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Metal-free synthesis of oxazolidine-2,4-diones and 3,3-disubstituted oxindoles *via* the ICl-induced cyclization

Wei Yi,[a] Xing-Xiao Fang,[a] Qing-Yun Liu[a] and Gong-Qing Liu[a]*

Dedication ((optional))

Abstract: A metal-free method for the construction of oxazolidine-2,4-diones and oxindoles was discussed. Using iodine monochloride (ICl) as both the reaction promoter and iodide source, the iodolactonization of N-Boc acrylamides proceeded readily and provided the corresponding iodo oxazolidine-2,4-diones and oxazolidin-2-ones in good isolated yields. The obtained oxazolidine-2,4-diones can be used as key intermediates in the synthesis of toloxatone. When N-alkyl-N-arylacrylamide derivatives were subjected to the same reaction, iodocarbocyclization products 3,3-disubstituted oxindoles were obtained. The obtained oxindoles can be used as key intermediates in the synthesis of the alkaloids (±)-esermethole and (±)-physostigmine.

Introduction

Oxazolidine-2,4-dione moiety is an ubiquitous structural feature in natural products, and it is listed among the most significant structural components of synthetic lead compounds that exhibit various biological activities including anticonvulsant,[1] antidiabetic,[2] antitumor,[3] anti-inflammatory activity[4] and cardiotonic[5] (Figure 1). Moreover, oxazolidine-2,4-dione are also frequently employed as synthons in organic synthesis since they can be further manipulated by various reactions such as hydrolysis to hydroxyamides[6]. Accordingly, over the years, a substantial amount of effort has been devoted to the development of novel methods for the synthesis of these compounds.[7] The most general methods for the preparation of compounds of this class are the condensation of α-hydroxy amides with dialkyl carbonates[8] or phosgene[2b, 9] and α-hydroxy esters with urea[10] or isocyanates[11] (Scheme 1a). However, this method requires preformed α-hydroxy amides or α-hydroxy esters as a substrate which are sometimes difficult to make. Additionally, the cyclizations of acrylic acid or propiolic acid derivatives with CO_2 is also an efficient route for the synthesis of oxazolidine-2,4-diones[12](Scheme 1b). However, transition-metal catalysts are often required to facilitate these reactions due to the thermodynamic and kinetic stability of carbon dioxide,[12e] which involve some drawbacks including their associated cost, toxicity as well as the issue of metal impurities. Finally, Li, Lu and coworkers prepared fluorinated oxazolidine-2,4-diones *via* an oxy-palladation and formal Wagner−Meerwein rearrangement cascade reaction[13] (Scheme 1c).

Despite these advances, general methods for the preparation of various oxazolidine-2,4-dione are still limited. Furthermore, a chromatographic step was often required for the removal of excess amount of reactants and/or catalysts in most cases. These drawbacks more or less limited the application of these methods in the preparation of structurally diverse oxazolidine-2,4-dione compounds. Given the great importance of electrophilic cyclization, development of a simple, practical, scalable electrophilic cyclization for the synthesis of the oxazolidine-2,4-dione framework as well as the application of these materials in the synthesis of bioactive compound seemed is very interesting to us. Herein, we report the ICl-mediated iodolactonization of unsaturated carbamates to prepare iodo-substituted oxazolidine-2,4-diones and oxazolidin-2-ones as a continuation of our investigation of the halocyclization of unfunctionalized olefins[14] (Scheme 1d).

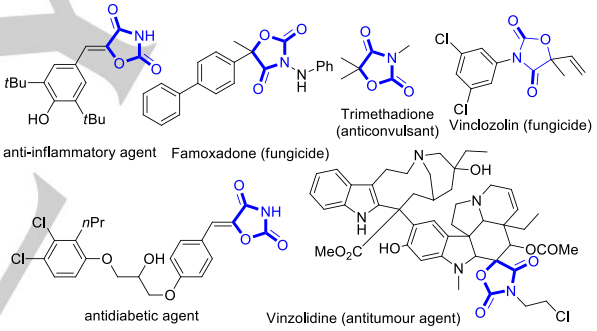
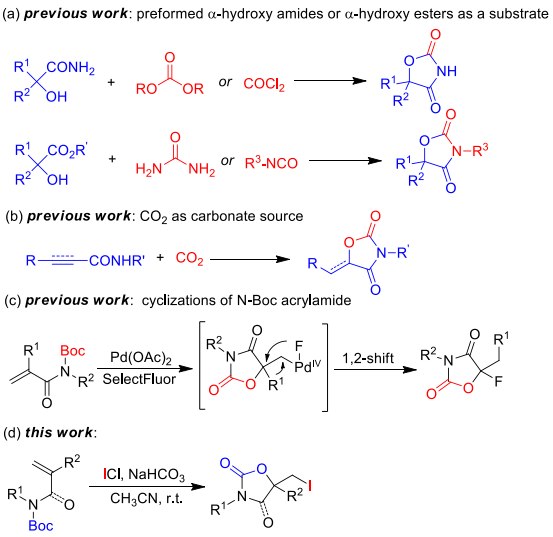


Figure 1. Examples of bioactive oxazolidine-2,4-dione-containing compounds.



Scheme 1. Synthesis of oxazolidine-2,4-diones.

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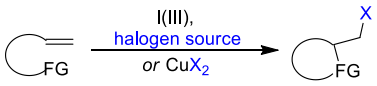
Results and Discussion

The iodocyclization of acrylamides is a direct and efficient method for accessing oxazolidine-2,4-dione derivatives due to their low cost and step economy (Scheme 1d). Moreover, the resulting iodinated products could be easily converted to many different oxazolidine-2,4-dione derivatives upon conventional nucleophilic substitution reactions, and this method thus offer an effective route to a variety of biologically active structures.

Recently, we have shown that intramolecular halocyclizations of unfunctionalized olefins could be realized by using hypervalent iodine[14a, 14b] or Cu(II)[14c, 14d] as the reaction promoters (Scheme 2). Given the importance of oxazolidine-2,4-diones, we would like to adopt the halocyclization of acrylamides to prepare these compounds as an extension of our ongoing work toward the cyclization of olefins (Scheme 1d).

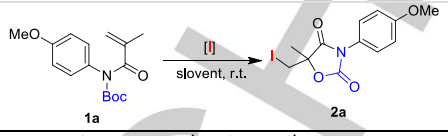


FG = NHR, OH, COOH

Scheme 2. Intramolecular halocyclizations.

With this in mind, we initially tested our previously reported protocols that could promote the intramolecular halocyclization of olefins. To our delight, (diacetoxyiodo)benzene in combination with potassium iodide[14a] or trimethylsilyl iodide[14b] was also effective for promoting the desired iodolactonization of N-Boc acrylamide **1a**, which normally are ineffective in similar transformations[15] (Table 1, entries 1−2). The *O*-cyclization product **2a** arose from nucleophilic attack of the carbamate carbonyl group on the double bond,[16] and the structure of this compound was established by two-dimensional (2D) NMR experiments and HRMS experiments. Molecular iodine and N-iodosuccinimide (NIS), which are commonly used in iodocyclization reactions,[17] could also be used for iodolactonization of **1a**, but the yields were generally lower than $PhI(OAc)_2$-induced reactions (entries 3−4). To our surprise, the reaction could be completed in 1 hour when iodine monochloride (ICl) was employed as the reaction promoter (entry 5). More importantly, we found that the desired product can also be isolated conveniently by simple extraction after quenching with a saturated aqueous $Na_2S_2O_3$ solution and chromatographic purification can be avoided. Encouraged by these preliminary results, reactions in different solvents were then carried out to find suitable reaction conditions (entries 6−9). Reactions in benzene or acetonitrile gave promising results. Acetonitrile was finally chosen as the reaction medium for further studies due to its low toxicity. Interestingly, products resulting from the participation of CH_3CN were not observed under the current conditions.[18] Finally, the investigation of the effect of base showed that the addition of sodium bicarbonate improved the yield of the reaction (entry 10). Other bases, such as sodium carbonate and triethylamine, were much less effective than sodium bicarbonate (entries 11−12).

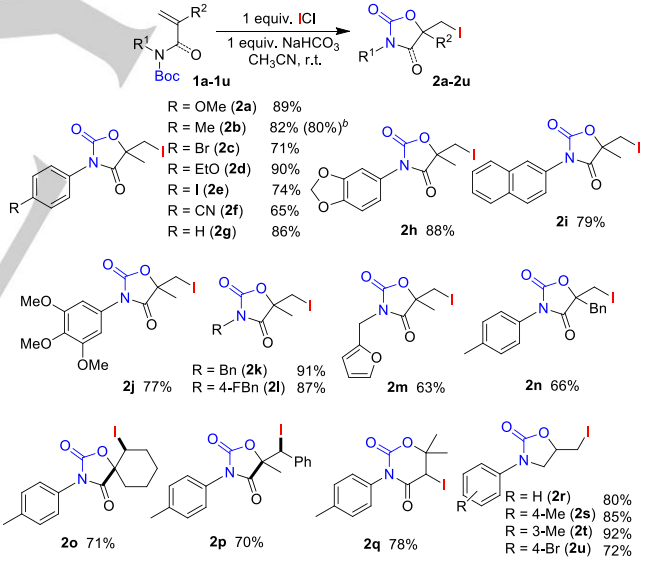
Table 1. Optimization of the conditions for the iodocarbocyclization.[a]



entry	reagent	solvent	time (h)	base	yield (%)[b]
1	$PhI(OAc)_2$, KI	CH_2Cl_2	24 h	-	79
2	$PhI(OAc)_2$, TMSI	CH_2Cl_2	24 h	-	80
3	I_2	CH_2Cl_2	24 h	-	70
4	NIS	CH_2Cl_2	24 h	-	62
5	ICl	CH_2Cl_2	1 h	-	84
6	ICl	hexane	1 h	-	75
7	ICl	acetone	1 h		60
8	ICl	benzene	1 h		86
'9	ICl	CH_3CN	1 h		85
10	ICl	CH_3CN	1 h	$NaHCO_3$	89
11	ICl	CH_3CN	1 h	Na_2CO_3	83
12	ICl	CH_3CN	1 h	Et_3N	N.R.

[a] The reaction was carried out with 0.5 mmol of **1a** in 20 mL of solvent, [b] isolated yield.

Scheme 3. Scope on cyclization of carbamate [a]

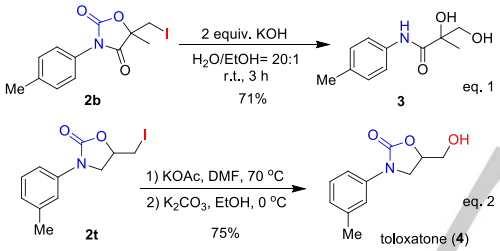


[a] The reaction was carried out with 0.5 mmol of substrate, 0.5 mmol of ICl, and 0.5 mmol of $NaHCO_3$ in 20 mL of CH_3CN. [b] 10 mmol scale

With the optimized conditions in hand, the substrate scope was studied, and the results are presented in Scheme 3. As shown in Scheme 3, good to excellent yields were obtained from a variety of N-Boc protected acrylamides (**2a**-**2q**). The reaction could also be scaled up to 10 mmol to give 2.76 g (80%) of product **2b**. It is remarkable that no additional iodination occured at furan moiety in **2m** under the current conditions. α, β-Substituted N-Boc acrylamides were also

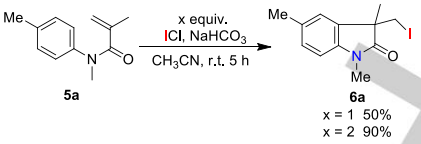
subjected to the process affording one single diastereomer in good yield (**2o** and **2p**). The relative configuration in **2o** and **2p** was assigned to *trans*, as expected for a cyclization *via* an intermediate iodonium ion. 1,1-Disubstituted olefin can also undergo cyclization under identical condition, but resulted exclusively in the formation of the six-membered ring product 1,3-oxazinane-2,4-dione **2q**. Moreover, allyl(phenyl)carbamates could all be cyclized under the optimal conditions, giving oxazolidinones **2r−2u** in satisfactory isolated yields.

To test the synthetic utility of current reaction, functional group transformations of obtained products were also pursued (Scheme 4). For example, the oxazolidinedione moiety in **2b** could be easily hydrolyzed under alkaline conditions. Simultaneously, iodine atom in **2b** was replaced by hydroxyl group, giving α-hydroxyamide **3** in good yield (Scheme4, eq. 1). In addition, the developed methodology was successfully applied to the synthesis of toloxatone (Humoryl®), an antidepressant medicine.[19] The obtained **2t** was treated with KOAc followed by saponification with K_2CO_3 in EtOH, giving toloxatone (**4**) in 75% overall yield over two steps (Scheme 4, eq. 2). This synthetic route has the advantage of being higher yielding compared to that reported in the literature.[20]



Scheme 4. Derivatization of obtained products

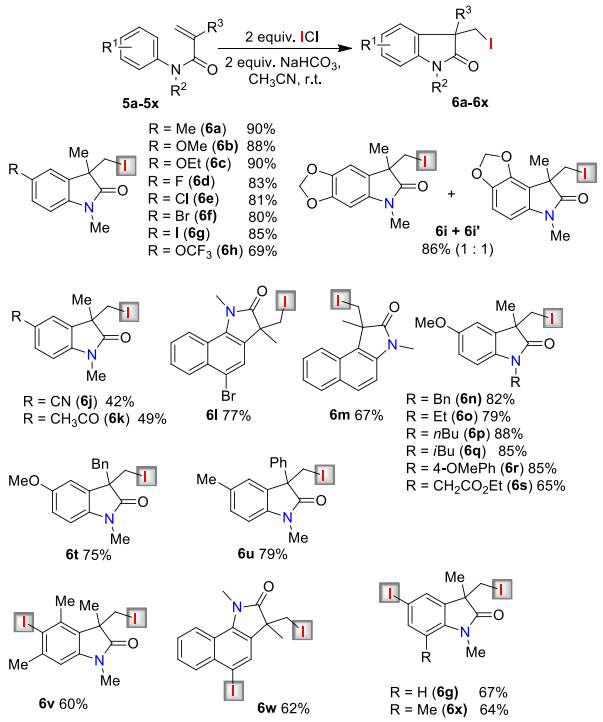
To further extend the application scope of ICl-promoted iodocyclization reactions, we next examined the acrylamide bearing different groups on the nitrogen atom. N-Acetyl or N-tosyl protected acrylamide failed to react, probably due to poor electron density. However, when N-methylacrylamide **5a** was subjected to reaction under the standard conditions, an iodocarbocyclization product oxindole **6a** was obtained as a sole product, albeit at a lower yield (Scheme 5), which was not consistent with the observations made by Zhu that the iodocarbocyclization of methacrylamide did not occur when ICl was used[21]. This can be attributed to the use of different solvents. Moreover, additional iodination of the benzene ring, which was frequently encountered in this process,[15a, 21] was not observed in the current system. By increasing the amount of ICl to 2.0 equiv., the isolated yield of **6a** increased to 90%. Compared with above iodolactonization, 2 equiv. ICl and long reaction times were essential to achieve satisfactory yields for current cases. This may be attributed to the lower nucleophilic character of the carbon atom than oxygen atom.



Scheme 5. Cyclization of N-methylacrylamide **5a**

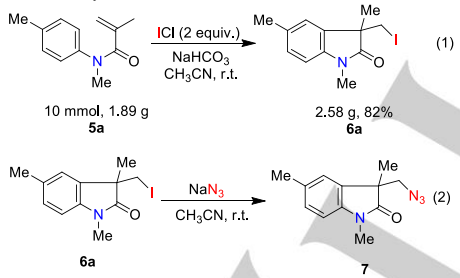
Oxindoles have been identified as having diverse properties such as antitumor,[22] anti-HIV,[23] antimalarial,[24] anti-inflammatory,[25] antibacterial,[26] antioxidant,[27] anti-Alzheimer's,[28] spermicidal,[29] kinase inhibitory,[30] and analgesic activity.[31] Moreover, oxindoles are important building blocks for the construction of other nitrogen-containing ring systems.[32] Thus, structurally diverse oxindole compounds were prepared using the developed method, and the results are summarized in Scheme 6. As shown in Scheme 6, the iodocarbocyclization of N-arylacrylamides proceeded readily and gave rise to the corresponding oxindole products in good isolated yields. The presence of an electron-donating group or a halide at the *para*-position of the anilide did not significantly influence the reaction outcome, and no additional iodination of the aromatic ring was observed in these cases (**6a−6h**). As expected, a 3,4-methylenedioxy-substituted anilide gave a mixture of two regioisomers (**6i**/**6i'**) in a 1.1:1 ratio. The anilides bearing a cyano or an acetyl moiety gave significantly lower yields probably due to the low reactivity of the substrate caused by the strong electron-withdrawing effects of the substituents (**6j** and **6k**). Naphthalene compounds worked well in the current reaction system, and the corresponding oxindoles were obtained in good yields (**6l** and **6m**). Furthermore, different alkyl, phenyl or benzyl substituents on the nitrogen atom had little impact on the course of the reaction (**6n−6s**). It is worth mentioning that the benzyl residue did not participate in the cyclization as none of the corresponding 1,2-dihydroisoquinolin-3(4*H*)-one was observed. Substrates with different substituents at the α-position of the Michael-acceptor unit were also investigated. Benzyl and phenyl groups at the α-position of the acrylamide were well-tolerated and afforded the corresponding iodo oxindoles in 75% and 79% yields, respectively (**6t** and **6u**). Again, no iodination of the electron rich-aromatic rings in **6t** and **6u** was detected. Whereas oxindoles with iodo-substitution of the aromatic ring were obtained in the case of acrylamides lacking a *para* substituent on the anilide (**6v−6x**). This might be attributed to the directing effect of the amino substituent, which caused the other positions on the phenyl ring to be less reactive than the C5 position.

Scheme 6. Scope of the iodocarbocyclization reaction. [a]



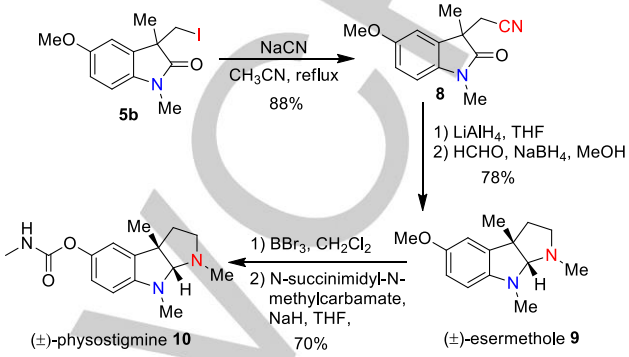
[a] The reaction was carried out with 0.5 mmol of substrate, 1.0 mmol of ICl, and 1.0 mmol of $NaHCO_3$ in 20 mL of CH_3CN, 5 h

The scalability of the current protocol was demonstrated by the gram-scale synthesis of oxindole **6a**. Iodocarbocyclization of N-arylacrylamide **5a** was carried out on a 10-mmol scale, and product **6a** was obtained in 82% yield after recrystallization (Scheme 7, eq. 1). Substitution of the exocyclic iodine atom in **6a** by sodium azide delivered compound **7** (Scheme 7, eq. 2), which could be converted to a potential antidepressant agent after simple derivatization.[33]



Scheme 7. Gram-scale iodocarbocyclization and derivatization of **5a**

To further highlight the utility of the developed methodology, we completed the total synthesis of the acetylcholinesterase inhibitor physostigmine, which was isolated from the seeds of the African Calabar bean *Physostigma Venenosum*.[34] The iodine atom in oxindole **5b** could be replaced by sodium cyanide, providing product **8** in 88% yield (Scheme 8). Compound **8** was converted into the natural product (±)-esermethole (**9**) by reductive cyclization, followed by N-methylation. Finally, using a slightly modified version of the conditions reported by Zhu,[35] compound **9** was transformed in two steps to (±)-physostigmine (**10**) (70% yield over two steps). Using this short and efficient route, the syntheses of (±)-esermethole and (±)-physostigmine were achieved in only three steps and 69% overall yield and five steps and 48% overall yield, respectively.



Scheme 8. Total synthesis of (±)-physostigmine

Conclusions

In summary, we have developed a metal-free method for the preparation of oxazolidine-2,4-diones and oxindole derivatives. Using iodine monochloride as both the reaction promoter and iodide source, oxazolidine-2,4-diones and 3-iodomethyloxindoles could be obtained in good isolated yields at ambient temperature without special procedures. The reaction could be carried out on a gram-scale, and the iodide substituent could be easily converted to other functional groups *via* conventional methods. The obtained products can be used as key intermediates in syntheses of bioactive compound such as toloxatone, (±)-esermethole and (±)-physostigmine. The good isolated yields, mild conditions, and operational simplicity make the current reaction an attractive method for the syntheses of a variety of medicinally and agrochemically relevant compounds.

Experimental Section

General Experimental Information. All reactions requiring the exclusion of air and/or moisture were conducted in flame-dried glassware under an argon atmosphere. Solvents were dried and distilled prior to use. Acetonitrile was dried over 3Å molecular sieves and distilled under an argon atmosphere. Cyclohexane, ethyl acetate and petroleum ether were purchased in technical quality and were purified by distillation. All other chemicals were purchased from commercial suppliers and used without prior purification unless otherwise stated. Flash column chromatography was performed on silica of 25−40 μm particle size. NMR spectra were recorded on 400 MHz spectrometers using standard pulse sequences. Chemical shifts are expressed in ppm relative to tetramethylsilane referenced to the residual solvent signals ($CDCl_3$: ^1H, δ = 7.26 ppm; ^{13}C, δ = 77.16 ppm).

HRMS–ESI was performed on a Q-TOF instrument with a dual source and a suitable external calibrant. Thin-layer chromatography (TLC) was carried out on 0.25 mm silica gel plates with a fluorescence indicator. Melting points were measured on an electrothermal apparatus with a digital thermometer. Substrates **1a**-**1u** and **5a**-**5x** were prepared according to the literature.[13, 36]

General procedure for the synthesis of oxazolidinediones: To a solution of N-Boc acrylamide (0.5 mmol, 1.0 equiv.) in acetonitrile (20 mL) were added ICl (0.5 mmol, 1.0 equiv.) and $NaHCO_3$ (0.5 mmol, 1.0 equiv.). The reaction mixture was stirred at room temperature until complete disappearance of the starting material as shown by TLC (usually 1-2 h). The reaction was next quenched with a saturated aqueous $Na_2S_2O_3$ solution and extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried and concentrated to give a crude residue, which was purified by flash column chromatography.

5-(Iodomethyl)-3-(4-methoxyphenyl)-5-methyloxazolidine-2,4-dione (**2a**). Compound **2a** was prepared according to the general procedure and isolated as a white solid (161 mg, 89% yield) after flash chromatography (petroleum ether/ethyl acetate = 10/1); mp = 129–131 °C. ^{1}H NMR, COSY (400 MHz, $CDCl_3$): δ/ppm =7.37 (d, *J* = 8.8 Hz, 2H, Ar-H2,6), 7.01(d, *J* = 8.8 Hz, 2H, Ar-H3,5), 3.85(s, 3H, -OMe), 3.69(d, *J* = 11.3 Hz, 1H, -$CH_aC\mathit{H}_b$I), 3.54(d, *J* = 11.3 Hz, 1H, -$C\mathit{H}_aCH_b$I), 1.85(s, 3H, -CH3). ^{13}C NMR, HSQC, HMBC (100 MHz, $CDCl_3$): δ/ppm =172.7(-NCO-), 160.0 (Ar-C4), 153.1(-NCO_2-), 127.2(Ar-C2,6), 123.5(Ar-C1), 114.7 (Ar-C3, 5), 83.2(-CO_2C-), 55.6(-OCH_3), 21.6 (-CH_3), 6.4(-CH_2I). IR (KBr): 3050, 2928, 1714, 1620, 1375, 1063, 795, 656, 648 cm^{-1}. ESI-HRMS: calc. for $[C_{12}H_{12}INO_4+H]^+$: m/z = 361.9889, found: 361.9879.

5-(Iodomethyl)-5-methyl-3-(*p*-tolyl)oxazolidine-2,4-dione (2b). Compound **2b** was prepared according to the general procedure and isolated as a yellow solid (141 mg, 82%) after flash chromatography (petroleum ether/ethyl acetate = 15/1); mp = 106–108 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ/ppm=7.32 (d, *J* = 8.6 Hz, 2H), 7.29 (d, *J* = 8.6 Hz, 2H), 3.67 (d, *J* = 11.3 Hz, 1H), 3.51 (d, *J* = 11.3 Hz, 1H), 2.39 (s, 3H), 1.83 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ/ppm= 171.5, 151.9, 138.4, 129.0, 127.0, 124.6, 82.1, 20.7, 20.2, 5.4. IR (KBr): 3021, 2982, 1720, 1649, 1500, 1218, 1021, 875, 737, 653 cm^{-1}. ESI-HRMS: calc. for $[C_{12}H_{12}INO_3+H]^+$: m/z = 345.9940, found: 345.9933.

3-(4-Bromophenyl)-5-(iodomethyl)-5-methyloxazolidine-2,4-dione (2c). Compound **2c** was prepared according to the general procedure and isolated as a brown solid (146 mg, 71% yield) after flash chromatography (petroleum ether/ethyl acetate = 15/1); mp = 135–136 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ/ppm= 7.63 (d, *J* = 8.7 Hz, 2H), 7.37 (d, *J* = 8.7 Hz, 2H), 3.68 (d, *J* = 11.3 Hz, 1H), 3.52 (d, *J* = 11.3 Hz, 1H), 1.84 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ/ppm= 172.2, 152.3, 132.6, 129.7, 127.1, 123.1, 83.3, 21.8, 6.1. IR (KBr): 3045, 2010, 1701, 1649, 1502, 1068, 873, 653 cm^{-1}. ESI-HRMS: calc. for $[C_{11}H_9BrINO_3+H]^+$: m/z = 409.8889, found: 409.8888.

3-(4-Ethoxyphenyl)-5-(iodomethyl)-5-methyloxazolidine-2,4-dione (2d). Compound **2d** was prepared according to the general procedure and isolated as a light red solid (169 mg, 90% yield) after flash chromatography (petroleum ether/ethyl acetate = 15/1); mp = 110–112 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ/ppm= 7.33 (d, *J* = 9.0 Hz, 2H), 6.98 (d, *J* = 9.0 Hz, 2H), 4.06 (q, *J* = 7.0 Hz, 2H), 3.68 (d, *J* = 11.2 Hz, 1H), 3.52 (d, *J* = 11.2 Hz, 1H), 1.84 (s, 3H), 1.43 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ/ppm= 172.7, 159.4, 153.1, 127.1, 123.0, 115.2, 83.1, 63.8, 21.8, 14.7, 6.3. IR (KBr): 3053, 3002, 1700, 1666, 1506, 1006, 845, 814, 701 cm^{-1}. ESI-HRMS: calc. for $[C_{13}H_{14}INO_4+H]^+$: m/z = 376.0046, found: 376.0043.

5-(Iodomethyl)-3-(4-iodophenyl)-5-methyloxazolidine-2,4-dione (2e). Compound **2e** was prepared according to the general procedure and isolated as a brown solid (169 mg, 74% yield) after flash chromatography (petroleum ether/ethyl acetate = 12/1); mp = 127–128 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ/ppm= 7.83 (d, *J* = 8.6 Hz, 2H), 7.23 (d, *J* = 8.6 Hz, 2H), 3.67 (d, *J* = 11.3 Hz, 1H), 3.52 (d, *J* = 11.3 Hz, 1H), 1.84 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ/ppm= 171.1, 151.2, 137.6, 129.4, 126.2, 93.6, 82.3, 20.7, 5.1. IR (KBr): 3010, 2956, 1705, 1628, 1503, 1056, 827, 679, 521 cm^{-1}. ESI-HRMS: calc. for $[C_{11}H_9I_2NO_3+H]^+$: m/z = 457.8750, found: 457.8741.

4-(5-(Iodomethyl)-5-methyl-2,4-dioxooxazolidin-3-yl)benzonitrile (2f). Compound **2f** was prepared according to the general procedure and isolated as a yellow solid (116 mg, 65% yield) after flash chromatography (petroleum ether/ethyl acetate = 12/1); mp = 156–158 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ/ppm= 7.81 (d, *J* = 8.7 Hz, 2H), 7.70 (d, *J* = 8.7 Hz, 2H), 3.69 (d, *J* = 11.3 Hz, 1H), 3.54 (d, *J* = 11.3 Hz, 1H), 1.87 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ/ppm= 170.8, 150.7, 133.6, 132.2, 124.7, 116.7, 111.7, 82.5, 20.7, 4.9. IR (KBr): 3011, 2979, 1703, 1640, 1498, 1037, 820, 710, 547 cm^{-1}. ESI-HRMS: calc. for $[C_{12}H_9IN_2O_3+Na]^+$: m/z = 378.9556, found: 378.9551.

5-(Iodomethyl)-5-methyl-3-phenyloxazolidine-2,4-dione (2g). Compound **2g** was prepared according to the general procedure and isolated as a white solid (142 mg, 86% yield) after flash chromatography (petroleum ether/ethyl acetate = 15/1); mp = 85–88 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ/ppm= 7.45 – 7.30 (m, 5H), 3.61 (d, *J* = 11.3 Hz, 1H), 3.45 (d, *J* = 11.3 Hz, 1H), 1.76 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ/ppm= 172.5, 152.8, 130.7, 129.4, 129.2, 125.7, 83.2, 21.8, 6.3. IR (KBr): 3013, 3000, 2878, 1700, 1604, 1499, 1099, 800, 640 cm^{-1}. ESI-HRMS: calc. for $[C_{11}H_{10}INO_3+H]^+$: m/z = 331.9784, found: 331.9777.

3-(Benzo[d][1,3]dioxol-5-yl)-5-(iodomethyl)-5-methyloxazolidine-2,4-dione (2h). Compound **2h** was prepared according to the general procedure and isolated as a yellow solid (165 mg, 88% yield) after flash chromatography (petroleum ether/ethyl acetate = 8/1); mp = 96–97 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ/ppm= 6.89 (s, 3H), 6.02 (s, 2H), 3.67 (d, *J* = 11.3 Hz, 1H), 3.51 (d, *J* = 11.3 Hz, 1H), 1.82 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ/ppm= 172.6, 152.9, 148.3, 148.2, 124.0, 120.0, 108.5, 107.1, 102.1, 83.2, 21.7, 6.4. IR (KBr): 3012, 2947, 2793, 1712, 1620, 1501, 1332, 1037, 817, 610, 573 cm^{-1}. ESI-HRMS: calc. for $[C_{12}H_{10}INO_5+H]^+$: m/z = 375.9684, found: 375.9678.

5-(Iodomethyl)-5-methyl-3-(naphthalen-2-yl)oxazolidine-2,4-dione (2i). Compound **2i** was prepared according to the general procedure and isolated as a yellow solid (150 mg, 79% yield) after flash chromatography (petroleum ether/ethyl acetate = 10/1); mp = 135–136 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ/ppm=

7.88 – 7.83 (m, 2H), 7.78 (dd, *J* = 5.6, 3.2 Hz, 2H), 7.44 (dt, *J* = 8.0, 2.1 Hz, 3H), 3.61 (d, *J* = 11.3 Hz, 1H), 3.44 (d, *J* = 11.3 Hz, 1H), 1.76 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ/ppm= 171.6, 151.8, 132.0, 131.9, 128.4, 127.2, 127.0, 126.8, 126.2, 125.9, 124.0, 121.8, 82.2, 20.7, 5.3. IR (KBr): 3023, 3000, 2901, 1714, 1625, 1504, 1138, 814, 711 cm^{-1}. ESI-HRMS: calc. for $[C_{15}H_{12}INO_3+H]^+$: m/z = 381.9940, found: 381.9932.

5-(Iodomethyl)-5-methyl-3-(3,4,5-trimethoxyphenyl)oxazolidine-2,4-dione (2j). Compound **2j** was prepared according to the general procedure and isolated as a brown solid (162 mg, 77% yield) after flash chromatography (petroleum ether/ethyl acetate = 5/1); mp = 93–95 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ/ppm= 6.64 (s, 2H), 3.86 (s, 6H), 3.85 (s, 3H), 3.68 (d, *J* = 11.3 Hz, 1H), 3.52 (d, *J* = 11.3 Hz, 1H), 1.84 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ/ppm= 171.5, 152.6, 151.7, 137.6, 125.1, 102.5, 82.1, 59.9, 55.3, 20.8, 5.4. IR (KBr): 3014, 2886, 1696, 1590, 1484, 1140, 1007, 814, 677, 532 cm^{-1}. ESI-HRMS: calc. for $[C_{14}H_{16}INO_6+H]^+$: m/z = 422.0101, found: 422.0094.

3-Benzyl-5-(iodomethyl)-5-methyloxazolidine-2,4-dione (2k). Compound **2k** was prepared according to the general procedure and isolated as a white solid (157 mg, 91% yield) after flash chromatography (petroleum ether/ethyl acetate = 6/1); mp = 85–87 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ/ppm= 7.45 – 7.41 (m, 2H), 7.36 – 7.31 (m, 3H), 4.70 (s, 2H), 3.53 (d, *J* = 11.3 Hz, 1H), 3.41 (d, *J* = 11.3 Hz, 1H), 1.70 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ/ppm= 173.1, 153.8, 134.4, 129.0, 128.8, 128.5, 83.4, 44.1, 21.9, 5.4. IR (KBr): 3029, 2999, 1700, 1627, 1499, 1402, 1076, 937, 826, 629, 573 cm^{-1}. ESI-HRMS: calc. for $[C_{12}H_{12}INO_3+H]^+$: m/z = 345.9940, found: 345.9938.

3-(4-Fluorobenzyl)-5-(iodomethyl)-5-methyloxazolidine-2,4-dione (2l). Compound **2l** was prepared according to the general procedure and isolated as a white solid (158 mg, 87% yield) after flash chromatography (petroleum ether/ethyl acetate = 15/1); mp = 81–82 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ/ppm= 7.41 (dd, *J* = 8.6, 5.3 Hz, 2H), 7.00 (t, *J* = 8.7 Hz, 2H), 4.67 (d, *J* = 14.5 Hz, 1H), 4.62 (d, *J* = 14.5 Hz, 1H), 3.52 (d, *J* = 11.3 Hz, 1H), 3.40 (d, *J* = 11.3 Hz, 1H), 1.69 (s, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ/ppm=113.1. ^{13}C NMR (100 MHz, $CDCl_3$): δ/ppm= 172.1, 161.7 (d, $J_{C\text{-}F}$ = 247.4 Hz), 152.7, 130.1 (d, $J_{C\text{-}F}$ = 8.3 Hz), 129. 2 (d, $J_{C\text{-}F}$ = 3.3 Hz), 114.7 (d, $J_{C\text{-}F}$ = 21.6 Hz), 82.4, 42.3, 20.8, 4.5. IR (KBr): 3057, 2745, 1701, 1593, 1499, 1400, 1283, 1130, 814, 726 504 cm^{-1}. ESI-HRMS: calc. for $[C_{12}H_{11}FINO_3+Na]^+$: m/z = 385.9665, found: 385.9662.

3-(Furan-2-ylmethyl)-5-(iodomethyl)-5-methyloxazolidine-2,4-dione (2m). Compound **2m** was prepared according to the general procedure and isolated as an oil (106 mg, 63% yield) after flash chromatography (petroleum ether/ethyl acetate = 6/1). ^{1}H NMR (400 MHz, $CDCl_3$): δ/ppm= 7.35 (dd, *J* = 1.8, 0.7 Hz, 1H), 6.42 (dd, *J* = 3.2, 0.7 Hz, 1H), 6.31 (dd, *J* = 3.2, 1.8 Hz, 1H), 4.71 (s, 2H), 3.52 (d, *J* = 11.3 Hz, 1H), 3.41 (d, *J* = 11.3 Hz, 1H), 1.71 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ/ppm= 171.6, 152.3, 146.2, 141.9, 109.6, 109.1, 82.5, 35.6, 20.8, 4.3. IR (KBr): 2998, 2768, 1701, 1614, 1499, 1342, 1283, 1173, 917, 824, 737, 640, 544 cm^{-1}. ESI-HRMS: calc. for $[C_{10}H_{10}INO_4+H]^+$: m/z = 335.9733, found: 335.9728.

5-Benzyl-5-(iodomethyl)-3-(*p*-tolyl)oxazolidine-2,4-dione (2n). Compound **2n** was prepared according to the general procedure and isolated as an oil (139 mg, 66% yield) after flash chromatography (petroleum ether/ethyl acetate = 15/1). ^{1}H NMR (400 MHz, $CDCl_3$): δ/ppm= 7.27 – 7.21 (m, 3H), 7.17 (dd, *J* = 6.4, 3.2 Hz, 2H), 7.08 (d, *J* = 8.3 Hz, 2H), 6.67 (d, *J* = 8.3 Hz, 2H), 3.70 (d, *J* = 11.3 Hz, 1H), 3.50 (d, *J* = 11.3 Hz, 1H), 3.25 (d, *J* = 13.9 Hz, 1H), 3.19 (d, *J* = 13.9 Hz, 1H), 2.24 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ/ppm= 170.5, 151.8, 138.4, 131.3, 129.1, 128.9, 127.8, 127.2, 126.5, 124.7, 85.4, 40.4, 20.2, 3.8. IR (KBr): 3011, 3009, 2927, 1701, 1625, 1456, 1329, 1257, 1152, 809, 678, 632, 506 cm^{-1}. ESI-HRMS: calc. for $[C_{18}H_{16}INO_3+H]^+$: m/z = 422.0253, found: 422.0250.

6-Iodo-3-(*p*-tolyl)-1-oxa-3-azaspiro[4.5]decane-2,4-dione (2o). Compound **2o** was prepared according to the general procedure and isolated as a white solid (137 mg, 71% yield) after flash chromatography (petroleum ether/ethyl acetate = 50/1); mp = 135–137 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ/ppm= 7.33 (d, *J* = 8.4 Hz, 2H), 7.29 (d, *J* = 8.4 Hz, 2H), 4.28 (dd, *J* = 13.0, 4.7 Hz, 1H), 2.71 (dd, *J* = 13.3, 3.9 Hz, 1H), 2.49 (dd, *J* = 13.7, 3.4 Hz, 1H), 2.40 (s, 3H), 2.11 (dt, *J* = 13.2, 3.7 Hz, 1H), 1.99 (dd, *J* = 13.2, 3.9 Hz, 1H), 1.91 (d, *J* = 17.3 Hz, 1H), 1.72 (dd, *J* = 13.6, 2.6 Hz, 1H), 1.42 (dt, *J* = 13.6, 3.7 Hz, 1H), 1.27 (d, *J* = 11.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ/ppm= 171.9, 153.0, 139.3, 130.0, 128.1, 125.8, 85.1, 35.8, 33.8, 29.9, 27.4, 21.4, 21.2. IR (KBr): 3017, 2976, 1704, 1615, 1447, 1400, 1253, 1009, 827, 736, 623 cm^{-1}. ESI-HRMS: calc. for $[C_{15}H_{16}INO_3+H]^+$: m/z = 386.0253, found: 386.0250.

5-(Iodo(phenyl)methyl)-5-methyl-3-(*p*-tolyl)oxazolidine-2,4-dione (2p). Compound **2p** was prepared according to the general procedure and isolated as an oil (147 mg, 70% yield) after flash chromatography (petroleum ether/ethyl acetate = 30/1). ^{1}H NMR (400 MHz, $CDCl_3$): δ/ppm= 7.43 (dd, *J* = 6.6, 2.8 Hz, 2H), 7.23 (dd, *J* = 4.9, 1.8 Hz, 3H), 7.03 (d, *J* = 8.1 Hz, 2H), 6.49 (d, *J* = 8.1 Hz, 2H), 5.26 (s, 1H), 2.22 (s, 3H), 1.82 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ/ppm= 168.7, 151.6, 138.3, 136.1, 128.9, 128.4, 128.3, 127.8, 126.5, 124.5, 86.5, 31.6, 24.2, 20.1. IR (KBr): 3018, 2993, 1721, 1623, 1487, 1321, 1276, 1101, 973, 873, 757, 637 cm^{-1}. ESI-HRMS: calc. for $[C_{18}H_{16}INO_3+H]^+$: m/z = 422.0253, found: 422.0249.

5-Iodo-6,6-dimethyl-3-(*p*-tolyl)-1,3-oxazinane-2,4-dione (2q). Compound **2q** was prepared according to the general procedure and isolated as a yellow solid (140 mg, 78% yield) after flash chromatography (petroleum ether/ethyl acetate = 6/1); mp = 163–164 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ/ppm= 7.29 (d, *J* = 8.3 Hz, 2H), 7.08 (d, *J* = 8.3 Hz, 2H), 4.77 (s, 1H), 2.40 (s, 3H), 1.82 (s, 3H), 1.71 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ/ppm= 167.1, 149.6, 139.3, 131.7, 130.2, 127.3, 78.1, 29.7, 28.4, 22.6, 21.3. IR (KBr): 3060, 3001, 2928, 1729, 1635, 1489, 1341, 1306, 1230, 914, 873, 733 cm^{-1}. ESI-HRMS: calc. for $[C_{13}H_{14}INO_3+ H]^+$: m/z = 360.0097, found: 360.0089.

5-(Iodomethyl)-3-phenyloxazolidin-2-one (2r). Compound **2r** was prepared according to the general procedure and isolated as a yellow solid (121 mg, 80% yield) after flash chromatography (petroleum ether/ethyl acetate = 6/1); mp = 92–94 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ/ppm= 7.53 – 7.50 (m, 2H), 7.39 – 7.34 (m, 2H), 7.14 (t, *J* = 7.4 Hz, 1H), 4.72 – 4.63 (m, 1H), 4.14 (t, *J* = 8.9

Hz, 1H), 3.76 (dd, *J* = 9.2, 6.1 Hz, 1H), 3.43 (dd, *J* = 10.4, 4.1 Hz, 1H), 3.34 (dd, *J* = 10.4, 7.9 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ/ppm= 153.0, 136.8, 128.1, 123.3, 117.4, 70.2, 49.9, 5.4. The data are in accordance with the literature.[16c]

5-(Iodomethyl)-3-(*p*-tolyl)oxazolidin-2-one (2s). Compound **2s** was prepared according to the general procedure and isolated as a yellow solid (135 mg, 85% yield) after flash chromatography (petroleum ether/ethyl acetate = 6/1); mp = 101–102 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ/ppm= 7.42 (d, *J* = 8.4 Hz, 2H), 7.19 (d, *J* = 8.4 Hz, 2H), 4.77 – 4.67 (m, 1H), 4.16 (t, *J* = 8.9 Hz, 1H), 3.78 (dd, *J* = 9.2, 6.1 Hz, 1H), 3.48 (dd, *J* = 10.3, 3.9 Hz, 1H), 3.35 (dd, *J* = 10.2, 8.6 Hz, 1H), 2.33 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ/ppm= 154.1, 135.3, 134.2, 129.7, 118.6, 71.3, 51.2, 20.8, 6.1. IR (KBr): 3011, 2967, 1695, 1506, 1416, 1305, 1039, 779, 590 cm^{-1}. ESI-HRMS: calc. for $[C_{11}H_{12}INO_2+H]^+$: m/z = 317.9991, found: 317.9987.

5-(Iodomethyl)-3-(*m*-tolyl)oxazolidin-2-one (2t). Compound **2t** was prepared according to the general procedure and isolated as an oil (146 mg, 92% yield) after flash chromatography (petroleum ether/ethyl acetate = 6/1). ^{1}H NMR (400 MHz, $CDCl_3$): δ/ppm= 7.29 (s, 1H), 7.23 (d, *J* = 8.6 Hz, 1H), 7.17 (t, *J* = 7.8 Hz, 1H), 6.89 (d, *J* = 7.3 Hz, 1H), 4.60 (ddd, *J* = 14.3, 8.3, 4.0 Hz, 1H), 4.06 (t, *J* = 8.9 Hz, 1H), 3.68 (dd, *J* = 9.3, 6.1 Hz, 1H), 3.36 (dd, *J* = 10.4, 4.0 Hz, 1H), 3.26 (dd, *J* = 10.4, 8.1 Hz, 1H), 2.29 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ/ppm= 153.0, 138.1, 136.7, 127.8, 124.2, 118.1, 114.5, 70.1, 50.0, 20.6, 5.3. IR (KBr): 3002, 2987, 1749, 1623, 1475, 1463, 1357, 1143, 1003, 955, 866, 741, 657 cm^{-1}. ESI-HRMS: calc. for $[C_{11}H_{12}INO_2+H]^+$: m/z = 317.9991, found: 317.9986.

3-(4-Bromophenyl)-5-(iodomethyl)oxazolidin-2-one (2u). Compound **2u** was prepared according to the general procedure and isolated as a white solid (137 mg, 72% yield) after flash chromatography (petroleum ether/ethyl acetate = 8/1); mp = 152–154 °C. ^{1}H NMR (400 MHz, DMSO): δ/ppm= 7.59 (d, *J* = 9.2 Hz, 2H), 7.55 (d, *J* = 9.2 Hz, 2H), 4.75 (td, *J* = 10.7, 5.2 Hz, 1H), 4.20 (t, *J* = 9.1 Hz, 1H), 3.67 (dd, *J* = 9.3, 6.0 Hz, 1H), 3.62 (t, *J* = 9.1 Hz, 1H), 3.57 (dd, *J* = 10.7, 4.8 Hz, 1H). ^{13}C NMR (100 MHz, DMSO): δ/ppm= 154.01, 138.0, 132.2, 120.5, 116.0, 71.5, 50.7, 10.0. IR (KBr): 3026, 3001, 2917, 1759, 1616, 1496, 1406, 1296, 1200, 1002, 931, 827, 713, 659 cm^{-1}. ESI-HRMS: calc. for $[C_{10}H_9BrINO_2+H]^+$: m/z = 381.8940, found: 381.8935.

Synthesis of α-hydroxyamide 3. Compound **2b** (173 mg, 0.5 mmol) and KOH (56 mg, 1 mmol) were dissolved in a mixture of H_2O and EtOH (10 mL, 20:1). The resulting mixture was stirred for 3 h. The solvent was evaporated, water (5 mL) was added and the mixture was extracted thrice with dichloromethane (15 mL). The combined extracts were dried over Na_2SO_4 and concentrated to give a crude residue, which was purified by flash column chromatography to give compound **3** as a white solid (74 mg, 71% yield). mp = 86–88 °C. ^{1}H NMR (400 MHz, $CDCl_3$): ^{1}H NMR (400 MHz, $CDCl_3$): δ/ppm= 8.75 (s, 1H), 7.39 (d, *J* = 8.4 Hz, 2H), 7.08 (d, *J* = 8.4 Hz, 2H), 4.08 (brs, 1H), 4.03 (d, *J* = 11.2 Hz, 1H), 3.53 (brs, 1H), 3.45 (d, *J* = 11.2 Hz, 1H), 2.29 (s, 3H), 1.37 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ/ppm= 172.5, 133.5, 133.3, 128.5, 118.9, 75.5, 66.6, 21.6, 19.8. IR (KBr): 3503, 3149, 2989, 2928, 1704, 1615, 1401, 1239, 1162, 976, 793 cm^{-1}. ESI-HRMS: calc. for $[C_{11}H_{15}INO_3+H]^+$: m/z = 210.1130, found: 210.1127.

Synthesis of toloxatone (**4**). The oxazolidinone **2t** (317 mg, 1 mmol) was dissolved in DMF (10 mL), and KOAc (490 mg, 5 mmol) was added to the solution. After stirring the mixture at 70 °C for 10 h, H_2O (20 mL) was added, and then the aqueous layer was extracted with CH_2Cl_2 (x 4). The organic layers were combined, washed with H_2O and brine, dried over Na_2SO_4 and concentrated. The residue was subsequently dissolved in EtOH (10 mL), and K_2CO_3 (690 mg, 5 mmol) was added to the solution at 0 °C. After stirring the mixture at 0 °C for 3 h, H_2O (10 mL) and CH_2Cl_2 (10 mL) were added, and then the aqueous layer was extracted with CH_2Cl_2 (x 3). The organic layers were combined, washed with H_2O and brine, dried over Na_2SO_4 and concentrated. Flash column chromatography (petroleum ether/ethyl acetate = 2/1) afforded toloxatone (**4**) as a white solid (155 mg, 75%). mp = 77 °C (ref,[20a] mp = 75–76 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ/ppm= 7.41 (s, 1H), 7.34 (d, *J* = 8.3 Hz, 1H), 7.31 – 7.26 (m, 1H), 6.98 (d, *J* = 7.4 Hz, 1H), 4.75 (ddd, *J* = 12.2, 7.3, 3.8 Hz, 1H), 4.05 (t, *J* = 8.8 Hz, 1H), 4.03 – 3.99 (m, 1H), 3.99 – 3.96 (m, 1H), 3.78 (dd, *J* = 12.5, 4.1 Hz, 1H), 2.39 (s, 3H), 1.72 (brs, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ/ppm= 154.8, 139.1, 138.1, 128.9, 125.1, 119.2, 115.5, 72.8, 62.9, 46.5, 21.6. The data are in accordance with the literature.[20a]

General procedure for the synthesis of iodinated oxindoles: To a solution of N-arylacrylamide (0.5 mmol, 1.0 equiv.) in acetonitrile (20 mL) were added ICl (1.0 mmol, 2.0 equiv.) and $NaHCO_3$ (1.0 mmol, 2.0 equiv.). The reaction mixture was stirred at room temperature until complete disappearance of the starting material as shown by TLC (usually 3-5 h). The reaction was next quenched with a saturated aqueous $Na_2S_2O_3$ solution and extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried and concentrated to give a crude residue, which was purified by flash column chromatography. In most of the reactions, the products obtained were essentially pure by NMR analysis and further silica gel chromatography was not necessary.

3-(Iodomethyl)-1,3,5,-trimethylindolin-2-one (**6a**). Compound **6a** was prepared according to the general procedure and isolated as a light red solid (142 mg, 90% yield) after flash column chromatography (petroleum ether/ethyl acetate = 8/1); mp = 68–70 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ/ppm= 7.05 (d, *J* = 7.2 Hz, 1H), 7.01 (s, 1H), 6.69 (d, *J* = 7.9 Hz, 1H), 3.44 (d, *J* = 9.7 Hz, 1H), 3.33 (d, *J* = 9.7 Hz, 1H), 3.14 (s, 3H), 2.29 (s, 3H), 1.43 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ/ppm= 176.8, 139.7, 131.6, 131.2, 127.8, 122.4, 107.0, 47.6, 25.2, 22.1, 20.2, 10.0. Spectral data are in agreement with literature values.[21]

3-(Iodomethyl)-5-methoxy-1,3-dimethylindolin-2-one (**6b**). Compound **6b** was prepared according to the general procedure and isolated as a white solid (146 mg, 88% yield) after flash column chromatography (cyclohexane/ethyl acetate = 3/1); mp = 96–97 °C (ref,[21] mp = 101 °C; ref,[37] mp = 94–95 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ/ppm= 6.91 (d, *J* = 2.5 Hz, 1H), 6.87 (dd, *J* = 8.4, 2.5 Hz, 1H), 6.80 (d, *J* = 8.4 Hz, 1H), 3.83 (s, 3H), 3.52 (d, *J* = 9.8 Hz, 1H), 3.42 (d, *J* = 9.8 Hz, 1H), 3.24 (s, 3H), 1.52 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ/ppm = 177.6, 156.1, 136.7,

133.9, 112.6, 110.4, 108.6, 55.8, 49.0, 26.4, 23.1, 10.8. Spectral data are in agreement with literature values.[21]

5-Ethoxy-3-(iodomethyl)-1,3-dimethylindolin-2-one (**6c**). Compound **6c** was prepared according to the general procedure and isolated as a colorless oil (155 mg, 90% yield) after flash column chromatography (cyclohexane/ethyl acetate = 6/1). ^{1}H NMR (400 MHz, $CDCl_3$): δ/ppm = 6.91 (d, *J* = 2.4 Hz, 1H), 6.86 (dd, *J* = 8.4, 2.4 Hz, 1H), 6.78 (d, *J* = 8.4 Hz, 1H), 4.05 (d, *J* = 7.0 Hz, 1H), 4.02 (d, *J* = 7.0 Hz, 1H), 3.52 (d, *J* = 9.8 Hz, 1H), 3.41 (d, *J* = 9.8 Hz, 1H), 3.23 (s, 3H), 1.51 (s, 3H), 1.43 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ/ppm = 177.6, 155.4, 136.6, 133.9, 113.3, 111.0, 108.6, 64.1, 49.0, 26.4, 23.1, 14.9, 10.9. IR (KBr): 2957, 2929, 1702, 1601, 1495, 1352, 1287, 1190, 1036, 838, 805, 736, 629 cm^{-1}. ESI–HRMS: calc. for $[C_{13}H_{16}INO_2+Na]^+$: m/z = 368.0123, found: 368.0114.

5-Fluoro-3-(iodomethyl)-1,3-dimethylindolin-2-one (**6d**). Compound **6d** was prepared according to the general procedure and isolated as a colorless oil (132 mg, 83% yield) after flash column chromatography (cyclohexane/ethyl acetate = 3/1). ^{1}H NMR (400 MHz, $CDCl_3$): δ/ppm = 7.06 – 7.02 (m, 2H), 6.81 (dd, *J* = 9.2, 4.1 Hz, 1H), 3.51 (d, *J* = 9.9 Hz, 1H), 3.40 (d, *J* = 9.9 Hz, 1H), 3.24 (s, 3H), 1.52 (s, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ/ppm= 120.0. ^{13}C NMR (100 MHz, $CDCl_3$): δ/ppm = 177.6, 159.3 (d, *J* = 241.2 Hz), 139.1, 134.2, 114.9 (d, *J* = 24.0 Hz), 111.0 (d, *J* = 24.9 Hz), 108.8 (d, *J* = 8.1 Hz), 49.1, 26.5, 23.0, 10.1. IR (KBr): 3061, 2927, 1711, 1610, 1484, 1347, 1245, 1126, 1096, 807, 626, 544 cm^{-1}. HRMS–ESI: calc. for $[C_{11}H_{11}FINO+H]^+$: m/z = 319.9948, found: 319.9959.

5-Chloro-3-(iodomethyl)-1,3-dimethylindolin-2-one (**6e**). Compound **6e** was prepared according to the general procedure and isolated as a yellow solid (136 mg, 81% yield) after flash column chromatography (petroleum ether/ethyl acetate = 8/1). mp = 68–70 °C (ref,[37] mp=79–81°C). ^{1}H NMR (400 MHz, $CDCl_3$): δ/ppm = 7.24 (dd, *J* = 8.3, 2.1 Hz, 1H), 7.18 (d, *J* = 2.0 Hz, 1H), 6.73 (d, *J* = 8.3 Hz, 1H), 3.44 (d, *J* = 9.9 Hz, 1H), 3.31 (d, *J* = 9.9 Hz, 1H), 3.16 (s, 3H), 1.44 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ/ppm= 176.4, 140.8, 133.2, 127.6, 127.1, 122.2, 108.2, 47.9, 25.4, 21.9, 8.9. Spectral data are in agreement with literature values.[37]

5-Bromo-3-(iodomethyl)-1,3-dimethylindolin-2-one (**6f**). Compound **6f** was prepared according to the general procedure and isolated as a colorless oil (151 mg, 80% yield) after flash column chromatography (cyclohexane/ethyl acetate = 3/1). ^{1}H NMR (400 MHz, $CDCl_3$): δ/ppm = 7.47 (dd, *J* = 8.3, 1.9 Hz, 1H), 7.39 (d, *J* = 1.9 Hz, 1H), 6.77 (d, *J* = 8.3 Hz, 1H), 3.52 (d, *J* = 9.9 Hz, 1H), 3.40 (d, *J* = 9.9 Hz, 1H), 3.24 (s, 3H), 1.53 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ/ppm= 177.3, 142.3, 134.6, 131.5, 126.0, 115.4, 109.8, 48.9, 26.4, 23.0, 9.9. IR (KBr): 3061, 2927, 2854, 1711, 1611, 1484, 1415, 1245, 1096, 1013, 808, 626, 544 cm^{-1}. HRMS–ESI: calc. for $[C_{11}H_{11}BrINO+H]^+$: m/z = 379.9147, found: 379.9138.

5-Iodo-3-(iodomethyl)-1,3-dimethylindolin-2-one (**6g**). Compound **6g** was prepared according to the general procedure and isolated as a white solid (181 mg, 85% yield) after flash column chromatography (cyclohexane/ethyl acetate = 4/1). mp = 126–127 °C (ref,[21] mp = 129–130 °C) ^{1}H NMR (400 MHz, $CDCl_3$): δ/ppm= 7.64 (dd, *J* = 8.2, 1.6 Hz, 1H), 7.53 (d, *J* = 1.6 Hz, 1H), 6.65 (d, *J* = 8.2 Hz, 1H), 3.52 – 3.45 (m, 1H), 3.39 – 3.33 (m, 1H), 3.21 (s, 3H), 1.50 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ/ppm= 177.2, 143.0, 137.5, 135.0, 131.5, 110.4, 85.2, 48.7, 26.4, 23.0, 10.0. Spectral data are in agreement with literature values.[21]

3-(Iodomethyl)-1,3-dimethyl-5-(trifluoromethoxy)indolin-2-one (**6h**). Compound **6h** was prepared according to the general procedure and isolated as a white solid (133 mg, 69% yield) after flash column chromatography (petroleum ether/ethyl acetate = 8/1). mp = 73-75°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ/ppm = 7.23 (d, *J* = 8.4 Hz, 1H), 7.19 (s, 1H), 6.88 (d, *J* = 8.4 Hz, 1H), 3.52 (d, *J* = 9.9 Hz, 1H), 3.42 (d, *J* = 9.9 Hz, 1H), 3.27 (s, 3H), 1.55 (s, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ/ppm= 58.3. ^{13}C NMR (100 MHz, $CDCl_3$): δ/ppm= 177.6, 144.8 (q, *J* = 2.0 Hz), 141.9, 134.1, 121.8, 119.3, 116.9, 108.7, 48.9, 26.5, 22.9, 9.8. IR (KBr): 3050, 2930, 1716, 1619, 1493, 1375, 1269, 1138, 817, 615, 548 cm^{-1}. HRMS–ESI: calc. for $[C_{12}H_{11}F_3INO_2+H]^+$: m/z = 385.9865, found: 385.9855.

7-(Iodomethyl)-5,7-dimethyl-5H-[1,3]dioxolo[4,5-f]indol-6(7H)-one, 8-(iodomethyl)-6,8-dimethyl-6H-[1,3]dioxolo[4,5-e]indol-7(8H)-one (**6i**+**6i'**). Compound **6i** and **6i'** was prepared according to the general procedure and isolated as a yellow oil (148 mg, 86% yield) after flash column chromatography (petroleum ether/ethyl acetate = 6/1). **6i/6i'**= 1.1/1. ^{1}H NMR (400 MHz, $CDCl_3$): δ/ppm = 6.77 (s, 1H-maj), 6.72 (s, 1H-min), 6.41 (s, 2H-maj, min), 5.90–5.80 (m, 4H-maj, min), 3.67 (d, *J* = 10.8 Hz, 1H-maj), 3.62 (d, *J* = 10.8 Hz, 1H-maj), 3.40 (d, *J* = 9.8 Hz, 1H-min), 3.28 (d, *J* = 9.8 Hz, 1H-min), 3.11 (s, 3H-min), 3.10 (s, 3H-maj), 1.39 (s, 3H-min), 1.31 (s, 3H-maj). ^{13}C NMR (100 MHz, $CDCl_3$): δ/ppm= 177.0, 176.8, 146.7, 146.6, 142.3, 136.7, 142.2, 136.5, 123.3, 122.0, 103.8, 103.3, 100.2, 91.2, 48.8, 48.1, 47.8, 25.5, 25.4, 21.9, 20.3, 10.3. IR (KBr): 3010, 2927, 1702, 1622, 1477, 1381, 1226, 1110, 1035, 925, 819, 698, 547 cm^{-1}. HRMS–ESI: calc. for $[C_{12}H_{12}INO_3+H]^+$: m/z = 345.9940, found: 345.9933.

3-(Iodomethyl)-1,3-dimethyl-2-oxoindoline-5-carbonitrile (**6j**). Compound **6j** was prepared according to the general procedure and isolated as a yellow solid (68 mg, 42% yield) after flash column chromatography (petroleum ether/ethyl acetate = 4/1). mp = 122–125 °C (ref,[21] mp = 138–140 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ/ppm = 7.61 (dd, *J* = 8.1, 1.6 Hz, 1H), 7.46 (d, *J* = 1.4 Hz, 1H), 6.89 (d, *J* = 8.2 Hz, 1H), 3.45 (d, *J* = 10.0 Hz, 1H), 3.34 (d, *J* = 10.0 Hz, 1H), 3.21 (s, 3H), 1.48 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ/ppm= 176.6, 146.1, 133.0, 132.7, 125.1, 118.0, 107.8, 104.9, 47.6, 25.6, 21.8, 8.1. Spectral data are in agreement with literature values.[21]

5-Acetyl-3-(iodomethyl)-1,3-dimethylindolin-2-one (**6k**). Compound **6k** was prepared according to the general procedure and isolated as a colorless oil (84 mg, 49% yield) after flash column chromatography (cyclohexane/ethyl acetate = 1/1). ^{1}H NMR (400 MHz, $CDCl_3$): δ/ppm = 8.00 (dd, *J* = 8.2, 1.8 Hz, 1H), 7.90 (d, *J* = 1.8 Hz, 1H), 6.94 (d, *J* = 8.2 Hz, 1H), 3.55 (d, *J* = 9.8 Hz, 1H), 3.44 (d, *J* = 9.8 Hz, 1H), 3.29 (s, 3H), 2.61 (s, 3H), 1.55 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ/ppm= 196.7, 178.3, 147.5, 132.9, 132.3, 130.7, 122.5, 107.7, 48.7, 26.6, 26.5, 22.8, 9.8. IR (KBr): 2967, 2928, 1714, 1605, 1465, 1436, 1355, 1260, 1170, 1011, 872, 740, 628 cm^{-1}. HRMS–ESI: calc. for $[C_{13}H_{14}INO_2+Na]^+$: m/z = 365.9967, found: 365.9983.

5-Bromo-3-(iodomethyl)-1,3-dimethyl-1H-benzo[g]indol-2(3H)-one (**6l**). Compound **6l** was prepared according to the general procedure and isolated as a brown solid (166 mg, 77% yield) after flash column chromatography (petroleum ether/ethyl acetate = 8/1). mp= 140–143 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ/ppm= 8.39 (d, *J* = 8.2 Hz, 1H), 8.30 – 8.19 (m, 1H), 7.60 (s, 1H), 7.55 – 7.46 (m, 2H), 3.76 (s, 3H), 3.52 (d, *J* = 9.9 Hz, 1H), 3.36 (d, *J* = 9.9 Hz, 1H), 1.50 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ/ppm= 178.2, 137.5, 131.5, 127.8, 127.7, 126.2, 125.7, 123.0, 121.4, 121.1, 115.6, 47.7, 30.0, 22.0, 8.6. IR (KBr): 3021, 2967, 2921, 1707, 1620, 1465, 1260, 1053, 800, 757, 688, 612, 516 cm^{-1}. HRMS–ESI: calc. for $[C_{15}H_{13}BrINO+H]^+$: m/z = 429.9303, found: 429.9291.

1-(Iodomethyl)-1,3-dimethyl-1H-benzo[e]indol-2(3H)-one (**6m**). Compound **6m** was prepared according to the general procedure and isolated as a yellow solid (118 mg, 67% yield) after flash column chromatography (petroleum ether/ethyl acetate = 8/1). mp= 129–130 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ/ppm= 8.00 – 7.87 (m, 2H), 7.80 (d, *J* = 8.5 Hz, 1H), 7.56 (t, *J* = 7.1 Hz, 1H), 7.41 (t, *J* = 7.6 Hz, 1H), 7.32 – 7.15 (m, 1H), 3.90 (d, *J* = 9.8 Hz, 1H), 3.84 (d, *J* = 9.8 Hz, 1H), 3.39 (s, 3H), 1.81 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ/ppm= 179.4, 141.1, 130.6, 130.0, 130.0, 129.3, 127.6, 124.0, 123.7, 120.9, 109.6, 50.8, 26.6, 22.3, 9.5. Spectral data are in agreement with literature values.[21]

1-Benzyl-3-(iodomethyl)-5-methoxy-3-methylindolin-2-one (**6n**). Compound **6n** was prepared according to the general procedure and isolated as a yellow solid (167 mg, 82% yield) after flash column chromatography (cyclohexane/ethyl acetate = 4/1). mp= 139–142 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ/ppm= 7.41 – 7.21 (m, 5H), 6.91 (d, *J* = 2.5 Hz,1H), 6.74 (dd, *J* = 8.5, 2.5 Hz, 1H), 6.65 (d, *J* = 8.5 Hz, 1H), 5.01 (d, *J* = 15.6 Hz, 1H), 4.88 (d, *J* = 15.7 Hz, 1H), 3.79 (s, 3H), 3.62 (d, *J* = 9.8 Hz, 1H), 3.49 (d, *J* = 9.8 Hz,1H), 1.59 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ/ppm = 177.7, 156.0, 135.7, 135.6, 134.0, 128.7, 127.6, 127.5, 112.5, 110.4, 109.8, 55.8, 49.1, 44.1, 23.7, 10.4. IR (KBr): 3010, 2927, 2868, 1704, 1600, 1493, 1351, 1288, 1037, 963, 804, 680, 629 cm^{-1}. HRMS–ESI: calc. for $[C_{18}H_{18}INO_2+Na]^+$: m/z = 430.0280, found: 430.0284.

1-Ethyl-3-(iodomethyl)-5-methoxy-3-methylindolin-2-one (**6o**). Compound **6o** was prepared according to the general procedure and isolated as a colorless oil (136 mg, 79% yield) after flash column chromatography (cyclohexane/ethyl acetate = 3/1). ^{1}H NMR (400 MHz, $CDCl_3$): δ/ppm = 6.90 (d, *J* = 2.5, 1H), 6.85 (dd, *J* = 8.5, 2.5 Hz, 1H), 6.81 (d, *J* = 8.5 Hz, 1H), 3.87 (dq, *J* = 14.3, 7.2 Hz,1H), 3.82 (s, 3H), 3.68 (dq, *J* = 14.3, 7.2 Hz, 1H), 3.53 (d, *J* = 9.8 Hz, 1H), 3.40 (d, *J* = 9.8 Hz, 1H), 1.51 (s, 3H), 1.29 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ/ppm = 177.1, 155.9, 135.7, 134.2, 112.6, 110.5, 108.7, 55.8, 48.8, 34.9, 23.0, 12.8, 10.8. IR (KBr): 3003, 2928, 2868, 1702, 1600, 1494, 1352, 1183, 1037, 804, 629, 588 cm^{-1}. HRMS–ESI: calc. for $[C_{13}H_{16}INO_2+Na]^+$: m/z =368.0123, found: 368.0128.

1-Butyl-3-(iodomethyl)-5-methoxy-3-methylindolin-2-one (**6p**). Compound **6p** was prepared according to the general procedure and isolated as a colorless oil (164 mg, 88% yield) after flash column chromatography (petroleum ether/ethyl acetate = 8/1). ^{1}H NMR (400 MHz, $CDCl_3$): δ/ppm= 6.90 (d, *J* = 2.4 Hz, 1H), 6.85 (dd, *J* = 8.5, 2.4 Hz, 1H), 6.81 (d, *J* = 8.5 Hz, 1H), 3.82 (s, 3H), 3.77 (dd, *J* = 14.2, 7.2 Hz, 1H), 3.64 (dt, *J* = 14.2, 7.2 Hz, 1H), 3.53 (d, *J* = 9.8 Hz, 1H), 3.42 (d, *J* = 9.8 Hz, 1H), 1.73 – 1.63 (m, 2H), 1.51 (s, 3H), 1.46 – 1.41 (m, 2H), 0.96 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ/ppm= 177.4, 155.5, 136.1, 134.2, 112.6, 110.4, 108.9, 55.8, 48.8, 40.0, 29.6, 23.3, 20.3, 13.8, 10.7. IR (KBr): 3030, 2957, 2929, 1701, 1600, 1435, 1352, 1287, 1037, 804, 629, 466 cm^{-1}. HRMS–ESI: calc. for $[C_{15}H_{20}INO_2+H]^+$: m/z = 374.0617, found: 374.0616.

3-(Iodomethyl)-1-isobutyl-5-methoxy-3-methylindolin-2-one (**6q**). Compound **6q** was prepared according to the general procedure and isolated as a colorless oil (158 mg, 85% yield) after flash column chromatography (petroleum ether/ethyl acetate = 8/1). ^{1}H NMR (400 MHz, $CDCl_3$): δ/ppm= 6.92 (d, *J* = 2.5 Hz, 1H), 6.85 (dd, *J* = 8.5, 2.5 Hz, 1H), 6.80 (d, *J* = 8.5 Hz, 1H), 3.84 (s, 3H), 3.60 – 3.55 (m, 1H), 3.54 (d, *J* = 3.4 Hz, 1H), 3.52 – 3.47 (m, 1H), 3.44 (d, *J* = 3.4 Hz, 1H), 2.18 (dp, *J* = 13.8, 6.9 Hz, 1H), 1.52 (s, 3H), 1.02 (d, *J* = 6.7 Hz, 3H), 0.99 (d, *J* = 6.7 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ/ppm= 177.7, 155.8, 136.5, 134.1, 112.5, 110.4, 109.2, 55.8, 48.8, 47.8, 27.2, 23.7, 20.5, 20.4, 10.6. IR (KBr): 3044, 2958, 2866, 1701, 1602, 1492, 1303, 1218, 1044, 806, 635, 599 cm^{-1}. HRMS–ESI: calc. for $[C_{15}H_{20}INO_2+H]^+$: m/z = 374.0617, found: 374.0618.

3-(Iodomethyl)-5-methoxy-1-(4-methoxyphenyl)-3-methylindolin-2-one (**6r**). Compound **6r** was prepared according to the general procedure and isolated as a white solid (180 mg, 85% yield) after flash column chromatography (petroleum ether/ethyl acetate = 8/1). mp= 119-122 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ/ppm= 7.37 (d, *J* = 8.8 Hz, 2H), 7.29 (s, 1H), 7.05 (d, *J* = 8.8 Hz, 2H), 6.93 (d, *J* = 2.4 Hz, 1H), 6.80 (dd, *J* = 8.6, 2.4 Hz, 1H), 3.88 (s, 3H), 3.85 (s, 3H), 3.67 (d, *J* = 9.7 Hz, 1H), 3.48 (d, *J* = 9.7 Hz, 1H), 1.65 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ/ppm= 177.4, 159.2, 156.3, 137.3, 133.6, 127.9, 127.3, 114.9, 112.8, 110.1, 109.9, 55.9, 55.6, 49.0, 23.1, 11.2. IR (KBr): 3006, 2963, 2836, 1709, 1602, 1512, 1431, 1297, 1027, 846, 823, 633, 609, 574 cm^{-1}. HRMS–ESI: calc. for $[C_{18}H_{18}INO_3+H]^+$: m/z = 424.0410, found: 424.0406.

Ethyl 2-(3-(iodomethyl)-5-methoxy-3-methyl-2-oxoindolin-1-yl)acetate (**6s**). Compound **6s** was prepared according to the general procedure and isolated as a yellow oil (131 mg, 65% yield) after flash column chromatography (petroleum ether/ethyl acetate = 6/1). ^{1}H NMR (400 MHz, $CDCl_3$): δ/ppm= 6.86 (d, *J* = 2.5 Hz, 1H), 6.75 (dd, *J* = 8.5, 2.5 Hz, 1H), 6.60 (d, *J* = 8.5 Hz, 1H), 4.46 (d, *J* = 17.5 Hz, 1H), 4.30 (d, *J* = 17.5 Hz, 1H), 4.13 (q, *J* = 7.1 Hz, 2H), 3.73 (s, 3H), 3.45 (d, *J* = 9.9 Hz, 1H), 3.37 (d, *J* = 9.9 Hz, 1H), 1.47 (s, 3H), 1.18 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ/ppm=176.6, 166.6, 155.2, 134.2, 132.6, 111.7, 109.5, 107.7, 60.7, 54.8, 47.9, 40.5, 22.6, 13.1, 9.2. IR (KBr): 2967, 2928, 1714, 1630, 1498, 1375, 1298, 1208, 1036, 805, 686, 628 cm^{-1}. HRMS–ESI: calc. for $[C_{15}H_{18}INO_4+H]^+$: m/z =404.0359, found: 404.0359.

3-Benzyl-3-(iodomethyl)-5-methoxy-1-methylindolin-2-one (**6t**). Compound **6t** was prepared according to the general procedure and isolated as a colorless solid (153 mg, 75% yield) after flash column chromatography (petroleum ether/ethyl acetate = 8/1). mp= 139–142 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ/ppm=7.05 – 6.99 (m, 3H), 6.79 (dd, *J* = 7.2, 2.1 Hz, 2H), 6.71

(d, *J* = 2.5 Hz, 1H), 6.69 (s, 1H), 6.47 (d, *J* = 8.9 Hz, 1H), 3.72 (s, 3H), 3.60 (d, *J* = 9.8 Hz, 1H), 3.41 (d, *J* = 9.8 Hz, 1H), 3.06 (d, *J* = 5.5 Hz, 2H), 2.91 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ/ppm= 175.3, 154.7, 136.3, 134.1, 130.3, 128.8, 126.7, 125.8, 111.9, 110.1, 107.3, 54.8, 53.9, 42.3, 25.1, 8.1. IR (KBr): 3055, 2920, 2831, 1708, 1632, 1496, 1288, 1076, 869, 804, 701, 531 cm^{-1}. HRMS–ESI: calc. for $[C_{18}H_{18}INO_2+H]^+$: m/z =408.0460, found: 408.0455.

3-(Iodomethyl)-1,5-dimethyl-3-phenylindolin-2-one (**6u**). Compound **6u** was prepared according to the general procedure and isolated as a yellow solid (149 mg, 79% yield) after flash column chromatography (petroleum ether/ethyl acetate = 8/1). mp= 122–125 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ/ppm= 7.48 (d, *J* = 8.1, 1.7 Hz, 2H), 7.37 – 7.28 (m, 3H), 7.26 – 7.20 (m, 2H), 6.86 (d, *J* = 7.8 Hz, 1H), 4.06 (d, *J* = 9.7 Hz, 1H), 3.79 (d, *J* = 9.7 Hz, 1H), 3.25 (s, 3H), 2.44 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ/ppm= 176.2, 141.7, 137.9, 132.3, 131.0, 129.4, 128.8, 128.0, 127.2, 125.7, 108.4, 56.7, 26.6, 21.4, 10.7. IR (KBr): 3020, 2965, 2935, 1715, 1619, 1498, 1350, 1074, 810, 723, 697, 551, 506 cm^{-1}. HRMS–ESI: calc. for $[C_{17}H_{16}INO+H]^+$: m/z = 378.0355, found: 378.0349.

5-Iodo-3-(iodomethyl)-1,3,4,6-tetramethylindolin-2-one (**6v**). Compound **6v** was prepared according to the general procedure and isolated as a yellow solid (136 mg, 60% yield) after flash column chromatography (petroleum ether/ethyl acetate = 8/1). mp= 120–123 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ/ppm= 6.71 (s, 1H), 3.67 (d, *J* = 9.9 Hz, 1H), 3.61 (d, *J* = 9.9 Hz, 1H), 3.24 (s, 3H), 2.56 (s, 3H), 2.48 (s, 3H), 1.60 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ/ppm= 178.0, 143.5, 142.6, 137.6, 127.9, 107.7, 102.1, 50.6, 26.3, 24.8, 21.4, 17.8, 8.5. IR (KBr): 2975, 2918, 1712, 1604, 1451, 1327, 1265, 1052, 959, 848, 808, 709, 604, 520 cm^{-1}. HRMS–ESI: calc. for $[C_{13}H_{15}I_2NO+H]^+$: m/z = 455.9321, found: 455.9309.

5-Iodo-3-(iodomethyl)-1,3-dimethyl-1H-benzo[g]indol-2(3H)-one (**6w**). Compound **6w** was prepared according to the general procedure and isolated as a yellow oil (148 mg, 62% yield) after flash column chromatography (cyclohexane/ethyl acetate = 5/1). ^{1}H NMR (400 MHz, $CDCl_3$): δ/ppm= 8.43 – 8.40 (m, 1H), 8.21 – 8.18 (m, 1H), 7.94 (s, 1H), 7.59 – 7.52 (m, 2H), 3.84 (s, 3H), 3.59 (d, *J* = 9.9 Hz, 1H), 3.43 (d, *J* = 9.9 Hz, 1H), 1.57 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ/ppm= 179.1, 139.6, 134.7, 133.9, 131.2, 129.6, 127.6, 126.7, 122.3, 122.2, 91.8, 48.5, 31.1, 23.0, 9.7. Spectral data are in agreement with literature values.[21]

5-Iodo-3-(iodomethyl)-1,3,7-trimethylindolin-2-one (**6x**). Compound **6x** was prepared according to the general procedure and isolated as a yellow solid (141 mg, 64% yield) after flash column chromatography (cyclohexane/ethyl acetate = 5/1). mp = 155–156 °C (ref,[21] mp = 160 °C; ref,[15a] mp = 159–161 °C) ^{1}H NMR (400 MHz, $CDCl_3$): δ/ppm= 7.33 (s, 1H), 7.27 (d, *J* = 1.3 Hz, 1H), 3.42 (d, *J* = 9.8 Hz, 1H), 3.42 (s, 3H), 3.25 (d, *J* = 9.8 Hz, 1H), 2.47 (s, 3H), 1.40 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ/ppm= 177.0, 139.9, 139.7, 134.4, 128.2, 121.3, 84.3, 47.0, 28.6, 22.2, 17.7, 9.3. Spectral data are in agreement with literature values.[21]

3-(Azidomethyl)-1,3,5-trimethylindolin-2-one (**7**). Compound **6a** was dissolved in 2 mL of DMF, the sodium azide was added, and the reaction mixture was stirred at room temperature overnight. Then 30 mL of CH_2Cl_2 was added, and the reaction mixture was washed with water, dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (petroleum ether/ethyl acetate=12:1) to give **7** as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ/ppm= 7.05 (s, 1H), 7.03 (d, *J* = 4.5 Hz, 1H), 6.69 (d, *J* = 7.8 Hz, 1H), 3.55 (s, 2H), 3.14 (s, 3H), 2.28 (s, 3H), 1.29 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ/ppm= 177.1, 140.1, 131.3, 130.4, 127.9, 122.9, 107.1, 56.2, 47.8, 25.4, 20.1, 19.5. Spectral data are in agreement with literature values.[38]

2-(5-Methoxy-1,3-dimethyl-2-oxoindolin-3-yl)acetonitrile (**8**). A solution of oxindole **5b** (331 mg, 1 mmol) and sodium cyanide (147 mg, 3 mmol) was refluxed in CH_3CN (20 mL) for 36 h. Water (10 mL) was added and the mixture was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were dried (Na_2SO_4) and concentrated to give a crude residue, which was purified by flash column chromatography (cyclohexane/ethyl acetate=2:1) to afford compound **8** (202 mg, 88%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ/ppm = 7.09 (d, *J* = 2.4 Hz, 1H), 6.88 (dd, *J* = 8.5, 2.5 Hz, 1H), 6.82 (d, *J* = 8.5 Hz, 1H), 3.82 (s, 3H), 3.22 (s, 3H), 2.86 (dd, *J* = 16.7 Hz, 1H), 2.56 (dd, *J* = 16.7, Hz, 1H), 1.52 (s, 3H).^{13}C NMR (100 MHz, $CDCl_3$): δ/ppm = 177.1, 156.4, 136.0, 132.2, 116.6, 113.5, 110.5, 109.1, 55.9, 45.2, 26.6, 26.3, 22.2. Spectral data are in agreement with literature values.[35]

(±)-Esermethole (**9**). Compound **8** (184 mg, 0.8 mmol) was dissolved in THF (20 mL), and $LiAlH_4$ (122 mg, 4 mmol) was added. The reaction mixture was stirred under an argon atmosphere for 1 h and then heated to reflux for 1 h and cooled to 0 ºC afterwards. A solution of NaOH (10% in water) was added carefully until a white solid precipitates. After filtration over $MgSO_4$ and evaporation of the solvent, the product was obtained as yellow oil, which was subsequently dissolved in MeOH (5 mL). Aqueous solution of HCHO (37 wt%, 4 mmol) was added at 0 °C under an argon atmosphere, and the mixture was stirred for 30 min. Then the mixture was cooled to 0 °C before $NaBH_4$ (62 mg, 1.6 mmol) was added slowly, and the solution was stirred for 15 h at room temperature. The mixture was quenched at 0 °C with water and extracted with CH_2Cl_2. The organic layers were then combined, washed with brine, dried (Na_2SO_4) and concentrated. The residue was purified by using flash column chromatography (CH_2Cl_2/MeOH= 10:1) to give **9** as a yellow oil (145 mg, 78%). ^{1}H NMR, COSY (400 MHz, $CDCl_3$): δ/ppm = 6.68 (dd, *J* = 8.3, 2.5 Hz, 1H, Ar-H6), 6.65 (d, *J* = 2.5 Hz, 1H, Ar-H4), 6.40 (d, *J* = 8.3 Hz, 1H, Ar-H7), 4.17 (s, 1H, H8a), 3.76 (s, 3H, C_5-OMe), 2.92 (s, 3H, N_8-C*H*$_3$), 2.86 – 2.80 (m, 1H, H2), 2.65 (td, *J* = 9.1, 6.6 Hz, 1H, H2), 2.57 (s, 3H, N_1-C*H*$_3$), 2.09 – 1.94 (m, 2H, H3), 1.47 (s, 3H, C_{3a}-C*H*$_3$). ^{13}C NMR, HSQC, HMBC (100 MHz, $CDCl_3$): δ/ppm = 153.2 (C5), 146.3 (C7a), 137.9 (C3b), 112.4 (C6), 109.7 (C4), 107.7 (C7), 98.0 (C8a), 56.0 (-OMe), 53.1 (C2), 52.9(C3a), 40.5 (C3), 38.1 (N_8-*C*H$_3$), 37.7 (N_1-*C*H$_3$), 27.3 (C_{3a}-*C*H$_3$). Spectral data are in agreement with literature values.[35]

(±)-Physostigmine (**10**). (±)-Esermethole **(9)** (116 mg, 0.5 mmol) was dissolved in CH_2Cl_2 (10 ml) and 1 M BBr_3 solution in DCM (1.5 mL, 1.5 mmol) was added dropwise to the above solution with stirring. The resulting mixture was stirred at room

temperature for 5 h. The reaction was then quenched with H_2O (1 mL) at 0 °C. The mixture was diluted with EtOAc (10 mL), washed with H_2O (5 mL). The organic phase was dried with Na_2SO_4 and evaporated to dryness. The crude product was used directly in the next step of the reaction without purification. The resulting phenol, NaH (60%, 44 mg, 1.1 mmol), and THF (5 mL) was stirred at 0 °C for 10 min before N-succinimidyl-N-methylcarbamate (95 mg, 0.55 mol) was added. The resulting mixture was stirred at Room temperature for 2 h, quenched with water, and extracted with CH_2Cl_2. The organic layers were then combined, washed with brine, dried (Na_2SO_4), and concentrated. The residue was purified by using flash column chromatography (CH_2Cl_2/MeOH = 15:1) to give **10** as a colorless oil (96 mg, 70%). ^{1}H NMR, COSY (400 MHz, $CDCl_3$): δ/ppm =6.83 (dd, *J* = 8.4, 2.4 Hz, 1H, Ar-H6), 6.78 (d, *J* = 2.4 Hz, 1H, Ar-H4), 6.37 (d, *J* = 8.4 Hz, 1H, Ar-H7), 5.00 (brs, 1H, CH_3NH-), 4.22 (s, 1H, H8a), 2.95 (s, 3H, N_8-CH_3), 2.88 (d, *J* = 4.9 Hz, 3H, CH_3NH-), 2.85 – 2.76 (m, 1H, H2), 2.66 (dt, *J* = 9.4, 7.8 Hz, 1H, H2), 2.57 (s, 3H, N_1-CH_3), 2.06 – 1.97 (m, 2H, H3), 1.45 (s, 3H, C_{3a}-CH_3)).^{13}C NMR, HSQC, HMBC (100 MHz, $CDCl_3$): δ/ppm =156.1 (-NHCO-), 149.3 (C7a), 143.3 (C5), 137.2 (C3b), 120.6 (C4), 116.2 (C4), 106.8 (C7), 97.8 (C8a), 53.1 (C2), 52.7 (C3a), 40.5 (C3), 37.9 (N_1-CH_3), 37.2 (N_8-CH_3), 27.7 (CH_3NH-), 27.1 (C_{3a}-CH_3). Spectral data are in agreement with literature values.[35]

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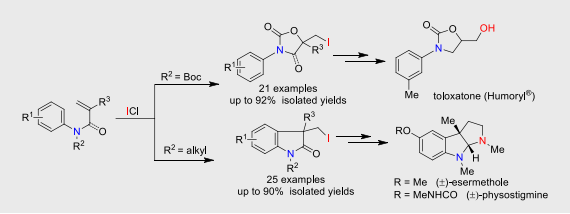

A metal-free method for the construction of oxazolidine-2,4-diones and oxindoles is reported herein. The resulting products can be used as key intermediates in syntheses of bioactive compound such as toloxatone, (±)-esermethole and (±)-physostigmine.

halocyclization.

Wei Yi, Xing-Xiao Fang, Qing-Yun Liu and Gong-Qing Liu [a]*

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Metal-free synthesis of oxazolidine-2,4-diones and 3,3-disubstituted oxindoles via the ICl-induced cyclization