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Journal Name

COMMUNICATION

Base Promoted Synthesis of Dibenzoxazepinamines and Quinazolinimines under Metal-free Conditions

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

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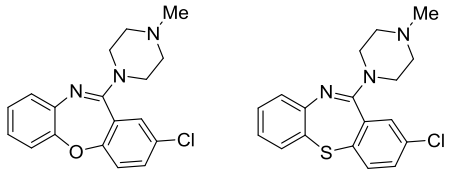
An interesting base promoted protocol for the synthesis of dibenzo[*b*,*f*][1,4]oxazepin-11-amines and quinazolinimines has been developed. Started from commercial available 2-fluorobenzonitriles, 2-aminophenols and 2-aminoehtanol good to excellent yields of the corresponding heterocycles can be achieved. Notablly, only K_3PO_4 or K_2CO_3 was required as the promoter here and the reaction can be easily performed in large scale.

Dibenzo[*b*,*f*][1,4]oxazepin-11-amines and its derivatives are important moieties because of their pharmacologically actives such as anti-inflammatory,[1] antidepressant,[2] antioxidant,[3] anti-tumor activities[4] and etc. (Scheme 1).[5] To our surprise, even though the accepted importance of these compounds, there is still no general procedure exist for their synthesis. Only two examples were reported recently by Jiang and co-workers. They using 2-(2-bromophenoxy)aniline and isocyanides as the substrates with palladium as the catalyst, the desired dibenzo[*b*,*f*][1,4]oxazepin-11-amines were produced in good yields.[6] Therefore, the research of general, convenient and practical strategies for the synthesis of these compounds is still of great importance and interests.

Transition metal catalysts have already become a true toolbox in modern organic synthesis which have also been verified by the Nobel Prize of Chemistry in 2001, 2005, and 2010.[7] These powerful catalysts have been applied in the heterocyclic compounds preparation as expected. However, as one of the main interests of heterocycles is their biological activity which is sensitive to the residual of metal catalyst in the final compounds and special attentions have to be paid to the product purification and impurity detection. Hence, synthetic procedures without the metal catalyst or additive are in need by the synthetic community. Under all these backgrounds and our own research interests on heterocycles synthesis, we wish to report here a practical procedure for the synthesis of dibenzoxazepinamines and related analogues under metal-free conditions.[9] Only K_3PO_4 or K_2CO_3 was required as the promotor here and the reaction can be easily performed in large scale.



Scheme 1: Selected examples of pharmacologically active dibenzoxazepinamines.

Initially, the effects of bases were tested with 2-fluorobenzonitrile (**1a**) and 2-aminophenol (**2a**) as the model substrates in DMF at 100 ℃ under air (Table 1, entries 1-6). In all the tested organic and inorganic bases, K_3PO_4 gave the best results and 95 % of the desired dibenzo[*b*,*f*][1,4]oxazepin-11-amine was isolated (Table 1, entry 4), while no product was detected with DBU as the base (Table 1, entry 6). Then the influences of solvents for this transformation were checked. Compared with using DMF as solvent, DMSO, DMAc, Toluene and 1,4-dioxane showed decreased yields (Table 1, entries 7-10).[9] Temperature was considered as another possibly effector for this method. However, no improvement appeared by either increasing the temperature to 130 ℃ or decreasing to 70 ℃ (Table 1, entries 11-12). In order to exclude the possibility of involve air in the reaction, a control reaction under argon atmosphere was performed and no influence on the yield was observed.

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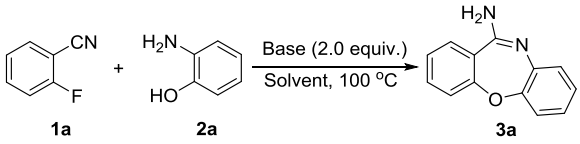
† Electronic Supplementary Information (ESI) available: [Analytic data and NMR spectrums]. See DOI: 10.1039/x0xx00000x

Table 1: Dibenzoxazepinamines synthesis: reaction conditions optimization.[a]



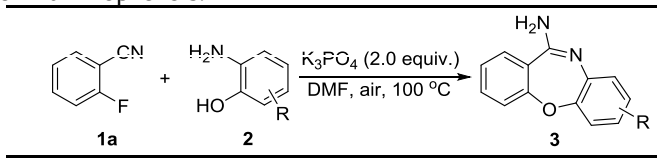
1a 2a 3a

Entry	Base	Solvent	T(°C)	Yield (%)[b]
1	Na_2CO_3	DMF	100	8
2	K_2CO_3	DMF	100	53
3	KO*t*Bu	DMF	100	89
4	K_3PO_4	DMF	100	95
5	DABCO	DMF	100	30
6	DBU	DMF	100	0
7	K_3PO_4	DMSO	100	34
8	K_3PO_4	DMAc	100	81
9	K_3PO_4	Toluene	100	24
10	K_3PO_4	Dioxane	100	57
11	K_3PO_4	DMF	130	66
12	K_3PO_4	DMF	70	25

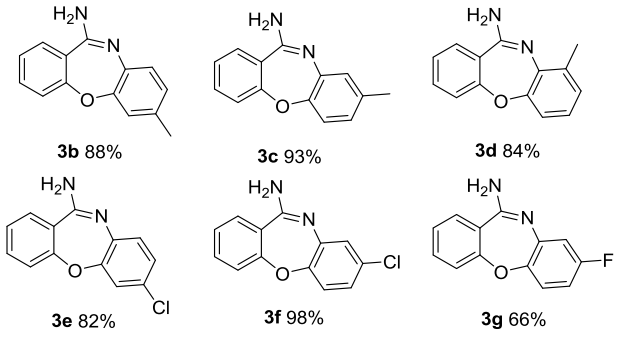
[a] Reaction conditions: **1** (1 mmol), **2** (1.5 mmol), base (2.0 equiv.), solvent (2 mL), 100 ℃, air, 6 h. [b] Isolated yield.

With the optimal reaction conditions in hand, the generality and limitation testing was performed subsequently. A variety of substituted 2-aminophenols were examined at the first stage. As shown in Table 2, both electronic-donating and electronic-withdrawing groups substituted substrates can gave the desired products with 2-aminophenol in good yields. Additionally, 2-aminopyridin-3-ol was shown can be applied as substrate as well and gave the corresponding benzo[*f*]pyrido[3,2-*b*][1,4]oxazepin-10-amine (**3h**) in 97 % isolated yield. Furthermore, the *ortho*-amino-substituted naphthalenols like 1-aminonaphthalen-2-ol and 3-aminonaphthalen-2-ol can are also suitable starting materials for this transformation and gave the corresponding products in good yields (**3i**, **3j**). In the case of 2-(methylamino)phenol, 51 % of 10-methyldibenzo[*b*,*f*][1,4]oxazepin-11(10*H*)-imine (**3k**) as the desired product was obtained.

Table 2: Dibenzoxazepinamines synthesis: substrates testing of 2-aminophenols.[a]

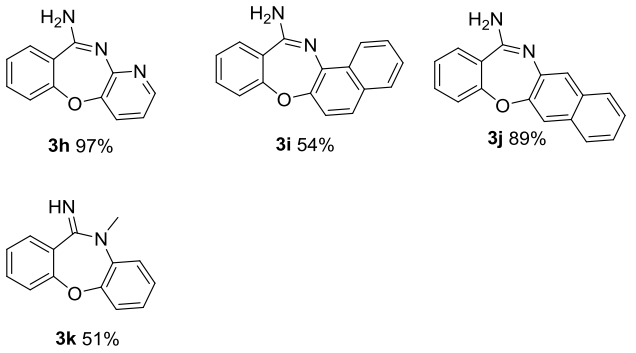


1a 2 3



3b 88% **3c** 93% **3d** 84%

3e 82% **3f** 98% **3g** 66%



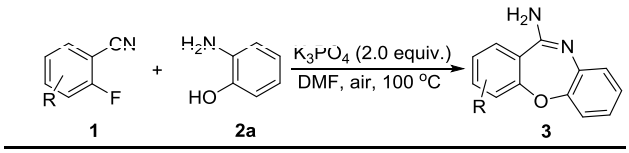
3h 97% **3i** 54% **3j** 89%

3k 51%

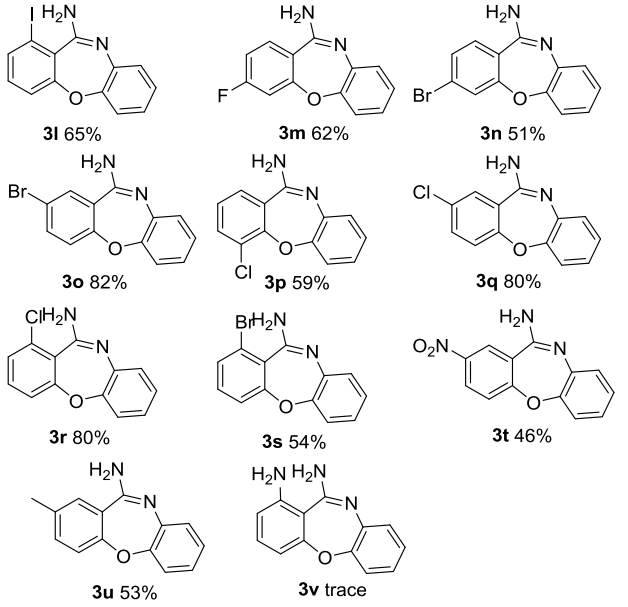
[a] Reaction conditions: **1a** (1 mmol), **2** (1.5 mmol), K_3PO_4 (2.0 equiv.), DMF (2 mL), 100 ℃, air, 6 h, isolated yields.

Then, various substituted 2-fluorobenzonitriles were tested with 2-aminophenol. As shown in Table 3, all the tested substrates provided moderate to good yields. This methodology showed good functional group tolerance whiles the electronic-withdrawing functional group shown positive effect than electronic-donating group. From the obtained results, it can be found that there is a significant differences in the yields of the desired compounds (**3n, 3o, 3s** and **3p, 3q, 3r**) when the same substituent is substituted in different position. This phenomenon might be able to be explained by the electron and steric effects of substituents on the nucleophilic substitution between -OH and -F and nucleophilic addition of $-NH_2$ to -CN. Only trace of desired product could be produced from 2-amino-6-fluorobenzonitrile and 2-aminophenol (**3v**), even prolong the reaction time and increase the reaction temperature.

Table 3: Dibenzoxazepinamines synthesis: Substrate testing of 2-fluorobenzonitriles.[a]



1 2a 3



3l 65% **3m** 62% **3n** 51%

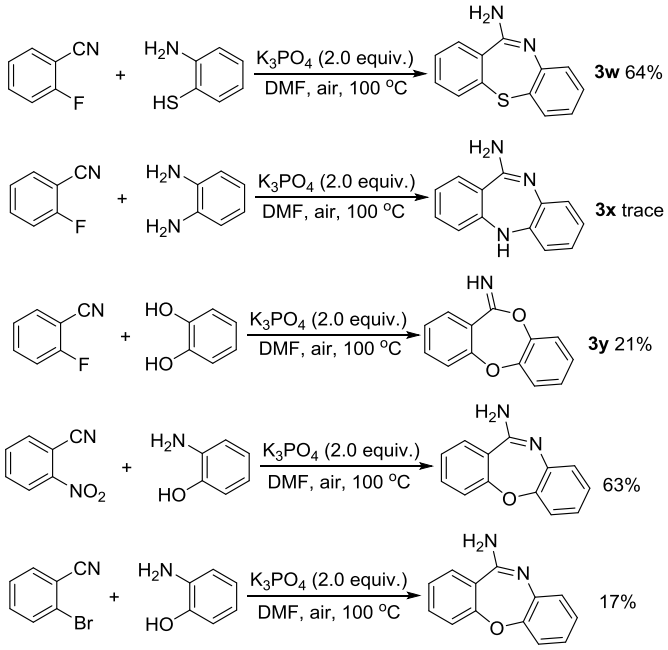
3o 82% **3p** 59% **3q** 80%

3r 80% **3s** 54% **3t** 46%

3u 53% **3v** trace

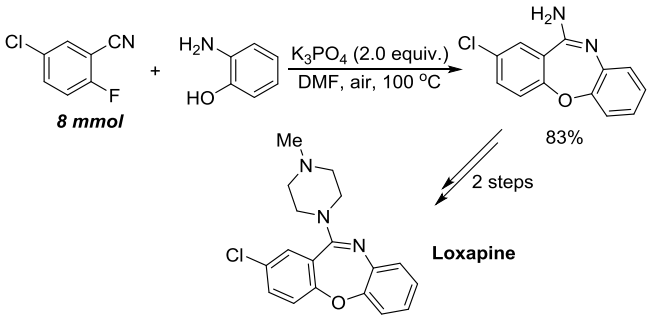
[a] Reaction conditions: **1** (1 mmol), **2a** (1.5 mmol), K_3PO_4 (2.0 equiv.), DMF (2 mL), 100 ℃, air, 6 h, isolated yields.

Encouraged by these results, we turned to the analogues of substrates testing (Scheme 2). Under the same reaction conditions, 64% of dibenzo[*b*,*f*][1,4]thiazepin-11-amine (**3w**) was isolated from the reaction between 2-fluorobenzonitrile and 2-aminobenzenethiol. However, only trace of the desired product can be detected by using benzene-1,2-diamine as the reaction partner. In the case of pyrocatechol, 21% of 11*H*-dibenzo[*b*,*e*][1,4]dioxepin-11-imine was isolated and together with a large amount of 2,2'-(1,2-phenylenebis(oxy))dibenzonitrile which is a result of the reaction of two molecules of 2-fluorobenzonitrile with one molecule of pyrocatechol. Then 2-nitrobenzonitrile and 2-bromobenzonitrile were tested because of their similarity with 2-fluorobenzonitrile. As we expected, moderate yield of the desired product can be produced from 2-nitrobenzonitrile and 2-aminophenol; while 17% yield with 2-bromobenzonitrile as their differences on leaving ability.



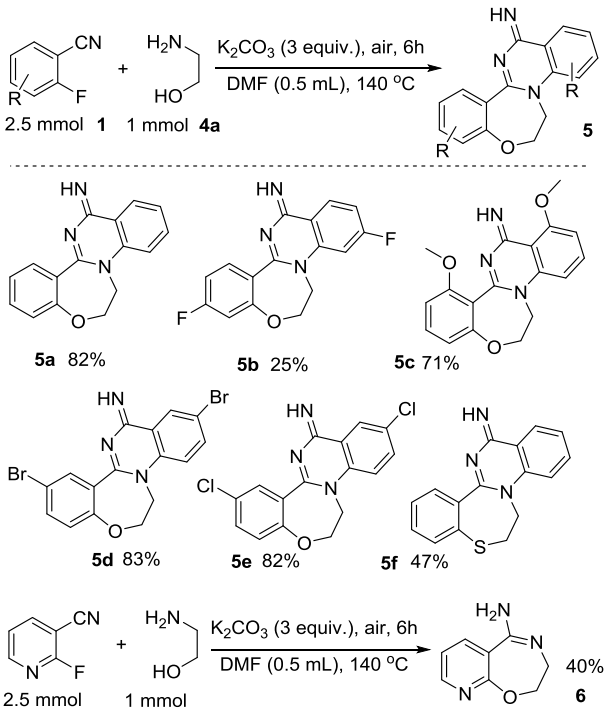
Scheme 2: Substrate analogues testing.

In order to prove the synthetic applicability of this procedure, we performed the reaction in large scale (Scheme 3). 5-Chlro-2-aminobenzonitrile was chosen as the substrate in 8 mmol scale in 16 mL of DMF, 83% of the corresponding product can be isolated. Notably, 2-chlorodibenzo[*b*,*f*][1,4]oxazepin-11-amine is a key intermediate for the synthesis of antidepressant drug, **Loxapine**.[2,3]

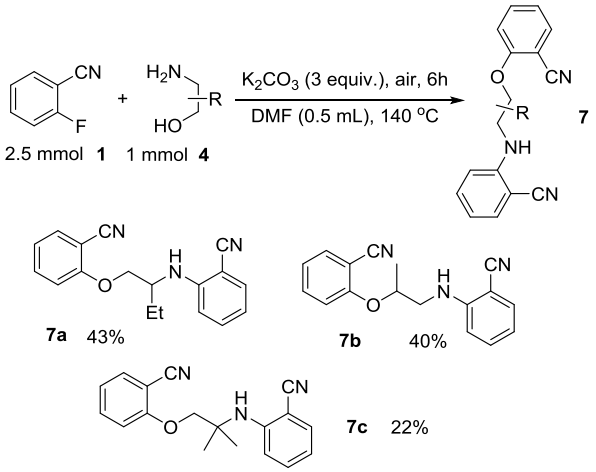


Scheme 3: Enlarged reaction.

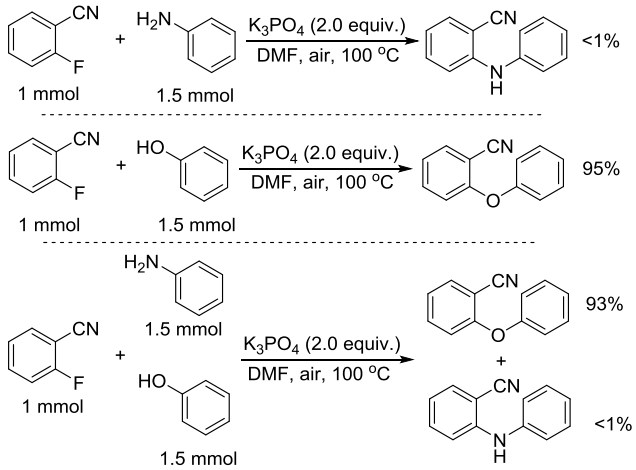
Moreover, only trace of the desired product was observed when 2-aminoethanol was applied as the substrate and together with certain amount of 1,2-dihydro-9*H*-benzo[6,7][1,4]oxazepino[4,5-*a*]quinazolin-9-imine. After some further optimizations, the yield of quinazolinimine can be improved to 82% by using 2.5 equiv. of 2-fluorobenzonitrile and with K_2CO_3 as the base (Scheme 4, **5a**). Some other 2-fluorobenzonitriles were tested as well, to our delight, moderate to good yields of the desired products can be isolated (Scheme 4). Interestingly, 2,3-dihydropyrido[3,2-*f*][1,4]oxazepin-5-amine was isolated in 40% yield when 2-fluoronicotinonitrile was applied as starting material (Scheme 4, **6**). However, in the testing of 2-aminoethanol derivatives, only non-cyclized products were detected (Scheme 5). Additionally, ethane-1,2-diol, ethane-1,2-diamine and 3-aminopropan-1-ol were tested with 2-fluorobenzonitrile as well. No desired product was observed in these cases.



Scheme 4: Reaction of 2-aminoethanol with 2-fluorobenzonitriles.

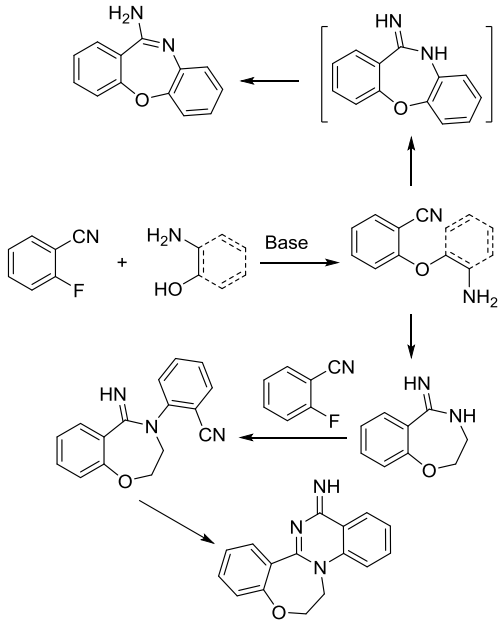


Scheme 5: Reaction of 2-aminoethanols with 2-fluorobenzonitrile.



Scheme 6: Control experiments.

Based on these results and the control experiments (Scheme 6), a most possible reaction pathway is proposed and shown in Scheme **7**.[8,10] The reaction starts with the base promoted nucleophilic substitution of 2-aminophenol/2-aminoethanol and 2-fluorobenzonitrile to give the corresponding aryl ether as the intermediate, and then followed by the addition of amino group to the cyano group. In the case of 2-aminophenol, the final product can be formed after rearrangement. When using 2-aminoethanol as substrate, another molecular of 2-fluorobenzonitrile joined in the reaction and gave the final product after nucleophilic substitution and addition.



Scheme 7: Proposed reaction mechanism.

In conclusion, a practical and efficient methodology for the synthesis of dibenzo[*b*,*f*][1,4]oxazepin-11-amines has been developed. With 2-fluorobenzonitriles and 2-aminophenols and their analogues as the substrates, the corresponding products can be isolated in good to excellent yield under metal-free conditions. Additionally, this methodology can be performed in large scale without any problem. Further, more complicated quinazolinimines can be produced when using 2-aminoethanol as the reaction partner.

The authors thank the state of Mecklenburg-Vorpommern, the Bundesministerium für Bildung und Forschung (BMBF), and the Deutsche Forschungsgemeinschaft for financial support. In addition, the research leading to these results has received funding from the Innovative Medicines Initiative Joint Undertaking (CHEM21) under grant agreement no. 115360, resources of which are composed of a financial contribution from the European Union's Seventh Framework Programme (FP7/2007–2013) and EFPIA companies in kind contribution. We also thank Dr. C. Fischer, S. Schareina, and Dr. W. Baumann for their excellent technical and analytical support. We also appreciate the general support from Prof. Matthias Beller.

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