127.44, 127.49, 128.13, 128.58, 129.01, 130.10, 130.57, 134.11, 136.08, 137.15, 139.77, 143.04, 143.22, 144.58, 147.64 ppm. $[M+1]^+$= 429 m/z.

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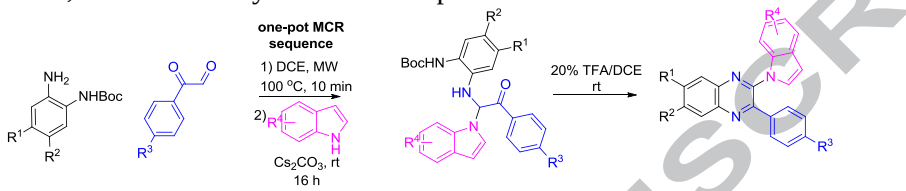
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Guillermo Martinez-Ariza, Muhammad Ayaz and Christopher Hulme*



A novel route to *N*-1-quinoxaline-indoles is presented. Base-catalyzed addition of indole to preformed α-iminoketones proceeds at the *N*-1 indole position and the subsequent adduct undergoes an acid-mediated Boc-deprotection, cyclization and oxidation generating *N*-1-quinoxaline-indoles in good yield in a succint three steps.

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