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Crafting mono- and novel bis-methylated pyrroloquinoxaline derivatives from a shared precursor and its application in the total synthesis of marinoquinoline A†

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The synthesis of mono- and novel bis-methylated pyrrolo[1,2-*a*]quinoxalines through the addition of unstable methyl radicals to aryl isocyanides is described contingent upon the reaction conditions employed. The strategy has been effectively employed in the total synthesis of the natural product marinoquinoline A.

Introduction

Nitrogen-containing heterocycles constitute a fundamental class of chemical compounds, playing a pivotal role in natural products, biologically active structures and compounds of significance in medicinal chemistry. The synthesis of pyrrolo[1,2-*a*]quinoxaline ring systems has been a subject of substantial research over the past century.[1,2] These compounds exhibit significant biological activity, with notable emphasis on the introduction of substitutions at the C-4 position of the pyrroloquinoxaline motif.[3] Such modifications yield structures that include having anticancer potential,[4] antimalarial properties,[5] and antiproliferative effects.[6] Moreover, these molecular structures have been identified as inhibitors of the human protein kinase CK2,[7] activators of glucagon receptors,[8] and agonists for 5-HT_3 receptors,[9] while also serving as building blocks for synthesising gamma aminobutyric acid (GABA) benzodiazepine receptor agonists and antagonists[10] thus prompting significant interest within the pharmaceutical sector.[11]

Traditional synthetic methods to access pyrroloquinoxalines substituted at the 4-position are toxic and dangerous.[12] Among the prevailing methodologies, the most prominent routes entail the reduction of 1-(2-nitrophenyl)pyrroles to their corresponding amino derivatives.[13] Treatment of the amino group with acid chlorides to generate the corresponding acetamides, followed by intramolecular cyclisation under Bischler–Napieralski conditions, thus furnishing the core of the 4-substituted pyrrolo[1,2-*a*]quinoxaline structure.[14] Another route encompasses the condensation of amino derivatives with aldehydes, followed by oxidation of the ensuing 4,5-dihydro pyrroloquinoxaline intermediate.[15] Several methods utilising the modified Pictet–Spengler reaction followed by oxidation have been reported for constructing 4-arylpyrrolo[1,2-*a*]quinoxalines.[16] Recently, a catalyst free electrochemical coupling of 2-isocyanobiphenyls and amines has been reported.[17] The limitation with all of these methods is that the substituent is only efficient with aryl groups.

The use of radical insertion reactions within isonitriles has arisen as an effective alternative method for the formation of nitrogen-based heterocycles, including phenanthridines, indoles, quinolines, quinoxalines and isoquinolines.[18] Addition of alkyl groups have been recently reported to isocyanides to form 4-substituted pyrrolo[1,2-*a*]quinoxalines.[19–25] The methyl group is one of the most widespread functional groups in small biologically active molecules. Over the past decade, the methyl group has gained much interest in the pharmaceutical field due to its ability to increase a drug's binding affinity and potency.[26] This phenomenon is known as the "magic-methyl effect" and is well established in medicinal chemistry.[27] Motivated by the recent advancements in the creation of nitrogen heterocyclic derivatives using biaryl isocyanides as radical acceptors we were interested in exploring whether methyl radicals could be used in a similar approach to create 4-methyl substituted pyrrolo[1,2-*a*]quinoxalines.

Results and discussion

1-(2-Isocyanophenyl)-1*H*-pyrrole **4a** was chosen as a model substrate for the radical addition of a methyl group. **4a** was prepared in a four-step procedure according to the literature in good yields.[19,28] A nucleophilic aromatic substitution between pyrrole and 2-fluoronitrobenzene, followed by a reduction using Pd/C and hydrazine hydrate furnished amine **2a**. Formylation,

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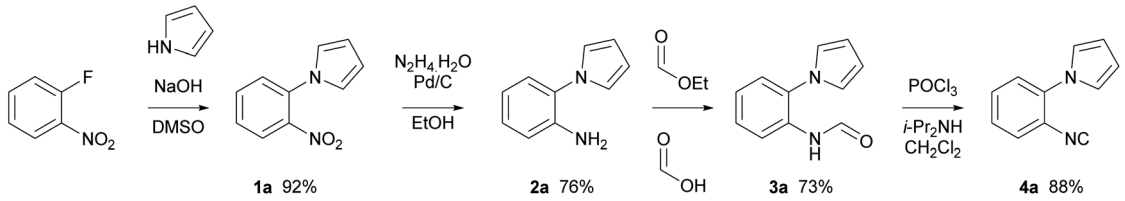
† Electronic supplementary information (ESI) available: Full experimental details and copies of ^{1}H and ^{13}C for novel compounds and cyclised product. See DOI: https://doi.org/10.1039/d3ra05952a



Scheme 1 Synthesis of isocyanide **4a**.

with ethyl formate and formic acid, followed by dehydration with phosphorus oxychloride in the presence of diisopropylamine resulted in the required cyclisation precursor **4a** in excellent yield (Scheme 1).[29]

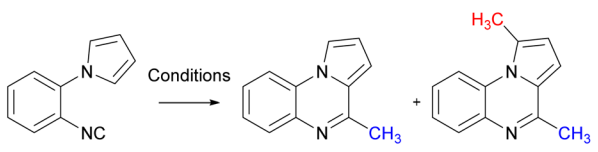
With the cyclisation precursor in hand, reported methods for the generation of methyl radicals were screened. The application of the photoredox catalysis conditions described by Jamison, utilising visible light, led to the isolation of the desired pyrroloquinoxaline **5a** in a yield of 30%, this was similar to that previously reported (Table 1, entry 1).[21]

The use of phenyliodine diacetate in the presence of 2-nitropropane and DBU resulted in the desired pyrroloquinoxaline **5a** in 45% yield. Notably, a minor amount of an unexpected bis-methylated pyrroloquinoxaline **6a** was also obtained in a yield of 10% (entry 2);[30] this is similar to the difluoromethyl radical addition reported previously in the 1 and 4 positions of a pyrroloquinoxaline.[20] When the sequential methylation and intramolecular aromatisation conditions employed by Dai were applied to aryl isocyanide **4a**, pyrroloquinoxaline **5a** was isolated in an encouraging 48% yield with no bis-methyl adduct **6a** observed (entry 3).[31] Cyclisation with dicumyl peroxide (DCP) in the presence of KF in *t*-BuOH resulted in pyrroloquinoxaline **5a** in 67% yield with 4% of **6a** in the reaction mixture observed by ^{1}H-NMR (entry 4).[32] Upon exposure to blue LED light, the reaction of **4a** with methylhydrazine hydrochloride in the presence of eosin B at room temperature, as well as blue LED-induced cyclisation in the absence of a photocatalyst with sodium methanesulfinate under aerobic conditions, yielded a mixture of pyrroloquinoxaline **5a** and **6a** (entries 5 and 6).[33,34] Using Fenton reaction conditions reported by Zhang led exclusively to the formation of bis-methyl pyrroloquinoxaline **6a** (entry 7).[35]

Encouraged by these results of selectively being able to favour mono-methyl radical addition over bis-methylation, these conditions were initially investigated. The use of DCP as a source of methyl radicals provided the greatest yield of pyrroloquinoxaline **5a**, albeit with trace amounts of **6a**. Conditions were further optimised for the methylation of 1-(2-isocyanophenyl)-1*H*-pyrrole **4a**. Using the conditions reported by Xu *et al.* for varying time periods revealed that heating for 12 hours resulted in only pyrroloquinoxaline **5a** (Table 2, entry 1).[32] Prolonged heating led to increased pyrroloquinoxaline **5a** yields accompanied by the formation of bis-methyl pyrroloquinoxaline **6a** (entries 2–4). Although heating for 18 hours showed formation of bis-methyl pyrroloquinoxaline **6a**, the desired product was formed in greatest yield. Altering the catalyst to CsF resulted in a decreased yield (entry 5) as observed previously.[32]

Given that the half-life of DCP is 10 hours at 117 °C and 1 hour at 137 °C,[36] adjusting the temperature to 100 °C resulted in 50% of pyrroloquinoxaline **5a** and recovered starting material **4a** (entry 6). Raising the temperature to 140 °C led to a reduced mixture of the pyrroloquinoxalines **5a** and **6a** (entry 7). To

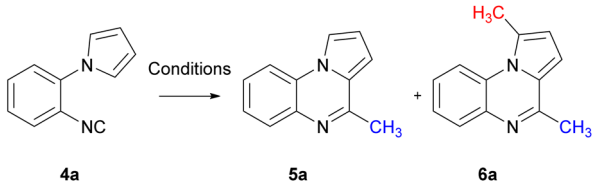
Table 1 Screening of methyl radical conditions



4a **5a** **6a**

Entry	Conditions	**5a** (%)	**6a** (%)
1	(1) $PhI(OAc)_2$ (1 equiv.), MeCOOH (2 equiv.) (2) [*fac*-Ir(ppy)$_3$] (1 mol%), 26 W fluorescent bulb, DMF, rt	30	—
2	$PhI(OAc)_2$ (2 equiv.) 2-nitropropane (1 equiv.), DBU (3 equiv.), CH_3CN, rt	45	10
3	DTBP (3 equiv.), $FeCl_2$ (20 mol%), Davephos (5 mol%), PhF, 130 °C	48	—
4	DCP (2 equiv.), KF (0.5 equiv.), *t*-BuOH, 120 °C	67	4
5	$MeNHNH_2 \cdot HCl$ (3 equiv.), K_2CO_3 (3 equiv.), eosin (5 mol%), 5 W blue LED, DMSO, air	32	24
6	$MeSO_2Na$ (4 equiv.), 24 W blue LED, EtOAc, rt, air	33	26
7	$FeCl_2$ (0.2 equiv.), 30% H_2O_2 (3 equiv.), DMSO, rt	—	88

Table 2 Optimisation of methyl radical addition to isocyanide 4

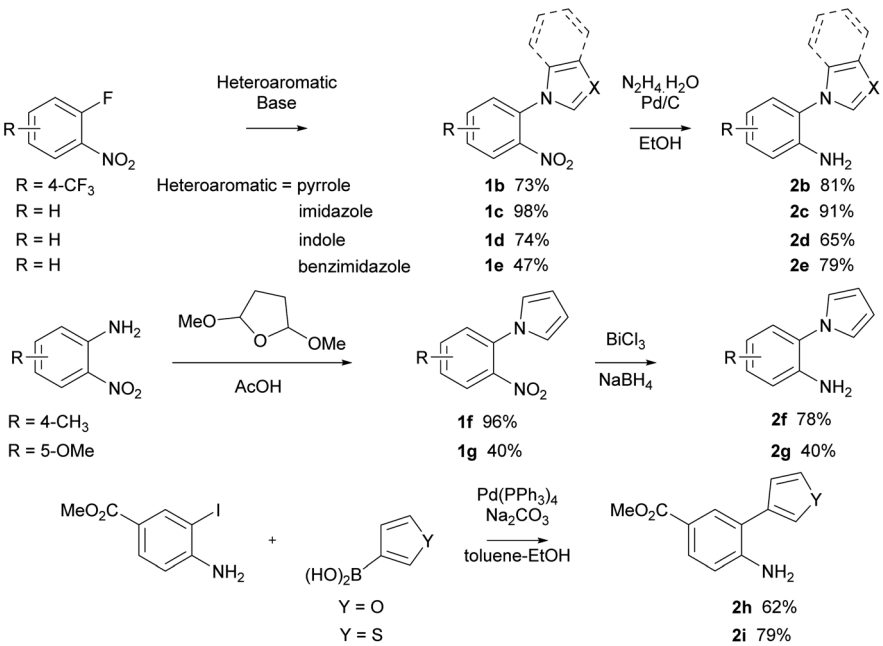


Entry	Catalyst (equiv.)	DCP equiv.	Time (h)	Temperature (°C)	**5a** (%)	**6a** (%)
1	KF (0.5)	2	12	120	52	—
2	KF (0.5)	2	18	120	74	3
3	KF (0.5)	2	24	120	67	4
4	KF (0.5)	2	48	120	65	12
5	CsF (0.5)	2	18	120	48	2
6	KF (0.5)	2	18	100	50	—
7	KF (0.5)	2	18	140	56	2
8	**KF (0.5)**	**1.1**	**18**	**120**	**84**	—
9	KF (0.5)	3	18	120	66	14
10[a]	KF (0.5)	1.1	18	120	76	—

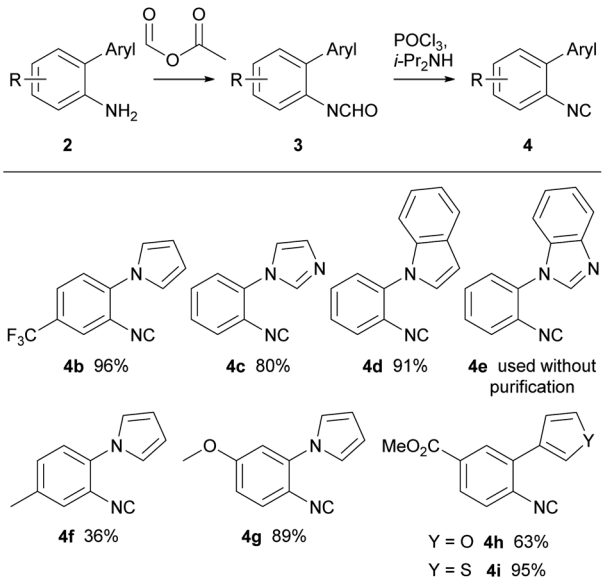
[a] Slow addition of DCP over 4 h.

curtail the bis-methylated product formation, the amount of DCP was explored. Using 1.1 equiv. of the initiator resulted in exclusive formation of **5a** in 84% yield (entry 8). Conversely of excess DCP, 3 equiv., increased the formation of the bis-product **6a** at the expense of **5a** (entry 9). Finally, slow addition of the radical initiator, DCP, over 4 hours resulted in a slightly lower yield of 76% of **5a**.

With optimised conditions for the methylation concomitant pyrroloquinoxaline formation, investigation of the cyclisation with analogous pyrrole and five-membered heterocycle substituted aryl isocyanides was conducted. The synthesis of arylamines involved three different approaches (Scheme 2). In the first method, arylamines were synthesised by nucleophilic aromatic substitution of nitrogen-containing ring systems with 2-fluoronitrobenzene. Subsequent reduction of the nitro intermediates (**1b–e**) using Pd/C and hydrazine hydrate yielded amines (**2b–e**) in yields ranging from 65–91%. Conversely, the Clauson–Kass reaction of electron-rich nitroanilines with 2,5-dimethoxytetrahydrofuran in acetic acid,[8] followed by reduction using $BiCl_3$–$NaBH_4$ resulted in amines **2f** and **2g**. The final



Scheme 2 Synthesis of biaryl amines **2**.



Scheme 3 Synthesis of isocyanides 4.

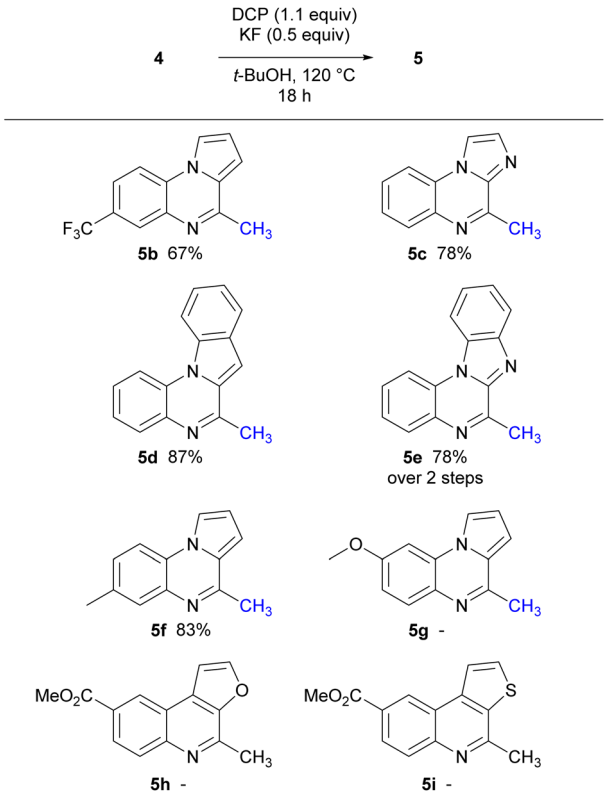
approach utilised the Suzuki–Miyaura reaction of aryl iodide and commercially available boronic acids to give the corresponding amines **2h** and **2i** in good yields.[37]

Subsequently, all the arylamines underwent a two-step conversion to the respective isocyanides. Formylation with formic acetic anhydride followed by dehydration using phosphorus oxychloride and diisopropylamine furnished isocyanides **4** in good yields (Scheme 3).

With the corresponding isocyanides **4** prepared, optimised mono-methylation/radical cyclisation conditions were employed using DCP and KF. The resulting 6-*endo* cyclisation gave a range of tri- and tetracyclic structures bearing a methyl group in the 2-position of the quinoline ring (Scheme 4).

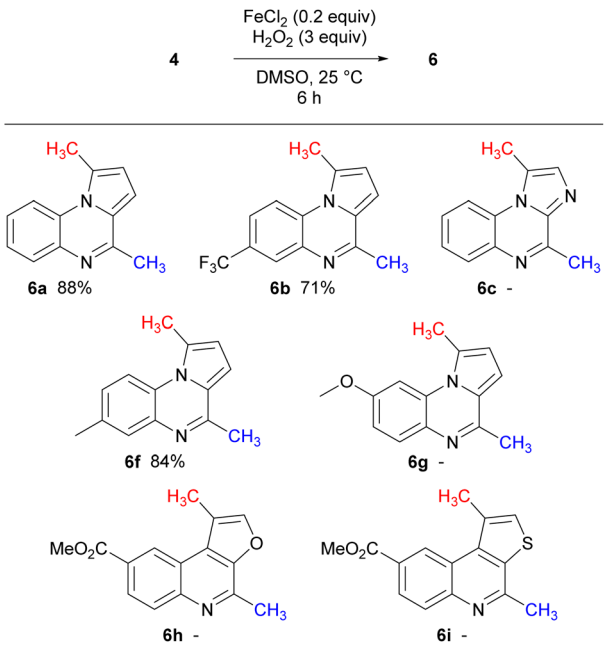
Precursors, **4b**, **4f**, and **4g**, were prepared to investigate the electronic effects of the cyclisation precursor and from the results attained it was evident cyclisation was favoured for most of the isocyanides apart from electron-rich isocyanide **4g**. Following this preliminary screen, isocyanides **4c–e** were reacted and successfully underwent 6-*endo* cyclisation to tricyclic and tetracyclic congeners. The slightly higher yields for **5d** and **5e** could be explained by the extended conjugation in comparison to the tricyclic counterparts. Furthermore, we explored oxygen and sulfur derivatives, **5h** and **5i**, although no discernible reactions were observed. The lack of reactivity is attributed to the presence of lone pairs of electrons on the heteroatom in thiophene and furan, which might impede the closure of the intermediate radical, thus explaining the absence of the expected ring-closing reactions.

As previously mentioned, bis-methylation was observed with isocyanide **4a** when Fenton conditions were subjected to the reaction conditions (Table 1, entry 7). Employing Fenton reaction conditions, isocyanides **4a–c** and **4f–h** were treated, yielding bis-methyl pyrroloquinoxalines **6a**, **6b** and **6f** in very good yields (Scheme 5). No mono-methylated products were observed in any case.



Scheme 4 Cyclisation using DCP to give tricyclic and tetracyclic derivatives.

Notably, decreasing the amount of DMSO used in the reaction below 10 equiv. resulted in lower yields. Interestingly, the imidazole isocyanide **4c** exclusively produced 4-methylimidazo[1,2-*a*]quinoxaline **5c**, even with prolonged reaction times and



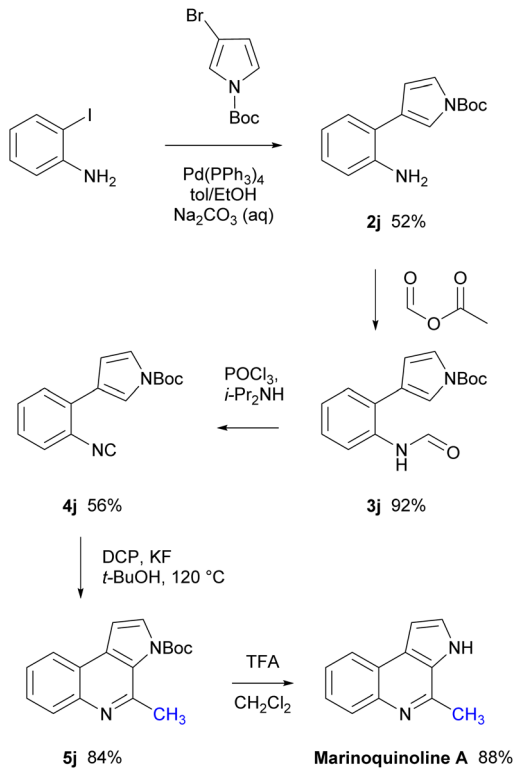
Scheme 5 Cyclisation using Fenton conditions for bis-methylation.

increased amount of radical initiator, possibly due to stabilisation of the resulting radical by the lone pair of electrons on the adjacent nitrogen atom. To date, only one example in the literature similar to electron rich methoxy isocyanide **4g** that has undergone radical cyclisation reported,[21] however the methoxy group is in the 7-position. In our hands, isocyanide **4g** displayed a lack of reactivity, possibly attributed to the presence of the electron-rich methoxy group, which seems to render the isocyanide nucleophilic.[38] This trend was similarly observed with the furan and thiophene derivatives.

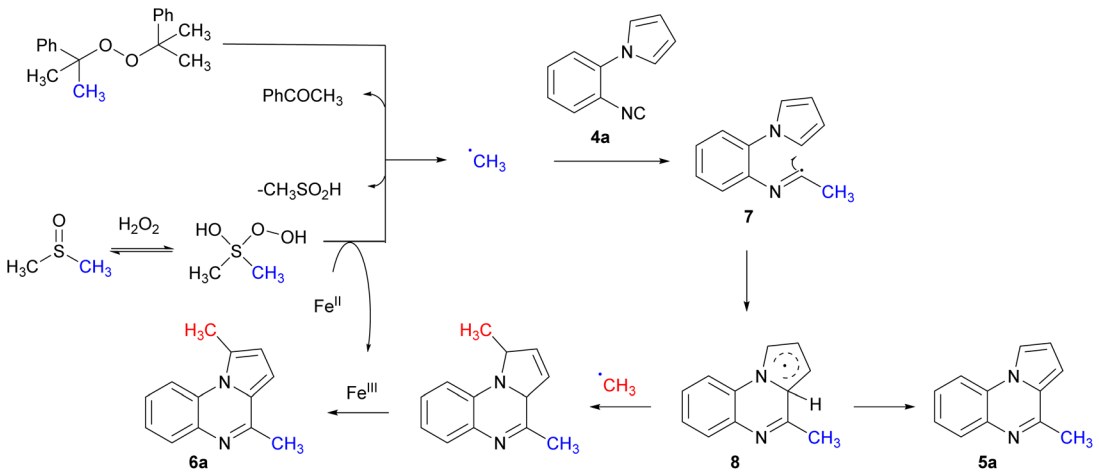
The mechanism for the mono- and bis-methylation was investigated for the *in situ* generation of methyl radicals. Initially, an inhibition reaction was carried out in the presence of 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) under standard reaction conditions. A complete suppression of methylation concomitant cyclisation was observed, and formation of a methyl-TEMPO adduct was observed by GC-MS. This indicates the methyl radical species is involved and initiates the reaction and is consistent with previous studies.[39] Based on this data, a plausible mechanism for the reaction is proposed (Scheme 6). Initiation begins with the homolysis of DCP, yielding acetophenone and a methyl radical *via* β-cleavage.[32] The methyl radical adds to the isocyanide to generate the α-imidoyl radical 7 which cyclises onto the aromatic ring to give radical **8**. H-abstraction by the cumyloxy or methyl radical results in the mono-methylated product **5a**. The bis-methylated pyrroloquinoxaline **6a** was observed when excess DCP was used, however was more predominant with Fenton conditions.

When mono-methylated pyrroloquinoxaline **5a** was subjected to $FeCl_2$, in H_2O_2 and DMSO only 17% of the bis-methylated pyrroloquinoxaline **6a** was isolated. Wan *et al.* observed a radical addition to form a bis-alkylated pyrroloquinoxaline.[20] This is proposed to occur *via* a direct C–H radical addition to the α-position of the pyrrole ring followed by a second radical addition to the isocyanide to form the α-imidoyl radical. This undergoes cyclisation followed by aromatisation to form the bis-alkylated pyrroloquinoxaline **6a**. This study features radical addition to produce the mono-alkylated product with no bis-alkylation product. A second radical addition was not efficient from the pyrroloquinoxaline **5a**. Thus, an alternative mechanism is proposed to form the bis-methylated pyrroloquinoxaline **6a**. Initial addition of the methyl radical followed by cyclisation. The resulting π-radical **8** is stabilised by resonance and allows for another methyl radical to trap the radical and yield the bis-methylated pyrrolines; this undergoes aromatisation to the pyrrole in the presence of iron.[40]

Marinoquinoline A is a methylated 3*H*-pyrrolo[2,3-*c*]quinoline natural product isolated from the marine gliding bacteria



Scheme 7 Total synthesis of marinoquinoline A.



Scheme 6 Proposed mechanism for methyl radical addition to form mono- or bis-methylated pyrroloquinoxaline.

Rapidithrix thailandica TISTR 1742 by Plubrukarn in 2008.[41] and displays inhibition against acetylcholinesterase ($IC_{50} = 4.9$ μM against *Torpedo californica* AChE).[42] To demonstrate the practical utility of the conditions developed herein, marinoquinoline A was successfully synthesised in five steps from commercially available starting materials (Scheme 7). Isocyanide **4j** was prepared through a Suzuki–Miyaura coupling between 2-iodoaniline and 3-bromopyrrole-1-carboxylic acid *tert*-butyl ester in good yield, followed by formylation with formic acetic anhydride and dehydration with phosphorous oxychloride in the presence of diisopropylamine. The key step was the radical methylation of **4j** using DCP to provide the 3*H*-pyrrolo[2,3-*c*]quinoline core structure **5j** in excellent yield. Consequent deprotection of the *N*-Boc group using TFA in CH_2Cl_2 resulted in marinoquinoline A in excellent yield.

Conclusions

To summarise, an effective approach has been tuned to yield selective mono- and bis-methylated pyrroloquinoxaline derivatives, contingent on the specific reaction conditions employed. Insights from mechanistic studies indicate that methylation at the 1-position occurs subsequent to the initial addition of the methyl radical to the α-imidoyl radical, rather than *via* direct addition to a double bond. The methodology has been applied to the synthesis of the natural product marinoquinoline A in very good yield overall and provides a route to novel methylated N heterocycles. Exploration of the reaction mechanism, biological activity, further applications of the methodology and functionalisation are currently underway.[43]

Experimental

General procedure for synthesis of compound 5

A mixture of isocyanide (1 equiv.), KF (0.5 equiv.), DCP (1.1 equiv.) and *t*-butanol (0.08 M) was heated at 120 °C in a sealed tube for 18 h. The mixture was allowed cool and concentrated under reduced pressure. The residue was purified by column chromatography (99 : 1 Hex : EtOAc) give mono-methylated products.

General procedure for synthesis of compound 6

A mixture of isocyanide (1 equiv.), $FeCl_3$ (0.2 equiv.), 30% w/w H_2O_2 (3 equiv.) and DMSO (0.083 M) was stirred at 25 °C under inert atmosphere for 6 h in a sealed tube. The mixture was extracted with ethyl acetate (3 × 5 mL) and water (3 × 5 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by column chromatography (99 : 1 Hex : EtOAc) give bis-methylated products.

Author contributions

MD: investigation, methodology, writing – original draft, writing – review & editing. NG: methodology, writing – review & editing. VT: methodology, writing – review & editing. ZR: methodology, writing – review & editing. DS: methodology, supervision, writing – review & editing. BP: conceptualization, funding acquisition, supervision, writing – original draft, writing – review & editing.

Conflicts of interest

There are no conflicts to declare.

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