Electronic Supplementary Information

$TiCl_4$ Catalyzed Tandem Construction of C-C and C-O Bonds: a Simple and One-Pot Atom-Economical Stereoselective Synthesis of Spiro-Oxindoles

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Contents

Experimental Section:

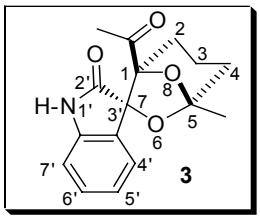
General Remarks: Melting points were recorded on a Superfit (India) capillary melting point apparatus and are uncorrected. IR spectra were recorded on a JASCO-FT-IR model 5300 spectrometer using solid samples as KBr plates. ^{1}H NMR (200 MHz / 400 MHz) and ^{13}C NMR (50 MHz / 100 MHz) spectra were recorded in deuterochloroform ($CDCl_3$) on a Bruker-AC-200/Bruker-AVANCE-400 spectrometer using tetramethylsilane (TMS, $\delta = 0$) as an internal standard. Elemental analyses were recorded on a Thermo Finnigan Flash EA 1112 analyzer. Mass spectra were recorded on either VG7070H mass spectrometer using EI technique or Shimadzu-LCMS-2010 A mass spectrometer. The X-ray diffraction measurements were carried out at 298 K on an automated Enraf-Nonious MACH 3 diffractometer using graphite monochromated, Mo-Kα ($\lambda = 0.71073$ Å) radiation with CAD4 software or the X-ray intensity data were measured at 298 K on a Bruker SMART APEX CCD area detector system equipped with a graphite monochromator and a Mo-Kα fine-focus sealed tube ($\lambda = 0.71073$ Å). 2-Acetyl-6-methyl-2,3-dihydro-4*H*-pyran (**2**) was prepared according to the literature procedure (K. Alder, H. Offermanns, E. Ruden, *Chem. Ber*.,1941, **74B**, 905).

General procedure:

[1*S*,5*S*,7(3′)*S*/1*R*,5*R*,7(3′)*R*]-[1-Acetyl-5-methyl-6,8-dioxabicyclo(3.2.1)octane]-7-spiro-3′-(indolin-2′-one) (3):

To a stirred solution of isatin (0.147 g, 1 mmol) in acetonitrile (5 mL) were successively added 2-acetyl-6-methyl-2,3-dihydro-4*H*-pyran (**2**) (0.28 g, 2 mmol) and $TiCl_4$ (0.1 mL, 2 M solution in CH_2Cl_2, 0.2 mmol) at room temperature. After stirring at room temperature for 6 h, water was added to the reaction mixture and extracted with ethyl acetate (2 X 10 mL). The combined organic layer was dried over anhyd. Na_2SO_4 and concentrated. The crude product thus obtained was purified by column chromatography (silica gel, 10% ethyl acetate in hexanes) to afford the desired compound **3** (0.212 g, 74 %) as a colorless solid.

m.p. : 163-165 ^{o}C



IR (KBr) : ν 3200-2800 (multiple bands), 1720, 1620 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) : δ 1.65-2.00 (m, 7H), 2.04 (s, 3H), 2.19-2.29 (m, 1H), 3.05-3.22 (m, 1H), 6.77 (d, 1H, *J* = 8.0 Hz), 6.96-7.04 (m, 1H), 7.19-7.25 (m, 1H), 7.43 (d, 1H, *J* = 7.6 Hz), 7.94 (b, 1H).

^{13}C NMR (50 MHz, $CDCl_3$) : δ 17.50, 25.48, 26.08, 27.42, 33.19, 83.67, 94.24, 110.18, 110.67, 122.70 124.74, 129.35, 130.22, 140.33, 174.22, 205.83.

EIMS (m/z) : 287 (M^+).

Analysis calcd for $C_{16}H_{17}NO_4$: C, 66.89; H, 5.96; N, 4.87.

Found : C, 66.72; H, 5.98; N, 4.87.

Crystal data for **3**: empirical formula, $C_{16}H_{17}NO_4$; formula weight, 287.31; crystal color, habit: colorless, rectangular; crystal dimensions, 0.52 X 0.48 X 0.42 mm; crystal system, triclinic; lattice type, primitive; lattice parameters, *a* = 7.508(17) Å, *b* = 8.223(7) Å, *c* = 12.453(8) Å; α = 77.46(6); β = 83.05(10); γ = 74.89(10); *V* = 722.8(18) Å^3; space group, P-1; (No: 2); *Z* = 2; D_{calcd} = 1.320 g / cm^3; F_{ooo} = 304; λ(Mo-K$_\alpha$) = 0.71073 Å; *R* (I≥2σ$_1$) = 0.0665, wR^2 = 0.1793. Detailed X-ray crystallographic data is available from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK (for compound **3** CCDC # 248071).

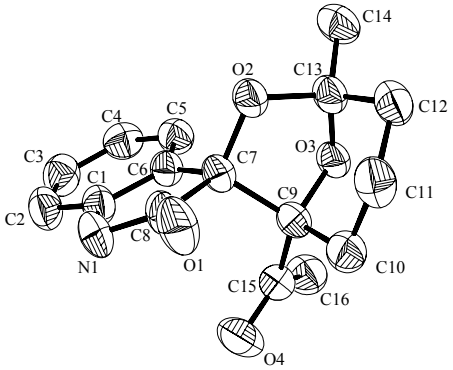
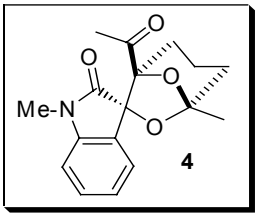


Fig.1. ORTEP diagram of compound **3**
(*Hydrogen atoms were omitted for clarity*)

[1*S*,5*S*,7(3′)*S*/1*R*,5*R*,7(3′)*R*]-[1-Acetyl-5-methyl-6,8-dioxabicyclo(3.2.1)octane]-7-spiro-3′-(1′-methylindolin-2′-one) (4):



4

Yield : 64 %

m.p. : 148-150 ^{o}C

IR (KBr) : ν 1718, 1707, 1608 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) : δ 1.62-2.00 (m, 7H), 2.01 (s, 3H), 2.18-2.30 (m, 1H), 3.08-3.40 (m,4H), 6.75 (d, 1H, *J* = 7.6 Hz), 6.96-7.11 (m, 1H), 7.24-7.40 (m, 1H), 7.44 (d, 1H, *J* = 7.6 Hz).

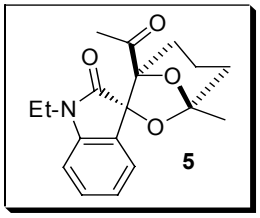
^{13}C NMR (50 MHz, $CDCl_3$) : δ 17.43, 25.40, 26.00, 26.43, 27.37, 33.16, 83.34, 94.00, 108.16, 110.48, 122.67, 124.24, 128.88, 130.19, 143.08, 171.99, 205.66.

LCMS (m/z) : 302 $(M+H)^{+}$.

Analysis calcd for $C_{17}H_{19}NO_4$: C, 67.76; H, 6.36; N, 4.65.

Found : C, 67.99; H, 6.35; N, 4.61.

[1*S*,5*S*,7(3′)*S*/1*R*,5*R*,7(3′)*R*]-[1-Acetyl-5-methyl-6,8-dioxabicyclo(3.2.1)octane]-7-spiro-3′-(1′-ethylindolin-2′-one) (5):



5

Yield : 69 %

m.p. : 131-132 ^{o}C

IR (KBr) : ν 1720, 1709, 1610 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$) : δ 1.27 (t, 3H, *J* = 6.8 Hz), 1.56-1.94 (m, 7H), 1.98 (s, 3H), 2.12-2.29 (m,1H), 3.06-3.30 (m, 1H), 3.64-3.88 (m, 2H), 6.75 (d, 1H, *J* = 7.8 Hz), 6.94-7.03 (m, 1H), 7.20-7.31 (m, 1H),7.43 (d, 1H, *J* = 8.0 Hz).

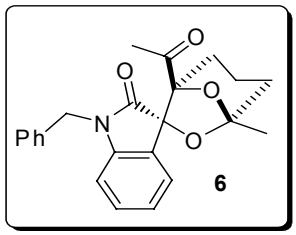
^{13}C NMR (50 MHz, $CDCl_3$) : δ 12.16, 17.37, 25.35, 25.91, 27.29, 33.12, 34.86, 83.28, 94.00, 108.19, 110.42, 122.43, 124.45, 128.98, 130.07, 142.08, 171.50, 205.46.

EIMS (m/z) : 315 (M^{+}).

Analysis calcd for $C_{18}H_{21}NO_4$: C, 68.55; H, 6.71; N, 4.44.

Found : C, 68.42; H, 6.74; N, 4.49.

[1*S*,5*S*,7(3′)*S*/1*R*,5*R*,7(3′)*R*]-[1-Acetyl-5-methyl-6,8-dioxabicyclo(3.2.1)octane]-7-spiro-3′-(1′-benzylindolin-2′-one) (6):



Yield : 70 %

m.p. : 141-143 ^{o}C

IR (KBr) : ν 1716, 1608 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$) : δ 1.63-2.00 (m, 7H), 2.04 (s, 3H), 2.19-2.37 (m, 1H), 3.09-3.36 (m, 1H), 4.79 & 5.07 (ABq, 2H, *J* = 15.8 Hz), 6.59 (d, 1H, *J* = 7.8 Hz), 6.92-7.05 (m, 1H), 7.08-7.20 (m, 1H), 7.22-7.51 (m, 6H).

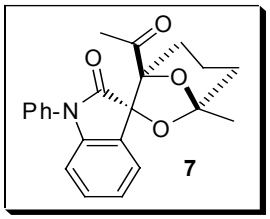
^{13}C NMR (50 MHz, $CDCl_3$) : δ 17.52, 25.50, 26.11, 27.56, 33.26, 44.23, 83.45, 94.24, 109.33, 110.64, 122.80, 124.32, 127.21, 127.57, 128.79, 129.10, 130.12, 135.48, 142.42, 172.35, 205.93.

LCMS (m/z) : 378 $(M+H)^{+}$.

Analysis calcd for $C_{23}H_{23}NO_4$: C, 73.19; H, 6.14; N, 3.71.

Found : C, 73.01; H, 6.19; N, 3.73.

[1*S*,5*S*,7(3′)*S*/1*R*,5*R*,7(3′)*R*]-[1-Acetyl-5-methyl-6,8-dioxabicyclo(3.2.1)octane]-7-spiro-3′-(1′-phenylindolin-2′-one) (7):



Yield : 56 %

m.p. : 125-126 ^{o}C

IR (KBr) : ν 1728, 1707, 1610 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$) : δ 1.62-2.00 (m, 7H), 2.04 (s, 3H), 2.15-2.30 (m, 1H), 3.06-3.32 (m, 1H), 6.64 (d, 1H, *J* = 7.8 Hz), 6.94-7.08 (m, 1H), 7.11-7.23 (m, 1H), 7.35-7.60 (m, 6H).

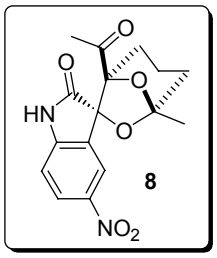
^{13}C NMR (50 MHz, $CDCl_3$) : δ 17.32, 25.47, 26.06, 27.43, 33.17, 83.60, 94.49, 109.36, 110.82, 123.06, 124.54, 126.88, 128.26, 128.52, 129.58, 130.06, 134.36, 143.30, 171.48, 205.83.

EIMS (m/z) : 363 (M^+).

Analysis calcd for $C_{22}H_{21}NO_4$: C, 72.71; H, 5.82; N, 3.85.

Found : C, 72.93; H, 5.80; N, 3.82.

[1*S*,5*S*,7(3′)*S*/1*R*,5*R*,7(3′)*R*]-[1-Acetyl-5-methyl-6,8-dioxabicyclo(3.2.1)octane]-7-spiro-3′-(5′-nitroindolin-2′-one) (8):



Yield : 48 %

m.p. : 214-216 ^oC

IR (KBr) : ν 3263, 1751, 1716, 1628 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$) : δ 1.65-2.05 (m, 7H), 2.08-2.26 (m, 4H), 2.96-3.20 (m, 1H), 6.88 (d, 1H, *J* = 8.6 Hz), 8.20 (dd, 1H, *J* = 8.6 & 1.8 Hz), 8.26 (d, 1H, *J* = 1.8 Hz), 8.44 (b, 1H).

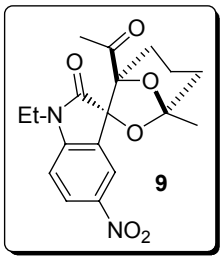
^{13}C NMR (50 MHz, $CDCl_3$) : δ 17.29, 25.53, 26.43, 27.26, 32.90, 83.04, 94.73, 110.07, 111.63, 120.17, 127.15, 130.63, 143.58, 146.18, 174.20, 206.98.

EIMS (m/z) : 332 (M^+).

Analysis calcd for $C_{16}H_{16}N_2O_6$: C, 57.83; H, 4.85; N, 8.43.

Found : C, 57.98; H, 4.82; N, 8.38.

[1*S*,5*S*,7(3′)*S*/1*R*,5*R*,7(3′)*R*]-[1-Acetyl-5-methyl-6,8-dioxabicyclo(3.2.1)octane]-7-spiro-3′-(1′-ethyl-5′-nitroindolin-2′-one) (9):



Yield : 50 %

m.p. : 168-170 ^oC

IR (KBr) : ν 1738, 1711, 1608 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$) : δ 1.31 (t, 3H, *J* = 7.8 Hz), 1.62-2.21 (m, 11H), 2.95-3.28 (m, 1H), 3.65-4.00 (m, 2H), 6.84 (d, 1H, *J* = 7.8 Hz), 8.20-8.31 (m, 2H).

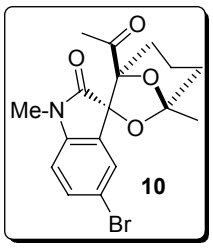
^{13}C NMR (50 MHz, $CDCl_3$) : δ 12.13, 17.25, 25.50, 26.15, 27.27, 33.00, 35.57, 82.67, 94.66, 107.85, 111.42, 119.86, 127.14, 130.39, 143.32, 148.02, 171.80, 206.12.

LCMS (m/z) : 383 $(M+ Na)^+$.

Analysis calcd for $C_{18}H_{20}N_2O_6$: C, 59.99; H, 5.59; N, 7.77.

Found : C, 59.80; H, 5.60; N, 7.81.

[1*S*,5*S*,7(3′)*S*/1*R*,5*R*,7(3′)*R*]-[1-Acetyl-5-methyl-6,8-dioxabicyclo(3.2.1)octane]-7-spiro-3′-(5′-bromo-1′-methylindolin-2′-one) (10):



Yield : 61 %

m.p. : 179-180 ^oC

IR (KBr) : ν 1728, 1709, 1621 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$) : δ 1.62-2.22 (m, 11H), 3.00-3.28 (m, 4H), 6.62 (d, 1H, *J* = 8.8 Hz), 7.40 (dd, 1H, *J* = 8.8 & 2.0 Hz), 7.50 (d, 1H, *J* = 2.0 Hz).

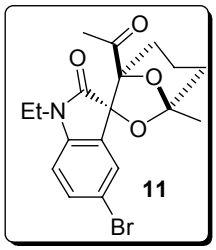
^{13}C NMR (100 MHz, $CDCl_3$) : δ 17.35, 25.55, 26.31, 26.64, 27.33, 33.04, 83.12, 94.20, 109.75, 110.89, 115.28, 127.23, 131.02, 132.95, 142.17, 171.43, 206.03.

LCMS (m/z) : 378 $(M-H)^-$, 380 $(M+2-H)^-$.

Analysis calcd for $C_{17}H_{18}NO_4Br$: C, 53.70; H, 4.77; N, 3.68.

Found : C, 53.79; H, 4.72; N, 3.64.

[1*S*,5*S*,7(3′)*S*/1*R*,5*R*,7(3′)*R*]-[1-Acetyl-5-methyl-6,8-dioxabicyclo(3.2.1)octane]-7-spiro-3′-(5′-bromo-1′-ethylindolin-2′-one) (11):



Yield : 44 %

m.p. : 137-140 ^oC

IR (KBr) : ν 1724, 1707, 1624 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$) : δ 1.25 (t, 3H, *J* = 6.8 Hz), 1.62-2.00 (m, 7H), 2.03-2.22 (m, 4H), 3.04-3.28 (m, 1H), 3.59-3.90 (m, 2H), 6.63 (d, 1H, *J* = 7.8 Hz), 7.38 (dd, 1H, *J* = 7.8 & 2.0 Hz), 7.52 (d, 1H, *J* = 2.0 Hz).

^{13}C NMR (50 MHz, $CDCl_3$) : δ 12.06, 17.30, 25.47, 26.08, 27.32, 33.06, 35.08, 83.11, 94.26, 109.72, 110.81, 114.98, 127.47, 131.28, 132.83, 141.28, 170.99, 205.65.

LCMS (m/z) : 394 $(M+H)^+$, 396 $(M+2+H)^+$

Analysis calcd for $C_{18}H_{20}NO_4Br$: C, 54.83; H, 5.11; N, 3.55.

Found : C, 54.63; H, 5.13; N, 3.58.

Crystal data for **11**: empirical formula, $C_{18}H_{20}BrNO_4$; formula weight, 394.26; crystal color, habit: colorless, rectangular; crystal dimensions, 0.51 X 0.45 X 0.30 mm; crystal system, monoclinic; lattice type, primitive; lattice parameters, a = 12.5767(8) Å, b = 9.3151(6) Å, c = 15.5341(11) Å; α = 90.00; β = 109.0860(10); γ = 90.00; V = 1719.8(2) Å^3; space group, P 2 (1)/n (No:14); Z = 4; D_{calcd} = 1.523 g / cm^3; F_{ooo} = 808; λ(Mo-K_α) = 0.71073 Å; R (I≥2σ_1) = 0.0402, wR^2 = 0.1123. Detailed X-ray crystallographic data is available from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK (for compound **11** CCDC # 248072).

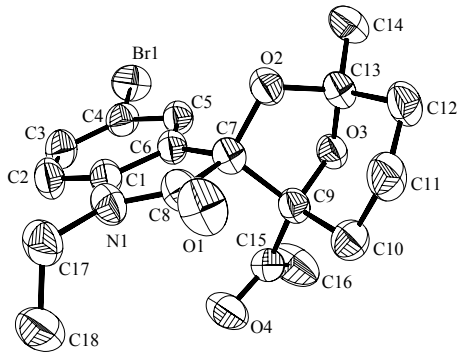
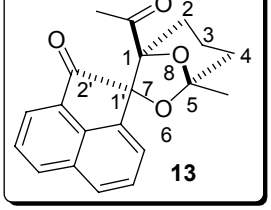


Fig.2. ORTEP diagram of compound **11**
(*Hydrogen atoms were omitted for clarity*)

[1*S*,5*S*,7(1′)*S*/1*R*,5*R*,7(1′)*R*]-[1-Acetyl-5-methyl-6,8-dioxabicyclo(3.2.1)octane]-7-spiro-1′-(1′,2′-dihydroacenaphthalene-2′-one) (13):



Yield : 72 %

m.p. : 147-149 ^{o}C

IR (KBr) : ν 1724, 1712, 1622 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) : δ 1.71-2.10 (m, 10H), 2.13-2.27 (m, 1H), 3.19-3.38 (m, 1H), 7.59-7.66 (m, 1H), 7.71-7.83 (m, 2H), 7.87 (d, 1H, *J* = 8.8 Hz), 8.00 (d, 1H, *J* = 6.8 Hz), 8.09 (d, 1H, *J* = 7.6, Hz).

^{13}C NMR (50 MHz, $CDCl_3$) : δ 17.57, 25.48, 25.72, 28.10, 33.38, 87.23, 94.95, 110.52, 120.95, 121.80, 125.85, 128.33, 128.50, 130.36, 131.63, 132.91, 138.93, 141.01, 198.91, 205.88.

EIMS (m/z) : 322 (M^+).

Analysis calcd for $C_{20}H_{18}O_4$: C, 74.52; H, 5.63.

Found : C, 74.70; H, 5.65.

Crystal data for **13**: empirical formula, $C_{20}H_{18}O_4$; formula weight, 322.34; crystal color, habit: colorless, rectangular; crystal dimensions, 0.50 X 0.45 X 0.40 mm; crystal system, monoclinic; lattice type, primitive; lattice parameters, *a* = 11.901(2) Å, *b* = 9.0504(13) Å, *c* = 14.859(6) Å; α = 90.00; β = 90.66(2); γ = 90.00; *V* = 1600.4(7) Å^3; space group, P 21/c (No: 14); *Z* = 4; D_{calcd} = 1.338 g / cm^3; F_{ooo} = 680; λ(Mo-K_α) = 0.71073 Å; *R* (I≥2σ_1) = 0.0712, wR^2 = 0.1754. Detailed X-ray crystallographic data is available from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK (for compound **13** CCDC # 248073).

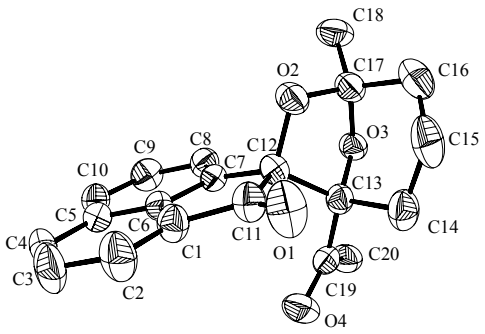
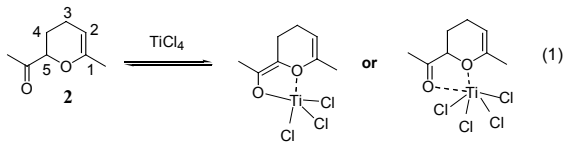


Fig.3. ORTEP diagram of compound **13**
(*Hydrogen atoms were omitted for clarity*)

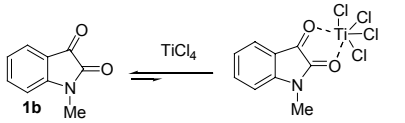
Towards understanding the actual role of titanium tetrachloride

With a view to understand the nature of the actual species formed in the reaction of 2-acetyl-6-methyl-2,3-dihydro-4*H*-pyran (**2**) with $TiCl_4$, we have recorded the ^1H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra of 2-acetyl-6-methyl-2,3-dihydro-4*H*-pyran (**2**) (1.0 eq.) in the presence of $TiCl_4$ (0.1 eq.) (the ratio of **2** and $TiCl_4$ is 1:0.1) in $CDCl_3$. In the ^1H NMR spectrum, the multiplet originally at δ 4.24-4.32 appears now as two multiplets, one at δ 4.15-4.25 (major) and the other one at δ 4.28-4.34 (minor) due to methine proton.[Δ] There is also some change in splitting pattern in the region δ 1.60–2.40. Similarly, ^{13}C NMR spectrum, shows some additional peaks at δ 207.34 (C=O), 106.16 (C2), 78.70(C5), 39.39 and 33.54(alkyl).[Δ] These results clearly indicate the possible formation of titanium enolate or complexation as shown in eqn. 1.



(1)

We have also recorded the ^1H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra of the 1-methylisatin (**1b**) (1.0 eq.) in the presence of $TiCl_4$ (0.2 eq.) (the ratio of **1b** and $TiCl_4$ is 1:0.2) in $CDCl_3$. ^1H NMR spectrum, shows there is not significant change in the chemical shift values and the pattern of the peaks from the original spectrum. Similar trend was also observed in the ^{13}C NMR spectrum. These results do not give any clear indication for strong complexation between 1-methylisatin (**1b**) and titanium tetrachloride in the present reaction conditions. However, we cannot rule out some kind of complexation between 1-methylisatin (**1b**) and titanium tetrachloride (eqn. 2).



(2)

[Δ] We also noticed that small variations in quantity of $TiCl_4$ effect the intensity of additional peaks in the ^1H NMR and ^{13}C NMR spectra.