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Pyrrolo[1,2-*a*]quinoxalines from chalcones: An alternate route

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ABSTRACT

The synthesis of 2,4-disubstituted pyrrolo[1,2-*a*]quinoxalines from chalcones is reported. The key steps used are polyphosphoric acid (PPA) assisted acyl rearrangement of the pyrrole ring and Fe catalyzed reduction-cyclization leading to 2,4-disubstituted pyrrolo[1,2-*a*]quinoxalines. Despite the utilization of comparatively unreactive aromatic ketones, modest to good yields were obtained.

Introduction

Pyrrolo[1,2-*a*]quinoxalines are an important synthetic target due to their diverse bioactivities and photophysical properties [1]. These compounds have shown potential as anti-leishmanial and antitumor compounds as well as central dopamine antagonists [2]. Additionally, compounds such as 1 and 2 also display 5-HT3 receptor and glucagon receptor antagonist activity, respectively (Fig. 1) [3,4].

Our group has an ongoing interest in the synthesis of fused heterocyclic systems and their applications [5]. With this experience, the synthesis of 2,4-disubstituted pyrrolo[1,2-*a*]quinoxalines were envisaged. The synthesis of these compounds can generally be segregated into two broad categories: (a) cyclization reactions carried out on 1-arylpyrroles and (b) conversion of propiolates or *N*-ylides to pyrrolo[1,2-*a*]quinoxalines *via* 1,3-dipolar cycloaddition [6]. Several alternative strategies have also been reported in the literature, relying mainly on specific precursors or catalysts. Ammermann and co-workers have demonstrated the synthesis of 1,4-disubstituted pyrrolo[1,2-*a*]quinoxalines *via* the annulation of 2-alkylquinoxalines. A unique feature of this reaction was incorporating a pyrrole ring in the last step using $Ir(acac)_3$ as the catalyst [7]. The synthesis of pyrrolo[1,2-*a*]quinoxalines was reported by Guiffer and co-workers *via* the condensation of 2-methylquinoxalines and ethyl bromopyruvate [8]. Wang and co-workers reported the one-pot, three-component synthesis of 4,5-dihydropyrrolo[1,2-*a*]quinoxaline under $BF_3.Et_2O$ catalysis using *o*-phenylenediami-

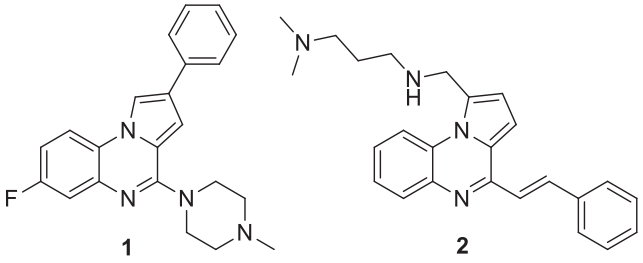
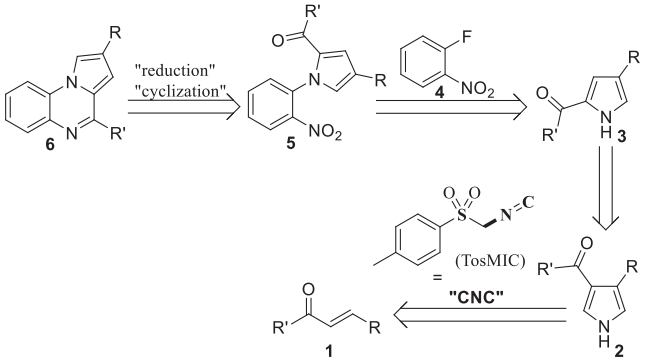


Fig. 1. Pyrrolo[1,2-*a*]quinoxaline compounds with 5-HT3 receptor and glucagon receptor antagonist activities.



Scheme 1. Retrosynthetic analysis for the synthesis of 2,4-disubstituted pyrrolo [1,2-*a*]quinoxalines.

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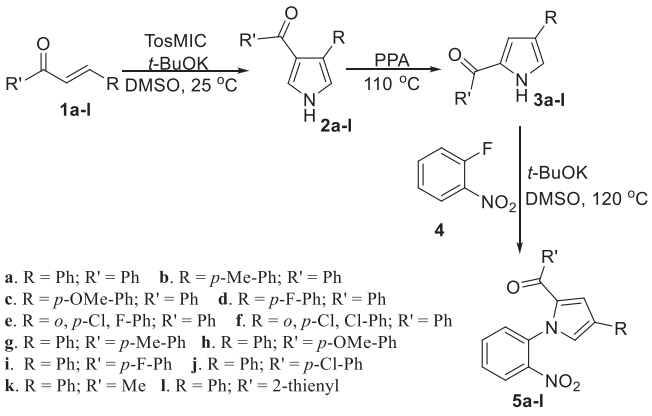


Scheme 2. Synthesis of *o*-nitrophenyl appended 2,4-disubstituted pyrroles 5a-l from chalcones.

nes, 2-alkoxy-2,3-dihydrofurans and ketones as substrates [9]. Zhang and co-workers reported the cyclization of 1-(*N*-arylpyrrol-2-yl)ethanone *O*-acetyl oximes for the synthesis of pyrrolo[1,2-*a*]quinoxalines and their indole congeners [10]. A palladium-catalyzed one-pot approach was reported by Keivanloo and co-workers for the synthesis of trisubstituted pyrrolo[1,2-*a*]quinoxalines using 3-substituted-2-chloroquinoxalines, propargyl bromides and diverse secondary amines as precursors [11]. Finally, Reddy and co-workers have reported the one-pot synthesis of pyrrolo[1,2-*a*]quinoxalines using 1-(2-aminophenyl)pyrrole and styrene as precursors with I_2/IBX in DMSO as the oxidant [12].

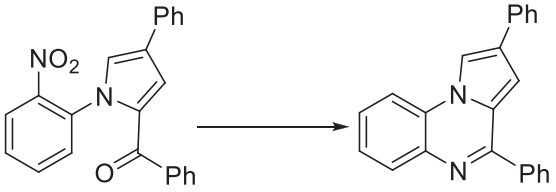
A literature search revealed that most of the recent efforts utilize precursors which are either difficult to synthesize or require expensive/difficult to handle transition metal catalysts. Additionally, in the cases with simple starting compounds, sufficient structural diversity of the final product is not possible. Our motivation was, therefore, to start with a precursor that can be easily synthesized and subsequently converted to the target compounds. Accordingly, a retrosynthetic approach was envisaged as shown in Scheme 1. The synthesis was proposed to start with chalcones 1, which would be coverted into 3,4-disubstituted pyrroles 2 using TosMIC (*p*-toluenesulfonylmethyl isocyanide). Subsequent rearrangement of the 3,4-disubstituted pyrroles would give their 2,4-disubstituted analogues. Finally, an S_NAr reaction, followed by reduction-cyclization would afford the desired 2,4-disubstituted pyrrolo[1,2-*a*]quinoxalines.

Results and discussion

Our efforts towards the synthesis of 2,4-disubstituted pyrrolo[1,2-*a*]quinoxalines started with the conversion of chalcones (1) to the corresponding 2,3-disubstituted pyrroles (2) using the well-known van Leusen synthesis [13]. The product bearing an acyl linkage was then treated with polyphosphoric acid at 110 °C to effect acyl rearrangement to the C-2 position of the pyrrole ring (Scheme 2) [14]. Subsequent steps involved an S_NAr reaction using rearranged pyrrole (3) and 1-fluoro-2-nitrobenzene (4) as substrates with $K^{+-}OC(CH_3)_3$ and DMSO as the base and solvent, respectively (Scheme 2).

Next, (1-(2-nitrophenyl)-4-phenyl-1*H*-pyrrol-2-yl)(phenyl) methanone (5a) was utilized as a model substrate to optimize the reaction conditions for the synthesis of 2,4-disubstituted pyrrolo[1,2-*a*]quinoxalines (Table 1). The main requirement of the final step was to sequentially carry out the selective reduction of the nitro group in the presence of a ketone functionality and imine formation-cyclization reactions. Initial attempts (Entries 1–2) carried out with $NaBH_4$ (5 equiv.) and $NiCl_2{\cdot}6H_2O$ (0.2 equiv.) in CH_3CN-H_2O [(1:2) and (9:1)] gave 2,4-diphenylpyrrolo[1,2-*a*]quinoxaline (6a) in 20% and 40% yield, respectively. Increasing the amount of $NiCl_2{\cdot}6H_2O$ to 0.5 equivalents in CH_3CN-H_2O (9:1)

Table 1
Optimization of the reaction conditions.

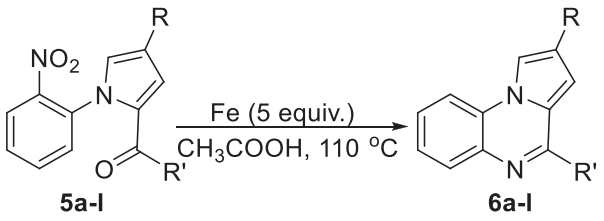


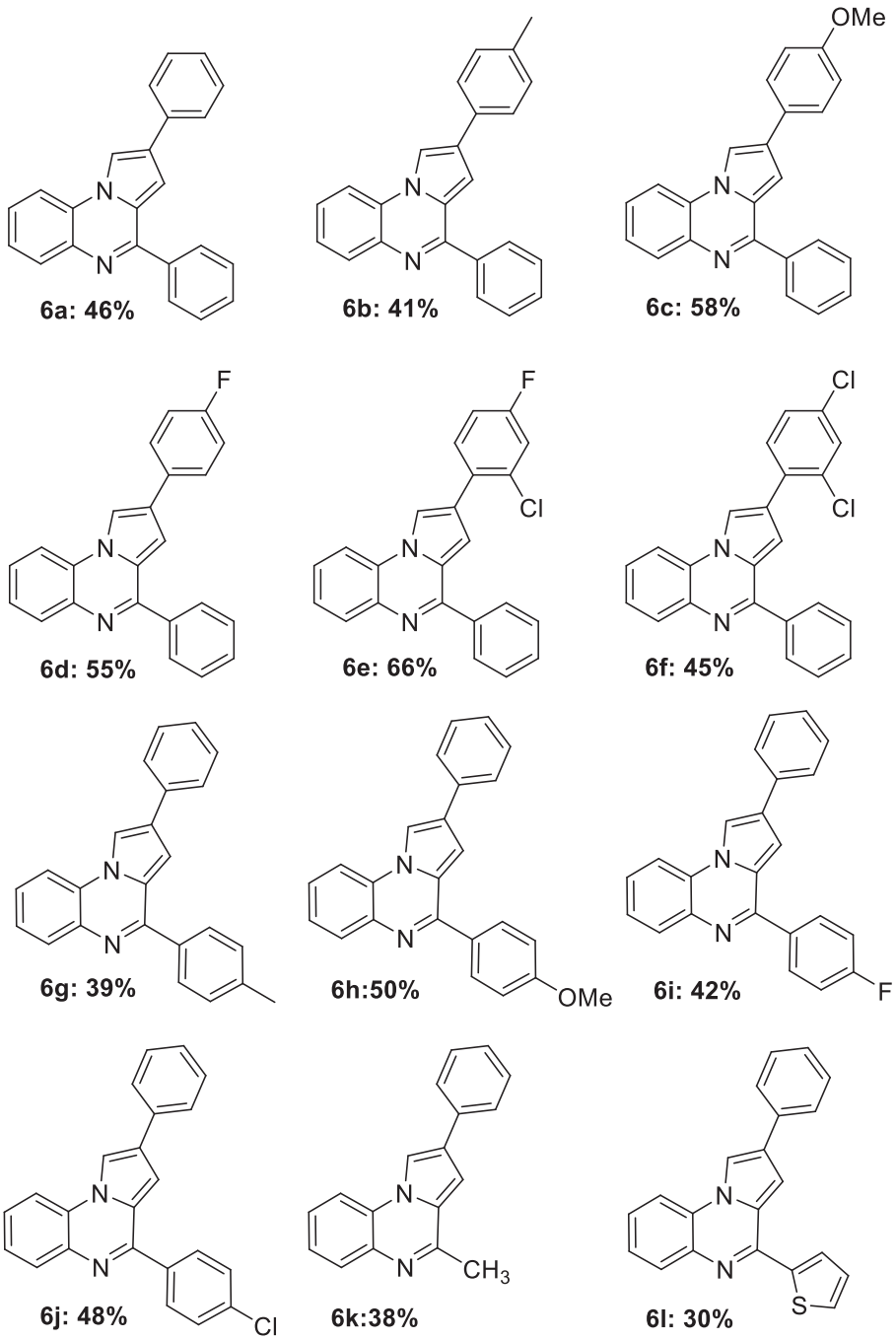
5a 6a

Entry	Reagent [equiv.]	Solvent	Temp. (°C)	Time (h)	Yield 6a (%)[a]
1	$NaBH_4/NiCl_2{\cdot}6H_2O$ [5/0.2]	CH_3CN-H_2O (1:2)	RT	0.5	20
2	$NaBH_4/NiCl_2{\cdot}6H_2O$ [5/0.2]	CH_3CN-H_2O (9:1)	RT	0.5	40
3	$NaBH_4/NiCl_2{\cdot}6H_2O$ [5/0.5]	CH_3CN-H_2O (9:1)	RT	0.5	38
4	$NaBH_4/NiCl_2{\cdot}6H_2O$ [5/0.2]	THF	RT	0.5	–
5	$NaBH_4/NiCl_2{\cdot}6H_2O$ [5/0.2]	THF-H_2O (1:1)	RT	0.5	40
6	$NaBH_4/NiCl_2{\cdot}6H_2O$ [5/0.2]	THF-H_2O (9:1)	RT	0.5	–
7	$Na_2S_2O_4$ [5]	EtOH-H_2O (1:1)	RT	0.5	–
8	Fe [5]	CH_3COOH	90	2	46
9	Fe [5]	EtOH-CH_3COOH-H_2O (2:2:1)	90	2	–
10	Fe [1][b]	CH_3COOH	90	2	–
11	Fe [3]	CH_3COOH	90	2	45
12	Fe [7]	CH_3COOH	90	2	38
13	$Fe/CaCl_2$ [5/0.2]	MeOH	70	12	–
14	Fe/NH_4Cl [5/5]	1,4-dioxane-H_2O (9:1)	90	12	–
15	Fe/NH_4Cl [5/5]	THF-H_2O (9:1)	90	12	–

[a] Isolated yields;
[b] Incomplete conversion, product was not isolated.

Table 2
Synthesis of various 2,4-disubstituted pyrrolo[1,2-*a*]quinoxalines.





(Entry 3) did not improve the yield (38%). Next, the reaction with $NaBH_4/NiCl_2{\cdot}6H_2O$ [5/0.2] in either THF or a THF-H_2O combination were carried out (Entries 4–6), which gave the highest yield of 40% when the THF-H_2O ratio was 1:1. The reaction was also attempted with sodium dithionite (Entry 7) based on literature precedence, which did not give 2,4-diphenylpyrrolo[1,2-*a*]quinoxaline 6a in

isolable yields [15]. When Fe was used to facilitate the reduction of the nitro group in acetic acid, the desired product was obtained in 46% yield (Entry 8). However, the reaction using Fe in EtOH:CH_3-COOH:H_2O (2:2:1) was not successful (Entry 9). Attempting the reaction with a reduced concentration of Fe (Entries 10, 11) gave 2,4-diphenylpyrrolo[1,2-*a*]quinoxaline 6a in 45% yield when three equivalents were used (Entry 11), while incomplete conversion was observed when one equivalent was used (Entry 10). When the reaction was carried out with an increased amount of Fe (Entry 12), 2,4-diphenylpyrrolo[1,2-*a*]quinoxaline 6a was obtained in 37% yield. The attempted reduction with Fe in combination with either $CaCl_2$ or NH_4Cl (Entries 13–15) did not give 2,4-diphenylpyrrolo [1,2-*a*]quinoxaline 6a. Based on the screening, reduction with five equivalents of Fe in acetic acid was identified as the optimized reaction conditions.

The optimized reaction conditions were subsequently used on various *N*-substituted pyrrole derivatives (Table 2). Initial attempts were carried out on substrates 5b-d with an unsubstituted benzoyl moiety at the 2-position and different *para*-substituted phenyl rings at the 4-position. Compounds 6b-d were obtained in 41–58% yield. The outcome of the reaction showed no dependence on the electron-withdrawing or electron-donating ability of the substituents, as comparable yields of 58% and 55% were obtained for 6c and 6d, respectively. Substrates 5e-f with di-substituted phenyl rings at the 4-position and an unsubstituted benzoyl moiety at the 2-position gave 6e in 66% yield and 6f in 45% yield. This outcome indicates the suitability of the reaction conditions even when using sterically encumbered substrates. Compounds 5g-i containing a substituted benzoyl group at the 2-position and an unsubstituted phenyl ring at the 4-position gave 2,4-disubstituted pyrrolo[1,2-*a*]quinoxalines 6 g-i in 39–50% yield. The comparatively better yield of 50% in the case of substrate 5 h with a *p*-methoxy substituent on the benzoyl moiety was surprising since the presence of an electron-donating group reduces the reactivity of the carbonyl carbon towards nucleophilic addition reaction. Finally, acetyl and 2-thienocarbonyl containing products 6 k and 6 l were obtained in 38% and 30% yield, respectively.

Although the yields obtained were only moderate, the fact that two consecutive reactions can be performed and the final nucleophilic addition can be successfully carried out on comparatively unreactive ketones means this alternative approach is useful.

Conclusion

In summary, an alternative strategy has been reported for the synthesis of pyrrolo[1,2-*a*]quinoxalines from readily available chalcones. The developed method allows the exclusive synthesis of 2,4-disubstituted pyrrolo[1,2-*a*]quinoxalines in four simple steps with modest overall yields. Given the importance of these scaffolds due to their attractive biological and photophysical properties, we believe that this method will find applications in medicinal and materials chemistry.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2021.153008.

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