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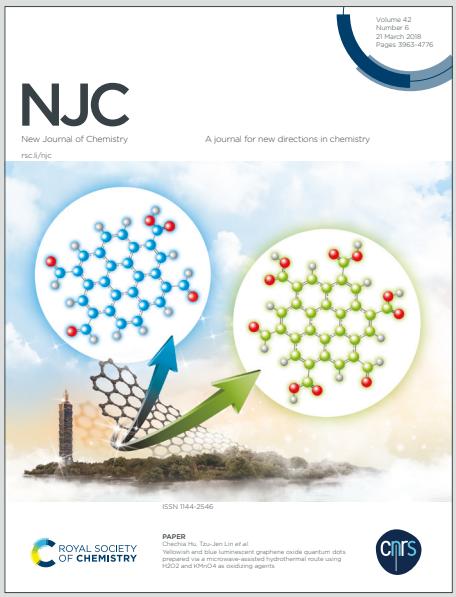

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ARTICLE

Terminal Methyl as a One-Carbon Synthon: Synthesis of Quinoxaline Derivatives *via* Radical-type Transformation†

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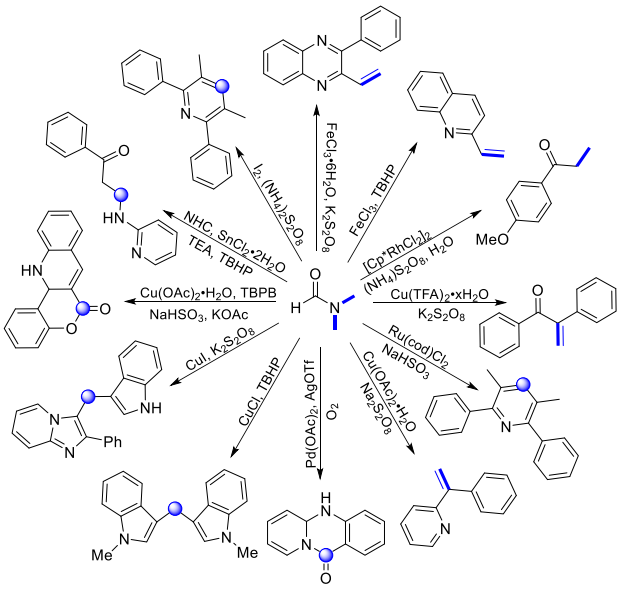
An iron-promoted method for the construction of pyrrolo[1,2-*a*]quinoxaline derivatives has been developed. Ferric chloride served as promoter and Lewis acid in the reaction. Solvents provided corresponding carbon sources simultaneously. A majority of solvents with terminal methyl group, including ethers, amines and dimethyl sulfoxide, were reactive for the synthesis of quinoxaline derivatives at the certain yields *via* C–H(sp^3) amination/C–O or C–N (C–S) cleavage. The method was applicable to a wide range of pyrrolo[1,2-*a*]quinoxaline and indolo[1,2-*a*]quinazoline substrates.

Introduction

As a common polar solvent, N, N-dimethylformamide (DMF) is also considered to be a versatile organic synthon for formylation[1], amination[2] and cyanation[3] of many complex organic compounds. It's not until Lou and Xu[4a] first reported an iron-catalyzed benzylic vinylation in 2012 that the utilization of DMF as methylenation agent have been gradually developed. Recently, the N-methyl moiety of DMF served not only for methylene insertion[4] but also for the transformation of $-CH_3$,[5] $-CH-$[6] and $-C=O$[7] as one-carbon synthon (Scheme 1).

Pyrrolo[1,2-*a*]quinoxaline derivatives, an important class of *N*-heterocyclic compounds, have rather widespread application in organic functional materials, pharmaceuticals and biological studies. In many cases, the functionalized pyrrolo[1,2-*a*]quinoxaline derivatives were proved to possess a wide range of biological and pharmaceutical properties, for example anti-ulcer,[8] antimalarial,[9] anti-HIV,[10] antitumor[11] and other activities. In addition, it has been used as 5-HT3 receptor agonists,[12] human protein kinase CK2 inhibitors,[13] PARP-1 inhibitors,[14] non-peptide glucagon receptor antagonists,[15] and so on. Furthermore, it can also be disposed as fluorescent probes for amyloid fibril.[16]

Nowadays multifarious synthesis ways have been reported to construct this structural skeleton. It was for the first time in 1966 that a method for the preparation of pyrrolo[1,2-*a*]quinoxaline through the reactions between 2-(1*H*-pyrrol-1-yl)aniline and formic acid under reflux conditions was reported by Cheesman and Tuck groups (Scheme 2, reaction 1).[17] Afterwards, numerous protocols for the construction of pyrrolo[1,2-*a*]quinoxalines have sprung up. Among these methodologies, the cyclization synthesis of substituted *N*-phenyl pyrroles has always been the most active part. Generally, a nitro or amino group at the 2-position in phenyl rings is more beneficial to the success of cyclization and aromatization. In 2012, Thiery and Pereira groups explored a synthetic method of quinoxaline derivatives in the condition of iron and HCl which adopted alcohols as raw materials through oxidation cyclization of nitrobenzene (Scheme 2, reaction 2a).[18] But the low yield of reaction was accompanied by the excessive use of iron and HCl. In 2015, Jayaprakash and co-workers reported an iodine-promoted synthetic pathway employing benzylamine and 2-(1*H*-pyrrol-1-yl)aniline as



Scheme 1. Reactions of DMF as methylenating agent

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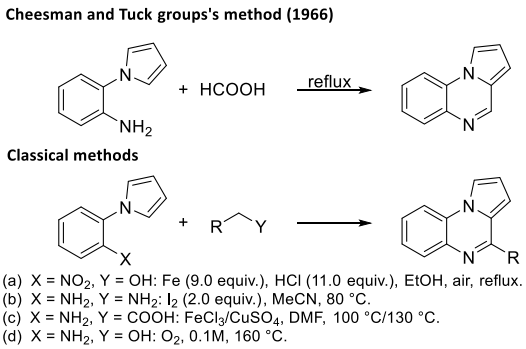
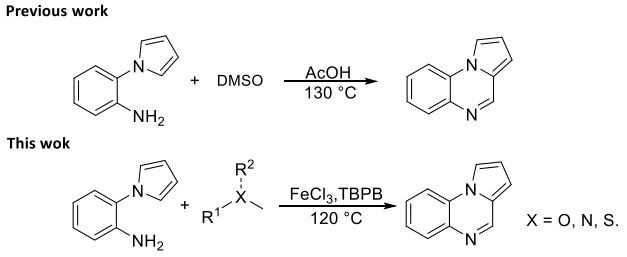
† Electronic Supplementary Information (ESI) available. See DOI: 10.1039/x0xx00000x



Scheme 2. Synthesis of Pyrrolo[1,2-*a*]quinoxaline

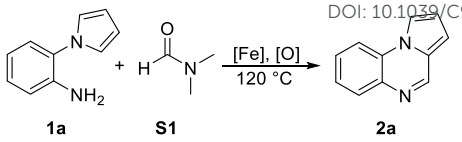
reaction substrates (Scheme 2, reaction 2b).[19] Nonetheless, there is still no solution to the excessive use of toxic additive. In the subsequent reports on the cyclochemistry of aniline, it was found that acids[20] and alcohols[21] could also be utilized as substrates to participate in the reaction for efficient synthesis of pyrrolo[1,2-*a*]quinoxaline under certain conditions. There are still many ineluctable imperfections in these methods yet, for instance, tedious procedure, complicated operation, toxic reagent, low productive, poor applicability and the like.

In 2017, a method of metal-free catalytic oxidation cyclization of 2-(1*H*-pyrrol-1-yl)aniline with dimethyl sulfoxide was developed for synthesizing various substituted pyrrolo[1,2-*a*]quinoxalines by our group (Scheme 3, reaction 1).[22] Nevertheless，methyl mercaptan was generated as environmentally unfriendly byproducts in the reaction which *S*-methyl group of DMSO was used as the carbon source. It is not difficult to find that all of the aforementioned methodologies were merely appropriate for such single substances as alcohols, amines or acids. Hence, we disclosed a novel and efficient approach to preparing pyrrolo[1,2-*a*]quinoxalines and indolo[1,2-*a*]quinoxalines *via* an iron-promoted sp^3 C–H activation and oxidative cyclization process (Scheme 3, reaction 2). Except that the solvents can be used as carbon sources, readily available Fe (III) which was a Lewis acid in place of Bronsted acid also acted as reaction facilitation. In comparison to the past limitations of single carbon sources, not only *S*-methyl group of DMSO but *N*-methyl group of amines and *o*-Methyl group of ethers can also be used as the carbon source in this reaction.



Scheme 3. Synthesis of Heterocyclic Compounds Employing Solvent as a One-Carbon Synthon

Table 1. Optimization of the Reaction Conditions[a]



1a **S1** **2a**

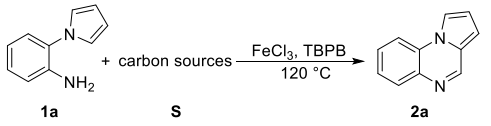
entry	[Fe]	[O]	T (°C)	yield (%)[b]
1	$FeCl_3$	TBHP	110	62
2	$FeCl_3$	TBHP	120	75
3	$FeCl_3$	TBHP	130	74
4	$FeBr_3$	TBHP	120	62
5	$Fe_2(SO_4)_3$	TBHP	120	37
6	$Fe(NO_3)_3{\bullet}9H_2O$	TBHP	120	trace
7	$FePO_4$	TBHP	120	39
8	$FeCl_3$	DTBP	120	41
9	**$FeCl_3$**	**TBPB**	**120**	**88**
10	$FeCl_3$	$K_2S_2O_8$	120	11
11	$FeCl_3$	$Na_2S_2O_8$	120	10
12	$FeCl_3$	$(NH_4)_2S_2O_8$	120	8
13	--	TBPB	120	n.d.
14	$FeCl_3$	--	120	9
15	$FeCl_3$	O_2	120	38
16	$FeCl_3$	N_2	120	8

[a]**1a** (0.3 mmol), DMF (2 mL), iron (0.3 mmol), oxidant (0.9 mmol), under air (unless otherwise noted), 120 °C (5~9 h). [b]Isolated yields.

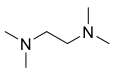
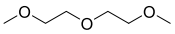
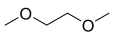
Results and discussion

Initially, the reaction of 2-(1*H*-pyrrol-1-yl)aniline **1a** (0.3 mmol) with the participation of $FeCl_3$ (0.3 mmol) and TBHP (0.9 mmol) stirred in 2 mL solvent (DMF) at 110 °C under air atmosphere for 5h was chosen as the model reaction to examine the diversity of reaction parameters and the desired product **2a** was gained in 62% yield (Table 1, entry 1). To our delight, a satisfactory yield of 75% was obtained at 120 °C (Table 1, entry 2). There was no significant change in the yield when the reaction was conducted at a relatively high temperature of 130 °C (Table 1, entry 3). The variable amount of neither Fe (III) nor oxidant increased the yield. Examinations of diverse iron salts, including $FeBr_3$, $Fe_2(SO_4)_3$, $Fe(NO_3)_3{\bullet}9H_2O$ and $FePO_4$, did not produce ideal results (Table 1, entries 4–7). Subsequently, when other oxidants such as DTBP, TBPB, $K_2S_2O_8$, $Na_2S_2O_8$ and $(NH_4)_2S_2O_8$ were examined, TBPB gave the best yield (88%) of all (Table 1, entries 8–12). When the reaction was carried out in the absence of iron, no target product was detected (Table 1, entry 13) and the yield of heterocyclic product was as low as 9% without TBPB (Table 1, entry 14), suggesting that ferric iron and TBPB was essential for the process. The yield of **2a** decreased precipitously to 38% when oxygen was employed as the

Table 2. Substrate Scope of Carbon Sources[a]



1a S 2a

entry	carbon sources		yield(%)[b]	entry	carbon sources		yield(%)[b]
1		**S2**	85	8		**S9**	36
2		**S3**	66	9		**S10**	32
3		**S4**	trace	10		**S11**	38
4		**S5**	62	11		**S12**	66
5		**S6**	15	12		**S13**	61
6		**S7**	trace	13		**S14**	55
7		**S8**	40	14		**S15**	58

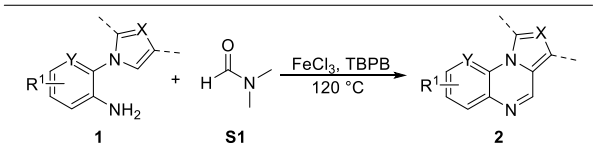
[a]**1a** (0.3 mmol), carbon source (2 mL), $FeCl_3$ (0.3 mmol), TBPB (0.9 mmol), under air (unless otherwise noted), 120 °C (5~10 h). [b]Isolated yields.

oxidant (Table 1, entry 15), which demonstrated that TBPB was not just an oxidant. As expected, the further experiment proved that oxidant was indispensable for this transformation (Table 1, entry 16). Thus, the optimal conditions were determined as described in entry 11.

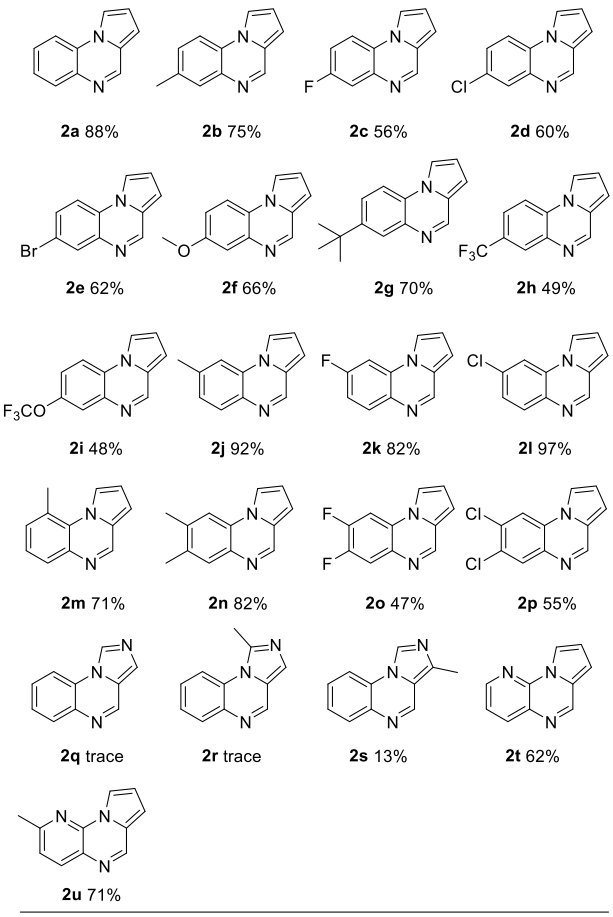
With the optimal reaction conditions established, we investigated the substrate scope of carbon sources for the route to pyrrolo[1,2-*a*]quinoxalines. The prospective product **2a** was obtained in excellent yield when DMA was employed as carbon source, while the secondary amine **S3** exhibited a lower reactivity than the tertiary **S2** (Table 2, entries 1–2). We therewith utilized the other two alternative amides of *N*,*N*-dimethyl benzamide **S4** and NMP **S5** to test this notable transformation founding that **S5** reacted well with a yield of 62% and when **S4** was substituted for **S5**, only a trace amount of **2a** was detected (Table 2, entries 3–4). Moreover，the reactions of aliphatic amines and aromatic amine **S8** also would generate **2a** in moderate yield, with the exception of 1-methylpyrrole **S7** (Table 2, entries 5–9). The reason we suspected that **S4** and **S7** have no yield was probably associated with the difference in the stability of the iminium intermediate in the reaction. Obviously, the yield of 4-methylmorpholine **S10** was superior to that of 1-methylpiperidine **S6**. Herein, considering the effect of ether bond, we explored the reaction under standard condition by using 1, 4-dioxane **S11** as carbon source. By comparison to **S10**, **S11** gave a slightly higher yield (Table 2, entries 10). Correspondingly, a series of chain ethers also achieved a good yield (Table 2, entries 11–13). Moreover, DMSO **S15** also gave the expected cyclization products **2a** in 58% yields. In summary, *N*-methyl was much more reactive than *o*-Methyl and *S*-methyl by contrast, and the reactions using heterocyclic amines and ethers as carbon sources were also feasible, albeit in somewhat low yields.

Having established the optimal carbon source **S1**, the substrate scope of the 2-(1*H*-pyrrol-1-yl) anilines with disparate substituents on the aromatic ring was surveyed. A majority of different substituted **1** was able to participate to achieve medium yield. Compared with **1** containing an electron-withdrawing group, that bearing an electron-donating

Table 3. Substrate Scope of 2-(1*H*-Pyrrol-1-yl) aniline[a,b]



1 S1 2



[a]**1** (0.3 mmol), DMF (2 mL), $FeCl_3$ (0.3 mmol), TBPB (0.9 mmol), under air (unless otherwise noted), 120 °C (5~12 h). [b]Isolated yields.

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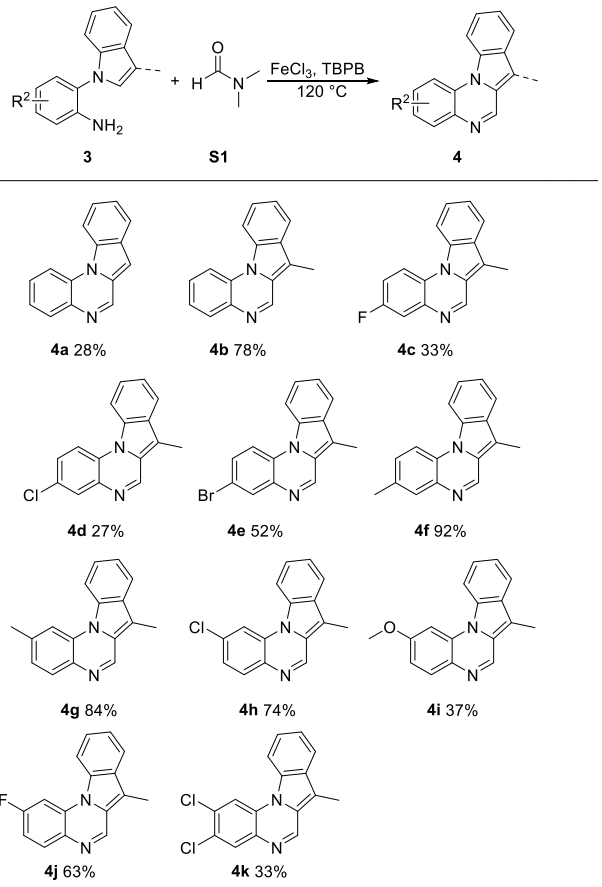
Table 4. Substrate Scope of 2-(1*H*-Indol-1-yl) aniline[a,b]

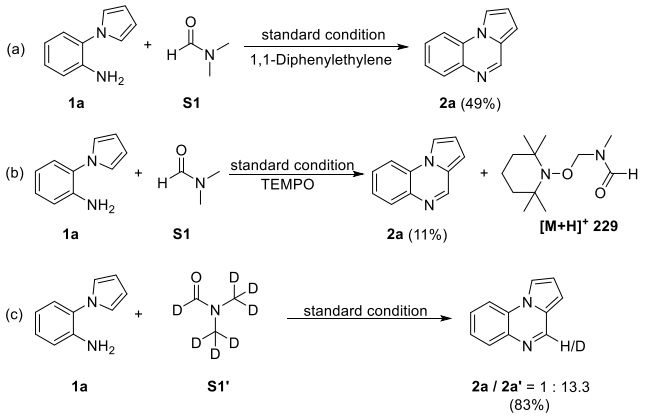


[a]**3** (0.3 mmol), DMF (2 mL), $FeCl_3$ (0.3 mmol), TBPB (0.9 mmol), under air (unless otherwise noted), 120 °C (24~72 h). [b]Isolated yields.

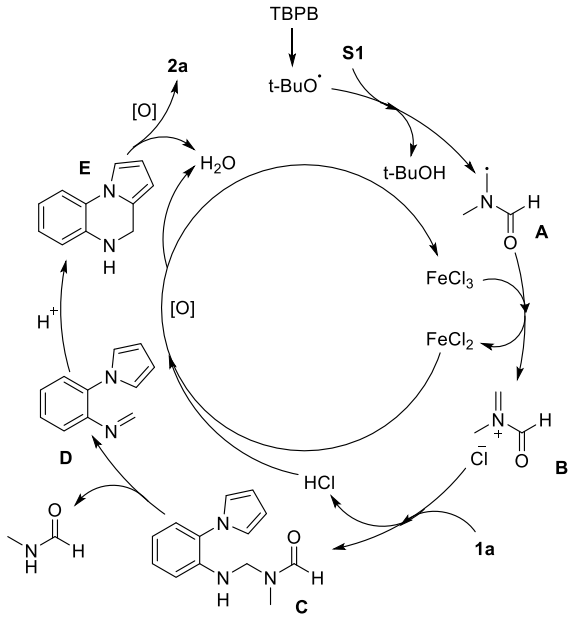
group was easier to have a more optimistic yield (Table 3, **2b**–**2f**). Interestingly, strong electron-donating and electron-withdrawing groups with steric hindrance had no significant impact on either the required reaction time or product yield (Table 3, **2g**–**2i**). Further results indicated that substituents at the 5-position on the ring have a better function on the reaction than groups located at the 4-position (Table 3, **2j**–**2l**). desired products in 71% yield (Table 3, **2m**). Furthermore, disubstituted substrates also smoothly furnished corresponding products, conforming to the above-mentioned law of electronic effect (Table 3, **2n**–**2p**). In the development of heterocyclic substrates, it was found that imidazolyl in place of pyrrolyl yielded only **2s** of 13% while the replacement of pyridine ring was efficiently engaged in the reaction (Table 3, **2q**–**2u**).

In light of these decent results, we decided to expand the range of pyrrolo[1,2-*a*]quinoxaline derivatives to investigate the versatility of the present method by substitution of the pyrrole ring with the indole ring. It turned out that 2-(1*H*-Indol-1-yl) aniline may took a longer reaction time affected by the possibility of steric hindrance and the yield of indolo[1,2-*a*]quinoxaline **4a** dropped sharply, with only 28% yield (Table 4, **4a**). Whereas, the yield got a visible improvement when there was a methyl group in indolyl ring (Table 4, **4b**). It seems that methyl group at the 3-position of indolyl should play a vital role in the reaction due to the influence of competitive reaction between the 2-position and 3-position of indolyl and the electron-donating effect of alkyl group. Distinct substituted 2-(3-methyl-1*H*-indol-1-yl) aniline exhibited favorable yield displaying the advantage of strong electron-donating group to yield (Table 4, **4c**–**4j**). Remarkably, 2-(3-methyl-1*H*-indol-1-yl) aniline having disubstituted chlorine was tolerated to give the desired product in 33% yield (Table 4, **4k**). Yet the effect of benzene ring on electronic density causes sluggish reactivity for the indole derivatives.

Meanwhile, several control experiments in regard to mechanistic investigations were carried out. In the presence of 4 equiv of 1,1-diphenylethylene as a radical scavenger, the extreme reduction of reaction yield occurred (Scheme 4a) and



Scheme 4. Control Experiments for Mechanistic Studies



Scheme 5. Plausible Reaction Mechanism

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the analogous result of TEMPO involvement was received (Scheme 4b), suggesting that a radical mechanism may be existed involved in this reaction. Additionally, the relevant free radical addition product of TEMPO was detected by HRMS implying that the corresponding radical was generated from DMF *via* C−H cleavage. Futher isotope experiments also proved that the one-carbon synthon was indeed from DMF (Scheme 4c). In the preliminary conditional screening, we were aware of that $FeCl_3$ and TBPB account for the crucial factor of reaction and not a single one can be omitted (Table 1, entries 15,16). TBPB was a radical initiator involved in the reaction as well as an oxidant (Table 1, entries 17,18).

On the basis of results described above and previous reports, a plausible mechanism is proposed by our group in Scheme 5. The initial reaction gives acylaminomethyl radical **A** through abstraction of hydrogen radical from sp^3 C−H bond of DMF **S1** by the *tert*-butoxy radical. In the presence of Fe (III), the radical **A** followed by the oxidation to acyliminium salt **B**.[23] Subsequently, nucleophilic addition of **1a** to **B** provides an intermediate **C** by removal of one molecular HCl. Imine **D** could be formed C−N cleavage together with an elimination of *N*-methylformamide from **C**. Ultimately, the target product **2a** is obtained through cyclization and oxidation under acidic condition. During transformation, the acid-base reaction between HCl and *t*-BuOFeCl_2 produced by the reaction of $FeCl_2$ and oxidant gave $FeCl_3$ to complete cycle of iron complexes.[24]

Conclusions

In summary, we have developed an interesting reaction for assembling pyrrolo[1,2-*a*]quinoxalines from 2-(1*H*-pyrrol-1-yl)anilines and various carbon sources. The synthesis method is applicable to multiple types of solvents with terminal methyl groups. At the same time, there are a great many advantages of available raw materials, simple operation, reaction efficiency, universal solvent applicability and wide substrates scope.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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Synthesis of Quinoxaline Derivatives with Terminal Methyl as a One-Carbon Synthon *via* Radical-type Transformation

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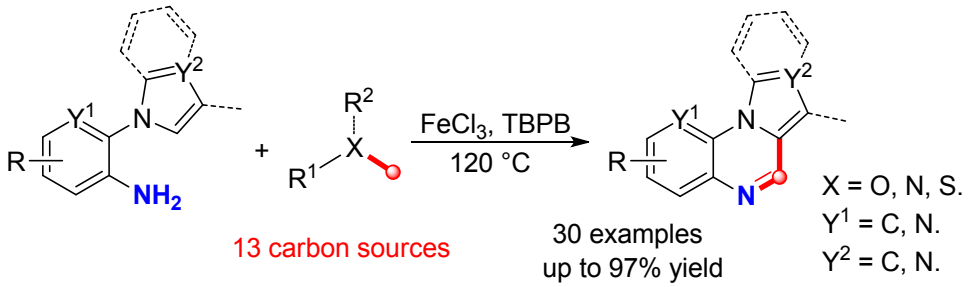
An iron-promoted method for the construction of pyrrolo[1,2-*a*]quinoxaline derivatives has been developed. Ferric chloride served as promoter and Lewis acid in the reaction. Solvents provided corresponding carbon sources simultaneously. Under the optimal reaction conditions, a variety of solvents were utilized as carbon sources for the synthesis of quinoxalines. A majority of solvents with terminal methyl group, including ethers, amines and dimethyl sulfoxide, were reactive for the synthesis of quinoxaline derivatives at the certain yields *via* radical-type transformation. The method was applicable to a wide range of pyrrolo[1,2-*a*]quinoxaline and indolo[1,2-*a*]quinazoline substrates.



Key words: Iron, Solvent, Terminal Methyl, Quinoxaline Derivatives.