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4-(Dimethylamino)pyridine-catalysed iodolactonisation of γ,δ-unsaturated carboxylic acids†

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4-(Dimethylamino)pyridine functioned as an excellent catalyst for iodolactonisation reactions of γ,δ-unsaturated carboxylic acids, affording γ-lactones, δ-lactones, or both under neutral conditions at room temperature. The effects of substrate structures on the iodolactonisation were investigated, and a catalytic mechanism is proposed.

Introduction

Five or six-membered lactones (γ- or δ-lactones) are present in a wide variety of natural products, and they also serve as building blocks and intermediates for the synthesis of natural products and pharmaceuticals.[1] Several strategies have been developed for the formation of lactones; among them, halolactonisation of unactivated olefins is a powerful and widely used method, since the resulting halogens on the lactones can provide flexible handles for further functionalisation. The reaction usually adopts olefinic acids as substrates and *N*-halosuccinimide as the halogen source, but the need for low temperature and the narrow substrate scope hinders the practical applications of this method.[2] Fortunately a combination of suitable catalysts and halogen sources has been found to accelerate the reaction, allow wider substrate scopes, or provide higher enantiomeric excesses. For example, Rousseau and coworkers adopted reactive bis(*sym*-collidine)iodine(I) hexafluorophosphate as the iodonium source to accomplish the medium-sized iodolactone formation;[3] Gao accomplished enantioselective iodolactonisations of *trans*-5-aryl-4-pentenoic acids with moderate enantiomeric excesses by using noncommercial chiral quaternary ammonium salts as chiral phase-transfer catalysts and *N*-iodosuccinimide (NIS) as the iodonium source;[4] Yeung found that the zwitterion formed from 3,5-(bistrifluoromethyl)phenyl isothiocyanate and *N*,*N*-dimethylaminopyridine (DMAP) could be used in the formation of seven- to nine-membered ring size lactones; however, when using *N*-chlorosuccinimide (NCS) and NIS instead of *N*-bromosuccinimide (NBS), the reaction yields were much lower.[5] He also developed some asymmetric bromolactonisation systems by using amino-thiocarbamate catalysts.[6]

DMAP has frequently been used to catalyse chemical reactions such as acylations,[7] esterifications,[8] Baylis–Hillman reactions,[9] and some other reactions.[10] Recently, as part of our ongoing investigation on the applications of DMAP in organic chemistry,[7e] we discovered that DMAP could act as an excellent catalyst for the iodolactonisation of γ,δ-unsaturated carboxylic acids with NIS as the iodonium source to form γ- and δ-lactones in high yields at room temperature, with reaction times ranging from 10 min to 2.5 h. Herein, we report the optimisation of the DMAP-catalysed iodolactonisation and the detailed investigation of the substrate scope, and a reasonable mechanism based on the results of preliminary NMR spectroscopy studies is proposed.

Results and discussion

The reaction conditions (the solvent and catalyst concentration) were optimised with 4-pentenoic acid (**1a**) as a model substrate (Table 1). In dichloromethane in the absence of a catalyst, **1a** was completely consumed within 2 h at room temperature, and the reaction proceeded *via* a 5-*exo* cyclisation to generate γ-lactone **2a** in 74% yield (entry 1). When 10 mol% DMAP was added to the reaction mixture, the reaction time was markedly shorter (10 min), and the yield increased to 99% (entry 2). A survey of other solvents (entries 3–8) revealed that the best results were obtained in dichloromethane. When the catalyst loading was reduced to 5 mol%, the reaction time increased to 30 min and the yield decreased slightly (entry 9). Therefore, all subsequent reactions were performed with 10 mol% DMAP at room temperature in dichloromethane.

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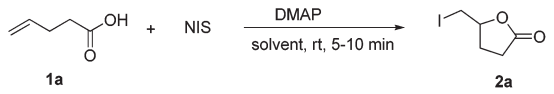
†Electronic supplementary information (ESI) available: GC spectra for Table 1, ^{1}H and ^{13}C NMR spectra for compounds **1** and **2**. See DOI: 10.1039/c5ob00806a

Table 1 DMAP-catalysed iodolactonisation of **1a**[a]



1a **2a**

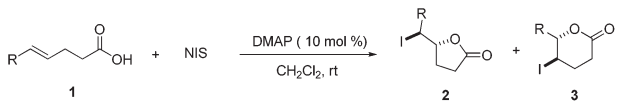
Entry	DMAP (mol%)	Time	Solvent	Conversion[b] (%)	Yield[b] (%)
1	None	2 h	CH_2Cl_2	100	74
2	10	10 min	CH_2Cl_2	100	99
3	10	10 min	CH_3CN	100	90
4	10	10 min	Acetone	100	88
5	10	10 min	MeOH	100	96
6	10	10 min	H_2O	100	94
7	10	10 min	Toluene	100	95
8	10	10 min	THF	100	92
9	5	30 min	CH_2Cl_2	100	95

[a] Reaction conditions: **1a** (2.5 mmol), NIS (3 mmol, 1.2 equiv.), and DMAP in 10 mL of solvent. [b] Conversion and yield determined by GC.

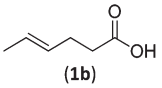
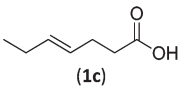
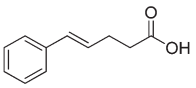
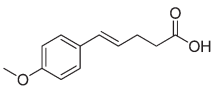
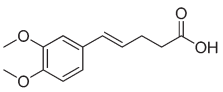
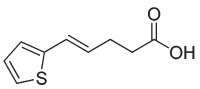
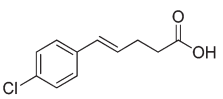
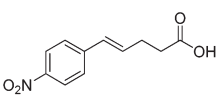
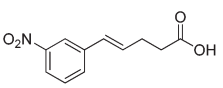
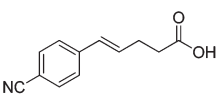
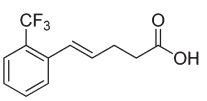
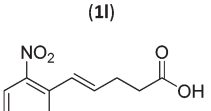
Under the optimised conditions (Table 1, entry 2), the substrate scope of the reaction was investigated with various 5-alkyl- and 5-aryl-4(*E*)-pentenoic acids (Table 2). All the tested substrates smoothly underwent iodolactonisation in the presence of 10 mol% DMAP and 1.2 equiv. of NIS at room temperature, although a longer reaction time was required for substrates with 5-aryl substituents. This increase in reaction time was likely due to both steric and electronic effects. It has previously been reported[4] that the products of iodolactonisation reactions of 4(*E*)-pentenoic acids depend on the electronic nature of the substituent at the 5-position. In our study, 5-alkyl-4(*E*)-pentenoic acid substrates mainly afforded γ-lactones, the structures of which were determined by H,H-COSY or by comparison with the literature data (entries 1 and 2). Iodolactonisation of 5-phenyl-4(*E*)-pentenoic acid (**1d**) generated both γ-lactone **2d** and δ-lactone **3d**, that is, products arising from 5-*exo* and 6-*endo* cyclisation, respectively, in a 25 : 75 ratio, as indicated by the analysis of the ^{1}H NMR spectrum of the crude reaction mixture (entry 3). Iodolactonisation of substrates with electron-rich aromatic rings, such as *p*-methoxyphenyl (**1e**), 3,4-dimethoxyphenyl (**1f**), and thienyl (**1g**), generated only δ-lactones (entries 4–6). Substrates with electron-deficient aromatic rings were well tolerated, but they preferentially afforded γ-lactones: specifically, mixtures of γ- and δ-lactones in ratios ranging from 25 : 1 to 100 : 1 were generated by the iodolactonisation reaction of 5-(4-chlorophenyl)-4(*E*)-pentenoic acid (**1h**) and the reactions of **1i**, **1j**, and **1k** (entries 7–10). Under the standard reaction conditions, a substrate bearing an electron-withdrawing CF_3 group at the *ortho* position of the aromatic ring (**1l**) gave only γ-lactone **2l** (entry 11).

It should be mentioned that although various *trans*-5-substituted-4-pentenoic acids afforded products arising from 5-*exo* or 6-*endo* cyclisation, all the products had high diastereomeric ratios because the iodolactonisation proceeded stereospecifically *via trans* nucleophilic addition to a cyclic iodonium intermediate.[1c] The relative configuration of the products is shown in Table 2. Furthermore, the fact that a 1 : 1 mixture of (*E*)- and

Table 2 Iodolactonisation of **1b–m** in the presence of DMAP[a]



1 **2** **3**

Entry	Substrate	Time	Yield[b] (%)	Product
1	 (**1b**)	10 min	92	**2b : 3b** 10 : 1
2	 (**1c**)	10 min	93	**2c : 3c** 10 : 1
3	 (**1d**)	2 h	86	**2d : 3d** 1 : 3
4	 (**1e**)	1 h	90	**3e**
5	 (**1f**)	1 h	92	**3f**
6	 (**1g**)	2 h	87	**3g**
7	 (**1h**)	2 h	84	**2h : 3h** 50 : 1
8	 (**1i**)	2.5 h	79	**2i : 3i** 100 : 1
9	 (**1j**)	2.5 h	73	**2j : 3j** 20 : 1
10	 (**1k**)	2.5 h	76	**2k : 3k** 50 : 1
11	 (**1l**)	2.5 h	70	**2l**
12	 (**1m** cis:trans 1:1)	2.5 h	75	**2m :** epimer 1 : 1

[a] Reaction conditions: **1b–m** (2.5 mmol), NIS (3 mmol, 1.2 equiv.), and DMAP in 10 mL of CH_2Cl_2. [b] Isolated yield.

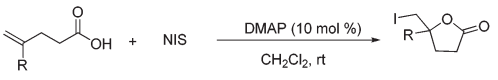
(*Z*)-**1m** afforded a pair of diastereoisomers of 5-*exo* lactone **2m** in a 1 : 1 ratio (entry 12) indicated that the reaction had a very high stereospecificity.

Next, we investigated the iodolactonisation reactions of 4-pentenoic acids with an aliphatic or aryl substituent at the 4-position (Table 3). We were delighted to find that all the tested substrates underwent iodolactonisation *via* 5-*exo* cyclisation in the presence of DMAP (10 mol%) to furnish γ-lactones in high yields as the only isolable products, although the 4-aryl-4-pentonic acids required slightly longer reaction times (entries 3–10). A substrate with a naphthyl group also underwent the DMAP-catalysed iodolactonisation smoothly (entry 11).

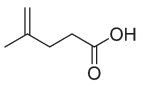
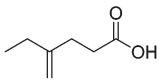
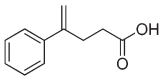
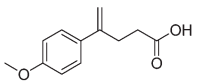
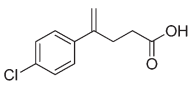
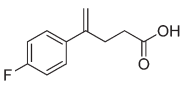
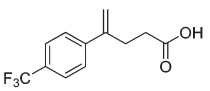
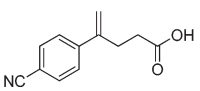
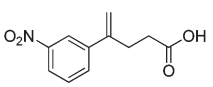
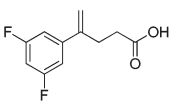
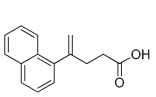
The good catalytic performance of DMAP in the above-described iodolactonisation reactions aroused our interest in its role in the reaction. We speculated that the electron-donating effect of the dimethylamino substituent increased the electron density of the pyridine ring, thus strengthening the nucleophilicity of the pyridine nitrogen atom, which was likely to have activated NIS to some extent. We used ^{1}H NMR spectroscopy to verify this speculation. The chemical shift of the methylene hydrogen atoms of NIS was at 3.04 ppm in deuterated chloroform, whereas the signal shifted upfield to 2.75 ppm in the presence of equimolar DMAP (Fig. 1). This result illustrates that the electron density of the dicarboximide ring was increased by the addition of DMAP. In contrast, DMAP and NBS could not form into a complex because no changes in the chemical shifts were found.[5] The nucleophilic nitrogen atom of the pyridine ring of DMAP can interact with the iodine atom of NIS, leading to an increase in the distance between the iodine atom and the nitrogen atom of NIS and movement of the electrons in the I–N bond toward the dicarboximide ring.

With this evidence in hand, we propose the following mechanism for the DMAP-catalysed iodolactonisation reactions (Scheme 1). NIS is initially activated by DMAP to form complex **I**, then the positively-charged iodonium atom adds to the double bond of the γ,δ-unsaturated carboxylic acid substrate to give iodonium intermediate **II**. Deprotonation of the carboxyl group by the succinimide anion and subsequent nucleophilic addition of the carbonyl oxygen to cyclic iodonium intermediate **II** afford the target γ- or δ-lactone with simultaneous release of DMAP. The 6-*endo* selectivity of the reactions of substrates with electron-rich aromatic rings may be due to the fact that these substrates can stabilise the developing positive charge at the benzylic position;[1c,11] whereas this circumstance is unfavorable in substrates with electron-poor aromatic rings, so they undergo the 5-*exo* mode of ring closure. Unlike aromatic rings, alkyl substituents cannot stabilise the developing positive charge, so alkyl-substituted substrates preferentially undergo the *exo* mode of ring closure, which is consistent with Baldwin's rules.[12] Substrates with substituents at the 4-position have no choice but to undergo 5-*exo* cyclisation, owing to the instability of the primary alkyl carbenium ions.

Table 3 Iodolactonisation of **1n–x** in the presence of DMAP[a]



1 **2**

Entry	Substrate	Time	Yield[b] (%)	Product
1	 (**1n**)	10 min	94	**2n**
2	 (**1o**)	10 min	94	**2o**
3	 (**1p**)	2 h	87	**2p**
4	 (**1q**)	1 h	89	**2q**
5	 (**1r**)	2 h	87	**2r**
6	 (**1s**)	2 h	86	**2s**
7	 (**1t**)	2.5 h	81	**2t**
8	 (**1u**)	2.5 h	85	**2u**
9	 (**1v**)	2.5 h	83	**2v**
10	 (**1w**)	2.5 h	70	**2w**
11	 (**1x**)	2 h	84	**2x**

[a] Reaction conditions: **1n–x** (2.5 mmol), NIS (3 mmol, 1.2 equiv.), and DMAP in 10 mL of CH_2Cl_2. [b] Isolated yield.

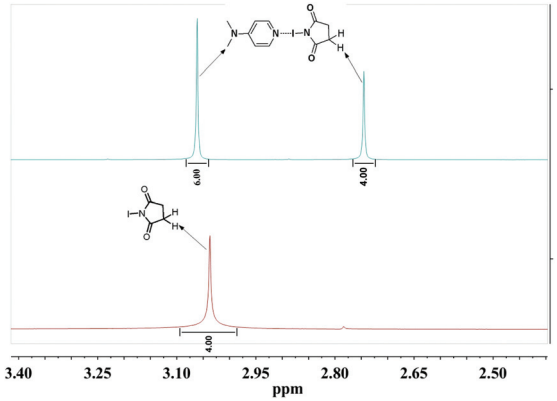
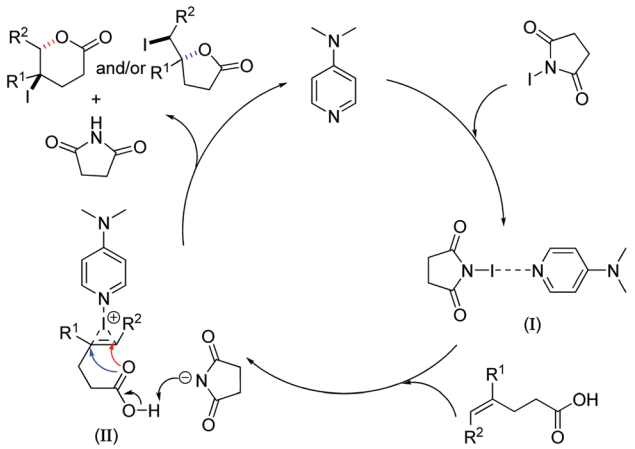


Fig. 1 ^{1}H NMR spectra of NIS alone (lower panel) and an equimolar mixture of DMAP and NIS (upper panel) in deuterated chloroform 10 min after mixing.



Scheme 1 Proposed mechanism of DMAP-catalysed iodolactonisation.

Conclusions

In summary, we used DMAP as a unique catalyst for iodolactonisation reactions in which DMAP served two purposes in the catalytic cycle: it activated NIS and stabilised the iodonium intermediate. ^{1}H NMR spectroscopy was used to support a proposed mechanism. With catalysis by DMAP, γ,δ-unsaturated carboxylic acids could be efficiently and regioselectively converted to γ- or δ-lactones under mild conditions.

Experimental section

^{1}H NMR and ^{13}C NMR spectra were recorded at 400 MHz using a Bruker AV400 spectrometer in $CDCl_3$ or DMSO-d_6 with tetramethylsilane as the internal standard. Chemical shift values (δ) are given in parts per million (ppm). Gas chromatograms were obtained using a Shimadzu GC-2014 FID detector. The melting points were determined using an X-4 Melting Point Apparatus with a Binocular Microscope and are uncorrected. High-Resolution Mass Spectra (HRMS) were recorded with an FT-ICR MS spectrometer (IonSpec, 7.0 T).

Synthesis of olefinic acids

(*E*)-5-Alkyl-4-pentenoic acids (**1b–c**), (*E*)-5-aryl-4-pentenoic acids (**1d–m**), 4-alkyl-4-pentenoic acids (**1n–o**) and 4-aryl-4-pentenoic acids (**1p–x**) were prepared according to literature procedures;[6,13,14] characterisation data for new compounds are reported in the ESI.†

General procedure for the DMAP-catalysed iodolactonisations

To a solution of γ-unsaturated carboxylic acid (2 mmol, 1.0 eq.), catalyst DMAP (0.2 mmol, 0.1 eq.) in CH_2Cl_2 (10 mL) in the dark was added NIS (2.4 mmol, 1.2 eq.). The resulting mixture was stirred at room temperature and monitored by TLC. After the reaction was complete, the reaction mixture was quenched with saturated Na_2SO_3 (20 mL), diluted with water (30 mL), and extracted with CH_2Cl_2 (3 × 10 mL). The combined extracts were washed with brine (20 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by flash column chromatography to give the corresponding product.

5-(Iodomethyl)dihydrofuran-2(3*H*)-one (2a). Colourless oil, yield: 94%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.61–4.55 (m, 1H), 3.45–3.36 (m, 2H), 2.71–2.57 (m, 2H), 2.55–2.45 (m, 1H), 2.05–1.96 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.4, 78.5, 28.9, 28.1, 8.4. HRMS (ESI): calcd for $C_5H_8IO_2$ $[M + H]^+$: 226.9563; found: 226.9561.

5-(1-Iodoethyl)dihydrofuran-2(3*H*)-one (2b) and 5-iodo-6-methyltetrahydro-2*H*-pyran-2-one (3b). Colourless oil; yield: 92%; ^{1}H NMR (400 MHz, $CDCl_3$) for **2b**: δ 4.19–4.30 (m, 2H), 2.51–2.67 (m, 2H), 2.45–2.51 (m, 1H), 1.99–2.05 (m, 1H), 1.97 (d, J = 6.2 Hz, 3H); for **3b**: δ 4.60–4.70 (m, 1H), 4.00–4.10 (m, 1H), 2.38–2.60 (m, 3H), 1.99–2.05 (m, 1H), 1.59 (d, J = 6.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) for **2b**: δ 176.4, 83.4, 29.5, 29.0, 27.9, 24.2; for **3b**: 169.8, 81.7, 32.1, 30.9, 24.3, 21.5; HRMS (ESI): calcd for $C_6H_{10}IO_2$ $[M + H]^+$: 240.9719; found: 240.9715. The ratio of integrals for H-6 of **2b** and **3b** was 10 : 1 observed by ^{1}H NMR spectroscopy.

5-(1-Iodopropyl)dihydrofuran-2(3*H*)-one (2c) and 6-ethyl-5-iodotetrahydro-2*H*-pyran-2-one (3c). Colourless oil; yield: 93%; ^{1}H NMR (400 MHz, $CDCl_3$) for **2c**: δ 4.41 (q, J = 7.2 Hz, 1H), 4.11 (td, J = 7.2 Hz, J = 3.6 Hz, 2H), 2.63–2.48 (m, 3H), 2.09–1.92 (m, 2H), 1.85–1.78 (m, 1H), 1.08 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) for **2c**: δ 176.5, 81.8, 41.9, 29.1, 29.0, 28.5, 13.7; for **3c**: 170.0, 85.9, 31.8, 30.8, 27.7, 22.4, 8.71; HRMS (ESI): calcd for $C_7H_{12}IO_2$ $[M + H]^+$: 254.9876; found: 254.9875. The ratio of integrals for methyl of **2c** and **3c** was 10 : 1 observed by ^{1}H NMR spectroscopy.

5-(Iodo(phenyl)methyl)dihydrofuran-2(3*H*)-one (2d) and 5-iodo-6-phenyltetrahydro-2*H*-pyran-2-one (3d). White solid; mp: 95 °C (decomposition); yield: 86%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39–7.30 (m, 5H), 5.55 (d, J = 8.0 Hz, 0.75H), 5.13 (d, J = 8.0 Hz, 0.25H), 4.88 (q, J = 8.0 Hz, 0.25H), 4.42 (q, J = 8.0 Hz, 0.75H), 2.89–2.81 (m, 0.75H), 2.73–2.67 (m, 0.75H),

2.60–2.53 (m, 0.75H), 2.48–2.33 (m, 1.50H), 2.19–2.12 (m, 0.25H); HRMS (ESI): calcd for $C_{12}H_{12}IO_2$ $[M + H]^+$: 302.9876; found: 302.9872. The ratio of integrals for H-6 of **2d** and **3d** was 1 : 3 observed by ^1H NMR spectroscopy.

5-Iodo-6-(4-methoxyphenyl)tetrahydro-2*H*-pyran-2-one (3e). White solid; mp: 65 °C (decomposition); yield: 90%; ^1H NMR (400 MHz, $CDCl_3$): δ 7.25 (d, J = 8.0 Hz, 2H), 6.91 (d, J = 8.0 Hz, 2H), 5.49 (d, J = 8.0 Hz, 1H), 4.41–4.36 (m, 1H), 3.82 (s, 3H), 2.87–2.79 (m, 1H), 2.74–2.66 (m, 1H), 2.55–2.47 (m, 1H), 2.46–2.38 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.4, 160.2, 129.8, 128.2, 114.0, 86.9, 55.3, 31.0, 30.7, 24.8; HRMS (ESI): calcd for $C_{12}H_{14}IO_3$ $[M + H]^+$: 332.9982; found: 332.9985.

6-(3,4-Dimethoxyphenyl)-5-iodotetrahydro-2*H*-pyran-2-one (3f). White solid; mp: 50 °C (decomposition); yield: 92%; ^1H NMR (400 MHz, $CDCl_3$): δ 6.90 (dd, J = 8.0 Hz, J = 2.0 Hz, 1H), 6.86 (d, J = 8.0 Hz, 1H), 6.81 (d, J = 2.0 Hz, 1H), 5.48 (d, J = 8.0 Hz, 1H), 4.41 (td, J = 8.0 Hz, J = 4.0 Hz, 1H), 3.90 (s, 3H), 3.89 (s, 3H), 2.87–2.79 (m, 1H), 2.75–2.67 (m, 1H), 2.54–2.39 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.4, 149.7, 149.1, 130.1, 119.8, 110.8, 109.6, 87.0, 56.0, 55.9, 31.0, 30.6, 24.7; HRMS (ESI): calcd for $C_{13}H_{16}IO_4$ $[M + H]^+$: 363.0093; found: 363.0085.

5-Iodo-6-(thiophen-2-yl)tetrahydro-2*H*-pyran-2-one (3g). White solid; mp: 60 °C (decomposition); yield: 87%; ^1H NMR (400 MHz, $CDCl_3$): δ 7.38 (d, J = 8.0 Hz, 1H), 7.13 (d, J = 8.0 Hz, 1H), 7.03 (t, J = 8.0 Hz, 1H), 5.82 (t, J = 8.0 Hz, 1H), 4.49 (d, J = 4.0 Hz, 1H), 2.87–2.79 (m, 1H), 2.73–2.67 (m, 1H), 2.54–2.48 (m, 1H), 2.42–2.35 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.5, 140.6, 127.2, 126.9, 126.5, 83.1, 30.8, 30.4, 24.2; HRMS (ESI): calcd for $C_9H_{10}IO_2S$ $[M + H]^+$: 308.9446; found: 308.9438.

5-((4-Chlorophenyl)iodomethyl)dihydrofuran-2(3*H*)-one (2h) and 6-(4-chlorophenyl)-5-iodotetrahydro-2*H*-pyran-2-one (3h). The ratio of integrals for H-6 of **2h** and **3h** was 50 : 1. Semi-solid; yield: 84%; ^1H NMR (400 MHz, $CDCl_3$): δ 7.36 (d, J = 8.0 Hz, 2H), 7.29 (d, J = 8.0 Hz, 2H), 5.06 (d, J = 8.0 Hz, 1H), 4.89 (q, J = 8.0 Hz, 1H), 2.68–2.51 (m, 3H), 2.15–2.05 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.0, 138.0, 134.4, 129.5, 129.1, 82.4, 32.7, 29.3, 29.0; HRMS (ESI): calcd for $C_{11}H_{10}ClIO_2Na$ $[M + Na]^+$: 358.9300; found: 358.9307.

5-(Iodo(4-nitrophenyl)methyl)dihydrofuran-2(3*H*)-one (2i) and 5-iodo-6-(4-nitrophenyl)tetrahydro-2*H*-pyran-2-one (3i). The ratio of integrals for H-6 of **2i** and **3i** was 100 : 1. White solid; mp: 120–121 °C; yield: 79%; ^1H NMR (400 MHz, $CDCl_3$): δ 8.19 (d, J = 8.8 Hz, 2H), 7.59 (d, J = 8.8 Hz, 2H), 5.09 (d, J = 9.2 Hz, 1H), 5.01 (dd, J = 16.0 Hz, J = 8.0 Hz, 1H), 2.78–2.69 (m, 1H), 2.65–2.60 (m, 2H), 2.19–2.09 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.7, 147.6, 146.8, 129.1, 124.1, 81.9, 30.5, 29.3, 29.2; HRMS (ESI): calcd for $C_{11}H_{10}INO_4Na$ $[M + Na]^+$: 369.9535; found: 369.9536.

5-(Iodo(3-nitrophenyl)methyl)dihydrofuran-2(3*H*)-one (2j) and 5-iodo-6-(3-nitrophenyl)tetrahydro-2*H*-pyran-2-one (3j). The ratio of integrals for H-6 of **2j** and **3j** was 25 : 1. White solid; mp: 143–144 °C; yield: 73%; ^1H NMR (400 MHz, $CDCl_3$): δ 8.28 (s, 1H), 8.14 (d, J = 8.0 Hz, 1H), 7.75 (d, J = 7.2 Hz, 1H), 7.52 (t, J = 8.0 Hz, 1H), 5.11 (d, J = 8.0 Hz, 1H), 5.03 (dd, J = 16.0 Hz, J = 8.0 Hz, 1H), 2.75 (dd, J = 12.0 Hz, J = 8.0 Hz, 1H), 2.63 (t, J = 8.0 Hz, 2H), 2.15 (t, J = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.8, 148.3, 141.9, 134.2, 130.1, 123.5, 122.9, 82.0, 30.7, 29.4, 29.2; HRMS (ESI): calcd for $C_{11}H_{10}INO_4Na$ $[M + Na]^+$: 369.9535; found: 369.9536.

5-(Iodo(2-nitrophenyl)methyl)dihydrofuran-2(3*H*)-one (2m) and its epimer. White solid; mp: 128–129 °C; yield: 75%; ^1H NMR (400 MHz, $CDCl_3$): δ 8.05 (dd, J = 8.0 Hz, J = 1.2 Hz, 0.5H), 7.92 (dd, J = 8.0 Hz, J = 1.2 Hz, 0.5H), 7.86 (ddd, J = 8.0 Hz, J = 1.2 Hz, 1H), 7.65 (td, J = 8.0 Hz, J = 1.2 Hz, 1H), 7.47 (td, J = 8.0 Hz, J = 1.2 Hz, 1H), 5.89 (d, J = 4.0 Hz, 0.73H), 5.86 (s, 0.27H), 5.17–5.12 (m, 0.5H), 4.37–4.33 (m, 0.5H), 2.85–2.71 (m, 1H), 2.70–2.62 (m, 1.44H), 2.62–2.44 (m, 0.56H), 2.26–2.05 (m, 1H). HRMS (ESI): calcd for $C_{11}H_{10}INO_4Na$ $[M + Na]^+$: 369.9535; found: 369.9536. The ratio of integrals for H-5 of diastereoisomers of **2m** was 1 : 1.

4-(Iodo(5-oxotetrahydrofuran-2-yl)methyl)benzonitrile (2k) and 4-(3-iodo-6-oxotetrahydro-2*H*-pyran-2-yl)benzonitrile (3k). The ratio of integrals for H-6 of **2k** and **3k** was 50 : 1. White solid; mp: 159 °C (decomposition); yield: 76%; ^1H NMR (400 MHz, $CDCl_3$): δ 7.62 (d, J = 8.0 Hz, 2H), 7.53 (d, J = 8.0 Hz, 2H), 5.05 (d, J = 12.0 Hz, 1H), 4.97 (dd, J = 16.0 Hz, J = 8.0 Hz, 1H), 2.73–2.67 (m, 1H), 2.65–2.59 (m, 2H), 2.17–2.07 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.8, 144.8, 132.7, 128.9, 118.3, 112.3, 81.9, 31.2, 29.3, 29.1; HRMS (ESI): calcd for $C_{13}H_{11}INO_4$ $[M + HCOO]^-$: 371.9739; found: 371.9736.

5-(Iodo(2-(trifluoromethyl)phenyl)methyl)dihydrofuran-2(3*H*)-one (2l). White solid; mp: 78–79 °C; yield: 70%; 1H NMR (400 MHz, $CDCl_3$): δ 7.83 (d, J = 8.0 Hz, 1H), 7.60–7.54 (m, 2H), 7.38 (t, J = 9.2 Hz, 1H), 5.40 (d, J = 13.2 Hz, 1H), 5.06 (dd, J = 15.0 Hz, J = 7.2 Hz, 2H), 2.72–2.58 (m, 3H), 2.22–2.17 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.8, 138.5, 132.7, 131.2, 128.4, 126.9 (q, $J_{C,F}$ = 29.7 Hz), 126.0 (q, $J_{C,F}$ = 5.8 Hz), 124.2 (q, $J_{C,F}$ = 272.4 Hz), 82.8, 29.0, 28.5, 25.7; HRMS (ESI): calcd for $C_{13}H_{11}F_3IO_4$ $[M + HCOO]^-$: 414.9660; found: 414.9655.

5-(Iodomethyl)-5-methyldihydrofuran-2(3*H*)-one (2n). Colourless oil; yield: 94%; ^1H NMR (400 MHz, $CDCl_3$): δ 3.45–3.38 (m, 2H), 2.76–2.61 (m, 2H), 2.37–2.29 (m, 1H), 2.19–2.12 (m, 1H), 1.63 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.8, 83.8, 32.8, 29.5, 26.0, 14.6; HRMS (ESI): calcd for $C_6H_{10}IO_2$ $[M + H]^+$: 240.9719; found: 240.9715.

5-Ethyl-5-(iodomethyl)dihydrofuran-2(3*H*)-one (2o). Colourless oil; yield: 94%; ^1H NMR (400 MHz, $CDCl_3$): δ 3.40–3.30 (m, 2H), 2.64–2.54 (m, 2H), 2.19–2.13 (m, 2H), 1.89–1.82 (m, 2H), 0.97–0.88 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.0, 86.1, 31.6, 30.7, 29.4, 13.3, 8.0; HRMS (ESI): calcd for $C_7H_{12}IO_2$ $[M + H]^+$: 254.9876; found: 254.9875.

5-(Iodomethyl)-5-phenyldihydrofuran-2(3*H*)-one (2p). Colourless oil; yield: 87%; ^1H NMR (400 MHz, $CDCl_3$): δ 7.39 (s, 5H), 3.63 (s, 2H), 2.77–2.48 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.3, 140.7, 128.8, 128.5, 124.9, 86.0, 33.9, 29.2, 16.5; HRMS (ESI): calcd for $C_{11}H_{12}IO_2$ $[M + H]^+$: 302.9876; found: 302.9868.

5-(Iodomethyl)-5-(4-methoxyphenyl)dihydrofuran-2(3*H*)-one (2q). Colourless oil; yield: 89%; ^1H NMR (400 MHz, $CDCl_3$): δ 7.24 (d, J = 8.0 Hz, 2H), 6.83 (d, J = 8.0 Hz, 2H), 3.74 (s, 3H), 3.52 (s, 2H), 2.71–2.60 (m, 2H), 2.59–2.54 (m, 1H), 2.52–2.41 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.5, 159.7, 132.4,

126.3, 114.1, 86.0, 55.4, 33.8, 29.3, 16.8; HRMS (ESI): calcd for $C_{12}H_{14}IO_3$ $[M + H]^+$: 332.9982; found: 332.9985.

5-(4-Chlorophenyl)-5-(iodomethyl)dihydrofuran-2(3*H*)-one (2r). Colourless oil; yield: 87%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37 (s, 2H), 7.36 (s, 2H), 3.59 (s, 2H), 2.81–2.68 (m, 2H), 2.60–2.50 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.0, 139.2, 134.6, 129.0, 126.4, 85.6, 33.9, 29.2, 15.7; HRMS (ESI): calcd for $C_{11}H_{11}ClO_2$ $[M + H]^+$: 336.9486; found: 336.9481.

5-(4-Fluorophenyl)-5-(iodomethyl)dihydrofuran-2(3*H*)-one (2s). Colourless oil; yield: 86%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39 (dd, J = 8.0 Hz, J = 4.0 Hz, 2H), 7.09 (t, J = 8.0 Hz, 2H), 3.60 (s, 2H), 2.82–2.50 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.0, 162.6 (d, $J_{C,F}$ = 247.0 Hz), 136.5 (d, $J_{C,F}$ = 3.0 Hz), 126.9 (d, $J_{C,F}$ = 9.0 Hz), 115.8 (d, $J_{C,F}$ = 9.0 Hz), 85.7, 33.9, 29.2, 16.0; HRMS (ESI): calcd for $C_{11}H_{11}FIO_2$ $[M + H]^+$: 320.9782; found: 320.9779.

5-(Iodomethyl)-5-(4-(trifluoromethyl)phenyl)dihydrofuran-2(3*H*)-one (2t). Colourless oil; yield: 81%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.68 (d, J = 8.0 Hz, 2H), 7.55 (d, J = 8.0 Hz, 2H), 3.62 (s, 2H), 2.83–2.73 (m, 2H), 2.65–2.53 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.8, 144.71, 130.9 (q, J = 32.0 Hz), 125.9 (q, J = 4.0 Hz), 125.5, 123.8 (q, J = 270.0 Hz), 85.6, 34.0, 29.1, 15.2; HRMS (ESI): calcd for $C_{13}H_{11}F_3IO_4$ $[M + HCOO]^-$: 414.9660; found: 414.9655.

4-(2-(Iodomethyl)-5-oxotetrahydrofuran-2-yl)benzonitrile (2u). White solid; mp: 138–139 °C; yield: 85%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.72 (d, J = 8.0 Hz, 2H), 7.54 (d, J = 8.0 Hz, 2H), 3.60 (s, 2H), 2.86–2.72 (m, 2H), 2.65–2.51 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.5, 146.0, 132.7, 125.9, 118.1, 112.7, 85.4, 33.9, 29.0, 14.7; HRMS (ESI): calcd for $C_{13}H_{11}INO_4$ $[M + HCOO]^-$: 371.9739; found: 371.9736.

5-(Iodomethyl)-5-(3-nitrophenyl)dihydrofuran-2(3*H*)-one (2v). Colourless oil; yield: 83%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.28 (s, 1H), 8.24 (d, J = 8.0 Hz, 1H), 8.21 (d, J = 8.0 Hz, 1H), 7.64 (t, J = 8.0 Hz, 1H), 3.67 (s, 2H), 2.91–2.81 (s, 2H), 2.76–2.68 (s, 1H), 2.63–2.54 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.5, 148.4, 143.2, 131.2, 130.1, 123.6, 120.2, 85.3, 33.8, 29.1, 15.0; HRMS (ESI): calcd for $C_{12}H_{11}INO_6$ $[M + HCOO]^-$: 391.9637; found: 391.9635.

5-(3,5-Difluorophenyl)-5-(iodomethyl)dihydrofuran-2(3*H*)-one (2w). White solid; mp: 61–62 °C; yield: 70%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.98 (d, J = 2.0 Hz, 1H), 6.96 (d, J = 2.0 Hz, 1H), 6.83 (tt, J = 8.0 Hz, J = 2.0 Hz, 1H), 3.60 (s, 2H), 2.85–2.71 (m, 2H), 2.64–2.54 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.5, 163.1 (dd, $J_{C,F}$ = 249.0, 13.0 Hz), 144.8 (t, $J_{C,F}$ = 9.0 Hz), 108.5 (dd, $J_{C,F}$ = 19.0, 8.0 Hz), 104.2 (t, $J_{C,F}$ = 25.0 Hz), 85.1, 33.9, 29.0, 14.6; HRMS (ESI): calcd for $C_{11}H_{10}F_2IO_2$ $[M + H]^+$: 338.9688; found: 338.9677.

5-(Iodomethyl)-5-(naphthalen-1-yl)dihydrofuran-2(3*H*)-one (2x). Semi solid; yield: 84%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.92–7.78 (m, 4H), 7.58–7.43 (m, 3H), 4.15 (d, J = 8.0 Hz, 1H), 3.81 (d, J = 11.6 Hz, 1H), 3.09–3.01 (m, 1H), 2.98–2.83 (m, 2H), 2.57–2.48 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.2, 136.0, 134.7, 130.0, 129.9, 128.7, 126.6, 125.8, 125.3, 123.9, 123.8, 86.9, 34.2, 29.2, 16.8; HRMS (ESI): calcd for $C_{15}H_{14}IO_2$ $[M + H]^+$: 353.0032; found: 353.0022.

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