

Short communication

Synthesis of 4-(2-Indenylethyl)morpholine and their cationic transition metal complexes

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The amido tethered ligand 4-(2-indenylethyl)morpholine (6) have been prepared in high yield (71%). All the compounds were fully characterized by NMR, IR, Mass Spec. and Microanalysis. Treatment of the lithio salt of (6) with TiCl₄:2THF in THF afforded the new complex 4-(2-indenylethyl)morpholinetitanium dichloride (7a) in 26% yield as viscous green oil while, treatment with ZrCl₂:2THF gave 4-(2-indenylethyl)morpholinezirconium dichloride (7b) in 63% yield as yellow solid. The new compounds (7a and 7b) were characterized by Mass Spectroscopy and Micro Analysis.

Key words: 4-(2-indenylethyl)morpholine, 4-(2-indenylethyl)morpholinetitanium, 4-(2-indenylethyl)morpholinezirconium dichloride.

INTRODUCTION

Complexation of transition metals to optically active cyclopentadienyl anions to form chiral metallocenes has emerged in recent years as serviceable catalysts for asymmetric synthesis and stereoselective organic transformations (Jordan et al., 1990; Nienkemper et al. 2008). Chiral bridged-metallocene of group IV transition metals have been utilized successfully in synthetic transformations such as hydrogenation (Pino, 1998), carbomagnesation (Morken et al., 1993), olefin epoxidation (Jordan et al., 1990), olefin isomerisation (Amor et al., 1996; Bryte et al., 2006), ketone reduction (Galtman and Moisa, 2000), allylation of aldehydes (Hideo et al., 1989) and in Diels - Alder reactions (Stille et al., 1989). The ansa-metallocenes (1) (ethylenebis(η⁵-4,5,6,7-tetrahydro-1-indenyl))titanium and zirconium dichloride first disclosed by Brintzinger are the most used reagents (Jordan et al., 1990). Bercaw et al. (1972) have recently introduced a novel chelating ligand system (2) in which one cyclopentadienyl moiety is linked via an NMe₂

or ethylene group to an amide ligand. The nitrogen atom (Figure 1) (Jordan et al., 1990) can act as a 2-electron donor site and can coordinate to metal centres; owing to the appropriate length and flexibility of the ethylene spacer between the cyclopentadienyl moiety and NMe₂ units. Intramolecular coordination to a Lewis acidic metal centre bonded to the cyclopentadienyl ring is quite favourable. The nitrogen atom can act as a Lewis base not only towards Lewis acidic metal centre but also towards more classical Lewis acids such as H⁺ and R⁺. Protonation or alkylation of the "N" atom generates an ammonium group, which will enhance the solubility of the relevant metal complexes in polar solvents such as water. Furthermore, the ammonium-substituted side arm will have electronic and steric properties distinctly different from those of the neutral NMe₂ substituted side arm. Reggio et al. (1998) studied the (E)- and (Z)-naphthylidene indene (C-2 H and C2 Me) (3) and their results indicate that the E geometric isomer in each pair of analogues is the isomer with the higher CB1 and CB2 affinities and the higher pharmacological potency.

Our intention (Figure 2) is to synthesize a cationic ligand containing immobilized nitrogen within a molecule,

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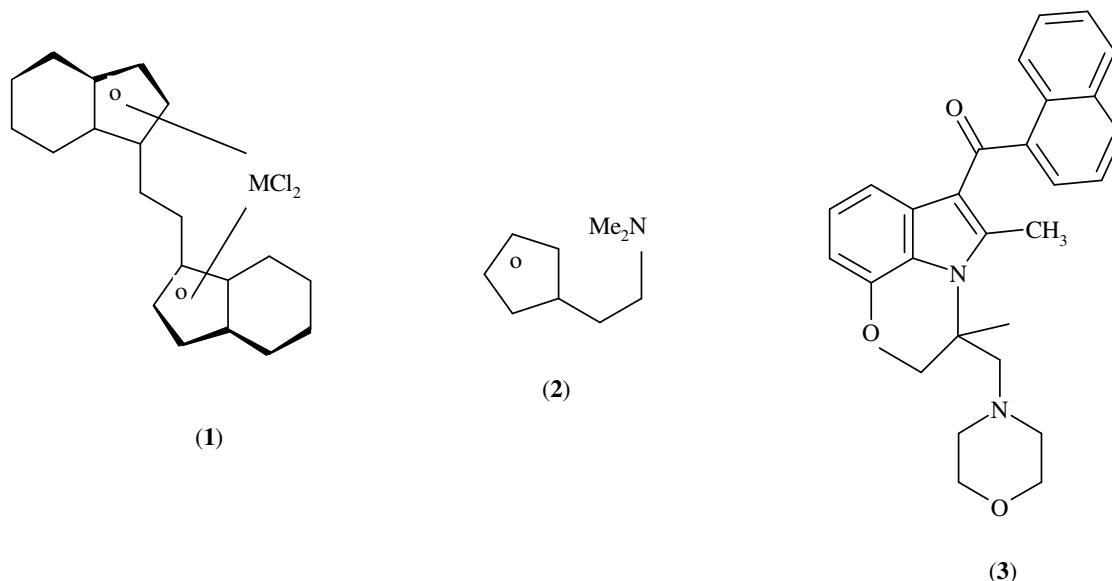


Figure 1. (1, 8, 9) 1a: M = Ti; 1b: = Zr.

metallate the ligand and examine the effect of the nitrogen on the stability of the complex obtained.

MATERIALS AND METHODS

Moisture- and air sensitive compounds were handled under an argon atmosphere using Schlenk techniques. Diethyl ether was distilled from benzophenone ketyl. The NMR, IR and Mass. Spec. were done at University of Manchester Institute of Science and Technology (UMIST) now The University of Manchester, Manchester, England.

Preparation of 4-(2-chloroethyl)morpholine (5)

N-(2-chloroethyl)morpholine hydrochloride (20.0 g, 10.8 mmol) (4) was dissolved in water (100 ml) and neutralized with aqueous sodium hydroxide to pH 11. The solution was extracted with dichloromethane, washed with water, dried over MgSO_4 and concentrated under reduced pressure. Distillation under vacuum afforded the pure product (5) as colourless oil, (17.2 g, 86% yield) b.p. 128-130°C (2 mm Hg). $^1\text{H NMR}$ (CDCl_3) δ 2.10 (s, 4H, H_3 , and H_6), 2.3 (t, 2H, $J = 5\text{Hz}$, H_2), 3.2 (t, 2H, $J = 5\text{Hz}$, H_1) 3.3 (br s, 4H, H_4 and H_5) ppm. $^{13}\text{C NMR}$ (CDCl_3) δ 40.6(C_2), 53.6 (C_3 and C_6), 60.0 (C_1), 66.7 (C_4 and C_5) ppm. IR ν_{max} (neat) 2950 s, 2860 m, 2830 m, 1460 s (C-N), 1355 m, 1300 s (C-O-C), 1260 s, 1120 m, 1010 s (C-N), 872 m, 620 w (C-Cl) cm^{-1} . Elemental analysis (Found: C, 48.5; H, 7.9; N, 9.2; Cl, 23.7 $\text{C}_6\text{H}_{12}\text{ONCl}$ requires C, 48.2; H, 8.1; N, 9.4; Cl, 23.8. MS (FAB): m/z M^+ 150.

Preparation of 4-(2-indenylethyl)morpholine (6)

To a flame-dried, three-necked round-bottom flask (250 ml) under argon was added freshly distilled indene (5.8 g, 5.8 ml, 5.0 mmol) in THF (50 ml) it was cooled to -78°C for 30 min. *n*-Butyllithium (20 ml, 5.0 mmol of 2.5 M solution in hexane) was added drop wise. The mixture was further stirred for 1 h at -78°C. N-(2-

chloroethyl)morpholine (5.0 g, 3.3 mmol) (5) in THF (20 ml) was cannulated into the reaction mixture. The reaction mixture was then stirred at room temperature for 18 h. The mixture was hydrolyzed by careful addition of water and the aqueous layer was extracted with diethyl ether (3 x 100 ml). The combined ether layers were dried over MgSO_4 and concentrated. The crude oil (10.9 g, 95%) was fractionally distilled under vacuum (in a sand-bath) to afford the product (6) (5.4 g, 23.0 mmol, 71%) as light brown oil. B.p. 230-236°C (1.0 mm Hg). $^1\text{H NMR}$ (CDCl_3) δ 2.75 (br s, 4H, H_1 and H_2), 2.90 (m, 4H, H_{12} and H_{15}), 3.5 (s, 2H H_5), 3.9 (m, 4H, H_{13} and H_{14}), 6.3 (s, 1H, H_4), 7.2-7.65 (complex, 4H, aromatic) ppm; ^{13}C (CDCl_3) δ 24.9 (C_2), 37.6 (C_5), 53.5 (C_{12}), 57.6 (C_1), 66.8 (C_{13}), 118.6 (C_7), 123.6 (C_{10}), 124.5 (C_8), 125.9 (C_9), 128.3 (C_4), 142.0 (C_3), 144.0 (C_6), 145.0 (C_{11}). IR ν_{max} (neat) 3070w, 3020, 2980, 2860, 2710, 1620, 1460, 1120, 1118s, 1005 cm^{-1} . (Found: C, 78.7; H, 8.4; N, 6.2. Calc for $\text{C}_{15}\text{H}_{19}\text{ON}$ requires C, 78.6; H, 8.3; N, 6.1; MS (FAB) m/z 230 M^+ 72%).

Preparation of N-(2-indenylethyl)morpholinetitanium dichloride (IV) (7a) using TiCl_4 :2THF

The compound TiCl_4 :2THF (7.0 g, 21.0 mmol) in THF (100 ml) was placed in a well-stoppered pressure-equalizing dropping funnel and a solution of litho N-(2-indenylethyl)morpholine (5.0 g, 21.0 mol) in THF (100 ml) was placed in another pressure equalizing dropping funnel. The two solutions were simultaneously added drop wise to a 500 ml three-neck flask containing THF (100 ml) maintained at 40°C over a period of 4.5 h under argon. The solution became brownish and was refluxed for a further 4 h and was finally flushed with dry HCl gas for 30 s during which time the colour changed to dark green. Solvent was removed under reduced pressure. Diethyl ether (2 x 20 ml) was used to slurry the green viscous oil which precipitated dark green solid. Ether was removed and the solid was dried under reduced pressure to ensure complete removal of solvent. The dry residue was slurried with ether (50 ml). The solid was washed successively with aqueous HCl (4 N, 2 x 20 ml), H_2O

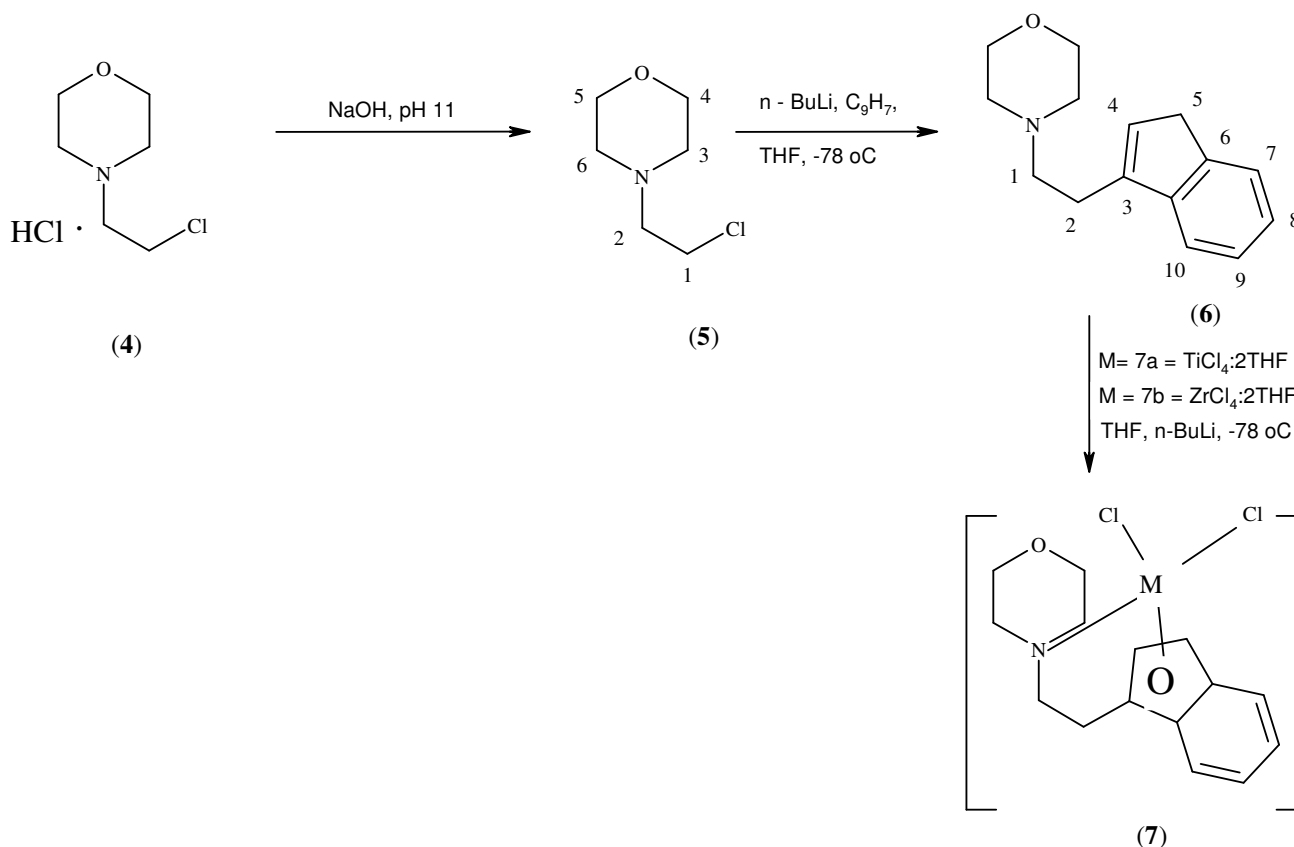


Figure 2. Synthesis of 4-(2-indenylethyl)morpholine and their complexes.

(2 x 20 ml), EtOH (2 x 20 ml), and ether (50 ml) and was dried through a stream of argon to yield (1.3 g, 26%) green viscous oil which was not soluble in NMR solvents. TLC showed it to contain two spots, the starting material (6) at an R_F value of 0.46 and a second spot the product (B) at R_F value of 0.34. (Found: C, 51.9; H, 5.7; N, 4.9; M 347. $\text{C}_{15}\text{H}_{19}\text{NOTiCl}_2$ requires C, 51.9; H, 5.5; N, 4.0 MS (FAB) m/z 160($\text{C}_{11}\text{H}_{12}\text{O}$) 94%, 229 ($\text{C}_{15}\text{H}_{19}\text{NO}$)23%, 291($\text{C}_4\text{H}_8\text{NO}$) $_2\text{TiCl}_2$ 86%, 347($\text{C}_{15}\text{H}_{19}\text{NOTiCl}_2$)52%).

Preparation of 4-(2-indenylethyl)morpholinezirconium dichloride (IV) (7b) using $\text{ZrCl}_4 \cdot 2\text{THF}$

A solution of N-(2-indenylethyl)morpholine (5.0 g, 21.0 mol) in THF (50 ml) was cooled to -78°C and was treated drop wise by syringe with a solution of n-butyllithium (8.4 ml of 2.5 M solution in hexane, 0.21 mol) in THF (50 ml) over 40 min under argon. The bright yellow solution formed was stirred for 1 h. It was then warmed to room temperature before being cannulated into a constant-addition dropping funnel and the solution was diluted to 100 ml. A solution of $\text{ZrCl}_4 \cdot 2\text{THF}$ (8.3 g, 21.0 mol) in THF (50 ml) was cannulated into a second constant-addition dropping funnel and the solution was diluted to 100 ml. The two solutions were simultaneously added drop wise to a 1-litre three-necked flask containing THF (250 ml) maintained at 25°C over a period of 3 h. The resultant solution was then stirred for 18 h. Solvent was removed under reduced pressure. Diethyl ether (2 x 20 ml) was used to slurry the brown residue and was also removed under reduced pressure to ensure complete

removal of THF. The dry residue was slurred with ether (50 ml), filtered, and washed with ether (50 ml). The yellow solid obtained was washed successively with aqueous HCl (4 N, 2 x 20 ml), H_2O (2 x 20 ml), ethanol (2 x 20 ml), and ether (20 ml) and was dried under argon to give the product (7b) in 63% (5.16 g) yield. The ^1H NMR (D_2O) spectrum of the yellow solid thus showed bands at δ 0.79 (s, 1H), 1.18 (s, 1H), 3.6 (m, 5H), 6.4 (d, J 3.1Hz, 1H), 6.7 (d, J 3.5, 1H). The MASS (FAB) (6b) gave the following fragments at 115($\text{C}_6\text{H}_{12}\text{NO}$)38%, 228($\text{C}_{15}\text{H}_{19}\text{NO}$)41%, 322($\text{C}_9\text{H}_7\text{Zr}$)84%, 393($\text{C}_{15}\text{H}_{19}\text{NOZrCl}_2$) $^{+2}$ 61%, 394($\text{C}_{15}\text{H}_{19}\text{NOZrCl}_2$) $^{+3}$ 51%. (Found: C, 69.1; H, 8.6; N, 2.8; M 390. $\text{C}_{15}\text{H}_{19}\text{NOZrCl}_2$ requires C, 46.3; H, 4.9; N, 3.6; Cl, 18.0).

RESULTS AND DISCUSSION

Neutralization of N-(2-chloroethyl)morpholine hydrochloride (4) (pH 11) with sodium hydroxide afforded the free base (5) in 86% yield (17.2 g) as colourless oil after ether extraction and fractional distillation in a sand-bath (b.p. 128-30/2 mm Hg). Compound (5) was fully characterized by ^1H , ^{13}C , IR, Microanalysis and Mass Spectroscopy. The reaction of the free base (5) with indenyllithium initially at -78°C and a gradual warming to room temperature for 18 h gave the desired product N-(2-indenylethyl)morpholine (6) in 71% (5.4 g) yield as light

brown oil which was purified by fractional distillation under vacuum in a sand bath (b.p. 230-236 °C, 1 mm Hg). The ^1H NMR spectrum showed a singlet at δ 2.75 ppm integrating for four protons $\text{N}(\text{-CH}_2)_2$ (H_1 and H_2) and a multiplet at δ 2.90 ppm integrating for four protons (H_{12} and H_{15}). The olefinic proton was a singlet at δ 3.5 ppm integrating for two protons (H_5) and a multiplet at δ 3.9 ppm for the four protons of the (H_{13} and H_{14}). At δ 6.3 ppm was a singlet integrating for two protons of H_3 while between δ 7.2-7.65 ppm were the aromatic protons integrating for the four protons of the aromatic ring ($\text{H}_7 - \text{H}_{10}$). The ^{13}C NMR spectrum exhibited 13 lines. The aromatic carbons of the ring were between 118.6 – 125.9 ppm, the olefinic carbon at 128.3 ppm while the three quaternary carbons were between δ 142.0-145.0 ppm. The IR spectrum showed bands at 2860 (C-H str.), 1460 m, 1120 m (C-O-C str.), 1110s, 1005 m (C-N str.) cm^{-1} . Microanalysis and mass spectrum (FAB) confirmed a molecular mass of 229 a.m.u. and a molecular formula of $\text{C}_{15}\text{H}_{19}\text{NO}$.

Reacting *n*-butyllithium with *N*-(2-indenylethyl)morpholine (6) gave an organometallic reagent *N*-(2-indenylethyl)morpholinolithium. Treatment of the organometallic reagent with $\text{TiCl}_4 \cdot 2\text{THF}$ and oxidation with dry HCl gas gave the expected product *N*-(2-indenylethyl)morpholinitanium dichloride (7a) in 18% yield as green viscous oil. The product, complex (7a) was characterized by microanalysis and mass spectroscopy. Thin layer chromatography gave two spots with distinct R_F values of 0.46 for starting material (6) and a new spot at R_F 0.34 for the product (7a). Attempted crystallization gave deposits that decompose once out of solution, on trying to isolate them and all attempts to sublime the product failed. The fragmentation pattern was interesting because the observed peaks at 160, 229 and 291 gave fragments of expected disconnection while the peak at 347 gave peak of expected product (7a), this sort of fragmentation was also observed by Zock et al. (2007) in their synthesis of a titanium complex. Microanalysis gave a matching percent composition. Treatment of the organometallic reagent *N*-(2-indenylethyl)morpholinolithium with solution of $\text{ZrCl}_4 \cdot 2\text{THF}$ and purification gave the product (7b) as yellow solid (3.15 g, 63%) yield which was not soluble in NMR solutions. Mass Spectroscopy gave fragmentations at 393 and 394 for the new cationic zirconocenes ($\text{C}_{15}\text{H}_{19}\text{NOZrCl}_2$) $^{+2}$ 61% and ($\text{C}_{15}\text{H}_{19}\text{NOZrCl}_2$) $^{+3}$ 51% respectively as our product (7b). Microanalysis also confirms the product. All attempts at crystallization of (7b) resulted in destruction of the substance.

Conclusion

The ligand *N*-(2-indenylethyl)morpholine was prepared, their titanium and zirconium complexes were synthesized. All attempts at crystallization of (7a and 7b)

resulted in destruction of the substance. Pasmann et al. (2008) had similar experience of not being able to obtain the crystals of their isodicyclopentadienide complexes. The new complexes obtained (7a and 7b) were not stabilized by the presence of nitrogen within the morpholine ring.

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