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An efficient synthesis of 3-(indol-3-yl)quinoxalin-2-ones with TfOH-catalyzed Friedel–Crafts type coupling reaction in air

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ABSTRACT

An efficient one-pot synthetic approach to access a variety of 3-(indol-3-yl)quinoxalin-2-ones from various quinoxalin-2-ones and very wide scope of indoles through TfOH-catalyzed Friedel–Crafts type coupling reaction in DMF has been developed. Only 10 mol % Brønsted acid as a catalyst, air as an oxidizer, and very wide range of substrates are the prominent advantages of this method.

The prevalence and diversity of aromatic nitrogen-containing heterocycles found in natural products and used in medicinal chemistry continue to fuel the development of new methods and strategies for their syntheses.[1] As one of an important class of nitrogen-containing heterocycle compounds, quinoxalin-2-ones, and their derivatives have been extensively studied during the past three decades and used as synthetic precursors for antihypertensives and analgesics.[2,3] Among them, 3-(indol-3-yl)quinoxalin-2-ones have proven to be a class of efficient small-molecule inhibitors for blocking abnormal PDGF-induced cell proliferation to treat proliferative disorders.[4,5] Despite this, the full potential of 3-(indol-3-yl)quinoxalin-2-ones has not been profoundly evaluated in part due to the scarcity of them. In addition, few efficient synthetic protocols have been reported for generating such 3-(indol-3-yl)quinoxalin-2-ones up to now.[5a,6] Moreover, some major drawbacks are obvious in the developed methods, such as using large amount acid as a promoter, harsh reaction conditions, high-cost oxidizer, and limited range of substrates. Accordingly, it is not only meaningful but also strongly required to develop more efficient approaches to access these compounds.

The Friedel–Crafts reaction promoted by Lewis acid or Brønsted acid is one of the most efficient methods for the construction of carbon–carbon bonds to aromatics and hetroaromatics.[7] Notably, the Friedel–Crafts type reaction of imines with indole has arisen increasing attention.[8] It has been well reported that the C-3 position of quinoxalin-2-ones is susceptible to nucleophilic attack and Friedel–Crafts type reaction is readily performed.[5] Based on these chem-information, we speculated that the reaction between quinoxalin-2-ones and highly nucleophilic reagents indoles[9] may be able to proceed smoothly under certain mild reaction conditions leading to 3-(indol-3-yl)quinoxalin-2-ones. However, through carefully researching literature, we found Aoki et al. reported the direct condensation of indole or 7-azaindole with various substituted quinoxalin-2-ones,[5a] but the reaction must be carried out in DMF with 10% (v/v to solvent DMF) TFA, and a large amount of MnO_2 was inevitable as an oxidizer for the oxidation to generate the desired products. In addition, there had been no reports on catalytic processes. Fortunately, we recently found a series of 3-(indol-3-yl)quinoxalin-2-ones could even be efficiently formed in one-pot through Friedel–Crafts type reaction between quinoxalin-2-ones[10] and indoles in air with 10 mol % trifluoromethanesulfonic acid (TfOH) as a catalyst. In this Letter, we hope to present the results of our studies.

At the outset of our study, we first examined the reaction of quinoxalin-2-one **1a** and indole (**2a**) with 10 mol % diphenyl phosphoric acid as a catalyst leading to 3-(indol-3-yl)quinoxalin-2-one (**3a**) for a screening solvent. With examination to a series of solvents, it revealed that dimethyl formamide (DMF) was superior to other solvents, such as DMSO, toluene, EtOAc, CH_2Cl_2, THF, and CH_3OH,[11] providing the desired product **3a** in 74% yield (Table 1, entry 1). In addition, this reaction worked well in dimethylacetamide (DMAC)

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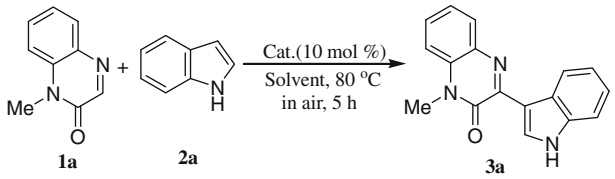
Table 1
Optimization of the reaction conditions[a]



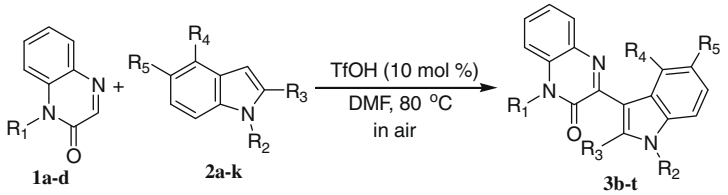
Entry	Cat	Solvent	Yield[b] (%)
1	$(PhO)_2PO_2H$	DMF	74
2	$(PhO)_2PO_2H$	DMAC	62
3	$(PhO)_2PO_2H$	NMP	71
4	F_3CCO_2H	DMF	60
5	TsOH	DMF	74
6	TfOH	DMF	95
7	$PhCO_2H$	DMF	42
8	H_2NSO_3H	DMF	38
9	DABCO	DMF	N.R.
10	DBU	DMF	N.R.
11	Cs_2CO_3	DMF	N.R.
12[c]	TfOH	DMF	Trace
13[d]	TfOH	DMF	60
14[e]	TfOH	DMF	93

[a] Unless otherwise noted, reactions were carried out with **1a** (0.4 mmol) and **2a** (0.8 mmol) in 1.0 mL solvent at 80 °C for 5 h in air.
[b] Yield of isolated product.
[c] The reaction was carried out with 10 mol % catalyst at room temperature for 5 h.
[d] The reaction was carried out with 5 mol % catalyst at 80 °C for 5 h.
[e] The reaction was carried out with 20 mol % catalyst at 80 °C for 5 h. TsOH = *p*-toluenesulfonic acid, TfOH = trifluoromethanesulfonic acid, N.R. = no reaction.

and *N*-methyl-2-pyrrolidinone (NMP), respectively, but the yields were slightly inferior to that in DMF (Table 1, entry 1 vs entries 2 and 3). We then turned our attention to the optimization of the same reaction in DMF aimed at improving the reaction efficiency. Among the various Brønsted acids surveyed (Table 1, entries 1 and 4–8), the best result was achieved by 10 mol % TfOH (Table 1, entry 6). However, attempting to perform this reaction with some base[12] as a catalyst, no any corresponding product was observed (Table 1, entries 9–11). This suggested that protonic acid-initiated Friedel–Crafts type reaction was crucial in this process. Unfortunately, when the reaction was carried out at room temperature, only trace amount product was obtained (Table 1, entry 12). Further examining to the catalyst loading, it revealed that 10 mol % catalyst loading was favorable and acceptable (Table 1, entry 6 vs entries 13 and 14). As a result, above-mentioned studies led us to conclude the optimal reaction conditions: quinoxalin-2-one **1a** and two-equivalent indole (**2a**) using 10 mol % TfOH as a catalyst in DMF (c = 0.4 M for **1a**) at 80 °C with opening to air.

Having established the optimal reaction conditions, the substrates' scope for the formation of 3-(indol-3-yl)quinoxalin-2-ones was investigated. As shown in Table 2, we firstly subjected 1-methly-quinoxalin-2-one (**1a**) to the reaction using various indole derivatives **2b–j** as partner, in general, these reactions proceeded smoothly and afforded the corresponding products with good yields (Table 2, entries 1–9). Particularly, the reaction was fast between **1a** and **2j** and completed even in 4 h while provided product **3j** with up to 92% yield (Table 2, entry 9). With further using free quinoxalin-2-one (**2b**) as a substrate to validate the generality and efficiency of our synthetic methodology, it was gratified that

Table 2
Extension of substrates for 3-(indol-3-yl)quinoxalin-2-ones synthesis[a]



1a, R_1=Me
1b, R_1=H
1c, R_1=Bn
1d, R_1=Allyl

2a, R_2=H, R_3=H, R_4=H, R_5=H
2b, R_2=H, R_3=Me, R_4=H, R_5=H
2c, R_2=H, R_3=OH, R_4=H, R_5=H
2d, R_2=H, R_3=H, R_4=Br, R_5=H
2e, R_2=H, R_3=H, R_4=OMe, R_5=H
2f, R_2=H, R_3=H, R_4=H, R_5=OMe
2g, R_2=H, R_3=H, R_4=H, R_5=OBn
2h, R_2=H, R_3=H, R_4=H, R_5=Br
2i, R_2=H, R_3=H, R_4=H, R_5=NO_2
2j, R_2=Bn, R_3=H, R_4=H, R_5=H

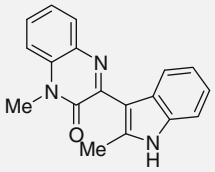
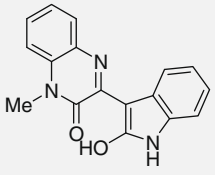
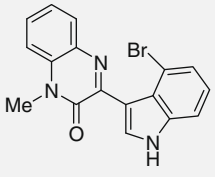
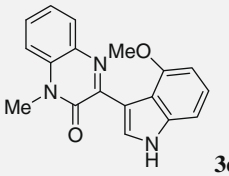
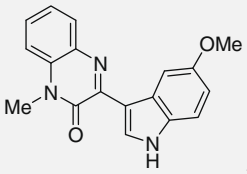
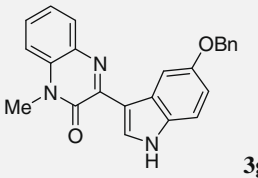
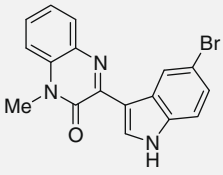
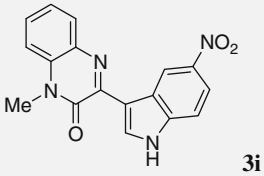
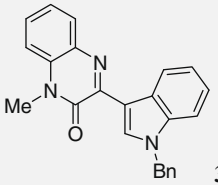
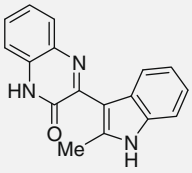
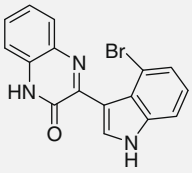
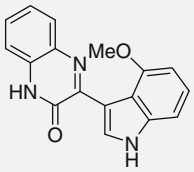
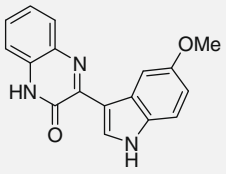
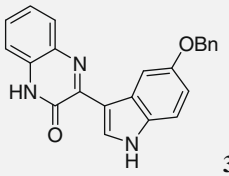
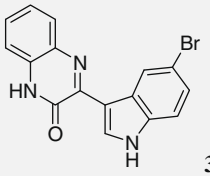
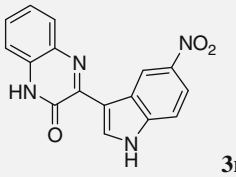
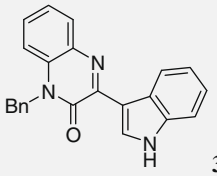
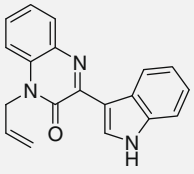
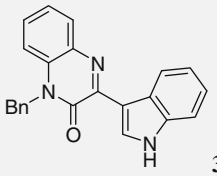
Entry	1	2	3	Time (h)	Yield[b] (%)
1	**1a**	**2b**	 **3b**	6	69
2	**1a**	**2c**	 **3c**	5	69
3	**1a**	**2d**	 **3d**	20	64

Table 2 (*continued*)

Entry	1	2	3	Time (h)	Yield[b] (%)
4	**1a**	**2e**	 **3e**	24	93
5	**1a**	**2f**	 **3f**	24	70
6	**1a**	**2g**	 **3g**	24	86
7	**1a**	**2h**	 **3h**	28	91
8	**1a**	**2i**	 **3i**	28	71
9	**1a**	**2j**	 **3j**	4	92
10	**1b**	**2b**	 **3k**	6	86
11	**1b**	**2c**	 **3l**	1	69
12	**1b**	**2d**	 **3m**	11	66

(*continued on next page*)

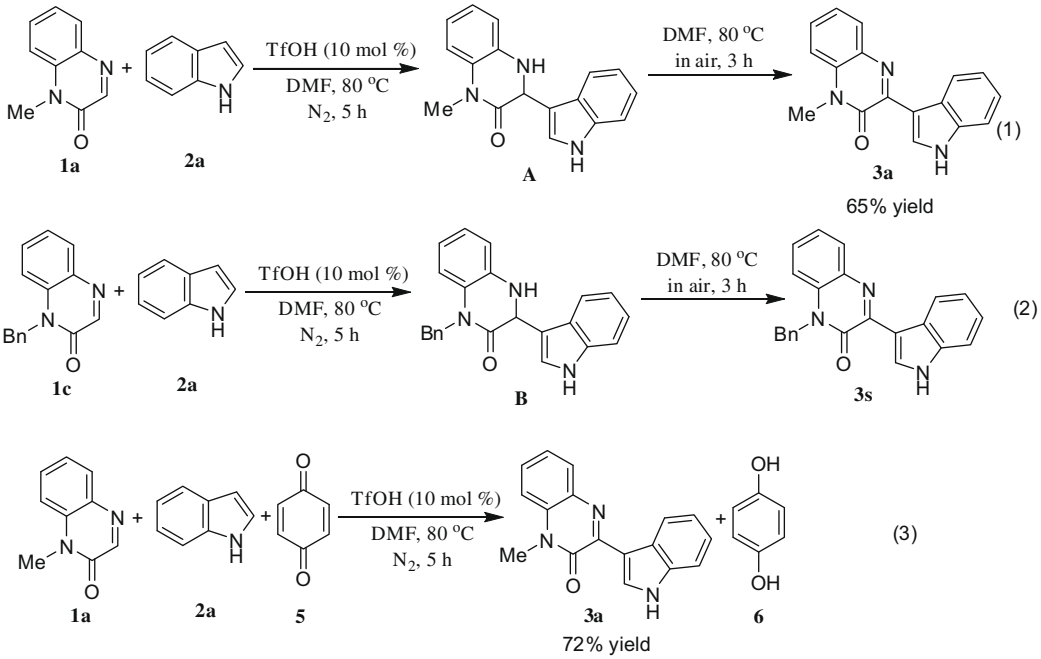
Table 2 (*continued*)

Entry	1	2	3	Time (h)	Yield[b] (%)
13	**1b**	**2e**	 **3n**	11	72
14	**1b**	**2f**	 **3o**	6	92
15	**1b**	**2g**	 **3p**	6	91
16	**1b**	**2h**	 **3q**	6	86
17	**1b**	**2i**	 **3r**	5	75
18	**1c**	**2a**	 **3s**	3	94
19	**1d**	**2a**	 **3t**	3	91
20	**1b**	**2a**	 **3u**	15	85[c]

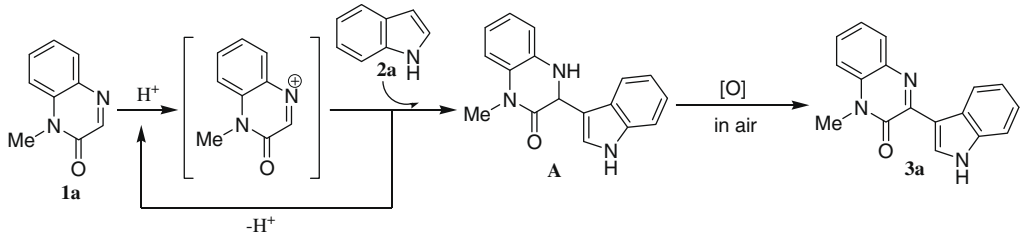
[a] Reactions were conducted using **1** (0.4 mmol), **2** (0.8 mmol), and TfOH (10 mol %) in 1.0 mL DMF at 80 °C in air.
[b] Yield of isolated product.
[c] The reaction was carried out in 5.0 g scale.

free quinoxalin-2-one (**2b**) also smoothly provided the desired products (**3k–r**) with 69–92% yields at the same optimal reaction conditions (Table 2, entries 10–18). It was worth mentioning this method could successfully yield **3m** with 69% yield only in 1 h (Table 2, entry 12). For other 1-substituted-quinoxalin-2-ones tested, such as **2c** and **2d** as substrates, it was found that both of them showed higher reactivity (3 h) in reaction with indole and afforded the corresponding products with 94% and 91% yield, respectively (Table 2, entries 18 and 19). Additionally, it is pertinent to note that we also demonstrated that the synthetic method described here could be carried out in large scale to 5.0 g, giving the desired product in 85% yield (Table 2. entry 20). Remarkably, very wide range of substrate was tolerated to this method as shown in Table 2.

To probe the reaction mechanism, the following three verification experiments were performed with 10 mol % TfOH in DMF,



Scheme 1. Verification experiments.



Scheme 2. Proposed mechanism for the transformation.

respectively (Scheme 1). In experiment (1), the reaction was carried out under argon atmosphere for 5 h leading to the only formation of **A**, as confirmed by crude ^{1}H NMR analysis. This suggested that acid-catalyzed Friedel–Crafts type reaction was the initial reaction. The same reaction mixture was opened to air and stirred at 80 °C for 3 h, after working up, the desired product **3a** was obtained with 65% yield. This revealed that the intermediate **A** was subjected to oxidation by air in the second period. To the experiment (2), we successfully obtained the intermediate **B**.[13] Additionally, in experiment (3), the mixture of **1a**, **2a**, 1,4-quinone (**5**),[14] and 10 mol % TfOH in DMF was vigorously stirred at 80 °C for 5 h under argon atmosphere, the reaction occurred well and the same desired product **3a** was formed with 72% isolated yield. Concurrently, hydroquinone (**6**), reduced product of 1,4-quinone (**5**), was observed as confirmed by TLC analysis. This also led us to ascertain that the reaction experienced tandem Friedel–Crafts and oxidation reactions.

Based on the above-mentioned results and on Aoki's study,[5] we postulate a mechanism for this transformation between quinoxalin-2-ones **1** and indoles **2** to yield various 3-(indol-3-yl)quinoxalin-2-ones **3** in Scheme 1. Firstly, quinoxalin-2-one (**1a**) was activated by Brønsted acid forming cationic intermediate, then the cationic intermediate and **2a** took Friedel–Crafts type reaction generating intermediate **A** while releasing catalyst acid. Finally, **A** underwent oxidation by air yielding the desired product **3a** (Scheme 2).

In summary, we have presented an efficient approach for the synthesis of various 3-(indol-3-yl)quinoxalin-2-ones through Friedel–Crafts type coupling reaction between quinoxalin-2-ones and indoles with catalytic amount TfOH (10 mol %) as a catalyst and using air as an oxidizer. This procedure tolerates to a wide range of substrates not only for quinoxalin-2-ones but also for indoles. Two verification experiments for the possible reaction mechanism have been successfully conducted. Further applications of quinoxalin-2-ones to synthesize a range of other aromatic nitrogen-containing heterocycles are currently in progress and will be reported in due course.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.02.031.

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10. Various quinoxalin-2-ones were prepared according to the reported procedure, see: McAtee, J. J.; Dodson, J. W.; Dowdell, S. E.; Girard, G. R.; Goodman, K. B.; Hilfiker, M. A.; Sehon, C. A.; Sha, D.; Wang, G. Z.; Wang, N.; Viet, A. Q.; Zhang, D.; Aiyar, N. V.; Behm, D. J.; Carballo, L. H.; Evans, C. A.; Fries, H. E.; Nagilla, R.; Roethke, T. J.; Xu, X.; Yuan, C. C. K.; Douglas, S. A.; Neeb, M. J. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 3500–3503.
11. Using DMSO, toluene, EtOAc, CH_2Cl_2, THF, and CH_3OH as solvents, respectively, only trace amount of the corresponding product was monitored by thin layer chromatography (TLC).
12. DABCO = 1,4-diazabicyclo[2.2.2]octane, DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene.
13. The corresponding *N*-benzyl intermediate **B** was successfully isolated and was ascertained by ^1H NMR and ^{13}C NMR spectra (See Supplementary data).
14. In this verification experiment, the reaction was run with the amount **1a**/**2a**/**5** = 0.4 mmol/0.8 mmol/0.5 mmol in 1.0 mL DMF.