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Titanium(III) chloride mediated synthesis of furan derivatives: Synthesis of (±)-evodone

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Abstract. Titanocene(III) chloride (Cp_2TiCl) mediated one-pot synthesis of furan derivatives has been accomplished. This radical method has been applied for the synthesis of a furanomonoterpene, evodone. Ti(III) species was prepared *in situ* from commercially available titanocene dichloride (Cp_2TiCl_2) and zinc dust in THF.

Keywords. Ti(III) chloride; radical; Furan derivatives; synthesis; Evodone.

1. Introduction

The synthesis of furan derivatives has become much significant due to their widespread occurrence in nature and versatile applications in medicinal chemistry and pharmaceutical industry.[1] Moreover, annulated furan derivatives such as tetrahydrobenzofurans and tetrahydronaphthofurans are widely used as key intermediates for the synthesis of many indispensable natural products and pioneer of other heterocyclic compounds.[2] Evodone, containing the tetrahydrobenzofuran moiety, is a furanomonoterpene isolated from *Evonia hortensis Forst* and exhibits strong germination inhibitory activity and stimulatory effect towards *Schizachyrium scoparium* seeds.[3] Although several useful and elegant procedures have been developed for the synthesis of active components of furan derivatives,[4] the use of the radical chemistry in this field is less explored. Srikrishna and Krishnan developed[5] a radical-induced synthesis of substituted furans from α-bromo-β-keto enolethers using tributyl tinhydride (TBTH) as the radical initiator with 35–69% yield. But the use of tin compounds has certain limitations due to their toxicity and difficulties in isolation of pure products free of tin residues. To overcome these difficulties alternative methods are still desirable.

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2. Experimental

All melting points were taken on a Gallenkamp melting point apparatus and are uncorrected. The ^1H and ^{13}C NMR were recorded in $CDCl_3$ using TMS as an internal standard on 300 and 75 MHz spectrometer (Bruker) respectively and IR were recorded using a Shimadzu FT IR-8300 instrument. High-resolution mass spectra were obtained using a Qtof Micro YA263 instrument. Diethyl ether, tetrahydrofuran and toluene were dried over sodium. Dimethyl sulfoxide was dried over sodium hydride. Dichloromethane was freshly distilled from phosphorus pentoxide. Pyridine was distilled over potassium hydroxide prior to use. Tosyl chloride was freshly crystallized from benzene prior to use. Petroleum ether of boiling range 60–80°C and silica gel of 60–120 mesh were used for column chromatography.

2.1 *Representative procedure for the radical cyclization reaction*

N-bromosuccinamide (356 mg, 2·0 mmol) was added to a stirred solution of **2a** (189 mg, 1·5 mmol) and propargyl alcohol (112 mg, 2·0 mmol) in dry benzene (10 mL) at 0°C during 30 min. The reaction mixture was allowed to stir for another 2 h. After completion of the reaction (monitored by TLC) the solvent was removed under reduced pressure and the residue was extracted with diethyl ether (3 × 50 mL). The organic layer was washed successively with water

(2 × 10 mL), brine (2 × 10 mL) and finally dried (Na_2SO_4). After removal of the solvent under reduced pressure, the crude residue (**3a** along with some other inidentified product) obtained was used without further purification for the radical cyclization reaction. A red solution of Cp_2TiCl_2 (747 mg, 3·0 mmol) in dry deoxygenated THF (40 mL) was stirred with activated zinc dust (393 mg, 6 mmol) under argon until it turned green. This green solution was transferred to a dropping funnel by a cannula and was added drop-wise slowly to a solution of the crude bromo compound **3a** in dry deoxygenated THF (20 mL) under argon atmosphere. The reaction mixture was then stirred for an additional 2 h. After completion of the reaction (monitored by TLC), it was decomposed slowly with 10% aqueous H_2SO_4. Most of the THF was removed under reduced pressure and resulting residue was extracted with diethyl ether (3 × 50 mL). The combined organic layer was washed successively with water (2 × 10 mL), brine (2 × 10 mL) and finally dried (Na_2SO_4). Solvent was removed under reduced pressure and the crude residue obtained was purified by column chromatography over silica gel (5% ethyl acetate in light petroleum) to obtain *3-methyl-6,7-dihydro-1-benzofuran-4(5H)-one* (**4a**) (143 mg, 63%) as a crystalline solid; m.p. 61–63°C; IR ν_{max} (KBr) 2950, 1668, 1562, 1386 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ (ppm) 2·09–2·18 (*m*, 5H), 2·46 (*t*, *J* = 6·3 Hz, 2H), 2·82 (*t*, *J* = 6·3 Hz, 2H), 7·05 (*brs*, 1H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ (ppm) 9·1, 22·8, 23·6, 38·4, 119·0, 120·4, 138·9, 167·4, 195·7; HRMS calcd for $C_9H_{10}O_2$ [M$^+$ + 1] 151·0754, found 151·0750.

2.1a *3,6,6-Trimethyl-6,7-dihydro-1-benzofuran-4(5H)-one* (**4b**): Viscous oil; IR ν_{max} (neat) 2960, 1678, 1562, 1436, 1286 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ (ppm) 1·14 (*s*, 6H), 2·20 (*d*, *J* = 0·9 Hz, 3H), 2·35 (*s*, 2H), 2·71 (*s*, 2H), 7·09 (*brs*, 1H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ (ppm) 9·1, 28·7 (2C), 35·3, 37·7, 52·8, 119·0, 119·4, 139·4, 166·7, 195·2; HRMS calcd for $C_{11}H_{14}O_2Na$ [M + Na]$^+$ 201·0892, found 201·0880.

2.1b *3-Methyl-6-phenyl-6,7-dihydro-1-benzofuran-4(5H)-one* (**4c**): Viscous oil; IR ν_{max} (neat) 2962, 1668, 1560, 1398 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ (ppm) 2·25 (*s*, 3H), 2·73–2·76 (*m*, 2H), 3·01 (*dd*, *J* = 10·9, 17·0 Hz, 1H), 3·14 (*dd*, *J* = 5·2, 17·0 Hz, 1H), 3·48–3·59 (*m*, 1H), 7·11 (*s*, 1H), 7·26–7·39 (*m*, 5H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ (ppm) 9·0, 31·4, 41·3, 45·6, 119·1, 120·3, 126·7 (2C), 127·1, 128·8 (2C), 139·4, 142·6, 166·6, 194·2; HRMS calcd for $C_{15}H_{14}O_2$ [M]$^+$ 227·1067, found 227·1065.

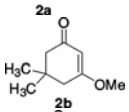
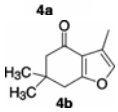
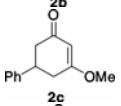
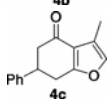
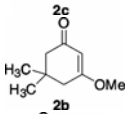
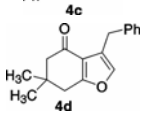
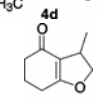
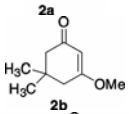
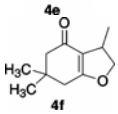
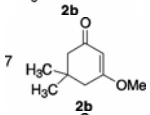
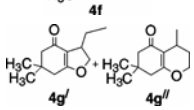
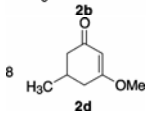
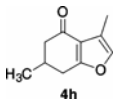
2.1c *3-Benzyl-6,6-dimethyl-6,7-dihydro-1-benzofuran-4(5H)-one* (**4d**): Viscous oil; IR ν_{max} (Neat) 2960, 1676, 1558, 1444, 1072 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ (ppm) 1·12 (*s*, 6H), 2·34 (*s*, 2H), 2·69 (*s*, 2H), 3·98 (*s*, 2H), 6·88 (*s*, 1H), 7·18–7·27 (*m*, 5H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ (ppm) 28·7 (2C), 30·5, 35·3, 37·7, 52·7, 118·7, 123·9, 126·3, 128·5 (2C), 128·9 (2C), 139·9, 140·1, 167·0, 194·8; HRMS calcd for $C_{17}H_{18}O_2Na$ [M + Na]$^+$ 277·1205, found 277·1208.

2.1d *3-Methyl-3,5,6,7-tetrahydro-1-benzofuran-4(2H)-one* (**4e**): Colourless oil; IR ν_{max} (neat) 2956, 1627, 1404, 1236, 1182 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ (ppm) 1·21 (*d*, *J* = 6·7 Hz, 3H), 1·97–2·06 (*m*, 2H), 2·30–2·43 (*m*, 4H), 3·24–3·35 (*m*, 1H), 4·08 (*dd*, *J* = 5·8, 9·2 Hz, 1H), 4·60 (*t*, *J* = 9·2 Hz, 1H), ^{13}C-NMR ($CDCl_3$, 75 MHz) δ (ppm) 19·5, 21·9, 24·1, 34·0, 36·8, 80·6, 118·2, 178·3, 195·9; HRMS calcd for $C_9H_{12}O_2Na$ [M + Na]$^+$ 175·0735, found 175·0737.

2.1e *3,6,6-Trimethyl-3,5,6,7-tetrahydro-1-benzofuran-4(2H)-one* (**4f**): Colourless oil; IR ν_{max} (neat) 2958, 1633, 1402, 1222, 1029 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ (ppm) 1·02 (*s*, 6H), 1·14 (*d*, *J* = 6·7 Hz, 3H), 2·13 (*s*, 2H), 2·20 (*s*, 2H), 3·18–3·28 (*m*, 1H), 4·03 (*dd*, *J* = 5·6, 9·2 Hz, 1H), 4·54 (*t*, *J* = 9·2 Hz, 1H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ (ppm) 19·3, 28·3, 28·8, 33·8, 34·1, 37·8, 51·2, 80·5, 116·5, 176·6, 194·8; HRMS calcd for $C_{11}H_{16}O_2Na$ [M + Na]$^+$ 203·1048, found 203·1040.

2.1f *3-Ethyl-6,6-dimethyl-3,5,6,7-tetrahydro-1-benzofuran-4(2H)-one* (**4g′**) *and 4,7,7-trimethyl-2,3,4,6,7,8-hexahydro-5H-chromen-5-one* (**4g″**): The compounds **4g′** and **4g″** were obtained from crude **3g** as an inseparable mixture in a 1 : 1 ratio. **4g′**: ^{1}H-NMR ($CDCl_3$, 300 MHz) δ (ppm) (only distinctive signals) 0·83 (*t*, J = 6·8 Hz, 3H), 3·16–3·23 (*m*, 1H), 4·24 (*dd*, *J* = 5·4, 9·3 Hz, 1H). **4g″**: ^{1}H-NMR ($CDCl_3$, 300 MHz) δ (ppm) (only distinctive signals) 1·34 (*d*, *J* = 6·8 Hz, 3H), 3·77–3·80 (*m*, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 10·7, 19·2, 25·6, 28·2, 28·3, 28·9, 29·2, 33·9 (2C), 37·8 (2C), 40·4, 46·8, 51·0, 51·2, 57·0, 74·6, 78·0, 112·2, 114·9, 176·9, 178·7, 194·2, 194·8; HRMS

Table 1. Titanocene(III) chloride mediated synthesis of furan derivatives.

Entry	Enol ether (**2**)	Reactant (alcohol used)	Furan derivative (**4**)	Yield (%)[a]
1	 **2a**		 **4a**	63
2	 **2b**		 **4b**	68
3	 **2c**		 **4c**	64
4	 **2b**		 **4d**	54
5	 **2a**		 **4e**	53
6	 **2b**		 **4f**	51
7	 **2b**		 **4g′** **4g″**	52[b]
8	 **2d**		 **4h**	58

[a]Yield refer to pure isolated product **4** from **2**. [b]Two isomers in 1 : 1 ratio

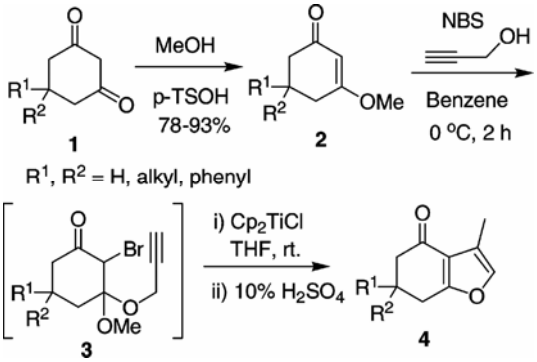
calcd for $C_{12}H_{18}O_2Na$ $[M + Na]^+$ 217·1204, found 217·1205.

2.1g *3,6,-Dimethyl-6,7-dihydro-1-benzofuran-4(5H)-one, Evodone* (**4h**): Compound **4h** (144 mg, 58%) was prepared from **2d** (210 mg, 1·5 mmol) through **3h** following the procedure deacribed for **4a** as a crystalline solid; m.p. 70–72°C (lit[3a] 73°C); IR ν_{max} (KBr) 2960, 1668, 1560, 1386, 1429 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ (ppm) 1·14 (*d*, J = 6·3 Hz, 3H), 2·16–2·24 (*m*, 4H), 2·36–2·52 (*m*, 3H), 2·89 (*dd*, J = 4·1, 16·2 Hz, 1H), 7·04 (*brs*, 1H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ (ppm) 8·9, 21·0, 30·8, 31·7, 46·7, 118·9, 120·0, 139·1, 167·1, 195·2; HRMS calcd for $C_{10}H_{12}O_2$ $[M^+ + 1]$ 165·0910, found 165·0918.

3. Results and discussion

Recently, it has been established[6] in our laboratory that α-bromocarbonyl compounds can be converted to tri-substituted tetrahydrofurans via intramolecular radical cyclization in the presence of titanocene(III) chloride as the radical initiator. Here, we describe a simple and useful method for the synthesis of substituted furans in considerable yields from α-bromo-β-keto enolethers using titanocene(III) chloride (Cp_2TiCl) as the radical source (scheme 1). Cp_2TiCl was prepared *in situ* from commercially available titanocene dichloride (Cp_2TiCl_2) and zinc dust in THF.[7]

Initially, the α-keto enolether **2** was prepared[8] from the 1,3-diketone **1** and methanol in good yield (scheme 1). The enolether **2** underwent bromopropargylation/allylation on treatment with N-bromosuccinimide and propagyl alcohol/allyl alcohol at 0°C to furnish **3** (80–90% purity, ^{1}H NMR) along with an inseparable unidentified product (10–20%). Unfortunately, several attempts to purify compound **3** failed due to its instability during chromatography. The crude bromo compound **3** in the presence of titanocene(III) chloride in THF followed by decomposition with 10% aqueous sulphuric acid afforded a mass which was purified by column chromatography to isolate the pure furan derivative **4** in considerable yield. Thus, a series of crude α-bromo carbonyl compounds were treated with titanocene(III) chloride in THF and the results are summarized in table 1.



Scheme 1. Synthesis of substituted furans.

All the products were characterized by IR, NMR and HRMS studies and by comparing the data with those of reported values.[4g,5] While radical cyclization of the crude bromoketones **3a–3f** afforded only a single furan derivative **4a–4f**, crude **3g** (entry 7, table 1) on treatment with Cp_2TiCl in THF afforded a non-separable mixture of two isomers **4g′** and **4g″** (52%) in the ratio of 1 : 1. The pyran derivative **4g″** was formed via 6-*endo-trig* radical cyclization.[9] The ratio of isomers was determined from the methyl signals in ^{1}H NMR spectrum of the crude compound appeared at δ 0·83 (*t*, $J = 6{\cdot}8$ Hz) for **4g′** and at δ 1·34 (*d*, $J = 6{\cdot}8$ Hz) for **4g″**.

This radical technology was then applied for the synthesis of a naturally occurring furanoterpene, evodone in good yield. Thus, the crude bromoketone (85% purity) obtained from **2d**, on radical cyclization reaction in the presence of Cp_2TiCl in THF at room temperature followed by acid treatment furnished (±)-evodone **(4h)** in 58% yield (table 1, entry 8). The spectral and analytical data are in good agreement with the reported values.[5]

4. Conclusions

In conclusion, we have developed a radical induced method for synthesis of furan derivatives using titanocene(III) chloride as the radical source. A furanoterpene, (±) evodone has been synthesized in good yield using this radical technology.

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