Catalysis Science & Technology

Accepted Manuscript

ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/catalysis

Journal Name

ARTICLE

Base-regulated tunable synthesis of pyridobenzoxazepinones and pyridobenzoxazines

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

DOI: 10.1039/x0xx00000x

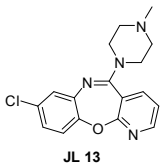
www.rsc.org/

Chaoren Shen[a] and Xiao-Feng Wu*[a]

A base-regulated one-pot protocol for the tunable synthesis of pyridobenzoxazepinones and pyridobenzoxazines has been developed. The preparation of pyridobenzoxazepinones is achieved in moderate to good yield by utilizing aromatic nucleophilic substitution(S_NAr, *O*-arylation)/carbonylation tandem reaction. Mechanistic studies suggest that S_NAr (*O*-arylation) proceeds prior to the aminocarbonylation. Through the regulation of bases, pyridobenzoxazines can be obtained via successive S_NAr (*O*-arylation and then *N*-arylation). Base is crucial for the regulation of the products.

Introduction

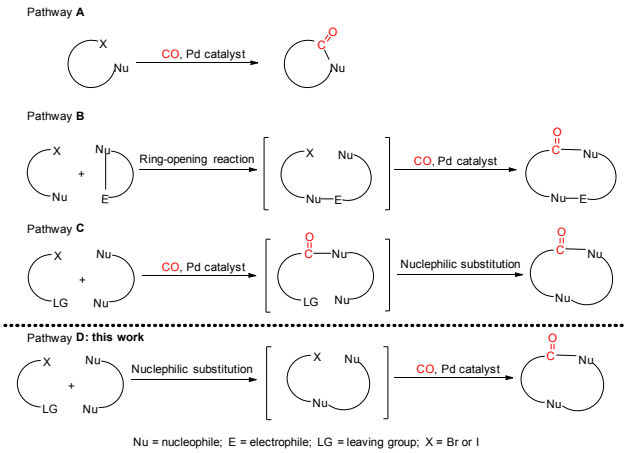
As the analogs of dibenzoxazepinone, dibenzoxazepine and its derivatives, pyridobenzoxazepines are the skeletons of some HIV inhibitors,[1] clozapine-like compound JL 13 with potential atypical antipsychotic activity (Fig. 1)[2] and its derivatives.[3] To the best of our knowledge, until now there are only two ways to obtain pyridobenzoxazepinones. One is from the condensation/nucleophilic aromatic substitution (S_NAr) sequence of 2-chloronicotinoyl chloride or 2-chloronicotinic acid with 2-aminophenol and the other is through Smiles rearrangement of *o*-chloronicotinamide with *o*-halogenated phenols.[4] Considering the following two factors that i) *o*-chloronicotinamides come from the 2-chloronicotinoyl chloride or 2-chloronicotinic acid; ii) substituted 2-chloronicotinoyl chloride and substituted 2-chloronicotinic acid usually are not readily available, developing more facile and novel methods of preparing pyridobenzoxazepinones that utilizing commercially available starting materials becomes important, useful and under current interests. With the developments of synthetic procedures, the discovery of new potential drug candidates with the backbone of pyridobenzoxazepinone can definitely be favored.



JL 13

Fig. 1 Potential atypical antipsychotic JL 13.

Based on our long-lasting interest on palladium-catalyzed carbonylative synthesis of heterocyclic compounds,[5] we intended to develop a simple method to prepare pyridobenzoxazepinone *via* palladium-catalyzed aminocarbonylation. The existing strategies involving palladium-catalyzed carbonylation to construct medium ring heterocycles are classified into three types (Scheme 1): (i) direct carbonylation of substrates (Pathway **A**);[6] (ii) utilizing sequential ring-opening/carbonylation or Baylis-Hillman reaction/carbonylation[7] process (Pathway **B**); (iii) employing carbonylation/S_NAr approach (Pathway **C**).[8] Thus in this manuscript we attempt to develop alternative one-pot tandem S_NAr/carbonylation protocol for preparing pyridobenzoxazepinones (Pathway **D**)[9] and report the pathways for base-regulated tunable synthesis of pyridobenzoxazepinones and pyridobenzoxazine.



Nu = nucleophile; E = electrophile; LG = leaving group; X = Br or I

Scheme 1. Existing strategies involving Pd-catalyzed carbonylation to construct medium ring heterocycles.

[a] Leibniz-Institut für Katalyse an der Universität Rostock *e.V.*, Albert-Einstein-Str. 29a, 18059 Rostock, Germany. E-mail: xiao-feng.wu@catalysis.de

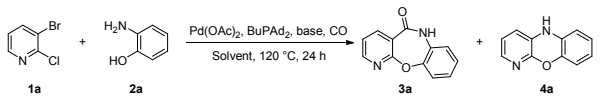
Electronic Supplementary Information (ESI) available: [analytic data and spectrums]. See DOI: 10.1039/x0xx00000x

Results and discussion

Because of the following two facts i) with most anionic and neutral reagents, the typical reactivity order of leaving groups in S_NAr is F > Cl ≈ Br > I;[10] ii) usually nucleophilic attack to a suitable leaving group on a π-deficient pyridine ring is more favourable at the α- and γ-position to the heteroatom,[11] commercially obtainable 3-bromo-2-chloropyridine (**1a**) and 2-aminophenol (**2a**) were employed as model substrates and $Pd(OAc)_2$**/**$BuPAd_2$ was adopted as catalyst for the initial investigation on the generation of pyridobenzoxazepinone compound **3a** (Table 1). An evaluation of different inorganic bases in dipolar aprotic solvent DMSO (Table 1, entries 1-5) indicated that base had significant influences on the selectivity of products. When Cs_2CO_3 was employed, the major product was switched from aminocarbonylative product **3a** to 5*H*-benzo[*b*]pyrido[3,2-*e*][1,4]oxazine **4a** (Table 1, entry 2). Employing Na_2CO_3 or $NaHCO_3$ as base can suppress the formation of product **4a (**Table 1, entries 4 and 5**)**. To make clear the role of palladium catalyst in the formation of **4a**, blank reaction without palladium catalyst and CO was conducted (Table 1, entry 6)**.** The result indicated that the generation of **4a** was through twice nucleophilic substitution between **1a** and **2a**. Apparently the nucleophilic substitution of aniline to C-Br bond overwhelmed the aminocarbonylation with the help of Cs_2CO_3. The distinct product selectivity with different bases is probably due to the different solubility of these bases in DMSO and the different basicity resulted from the difference on solubility.[12] Further investigation on solvents effect showed that in other dipolar aprotic solvents such as DMF, DMAc and NMP (Table 1, entries 7-9) no better selectivity can be achieved than in DMSO. Reducing the loading of palladium catalyst also results in a drop of yield (Table 1, entry 10). Replacing $BuPAd_2$ with PPh_3 leads to the slight drop on the yield (Table 1, entry 11). While the reaction time was shortened to 12 h, distinct difference was displayed on the yield between employing $BuPAd_2$ and PPh_3 (Table 1, entries 12 and 13). Finally the $Pd(OAc)_2$/$BuPAd_2$/Na_2CO_3/DMSO was found to be the optimized catalytic system for the generation of pyridobenzoxazepinones and the collaboration of Cs_2CO_3 and DMSO is suitable for the preparation of pyridobenzoxazines.

To gain some insight into this interesting selectivity switch and clarify the sequence between S_NAr (*O*-arylation) and carbonylation, a set of control experiments were conducted. The result of reaction of **1a** with 1.0 equivalent aniline and 1.0 equivalent phenol without palladium catalyst under the optimized conditions (Scheme 2, part a) showed that no 3-bromo-*N*-phenylpyridin-2-amine, the nucleophilic substitution product of aniline, was generated. However the yield of 3-bromo-2-phenoxypyridine determined by GC and GC-MS was only *ca.* 34% and **1a** still exists even after 24 h. As shown in Schemes 2b, 2c and 2d, **5a** can be confirmed as the intermediate for further transformation.

Table 1 Optimization of reaction conditions.[a]

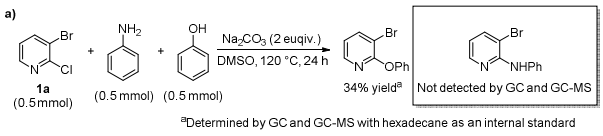


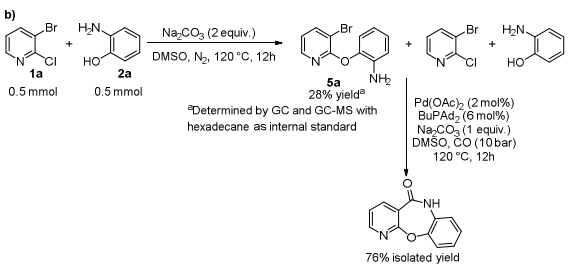
1a 2a 3a 4a

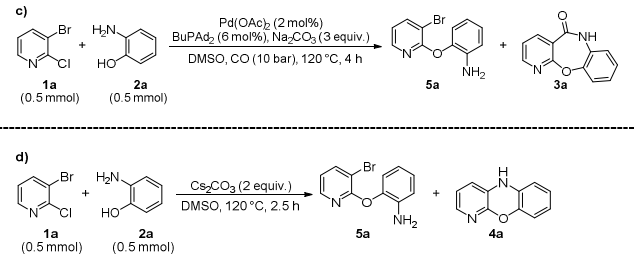
Entry	Base	Solvent	**3a** : **4a**[b]	Yield[c]
1	K_3PO_4	DMSO	48 : **52**	43
2	Cs_2CO_3	DMSO	17 : **83**	(51)
3	K_2CO_3	DMSO	**83** : 17	(53)
4	Na_2CO_3	DMSO	> **99** : 1	81 (77)
5	$NaHCO_3$	DMSO	> **99** : 1	(56)
6	Cs_2CO_3	DMSO	0 : **100**	(71)[d]
7	Na_2CO_3	DMF	**63** : 37	42
8	Na_2CO_3	DMA	**69** : 31	47
9	Na_2CO_3	NMP	**85** : 15	40
10	Na_2CO_3	DMSO	> **99** : 1	(60)[e]
11	Na_2CO_3	DMSO	> **99** : 1	(71)[f]
12	Na_2CO_3	DMSO	> **99** : 1	(78)[g]
13	Na_2CO_3	DMSO	> **99** : 1	46[f,g,h]

[a] Unless otherwise stated, the reaction was conducted on a 0.50 mmol scale (0.50 mmol **1a**, 0.50 mmol **2a**, 2 mol% $Pd(OAc)_2$, 6 mol% $BuPAd_2$, 1.5 mmol base, 10 bar CO) with 2.0 mL solvent. Reaction temperature was 120 °C. Reaction was 24 h. [b] The ratio of **3a** and **4a** determined by GC and GC-MS with hexadecane as an internal standard. [c] Yields refer to the yields of major product and they were determined by GC and GC-MS with hexadecane as an internal standard; yields in parentheses are for the isolated major product. Ad = adamantyl, Bu = *n*-butyl, DMA = *N*, *N*′-dimethylacetamide, DMF = *N*, *N*′-dimethylformamide, DMSO = dimethyl sulfoxide, NMP = *N*-methyl-2-pyrrolidone. [d] No Pd catalyst and CO. [e] 1 mol% $Pd(OAc)_2$, 3 mol% $BuPAd_2$. [f] 6 mol% PPh_3 instead of 6 mol% $BuPAd_2$. [g] Reaction time was shortened to 12 h.[h] 2-((3-bromopyridin-2-yl)oxy)aniline was detected by GC and GC-MS.

Investigations on the base effect in the blank reaction between **1a** and **2a** (Table 2) revealed that different from the effect of Cs_2CO_3, K_2CO_3 and DBU (Table 2, entries 1-3), Na_2CO_3 is not able to promote the nucleophilic cyclization of intermediate **5a**. And compared with results of the other three bases, the S_NAr of phenol group to the C-Cl bond of **1a** is sluggish in the presence of Na_2CO_3. Even after 24 hours, the conversion of **1a** only reached 39% (Table 2, entry 4).

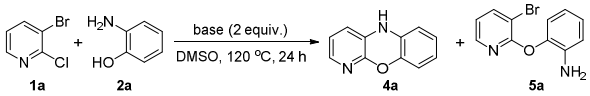






Scheme 2 Control experiments.

Table 2 Investigation on effect of bases.[a]

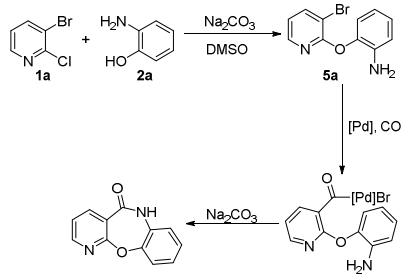


Entry	Base	**4a** : **5a**[b]	Conversion of **1a**[c]
1	Cs_2CO_3	> 99 : 1	> 99%
2	K_2CO_3	44 : 56	> 99%
3	DBU	47 : 53	> 99%
4	Na_2CO_3	< 1 : 99	39%

[a] The reaction was conducted on a 0.50 mmol scale (0.50 mmol **1a**, 0.50 mmol **2a**, 1.0 mmol base, 0.10 mL hexadecane as an internal standard and 2.0 mL DMSO). DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene. [b] The ratio of **4a** and **5a** was determined by GC and GC-MS with hexadecane as an internal standard. [c] The conversion of **1a** was determined by GC and GC-MS with hexadecane as an internal standard.

With our expectation, the nucleophilic aromatic substitution should precede the aminocarbonylation.[13] The outcome of a two-step reaction (Scheme 2, part b) as well as the side product observed during the optimization of conditions (Table 1, entry 13) suggested that the product **3a** was converted from the intermediate **5a**. And the rate of S_NAr (*O*-arylation) is slower than the rate of carbonylation catalyzed by $Pd(OAc)_2$-$BuPAd_2$. When we shortened the time of model reaction to 4 hours, the intermediate **5a** was also observed by GC and GC-MS (Scheme 2, part c). Shortening the reaction time also helps us to observe the intermediate **5a** during the formation of **4a** (Scheme 2, part d). It implied that the Cl atom at the 2-position of pyridine ring leaves prior to the Br at the 3-position of pyridine ring during the formation of **4a**.[14] Considering the possible impact of trace moisture brought into the reaction system by hygroscopic base and solvent, blank reaction of **1a** only with Na_2CO_3 or Cs_2CO_3 in DMSO was conducted.[15] No hydrolysis product of **1a** and no conversion of **1a** were detected.

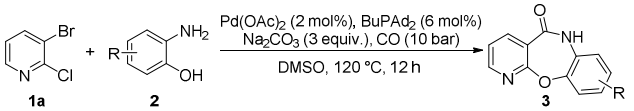
Based on the above results from the control experiments and investigations on base effects, a plausible mechanism is proposed in Scheme 3. Firstly, the nucleophilic aromatic substitution between 2-aminophenol and 3-bromo-2-chloropyridine occurs. With the help of Na_2CO_3 in DMSO, the intermediate **5a** is formed and no further intramolecular nucleophilic substitution of **5a** occurs. Then **5a** is converted to acylpalladium species through the oxidative addition with Pd(0) under CO atmosphere. Finally, the product is generated from the intramolecular cyclization of acylpalladium species with amino group. The second step reaction that consuming the intermediate **5a** accelerate the conversion of **1a** and **2a**, and subsequently drive the proceeding of the reaction.

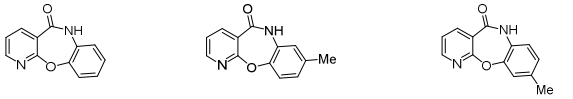


Scheme 3 Proposed reaction mechanism.

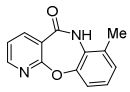
With the optimized conditions in hand, we set out to investigate the scope of the 2-aminophenol substrates (Table 3). A range of 2-aminophenol possessing methyl, halogen at various positions and *ortho*-amino naphthol (all commercially available) were subjected to the optimized conditions described above (**3b**-**3i**). For *para*- or *meta*-substituted 2-aminophenol and 3-amino-2-naphthol, the corresponding pyridobenzoxazepinones were obtained in moderate to good yields (**3b**, **3c**, **3e**-**3h**). However for 2-amino-3-methylphenol (**3c**) and 1-amino-2-naphthol hydrochloride (**3i**), the yields of the desired products are lower, which is probably due to the steric hindrance around the amino group of the intermediates. Compound JL 13 (Fig. 1) and its analogues can be synthesized from the product **3e** *via* an iminochloride-intermediated process or a synthetic method of amidine developed by Fryer and co-workers (Scheme 4).[3b,16] Moderate yield is obtained for the *N*-substituted 2-aminophenol (**3j**). Because of the weak nucleophilicity of 3-amino-2-hydroxypyridine resulted from the hydroxypyridine-pyridone equilibrium in polarized solvent,[17] dipyrido[2,3-*b*:3',2'-*f*][*1,4*]oxazepin-6(5*H*)-one cannot be prepared with this protocol (**3k**).

Table 3 Substrate scope of 2-aminophenols.[a]

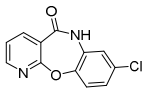




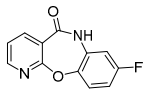
3a, 77% **3b**, 81% **3c**, 74%



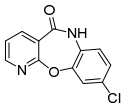
3d, 30%



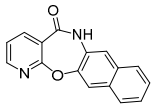
3e, 68%



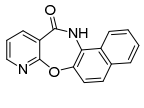
3f, 65%



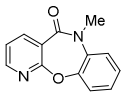
3g, 62%



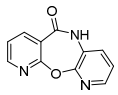
3h, 79%



3i, 41%[b]

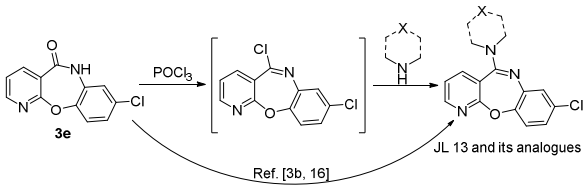


3j, 58%



3k, 0%

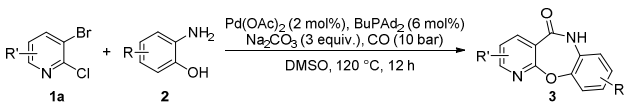
[a] Unless otherwise stated, the reaction was conducted on a 0.50 mmol scale (0.50 mmol **1a**, 0.50 mmol **2**, 2 mol% $Pd(OAc)_2$, 6 mol% $BuPAd_2$, 1.5 mmol Na_2CO_3, 10 bar CO) with 2.0 mL DMSO. Reaction temperature was 120 °C. Reaction was 24 h. Yield of the isolated product. [b] 1-amino-2-naphthol hydrochloride was used and 2.0 mmol Na_2CO_3 instead of 1.5 mmol Na_2CO_3.

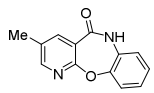


Scheme 4 Conversion of compound **3e** to JL 13 and its analogues.

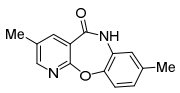
Then combinatorial reactions of several commercially available substituted 3-bromo-2-chloropyridines with various substituted 2-aminophenols were conducted to verify the broad-spectrum on substrates of this protocol (Table 4). Except two examples **3o** and **3w,** moderate to good yields were achieved for the rest of the substrates (**3l**-**3n**, **3p**-**3v**, **3x**-**3y**). Similar with the results in Table 3, the yields in reactions of 3-position substituted 2-aminophenol (**3o**, **3w**) is low, which is caused by the congested environment around the amino group of intermediates. Additionally, 2-aminobenzenethiol can be applied as the coupling partner as well. 62-69% of the desired benzo[*b*]pyrido[3,2-*f*][1,4]thiazepin-5(6*H*)-ones were isolated without any further optimization (**3z, 3aa**). To our surprise, no target product was formed when pyrocatechol and benzene-1,2-diamine reacted with 3-bromo-2-chloropyridine under our reaction conditions. Moreover, palladium black was formed immediately when we attempt in using 2-aminoethane-1-thiol and 2-aminoethan-1-ol as the reaction partner which might due to the good coordination and reducing properties of them.

Table 4 Reaction of substituted 3-bromo-2-chloropyridines with substituted 2-aminophenols.[a]

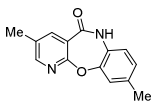




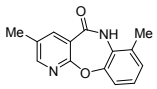
3l, 80%



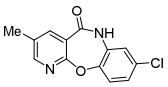
3m, 74%



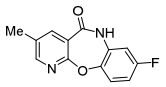
3n, 75%



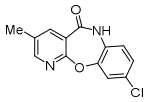
3o, 35%



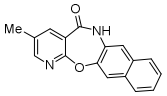
3p, 71%



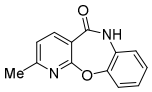
3q, 70%



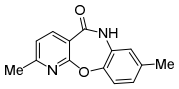
3r, 74%



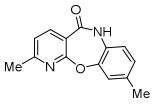
3s, 76%



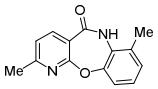
3t, 82%



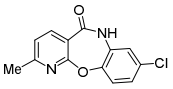
3u, 85%



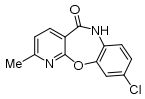
3v, 71%



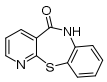
3w, 27%



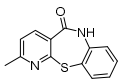
3x, 69%



3y, 81%



3z, 69%

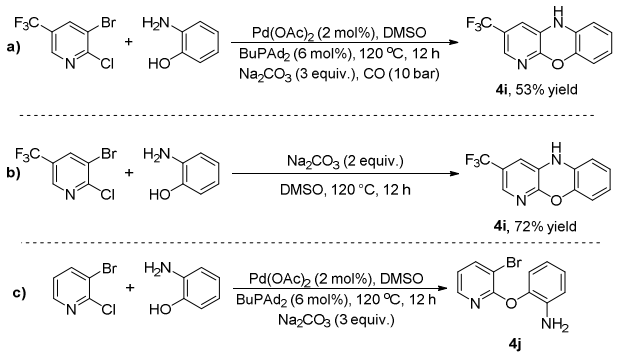


3aa, 62%

[a] Unless otherwise stated, the reaction was conducted on a 0.50 mmol scale (0.50 mmol **1a**, 0.50 mmol **2**, 2 mol% $Pd(OAc)_2$, 6 mol% $BuPAd_2$, 1.5 mmol Na_2CO_3, 10 bar CO) with 2.0 mL DMSO. Reaction temperature was 120 °C. Reaction was 24 h. Yield of the isolated product.

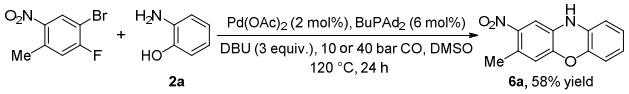
However when this protocol was applied to the reaction between 3-bromo-2-chloro-5-(trifluoromethyl)pyridine and 2-aminophenol, even in the pressure of 10 bar carbon monoxide, palladium-catalyzed aminocarbonylation was inhibited and pyridobenzoxazine product **4h** was formed (Scheme 5, a). Through the reaction without palladium catalyst and CO, it is confirmed that the formation of C-N bond is through the nucleophilic attack of $-NH_2$ to C-Br bond at the 3-position of pyridine ring (Scheme 5, b). This phenomenon is blamed to the electronic effect from the introduction of strong electron-withdrawing $-CF_3$ group into the pyridine ring. This helps the nucleophilic substitution overwhelming the oxidative addition of Pd(0) on C(sp^2)-Br bond. In addition, only non-cyclized

intermediate (**4j**) was formed when we perform our model reaction in the absence of CO (Scheme 5, c) which also explains the importance of the base (compared with Table 6).



Scheme 5 Reactions between 3-bromo-2-chloro-5-(trifluoromethyl)pyridine and 2-aminophenol.

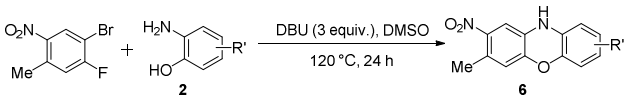
The similar situation was encountered when we attempted to achieve the sequential S_NAr(*O*-arylation)/caronylation process to prepare 3-methyl-2-nitrodibenzo[*b*,*f*][1,4]oxazepin-11(10*H*)-one, the analogue of tricyclic antidepressant nitroxazepine. Although in the atmosphere of 10 bar CO and the existence of palladium catalyst, the carbonylation was prevented by the nucleophilic substitution (*N*-arylation) and 3-methyl-2-nitro-10*H*-phenoxazine was obtained in moderate yield (Scheme 6). Even the pressure rises to 40 bar, there is no impact on product and yield.

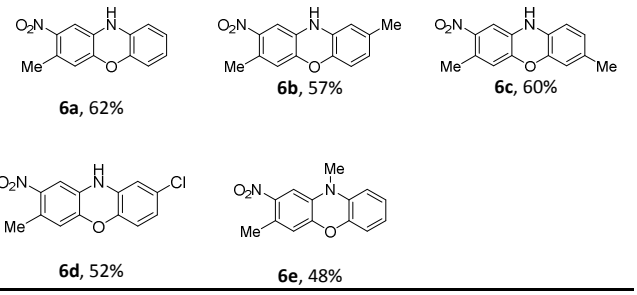


Scheme 6 Reaction of 1-bromo-2-fluoro-4-methyl-5-nitrobenzene with 2-aminophenol.

For the reaction between 1-bromo-2-fluoro-4-methyl-5-nitrobenzene and substituted 2-aminophenols, the consequences resemble to the reaction between 1-bromo-2-fluoro-4-methyl-5-nitrobenzene and **1a.** Whether there is CO atmosphere and palladium catalyst or not, the products are always substituted 3-methyl-2-nitro-10*H*-phenoxazine (Table 5).

Table 5 Reaction of 1-bromo-2-fluoro-4-methyl-5-nitrobenzene with substituted 2-aminophenol.

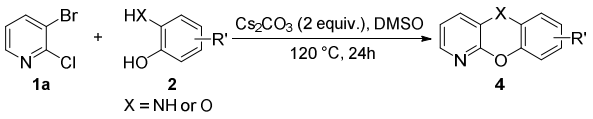


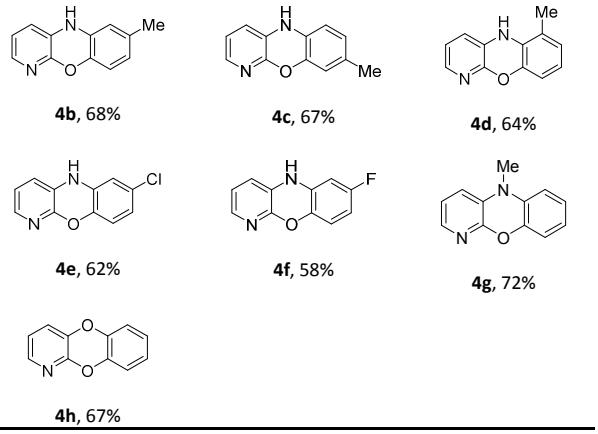


[a] Unless otherwise stated, the reaction was conducted on a 0.50 mmol scale (0.50 mmol , 0.50 mmol **2**, 1.0 mmol Cs_2CO_3) with 2.0 mL DMSO. Reaction temperature was 120 °C. Reaction was 24 h. Yield of the isolated product.

Through the regulation on base, benzo[5,6][1,4]dioxino[2,3-*b*]pyridine and 5*H*-benzo[*b*]pyrido[3,2-*e*][1,4]oxazine with different substituent group can be obtained in moderate yield (Table 6). Compared with the only two reports about the preparation of benzo[5,6][1,4]dioxino[2,3-*b*]pyridine and 5*H*-benzo[*b*]pyrido[3,2-*e*][1,4]oxazine which respectively involves multistep procedure or using metallic potassium,[14b,18] this pathway is relatively simple and mild.

Table 6 Preparation of substituted 5*H*-benzo[*b*]pyrido[3,2-*e*][1,4]oxazine[a]





[a] Unless otherwise stated, the reaction was conducted on a 0.50 mmol scale (0.50 mmol 1-bromo-2-fluoro-4-methyl-5-nitrobenzene, 0.50 mmol **2**, 1.0 mmol Cs_2CO_3) with 2.0 mL DMSO. Reaction temperature was 120 °C. Reaction was 24 h. Yield of the isolated product.

Conclusions

In conclusion, a base-regulated one-pot one-step protocol for the tunable synthesis of pyridobenzoxazepinones and pyridobenzoxazines from commercially available starting

materials has been developed. Moderate to good yields are achieved for the preparation of pyridobenzoxazepinones and pyridobenzoxazines. Studies on mechanism disclose that base plays an important role in the tuning of products.

Acknowledgements

The authors thank the state of Mecklenburg-Vorpommern, the Bundesministerium für Bildung und Forschung (BMBF), and the Deutsche Forschungsgemeinschaft for financial support. Thanks also go to China Scholarship Council (CSC) for its financial support to C. Shen. We also thank Andreas Hutter, Andreas Koch, Dr Christine Fischer, Susanne Schareina, and Dr Wolfgang Baumann for their excellent technical and analytical support. We also appreciate the general support from Prof. Matthias Beller.

Experimental

Representative procedure for the synthesis of pyridobenzoxazepinones

A Wheaton vial (4 mL) equipped with a septum, a small cannula was charged with $Pd(OAc)_2$ (2 mol%), $BuPAd_2$ (6 mol%), 3-bromo-2-chloropyridine (0.5 mmol), 2-aminophenol (0.5 mmol), sodium carbonate (1.5 mmol) and a magnetic stirring bar. The vial was purged with argon before DMSO (2.0 mL) was injected by using a syringe. The vial (or several vials) was placed in an alloy plate, which was transferred into a 300 mL autoclave of the 4560 series from Parr Instruments under argon atmosphere. After flushing the autoclave three times with CO, a pressure of 10 bar of CO was adjusted at ambient temperature. Afterwards the reaction was performed for 12 h at 120°C. After the reaction was complete, the autoclave was cooled down with ice-water mixture to room temperature and the pressure was released carefully. The solution was diluted with acetone and then silica gel was added into the solution. After evaporation of the organic solvent, the crude product was purified by column chromatography using ethyl acetate/*n*-pentane.

Representative procedure for the synthesis of pyridobenzoxazepinones

To an oven-dried 10 mL Schlenk tube was added 3-bromo-2-chloropyridine (0.50 mmol), 2-aminophenol (0.50 mmol), cesium carbonate (1.0 mmol) and a magnetic stirring bar. The Schlenk tube was purged with argon before DMSO (2.0 mL) was injected by using a syringe. Then the reaction was performed for 24 h at 120°C. After the reaction was completed, the reaction mixture was diluted with acetone and then silica gel was added into the solution. After evaporation of the organic solvent, the crude product was purified by column chromatography using ethyl acetate/*n*-pentane.

Benzo[*b*]pyrido[3,2-*f*][1,4]oxazepin-5(6*H*)-one: White solid; **^{1}H NMR (300 MHz, [D$_6$]DMSO)**: δ = 10.76 (br s, 1H), 8.51 (dd, *J* = 1.8, 4.7 Hz, 1H), 8.27 (dd, *J* = 1.8, 7.5 Hz, 1H), 7.46 (dd, *J* = 4.8, 7.7 Hz, 1H), 7.34 (dd, *J* = 1.8, 7.4 Hz, 1H), 7.26-7.14 (m, 3H). **^{13}C NMR (75 MHz, [D$_6$]DMSO)**: δ = 164.4, 162.3, 152.4, 148.1, 142.4, 130.5, 126.4, 125.6, 122.5, 121.9, 121.7, 120.0. **GC-MS (EI, 70 eV)**: m/z (%) = 212 (100), 184 (36), 155 (41), 130 (9), 77 (11), 52 (11). **HRMS (EI)**: calcd. for $[C_{12}H_8O_2N_2]^+$ 212.05803, found 212.05831.

8-Methylbenzo[*b*]pyrido[3,2-*f*][1,4]oxazepin-5(6*H*)-one: White solid; **^{1}H NMR (300 MHz, [D$_6$]DMSO)**: δ = 10.69 (br s, 1H), 8.49 (dd, *J* = 1.8, 4.8 Hz, 1H), 8.26 (dd, *J* = 2.1, 7.7 Hz, 1H), 7.45 (dd, *J* = 4.8, 7.8 Hz, 1H), 7.21 (d, *J* = 9.0 Hz, 1H), 6.98 (s, 1H), 6.98-6.65 (m, 1H), 2.25 (s, 3H). **^{13}C NMR (100MHz, [D$_6$]DMSO)**: δ = 164.5, 162.5, 152.3, 146.0, 142.3, 135.7, 130.1, 126.0, 122.4, 121.8, 121.5, 120.1, 20.3. **GC-MS (EI, 70 eV)**: m/z (%) = 226 (100), 211 (11), 197 (64), 183 (7), 169 (24), 155 (12), 77 (14), 51 (8). **HRMS (EI)**: calcd. for $[C_{13}H_{10}O_2N_2]^+$ 226.07368, found 226.07358.

9-Methylbenzo[*b*]pyrido[3,2-*f*][1,4]oxazepin-5(6*H*)-one: Pale yellow solid; **^{1}H NMR (300 MHz, [D$_6$]DMSO)**: δ = 10.64 (br s, 1H), 8.49 (dd, *J* = 2.1, 4.5 Hz, 1H), 8.25 (dd, *J* = 2.1, 7.5 Hz, 1H), 7.45 (dd, *J* = 4.8, 7.8 Hz, 1H), 7.16 (s, 1H), 7.08-7.00 (m, 2H), 2.26 (s, 3H). **^{13}C NMR (75 MHz, [D$_6$]DMSO)**: δ = 164.9, 162.9, 152.8, 148.5, 142.8, 135.9, 128.3, 127.3, 123.0, 122.6, 122.0, 120.6, 20.6. **GC-MS (EI, 70 eV)**: m/z (%) = 226 (100), 211 (5), 197 (79), 169 (41), 77 (44), 65 (24), 50 (41), 39 (30). **HRMS (EI)**: calcd. for $[C_{13}H_{10}O_2N_2]^+$ 226.07368, found 226.07395.

7-Methylbenzo[*b*]pyrido[3,2-*f*][1,4]oxazepin-5(6*H*)-one: Pale yellow solid; **^{1}H NMR (300 MHz, [D$_6$]DMSO)**: δ = 10.17 (br s, 1H), 8.48 (dd, *J* = 2.1, 4.8 Hz, 1H), 8.22 (dd, *J* = 2.1, 7.7 Hz, 1H), 7.46 (dd, *J* = 4.8, 7.8 Hz, 1H), 7.21-7.16 (m, 1H), 7.11-7.08 (m, 2H), 2.34 (s, 3H). **^{13}C NMR (75 MHz, [D$_6$]DMSO)**: δ = 165.2, 163.4, 152.6, 150.7, 142.5, 132.2, 129.4, 128.4, 126.2, 123.1, 121.1, 119.9, 18.3 (d, *J* = 3.0 Hz). **GC-MS (EI, 70 eV)**: m/z (%) = 226 (100), 211 (14), 197 (70), 183 (19), 169 (49), 77 (67), 65 (41), 50 (48), 39 (46). **HRMS (EI)**: calcd. for $[C_{13}H_{10}O_2N_2]^+$ 226.07368, found 226.07401.

8-Chlorobenzo[*b*]pyrido[3,2-*f*][1,4]oxazepin-5(6*H*)-one: White solid; **^{1}H NMR (300 MHz, [D$_6$]DMSO)**: δ = 10.83 (br s, 1H), 8.52 (dd, *J* = 2.1, 4.8 Hz, 1H), 8.28 (dd, *J* = 1.8, 7.7 Hz, 1H), 7.49 (dd, *J* = 4.8, 7.8 Hz, 1H), 7.40-7.36 (m, 1H), 7.23-7.20 (m, 2H). **^{13}C NMR (75 MHz, [D$_6$]DMSO)**: δ = 164.2, 161.8, 152.6, 146.7, 142.5, 132.0, 129.9, 125.1, 123.5, 122.7, 121.0, 119.7. **GC-MS (EI, 70 eV)**: m/z (%) = 246 (100), 218 (28), 211 (65), 183 (43), 155 (85), 77 (76), 63 (46), 50 (78), 38 (27). **HRMS (EI)**: calcd. for $[C_{12}H_7O_2N_2Cl]^+$ 246.01906, found 246.01951; calcd. for $[C_{12}H_7O_2N_2{}^{31}Cl]^+$ 248.01676.

8-Fluorobenzo[*b*]pyrido[3,2-*f*][1,4]oxazepin-5(6*H*)-one: Pale pink solid; **^{1}H NMR (300 MHz, [D$_6$]DMSO)**: δ = 10.83 (br s, 1H), 8.52 (dd, *J* = 2.1, 4.8 Hz, 1H), 8.27 (dd, *J* = 2.1, 7.5 Hz, 1H), 7.48 (dd, *J* = 4.8, 7.5 Hz, 1H), 7.42-7.37 (m ,1H), 7.04-6.99 (m, 2H); **^{19}F NMR (282 MHz, [D$_6$]DMSO)**: δ = -115.46 (m); **^{13}C NMR (100 MHz, [D$_6$]DMSO)**: δ = 164.3, 162.1, 159.2 (d, *J* = 241 Hz), 152.6, 144.3 (d, *J* = 3.0 Hz), 142.5, 132.0 (d, *J* = 12.0 Hz), 123.3 (d, *J* = 9.0 Hz), 122.7, 119.8, 111.8 (d, *J* = 23.0 Hz), 108.1 (d, *J* = 27.0 Hz). **GC-MS (EI, 70 eV)**: m/z

(%) = 230 (100), 202 (35), 173 (66), 147 (17), 77 (44), 50 (50). **HRMS (EI)**: calcd. for $[C_{12}H_7O_2N_2F_1]^+$ 230.04861, found 230.04875.

9-Chlorobenzo[*b*]pyrido[3,2-*f*][1,4]oxazepin-5(6*H*)-one: White solid; **^{1}H NMR (300 MHz, [D$_6$]DMSO)**: δ = 10.83 (br s, 1H), 8.52 (dd, *J* = 2.1, 4.8 Hz, 1H), 8.28 (dd, *J* = 2.1, 7.5Hz, 1H), 7.49 (dd, *J* = 4.8, 7.5 Hz, 1H), 7.46 (d, *J* = 2.4 Hz, 1H), 7.33 (dd, *J* = 2.4, 8.4 Hz, 1H), 7.20 (d, *J* = 8.7 Hz, 1H). **^{13}C NMR (75 MHz, [D$_6$]DMSO)**: δ = 164.6, 162.2, 153.0, 148.8, 143.0, 130.3, 129.2, 127.0, 123.4, 122.4, 122.4, 120.3. **GC-MS (EI, 70 eV)**: m/z (%) = 246 (95), 211 (100), 183 (46), 155 (34), 77 (18). **HRMS (EI)**: calcd. for $[C_{12}H_7O_2N_2Cl]^+$ 246.01906 found 246.01935, calcd. for $[C_{12}H_7O_2N_2{}^{37}Cl]^+$ 246.01611, found 248.01628.

Naphtho[2,3-*b*]pyrido[3,2-*f*][1,4]oxazepin-5(6*H*)-one: White solid; **^{1}H NMR (300 MHz, [D$_6$]DMSO)**: δ = 11.06 (br s, 1H), 8.54 (dd, *J* = 2.1, 4.8 Hz, 1H), (d, *J* = 2.1, 7.7 Hz, 1H), 7.95 (s, 1H), 7.93-7.84 (m, 2H), 7.67 (s, 1H), 7.51-7.45 (m, 3H). **^{13}C NMR (75 MHz, [D$_6$]DMSO)**: δ = 165.1, 162.2, 153.0, 148.3, 142.8, 131.5, 131.1, 130.3, 127.7, 127.4, 126.9, 126.3, 123.2, 120.5, 119.4, 119.1. **GC-MS (EI, 70 eV)**: m/z (%) = 262 (100), 234 (37), 205 (52), 114 (13). **HRMS (EI)**: calcd. for $[C_{16}H_{10}O_2N_2]^+$ 262.07368, found 262.07392.

Naphtho[2,1-*b*]pyrido[3,2-*f*][1,4]oxazepin-12(13*H*)-one: White solid; **^{1}H NMR (300 MHz, [D$_6$]DMSO)**: δ = 11.03 (br s, 1H), 8.51 (dd, *J* = 1.8, 4.8 Hz, 1H), 8.27 (dd, *J* = 2.1, 7.7 Hz, 1H), 8.22 (d, *J* = 8.4 Hz, 1H), 7.97 (d, *J* = 7.5 Hz, 1H), 7.84 (d, *J* = 8.7 Hz, 1H), 7.66-7.53 (m, 2H), 7.55 (d, *J* = 8.7 Hz, 1H), 7.47 (dd, *J* = 4.8, 7.5 Hz, 1H). **^{13}C NMR (100 MHz, [D$_6$]DMSO)**: δ = 165.2, 163.5, 152.1, 146.7, 142.2, 131.5, 128.1, 126.8, 126.7, 126.1, 124.5, 122.7, 122.6, 121.0, 120.6. **GC-MS (EI, 70 eV)**: m/z (%) = 262 (100), 234 (41), 205 (59). **HRMS (EI)**: calcd. for $[C_{16}H_{10}O_2N_2]^+$ 262.07368, found 262.07381.

6-Methylbenzo[*b*]pyrido[3,2-*f*][1,4]oxazepin-5(6*H*)-one: Solid white; **^{1}H NMR (300 MHz, [D$_6$]DMSO)**: δ = 8.47 (dd, *J* = 0.9, 4.1 Hz 1H), 8.25 (dd, *J* = 1.5, 7.8 Hz, 1H), 7.53-7.26 (m, 5H), 3.51 (s, 3H). **^{13}C NMR (75 MHz, [D$_6$]DMSO)**: δ = 163.9, 163.2, 151.9, 150.5, 142.7, 134.8, 126.7, 126.6, 123.2, 122.6, 121.8, 120.2, 36.1. **GC-MS (EI, 70 eV)**: m/z (%) = 226 (100), 209 (9), 197 (24), 181 (23), 169 (31). **HRMS (EI)**: calcd. for $[C_{13}H_{10}O_2N_2]^+$ 226.07368, found 226.07387.

3-Methylbenzo[*b*]pyrido[3,2-*f*][1,4]oxazepin-5(6*H*)-one: White solid; **^{1}H NMR (300 MHz, [D$_6$]DMSO)**: δ = 10.69 (br s, 1H), 8.31 (s, 1H), 8.06 (s, 1H), 7.32 (d, *J* = 8.4 Hz, 1H), 7.22-7.13 (m, 3H), 2.32 (s, 3H). **^{13}C NMR (75 MHz, [D$_6$]DMSO)**: δ = 165.1, 161.0, 152.6, 148.8, 142.7, 132.4, 131.0, 126.7, 126.0, 122.3, 122.2, 119.7, 17.3. **GC-MS (EI, 70 eV)**: m/z (%) = 226 (100), 198 (36), 169 (24). **HRMS (EI)**: calcd. for $[C_{13}H_{10}O_2N_2]$ 226.07368, found 226.07372.

3,8-Dimethylbenzo[*b*]pyrido[3,2-*f*][1,4]oxazepin-5(6*H*)-one: Pale yellow solid, **^{1}H NMR (300 MHz, [D$_6$]DMSO)**: δ = .10.63 (br s, 1H), (dd, *J* = 0.9, 2.3 Hz, 1H), (dd, *J* = 0.9, 2.3 Hz, 1H), 7.19 (d, *J* = 7.8 Hz, 1H), 6.98-6.93 (m, 2H), 2.31 (s, 3H), 2.24 (s, 3H). **^{13}C NMR (75 MHz, [D$_6$]DMSO)**: δ = 164.6, 160.7, 152.0, 146.2, 142.1, 135.6, 131.7, 130.1, 125.9, 121.8, 121.4, 119.2, 20.3, 16.8. **GC-MS (EI, 70 eV)**: m/z (%) = 240 (100), 225 (13), 211 (67), 183 (17). **HRMS (EI)**: calcd. for $[C_{14}H_{12}O_2N_2]^+$ 240.08933, found 240.08975.

3,9-Dimethylbenzo[b]pyrido[3,2-f][1,4]oxazepin-5(6*H*)-one: Pale yellow solid, **^{1}H NMR (300 MHz, [D$_6$]DMSO)**: δ = 10.59 (br s, 1H), 8.29 (dd, *J* = 0.6, 2.6 Hz, 1H), 8.05 (dd, *J* = 0.6, Hz, 1H), 7.14 (s, 1H), 7.07-6.99 (m, 2H), 2.31 (s, 3H), 2.26 (s, 3H). **^{13}C NMR (75 MHz, [D$_6$]DMSO)**: δ = 165.0, 161.1, 152.5, 148.7, 142.6, 135.8, 132.3, 128.3, 127.2, 122.5, 121.9, 119.8, 20.5, 17.3. **GC-MS (EI, 70 eV)**: m/z (%) = 240 (100), 211 (55), 197 (9), 183 (18). **HRMS (EI)**: calcd. for $[C_{14}H_{12}O_2N_2]^+$ 240.08933, found 240.08955.

3,7-Dimethylbenzo[*b*]pyrido[3,2-*f*][1,4]oxazepin-5(6*H*)-one: GC-MS (EI, 70 eV): m/z (%) = 240 (100), 223 (13), 211 (65), 196 (19), 183 (39), 77 (21), 65(22), 51 (29), 39 (42). **HRMS (EI)**: calcd. for $[C_{14}H_{12}O_2N_2]^+$ 240.08933, found 240.08958

8-Chloro-3-methylbenzo[*b*]pyrido[3,2-*f*][1,4]oxazepin-5(6*H*)-one: Pale yellow solid; **^{1}H NMR (300 MHz, [D$_6$]DMSO)**: δ = 10.77 (br s, 1H), 8.32 (dd, *J* = 0.9, 2.7 Hz, 1H), 8.07 (d, *J* = 0.9, 2.6 Hz, 1H), 7.35 (dd, *J* = 1.2, 7.8 Hz, 1H), 7.22-7.18 (m, 2H), 2.31 (s, 3H). **^{13}C NMR (75 MHz, [D$_6$]DMSO)**: δ = 164.9, 160.5, 152.8, 147.4, 142.8, 132.7, 132.5, 130.3, 125.6, 123.9, 121.5, 119.4, 17.3. **GC-MS (EI, 70 eV)**: m/z (%) = 260 (100), 231 (25), 225 (68), 197 (33), 169 (41). **HRMS (EI)**: calcd. for $[C_{13}H_9O_2Cl]^+$ 260.03471, found 260.03481; calcd. for $[C_{13}H_9O_2{}^{37}Cl]^+$ 262.03176, found 262.03243.

8-Fluoro-3-methylbenzo[*b*]pyrido[3,2-*f*][1,4]oxazepin-5(6*H*)-one: White solid; **^{1}H NMR (300 MHz, [D$_6$]DMSO)**: δ = 10.78 (br s, 1H), 8.32 (dd, *J* = 0.9, 2.4 Hz, 1H), 8.07 (dd, *J* = 0.9, 2.7 Hz, 1H), 7.38-7.33 (m, 1H), 7.03-6.97 (m, 2H), 2.32 (s, 3H). **^{19}F NMR (282 MHz, [D$_6$]DMSO)**: δ = -115.6 (m). **^{13}C NMR (75 MHz, [D$_6$]DMSO)**: δ = 164.9, 159.6 (d, *J* = 240.8 Hz), 160.8, 152.8, 144.9 (d, *J* = 4.5 Hz), 142.7, 132.6, 132.4 (d, *J* = 11.3 Hz), 123.7 (d, *J* = 9.8 Hz), 119.5, 112.3 (d, *J* = 23.3 Hz), 108.6 (d, *J* = 27.0 Hz), 17.3. **GC-MS (EI, 70 eV)**: m/z (%) = 244 (100), 215 (34), 187 (25). **HRMS (EI)**: calcd. for $[C_{13}H_9O_2N_2F]^+$ 244.06426, found 244.06486.

9-Chloro-3-methylbenzo[b]pyrido[3,2-f][1,4]oxazepin-5(6H)-one: White solid; **^{1}H NMR (300 MHz, [D$_6$]DMSO)**: δ = 10.78 (br s, 1H), 8.33 (dd, *J* = 0.9, 1.2 Hz, 1H), 8.08 (dd, *J* = 0.9, 2.6 Hz, 1H), 7.44 (d, *J* = 2.4 Hz, 1H), 7.31 (dd, *J* = 2.4, 8.4 Hz, 1H), 7.19 (d, *J* = 8.7 Hz, 1H), 2.32 (s, 3H). **^{13}C NMR (100 MHz, [D$_6$]DMSO)**: δ = 164.2, 159.9, 152.2, 148.5, 142.3, 132.3, 129.8, 128.7, 126.3, 122.8, 121.8, 119.0, 16.8. **GC-MS (EI, 70 eV)**: m/z (%) = 260 (100), 231 (22), 225 (77), 197 (41), 169 (23), 78 (30), 63 (55), 51 (49), 39 (34). **HRMS (EI)**: calcd. for $[C_{13}H_9N_2O_2Cl]^+$ 260.03471, found 260.03499; calcd. for $[C_{13}H_9N_2O_2{}^{37}Cl]^+$ 262.03176, found 262.03239.

3-Methylnaphtho[2,3-*b*]pyrido[3,2-*f*][1,4]oxazepin-5(6*H*)-one: Pale pink solid; **^{1}H NMR (300 MHz, [D$_6$]DMSO)**: δ = 10.99 (br s, 1H), 8.34 (s, 1H), 8.09 (s, 1H), 7.92 (s, 1H), 7.92-7.83 (m, 2H), 7.65 (s, 1H), 7.50-7.42 (m, 2H), 2.32 (s, 3H). **^{13}C NMR (75 MHz, [D$_6$]DMSO)**: δ = 165.2, 160.4, 152.7, 148.5, 142.6, 132.6, 131.4, 131.1, 130.4, 127.7, 127.4, 126.9, 126.3, 119.7, 119.2, 119.0, 17.3. **GC-MS (EI, 70 eV)**:

m/z (%) = 276 (100), 248 (39), 220 (42), 205 (12). **HRMS (EI)**: calcd. for $[C_{17}H_{12}O_2N_2]^+$ 276.08933, found 276.08920.

2-Methylbenzo[*b*]pyrido[3,2-*f*][1,4]oxazepin-5(6*H*)-one: White solid; **^{1}H NMR (300 MHz, [D$_6$]DMSO)**: δ = 10.64 (br s, 1H), 8.14 (d, *J* = 7.8 Hz, 1H), 7.33 (dd, *J* = 1.5, 7.7 Hz, 1H), 7.30 (d, *J* = 7.8 Hz, 1H), 7.24-7.12 (m, 3H), 2.49 (s, 3H, overlapped by the solvent residual peak of [D$_6$]DMSO),. **^{13}C NMR (75 MHz, [D$_6$]DMSO)**: δ = 165.1, 163.0, 162.1, 148.5, 142.9, 131.1, 126.8, 125.9, 122.4, 122.2, 122.1, 117.3, 24.2. **GC-MS (EI, 70 eV)**: m/z (%) = 226 (100), 211 (4), 198 (67), 182 (13), 169 (39), 64 (51), 52 (88), 39 (42). **HRMS (EI)**: calcd. for $[C_{13}H_{10}O_2N_2]^+$ 226.07368, found 226.07392.

2,8-Dimethylbenzo[*b*]pyrido[3,2-*f*][1,4]oxazepin-5(6*H*)-one: White solid; **^{1}H NMR (300 MHz, [D$_6$]DMSO)**: δ = 10.57 (br s, 1H), 8.12 (d, *J* = 7.8 Hz, 1H), 7.29 (d, *J* = 7.8 Hz, 1H), 7.20 (d, *J* = 8.7 Hz, 1H), 6.96-6.93 (m, 2H), 2.50 (s, 3H, overlapped by the solvent residual peak of [D$_6$]DMSO), 2.24 (s, 3H). **^{13}C NMR (100 MHz, [D$_6$]DMSO)**: δ = 164.6, 162.3, 161.8, 145.9, 142.4, 135.6, 130.2, 125.8, 121.7, 121.6, 121.6, 116.86, 23.7, 20.3. **GC-MS (EI, 70 eV)**: m/z (%) = 240 (100), 225 (15), 211 (87), 197 (12), 183 (23), 169 (18), 65 (33), 52 (26), 39 (39). **HRMS (EI)**: calcd. for $[C_{14}H_{12}O_2N_2]^+$ 240.08933, found 240.08944.

2,9-Dimethylbenzo[b]pyrido[3,2-f][1,4]oxazepin-5(6*H*)-one: White solid; **^{1}H NMR (300 MHz, [D$_6$]DMSO)**: δ = 10.55 (br s, 1H), 8.12 (d, *J* = 7.8 Hz, 1H), 7.29 (d, *J* = 7.8 Hz, 1H), 7.16 (s, 1H), 7.07-7.00 (m, 2H), 2.48 (s, 3H, overlapped by the solvent residual peak of [D$_6$]DMSO) , 2.26 (s, 3H). **^{13}C NMR (75 MHz, [D$_6$]DMSO)**: δ = 164.5, 162.3, 161.7, 147.9, 142.3, 135.2, 127.9, 126.7, 122.1, 121.7, 121.3, 116.9, 23.7, 20.0. **GC-MS (EI, 70 eV)**: m/z (%) = 240 (100), 211 (89), 197 (15), 183 (31), 169 (19), 65 (51), 51 (35), 39 (39). **HRMS (EI)**: calcd. for $[C_{14}H_{12}O_2N_2]^+$ 240.08933, found 240.08958.

2,7-Dimethylbenzo[*b*]pyrido[3,2-*f*][1,4]oxazepin-5(6*H*)-one: White solid; **^{1}H NMR (300 MHz, [D$_6$]DMSO)**: δ = 10.05 (br s, 1H), (d, *J* = 7.5 Hz, 1H), (dd, *J* = 0.6, 7.8 Hz, 1H), 7.20-7.16 (m, 1H), 7.117.05 (m, 2H), 2.48 (s, 1H), 2.33 (s, 3H). **^{13}C NMR (75 MHz, [D$_6$]DMSO)**: δ = 165.3, 162.6, 150.7, 144.2, 142.6, 134.7, 132.0, 129.5, 128.3, 126.1, 122.4, 121.4, 119.9, 117.9, 112.5, 24.2, 18.3. **GC-MS (EI, 70 eV)**: m/z (%) = 240 (100), 225 (17), 211 (52), 183 (17). **HRMS (EI)**: calcd. for $[C_{14}H_{12}O_2N_2]^+$ 240.08933, found 240.08972.

8-Chloro-2-methylbenzo[*b*]pyrido[3,2-*f*][1,4]oxazepin-5(6*H*)-one: White solid; **^{1}H NMR (300 MHz, [D$_6$]DMSO)**: δ = 10.73 (br s,1H), 8.15 (d, *J* = 7.8 Hz, 1H), 7.37 (d, *J* = 9.0 Hz, 1H), 7.33 (d, *J* = 7.5 Hz, 1H), 7.22-7.18 (m, 2H), 2.50 (s, 3H, overlapped by the solvent residual peak of [D$_6$]DMSO). **^{13}C NMR (75 MHz, [D$_6$]DMSO)**: δ = 164.3, 162.7, 161.1, 146.7, 142.6, 132.1, 129.8, 124.9, 123.6, 122.0, 120.9, 116.5, 23.7. **GC-MS (EI, 70 eV)**: m/z (%) = 260 (100), 231 (33), 225 (78), 197 (56), 169 (60), 91 (37), 78 (58), 63 (83), 51 (60), 39 (48). **HRMS (EI)**: calcd. for $[C_{13}H_9O_2N_2Cl]^+$ 260.03471, found 260.03503.

9-Chloro-2-methylbenzo[*b*]pyrido[3,2-*f*][1,4]oxazepin-5(6*H*)-one: White solid; **^{1}H NMR (300 MHz, [D$_6$]DMSO)**: δ = 10.73 (br s, 1H), 8.15 (d, *J* = 7.8 Hz, 1H), 7.46 (d, *J* = 2.1 Hz, 1H), 7.35-7.30 (m, 2H), 7.19 (d, *J* = 8.7 Hz, 1H), 2.50 (s, 3H, overlapped by the solvent residual peak of [D$_6$]DMSO). **^{13}C NMR (100 MHz, [D$_6$]DMSO)**: δ = 164.2, 162.7, 161.0, 148.3, 142.5, 129.9, 128.6, 126.3, 122.8, 122.1, 121.9, 116.6, 23.7. **GC-MS (EI, 70 eV)**: m/z (%) = 260 (99.5), 231 (15), 225 (100), 197 (45), 169 (20). **HRMS (EI)**: calcd. for $[C_{13}H_9O_2N_2Cl]^+$ 260.03471, found 260.03459; calcd. for $[C_{13}H_9O_2N_2{}^{37}Cl]^+$ 262.03176, found 262.03256.

5*H*-Benzo[*b*]pyrido[3,2-*e*][1,4]oxazine: White solid; **^{1}H NMR (300 MHz, [D$_6$]DMSO)**: δ = 9.00 (br s, 1H), 7.53 (dd, *J* = 1.5, 5.1 Hz, 1H), 6.88 (d, *J* = 0.9, 7.8 Hz, 1H), 6.79-6.74 (m, 1H), 6.66-6.53 (m, 4H). **^{13}C NMR (75 MHz, [D$_6$]DMSO)**: δ = 145.9, 142.2, 141.6, 139., 131.3, 124.1, 121.2, 120.5, 116.4, 114.9, 114.0. **GC-MS (EI, 70 eV)**: m/z (%) = 184 (100), 155 (29), 129 (8), 92 (12). **HRMS (EI)**: calcd. for $[C_{11}H_8ON_2]^+$ 184.06311, found 184.06293.

7-Methyl-5*H*-benzo[*b*]pyrido[3,2-*e*][1,4]oxazine: White solid; **^{1}H NMR (300 MHz, [D$_6$]DMSO)**: δ = 8.97 (br s, 1H), 7.52 (dd, *J* = 1.5, 5.1 Hz, 1H), 6.88-6.85 (m, 1H), 6.56-6.52 (m, 2H), 6.44-6.39(m, 2H), 2.10 (s, 3H), **^{13}C NMR (75 MHz, [D$_6$]DMSO)**: δ = 145.9, 141.4, 140.1, 139.1, 133.0, 130.9, 121.3, 120.4, 116.4, 114.6, 114.5, 20.3. **GC-MS (EI, 70 eV)**: m/z (%) = 198 (100), 169 (15), 155 (7), 99 (7). **HRMS (EI)**: calcd. for $[C_{12}H_{10}ON_2]^+$ 198.07876, found 198.07861.

8-Methyl-5*H*-benzo[*b*]pyrido[3,2-*e*][1,4]oxazine: White solid; **^{1}H NMR (300 MHz, [D$_6$]DMSO)**: δ = 8.90 (br s, 1H), 7.51 (dd, *J* = 1.5, 5.1 Hz, 1H), 6.88-6.85 (m, 1H), 6.59-6.46 (m, 4H), 2.10 (s, 3H), **^{13}C NMR (75 MHz, [D$_6$]DMSO)**: δ = 146.1, 142.0, 141.5, 138.9, 130.4, 128.6, 124.2, 122.6, 120.4, 115.6, 113.8, 20.1. **GC-MS (EI, 70 eV)**: m/z (%) = 198 (100), 169 (11), 116 (9). **HRMS (EI)**: calcd. for $[C_{12}H_{10}ON_2]^+$ 198.07876, found 198.07876.

6-Methyl-5*H*-benzo[*b*]pyrido[3,2-*e*][1,4]oxazine: Light yellow solid; **^{1}H NMR (300 MHz, [D$_6$]DMSO)**: δ = 8.26 (br s, 1H), 7. 56 (d, *J* = 4.8 Hz, 1H), 6.89 (d, *J* = 7.8 Hz, 1H), 6.64-6.48 (m, 4H), 2.09 (s, 3H). **^{13}C NMR (75 MHz, [D$_6$]DMSO)**: δ = 146.5, 142.7, 141.8, 139.6, 129.6, 126.2, 123.4, 121.3, 120.9, 117.3, 113.3, 17.3. **GC-MS (EI, 70 eV)**: m/z (%) = 198 (100), 169 (15), 99 (7). **HRMS (EI)**: calcd. for $[C_{12}H_{10}ON_2]^+$ 198.07876, found 198.07874.

7-Chloro-5*H*-benzo[*b*]pyrido[3,2-*e*][1,4]oxazine: White solid; **^{1}H NMR (300 MHz, [D$_6$]DMSO)**: δ = 9.20 (br s, 1H), 7.56 (dd, *J* = 1.5, 5.1 Hz, 1H), (d, *J* = 7.8 Hz, 1H), 6.66-6.57 (m, 4H). **^{13}C NMR (75 MHz, [D$_6$]DMSO)**: δ = 145.0, 141.8, 141.2, 138.8, 132.95, 127.5, 120.9, 120.3, 117.1, 116.3, 113.3. **GC-MS (EI, 70 eV)**: m/z (%) = 218 (100), 183 (14), 155 (29), 109 (11). **HRMS (EI)**: calcd. for $[C_{11}H_7ON_2Cl]^+$ 218.02414, found 218.02456.

7-Fluoro-5*H*-benzo[*b*]pyrido[3,2-*e*][1,4]oxazine: White solid; **^{1}H NMR (300 MHz, [D$_6$]DMSO)**: δ = 9.19 (br s, 1H), 7.56 (dd, *J* = 1.5, 5.1Hz, 1H), 6.92 (dd, *J* = 0.6, 7.2 Hz, 1H), 6.69-6.59 (m, 2H), 6.46-6.36 (m, 2H). **^{13}C NMR (75 MHz, [D$_6$]DMSO)**: δ = 158.5 (d, *J* = 236.3 Hz), 144.9, 141.7, 138.9, 138.5 (d, *J* = 3.0 Hz), 132.8 (d, *J* = 11.3 Hz), 120.8, 117.1, 115.7 (d, *J* = 9.8 Hz), 106.3 (d, *J* = 22.5 Hz), 101.0 (d, *J* =

27.8 Hz). **^{19}F NMR (282 MHz, [D$_6$]DMSO)**: δ = -118.8 (m); **GC-MS (EI, 70 eV)**: m/z (%) = 202 (100), 173 (29), 101 (13). **HRMS (EI)**: calcd. for $[C_{11}H_7ON_2F]^+$ 202.05369, found 202.05378.

5-Methyl-5*H*-benzo[*b*]pyrido[3,2-*e*][1,4]oxazine: White solid; **^{1}H NMR (300 MHz, [D$_6$]DMSO)**: δ = 7.66-7.64 (m, 1H), 6.95-6.87 (m, 2H), 6.75-6.70 (m, 3H), 6.65-6.60 (m, 1H), 3.16 (s, 3H). **^{13}C NMR (75 MHz, [D$_6$]DMSO)**: δ = 146.2, 143.8, 141.7, 140.6, 133.5, 124.8, 122.2, 120.9, 117.1, 115.3, 113.3, 113.3, 28.5. **GC-MS (EI, 70 eV)**: m/z (%) = 198 (100), 183 (86), 169 (6). **HRMS (EI)**: calcd. for $[C_{12}H_{10}ON_2]^+$ 198.07876, found 198.07824.

3-(Trifluoromethyl)-5*H*-benzo[*b*]pyrido[3,2-*e*][1,4]oxazine: Pale yellow solid; **^{1}H NMR (300 MHz, [D$_6$]DMSO)**: δ = 9.69 (br s, 1H), 7.86 (q, *J* = 1.2 Hz, 1H), 7.15 (d, J = Hz, 1H), 6.84-6.78 (m, 1H), 6.73-6.66 (m, 2H), 6.63-6.60 (m, 1H). **^{19}F NMR (292 MHz, [D$_6$]DMSO)**: δ = -60.04 (s). **^{13}C NMR (75 MHz, [D$_6$]DMSO)**: δ = 149.6, 142.5, 139.8, 139.6, 130.3, 124.2 (q, *J* = 269 Hz) , 117.9 (q, *J* = 32.2 Hz), 116.9, 115.6, 115.1. **GC-MS (EI, 70 eV)**: m/z (%) = 252 (100), 223 (15), 126 (10). **HRMS (EI)**: calcd. for $[C_{12}H_7ON_2F]^+$ 252.05050, found 252.05056.

Benzo[5,6][1,4]dioxino[2,3-*b*]pyridine: White solid; **^{1}H NMR (300 MHz, [D$_6$]DMSO)**: δ = 7.83-7.82 (m, 1H), 7.44-7.40 (m, 1H), 7.11-7.00 (m, 5H). **^{13}C NMR (75 MHz, [D$_6$]DMSO)**: δ = 148.7, 141.6, 141.2, 140.6, 137.4, 124.8, 124.6, 124.4, 121.5, 116.9, 116.2. **GC-MS (EI, 70 eV)**: m/z (%) = 185 (100), 129 (11), 102 (13), 93 (9). **HRMS (ESI)**: calcd. for $[C_{11}H_7NO_2+H]^+$ 186.05495, found 186.05504.

3-Methyl-2-nitro-10*H*-phenoxazine: Dark red powder, **^{1}H NMR (300 MHz, [D$_6$]DMSO)**: δ = 9.26 (br s, 1H), 7.30 (s, 1H), 6.83-6.77 (m, 1H), 6.72-6.65 (m, 2H), 6.55 (d, *J* = 7.2 Hz, 1H), 6.34 (s, 1H), 2.40 (s, 3H). **^{13}C NMR (75 MHz, [D$_6$]DMSO)**: δ = 142.2, 140.4, 139.1, 138.1, 132.8, 129.4, 124.3, 122.2, 115.2, 114.8, 114.2, 111.4, 20.9; **GC-MS (EI, 70 eV)**: m/z (%) = 242 (100), 225 (13), 212 (12), 196 (97), 167 (33). **HRMS (ESI)**: calcd. for $[C_{13}H_{10}N_2O_3 - H]^-$ 241.06187, found 241.06206.

2,7-Dimethyl-3-nitro-5*H*-benzo[*b*]pyrido[3,2-*e*][1,4]oxazine: Brown solid, **^{1}H NMR (300 MHz, [D$_6$]DMSO)**: δ = 9.16 (br s, 1H), 7.26 (s, 1H), 6.55-6.46 (m, 2H), 6.34-6.33 (m, 1H), 6.32-6.31 (m, 1H), 2.49 (s, 3H), 2.10 (s, 3H). **^{13}C NMR (75 MHz, [D$_6$]DMSO)**: δ = 141.0, 140.5, 139.6, 138.6, 133.9, 133.1, 129.5, 122.9, 115.5, 115.4, 115.2, 111.8, 21.4, 20.7. **GC-MS (EI, 70 eV)**: m/z (%) = 256 (100), 239 (12), 226 (10), 210 (97), 180 (14), 167 (17). **HRMS (EI)**: calcd. for $[C_{14}H_{12}O_3N_2]^+$ 256.08424, found 256.08438.

2,8-Dimethyl-3-nitro-5*H*-benzo[*b*]pyrido[3,2-*e*][1,4]oxazine: Dark red solid, **^{1}H NMR (300 MHz, [D$_6$]DMSO)**: δ = 9.15 (br s, 1H), 7.27-7.25 (m, 1H), 6.60-6.57 (m, 1H), 6.50-6.43 (m, 2H), 6.30-6.28 (m, 1H), 2.39 (s, 3H), 2.11 (s, 3H). **^{13}C NMR (75 MHz, [D$_6$]DMSO)**: δ = 141.9, 140.3, 138.7, 138.3, 132.9, 131.7, 126.7, 124.4, 115.8, 114.7, 114.0, 111.4, 21.0, 20.1. **GC-MS (EI, 70 eV)**: m/z (%) = 256 (100), 239 (10), 226 (11), 210 (97), 180 (14), 167 (16). **HRMS (EI)**: calcd. for $[C_{14}H_{12}O_3N_2]^+$ 256.08424, found 256.08439.

7-Chloro-2-methyl-3-nitro-5*H*-benzo[*b*]pyrido[3,2-*e*][1,4]oxazine: Dark red solid, **^{1}H NMR (300 MHz, [D$_6$]DMSO)**: δ = 9.33 (br s, 1H), 7.29 (s, 1H), 6.72-6.64 (m, 2H), 6.52 (d, *J* = 2.4 Hz, 1H), 6.36 (s, 1H), 2.39 (s, 3H). **^{13}C NMR (75 MHz, [D$_6$]DMSO)**: δ = 141.1, 140.3, 139.7, 137.0, 132.7, 131.1, 127.6, 121.3, 116.5, 115.3, 113.5, 111.6, 20.7. **HRMS (ESI)**: calcd. for $[C_{13}H_9ClN_2O_3 - H]^-$ 275.02289, found 275.02344; calcd. for $[C_{13}H_9{}^{37}ClN_2O_3 - H]^-$ 277.02036, found 277.02079.

2,5-Dimethyl-3-nitro-5*H*-benzo[*b*]pyrido[3,2-*e*][1,4]oxazine: Dark red solid, **^{1}H NMR (300 MHz, [D$_6$]DMSO)**: δ = 7.33 (s, 1H), 6.96-6.90 (m, 1H), 6.86-6.79 (m, 2H), 6.76-6.73(m, 2H), 3.13 (s, 3H), 2.48 (s, 3H partially overlapped by the solvent residual peak of [D$_6$]DMSO). **^{13}C NMR (75 MHz, [D$_6$]DMSO)**: δ = 143.7, 141.9, 139.6, 139.4, 132.6, 131.9, 124.5, 122.8, 115.1, 114.6, 113.3, 110.8, 31.2, 20.9. **GC-MS (EI, 70 eV)**: m/z (%) = 256 (100), 239 (10), 226 (7), 210 (74), 195 (52). **HRMS (EI)**: calcd. for $[C_{14}H_{12}O_3N_2]^+$ 256.08424, found 256.08482.

Notes and references

1 (a) J. M. Klunder, K. D. Hargrave, M. West, E. Cullen, K. Pal, M. L. Behnke, S. R. Kapadia, D. W. McNeil, J. C. Wu, G. C. Chow and J. Adams, *J. Med. Chem.*, 1992, **35**, 1887-1897; (b) M. M. Morelock, L. L. Choi, G. L. Bell and J. L. Wright, *J. Pharm. Sci.*, 1994, **83**, 948-952.

2 (a) J.-F. F. Liébgeois, F. A. Rogistert, Jacques Bruhwyler, J. Damas, T. P. Nguyen, M.-O. Inarejos, E. M. G. Chleide, M. G. A. Mercier, and J. E. Delarge, *J. Med. Chem.*, 1994, **37**, 519; (b) J. Bruhwyler, J.-F. Liégeois, J. Bergman, G. Carey, A. Goudie, A. Taylor, H. Meltzer, J. Delarge and J. Gécyz, *Pharmacol. Res.*, 1997, **36**, 255-263; (c) R. Invernizzi, C. Garavaglia, R. Samanin, Naunyn Schmiedebergs *Arch. Pharmacol.*, 2000, **361**, 298-302; (d) B. A. Ellenbroek, J.-F. Liégeois, J. Bruhwyler and A. R. Cools, *J. Pharmacol. Exp. Ther.*, 2001, **298**, 386-391; (e) B. A. Ellenbroek and J.-F. Liégeois, *CNS Drug Rev.*, 2003, **9**, 41-56; (f) F. I. Tarazi, T. Moran-Gates, M. P. Gardner, A. Graulich, C. Lamy and J.-F. Liégeois, *J. Mol. Neurosci.*, 2007, **32**, 192-198; (g) A. J. Goudie, J. C. Cole and H. R. Sumnall, *Behav. Pharmacol.*, 2007, **18**, 9-17; (h) B. Capuano, I. T. Crosby, F. M. McRobb, D. A. Taylor, A. Vom and W. W. Blessing, *Prog. Neuropsychopharmacol. Biol. Psych.*, 2010, **34**, 136-142.

3 (a) J.-F. Liégeois, L. Eyrolles, B. A. Ellenbroek, C. Lejeune, P. Carato, J. Bruhwyler, J. Géczy, J. Damas, and J. Delarge, *J. Med. Chem.*, 2002, **45**, 5136-5149; (b) J.-F. Liégeois, M. Deville, S. Dilly, C. Lamy, F. Mangin, M. Résimont, and F. I. Tarazi, *J. Med. Chem.*, 2012, **55**, 1572-1582.

4 N. C. Ganguly, P. Mondal, S. Roya and P. Mitra, *RSC Adv.*, 2014, **4**, 55640-55648.

5 Selected very recent examples, see: a) J. Chen, K. Natte, A. Spannenberg, H. Neumann, P. Langer, M. Beller and X.-F. Wu, *Angew. Chem., Int. Ed.*, 2014, **53**, 7579-7583; J. Chen, K. Natte, A. Spannenberg, H. Neumann, P. Langer, M. Beller and X.-F. Wu, *Angew. Chem.*, 2014, **126**, 7709-7713; (b) Jianbin Chen, K. Natte, A. Spannenberg, H. Neumann, M. Beller and X.-F. Wu, *Chem. Eur. J.*, 2014, **20**, 14189-14193; (c) C. Shen, N. Y. T. Man, S. Stewart and X.-F. Wu *Org. Biomol. Chem.*, 2015, **13**, 4422-4425.

6 (a) S.-M. Lu and H. Alper, *J. Am. Chem. Soc.*, 2005, **127**, 14776-14784; (b) Q. Yang, H. Cao, A. Robertson and H. Alper, *J. Org. Chem.*, 2010, **75**, 6297-6299.

7 (a) G. Chouhan and H. Alper, *Org. Lett.*, 2010, **12**, 192-195; (b) F. Zeng and H. Alper, *Org. Lett.*, 2010, **12**, 5567-5569; (c) H. Li, A. Spannenberg, H. Neumann, M. Beller and X.-F. Wu, *Chem. Commun.*, 2014, **50**, 2114-2116.

8 (a) J. Chen, K. Natte, H. Neumann and X.-F. Wu, *Chem. Eur. J.*, 2014, **20**, 16107-16110; (b) C. Shen, H. Neumann and X.-F. Wu, *Green Chem.*, 2015, **17**, 2994-2999.

9 Selected very recent examples of tandem reaction involving S_NAr: a) G.-P. Lu and C. Cai, *RSC Adv.*, 2014, **4**, 59990-59996; b) R. Hudson, N. P. Bizier, K. N. Esdale and J. L. Katz, *Org. Biomol. Chem.*, 2015, **13**, 2273-2284; c) M. S. Mayo, X. Yu, X. Feng, Y. Yamamoto and M. Bao, *J. Org. Chem.*, 2015, 2015, **80**, 3998–4002; d) M. Koy, K. M. Engle, L. M. Henling, M. K. Takase and R. H. Grubbs, *Org. Lett.*, 2015, **17**, 1986–1989; e) K. M. Engle, S.-X. Luo and R. H. Grubbs, *J. Org. Chem.*, 2015, **80**, 4213-4220.

10 a) J. F. Bunnett and R. E. Zahler, *Chem. Rev.*, 1951, **49**, 273-412; b) J. F. Bunnett, *Q. Rev. Chem. Soc.*, 1958, **12**, 1-16; selected recent examples about nucleophilic attack to chloride atom at the 2-position on a pyridine ring: c) R. A. Bunce, S. T. Squires and B. Nammalwar, *J. Org. Chem.*, 2013, **78**, 2144-2148; d) X. Jia, L. Yu, J. Liu, Q. Xu, M. Sickert, L. Chen and M. Lautens, *Green Chem.*, 2014, **16**, 3444-3449.

11 F. Terrier, *Modern Nucleophilic Aromatic Substitution*, 2013, *pp* 11-12.

12 J. A. Cella and S. W. Bacon, *J. Org. Chem.*, 1984, **49**, 1122-1125.

13 Examples for the carbonylation on the C-Cl bond at the 2-position of pyridine ring: (a) Y. Bessard and J. P. Roduit, *Tetrahedron*, 1999, **55**, 393-404; (b) M. Beller, W. Mägerlein, A. F. Indolese, C. Fischer, *Synthesis*, 2001, 1098-1109; (c) R. Crettaz , J. Waser and Y. Bessard, *Org. Proc. Res. Dev.*, 2001, **5**, 572-574; (d) J. Albaneze-Walker, C. Bazaral, T. Leavey, P. G. Dormer and J. A. Murry, *Org. Lett.*, 2004, **6**, 2097-2100.

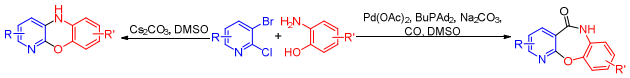
14 Examples for the S_NAr occurrence on the 3-position of pyridine or the *meta*-positon of electron-withdrawing group substituted phenyl ring: (a) J. S. Anderson and K. C. Brown, *Synth. Comm.*, 1983, **13**, 233-236; (b) H. H. Lee and W. A. Denny, *J. Chem. Soc., Perkin Trans. 1*, 1990, 1071-1074; (c) G. C. Eastmond and J. Paprotny, *Chem. Lett.*, 1999, **28**, 479-480; (d) H. H. Lee, B. D. Palmer, M. Boyd, B. C. Baguley and W. A. Denny *J. Med. Chem.*, 1992, **35**, 258-266. Examples for the case that the S_NAr occurs on the 2-position of 3-bromo-2-chloropyridine or 2,3-dichloropyridine while the 3-position is unaffected: (e) L. Testaferri, M. Tiecco, M. Tingoli, D. Bartoli and A. Massoli *Tetrahedron*, 1985, **41**, 1373-1384; (f) Y. Cheng, B. K. Albrecht, J. Brown, J. L. Buchanan, W. H. Buckner, E. F. DiMauro, R. Emkey, R. T. Fremeau, Jr., J.-C. Harmange, B. J. Hoffman, L. Huang, M. Huang, J. H. Lee, F.-F. Lin, M. W. Martin, H. Q. Nguyen, V. F. Patel, S. A. Tomlinson, R. D. White, X. Xia, and S. A. Hitchcock, *J. Med. Chem.*, 2008, **51**, 5019-5034; (g) M. G. Kale, A. Raichurkar, S. Hameed P, D. Waterson, D. McKinney, M. R. M., U. Kranthi, K. Koushik, L. K. Jena, V. Shinde, S. Rudrapatna, S. Barde, V. Humnabadkar, P. Madhavapeddi, H. Basavarajappa, A. Ghosh, VK Ramya, S. Guptha, S. Sharma, P. Vachaspati, K. N. M. Kumar, J. Giridhar, J. Reddy, V. Panduga, S. Ganguly, V. Ahuja, S. Gaonkar, C. N. N. Kumar, D. Ogg, J. A. Tucker, P. A. Boriack-Sjodin, S. M. de Sousa, V. K. Sambandamurthy and S. R. Ghorpade, *J. Med. Chem.*, 2013, **56**, 8834−8848; (h) S. Röver, M. Andjelkovic, A. Bénardeau, E. Chaput, W. Guba, P. Hebeisen, S. Mohr, M. Nettekoven, U. Obst, W. F. Richter, C. Ullmer, P. Waldmeier and M. B. Wright, *J. Med. Chem.*, 2013, **56**, 9874-9896.

15 The reaction was conducted on a 0.50 mmol scale (0.50 mmol **1a**, 1.5 mmol Na_2CO_3 or Cs_2CO_3, 0.10 mL hexadecane as an internal standard and 2.0 mL DMSO). The conversion of **1a** was determined by GC and GC-MS with hexadecane as an internal standard.

16 R. I. Fryer, J. V. Earley, G. F. Field, W. Zally and L. H. Sternbach, *J. Org. Chem.*, 1969, **34**, 1143-1145.

17 (a) M. Chevrier, Olivier Bensaude, J. Guillerez and J.-E. Dubois, *Tetrahedron Lett.*, 1980, **21**, 3359-3362; (b) P. Beak, J. B. Covington, S. G. Smith, J. M. White and J. M. Zeigler, *J. Org. Chem.*, 1980, **45**, 1354-1362.

18 Y. Ito and Y. Hamada, *Chem. Pharm. Bull.*, 1978, **26**, 1375-1383.



A base-regulated one-pot protocol for the tunable synthesis of pyridobenzoxazepinones and pyridobenzoxazines has been developed. Pyridobenzoxazepinones and pyridobenzoxazines were produced in good yields selectively.