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Iodine as a mild and efficient catalyst for the diastereoselective synthesis of δ-silyloxy-γ-lactones

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ABSTRACT

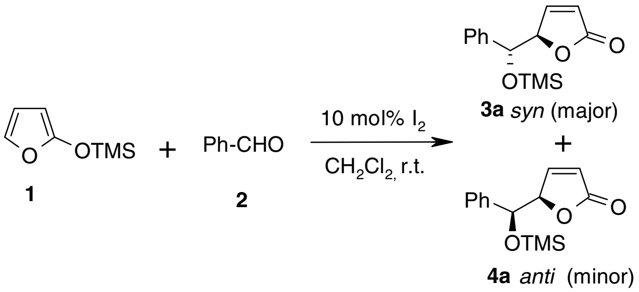
Aldehydes undergo smooth nucleophilic addition with 2-trimethylsilyloxyfuran in the presence of 10 mol % of iodine under mild and neutral conditions to produce the corresponding δ-silyloxy-α,β-unsaturated-γ-lactones in high yields and with moderate diastereoselectivity. *ortho*-Substituted benzaldehydes afford the *syn*-isomer predominantly. The use of iodine makes this procedure quite simple, more convenient and cost-effective.

Lewis acid-catalyzed carbon–carbon bond forming reactions are of prime importance in organic synthesis because of their mild reaction conditions, unique reactivity and improved selectivities.[1] Butenolides (α,β-unsaturated-γ-lactones) are versatile building blocks for the synthesis of several biologically active natural products such as cavernosine,[2] A26771B[3] and many others.[4] The catalytic coupling of 2-(trimethylsilyloxy)furan with aldehydes in the presence of Lewis acids is one of the most efficient methods for the synthesis of δ-hydroxy-α,β-unsaturated-γ-lactones.[5] Lewis acids such as $BF_3{\cdot}OEt_2$, TMSOTf, $ZnCl_2$, $TiCl_4$, $SnCl_4$, $SiCl_4$ and silyl triflates have been known to catalyze this reaction under strictly anhydrous conditions.[6,7] The presence of even a small amount of water results in lower yields probably due to the rapid decomposition or deactivation of the promoters. Recently, bismuth triflate was found to catalyze this reaction at low temperature (−78 °C).[8] However, the high cost, stringent conditions and moisture sensitivity of some of these reagents limit their use in large scale synthesis. Therefore, the development of new reagents that are more efficient leading to convenient procedures with improved yields and selectivity is desirable.

Recently, molecular iodine has received considerable attention as an inexpensive, non-toxic and readily available catalyst for various organic transformations affording the corresponding products with high selectivity and in excellent yields. The mild Lewis acidity associated with iodine has enhanced its use in organic synthesis to perform several organic transformations using stoichiometric levels to catalytic amounts.[9]

In continuation of our interest on catalytic applications of molecular iodine,[10] we herein report a simple, convenient and metal free synthesis of δ-silyloxy-α,β-unsaturated-γ-lactones by means of coupling of 2-(trimethylsilyloxy)furan with various aldehydes under mild conditions. Thus, treatment of 2-(trimethylsilyloxy)furan (**1**) with benzaldehyde (**2**) in the presence of 10 mol % of I_2 afforded the corresponding δ-silyloxy-α,β-unsaturated-γ-lactone in 89% yield as a mixture of *syn*:*anti*-isomers (**3a**/**4a**, 70:30; Scheme 1).

This result provided the incentive for further study with aldehydes such as 2-methoxy-, 2,5-dimethoxy-, 2,4-dimethoxy-, 3,4,5-trimethoxy-, 4-methyl-, 4-nitro-, 4-chloro- and 3,4-methylenedioxy-benzaldehyde. Interestingly, these substituted aryl



Scheme 1. Reaction of benzaldehyde with 2-(trimethylsilyloxy)furan.

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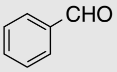
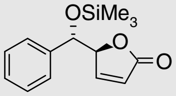
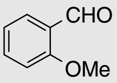
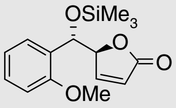
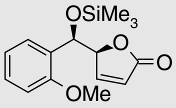
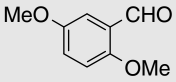
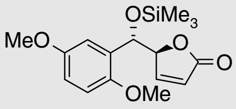
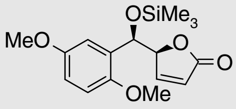
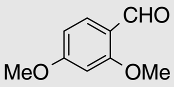
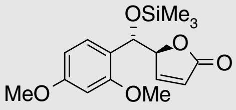
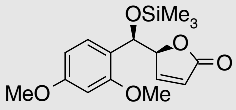
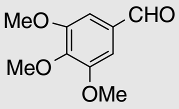
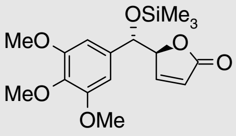
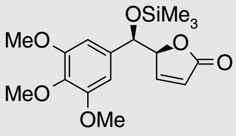
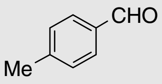
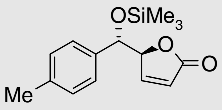
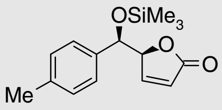
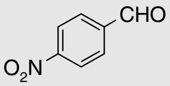
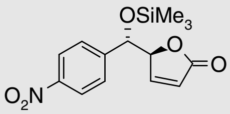
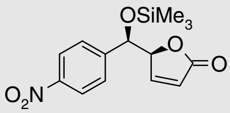
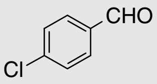
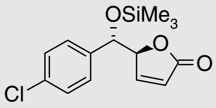
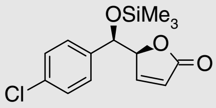
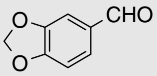
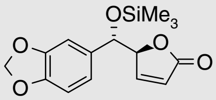
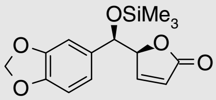
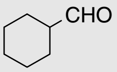
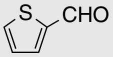
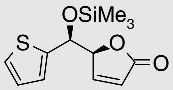
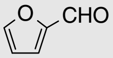
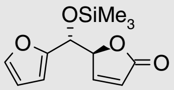
Table 1
Iodine-catalyzed preparation of butenolides from aldehydes and 2-(trimethylsiloxy)furan

Entry	Aldehyde	Product[a]		Time (h)	Yield[b] (%)	*syn*:*anti*[c]
a				4.0	89	70:30
b				3.5	92	75:25
c				3.0	90	78:22
d				3.5	88	75:25
e				4.0	85	70:30
f				5.0	82	72:28
g				4.5	80	67:33
h				5.0	83	70:30
i				4.0	85	70:30
j				5.0	83	65:35
k				4.0	89	60:40
l				4.0	85	75:25

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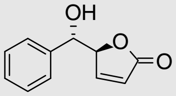
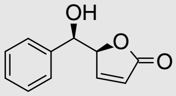
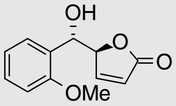
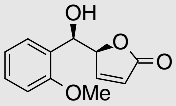
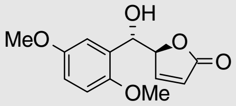
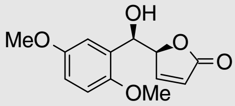
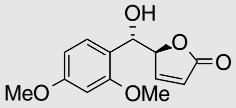
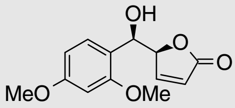
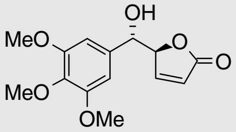
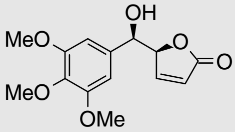
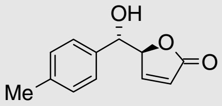
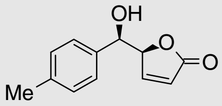
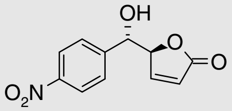
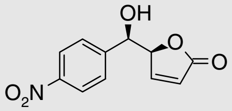
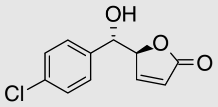
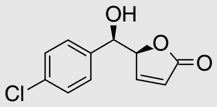
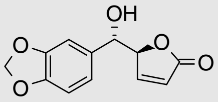
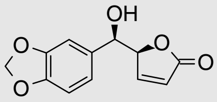
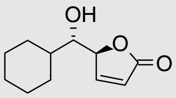
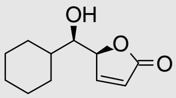
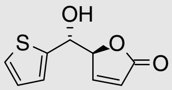
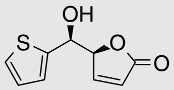
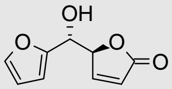
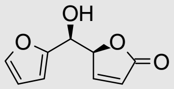
[a] The products were characterized by ^{1}H NMR, IR and mass spectrometry.

[b] Yield refers to pure products after chromatography.

[c] *Syn* and *anti* ratio was determined by ^{1}H NMR spectroscopy of the crude products.

Table 2
Optimization of the reaction conditions

Entry	Product[a]		Time (h)	Yield[b] (%)	*syn*:*anti*[c]
a			3.5	85	80:20
b			4.0	87	85:15
c			3.0	82	85:15
d			4.0	81	80:20
e			4.0	80	73:27
f			5.0	75	78:22
g			5.5	72	73:27
h			4.5	74	75:24
i			4.5	78	73:27
j			4.0	73	75:25
k			4.0	82	66:34
l			4.0	78	78:22

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[a] The reactions were carried out at −78 °C.

[b] Yield refers to pure products after chromatography.

[c] *Syn* and *anti* ratio was determined by ^{1}H NMR spectroscopy of the crude products.

aldehydes reacted well with 2-(trimethylsilyloxy)furan to provide the corresponding butenolides in high to excellent yields (Table 1). The reactions proceeded smoothly at room temperature under mild and neutral conditions. In most cases, the products were obtained as a mixture of *syn*- and *anti*-isomers, favouring the *syn*-isomer, which could be easily separated by column chromatography. The stereochemistry (*syn* and *anti*) of the products was assigned on the basis of the coupling constants of the protons in the ^{1}H NMR spectra of the products and also by comparison with authentic samples.[5–8] Both electron-rich and electron-deficient aromatic aldehydes participated effectively in this reaction. Aliphatic aldehydes such as cyclohexanecarboxaldehyde also reacted well with 2-(trimethylsilyloxy)furan to afford the corresponding γ-butyrolactone in 83% yield with moderate diastereoselectivity (Table 1, entry j). Similarly, heteroaromatic substrates such as thiophene-2-carboxaldehyde and furfural gave the respective butenolides in high yields (Table 1, entries k and l).[11]

The product ratio was determined by ^{1}H NMR spectroscopy of the crude products. In the case of *ortho*-substituted benzaldehydes, the products were formed with high *syn*-selectivity (Table 1, entries b–d). However, the diastereoselectivity could be improved by carrying out the reactions at -78 °C in diethyl ether, but the products were obtained as hydroxy compounds instead of OTMS ethers, and the results are presented in Table 2.

However, in the absence of iodine, the reaction did not proceed even after a long reaction time. Furthermore, the use of the tri-*n*-butyltin derivative of furan in place of 2-(trimethylsilyloxy)furan did not yield the desired product under these reaction conditions, perhaps because iodine does not interact with tri-*n*-butyltin. Thus, the combination of 2-(trimethylsilyloxy)furan and iodine is a useful method for addition of TMS to aldehydes. Interestingly, a catalytic amount of TMSI was also found to be an equally effective catalyst for this conversion. No additives or activators were required for the activation of the aldehyde. In all cases, the reactions proceeded smoothly at room temperature under the influence of 10 mol % of iodine, and the yields were generally high to excellent. The trimethylsilyl ethers of the butenolides were treated with 10% aqueous HCl (1 mL) in ether (5 mL) at 0 °C for 10–20 min to afford the corresponding δ-hydroxy-butenolides in quantitative yields. The advantages of this method are high conversions, ready availability of the catalyst, high atom efficiency, no salt formation and avoidance of heavy transition metal catalysts.

In summary, molecular iodine has proved to be an effective catalyst in promoting Mukaiyama-type aldol reactions of 2-(trimethylsilyloxy)furan with various aromatic and aliphatic aldehydes to produce δ-silyloxy butenolides.

Acknowledgement

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References and notes

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11. *General procedure*: To a stirred solution of aldehyde (1 mmol) and 2-(trimethylsilyloxy)furan (1.5 mmol) in dichloromethane (10 mL), iodine (10 mol %) was added at 0 °C and the mixture was stirred for the appropriate time (Table 1). After complete conversion as indicated by TLC, the reaction mixture was quenched with water (10 mL) and extracted with dichloromethane (3 × 15 mL). The combined extracts were washed with a 15% solution of aqueous sodium thiosulfate, dried over anhydrous Na_2SO_4, concentrated in vacuo and purified by column chromatography on silica gel (Merck 100–200 mesh, ethyl acetate/hexane, 1:9) to afford pure butenolide. *Spectral data for selected products*: Compound **3b**: Solid, mp 95–97 °C; IR (KBr): ν_{max} 2959, 2896, 1758, 1599, 1488, 1338, 1091, 1047, 932, 749 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.10 (s, 9H), 3.92 (s, 3H), 5.22–5.26 (m, 1H), 5.46 (d, $J = 3.0$ Hz 1H), 6.09 (dd, $J = 1.5$ and 6.0 Hz, 1H), 6.88 (d, $J = 8.3$ Hz, 1H), 6.98 (t, $J = 7.5$ Hz, 1H), 7.08 (dd, $J = 1.5$ and 6.0 Hz, 1H), 7.25–7.32 (m, 1H), 7.41 (d, $J = 7.5$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.9, 156.2, 153.4, 129.6, 127.7, 123.4, 121.4, 110.7, 85.7, 68.9, 55.9, 0.3; LC–MS: *m*/*z*: 315 (M+Na), 151; HRMS calcd for $C_{15}H_{20}O_4SiNa$: 315.1028, found: 315.1017. Compound **4b**: Liquid, IR (KBr): ν_{max} 2956, 2847, 1761, 1599, 1490, 1364, 1082, 1026, 905, 876, 756 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.08 (s, 9H), 3.86 (s, 3H), 5.04–5.16 (m, 2H), 6.07 (dd, $J = 2.2$ and 6.0 Hz, 1H), 6.86 (d, $J = 8.3$ Hz, 1H), 6.99 (t, $J = 7.5$ Hz, 1H), 7.09 (dd, $J = 1.5$ and 6.0 Hz, 1H), 7.23–7.31 (m, 1H), 7.48 (dd, $J = 1.5$ and 7.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.4, 155.6, 154.0, 129.3, 128.3, 122.4, 120.9, 110.4, 86.9, 68.8, 55.5, 0.06; LC–MS: *m*/*z*: 315 (M+Na), 151; HRMS calcd for $C_{15}H_{20}O_4SiNa$: 315.1028, found: 315.1022. HRMS calcd for $C_{15}H_{20}O_4SiNa$: 315.1028, found: 315.1017. Compound **3c**: Solid, mp 134–136 °C; IR (KBr): ν_{max} 2960, 2896, 1756, 1593, 1496, 1377, 1096, 1049, 930, 750 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.09 (s, 9H), 3.76 (s, 3H), 3.84 (s, 3H), 5.20–5.24 (m, 1H), 5.40 (d, $J = 3.1$ Hz, 1H), 6.07 (dd, $J = 1.5$ and 5.4 Hz, 1H), 6.74–6.77 (m, 2H), 6.94 (d, $J = 2.3$ Hz, 1H), 7.07 (dd, $J = 1.5$ and 5.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.5, 154.1, 153.0, 150.0, 128.6, 123.1, 113.4, 111.3, 85.2, 68.5, 55.9, 0.01; LC–MS: *m*/*z*: 345 (M+Na), 181, 102; HRMS calcd for $C_{16}H_{22}O_5SiNa$: 345.1134, found: 345.1129. Compound **4c**: Solid, mp 126–128 °C; IR (KBr): ν_{max} 2953, 2839, 1754, 1593, 1495, 1356, 1100, 1042, 908, 847, 755 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.07 (s, 9H), 3.76 (s, 3H), 3.77 (s, 3H), 4.99–5.10 (m, 2H), 6.04 (dd, $J = 1.5$ and 5.4 Hz, 1 H), 6.73 (d, $J = 1.5$ Hz, 2H), 6.98–7.08 (m, 2H);^{13}C NMR (75 MHz, $CDCl_3$): δ 173.7, 154.2, 150.2, 129.4, 122.8, 114.4, 114.3, 111.8, 87.2, 69.2, 56.3, 56.2, 0.4; LC–MS: *m*/*z*: 345 (M+Na), 181, 102; HRMS calcd for $C_{16}H_{22}O_5SiNa$: 345.1134, found: 345.1135.