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Acetic Acid Catalysed One-Pot Synthesis of Pyrrolo[1,2-*a*]quinoxaline Derivatives

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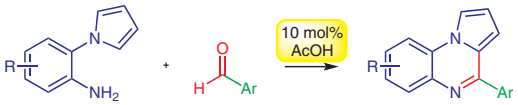

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Abstract An efficient acetic acid catalysed reaction has been developed for the synthesis of 4-aryl substituted pyrrolo[1,2-*a*]quinoxalines from readily available starting materials. A range of structures have been synthesised in very good to excellent yields. The one-pot reaction proceeds through imine formation, cyclisation followed by air oxidation.

Key words pyrrolo[1,2-*a*]quinoxaline, catalysis, Pictet–Spengler reaction, 1-(2-aminophenyl)pyrroles, biological heterocycles

The pyrrolo[1,2-*a*]quinoxaline scaffold is present in various heterocyclic compounds that exhibit an extensive range of pharmacological profiles.[1] In particular, substitution at the C-4 position of the pyrroloquinoxaline motif results in derivatives that possess biological activities such as anticancer,[2] antimalarial,[3] and antiproliferative effects.[4] Additionally, these structures have been reported as inhibitors of the human protein kinase CK2,[5] glucagon receptor agonists,[6] and $5HT_3$ receptor agonists,[7] and have been applicable in the synthesis of GABA benzodiazepine receptor agonists and antagonists.[8] Some of these compounds have also exhibited unique fluorescence properties, enabling uses for amyloid fibril detection.[9] For this reason, the efficient synthesis of 4-substituted pyrrolo[1,2-*a*]quinoxalines has gained much attention and is a highly desirable target in drug discovery. Various methods have been developed for the synthesis of 4,5-dihydropyrrolo[1,2-*a*]quinoxalines and unsubstituted pyrrolo[1,2-*a*]quinoxalines;[10] however, a survey of the literature revealed that few methods have been reported for the more active 4-substituted derivatives (Scheme 1).[11] A rare one-pot iron-promoted reduction of 1-(2-nitrophenyl)pyrroles, oxidation of alcohols followed by cyclisation and heterocycle oxidation in a cascade has been reported by Pereira.[12] A novel activated carbon/water catalytic system has recently been reported by Wang between 1-(2-nitrophenyl)pyrroles and aryl amines for the synthesis of pyrrolo[1,2-*a*]quinoxalines.[13] The radical addition of isocyanides has been reported by Hilton.[14] However, the most common methods to synthesise 4-substituted derivatives involve the reduction of 1-(2-nitrophenyl)pyrroles to the corresponding amino derivatives.[15] Treatment of the amino group with acid chlorides to form the corresponding acetamides followed by intramolecular cyclisation under Bischler–Napieralski conditions formed the 4-substituted pyrrolo[1,2-*a*]quinoxaline core.[16] Another approach involved the condensation between amino derivatives and aldehydes followed by oxidation of the 4,5-dihydro pyrroloquinoxaline intermediate.[17] A modified Pictet–Spengler reaction using benzotriazole followed by oxidation with MnO_2 has been reported as a one-pot procedure to construct 4-arylpyrrolo[1,2-*a*]quinoxalines.[18] Huo reported a metal-free variation of the Pictet–Spengler reaction meditated by TEMPO oxoammonium salts.[19] Recently, Krishna reported a one-pot copper-catalysed synthesis of pyrrolo[1,2-*a*]quinoxalines from 1-(2-aminophenyl)pyrroles and aldehydes.[20] These multistep syntheses have led to moderate yields and, in most cases, require the use of toxic reagents. Therefore, it is highly desirable to develop an efficient, nontoxic and convenient approach for the synthesis of 4-substituted pyrroloquinoxalines.

To identify the optimal reaction conditions, commercially available 1-(2-aminophenyl)pyrrole and benzaldehyde were initially used as model substrates. Reaction in the absence of an acid catalyst resulted in neither compounds **3a** nor **4a** (Table 1, entry 1). The efficiency of different acid catalysts was explored at 60 °C (entries 2–6) under an inert atmosphere. In the presence of concentrated hydrochloric acid or *p*-TSA no reaction was observed, and only small amounts of the desired cyclised product **3a** was ob-

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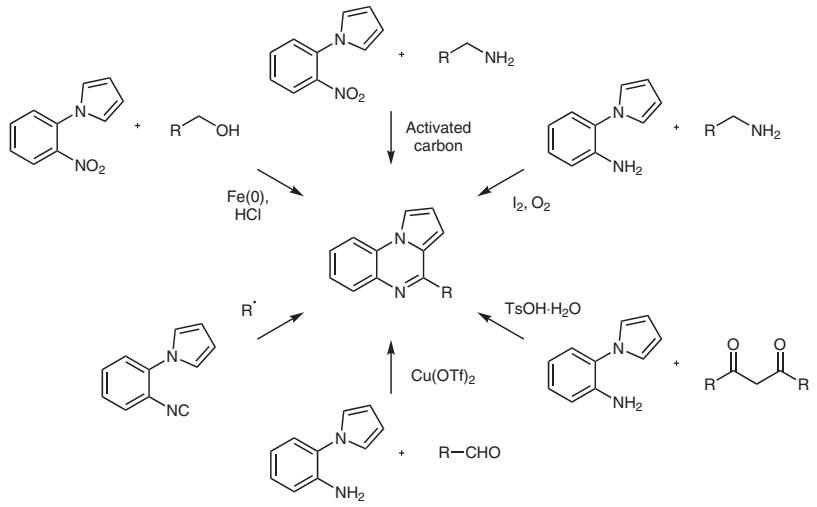
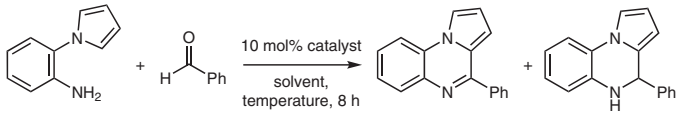


Scheme 1 Previous approaches to pyrrolo[1,2-*a*]quinoxalines[12–15,19]

tained with zinc chloride and trifluoroacetic acid. Reaction with acetic acid resulted in 55% yield of **3a**, with small amounts of the 4,5-dihydropyrroloquinoxaline **4a** observed by NMR analysis. The 4,5-dihydropyrroloquinoxaline **4a** oxidised to **3a** on standing at room temperature, as observed by Verma.[18] Further optimisation in the presence of air resulted in the greatest yield of **3a** at 89%, suggesting air oxidation was promoting aromaticity. No obvious improvements were observed when screening different solvents (entries 8–11). The reaction was explored at different tem-

Table 1 Optimisation of Reaction Conditions[a]



1a **2a** **3a** **4a**

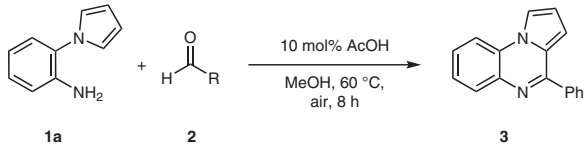
Entry	Acid	Atmosphere	Solvent	Temp. (°C)	Yield of **3a** (%)
1	–	N_2	MeOH	60	–
2	*p*TSA	N_2	MeOH	60	–
3	$ZnCl_2$	N_2	MeOH	60	14
4	HCl	N_2	MeOH	60	–
5	AcOH	N_2	MeOH	60	55
6	TFA	N_2	MeOH	60	9
7	**AcOH**	**air**	**MeOH**	**60**	**89**
8	AcOH	air	THF	60	51
9	AcOH	air	EtOAc	60	43
10	AcOH	air	MeCN	60	61
11	AcOH	air	toluene	60	58
12	AcOH	air	MeOH	25	20
13[b]	AcOH	air	MeOH	80	75
14[c]	AcOH	air	MeOH	60	trace
15[d]	AcOH	air	MeOH	60	50

[a] Reactions were carried out using 1-(2-aminophenyl)pyrrole (1 equiv) and benzaldehyde (1 equiv).
[b] Experiment was carried out in a sealed tube.
[c] Experiment was carried using 5 mol% catalyst.
[d] Experiment was carried using 5 equiv benzaldehyde.

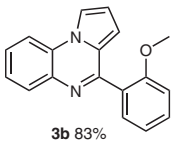
peratures (entries 7, 12, and 13), and a mixture of **3a** and **4a** was observed at 25 °C.[21] The highest-yielding reaction was observed at 60 °C. When the catalyst loading was halved to 5 mol% only a trace amount of the desired product was observed (entry 14), with the 4,5-dihydro pyrroloquinoxaline **4a** isolated as the major product. When the stoichiometry of benzaldehyde was increased five-fold, the yield decreased to 50% and isolation was problematic (entry 15).

With optimised conditions in hand, the reaction was further studied to extend the scope and generality of the protocol and to afford a series of 4-arylpyrrolo[1,2-*a*]quinoxaline derivatives in good to excellent yields (Table 2). Initially, electron-rich benzaldehydes were reacted to provide the corresponding pyrroloquinoxalines **3b–d** in 83–85% yield. In the presence of electron-withdrawing nitro groups, the position of the substituent affected the outcome of the reaction. Use of 3-nitrobenzaldehyde resulted in the 4,5-dihydropyrroloquinoxaline in a low yield; whereas the *p*-substituted reactant resulted in 82% yield of **3f**. Encouraged by this result, a series of halogen-substituted benzaldehydes was examined, and the resultant *o*- and *p*-substituted products **3h** and **3j** were produced in 87% and 84% yield, respectively. However, the *m*-substituted halogen benzaldehydes **2g** and **2i** resulted in an inseparable mixture of the aromatised product **3g** and **3i**, and the 4,5-dihydropyrroloquinoxaline **4g** and **4i**. Thiophene-2-carboxaldehyde and further functionalised benzaldehydes were efficiently employed to produce pyrroloquinoxalines **3k–o** in 83–88% yield.

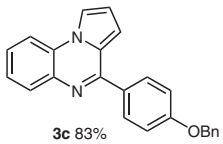
Table 2 Synthesis of Analogues **3b–o**



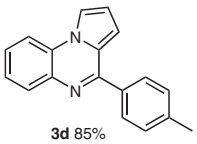
1a **2** **3**



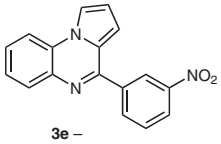
3b 83%



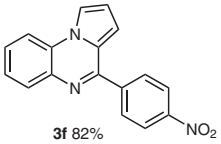
3c 83%



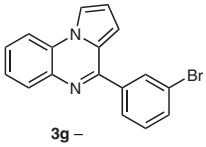
3d 85%



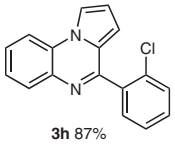
3e –



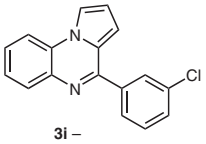
3f 82%



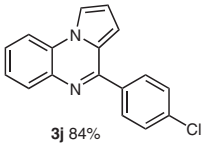
3g –



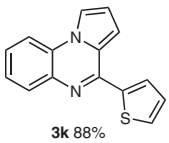
3h 87%



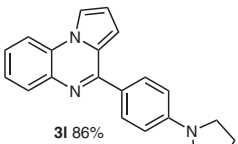
3i –



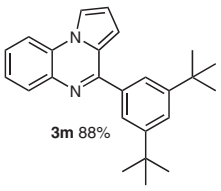
3j 84%



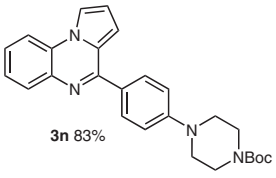
3k 88%



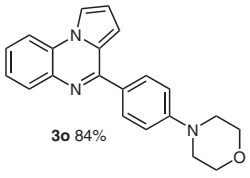
3l 86%



3m 88%

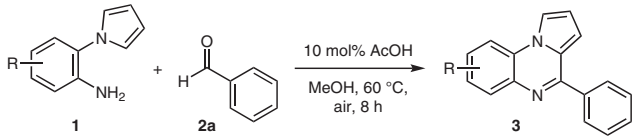


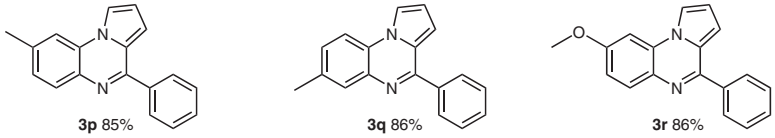
3n 83%

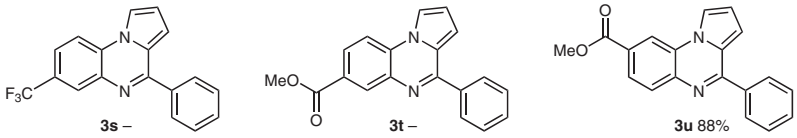


3o 84%

Table 3 Synthesis of Analogues **3p–u**





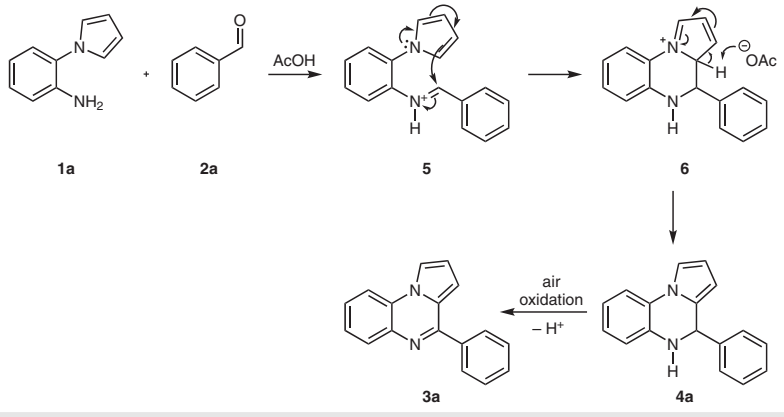


Next, the substrate scope with substituted anilines was investigated (Table 3). Use of electron-rich anilines resulted in excellent yields of pyrroloquinoxalines **3p–u**.

Unfortunately, no reaction was observed when a CF_3 group was appended to the aniline ring. To explore electron-deficient substrates further, methyl benzoates **1t** and **1u** were tested (Table 3). When the ester group was in the same position as the trifluoromethyl group (**1s**) no reaction was observed. Compounds **3s** and **3t** possess electron-deficient groups in the *para* position to the pyrrole and were unreactive as a result of conjugation of the pyrrole nitrogen lone pair of electrons into the electron-withdrawing group.[23] This was confirmed when ester **1u** was prepared by using a known procedure and produced the corresponding pyrroloquinoxaline **3u** in excellent yield.

Based on previous reports, a plausible mechanism for the synthesis of pyrrolo[1,2-*a*]quinoxaline is proposed in Scheme 2. The reaction occurs by initial condensation of aminophenylpyrrole **1** and aldehyde **2** to afford the iminium intermediate **5**. This undergoes intramolecular electrophilic addition in a Pictet–Spengler type reaction to give dihydro derivative **4**, which oxidises in the presence of air to the corresponding aromatic pyrroloquinoxaline **3**.

In summary, a facile method for the synthesis of pyrrolo[1,2-*a*]quinoxalines **3** using the Pictet–Spengler reaction has been developed by using a catalytic amount of acetic acid.[22] A range of compounds has been prepared in high yields under mild conditions. It has been shown that the position of the electron-withdrawing groups is crucial; when the group is in a deactivating position the reaction does not proceed due to conjugation with the pyrrole nitrogen lone pair of electrons. Synthetic applications to biologically active compounds using this methodology are under way.



Scheme 2 Proposed mechanism for acetic acid catalysed synthesis of pyrroloquinoxaline **3**.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0039-1690724.

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(22) **Typical Procedure for the Synthesis of Pyrrolo[1,2-*a*]quinoxaline 3a**: To a solution of 2-(1*H*-pyrrol-1-yl)aniline (1 equiv) in methanol (5 mL) were added benzaldehyde (1 equiv) and acetic acid (0.1 equiv) and the mixture was heated to 60 °C for 8 h. The reaction mixture was allowed to cool to room temperature and the solvent was removed under reduced pressure. The crude reaction mixture was purified by column chromatography to give 2-substituted pyrrolo[1,2-*a*]quinoxaline **3a** as a pale-yellow solid; mp 118–120 °C. IR (neat): 2929 (CH) cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 8.07 (dd, *J* = 7.7, 1.4 Hz, 1 H, Ar*H*), 7.99–8.04 (m, 5 H, 5 × Ar*H*), 7.88 (dd, *J* = 8.0, 1.4 Hz, 1 H, Ar*H*), 7.01 (dd, *J* = 3.8, 1.3 Hz, 1 H, Ar*H*), 6.90 (dd, *J* = 3.9, 2.7 Hz, 1 H, Ar*H*). ^{13}C (126 MHz, $CDCl_3$): δ = 154.4 (C), 138.4 (C), 136.2 (C), 130.2 (CH), 129.7 (CH), 128.6 (2 × CH), 128.5 (2 × CH), 127.4 (CH), 127.1 (C), 125.3 (C), 125.2 (CH), 114.5 (CH), 113.9 (CH), 113.6 (CH), 108.7 (CH). MS: *m*/*z* (%) = 244 (100) $[M + H]^+$.

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