

A new catalyst for aldol condensation reactions

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Abstract: A new manganese complex was synthesised incorporating 1,2-diaminobenzene linked ketopinic acid scaffold, and successfully utilised as catalyst in the aldol condensation reactions of benzaldehyde with various aliphatic ketones to obtain products with excellent yield of >99 %.

Keywords: Lewis acid, manganese, 1,2-diaminobenzene, catalysis, aldol condensation

Introduction

Aldol condensation reaction as C—C bond formation reaction continued to provide opportunity for the synthesis of valuable intermediates, natural products, as well as other biologically important compounds (Vashchenko, 2007; Badia, 2004; Heathcock, 1971). One major concern with some of the reported methodologies has always been the issue of atom economy (Masaharu, 2015; Ziuu, 2008). Although number of attempts which employ catalysts was made to improve the condition, it however usually incorporates the use of harsh temperature (Kottapalli, 1998; Climent, 1995; Tichit, 1995; Corma, 1991; Corma, 1990). In this work, a new organic-metal complex based on ketopinic acid scaffold and manganese was constructed and tested as catalyst in the aldol condensation of various aliphatic substrates at a mild temperature.

Experimental

Reagent-grade ethanol was used as received from commercial source, tetrahydrofuran was distilled from benzophenone/ketyl solutions and chloroform was purified by passing through a column of basic alumina. Analytical thin-layer chromatography was performed on ALUGRAM XTRA silica gel 0.2 mm (containing a fluorescent indicator at 254 nm). Flash chromatography was performed on MN Kieselgel 60 0.063-0.2 mm/70-230 mesh. All other reagents were purchased from Aldrich and used as received. All NMR spectra were recorded on Bruker Avance III HD spectrometer (400 and 600 MHz). All signals were expressed as ppm down field from TMS, referenced to the residual protonated solvent signals in ¹H NMR (7.26 ppm) and to the deuterated carbon signals in ¹³C NMR (77.36 ppm). IR spectral measurements were carried out on a Perkin Elmer spectrum 400 spectrometer

(ATR). Elemental analyses were conducted using an Elementar Vario micro cube. Melting points were determined by means of a Reichert apparatus and are uncorrected.

2,2'-(1,2-phenylenebis(azan-1-yl-1-ylidene))bis(7,7-dimethylbicyclo[2.2.1]heptane-1-carboxylic acid) 3

Ketopinic acid (382 mg, 2.096 mmol) was dissolved in CHCl₃ (5 mL) and 1,2-diaminobenzene (114 mg, 1.048 mmol), acetic acid (0.1 mL) were added successively at room temperature. After 36 h of reflux, a dark-pink solid precipitated out which was purified by trituration in chloroform to afford the product as a pale pink solid (0.97g, 90 %), m.p. 162–168 °C; δ_H (400 MHz; CD₃OD) 0.78 (s, 3H), 0.99 (s, 3H), 1.02 (s, 3H), 1.13 (s, 3H), 1.45–1.46 (m, 2H), 1.71–1.82 (m, 6H), 2.08–2.10 (m, 2H), 2.26–2.27 (m, 2H), 2.49–2.66 (m, 4H), 2.97–2.99 (m, 2H), 7.20 (s, 2H), 7.47 (s, 2H); δ_C (100 MHz; CD₃OD) 16.9 (CH₃), 24.6 (CH₃), 24.6 (CH₃), 24.8 (CH₃), 26.6, 27.0 (C7,7'), 29.1, 30.0 (C5,5'), 30.2, 30.7 (C4,4'), 45.1, 45.2 (C3,3'), 51.5 (C6,6'), 56.4, 56.6 (C1,1'), 115.2 (C13,13'), 123.9, 124.0 (C12,12'), 138.1, 138.2 (C11,11'), 156.2, 156.4 (C2,2'), 177.5, 179.2 (C10,10'). IR (neat, cm⁻¹) 2962, 2443, 2013, 1760, 1554. Anal. Calcd for C₂₆H₃₂N₂O₄ %: C, 71.53; H, 7.39; N, 6.42. Found: C, 71.54; H, 7.42; N, 6.43.

2,2'-(1,2-phenylenebis(azan-1-yl-1-ylidene))bis(7,7-dimethylbicyclo[2.2.1]heptane-1-carboxylato manganese (III) chloride 4

Solution of ligand **3** (117 mg, 0.268 mmol) and KOH (0.5M, 8 mL) in ethanol were allowed to reflux with Mn(OAc)₂ · 4H₂O (138 mg, 0.563 mmol) under nitrogen atmosphere for 12 h. The reaction mixture was then cooled to room temperature and then brine (8 mL) was added to give a biphasic solution which was later filtered and concentrated *in vacuo*. The residue obtained was redissolved in dichloromethane and removed the aqueous

layer using separating funnel. After concentrating the organic layer, the resulting complex was recrystallized from acetonitrile to furnish a brown amorphous powder (77 mg, 55 % yield). Calculated for $C_{26}H_{30}ClMnN_2O_4$: C, 61.38; H, 7.55; N, 4.77. Found: C, 60.75; H, 8.51; N, 4.79 IR (neat, cm^{-1}): 1740 (C=O), 1689 (C=N).

Typical procedure for the aldol condensation reactions

Potassium hexamethyldisilazide (KHMDs, 43.2 μ L, 0.0216 mmol, 0.5M in toluene) and a solution of water (48 μ L, 0.048 mmol, 1M in THF) were vigorously stirred for 20 min. This was followed with the addition of ketone (15 mmol) and further stirring for additional 10 min. To the resulting solution, catalyst **4** (79 mg, 10 mole %) and aldehyde (1.5 mmol) in THF (0.5 mL) were added. The mixture was continuously stirred with regular monitoring by 1H NMR.

(Z)-2-benzylidenecyclohexanone **7**

Yellow oil; >99 % yield, δ_H (600 MHz; $CDCl_3$) 1.50 (q, $J = 2.0$ Hz, CH_2), 1.55 (q, $J = 2.3$ Hz, CH_2), 1.57 (t, $J = 3.1$ Hz, CH_2), 1.63 (t, $J = 3.1$ Hz, CH_2), 6.88 (s, 2H), 7.32–7.33 (m, 2H), 7.40 (s, 1H), 7.61 (s, 1H), δ_C (100 MHz; $CDCl_3$) 22.2 ($2 \times CH_2$), 24.3 (CH_2), 35.0 (CH_2), 128.2 ($2 \times ArC$), 128.3 ($2 \times ArC$), 128.4 (ArC), 133.1 (ArC), 134.0 (CH), 139.5 (C), 198.3 (C=O). IR (neat, cm^{-1}) 3038, 1671, 1638, 1450.

(E)-2-benzylidene-6-methylcyclohexanone **9a**

Yellow oil; >99 % yield; δ_H (600 MHz; $CDCl_3$) 1.22 (d, $J = 1.2$ Hz, CH_3), 1.23–1.24 (m, 2H), 1.32–1.36 (m, 2H), 2.10–2.12 (m, 2H), 2.22–2.32 (m, 2H), 6.89 (s, 2H), 7.41–7.43 (m, 2H), 7.54 (s, 1H), 7.81 (s, 1H). δ_C (100 MHz; $CDCl_3$) 16.2 (CH_3), 26.3 (CH_2), 29.2 (CH_2), 30.6 (CH_2), 40.6 (C- CH_3), 133.2 ($2 \times ArC$), 136.3 ($2 \times ArC$), 136.7 (ArC), 134.2 (CH), 134.8 (ArC), 140.1 (C), 199.3 (C=O). IR (neat, cm^{-1}) 3045, 1674, 1632, 1447.

(E)-2-benzylidene-4-methylcyclohexanone **9b**

Yellow oil; >99 % yield, δ_H (600 MHz; $CDCl_3$) 0.99 (d, $J = 0.5$ Hz, CH_3), 1.62–1.68 (m, 2H), 1.85–1.93 (m, 2H), 2.33–2.80 (m, 2H), 2.86–2.93 (m, 1H), 3.20–3.52 (m, 1H), 3.62–3.72 (m, 1H), 7.02 (s, CH), 7.61–7.68 (m, 2H), 7.72 (s, 1H), 7.84 (s, 1H). δ_C (100 MHz; $CDCl_3$) 16.2 (CH_3), 26.3 (CH_2), 29.2 (CH_2), 30.6 (CH_2), 40.3 (C- CH_3), 133.2 ($2 \times ArC$), 136.3 ($2 \times ArC$), 136.7 (ArC), 134.2 (CH), 134.8 (ArC), 140.1 (C), 199.5 (C=O). IR (neat, cm^{-1}) 3044, 1675, 1632, 1447.

Trans-1-phenylhept-1-en-3-one **9c**

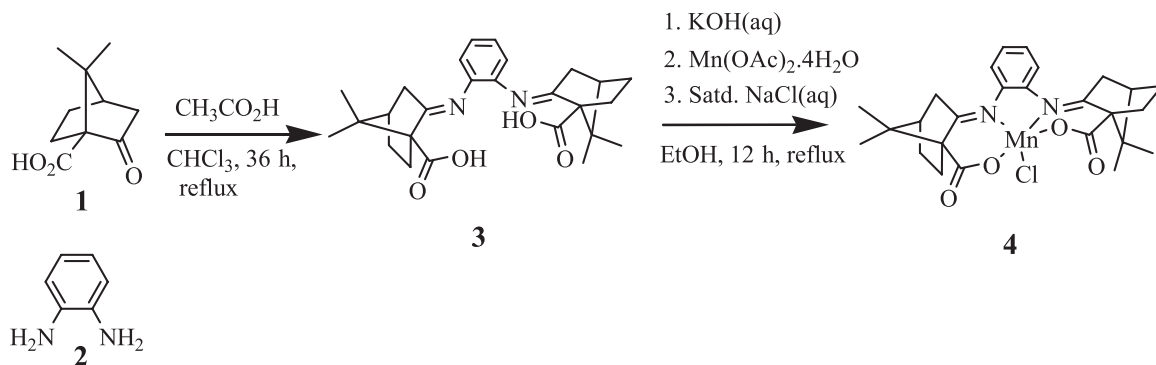
Yellow oil; >99 % yield, δ_H (600 MHz; $CDCl_3$) 0.96 (t, $J = 0.9$ Hz, 3H), 1.52–1.59 (m, 4H), 3.20 (t, $J = 3.1$ Hz, 2H), 6.53 (d, $J = 12.0$ Hz, 1H), 6.66 (d, $J = 12.0$ Hz, 1H), 6.83 (d, $J = 6.5$, 2H), 7.66–7.68 (m, 3H). δ_C (100 MHz; $CDCl_3$) 12.3 (CH_3), 23.4 (CH_2), 28.6 (CH_2), 40.2 (CH_2), 128.3 (CH), 129.0 ($2 \times ArC$), 131.1 ($2 \times ArC$), 135.1 (ArC), 140.1 (ArC), 147.2 (CH), 199.5 (C=O). IR (neat, cm^{-1}) 3051, 1668, 1646, 1510.

Cis-4,4-dimethyl-1-phenylpent-1-en-3-one **9d**

Yellow oil; >99 % yield, δ_H (600 MHz; $CDCl_3$) 1.51 (s, 9H), 6.93 (d, $J = 6.0$ Hz, 1H), 7.43 (d, $J = 6.0$ Hz, 1H), 7.66–7.68 (m, 2H), 7.72–7.75 (m, 3H). δ_C (100 MHz; $CDCl_3$) 33.2 (CH_3), 43.1 [$C(CH_3)_3$], 127.3 (CH), 129.1 ($2 \times ArC$), 129.8 ($2 \times ArC$), 133.10 (ArC), 138.0 (ArC), 140.2 (CH), 198.5 (C=O). IR (neat, cm^{-1}) 3055, 1671, 1644, 1525.

Results and Discussion

The ligand **3** reported by Yang 2003 was synthesised using the standard procedure, followed by the complexation step (Scheme 1) to obtain the new Mn(III) complex **4** (Kureshy 1997). Thus, the synthesis was carried out by refluxing ketopinic acid **1** with the 1,2-diaminobenzene **2** and a catalytic amount of glacial acetic acid, using chloroform as solvent (Scheme 1). Condensation of ketopinic acid



Scheme 1. Synthesis of ketopinic acid-derived complex.

(2 equiv.), with the 1,2-diaminobenzene as a linker enabled the generation of the C-2 symmetry and expand the space occupied by the ligand on each face of the final complex. It was hoped that the position of the manganese atom tightly situated at the centre of the ketopinic acid moieties would enhance the coordination of the electrophilic centres of the substrates in the course of the reaction.

The catalytic activity of complex **4** was investigated following the procedure reported by Yoshikawa 1999 with modification. Hence benzaldehyde was reacted with cyclohexanone in different ethereal solvents and at three catalyst loadings (Table 1). The results shows that THF is the most efficient solvent as it allows the formation of the aldol product in >99 % yield at relatively shorter time. Attempt to reduce the catalyst loading result in longer duration of the reaction. Although not given in Table 1, but the method development reveals that any attempt to reduce the cyclohexanone equivalent furnish the corresponding aldol in negligible amount. In fact it could only be detected in the ^1H NMR spectroscopic analysis of the crude mixture.

Based on the catalyst performance, other substrates were explored to further ascertain its efficacy. The results (Table 2) demonstrate that the catalyst has relatively wide spectrum of activity.

Conclusions

Ketopinic acid was successfully employed as a scaffold in the synthesis of a manganese (III) complex.

The complex thus obtained was used in the aldol condensation reactions of benzaldehyde with various aliphatic ketones. Interestingly it was found that irrespective of the structure of the aliphatic ketone, the yield of the products was apparently excellent in less than an hour.

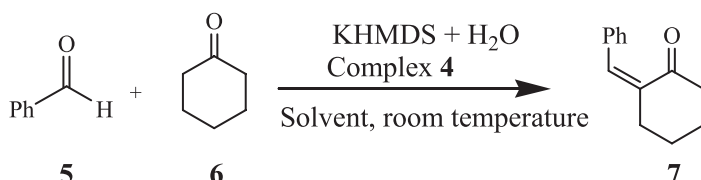
Acknowledgements

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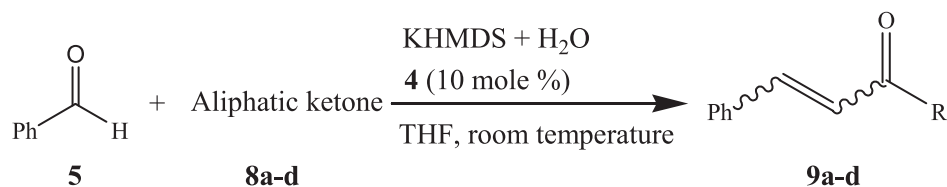
Tab. 1. Aldol condensation of benzaldehyde with cyclohexanone in three different solvents in the presence of complex **4**^a.

			
Solvent	4 (mole %)	Time (h)	Yield (%) ^b
THF	1	18	>99
	5	13	>99
	10	4	>99
EtOAc	1	24	>99
	5	24	>99
	10	24	>99
Dioxane	1	24	trace
	5	20	trace
	10	1	trace

^aBenzaldehyde (1.5 mmol), cyclohexanone (15 mmol). *Cis* assignment for **7** was determined using DFT calculation of the lowest-energy isomer.

^bDetermined by ^1H NMR spectroscopic analysis of the reaction mixture.

Tab. 2. Aldol condensation of various aliphatic substrates in the presence of **4** (10 mole %)¹



Aliphatic ketone			
a	2-Methylcyclohexanone		
b	4-Methylcyclohexanone		
c	2-Hexanone		
d	Pinacolone		

Aldol product, 9	Time (mins)	Yield (%) ²
 a	31	>99
 b	41	>99
 c	42	>99
 d	49	>99

¹Benzaldehyde (1.5 mmol), Ketone (15 mmol). Geometrical assignment for **9a** and **9b** was determined using DFT calculation of the lowest energy isomers.

²Determined by the analysis of the reaction mixture using ¹H NMR spectroscopy.

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