Organic & Biomolecular Chemistry

RSC Publishing

PAPER

View Article Online
View Journal | View Issue

Cite this: *Org. Biomol. Chem.*, 2013, **11**, 6520

A convenient method to construct (*Z*)-oxazines *via* 6-*exo-dig* iodocyclization and synthesis of indolin-3-one†

Jaya Kishore Vandavasi,‡[a] Kung-Kai Kuo,‡[b] Wan-Ping Hu,[c] Ho-Chanu Shen,[a] Wei-Sheng Lo[a] and Jeh-Jeng Wang*[a]

Received 20th June 2013,
Accepted 26th July 2013

DOI: 10.1039/c3ob41272e

www.rsc.org/obc

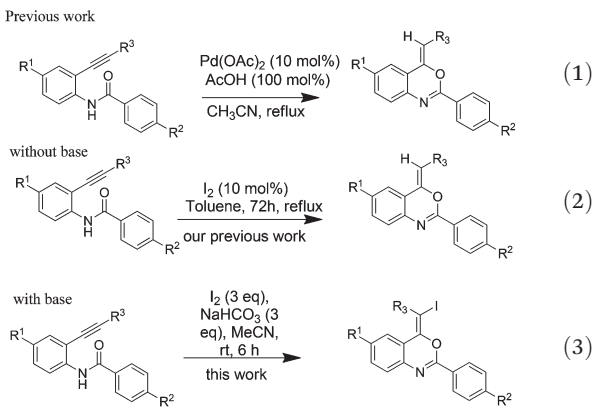
An efficient regio-, stereo- and chemo-specific synthesis of 1,3-benzoxazines *via* 6-*exo-dig* cyclization to afford the *Z*-isomer is reported. The structure and connectivity were confirmed unambiguously on the basis of ^{1}H NMR, NOESY, and ORTEP. Furthermore, DFT studies revealed that the *Z*-isomer was more stable than the *E*-isomer. Iodine substituted 1,3-benzoxazines were very useful precursors for cross coupling reactions. Suzuki reaction was carried out successfully and the resulting product was transformed to 1-(4-nitrobenzoyl)-2,2-diphenylindolin-3-one in the presence of a Lewis acid.

Introduction

Heterocyclic compounds[1] are valuable structural motifs present in many natural products and biologically active molecules.[2] Among them, nitrogen and oxygen containing fused aryl heterocycles occur widely in biologically active compounds.[2–4] In particular, oxazines[5] are generally found in many biologically important molecules[6] and their substructure is a component of naturally occurring active compounds.[7] In the last decade, great advancements have been made in the synthesis of 1,3-benzoxazines[8–14] *via* halocyclization.[15–18] However, these methods have some limitations, including harsh conditions, prolonged reaction times and poor selectivity. In this class, the most adorable way has been intramolecular nucleophilic attack of heteroatoms on C–C multiple bonds such as alkynes,[19–21] alkenes[22] and allenes,[23] which is one of the most powerful alterations. Halocyclization of alkyne onto amide involves various challenges such as (i) regioselectivity: nucleophile attack on alkyne follows two approaches such as *exo-* or *endo-dig* cyclization,[24] (ii) chemoselectivity: competition between oxygen and nitrogen as nucleophiles,[25] and (iii) stereospecificity: to obtain a single geometrical isomer (*E* or *Z*).[26]

In 2011, Saito and co-workers successfully produced 4-alkylidene-4*H*-3,1-benzoxazines, eqn (1),[10] *via* 6-*exo-dig* cyclization of *N*-acyl-*o*-alkynyl anilines. In our previous work we reported an efficient method for the synthesis of 1,3-benzoxazine derivatives in the presence of iodine, eqn (2).[21] Preceding results lack iodine substituents, which would be helpful for further diversifications. Considering the importance of iodine substituted 1,3-oxazines and the drawbacks of the existing methods, the perusal and development of an alternative method for constructing such an appropriate design is still attractive.

Iodine substituted 1,3-benzoxazines were very useful precursors for cross coupling reactions. In this aspect, we performed a Suzuki reaction to afford the desired product from an iodo derivative. Further, we developed a new strategy to construct indolin-3-ones,[27–34] in the presence of a Lewis acid as a catalyst, from compound **5a**. Indolin-3-ones also have an important function in biological and pharmaceutical activities.



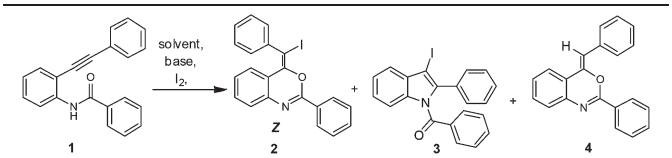
[a]*Department of Medicinal and Applied Chemistry, Kaohsiung Medical University, Kaohsiung, Taiwan. E-mail: jjwang@kmu.edu.tw*
[b]*Department of Surgery, School of Medicine, Kaohsiung Medical University, Kaohsiung, Taiwan*
[c]*Department of Biotechnology, Kaohsiung Medical University, Kaohsiung, Taiwan*
†Electronic supplementary information (ESI) available. CCDC 834780, 834782, 834785, 834787, 834788, 834789, 837880, 951676 and 951677. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c3ob41272e
‡Equally contributed.

Recently, we have successfully synthesized a series of oxaza heterocycles in the presence of a base,[19] a Lewis acid[20] and iodine, eqn (2).[21] Encouraged by the above results and our ongoing work on the synthesis of heterocycles by electrophilic cyclization of alkynes, herein we report a novel synthetic pathway to synthesize the (*Z*)-4-(iodo-methylene)-2-aryl-4*H*-benzo[*d*]-[1,3]oxazines, eqn (3).

Results and discussion

In the preliminary investigation, we screened the reaction of 2-alkylidene benzamides **1** in the presence of iodine (3.0 equiv.), $NaHCO_3$ and toluene at 120 °C (Table 1, entry 1). Under these conditions the chemoselectivity was at a moderate level as compound **2** (60%) and compound **3** (24%) yields (Table 1, entry 1) and the same result was observed in nitromethane as a solvent (Table 1, entry 2). Surprisingly high chemoselectivity was observed in THF and CH_3CN, with traces of compound **3** (Table 1, entries 3 and 5). In acetone, the reaction performance to afford the desired compound was very low (Table 1, entry 4). With halogenated solvents, the chemoselectivity was enriched with 75–80% yield of compound **2** and 11–18% yield of compound **3** (Table 1, entries 6 and 7). In a polar solvent like DMF, the reaction yield was low (Table 1, entry 8) and, in terms of protic solvents, the reaction yield was very low in ethanol (Table 1, entry 10) and cyclization was not successful in methanol (Table 1, entry 9). Subsequently, some

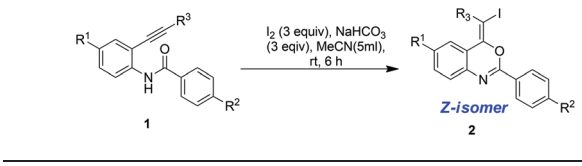
Table 1 Optimization studies[a,b,c,g]

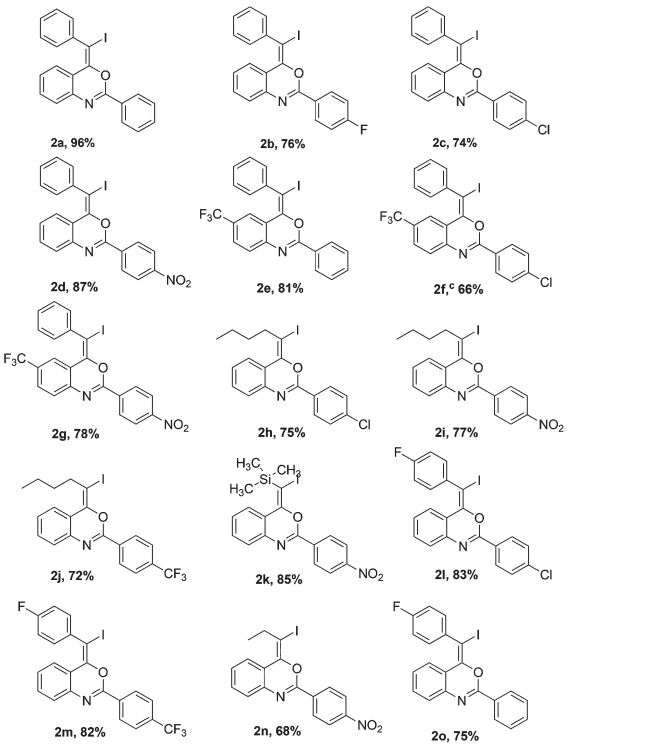


Entry	Solvent	Temp. [°C]	Time [h]	I_2 [eq.]	**2** [%]	**3** [%]
1	Toluene	120	24	3	60	24
2	$MeNO_2$	120	24	3	60	21
3	THF	80	24	3	90	Traces
4	Acetone	80	24	3	30	12
5	MeCN	80	24	3	92	Traces
6	CH_2Cl_2	60	24	3	75	18
7	DCE	60	24	3	80	11
8	DMF	120	24	3	50	8
9	MeOH	100	24	3	0	0
10	EtOH	100	24	3	30	5
11[d]	MeCN	80	6	3	10	Traces
12[e]	MeCN	80	6	3	20	16
13[f]	MeCN	80	6	3	90	Traces
14	MeCN	80	6	1	53	Traces
15	MeCN	80	6	2	71	Traces
16	MeCN	80	6	5	91	Traces
17	MeCN	80	6	—	0	0
18	MeCN	28	6	3	96	0

[a] Reaction conditions: compound **1** (1 equiv.), iodine, $NaHCO_3$ (3 equiv.) and solvent (5 mL). [b] Stereochemistry was determined on the basis of ^{1}H NMR. [c] Isolated yields. [d] K_2CO_3. [e] Cs_2CO_3. [f] Na_2CO_3. [g] Compound **4** was not observed.

Table 2 Iodine mediated regio- and stereoselective cyclization[a,b]





[a] Stereochemistry was determined on the basis of ^{1}H NMR. [b] Isolated yields. [c] Traces of *E*-isomer were observed by ^{1}H NMR.

other bases were also evaluated using CH_3CN as a solvent; among them $NaHCO_3$ resulted well (Table 1, entry 18). Notably, the yield of compound **2** was high in the presence of I_2 (3 equiv.), $NaHCO_3$ (3 equiv.) and CH_3CN at 28 °C for 6 h, which was thus found to be the optimum reaction condition (Table 1, entry 18).

The scope and generality of this transformation with other 2-alkylidene benzamides were investigated (Table 2). Reactions were well tolerated with electron-withdrawing and electron-donating groups on benzene. *Z*-Isomer was exclusively obtained in each case without any trace amount of *E*-isomer, even when the reaction was performed with aryl or alkyl substituent (R^3). The structures of compounds **2c** and **2j** were confirmed using the ORTEP diagram (Fig. 1).

Stereochemistry was confirmed on the basis of ^{1}H NMR, NOESY and single crystal X-ray. The two protons are mentioned in Fig. 2 as the NOE effect. By considering all these facts, the stereochemistry confirmed that the *Z*-form was obtained exclusively, and DFT M06-2x/6-31G* calculations revealed that the *Z*-form is more stable than the *E*-form by

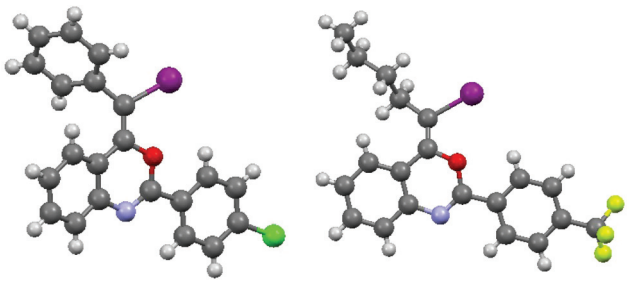


Fig. 1 ORTEP diagram of compounds **2c** and **2j**.

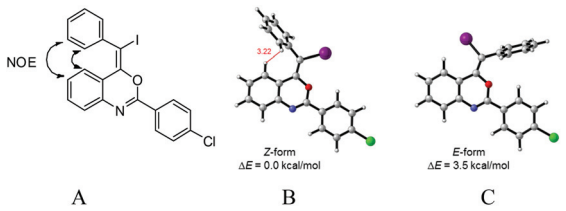
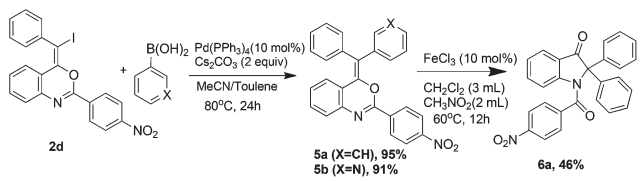


Fig. 2 Stereochemistry assignment based on ^{1}H NMR and NOESY of compound **2** (A) and density functional theory M06-2X/6-31G* optimized structures of *Z*- and *E*-form (B and C).



Scheme 1 Suzuki reaction and rearrangement in the presence of $FeCl_3$.

3.5 kcal mol^{-1} (Fig. 2B and C) and the H–H distance is 3.224 Å (Fig. 2B).

Further, to study the applications of the desired compound **2**, we performed the Suzuki reaction successfully with high yields to afford compound **5**. Interestingly, compound **5a** underwent further transformation in the presence of a Lewis acid such as $FeCl_3$ to afford compound **6a** in 46% yield (Scheme 1). The structures of compounds **5b** and **6a** were confirmed using the ORTEP diagram (Fig. 3).

Conclusion

The reaction was fine tuned with a base to afford the (*Z*)-4-(iodo-methylene)-2-aryl-4*H*-benzo[*d*]-[1,3]oxazines in the presence of I_2 *via* 6-*exo-dig* iodocyclization with high stereo-, regio- and chemoselectivity. Stereochemistry of *Z*-isomer was confirmed by ^{1}H NMR, NOESY and ORTEP. The DFT calculations M06-2x/6-31G* also revealed that the *Z*-form is more stable than the *E*-form by 3.5 kcal mol^{-1}. Iodine substituted molecules have many applications in synthetic chemistry. We have succeeded with Suzuki reaction, which has afforded the desired product in high yields. The Suzuki product in the presence of a Lewis acid such as $FeCl_3$ also transformed to 1-(4-nitrobenzoyl)-2,2-diphenylindolin-3-one.

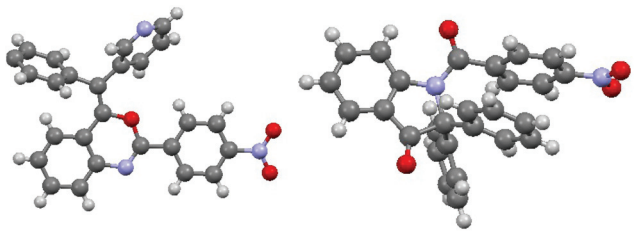


Fig. 3 ORTEP diagram of compounds **5b** and **6a**.

Experimental

Experimental details: Melting points are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded on a 400 MHz instrument using $CDCl_3$ as a solvent. ^{1}H NMR chemical shifts are referenced to TMS (0 ppm) or $CDCl_3$ (7.26 ppm). ^{13}C NMR was referenced to $CDCl_3$ (77.0 ppm). Multiplicities were denoted as s, d, t, and q. Mass spectra and high resolution mass spectra (HRMS) were measured using the electron-impact (EI, 70 eV) technique. Flash column chromatography was carried out over silica gel 60 (230–400 mesh).

Compound 1

Compound **1** was synthesized using previously reported protocols.[21]

General procedure for the synthesis of iodomethylene benzoxazines 2a–2o

A mixture of the corresponding compound **1** (1.0 mmol), iodine (3.0 mmol) and $NaHCO_3$ (3.0 mmol) was taken in dry acetonitrile (10.0 mL) in a flask under an argon atmosphere and stirred for 6 h at room temperature. The reaction was monitored by TLC analysis. The formed product was extracted with ethyl acetate by washing with water, saturated $Na_2S_2O_3$ solution and brine. The organic layer was separated and concentrated under reduced pressure. The crude residue obtained was chromatographed over silica gel using an ethyl acetate–hexane mixture as an eluent to obtain title compound **2**.

4-(Iodo(phenyl)methylene)-2-phenyl-4*H*-benzo[*d*][1,3]oxazine (2a). The title compound **2a** was prepared according to the general procedure and purified by column chromatography to obtain a yellow solid (96%). Mp = 102–104 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.45 (d, J = 5.6 Hz, 2H), 7.58–7.31 (m, 9H), 7.26 (td, J = 7.6 Hz and 1.4 Hz, 1H), 6.81 (td, J = 7.6 Hz and 1.4 Hz, 1H), 6.56 (dd, J = 8.4 Hz and 1.2 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 155.6, 145.4, 141.7, 140.4, 132.0, 130.6, 129.8, 129.3, 128.6, 128.4, 126.7, 126.2, 126.1, 120.2, 75.0. HRMS (ESI, m/z) for $C_{21}H_{15}INO$, calcd: 424.0198, found: 424.0200. Anal. calcd for: $C_{21}H_{14}INO$; C, 59.59; H, 3.33; N, 3.31; found: C, 59.37; H, 3.33; N, 3.32.

2-(4-Fluorophenyl)-4-(iodo(phenyl)methylene)-4*H*-benzo[*d*]-[1,3]oxazine (2b). The title compound **2b** was prepared

according to the general procedure and purified by column chromatography to obtain a yellow solid (76%). Mp = 109–111 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.45 (d, J = 5.2 Hz, 2H), 7.41–7.15 (m, 9H), 6.80 (td, J = 8.4 Hz and 1.6 Hz, 1H), 6.55 (dd, J = 8.0 Hz and 1.2 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 166.5, 164.0, 154.7, 145.3, 141.6, 140.3, 132.8, 130.7, 130.6, 129.8, 129.3, 128.6, 126.8 (d, J = 31.0 Hz), 126.7, 126.3, 126.1, 120.1, 115.7, 115.5, 75.2. HRMS (ESI, m/z) for $C_{21}H_{14}FINO$, calcd: 442.0104, found: 442.0101. Anal. calcd for $C_{21}H_{13}FINO$: C, 57.16; H, 2.97; N, 3.17; found: C, 57.15; H, 3.07; N, 3.12.

2-(4-Chlorophenyl)-4-(iodo(phenyl)methylene)-4*H*-benzo[*d*][1,3]oxazine (2c). The title compound **2c** was prepared according to the general procedure and purified by column chromatography to obtain a yellow solid (74%). Mp = 151–153 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.37 (d, J = 8.8 Hz, 2H), 7.48 (d, J = 8.8 Hz, 2H), 7.40 (d, J = 4.8 Hz, 4H), 7.37–7.31 (m, 2H), 7.26 (td, J = 8.0 Hz and 1.2 Hz, 1H), 6.81 (td, J = 8.0 Hz and 1.2 Hz, 1H), 6.55 (d, J = 8.0 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 154.7, 145.2, 141.6, 140.2, 138.2, 130.6, 129.8, 129.7, 129.3, 129.1, 128.8, 128.7, 126.9, 126.3, 126.2, 126.1, 75.3. HRMS (ESI, m/z) calcd for $C_{21}H_{14}IINO$: 457.9809, found: 457.9807. Anal. calcd for: $C_{21}H_{13}IINO$; C, 55.24; H, 2.91; N, 3.10; found: C, 55.11; H, 2.86; N, 3.06.

4-(Iodo(phenyl)methylene)-2-(4-nitrophenyl)-4*H*-benzo[*d*][1,3]oxazine (2d). The title compound **2d** was prepared according to the general procedure and purified by column chromatography to obtain a yellow solid (87%). Mp = 247–249 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.61 (d, J = 8.8 Hz, 2H), 8.37 (d, J = 8.8 Hz, 2H), 7.44–7.26 (m, 7H), 6.87 (td, J = 8.4 Hz and 1.2 Hz, 1H), 6.57 (d, J = 8.4 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 154.6, 149.8, 145.0, 141.3, 139.7, 136.4, 130.8, 129.7, 129.4, 129.2, 128.8, 127.8, 126.6, 126.4, 123.6, 120.3, 76.0. HRMS (ESI, m/z) calcd for $C_{21}H_{13}IN_2O_3Na$: 490.9869, found: 490.9865. Anal. calcd for: $C_{21}H_{13}IN_2O_3$; C, 55.80; H, 2.84; N, 6.08; found: C, 53.87; H, 2.80; N, 5.98.

4-(Iodo(phenyl)methylene)-2-phenyl-6-(trifluoromethyl)-4*H*-benzo[*d*][1,3]oxazine (2e). The title compound **2e** was prepared according to the general procedure and purified by column chromatography to obtain a yellow solid (81%). Mp = 139–141 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.44 (d, J = 7.2 Hz, 2H), 7.59 (t, J = 7.2 Hz, 1H), 7.52 (t, J = 7.2 Hz, 1H), 7.46–7.35 (m, 8H), 6.71 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 157.3, 144.4, 143.1, 132.6, 130.1, 129.6, 129.3, 129.2, 129.1, 128.7, 128.5, 128.3, 128.2, 127.0 (q, J = 3.8 Hz), 126.5, 123.6 (q, J = 3.8 Hz), 123.2 (q, J = 270.7 Hz), 120.5. HRMS (ESI, m/z) for $C_{22}H_{14}F_3INO$, calcd: 492.0067, found: 492.0069. Anal. calcd for: $C_{22}H_{13}F_3INO$; C, 53.79; H, 2.67; N, 2.85; found: C, 53.74; H, 2.68; N, 2.88.

2-(4-Chlorophenyl)-4-(iodo(phenyl)methylene)-6-(trifluoromethyl)-4*H*-benzo[*d*][1,3]oxazine (2f). The title compound **2f** was prepared according to the general procedure and purified by column chromatography to obtain a yellow solid (66%). Mp = 183–184 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.36 (d, J = 9.2 Hz, 2H), 7.51–7.34 (m, 9H), 6.70 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 162.8, 156.4, 144.2, 142.9, 140.7, 139.0, 130.0, 129.7, 129.5, 129.3, 129.2, 129.1, 128.9, 128.6 (q, J = 16.7 Hz), 128.3, 126.5, 123.6 (q, J = 3.7 Hz), 120.5. HRMS (ESI, m/z) for $C_{22}H_{13}ClF_3INO$ [$(M + H)^+$] calcd: 525.9677, found: 525.9679. Anal. calcd for $C_{22}H_{12}ClF_3INO$; C, 50.26; H, 2.30; N, 2.66; found: C, 50.20; H, 2.34; N, 2.66.

4-(Iodo(phenyl)methylene)-2-(4-nitrophenyl)-6-(trifluoromethyl)-4*H*-benzo[*d*][1,3]oxazine (2g). The title compound **2g** was prepared according to the general procedure and purified by column chromatography to obtain an orange solid (78%). Mp = 172–174 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.61 (d, J = 9.2 Hz, 2H), 8.37 (d, J = 9.2 Hz, 2H), 7.51–7.37 (m, 7H), 6.73 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 155.2, 150.1, 143.9, 142.3, 140.3, 135.8, 129.7, 129.5, 129.4, 129.2, 127.3 (q, J = 3.8 Hz), 124.1 (q, J = 270.0 Hz), 123.8 (q, J = 3.8 Hz), 123.7, 120.7, 78.1. HRMS (ESI, m/z) for $C_{22}H_{13}F_3IN_2O_3$, calcd: 536.9923, found: 536.9921. Anal. calcd for: $C_{22}H_{12}F_3IN_2O_3$; C, 49.28; H, 2.26; N, 5.22; found: C, 49.37; H, 2.32; N, 5.28.

2-(4-Chlorophenyl)-4-(1-iodopentylidene)-4*H*-benzo[*d*][1,3]oxazine (2h). The title compound **2h** was prepared according to the general procedure and purified by column chromatography to obtain a yellow solid (75%). Mp = 80–82 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.26 (d, J = 8.8 Hz, 2H), 7.40–7.29 (m, 5H), 7.19 (t, J = 8.0 Hz, 1H), 2.81 (t, J = 8.0 Hz, 2H), 1.72–1.64 (m, 2H), 1.45–1.35 (m, 2H), 0.93 (t, J = 7.2 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 155.7, 143.7, 140.9, 138.2, 130.5, 129.9, 129.2, 128.7, 127.0, 125.8, 125.3, 120.8, 87.1, 38.7, 32.0, 21.9, 13.9. HRMS (ESI, m/z) calcd for $C_{19}H_{18}ClINO$: 438.0122, found: 438.0119. Anal. calcd for: $C_{19}H_{17}ClINO$; C, 52.14; H, 3.91; N, 3.20; found: C, 52.09; H, 4.05; N, 3.13.

4-(1-Iodopentylidene)-2-(4-nitrophenyl)-4*H*-benzo[*d*][1,3]oxazine (2i). The title compound **2i** was prepared according to the general procedure and purified by column chromatography to obtain a yellow solid (77%). Mp = 142–144 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.55 (d, J = 8.8 Hz, 2H), 8.32 (d, J = 8.8 Hz, 2H), 7.47–7.40 (m, 3H), 7.32 (t, J = 8.0 Hz, 1H), 2.89 (t, J = 8.0 Hz, 2H), 1.79–1.72 (m, 2H), 1.53–1.44 (m, 2H), 1.01 (t, J = 7.2 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 154.5, 149.7, 143.4, 140.3, 136.4, 130.6, 129.3, 127.9, 126.3, 125.4, 123.5, 120.9, 87.7, 38.7, 31.9, 21.9, 13.9. HRMS (ESI, m/z) calcd for $C_{19}H_{18}IN_2O_3$: 449.0362, found: 449.0360. Anal. calcd for: $C_{19}H_{17}IN_2O_3$; C, 50.91; H, 3.82; N, 6.25; found: C, 51.05; H, 3.77; N, 6.25.

4-(1-Iodopentylidene)-2-(4-(trifluoromethyl)phenyl)-4*H*-benzo[*d*][1,3]oxazine (2j). The title compound **2j** was prepared according to the general procedure and purified by column chromatography to obtain a yellow solid (72%). Mp = 80–82 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.50 (d, J = 8.8 Hz, 2H), 7.74 (d, J = 8.8 Hz, 2H), 7.45–7.38 (m, 3H), 7.29 (t, J = 8.0 Hz, 1H), 2.89 (t, J = 8.0 Hz, 2H), 1.79–1.72 (m, 2H), 1.53–1.43 (m, 2H), 1.00 (t, J = 7.2 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 155.2, 143.6, 140.6, 134.0, 133.2 (q, J = 33 Hz), 130.5, 128.8, 127.4, 126.1, 125.3 (q, J = 3 Hz), 123.8 (q, J = 270.0 Hz), 120.9, 87.3, 38.4, 32.0, 22.0, 13.9. HRMS (ESI, m/z) calcd for $C_{20}H_{18}F_3INO$: 472.0385, found: 472.0383. Anal. calcd for: $C_{20}H_{17}F_3INO$; C, 50.97; H, 3.64; N, 2.97; found: C, 50.91; H, 3.68; N, 2.98.

4-(Iodo(trimethylsilyl)methylene)-2-(4-nitrophenyl)-4*H*-benzo[*d*][1,3]oxazine (2k). The title compound **2k** was prepared according to the general procedure and purified by column chromatography to obtain a sticky yellow compound (85%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.62 (d, J = 8.8 Hz, 2H), 8.34 (dd, J = 8.8 Hz, 2H), 7.55–7.29 (m, 4H), 0.38 (s, 9H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 152.5, 149.7, 140.9, 136.4, 131.9, 129.4, 128.6, 127.8, 127.3, 125.7, 123.6, 121.3, 82.4, 2.4. HRMS (ESI, m/z) calcd for $C_{18}H_{18}IN_2O_3Si$ [$(M + H)^+$]: 465.0136, found: 465.0133. Anal. calcd for: $C_{18}H_{17}IN_2O_3Si$; C, 46.56; H, 3.69; N, 6.03; found: C, 46.29; H, 3.58; N, 6.05.

2-(4-Chlorophenyl)-4-((4-fluorophenyl)iodomethylene)-4*H*-benzo[*d*][1,3]oxazine (2l). The title compound **2l** was prepared according to the general procedure and purified by column chromatography to obtain a sticky yellow compound (83%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.37 (d, J = 8.4 Hz, 2H), 7.49 (d, J = 8.4 Hz, 2H), 7.41–7.26 (m, 4H), 7.10 (t, J = 8.4 Hz, 2H), 6.86 (dt, J = 8.0 Hz, J = 1.2 Hz, 1H), 6.57 (dd, J = 8.0 Hz, J = 1.2 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 163.8, 161.3, 154.7, 145.6, 140.3, 138.4, 137.7, 131 (d, $^3J_{C-F}$ = 8.3 Hz), 130.9, 129.7, 128.8, 127.1, 126.2 (d, $^2J_{C-F}$ = 18.9 Hz), 120.0, 116.5 (d, $^1J_{C-F}$ = 21.9 Hz), 73.9. HRMS (ESI, m/z) for $C_{22}H_{13}ONClFI$ [$(M + H)^+$] calcd 475.9717, found: 475.9709. Anal. calcd for $C_{21}H_{12}ClFINO$ C, 53.02; H, 2.54; N, 2.94; found: C, 52.67,H, 2.57; N 2.91.

4-((4-Fluorophenyl)iodomethylene)-2-(4-(trifluoromethyl)-phenyl)-4*H*-benzo[*d*][1,3]oxazine (2m). The title compound **2m** was prepared according to the general procedure and purified by column chromatography to obtain a sticky yellow compound (82%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.53 (d, J = 8.0 Hz, 2H), 7.77 (d, J = 8.4 Hz, 2H), 7.43–7.22 (m, 4H), 7.10 (t, J = 8.8 Hz, 2H), 6.89 (dt, J = 8.0 Hz and 1.2 Hz, 1H), 6.58 (dd, J = 8.0 Hz and 1.2 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 163.9, 161.4, 154.2, 145.5, 140.0, 137.6 (d, J = 3.8 Hz), 134.0, 133.6, 133.3, 131.8 (d, J = 8.3 Hz), 130.9, 128.0, 127.5, 126.6, 126.2, 125.5, 125.4, 125.39, 125.2, 124.1 (q, J = 273.2 Hz), 116.5 (d, J = 21.2 Hz). HRMS (ESI, m/z) for $C_{22}H_{13}ON\,F_4I$ [$(M + H)^+$] calcd: 508.9987, found 509.9972; Anal. calcd for $C_{22}H_{12}F_4INO$: C, 51.89; H, 2.38; N, 2.75; found: C, 51.95; H, 2.41; N, 2.79.

4-((4-Ethylphenyl)iodomethylene)-2-(4-nitrophenyl)-4*H*-benzo[*d*][1,3]oxazine (2n). The title compound **2n** was prepared according to the general procedure and purified by column chromatography to obtain an orange solid (68%). Mp = 219–221 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.60 (d, J = 8.8 Hz, 2H), 8.57 (d, J = 8.8 Hz, 2H), 7.37–7.23 (m, 6H), 6.88 (td, J = 8.0 Hz and 1.2 Hz, 1H), 6.62 (dd, J = 8.0 Hz and 1.2 Hz, 1H), 2.71 (q, 7.6 Hz, 2H), 1.29 (t, 7.6 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 153.6, 149.8, 145.2, 144.7, 139.6, 138.5, 136.5, 130.7, 129.6, 129.2, 128.9, 127.8, 126.6, 126.3, 123.6, 120.4, 76.6, 28.6, 15.3. HRMS (ESI, m/z) calcd for $C_{23}H_{18}IN_2O_3$: 497.0362, found: 497.0360. Anal. calcd for: $C_{23}H_{17}IN_2O_3$; C, 55.44; H, 3.38; N, 5.57; found: C, 55.66; H, 3.45; N, 5.64.

4-((4-Fluorophenyl)iodomethylene)-2-phenyl-4*H*-benzo[*d*][1,3]oxazine (2o). The title compound **2o** was prepared according to the general procedure and purified by column chromatography to obtain a yellow solid (85%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.43 (td, J = 8.8 Hz and 1.6 Hz, 2H), 7.88–7.48 (m, 3H), 7.43–7.22 (m, 4H), 7.13–7.04 (m, 2H), 6.93–6.89 (dt, J = 7.6 Hz and 1.2 Hz, 1H), 6.56 (dd, J = 8.8 Hz and 1.2 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 163.8, 161.3, 155.6, 145.8, 140.5, 137.9, 137.8, 132.0 (d, J = 15.9 Hz), 131.8, 130.8, 130.6, 128.46, 128.45, 126.8, 126.3, 126.1, 116.4 (d, J = 21.9 Hz), 73.5. HRMS (ESI, m/z) for $C_{21}H_{13}FINO$, calcd: 442.0113, found: 442.0110. Anal. calcd for $C_{21}H_{13}FINO$: C, 57.16; H, 2.97; N, 3.17; found: C, 57.19; H, 2.99; N, 3.16.

4-(Diphenylmethylene)-2-(4-nitrophenyl)-4*H*-benzo[*d*][1,3]-oxazine (5a). A mixture of (*Z*)-4-(iodo(phenyl)methylene)-2-(4-nitrophenyl)-4*H*-benzo[*d*][1,3]oxazine (**2d**) (50 mg, 1.0 mmol), $Pd(PPh_3)_4$ (12.33 mg, 10 mol%), Cs_2CO_3 (75.21 mg, 2 equiv.), and phenylboronic acid (15.51 mg, 1.2 equiv.) in acetonitrile–toluene (1 : 1 mL) in a flask under an argon atmosphere was stirred for 24 h at 80 °C. The reaction was monitored by TLC analysis. After the reaction was complete, the mixture was poured into ethyl acetate, filtered and evaporated under vacuum. The crude mixture was carried to the next reaction, crude yield (42.4 mg, 95%).

2-(4-Nitrophenyl)-4-(phenyl(pyridin-3-yl)methylene)-4*H*-benzo-[*d*][1,3]oxazine (5b). The title compound was prepared according to the procedure for **5a** and purified by column chromatography to obtain a red solid **5b** (91%). Mp = 198–200 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.79 (s, 1H), 8.56 (d, J = 4 Hz, 1H), 8.20 (td, J = 9.2 Hz and 2.0 Hz, 2H), 8.02 (td, J = 8.8 Hz and 2.4 Hz, 2H), 7.64–7.61 (m, 1H), 7.40–7.27 (m, 8H), 6.93–6.89 (m, 1H), 6.72 (dd, J = 8.0 Hz and 1.2 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 153.4, 150.6, 149.5, 147.9, 142.3, 140.5, 138.9, 136.9, 136.5, 135.7, 130.7, 130.5, 129.4, 128.6, 128.2, 127.5, 127.2, 126.5, 123.5, 123.1, 121.1, 118.1. HRMS (ESI, m/z) for $C_{26}H_{18}N_3O_3$, calcd: 420.1348, found: 420.1350.

1-(4-Nitrobenzoyl)-2,2-diphenylindolin-3-one (6a). A crude mixture of 4-(diphenylmethylene)-2-(4-nitrophenyl)-4*H*-benzo-[*d*][1,3]oxazine (**5a**) (30 mg, 1.0 mmol) and $FeCl_3$ (1.1 mg, 10 mol%) in dichloromethane–nitromethane (1 : 0.7 mL) in a flask under an argon atmosphere was stirred for 12 h at 60 °C. The reaction was monitored by TLC analysis. The formed product was extracted with ethyl acetate by washing with water and brine. The organic layer was separated and concentrated under reduced pressure. The crude residue obtained was chromatographed over silica gel using an ethyl acetate–hexane mixture as an eluent to obtain the title compound as a white solid **6a** (46%). Mp = 210–212 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.04 (d, J = 8.4 Hz, 2H), 7.79 (dd, J = 7.6 Hz and 0.8 Hz, 1H), 7.57 (t, J = 7.2 Hz, 1H), 7.37–7.25 (m, 14H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 197.9, 152.6, 141.9, 136.9, 136.2, 128.7, 128.5, 128.4, 128.1, 125.7, 125.3, 123.5, 122.7, 117.8. HRMS (ESI, m/z) for $C_{27}H_{18}N_2O_4Na$, calcd: 457.1164, found: 457.1165.

Acknowledgements

We thank the National Science Council of the Republic of China for financial support. We are thankful to Dr Hsing-Yin Chen for performing the DFT calculations.

Notes and references

1 G. Rassu, F. Zanardi, L. Battistini and G. Casiraghi, *Chem. Soc. Rev.*, 2000, **29**, 109–118.
2 P. G. Baraldi, G. Saponaro, A. R. Moorman, R. Romagnoli, D. Preti, S. Baraldi, E. Ruggiero, K. Varani, M. Targa, F. Vincenzi, P. A. Borea and M. A. Tabrizi, *J. Med. Chem.*, 2012, **55**, 6608–6623.
3 R. C. Rizzo, M. U. Blagovic, D. P. Wang, E. K. Watkins, M. B. K. Smith, R. H. Smith, J. Triado-Rives and W. L. Jorgensen, *J. Med. Chem.*, 2002, **45**, 2970–2987.
4 T. S. A. Heugebaert, B. I. Roman and C. V. Stevens, *Chem. Soc. Rev.*, 2012, **41**, 5626–5640.
5 Y. R. Zhang, J. W. Xie, X. J. Huang and W. D. Zhu, *Org. Biomol. Chem.*, 2012, **10**, 6554–6561.
6 W. Li, X. Duan, H. Yan and H. Xin, *Org. Biomol. Chem.*, 2013, **11**, 4546–4550.
7 Y. Sugimoto, T. Otani, S. Oie, K. Wierzba and Y. Yamada, *J. Antibiot.*, 1990, **43**, 417–421.
8 K. Kobayashi, Y. Okamura and H. Konishi, *Synthesis*, 2009, 1494–1498.
9 K. Kobayashi, Y. Okamura, S. Fukamachi and H. Konishi, *Heterocycles*, 2010, **81**, 1253–1259.
10 T. Saito, S. Ogawa, N. Takei, N. Kutsumura and T. Otani, *Org. Lett.*, 2011, **13**, 1098–1101 and references therein.
11 N. T. Patil and Y. Yamamoto, *Chem. Rev.*, 2008, **108**, 3395–3442.
12 M. Costa, N. Della Cà, B. Gabriele, C. Massera, G. Salerno and M. Soliani, *J. Org. Chem.*, 2004, **69**, 2469–2477.
13 T. Ishida, S. Kikuchi, T. Tsubo and T. Yamada, *Org. Lett.*, 2013, **15**, 848–851.
14 S. Cacchi, G. Fabrizi and L. M. Parisi, *Org. Lett.*, 2003, **5**, 3843–3846.
15 A. Palisse and S. F. Kirsch, *Org. Biomol. Chem.*, 2012, **10**, 8041–8047.
16 R. Sanz, A. Martınez, P. G. Garcıa, M. A. F. Rodrıguez, M. A. Rashida and F. Rodrıguez, *Chem. Commun.*, 2010, **46**, 7427–7429.
17 B. Godoi, R. F. Schumacher and G. Zeni, *Chem. Rev.*, 2011, **111**, 2937–2980.
18 A. V. Gulevich, A. S. Dudnik, N. Chernyak and V. Gevorgyan, *Chem. Rev.*, 2013, **113**, 3084–3213.
19 J. K. Vandavasi, W. P. Hu, H. Y. Chen, G. C. Senadi, C. Y. Chen and J. J. Wang, *Org. Lett.*, 2012, **14**, 3134–3137.
20 G. C. Senadi, W. P. Hu, J. S. Hsiao, J. K. Vandavasi, C. Y. Chen and J. J. Wang, *Org. Lett.*, 2012, **14**, 4478–4481.
21 W. C. Lee, H. C. Shen, W. P. Hu, W. S. Lo, C. Murali, J. K. Vandavasi and J. J. Wang, *Adv. Synth.Catal.*, 2012, **354**, 2218–2228 and references therein.
22 D. S. Hamilton and D. A. Nicewicz, *J. Am. Chem. Soc.*, 2012, **134**, 18577–18580.
23 M. S. Jung, W. S. Kim, Y. H. Shin, H. J. Jin, Y. S. Kim and E. J. Kang, *Org. Lett.*, 2012, **14**, 6262–6265.
24 K. Gilmore and I. V. Alabugin, *Chem. Rev.*, 2011, **111**, 6513–6556.
25 S. X. Xu, L. Hao, T. Wang, Z. C. Ding and Z. P. Zhan, *Org. Biomol. Chem.*, 2013, **11**, 294–298.
26 A. Feula, S. S. Dhillon, R. Byravan, M. Sangha, R. Ebanks, M. A. H. Salih, N. Spencer, L. Male, I. Magyary, W. P. Deng, F. Müller and J. S. Fossey, *Org. Biomol. Chem.*, 2013, **11**, 5083–5093.
27 P. N. Wyrembak and A. D. Hamilton, *J. Am. Chem. Soc.*, 2009, **131**, 4566–4567.
28 K. Okuma, N. Matsunaga, N. Nagahora, K. Shiojia and Y. Yokomorib, *Chem. Commun.*, 2011, **47**, 5822–5824.
29 T. Kawasaki, W. Takamiya, N. Okamoto, M. Nagaoka and T. Hirayama, *Tetrahedron Lett.*, 2006, **47**, 5379–5382.
30 Y. Liu and W. W. McWhorter, *J. Org. Chem.*, 2003, **68**, 2618–2622.
31 R. Abonia, P. Cuerbo, J. Castillo, B. Insuasty, J. Quiroga, M. Nogueras and J. Cobo, *Tetrahedron Lett.*, 2008, **49**, 5028–5031.
32 R. R. Schmidt and B. Beitzke, *Chem. Ber.*, 1983, **116**, 2115–2135.
33 J. B. Peng, Y. Qi, A. J. Ma, Y. Q. Tu, F. M. Zhang, S. H. Wang and S. Y. Zhang, *Chem.–Asian J.*, 2013, **8**, 883–887.
34 W. Sun, L. Hong and R. Wang, *Chem.–Eur. J.*, 2011, **17**, 6030–6033.