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Short Communication

Regioselective Synthesis of γ -Butenoildes Mediated by Silvertrifluroacetate with B-Halo Acetals

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Abstract

γ-Butenoildes were prepared by 1,4 addition of β-halo acetals with 2-(tert-butyldimethylsiloxy)-3-methylfuranone mediated by silvertrifluroacetate in one step with high regioselectivity The structures of these products were determined using ^1H NMR, ^{13}C NMR, Mass spect. and IR analysis

Keywords: γ-Butenoildes, 1,4 addition, β-halo acetals, 2-(tert-butyldimethylsiloxy)-3-methylfuranone

Introduction

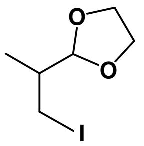
γ-Butenoildes have remained key precursors towards the synthesis of complex many biologically active natural products. More recently γ-Butenoildes could emerge to be important synthons for the synthesis of complex iridolactones; Brassoside and littaralissone are typical example.[1,2] In our previous report,[3] we have shown an efficient synthesis of 5-(But-3-enyl)-3-methylfuran-2(5H)-one via 1,4 addition with 4-iodobutene with high regioselectivity. This successful preparation led us to investigate other well functionalized systems as such plans to try to implement the second strategy began. The key ingredient of this strategy, a β-haloacetal **(241)** could offer the opportunity to furnish the much sought-after butenolides side chain with high regioselectivity (Scheme 1).

Material and Methods

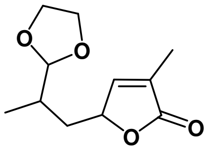
Commercial reagents were obtained from Aldrich and Lancaster chemical suppliers and were used directly as supplied or purified prior to use following the guidelines of Perrin and Amarego.[7] Dichloromethane and acetonitrile were refluxed over and distilled from CaH_2 prior to use. Diethyl ether and ethanol were obtained dry from Aldrich. THF was dried by distillation from the sodium benzophenone ketyl radical under nitrogen. Light petroleum is the fraction of petroleum ether boiling in the range 30-40 °C, and it was fractionally distilled through a 36 cm Vigreux column before use. Non-aqueous reagents were transferred under argon *via* syringe. Organic solutions were concentrated under reduced pressure on a Büchi rotary evaporator using a water bath. Thin-layer chromatography (TLC) was performed on Merck aluminium-backed plates coated with 0.2 mm silica gel 60-F plates. Visualization of the developed chromatogram was performed by UV fluorescence quenching at 254nm, or by staining with a $KMnO_4$ solution.

^1H and ^{13}C NMR spectra were recorded on a Bruker DPX250 (250 MHz for protons) and a Brüker AMX400 (400 MHz for protons). Data for ^1H NMR are reported as follows: chemical shift (δ-ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), integration, coupling constant in (Hz). Data for ^{13}C NMR spectra are reported in terms of chemical shift (ppm) down field from TMS. IR spectra were recorded on a Perkin Elmer Paragon 1000 or a Perkin Elmer 881 spectrometer as a thin film between sodium chloride plates or as a KBr disk. All absorptions are reported in terms of frequency of absorption (cm^{-1}).Mass spectrometric data were recorded on VG Autospec, under conditions of chemical ionisation (C.I) using ammonia as the ionising source. Peaks are quoted in the form *($^m/z$)* (relative intensity).

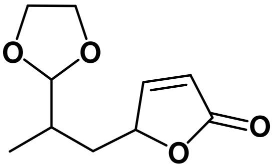
2-(iodopropan 2-yl)-1, 3-dioxalane (217)[4] : To a solution of methacrolein (241) (1.70 g, 24.3 mmol, 1.00 equiv), of sodium iodide (4.40 g, 29.5 mmol, 1.20 equiv) in acetonitrrile (60 mL) was rapidly added with vigorous stirring chlorotrimethylsilane (3.80 g, 34.9 mmol, 1.20 equiv). The resulting suspension was stirred for 5 minutes after which the reaction mixture was poured into (80 mL) of (5%) $NaHCO_3$ overlaid with (100 mL) of pentane. This produced after thorough mixing three distinct layers. The lower aqueous layer was removed and the remaining layers were washed with (5%) $Na_2S_2O_3$ (8 x 60 mL) and saturated NaCl (60 mL) until only a single organic layer was evident. The pentane layer was dried over K_2CO_3 and the solvent removed *in vacou*. Column chromatography on neutral alumina with hexane afforded the title compound as a colourless oil (4.92 g, 84%); υ_{max} (thin film/cm^{-1}), 2967, 2935, 2882, 1461, 1426, 726; δ_H (250 MHz, $CDCl_3$) 4.68 (1H, d, *J* 4.6 Hz, CHO_2), 3.92-3.78 (4 H, m, OCH_2CH_2O), 3.26 (1H, dd, *J* 4.5 Hz, CHI), 3.05 (1H, dd, *J* 4.5 Hz, CHI), 1.81-1.73 (1H, m, $CHCH_2I$), 1.02 (3H, d, *J* 3.5 Hz CH_3CH); δ_C (62.5 MHz, $CDCl_3$) 105.0, 64.2, 64.3, 38.3, 14.5, 8.3; $^{m}/_{z}$ (C.I) 242 (MH^+, 15 %), 115 (100%), 114 (2.3%), 113 (4.1%), 101 (1.7%), $C_6H_{13}IO_2$, requires 242.9882, found 242.9878

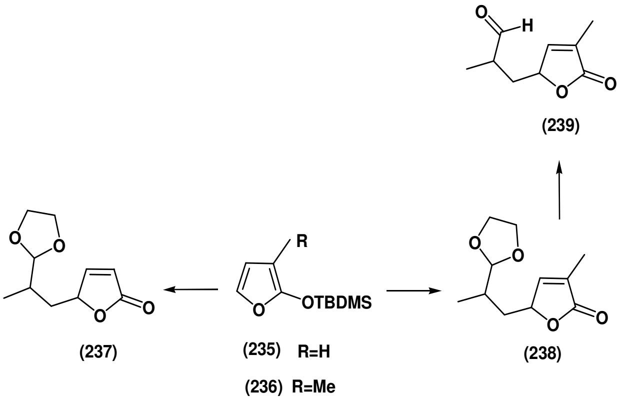


5-(2-(1, 3-dioxalan-2yl) propyl)-3-methylfuran-2-(5*H*)-one (156): To a stirred suspension of silver trifluoroacetate (140 mg, 0.63 mmol, 1.30 equiv) in dry DCM (4 mL) under argon at -78 °C was added 2-(*tert*-butyldimethyl siloxy)-3-methylfuran (125) (100 mg, 0.5 mmol, 1.00 equiv), followed by dropwise addition of 2-(iodopropan 2-yl)-1, 3-dioxalane (217) (0.12 g, 0.63 mmol, 1.30 equiv) over a period of 10 minutes. The temperature was increased to 10 °C over 4 hours. The mixture was filtered through Celite® washing with ether (4 x 10 mL). The solvent was removed carefully removed under reduced pressure and the residue was purified by flash chromatography on silica, eluting with hexane : ether (2:1) to afford a colourless oil (58 mg, 55%); υ_{max} (thin film/cm^{-1}), 2979, 2875, 2254, 1734, 1657, 734; δ_H (250 MHz, $CDCl_3$) 6.97 (1H, bd, *J* 1.6 Hz, CH=C), 6.97 (1H, bd, *J* 1.6 Hz, CH=C) 4.97-4.93 (1H, m, CHO), 4.97-4.93 (1H, m, CHO), 4.63 (1H, d, *J* 4.4 Hz, CHO_2), 4.61 (1H, d, *J* 4.1 Hz, CHO_2), 3.87-3.76 (4H, m, OCH_2CH_2O), 3.87-3.76 (4H, m, OCH_2CH_2O), 1.95-1.90 (1H, m, $CHCH_3$), 1.95-1.90 (1H, m $CHCH_3$), 1.83 (3H, bs, CH_3C=C), 1.83 (3H, bs, CH_3C=C), 1.78-1.38 (2H, dm, CH_2), 1.78-1.38 (2H, dm, CH_2), 0.94 (3H, bd, *J* 5.2 Hz, *J* 1.7 Hz, CH_3CH), 0.94 (3H, bd, *J* 5.2 Hz, *J* 1.7 Hz, CH_3CH); δ_C (62.5 MHz, $CDCl_3$) 173.3, 148.2, 147.9, 128.8, 128.7, 128.7, 106.0, 79.3, 78.0, 63.9, 63.9, 34.6, 34.2, 33.2, 32.6, 24.6, 14.5, 13.3, 9.60; $^{m}/_{z}$ (C.I) 213 (MH^+, 100%), 169 (40%),102 (30%),101 (11.4%), $C_{11}H_{18}O_2$, requires 213.1128, found 213.1127.



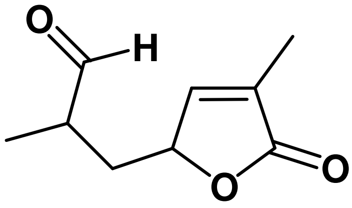
5-(2-(1, 3-dioxalan-2yl) propyl) furan-2-(5*H*)-one (242): To a stirred suspension of silvertrifluoroacetate (290 mg, 1.3 mmol, 1.30 equiv) in dry DCM (10 mL) under argon at -78 °C was added 2-(*tert*-butyldimethyl siloxy)-3-methylfuran (235) (200 mg, 1.0 mmol, 1.00 equiv), followed by drop wise addition of 2-(iodopropan 2-yl)-1, 3-dioxalane (217) (334 mg, 1.3 mmol, 1.3 equiv) over a period of 10 minutes. The temperature was increased to 10 °C over 4 hours. The mixture was filtered through Celite® washing with ether (4 x 15 mL).The solvent was removed carefully removed under reduced pressure and the residue was purified by flash chromatography on silica, eluting with hexane : ether (2:1) to afford a colourless oil (142 mg, 71%); υ_{max} (thin film/cm^{-1}), 2989, 2975, 2244, 1733, 1618, 734; δ_H (250 MHz, $CDCl_3$) 7.53 (1H, bt, *J* 5.0 Hz, *J* 2.5 Hz, CH=CH), 7.53 (1H, bt, *J* 5.0 Hz, *J* 2.5 Hz, CH=CH), 6.11 (1H, bd, *J* 2.5 Hz, CH=CH) 6.11 (1H, bd, *J* 2.5 Hz, CH=CH), 5.27-5.17 (1H, m, CHO), 5.27-5.17 (1H, m, CHO), 4.73 (1H, bt, *J* 5.0 Hz, CHO_2), 4.73 (1H, bt *J* 5.0 Hz, CHO_2), 3.99-3.83 (4H, m, OCH_2CH_2O), 3.99-3.83 (4H, m, OCH_2CH_2O), 2.11-2.00 (1H, m, $CHCH_3$), 211-2.00 (1H, m $CHCH_3$), 1.97-1.80 (1H, dm, CH_2), 1.97-1.80 (1H, dm, CH_2), 1.65-1.42 (1H, dm, CH_2), 1.65-1.42 (1H, dm, CH_2), 1.05 (3H, bd, *J* 2.5 Hz, CH_3CH), 1.05 (3H, bd, *J* 2.5 CH_3CH); δ_C (62.5 MHz, $CDCl_3$) 157.1, 156.8, 121.2, 121.1, 106.6, 106.9, 82.7, 81.5, 64.9, 64.7, 34.1, 33.9, 33.5, 14.3, 14.1; $^{m}/_{z}$ (C.I) 199 (MH^+, 100%), 198 (36%), 180 (35%), 156 (19%), $C_{10}H_{15}O_4$, requires 199.0971, found 199.0974.





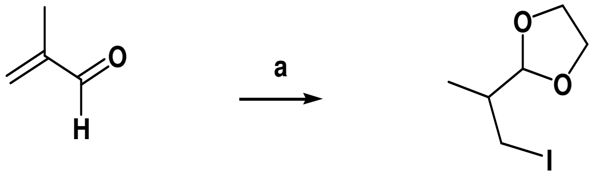
Scheme-1

2-methyl-3-(4-methyl-5-oxo-2,5-dihydrofuran-2-yl) propanal (157): A solution of 5-[2-(1, 3-dioxalan-2yl)propyl]-3-methylfuran -2-(5H)-one (156) (100 mg, 0.47 mmol, 1.00 equiv) in (12 mL) acetone/water (5:1, 12 mL) was treated with pTSOH (116 mg, 0.47 mmol, 0.99 equiv) and the resulting solution was heated at reflux for 3 h. The reaction was cooled and quenched with saturated $NaHCO_3$ solution, extracted with ether (5 x 4 mL), dried with Na_2SO_4 and concentrated *in vacuo.* Purification of the residue by column chromatography on silica eluting with hexane : ethyl acetate (1:1) afforded the title compound as a pale yellow oil (34 mg, 43%); υ_{max} (thin film/cm^{-1}), 2978, 2929, 2874, 1752, 1718; δ_H (250 MHz, $CDCl_3$) 9.67 (1H, bd, *J* 9.8 Hz, CHO), (1H, bd, *J* 9.8 Hz, CHO), 7.07 (1H, bd, *J* 3.1 Hz, CH=C), 7.07 (1H, bd, *J* 3.1 Hz, CH=C), 5.03-4.94 (1H, m, CHO), 5.03-4.94 (1H, m, CHO), 2.74-2.63 (1H, m, $CHCH_3$), 2.74-2.63 (1H, m, $CHCH_3$), 2.29-2.18 (1H, m, CH_2), 2.24-2.22 (1H, m, CH_2), 2.04-1.97 (1H, m, CH_2), 2.05-1.97 (1H, m, CH_2), 1.93-1.92 (1H, m, CH_2), 1.93-1.92 (1H, m, CH_2), 1.92 (3H, bs CH_3C=C), 1.92 (3 H, bs CH_3C=C), 1.81-1.76 (1H, m, CH_2), 1.42-1.26 (1H, m, CH_2), 1.25 (3H, bd, *J* 5.2 Hz, CH_3CH), 1.22 (3H, bd, *J* 5.3 Hz, CH_3CH); δ_C (62.5 MHz, $CDCl_3$) 203.7, 203.6, 169.8, 169.4, 148.8, 148.8, 79.6, 78.9, 43.5, 42.9, 34.7, 33.9, 30.1, 14.9, 13.9, 11.1; $^{m}/_{z}$ (C.I) 169 (MH^+, 100 %), 130 (80%), 111 (45%), $C_9H_{13}IO_3$, requires 169.0865, found ,169.0865



Results and Discussion

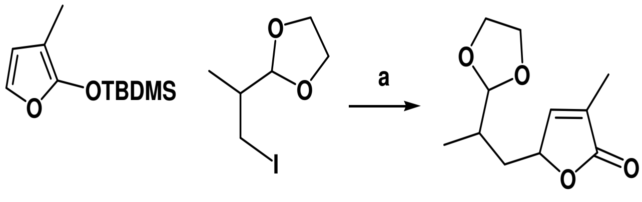
Larson,[4] reported a much improved method for the preparation of β-halo acetals, which employs chlorotrimethylsilane and sodium iodide in acetonitrile *in lieu* of the more difficult to handle iodotrimethylsilane Scheme 2. 0. Thus, addition of chlorotrimethylsilane to a rapidly stirred solution of methacrolein and sodium iodide produced an immediate precipitate and a yellow solution, which became dark orange with time. The addition of ethylene glycol and workup gave **(241)** in 84% yield. The ^{1}H NMR spectrum showed the appearance of a four proton multiplet at δ 3.89-3.80 ppm characteristic of the dioxalane protons and two multiplets integrating to two protons, a multiplet at δ 3.25-3.23 ppm and at δ 3.08-3.01 ppm due to the diastereotopic methylene (CH_2I) group. Mass spectrometric analysis confirmed the mass ion to be *m/z* 242 Scheme 2.13.



(240) **(241)**

(a) $(CH_2OH)_2$, NaI, Me_3SiCl, acetonitrile, 84%
Scheme-2

Synthesis of 5-(2-(1, 3-dioxolan-2yl) propyl)-3-methylfuran-2-(5H)-one: The simple transformation necessary to convert (236) to (238) was anticipated to proceed through condensation with (241). Subsequently the condensation went according to plan through the agency of 2-(iodopropan-2-yl)-1,3-dioxolane (241) and 2-(*tert*-butyldimethylsiloxy)-3-methylfuranone (236) in DCM and silver trifluoroacetate to furnish 5-(2-(1,3-dioxalan-2yl)propyl)-3-methylfuran-2-(5H)-one (156) as a pair of diastreoisomers with an overall yield of 55%. The diastereoisomers were not separated at this stage in order to establish the validity of the cyclization protocol. The ^{1}H NMR spectrum showed overlap of the resonances corresponding to the two diastreoisomers, with a broad doublet at δ 6.97 ppm corresponding to the olefinic proton of the lactone and a multiplet at δ 4.97-4.93 ppm for the lactone methine proton. Mass spectrometric analysis confirmed the mass ion to be *m/z* 212. The IR spectrum amongst other things exhibited a characteristic carbonyl band at 1734 cm^{-1} in accord with that expected for α-β unsaturated ester in a five-membered ring Scheme 3.0.

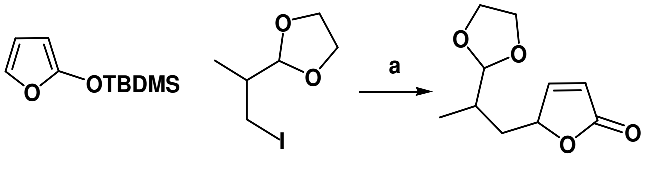


(236) **(241)** **(rac)-(238)**

(a) silver trifluoroacetate, DCM, 55%
Scheme-3

The successful preparation of 5-(2-(1, 3-dioxalan-2yl) propyl)-3-methylfuran-2-(5H)-one **(156)** opened the pathway towards the preparation of other model analogues to test the validity of the cyclization methods. As outlined earlier, such a reaction was to proceed through condensation with 2-(*tert*-butyldimethylsiloxy)furan **(235)**. Consequently protected furan **(235)** was converted in 71% yield to 5-(2-(1, 3-

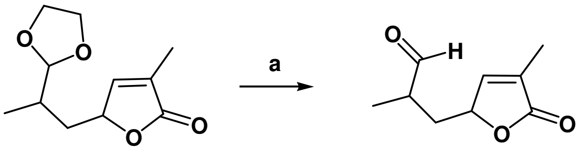
dioxalan-2yl) propyl) furan-2-(5H)-one **(242)**. The IR spectrum of **(242)** showed the ester at 1741 cm^{-1} and an absorption corresponding to a (C=C) double bond appeared at 1640 cm^{-1}. The ^{1}H NMR spectrum not only revealed the disappearance of the two sharp singlet resonances due to the *tert*-butyl and dimethyl groups, but also revealed a signal at δ 4.73 ppm (*J* 5.0 Hz) corresponding to the methine in the lactone. The diastereotopic methylene protons appeared as two double multiplets, at δ 1.97-1.80 ppm and at δ 1.97-1.80 ppm Scheme 2.15.



(235) **(241)** **(rac)-(237)**

(a) silver trifluoroacetate, DCM, 71%
Scheme - 4

The preparation of these key intermediates **(237)** and **(238)** set the stage for the synthesis of the desired aldehyde under mild acid conditions.[5, 6] We chose initially to attempt the reaction with PTSA in acetone/water (5:1), this being the most conventional and straightforward method for the removal of the dioxolane. Purification of the residue by column chromatography on silica eluting with hexane-ethyl acetate (1:1) afforded compound **(238)** from **(239)**, as a pair of diastereoisomers in 43% yield. The ^{1}H NMR spectrum showed a pair of overlapping doublets (*J* 1.0 Hz) centred at δ 9.67 ppm corresponding to the terminal aldehyde and the resonances due to dioxolane were absent. The IR spectrum showed two characteristic absorptions at 1752 cm^{-1} due to the lactone, and 1718 cm^{-1}, clear evidence for C=O stretching of an aldehyde. Mass spectrometric analysis confirmed the molecular ion to be *m/z* 168 Scheme 5.0.



(238) **(rac)-(239)**

(a) TsOH, acetone/water, reflux, 43%
Scheme-5

Conclusion

The synthesis on a suitable scale of the key γ-Butenoildes mediated by Silvertrifluroacetate with β-halo acetals was efficiently pursued. Our initial inspection of the intermediate (235) and (236) suggests that it could be conveniently assembled by coupling the C-5 cabanion β-halo acetals went smooth with high regioselectivity.

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