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Iodine-catalyzed 1,4-addition of 2-(trimethylsilyloxy)furan to α,β-unsaturated ketones: a facile synthesis of γ-butenolides

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The α,β-unsaturated compounds undergo smooth conjugate addition with 2-(trimethylsilyloxy)furan (TMSF) in the presence of 10 mol % of iodine under mild and neutral conditions to afford the corresponding γ-substituted butenolides in high yields and with good diastereoselectivity. The use of iodine makes this procedure simple, convenient and cost effective.

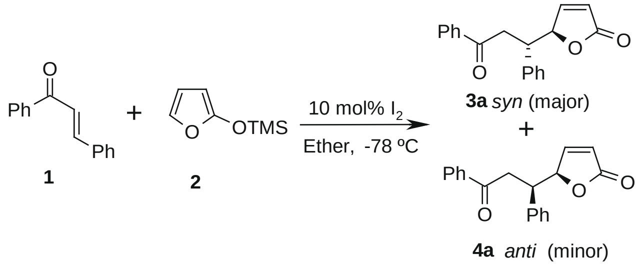
Butenolides (α,β-unsaturated-γ-lactones) are versatile building blocks for the synthesis of biologically active natural products such as mitomycins,[1] cavernosine,[2] A26771B[3] and many others.[4] They also serve as precursors for the synthesis of highly substituted chiral γ-lactones.[5] Lewis acid promoted Michael addition is one of the most important carbon–carbon bond forming reactions in organic synthesis. In particular, acid-catalyzed addition of 2-(trimethylsilyloxy)furan to α,β-unsaturated ketone is very attractive as it provides γ-substituted butenolides which are key intermediates in natural products synthesis.[6] Typically, Lewis acids such as $SnCl_4$, $Sc(OTf)_3$, $Cu(OTf)_2$ and lanthanide triflates have been utilized to accomplish this reaction under strictly anhydrous conditions.[6,7] However, Diels–Alder adduct was the major side product in these acid-catalyzed Michael additions. Alternatively, TBAF has been used to catalyze this reaction at low temperature (−78 °C).[8] However, the high cost, stringent conditions and moisture sensitivity 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 in organic synthesis because of its low cost, non-toxicity and ready availability. 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]

Following our interest in the catalytic uses of molecular iodine,[10] we herein report a simple, convenient and metal free synthesis of γ-substituted butenolides by means of addition of 2-(trimethylsilyloxy)furan onto α,β-unsaturated systems. Thus, treatment of chalcone (**1**), with 2-(trimethylsilyloxy)furan (**2**) in the presence of 10 mol % of I_2 at −78 °C gave the corresponding 5-(3-oxo-1,3-diphenylpropyl)furan-2(5*H*)-one in 89% yield as a mixture of *syn*:*anti*-isomers (**3a**:**4a**, 90:10; Scheme 1).

This result provided the incentive for further study with various α,β-unsaturated ketones. Interestingly, several substrates derived from both aromatic and aliphatic aldehydes or ketones participated well in this reaction (Table 1, entries **b–h**). Other conjugated ketones such as methylvinylketone and cyclohexenone were also effective for this transformation (Table 1, entries **i** and **j**).

Next, we attempted the conjugate addition of 2-(trimethylsilyloxy)furan with other unsaturated systems such as β-nitrostyrene and 2-benzylidenemalononitrile. Interestingly, these substrates



Scheme 1. Preparation of **3a** and **4a** from chalcone and 2-(trimethylsilyloxy) furan.

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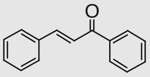
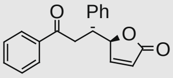
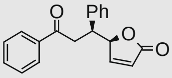
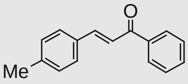
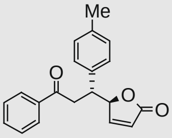
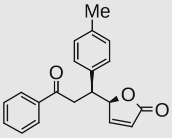
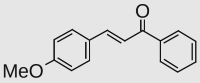
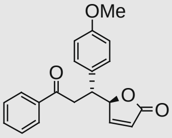
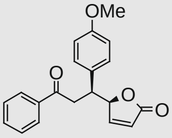
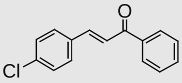
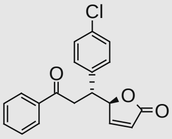
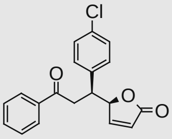
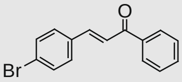
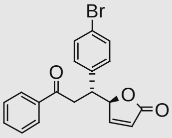
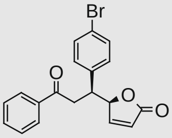
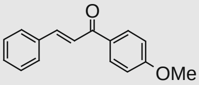
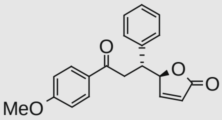
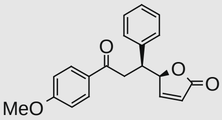
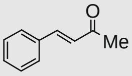
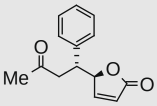
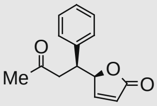
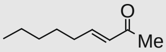
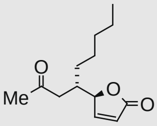
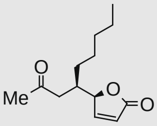
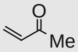
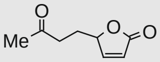
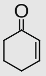
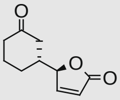
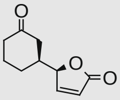
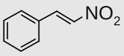
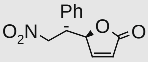
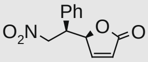
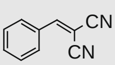
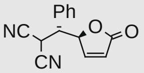
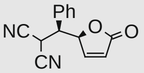
Table 1
Iodine-catalyzed preparation of butenolides from α,β-unsaturated ketones and 2-(trimethylsiloxy)furan

Entry	Aldehyde	Product[a]		Time (h)	Yield[b] (%)	*syn*:*anti*[c]
a				3.0	89	90:10
b				3.0	91	90:10
c				2.0	93	87:13
d				3.5	88	89:11
e				4.0	85	85:15
f				2.5	92	89:11
g				3.0	90	80:20
h				3.5	91	75:25
i				2.5	93	—
j				3.0	92	70:30
k				4.0	85	92:8
l				4.0	82	60:40

[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.

also underwent smooth 1,4-addition under similar reaction conditions (Table 1, entries **k** and **l**). In all cases, the reactions proceeded smoothly at −78 °C under extremely 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.[6–8] The product ratio was determined by ^{1}H NMR spectroscopy of the crude products. However, in the absence of iodine, the reaction did not proceed even after a long reaction time. The combination of 2-(trimethylsilyloxy)furan and iodine is a useful method for the addition of TMSF to activated unsaturated systems. 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 enones. In general, the reactions proceeded smoothly under the influence of 10 mol % of molecular iodine, and the yields were generally high to excellent. The advantages of this method are high conversions, ready availability of the catalyst, high efficiency, no salt formation and avoidance of heavy transition metal catalysts. The scope of this methodology is illustrated with respect to various activated unsaturated systems, and the results are presented in Table 1.[11]

In summary, molecular iodine has proved to be an effective catalyst in promoting conjugate addition of 2-(trimethylsilyloxy)furan with various α,β-unsaturated systems to produce functionalized butenolides.

Acknowledgement

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11. *General procedure*: To a stirred solution of α,β-unsaturated compound (1 mmol) and 2-(trimethylsilyloxy)furan (1.5 mmol) in diethyl ether (10 mL), iodine (10 mol %) was added at −78 °C, and the resulting mixture was allowed to stir at the same temperature 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**: *(5R)-5-[(1R)-1-(4-methylphenyl)-3-oxo-3-phenylpropyl]-2,5-dihydro-2-furanone*: Solid, mp 129–131 °C; IR (KBr) ν_{max}: 3092, 3027, 2921, 1790, 1750, 1674, 1596, 1513, 1372, 1264, 1101, 1015, 893, 814, 756 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.31 (s, 3H), 3.33–3.65 (m, 3H), 5.17–5.21 (m, 1H), 6.02 (dd, J = 2.6, 5.2 Hz, 1H), 7.02–7.57 (m, 8H), 7.85 (d, J = 7.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.9, 40.1, 43.9, 85.8, 121.7, 127.8, 128.1, 128.5, 129.1, 129.4, 133.1, 136.5, 137.1, 156.5, 172.6, 197.3; ESI-MS: *m/z*: 329 (M+Na); HRMS calcd for $C_{20}H_{18}O_3Na$: 329.1153, found: 329.1168. Compound **3i**: *(5S)-5-(3-oxobutyl)-2,5-dihydro-2-furanone:* Liquid, IR (KBr) ν_{max}: 3093, 2926, 1753, 1712, 1602, 1420, 1362, 1164, 1105, 1015, 918, 819, 772 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.66–1.82 (m, 1H), 2.08–2.26 (m, 4H), 2.49–2.74 (m, 2H), 5.07 (dd, J = 1.5, 8.3 Hz, 1H), 6.08 (d, J = 6.0 Hz, 1H), 7.43 (dd, J = 1.5, 6.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 26.4, 29.8, 37.8, 81.9, 121.3, 156.1, 172.6, 207.0; ESI-MS: *m/z*: 177 (M+Na); HRMS calcd for $C_8H_{10}O_3Na$: 177.0527, found: 177.0535. Compound **3j:** *(5R)-5-[(1R)-3-oxocyclohexyl]-2,5-dihydro-2-furanone*: Liquid, IR (KBr) ν_{max}: 2933, 1752, 1709, 1451, 1422, 1312, 1163, 1097, 1023, 901, 819, 753 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.44–2.50 (m, 9H), 5.02 (dd, J = 1.5, 3.7 Hz, 1H), 6.16 (dd, J = 2.2, 6.0 Hz, 1H), 7.42 (dd, J = 1.5, 6.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.4, 27.4, 40.7, 41.3, 43.5, 85.3, 122.1, 154.2, 172.3, 209.3; ESI-MS: *m/z*: 203 (M+Na); HRMS calcd for $C_{10}H_{12}O_3Na$: 203.0684, found: 203.0694.