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*Short Communication*

# Samarium (II) Iodide Mediated Synthesis of 3,5-dimethyl-hexahydrocyclopenta[b]furnan-2-one

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## Abstract

*Selective reduction of the aldehyde of (157) with sodium borohydride gave the alcohol (243) with an excellent yield of 80%. The alcohol was then converted to alkyl Iodide which was readily reduced with $SmI_2$ in $NiI_2$ to give carbocyclic compound (220) with overall yield of 74%. The structures of these products were determined using $^1H$ NMR, $^{13}C$ NMR, Mass spect. and IR analysis*

**Key Words:** Selective reduction, aldehyde, $SmI_2$, $NiI_2$, carbocyclic.

## Introduction

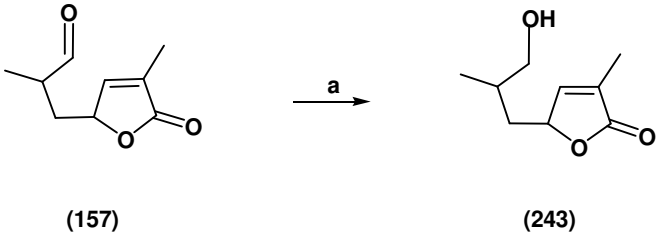
In our previous report[1], we showed an efficient regioselective synthesis of γ-butenoildes mediated by silvertrifluroacetate with β-halo acetals. Herein it is our desire to demonstrate the versatility of samarium diiodide ($SmI_2$) medited cyclization of γ-butenoildes. Samarium diiodide ($SmI_2$) is a strong single electron transfer reagent for promoting reduction and has been used in many important synthetic reactions reported successful reduction of organic halides by $SmI_2$ in THF[2]. Later it was shown that these reactions are faster when hexamethylphosphoramide is incorporated to the reaction mixture[3]. Over the years there was increasing efforts directed at finding other promoters of $SmI_2$ reduction. Some of the alternatives includes N,N-dimethylpropyleneurea, transition metal salts such as $NiI_2$. In our attempt to synthesize 3,5-dimethyl-hexahydrocyclopenta[b]furnan-2-one. It was decided to consider the chemistry reported by Molander in which alkyl halides act as a precursor in an intramolecular conjugate addition to α,β-unsaturated lactones[4].

## Material and Methods

Commercial reagents were obtained from Aldrich and Lancaster chemical suppliers and were used directly as supplied or purified prior to use. Dichloromethane was 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 $^oC$, 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).

## Results and Discussion

Initially, selective reduction of the aldehyde of **(157)** with sodium borohydride furnished the alcohol **(243)**[5]**.** sodium borohydride was added to a solution of aldehyde **(157)** in ethanol at room temperature and the reaction mixture was stirred for further 30 minutes. Colourless oil was obtained after column chromatography and this was shown to be the desired alcohol, isolated in 80% yield. The $^1H$ NMR showed the disappearance of the aldehyde peak and the presence of a multiplet at δ 3.59-3.41 ppm indicated a methylene group adjacent to a hydroxyl. A broad absorption in the IR centred at 3648 $cm^{-1}$ also indicated the presence of the alcohol. Mass spectrometric analysis confirmed the mass ion to be *m/z* 170 scheme 1.10.

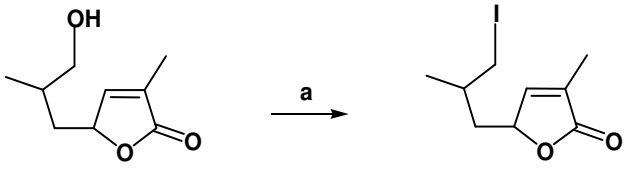



**(157)** **(243)**

(a) $NaBH_4$, ethanol, 80%

**Scheme 1.10**

The conversion of the alcohol to alkyl halides has also been reported using hydrogen chloride in toluene[6] and phosphorus trichloride or phosphorus pentachloride in petroleum ether. These methods give mixtures of alkyl halides, which became difficult to separate; tedious fractionation was required to isolate the alky halides[7]. It was envisaged that this procedure could mediate the conversion of the alcohol **(243)** to the corresponding alkyl iodide **(218)** in moderate yield without any problem. Initially 5-(3-hydroxy-2-methyl-2-methylpropyl)-3-methylfuran-2(5H)-one **(243)** was added to a stirred solution of triphenylphosphine, iodine and imidazole in anhydrous DCM. Once the reaction was complete the mixture was concentrated in *vacuo* and was rapidly purified by flash column chromatography on silica gel to afford **(218)** in 42% yield. $^1$H NMR analysis indicated the material to be the desired iodide with the position of the methylene adjacent to the alcohol moving from δ 3.59-3.41 ppm to δ 3.28-3.15 ppm confirming a methylene adjacent to iodine scheme 2.10.

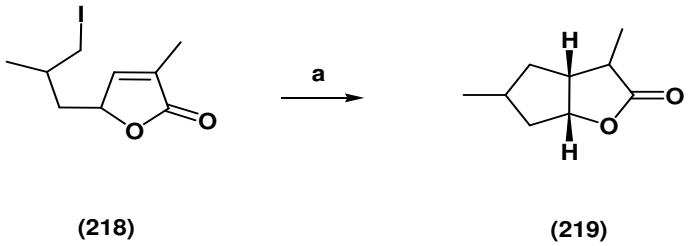



**(243)** **(218)**

(a) imidazole, $PPh_3$, $I_2$, DCM, 25$^o$C, 42%

**Scheme 2.10**

Following the radical cyclization procedure reported by Molander *et al*[8] , $NiI_2$ was added to a solution of $SmI_2$ in THF and the mixture was cooled to -78 $^o$C. After addition of **(218)** (0.08 mmol) in THF the resulting mixture was stirred for 1 hour, when TLC analysis indicated two spots with one corresponding to the staring material. However, after work up the $^1$H NMR spectrum showed the starting material had been recovered. At this point this radical approach was abandoned, the reason being that the final reaction would lead to a product that could not be readily functionalized further scheme 3.10.

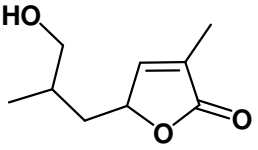



**(218)** **(219)**

(a) $NiI_2$, $SmI_2$, THF

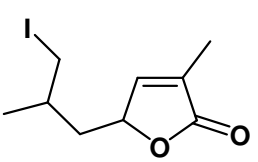
**Scheme 3.10**

**Experimental Procedures: 5-(3-hydroxy-2-methylpropyl)-3-methylfuran-2(5*H*)one (243):**




To a stirred solution of 2-methyl-3-(4-methyl-5-oxo-2, 5-dihydrofuran-2-yl) propanal **(157)** (50.0 mg, 0.30 mmol 1.00 equiv) in ethanol (4 mL) in an Erlenmeyer flask was added $NaBH_4$ at room temperature (14.5 mg, 0.38 mmol, 1.30 equiv) in small portions over 15 minutes. The reaction mixture was stirred for further 30 minutes and then poured into ice water (3 mL). Six drops of dilute hydrochloric acid (5%) were added; the organic layer was extracted with ether (2 x 6 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Column chromatography on silica eluting with ether : hexane (5:1) afforded the desired compound as a colourless oil (41 mg, 80%); $\upsilon_{max}$ (thin film/cm$^{-1}$), 3750, 3649, 3566, 2985, 1734, 1653; $\delta_H$ (250 MHz, $CDCl_3$) 6.98 (1H, bd, *J* 1.6 Hz, CH=C), (1H, bd, *J* 1.6 Hz, CH=C), 5.00-4.91 (1H, m, CHO), 5.00-4.91 (1H, m, CHO), 3.59-3.41 (2H, m $CH_2OH$), (2H, m $CH_2OH$), 1.88-1.85 (2H, m, $CHCH_3$), 1.88-1.85 (2H, m, $CHCH_3$), 1.86 (3H, bs, $CH_3C$=), 1.86 (3H, bs, $CH_3C$=C), 1.59-1.49 (2H, m, $CH_2$), 1.59-1.49 (2H, m, $CH_2$), 0.95 (3H dd, *J* 2.0 $CH_3CH$), 0.95 (3H dd, *J* 2.0 Hz, $CH_3CH$); $\delta_C$ (62.5 MHz, $CDCl_3$) 176.3, 149.7, 149.5, 130.2, 129.5, 80.2, 79.9, 68.3, 67.7, 38.0, 37.7, 33.5, 33.3, 17.6, 16.9; $^m/_z$ (C.I) 171 ($MH^+$, 63%), 153 (100%), 97 (79%), $C_9H_{15}O_3$, requires 171.1022, found ,171.1021

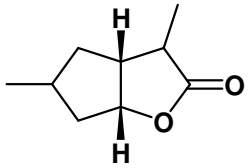
**5-(3-iodo-2-methylpropyl)-3-methylfuran-2(5*H*)one (218):**




To a stirred solution of triphenylphosphine (61.0 mg, 0.23, mmol, 1.30 equiv) in anhydrous DCM (2 mL) under argon was added imidazole (12.3 mg, 0.18 mmol, 1.00 equiv). Once the imidazole had dissolved, iodine (45.6 mg, 0.18 mmol, 1.00

equiv) was added and a white suspension formed. A solution of 5-(3-hydroxy-2-methylpropyl)-3-methylfuran-2(5*H*) one **(243)** (30.0 mg, 0.18 mmol, 1.00 equiv) in anhydrous DCM was added *via* syringe and stirring was continued for 45 minutes at room temperature. The reaction mixture was concentrated *in vacuo* and the crude product was rapidly purified by flash column chromatography on silica eluting with hexane : ethyl acetate (2:1) to afford the title compound as a colourless oil (21 mg, 42%); $\upsilon_{max}$ (thin film/cm$^{-1}$), 3448, 2978, 2929, 2874, 1750; $\delta_H$ (250 MHz, $CDCl_3$) 6.97 (2H, bd, *J* 1.5 Hz, C**H**=C), (1H, bd, *J* 1.5 Hz, C**H**=C), 4.85-4.84 (1H, m, C**H**O), 3.28-3.15 4.85-4.84 (1H, m, C**H**O), 3.28-3.15 (1H, m C$\mathbf{H}_2$I), 1.86-1.85 (1H, m, C**H**$CH_3$), 1.86-1.85 (1H, m, C**H**$CH_3$) 1.85 (3H, bs, C$\mathbf{H}_3$C=), 1.85 (3H, bs, C$\mathbf{H}_3$C=C), 1.03 (2H, d, *J* 6.4 C$\mathbf{H}_2$), 1.01 (2H, d, *J* 4.4 C$\mathbf{H}_2$), 0.78 (3H dd, *J* 2.0, C$\mathbf{H}_3$CH), 0.78 (3H dd, *J* 2.0, C$\mathbf{H}_3$CH); $^m/_z$ (C.I) 281 (MH$^+$, 100%), 153 (63%), 130 (29%), $C_9H_{14}IO_2$, requires 281.1003, found , 281.0029

**5-methyl-3-methylene-hexahydropenta[b]furan-2-one (220)**




To a stirred solution of $SmI_2$ (147 mg, 0.36, mmol, 1.30 equiv) in anhydrous THF (5 mL) under argon was added $NiI_2$ (43.82 mg, 0.14 mmol, 0.50 equiv), the mixture was cooled to -78 $^oC$ and **5**-(3-iodo-2-methylpropyl)-3-methylfuran-2(5*H*)one (218) (80.0 mg, 0.28 mmol, 1.00 equiv) was added. The reaction was allowed to stir overnight and was concentrated *in vacuo.* (5 mL) of water was added and the organic layer was extracted with ether (2x 7 mL), dried over $MagSO_4$ and concentrated in *vacuo* and the crude product was rapidly purified by flash column chromatography on silica eluting with petroleum ether : ethyl acetate (2:1) to afford the title compound as a colourless oil (32 mg, 74%); $\upsilon_{max}$ (thin film/cm$^{-1}$), 2922, 2919, 1728, $\delta_H$ (250 MHz, $CDCl_3$) 4.41-4.39 (1H, m, C**H**O), 2.41 (1H, m, C**H**CHO), 1.29 (3H, d, *J* 3.4 C$\mathbf{H}_3$CO), 1.09 (3H, d, *J* 3.4 $CH_3$CH); $\delta_C$ (62.5 MHz, $CDCl_3$) 171.2, 84.3, 46.7, 44.9, 41.3, 41.1, 31.1, 20.4, 13.9; $^m/_z$ (C.I) 281 (MH$^+$, 100%), 139 (29%), 124 (41%), $C_9H_{14}O_2$, requires 154.0994, found , 152.0993

## Conclusion

The result demonstrated the versatility of Samarium (II) Iodide as a potential promoter in the synthesis of bicyclic lactones in which alkyl halides act as a precursor in an intramolecular conjugate addition to α,β-unsaturated lactones. These lactones are recurrent features of many biologically active natural products

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