

Cite this: *RSC Adv.*, 2017, 7, 51972Received 18th August 2017
Accepted 30th October 2017

DOI: 10.1039/c7ra09160e

rsc.li/rsc-advances

Efficient synthesis of benzene-fused 6/7-membered amides *via* Xphos Pd G2 catalyzed intramolecular C–N bond formation†

Zhou Xu,^a Ke Li,^b Rongliang Zhai,^{ab} Ting Liang,^{ab} Xiaodie Gui^a and Rongli Zhang^b

An efficient approach for benzene-fused 6/7-membered amides *via* intramolecular amidation of aryl chlorides catalyzed by a Buchwald–Hartwig second generation Pd catalyst (Xphos Pd G2) has been successfully developed. This catalyst system allows the primary amides which have only modest nucleophilicity to be coupled successfully even with electron rich aryl chlorides in short reaction time. The intramolecular amidation reaction also has good chemoselectivity and excellent functional group compatibility.

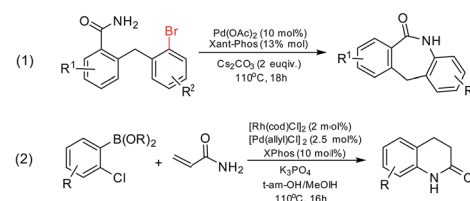
Introduction

Benzene-fused amides are important organic compounds commonly encountered in biologically relevant natural or synthetic pharmaceutical compounds.^{1–3} Some methods were developed towards the synthesis of these scaffolds which are mainly benzene-fused 6-membered amides known as 2*H*-1,4-benzoxazin-3-(4*H*)-one derivatives.^{4–6} However, the substituent diversity in the products is limited and more importantly, it is difficult to synthesize benzene-fused seven-membered amides.

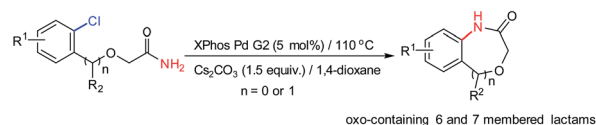
Organic halides are some of the most common industrially used compounds and widely used as starting materials for many chemical transformations. The efficient cleavage of C–X (X = halogen atom) bonds has been actively studied by organic chemists. Among them, palladium catalysts developed by Buchwald and Hartwig proved to be the most useful ones for the C–N bond formation.^{7,8} The amination of aryl halogens by transition metal catalyzed coupling methodology has been the subject of significant interest during past few decades, but the amidation reaction has not yet fully studied. Electron-deficient amides have been difficult coupling partners due to their modest nucleophilicity and intolerance of strong base. Although, amidation of aryl bromides and iodides have become the well-established processes in the reaction,^{9–12} however, largely absent from the literature on Pd-catalyzed amidation reactions is the description of an efficient method for coupling aryl chlorides.

To the best of our knowledge, there are limited literature reports the intramolecular amidation of aryl chlorides which can

Previous work



Our result



Scheme 1 Benzene-fused amides: prior arts and design.

construct the valuable molecular structure of benzene-fused amides. Laha *et al.* reported the synthesis of dibenzoazepinones *via* the intramolecular amination of aryl bromide (not aryl chlorides) in 18 h with yield of 68–94%.¹³ While, Lautens *et al.* reported the synthesis of 3,4-dihydroquinolinones *via* the reaction between arylboronic acid and acrylamide (Scheme 1).¹⁴

As part of our continuing efforts for accessing biologically hetero compounds by metal-catalyzed reactions,¹⁵ herein, we report a facile, efficient, convenient and generally applicable method for the intramolecular amidation of organic halides to synthesize oxo-containing 6/7 membered benzene-fused amides with excellent yield using commercial available XPhos Pd G2 as the catalyst.

Results and discussion

At the outset of our investigation, we employed **1a** as the substrate for the preparation of the desired benzene-fused 7-membered amide **2a**. After considerable amount of efforts on

^aDepartment of Chemistry, Xuzhou Medical University, Xuzhou 221004, China. E-mail: xuzhou@xzmmu.edu.cn

^bJiangsu Key Laboratory of New Drug Research and Clinical Pharmacy, Xuzhou Medical University, Xuzhou 221004, China

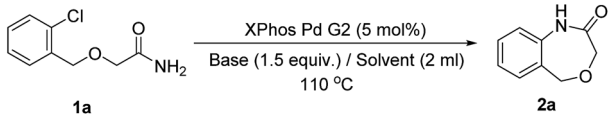
† Electronic supplementary information (ESI) available. See DOI: 10.1039/c7ra09160e



condition discovery and optimization, we were able to obtain **2a** with 97% isolated yield in 5 h.

The reaction conditions, as shown in the equation in Table 1, including the use of Xphos Pd G2 as the most effective catalyst, 1,4-dioxane as the optimal solvent, and Cs₂CO₃ as the base. Indeed, other catalysts, such as Ph₃PPdCl, JohnPhos Pd G2, Xphos PdCl₂ all fared much worse than Xphos Pd G2 in terms of reaction rate and efficiency (entries 1–3 vs. 5). We also performed the reaction with catalysts Xphos Pd G1, Xphos Pd G3 and Xphos Pd G4. All of them gave almost the same result with Xphos Pd G2 (entries 4–7). However, Xphos Pd G2 is the cheapest one. Thus, we chose it as catalyst for further investigation. The combination of Pd(OAc)₂ and ligand Xphos cannot proceed the transformation either (entry 8). The reaction can be faster and more efficiency when Cs₂CO₃ was used as the base instead of K₂CO₃ (entry 5 vs. entry 9). The best solvent for the reaction is 1,4-dioxane. Toluene is equal efficiency, but DMSO or DMF doesn't work for the reaction (entries 10, 12 and 13). The substrate **1a** can also convert smoothly to product **2a** at 80 °C, but requires longer reaction time (entry 14). Lowering the reaction temperature to 50 °C, the reaction could hardly happen and only trace product observed even prolonging the reaction time to 36 h (entry 15). Substrate concentration has limited effect on the reaction. When the concentration of the substrate

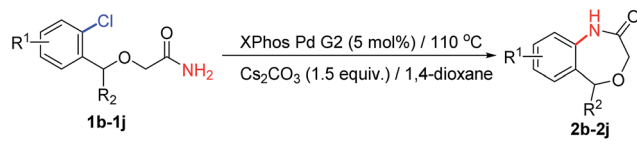
Table 1 Optimization for the reaction condition^a



Entry	Catalyst	Base	Solvent	Time	Yield ^b
1	PPh ₃ PdCl	K ₂ CO ₃	1,4-Dioxane	24 h	NR
2	Johnphos Pd	K ₂ CO ₃	1,4-Dioxane	24 h	18%
3	Xphos PdCl ₂	K ₂ CO ₃	1,4-Dioxane	24 h	84%
4	Xphos Pd G1	K ₂ CO ₃	1,4-Dioxane	5 h	95%
5	Xphos Pd G2	K ₂ CO ₃	1,4-Dioxane	5 h	97%
6	Xphos Pd G3	K ₂ CO ₃	1,4-Dioxane	5 h	94%
7	Xphos Pd G4	K ₂ CO ₃	1,4-Dioxane	5 h	97%
8	Pd(OAc) ₂ /Xphos	K ₂ CO ₃	1,4-Dioxane	24 h	NR
9	XPhos Pd G2	Cs ₂ CO ₃	1,4-Dioxane	2 h	99%
10	XPhos Pd G2	Cs ₂ CO ₃	DMSO	24 h	Trace
11	XPhos Pd G2	Cs ₂ CO ₃	H ₂ O	24 h	14%
12	XPhos Pd G2	Cs ₂ CO ₃	MePh	8 h	96%
13	XPhos Pd G2	Cs ₂ CO ₃	DMF	24 h	NR
14 ^c	XPhos Pd G2	Cs ₂ CO ₃	1,4-Dioxane	8 h	98%
15 ^d	XPhos Pd G2	Cs ₂ CO ₃	1,4-Dioxane	36 h	Trace
16 ^e	XPhos Pd G2	Cs ₂ CO ₃	1,4-Dioxane	4 h	97%
17 ^f	XPhos Pd G2	Cs ₂ CO ₃	1,4-Dioxane	4 h	96%
18 ^g	XPhos Pd G2	Cs ₂ CO ₃	1,4-Dioxane	2.5 h	97%
19 ^h	XPhos Pd G2	Cs ₂ CO ₃	1,4-Dioxane	12 h	Trace
20 ⁱ	XPhos Pd G2	Cs ₂ CO ₃	1,4-Dioxane	24 h	84%

^a The reactions were carried in Schlenk flasks. **1a** (0.5 mmol), Pd* (5 mol%), solvent (2 ml), base (1.5 equiv.), 110 °C. ^b Isolated yield. ^c The reaction temperature is 80 °C. ^d The reaction temperature is 50 °C. ^e Substrate concentration is 0.25 M. ^f Substrate concentration is 0.5 M. ^g The catalyst loading is 7.5 mol%. ^h The catalyst loading is 2.5 mol%. ⁱ H₂O (5 μl) was added.

Table 2 Formation of benzene-fused 7-membered amide: reaction scopes^{a,b}

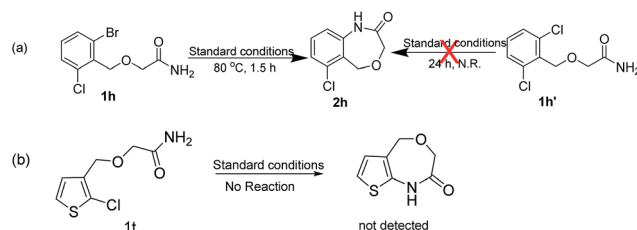


1	Me	5 h, 2b (96%)
2	F	4.5 h, 2c (94%)
3	F ₃ C	4.5 h, 2d (90%)
4	F ₃ C	4.5 h, 2e (92%)
5	OMe	5.5 h, 2f (90%)
6	Me	5.5 h, 2g (89%)
7	Cl	6 h, 2h (83%)
8	Me	4.5 h, 2i (89%)
9	Me	5.5 h, 2j (85%)

^a The reactions were carried in Schlenk flask under Ar. **1b–1j** (0.5 mmol), Xphos Pd G2 (5 mol%), 1,4-dioxane (2 ml), Cs₂CO₃ (1.5 equiv.), 110 °C. ^b Isolated yield.

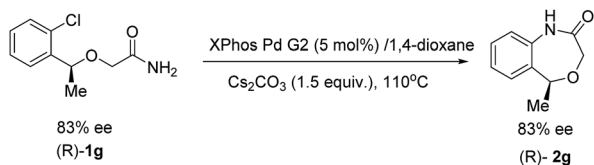
was 0.25 M, it gave the best result with 99% yield. Increasing or decreasing the concentration of **1a**, both gave slightly lower yield (entries 16 and 17). Higher the catalyst loading can faster the reaction with same yield (entry 18). Lowering the catalyst loading to 2.5% makes the reaction much difficult to proceed (entry 19). Small amount of water could hinder the reaction and slow down the reaction rate and yield (entry 20).

With the optimal conditions (Table 1, entry 9) in hand, we then set out to explore the substrate scope of the reaction for constructing benzene-fused 7-membered amides. As shown in Table 2, even electron-rich aryl chlorides can furnish the transformation in short time. A methyl (entry 1), a fluoro (entry 2), a trifluoromethyl (entries 3 and 4) or methoxyls (entry 5) substitution at the benzene ring were readily allowed and these reactions proceeded smoothly to afford the corresponding benzene-fused amides in good to excellent yields. In the case of



Scheme 2 (a) Chemoselectivity of the reaction. (b) Unsuccessful example.



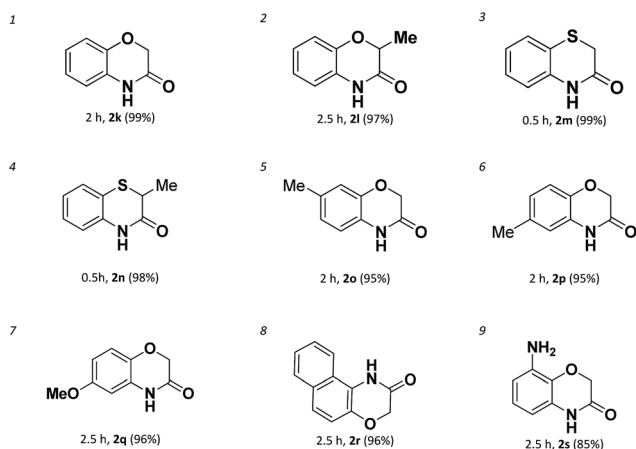
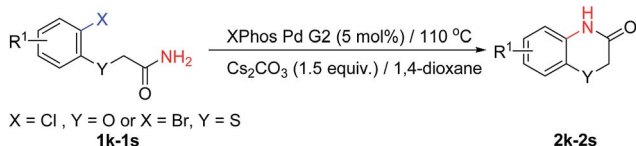
Scheme 3 (R)-**2g** was formed without detectable ee erosion.

2-(1-phenylethoxy)acetamide as the substrate, **2g** could be obtained with 89% yield in 5.5 h, which the reaction time was longer than that of **2a**.

The chemoselectivity of the system was also briefly explored. When there are more than one chloro-groups on the ring, the reaction can hardly proceed. For example, as shown in Scheme 2, when **1h'** was used as the substrate, only trace of **2h** was observed by NMR. Fortunately, when **1h** was used instead of **1h'**, **2h** could be achieved successfully with 83% yield (entry 7) which indicated that the reaction had good chemoselectivity.

Unfortunately, when we explored this chemistry with thiophene substrate, no expected product was observed (Scheme 2b). For other heteroaromatic amides **1i-1j**, the amidation reaction could proceed smoothly. When (1-(pyridin-3-yl)ethoxy)acetamide **1i** was used, **2i** could be obtained with 89% yield in 4.5 h (entry 8). Oxazepino[5,6-*b*]quinolin-2(3*H*)-one **2j** was also obtained with good yield (entry 9).

When Table 2, entry 6 was performed using the (*R*)-substrate (83% ee) under the optimal conditions, (*R*)-**2g** was formed without detectable ee erosion (Scheme 3).

Table 3 Formation of benzene-fused 6-membered amide: reaction scopes.^{a,b}

^a The reactions were carried in Schlenk flask under Ar. Substrate **1k-1s** (0.5 mmol), Xphos Pd G2 (5 mol%), 1,4-dioxane (2 ml), Cs₂CO₃ (1.5 equiv.), 110 °C. ^b Isolated yield.

With the success in the formations of benzene-fused seven membered rings, we subsequently turned to explore the 6-membered ring formation. As expected, the benzene-fused 6-membered rings are much easier formed than the seven membered ones both in efficiency and yields. We found a broad range of 6-membered ring amides possessing various functional groups could be achieved with high yields in short reaction times (Table 3).

However, it needs to point out that the substrate used for the formation of **2n** is aryl bromide (entry 4). The intramolecular amidation reaction could not proceed when the corresponding aryl chloride was used. Electron-rich aryl chlorides can also couple with amides successfully in short time affording the products in excellent yields (entries 5–7). For the sterically hindered aryl chloride, the amidation reaction was successfully proceeded affording **2r** in 96% yield (entry 8). Even for 2-(2-aminophenoxy)acetamide which has a very strong electron donating amino-group which deactivated the C–Cl bond could also undergo the intramolecular amidation and gives product **2s** in 85% yield (entry 9).

Conclusions

In conclusion, an efficient protocol for C–N cross-coupling reactions has been described. This catalyst system allows the primary amides which have only modest nucleophilicity could couple successfully even with electron rich aryl chlorides which can afford valuable benzene-fused 6/7-membered amides with high yield in short reaction time. The catalyst system also has good chemoselectivity and excellent functional group compatibility which supplies an important alternative way to the synthesis of benzene-fused 6/7-membered amides.

Experimental section

General experimental methods

Commercially available reagents were used without further purification. The solvents used for experiment research were all through pretreatment on condition of anaerobic and without water. Reactions were monitored by thin layer chromatography (TLC) using silicycle precoated silica gel plates. Flash column chromatography was performed over silicycle silica gel (300–400 mesh). ¹H NMR and ¹³C NMR spectra were recorded on JMTC-400/54/SS 400 MHz spectrometers using residue solvent peaks as internal standards (¹H: 7.26 ppm; ¹³C: 77.00 ppm). Infrared spectra were recorded with a PerkinElmer Spectrum Two FT-IR spectrometer and are reported in reciprocal centimeter (cm⁻¹). Mass spectra were recorded with MicroTof-II using electron spray ionization (MeOH or CH₃CN as solvent) or Waters GCT Premier time-of-flight mass spectrometer with a field ionization (FI) ion source.

General procedure for the synthesis of benzene-fused 6/7-membered amides

2-((2-chlorobenzyl)oxy)acetyl chloride **1** (0.25 mmol), Cs₂CO₃ (122.65 mg, 0.375 mmol) and Pd Xphos G2 (9.8 mg, 0.0125



mmol) were added into Schlenk tube. The mixture was stirred under argon and dry 1,4-dioxane (1 ml) was added and heated to 110 °C. The reaction was monitored by TLC. After the reaction finished, the product was isolated with column chromatography.

3,5-Dihydrobenzo[e][1,4]oxazepin-2(H)-one 2a

99% yield, m.p. 156–157 °C; ¹H NMR (400 MHz, CDCl₃): δ ppm 4.58 (s, 2H), 4.75 (s, 2H), 6.87 (d, *J* = 8.0 Hz, 1H), 7.06 (t, *J* = 7.6 Hz, 1H), 7.14 (d, *J* = 7.2 Hz, 1H), 7.26–7.27 (m, 1H), 7.72 (s, 1H); ¹³C NMR (100 MHz, CDCl₃): δ ppm 72.8, 73.5, 119.2, 123.7, 128.6, 128.7, 129.2, 135.7, 173.2; IR ν (cm⁻¹): 3357.3, 3171.4, 1635.8, 1431.5, 1377.8; HRMS calcd for C₉H₉NO₂ (M - H)⁺ 162.0555, found 162.0559.

8-Methyl-3,5-dihydrobenzo[e][1,4]oxazepin-2(H)-one 2b

96% yield, m.p. 154–155 °C; ¹H NMR (400 MHz, CDCl₃): δ ppm 2.33 (s, 3H), 4.57 (s, 2H), 4.70 (s, 2H), 6.79 (s, 1H), 6.87 (d, *J* = 7.6 Hz, 1H), 7.02 (d, *J* = 7.6 Hz, 1H), 8.75 (s, 1H); ¹³C NMR (100 MHz, CDCl₃): δ ppm 21.0, 72.5, 73.3, 119.9, 124.5, 125.9, 128.4, 135.7, 139.3, 173.5; IR ν (cm⁻¹): 3377.0, 3184.2, 2962.5, 1656.5, 1259.5; HRMS calcd for C₁₀H₁₁NO₂ (M + Na)⁺ 200.0687, found 200.0673.

8-Fluoro-3,5-dihydrobenzo[e][1,4]oxazepin-2(H)-one 2c

94% yield, m.p. 166–167 °C; ¹H NMR (400 MHz, *d*⁶-DMSO): δ ppm 4.43 (s, 2H), 4.65 (s, 2H), 6.79 (dt, *J*¹ = 8.0 Hz, *J*² = 2.4 Hz, 1H), 6.92 (dd, *J*¹ = 10.4 Hz, *J*² = 2.4 Hz, 1H), 7.17 (d, *J* = 8.4 Hz, 1H), 10.30 (s, 1H); ¹³C NMR (100 MHz, *d*⁶-DMSO): δ ppm 71.7, 73.8, 106.2 (d, *J* = 25.8 Hz), 109.4 (d, *J* = 21.1 Hz), 126.0 (d, *J* = 2.8 Hz), 130.6 (d, *J* = 9.6 Hz), 139.1 (d, *J* = 10.5 Hz), 162.3 (d, *J* = 41.4 Hz), 173.4; ¹⁹F NMR: -113.9; IR ν (cm⁻¹): 3194.0, 3066.2, 1661.0, 1603.5, 1372.5; HRMS calcd for C₉H₈FNO₂ (M + Na)⁺ 204.0437, found 204.0430.

7-(Trifluoromethyl)-3,5-dihydrobenzo[e][1,4]oxazepin-2(1H)-one 2d

90% yield, ¹H NMR (400 MHz, CDCl₃): δ ppm 4.62 (s, 2H), 4.78 (s, 2H), 7.24–7.31 (m, 3H), 8.91 (s, 1H); ¹³C NMR (100 MHz, CDCl₃): δ ppm 70.1, 70.2, 123.9 (q, *J* = 3.9 Hz), 124.5 (q, *J* = 267.2 Hz), 126.2 (q, *J* = 3.9 Hz), 129.3, 131.8 (q, *J* = 32.6 Hz), 133.5, 138.6, 171.6; ¹⁹F NMR: δ ppm 78.8; IR ν (cm⁻¹): 2979.8, 1663.7, 1334.6, 1121.5; HRMS calcd for C₁₀H₈F₃NO₂ (M - H) 230.0427, found 230.0425.

8-(Trifluoromethyl)-3,5-dihydrobenzo[e][1,4]oxazepin-2(H)-one 2e

92% yield, m.p. 128–129 °C; ¹H NMR (400 MHz, CDCl₃): δ ppm 4.56 (s, 2H), 4.77 (s, 2H), 7.09 (d, *J* = 8.4 Hz, 1H), 7.37 (s, 1H), 7.53 (d, *J* = 8.4 Hz, 1H), 9.44 (s, 1H); ¹³C NMR (100 MHz, CDCl₃): δ ppm 72.9, 74.0, 119.6, 123.9 (q, *J* = 270.2 Hz), 125.7 (q, *J* = 32.6 Hz), 125.7 (q, *J* = 3.9 Hz), 126.4 (q, *J* = 3.9 Hz), 129.2, 138.9, 174.5; ¹⁹F NMR: δ ppm 62.1; IR ν (cm⁻¹): 2919.9, 1658.6, 1447.8, 1084.8, 656.7; HRMS calcd for C₁₀H₈F₃NO₂ (M - H)⁺ 230.0427, found 230.0429.

8,9-Dimethoxy-3,5-dihydrobenzo[e][1,4]oxazepin-2(H)-one 2f

90% yield, m.p. 148–149 °C; ¹H NMR (400 MHz, CDCl₃): δ ppm 3.87 (s, 3H), 3.88 (s, 3H), 4.61 (s, 2H), 4.67 (s, 2H), 6.58 (d, *J* = 8.8 Hz, 1H), 6.78 (d, *J* = 8.8 Hz, 1H), 8.30 (s, 1H); ¹³C NMR (100 MHz, CDCl₃): δ ppm 55.9, 60.8, 72.9, 74.1, 106.6, 121.8, 122.8, 129.5, 136.8, 152.3, 172.4; IR ν (cm⁻¹): 3195.3, 1661.6, 1391.6, 1112.3. HRMS calcd for C₁₁H₁₃NO₄ (M + Na)⁺ 246.0742, found 246.0736.

5-Methyl-3,5-dihydrobenzo[e][1,4]oxazepin-2(H)-one 2g

89% yield, m.p. 120–121 °C; ¹H NMR (400 MHz, CDCl₃): δ ppm 1.64 (d, *J* = 6.4 Hz, 3H), 4.54 (d, *J* = 2.4 Hz, 2H), 4.78 (q, *J* = 6.4 Hz, 1H), 6.99 (dd, *J*¹ = 8.4 Hz, *J*² = 0.4 Hz, 1H), 7.01 (td, *J*¹ = 7.6 Hz, *J*² = 0.4 Hz, 1H), 7.23–7.29 (m, 2H), 8.68 (s, 1H); ¹³C NMR (100 MHz, CDCl₃): δ ppm 19.0, 71.1, 75.2, 120.0, 123.9, 125.9, 128.8, 132.7, 136.0, 173.7; IR ν (cm⁻¹): 3196.7, 3065.5, 2997.0, 2903.1, 1656.9; HRMS calcd for C₁₀H₁₁NO₂ (M - H)⁺ 176.0721, found 176.0725. For corresponding chiral *R*-2g: -78° (c 0.10, acetone), 83% ee (determined by a chiral AD-H column, ¹PrOH/hexane = 10/90, *t*_{major} = 14.26 min, *t*_{minor} = 15.40 min).

6-Chloro-3,5-dihydrobenzo[e][1,4]oxazepin-2(H)-one 2h

83% yield, m.p. 172–173 °C; ¹H NMR (400 MHz, CDCl₃): δ ppm 4.52 (s, 2H), 4.99 (s, 2H), 6.78 (d, *J* = 7.6 Hz, 1H), 7.11–7.19 (m, 2H), 7.70 (s, 1H); ¹³C NMR (100 MHz, CDCl₃): δ ppm 69.8, 73.1, 118.2, 124.9, 126.6, 129.2, 133.7, 137.5, 173.0; IR ν (cm⁻¹): 3246.6, 2918.9, 1671.0, 1480.4, 1258.1; HRMS calcd for C₉H₈ClNO₂ (M + Na)⁺ 220.0141, found 220.0143.

5-Methyl-3,5-dihydropyrido[2,3-*e*][1,4]oxazepin-2(H)-one 2i

89% yield, m.p. 106–106.5 °C; ¹H NMR (400 MHz, CDCl₃): δ ppm 1.64 (d, *J* = 6.4 Hz, 3H), 4.64 (d, *J* = 6.0 Hz, 2H), 4.73 (q, *J* = 6.4 Hz, 1H), 7.04 (dd, *J*¹ = 7.6 Hz, *J*² = 4.8 Hz, 1H), 7.53 (d, *J* = 7.8 Hz, 1H), 8.40 (d, *J* = 4.8 Hz, 1H), 9.38 (s, 1H); ¹³C NMR (100 MHz, CDCl₃): δ ppm 18.9, 72.2, 75.0, 118.7, 127.4, 134.7, 147.6, 149.1, 173.0; IR ν (cm⁻¹): 3180.4, 1662.7, 1634.3, 1401.8, 1315.7; HRMS calcd for C₉H₁₀N₂O₂ (M + Na)⁺ 201.0640, found 201.0623.

8-Methyl-3,5-dihydro-[1,4]oxazepino[5,6-*b*]quinolin-2(H)-one 2j

85% yield, m.p. 134–135 °C; ¹H NMR (400 MHz, CDCl₃): δ ppm 2.51 (s, 3H), 4.69 (s, 2H), 4.85 (s, 2H), 7.51 (d, *J* = 7.6 Hz, 2H), 7.77 (d, *J* = 8.4 Hz, 1H), 7.80 (s, 1H), 8.47 (s, 1H); ¹³C NMR (100 MHz, CDCl₃): δ ppm 21.5, 72.2, 74.3, 123.3, 125.0, 126.1, 127.2, 132.8, 135.7, 145.0, 147.6, 172.3; IR ν (cm⁻¹): 2919.9, 1658.6, 1447.8, 1084.8, 656.7; HRMS calcd for C₁₃H₁₂N₂O₂ (M - H)⁺ 227.0821, found 227.0848.

2H-Benzo[*b*][1,4]oxazin-3(4H)-one 2k^{6a,16,17}

Known compound, 99% yield; ¹H NMR (400 MHz, CDCl₃): δ ppm 4.63 (s, 2H), 6.82–6.98 (m, 4H), 8.07 (s, 1H); ¹³C NMR (100 MHz, CDCl₃): δ ppm 67.2, 116.0, 116.8, 122.7, 124.3, 126.0, 143.6, 165.9.



2-Methyl-2H-benzo[b][1,4]oxazin-3(4H)-one 2l¹⁷

Known compound, 97% yield; ¹H NMR (400 MHz, CDCl₃): δ ppm 1.59 (d, *J* = 6.8 Hz, 3H), 4.67 (q, *J* = 6.8 Hz, 1H), 6.88–6.89 (m, 1H), 6.96–6.97 (m, 3H), 9.68 (s, 1H); ¹³C NMR (100 MHz, CDCl₃): δ ppm 16.2, 73.2, 115.9, 117.0, 122.6, 124.1, 126.4, 143.1, 168.9.

2H-Benzo[b][1,4]thiazin-3(4H)-one 2m^{18,19}

Known compound, 99% yield; ¹H NMR (400 MHz, CDCl₃): δ ppm 3.44 (s, 2H), 6.90 (d, *J* = 8.0 Hz, 1H), 7.01 (dt, *J*¹ = 8.0 Hz, *J*² = 1.2 Hz, 1H), 7.17 (dt, *J*¹ = 7.6 Hz, *J*² = 1.2 Hz, 1H), 7.31 (d, *J* = 7.8 Hz, 1H), 9.11 (s, 1H); ¹³C NMR (100 MHz, CDCl₃): δ ppm 29.9, 117.4, 119.9, 123.9, 127.2, 127.8, 136.3, 166.4;

2-Methyl-2H-benzo[b][1,4]thiazin-3(4H)-one 2n^{18,19}

Known compound, 98% yield; ¹H NMR (400 MHz, CDCl₃): δ ppm 1.50 (d, *J* = 7.2 Hz, 3H), 3.56 (q, *J* = 7.2 Hz, 1H), 6.89 (d, *J* = 8.4 Hz, 1H), 7.02 (t, *J* = 6.8 Hz, 1H), 7.18 (t, *J* = 8.0 Hz, 1H), 7.30–7.31 (m, 1H), 8.86 (s, 1H); ¹³C NMR (100 MHz, CDCl₃): δ ppm 15.4, 37.0, 116.9, 119.4, 123.8, 127.1, 128.1, 136.0, 168.9.

7-Methyl-2H-benzo[b][1,4]oxazin-3(4H)-one 2o¹⁸

Known compound, 95% yield; ¹H NMR (400 MHz, CDCl₃): δ ppm 2.28 (s, 3H), 4.60 (s, 2H), 6.67 (s, 1H), 6.78 (d, *J* = 8.0 Hz, 1H), 6.87 (d, *J* = 8.4 Hz, 1H), 9.41 (s, 1H); ¹³C NMR (100 MHz, CDCl₃): δ ppm 20.7, 67.2, 116.5, 116.7, 120.3, 124.7, 125.8, 132.5, 166.6.

6-Methyl-2H-benzo[b][1,4]oxazin-3(4H)-one 2p^{18,19}

Known compound, 95% yield; ¹H NMR (400 MHz, CDCl₃): δ ppm 2.28 (s, 3H), 4.60 (s, 2H), 6.67 (s, 1H), 6.78 (dd, *J*¹ = 8.4 Hz, *J*² = 1.2 Hz, 1H), 6.86 (d, *J* = 7.6 Hz, 1H), 9.36 (s, 1H); ¹³C NMR (100 MHz, CDCl₃): δ ppm 20.6, 67.2, 116.4, 116.5, 124.7, 125.7, 132.5, 141.4, 166.7.

6-Methoxy-2H-benzo[b][1,4]oxazin-3(4H)-one 2q^{18,19}

Known compound, 96% yield; ¹H NMR (400 MHz, CDCl₃): δ ppm 3.76 (s, 3H), 4.57 (s, 2H), 6.40 (d, *J* = 2.4 Hz, 1H), 6.50 (dd, *J*¹ = 8.6 Hz, *J*² = 3.2 Hz, 1H), 6.85 (d, *J* = 8.8 Hz, 1H), 8.93 (s, 1H); ¹³C NMR (100 MHz, CDCl₃): δ ppm 55.8, 67.4, 102.1, 108.8, 117.2, 126.8, 137.6, 155.3, 166.6.

1H-Naphtho[2,1-b][1,4]oxazin-2(3H)-one 2r

96% yield, m.p. 207–208 °C; ¹H NMR (400 MHz, CDCl₃): δ ppm 4.76 (s, 2H), 7.22 (d, *J* = 8.2 Hz, 1H), 7.43 (td, *J*¹ = 7.8 Hz, *J*² = 0.8 Hz, 1H), 7.54 (d, *J* = 9.2 Hz, 1H), 7.58 (td, *J*¹ = 7.8 Hz, *J*² = 1.2 Hz, 1H), 7.83 (d, *J* = 8.4 Hz, 1H), 7.94 (d, *J* = 8.0 Hz, 1H), 9.66 (s, 1H); ¹³C NMR (100 MHz, CDCl₃): δ ppm 67.5, 117.4, 118.7, 119.0, 123.0, 124.3, 124.7, 127.0, 128.7, 130.0, 140.6, 166.0; IR ν (cm⁻¹): 3189.9, 2961.3, 2877.5, 1681.8, 1458.9; HRMS calcd for C₁₂H₉NO₂ (M + Na)⁺ 222.0531, found 222.0527.

8-Amino-2H-benzo[b][1,4]oxazin-3(4H)-one 2s²⁰

Known compound, 85% yield; ¹H NMR (400 MHz, CDCl₃): δ ppm 4.73 (s, 2H), 6.73 (dd, *J*¹ = 8.0 Hz, *J*² = 1.2 Hz, 1H), 6.90 (t, *J* = 8.0 Hz, 1H), 7.06 (dd, *J*¹ = 8.0 Hz, *J*² = 1.2 Hz, 1H), 8.61 (s, 1H); ¹³C NMR (100 MHz, CDCl₃): δ ppm 67.4, 114.3, 122.2, 122.9, 125.1, 127.1, 139.8, 165.4.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

The authors thank the Natural Science Foundation of the Jiangsu Higher Education (Grant No. 15KJB150029), the Project of Science and Technology of Xuzhou Government (No. KC16SG250) and the Natural Science Foundation of Jiangsu Province (Grants No. BK 20171175). The work is also sponsored by Qing Lan Project of Jiangsu Province and Zhen Xing Project of XZMC.

Notes and references

- (a) H. Otsuka, Y. Hirani, T. Nagao and K. Yamasaki, *J. Nat. Prod.*, 1988, **51**, 74; (b) A. S. Bourlot, I. Sanchez, G. Dureng, G. Guillaumet, R. Massingham, A. Monteil, E. Winslow, M. D. Pujol and J. Y. Merour, *J. Med. Chem.*, 1998, **41**, 3142; (c) D. A. Dudley, A. M. Bunker, L. Chi, W. L. Cody, D. R. Holland, D. P. Ignasiak, N. Janiczek-Dolphin, T. B. McClanahan, T. E. Mertz, L. S. Narasimhan, S. T. Rapundalo, J. A. Trautschold, C. A. Van Huis and J. J. Edmunds, *J. Med. Chem.*, 2000, **43**, 4063; (d) R. Fringuelli, D. Pietrella, F. Schiaffella, A. Guarraci, S. Perito, F. Bistoni and A. Vecchiarelli, *Bioorg. Med. Chem.*, 2002, **10**, 1681.
- T. B. Lanni Jr, K. L. Greene, C. N. Kolz, K. S. Para, M. Visnick, J. L. Mobley, D. T. Dudley, T. J. Baginski and M. B. Liimatta, *Bioorg. Med. Chem. Lett.*, 2007, **17**, 756.
- C. Su, C. Tseng, C. Ramesh, H. Liu, C. Huang and C. Yao, *Eur. J. Med. Chem.*, 2017, **132**, 90.
- H. Chan, *Synthesis*, 1984, **10**, 851.
- (a) T. Miki, M. Kori, H. Mabuchi, H. Banno, R. Tozawa, M. Nakamura, S. Itokawa, Y. Sugiyama and H. Yukimasa, *Bioorg. Med. Chem.*, 2002, **10**, 401; (b) E. Feng, H. Huang, Y. Zhou, D. Ye, H. Jiang and H. J. Liu, *J. Org. Chem.*, 2009, **74**, 2846; (c) A. Sharifi, M. Barzandeh, A. Saeed and M. Mirzaei, *Tetrahedron Lett.*, 2010, **51**, 1852; (d) D. Chen, Z. Wang and W. Bao, *J. Org. Chem.*, 2010, **75**, 5768.
- (a) D. Chen, G. Shen and W. Bao, *Org. Biomol. Chem.*, 2009, **7**, 4067; (b) A. Sharifi, M. Ansari, H. Darabi and M. Abaee, *Tetrahedron Lett.*, 2016, **57**, 529.
- (a) J. F. Hartwig, *Acc. Chem. Res.*, 1998, **31**, 852; (b) J. F. Hartwig, *Acc. Chem. Res.*, 2008, **41**, 1534.
- (a) J. P. Wolfe, S. Wagaw, J. F. Marcoux and S. L. Buchwald, *Acc. Chem. Res.*, 1998, **31**, 805; (b) A. R. Muci and S. L. Buchwald, *Top. Curr. Chem.*, 2002, **219**, 131.



- 9 (a) B. P. Fors, P. Krattiger, E. Strieter and S. L. Buchwald, *Org. Lett.*, 2008, **10**, 16; (b) D. S. Surry and S. L. Buchwald, *Chem. Sci.*, 2011, **2**, 27.
- 10 B. C. Hamann and J. F. Hartwig, *J. Am. Chem. Soc.*, 1998, **120**, 7369.
- 11 N. C. Bruno, N. Niljianskul and S. L. Buchwald, *J. Org. Chem.*, 2014, **79**, 4161.
- 12 N. A. Isley, S. Dobarco and B. H. Lipshutz, *Green Chem.*, 2014, **16**, 1480.
- 13 J. K. Laha, P. U. Shah and K. P. Jethava, *Chem. Commun.*, 2013, **49**, 7623.
- 14 L. Zhang, L. Sonaglia, J. Stacey and M. Lautens, *Org. Lett.*, 2013, **15**, 2128.
- 15 (a) Z. Xu, H. Chen, Z. Wang, A. Ying and L. Zhang, *J. Am. Chem. Soc.*, 2016, **138**, 5515; (b) Z. Xu, R. L. Zhai, T. Liang and L. Zhang, *Chem.–Eur. J.*, 2017, **23**, 14133.
- 16 P. Stefanic, K. Turnsek and D. Kikelj, *Tetrahedron*, 2003, **59**, 7123.
- 17 (a) S. Ceylan, L. Coutable, J. Wegner and A. Kirschning, *Chem.–Eur. J.*, 2011, **17**, 1884; (b) C. Rajitha, P. K. Dubey, V. Sunku, F. J. Piedrafita, V. R. Veeramani and M. Pal, *Eur. J. Med. Chem.*, 2011, **46**, 4887.
- 18 W. S. Huang, R. Xu, R. Dodd and W. C. Shakespeare, *Tetrahedron Lett.*, 2013, **54**, 5214.
- 19 F. Babudri, S. Florio, G. Indelicati and G. Trapani, *J. Org. Chem.*, 1983, **48**, 4082.
- 20 P. Smid, H. Coolen, H. G. Keizer, R. Hes, J. Moes, A. P. Hartog, B. Stork, R. H. Plekkenpol, L. C. Niemann, C. Stroomer, M. Tulp, H. Stuijvenberg, A. McCreary, M. Hesselink, H. J. Arnoud and C. G. Kruse, *J. Med. Chem.*, 2005, **48**, 6855.

