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Selective Synthesis of Bis(indolyl)methanes Under Solvent Free Condition Using Glucopyranosylamine Derived *cis*-Dioxo Mo(VI) Complex as an Efficient Catalyst

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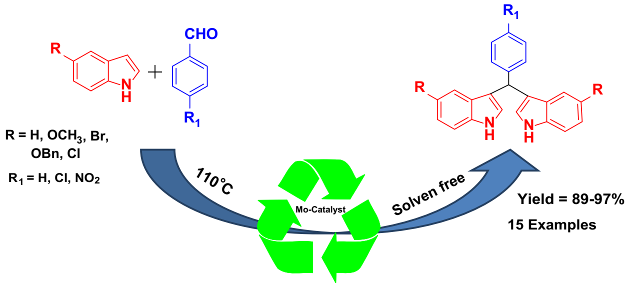
Abstract *cis*-Dioxomolybdenum(VI) complex of 4,6-*O*-ethylidene-*β*-D-glucopyranosylamine derived ligand has been used as an efficient catalyst in the selective synthesis of a series of bis(indolyl)methanes (BIMs) by condensing indole derivatives with carbonyl compounds. The adopted synthetic procedure is green in nature as solvent free reactions have been carried out using naturally occurring D-glucose derived ligands. Total 15 BIMs have been synthesised including four new ones, which have been characterized by mp, FTIR, NMR and mass spectroscopy. The catalyst has afforded good to excellent yield of BIMs in short reaction time and the former has been recycled five times without any significant loss in it's catalytic efficiency.

Graphical Abstract



Keywords Glucopyranosylamine · Bis(indolyl)methanes · Solvent free reaction · *cis*-Dioxomolybdenum(VI) complex

1 Introduction

Bis(indolyl)methanes (BIMs) are important class of compounds, which attracts the attention of chemists, biologist and pharmacists due to its application as anti-cancer, anti-bacterial, anti-inflammatory and analgesic agent [1–7]. Researchers are not only isolating this class of compounds from natural sources [8–10], but also developing new methodologies to synthesize them in laboratories. Condensation of indole derivatives with carbonyl compounds leads to the formation of BIMs, and reports are available, where $CuBr_2$ [11], I_2 [12], CAN [13], NBS [14], $InCl_3$, $In(OTf)_3$ [15], and BF_3 [16] have been used as the catalyst for such reactions. Few drawbacks of these methodologies include the use of high temperature, volatile organic solvents, toxic reagents, tedious work-up, poor yields etc., and hence developments of new procedures are desired to circumvent the limitations.

Under green methodologies, few reports are available where synthesis of BIMs has been carried out under neat reaction condition using organic and inorganic catalysts like oxalic acid, trityl chloride, ionic liquids, I_2, HBF_4–SiO_2, ZnO, $CeCl_3{\cdot}7H_2O$–NaI–SiO_2, modified zirconia etc. [17]. Researchers have performed such reactions in environmentally benign solvents like water, glycerol [18] and ionic liquids [17, 19], and also explored the reactions at room to moderate temperature [17, 20]. Recently, ammonium niobium oxalate catalyzed synthesis of BIMs under conventional heating in water and under ultrasonic irradiation in glycerol has been reported by Mendes et al, [18].

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This report suggests that the reaction under ultrasonic irradiation condition completes much faster than that under conventional heating condition with comparable yields.

Molybdenum complexes control several biochemical reactions in the form of nitrogenase, nitrate reductase, DMSO reductase, xanthine oxidase etc. [21, 22]. Several molybdenum complexes have also been used in industrial ammoxidation of olefins [23], olefin epoxidation [24], olefin metathesis [25] etc. D-Glucose is a naturally occurring compound and only few reports are available on the molybdenum complexes of its derivatives [26–28]. The catalytic reactions of sugar derived molybdenum complexes are in it's infant stage and to the best of our knowledge only two reports are available in this area. Zhao et al., have reported the epoxidation of cyclooctene and *cis*-, *trans*-β-methylstyrene using D-glucose derived ligands [26], and we have explored the selective oxidation of organic sulfides into corresponding sulfoxides [27] using *cis*-dioxomolybdenum(VI) complexes of 4,6-*O*–ethylidene-β-D-glucopyranosylamine derived ligands. Generally sugar derived complexes are assumed to be labile, however these two reports went against the general belief, which prompted us to explore new applications of such complexes in catalysis. Along this line, we successfully synthesized a series of BIMs using 4,6-*O*-ethylidene-*N*-(2-hydroxybenzylidene)-β-D-glucopyranosylamine derived Mo(VI) complex (*Mo-catalyst*; Fig. 1) as catalyst. We have optimized the coupling conditions of indole derivatives and carbonyl compounds with respect to catalytic loading, reaction solvent and recyclability of catalyst, to afford the best yields of BIMs. Hence, this paper deals with the details of first catalytic application of sugar derived Mo(VI) complex in BIMs synthesis.

2 Experimental

2.1 General Procedure for the Selective Synthesis of BIMs Under Optimized Condition

A mixture of respective aldehyde (0.5 mmol), indole (1.0 mmol) and *Mo-catalyst* (0.05 mmol) were stirred at 110 °C for appropriate time period. The resultant semisolid was triturated with ethyl acetate (3 × 5 mL) to transfer the product into the organic phase. The combined organic solution was concentrated under reduced pressure and pure product was isolated by column chromatography using *n*-hexane–ethyl acetate (8:2) as eluent on silica gel column.

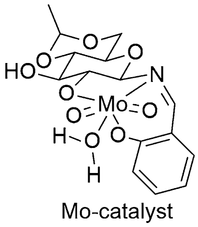

Fig. 1 Structure of (4,6-*O*-ethylidene-*N*-(2-hydroxybenzylidene)-β-D-glucopyranosylamine derived *cis*-dioxo Mo(VI) complex

2.2 Synthesis of 3,3′-(Phenylmethylene)bis(5-(benzyloxy)-1*H*-indole) (3dA)

This compound was synthesized following the above mentioned general procedure using benzaldehyde (0.050 g, 0.5 mmol), 5-(benzyloxy)-1*H*-indole (0.223 g, 1.0 mmol), and *Mo-catalyst* (0.023 g, 0.05 mmol). Yield: 0.241 g (91.0 %); mp 68–70 °C; IR (KBr; cm^{-1}) 3418, 1481, 1180; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.76 (br, 2H, NH), 7.44–7.19 (m, 17H, ArH), 6.99–6.91 (m, 4H, ArH), 6.58 (br, 2H, ArH), 5.78 (s, 1H, methylene CH), 4.95 (s, 4H, benzyl CH_2); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 152.8, 143.9, 137.6, 132.0, 128.7, 128.5, 128.3, 127.7, 127.4, 126.2, 124.5, 119.2, 112.6, 111.8, 103.5, 70.8, 40.3; HRMS m/z calcd. for (M^+) $C_{37}H_{30}N_2O_2$ 534.2307; found 534.2326.

2.3 Synthesis of 3,3′-((4-Chlorophenyl)methylene)bis(5-(benzyloxy)-1*H*-indole) (3dB)

This compound was synthesized using 4-chlorobenzaldehyde (0.070 g, 0.5 mmol), 5-(benzyloxy)-1*H*-indole (0.223 g, 1.0 mmol), and *Mo-catalyst* (0.023 g, 0.05 mmol). Yield: 0.266 g (93.5 %); mp 89–90 °C; IR (KBr; cm^{-1}) 3410, 1481, 1180; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.83 (br, 2H, NH), 7.42–7.32 (m, 10H, ArH), 7.28–7.23 (m, 6H, ArH), 6.96 (dd, $J = 8.8$, 2.4 Hz, 2H, ArH), 6.89 (d, $J = 2.4$ Hz, 2H, ArH), 6.58 (d, $J = 1.6$ Hz, 2H, ArH), 5.73 (s, 1H, methylene CH), 4.98 (s, 4H, benzyl CH_2); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 152.8, 142.4, 137.5, 132.0, 131.7, 130.0, 128.4, 128.4, 127.7, 127.6, 127.2, 124.5, 118.6, 112.8, 111.8, 103.4, 70.8, 39.7; HRMS m/z calcd. for $(M + H)^+$ $C_{37}H_{30}ClN_2O_2$ 569.1996; found 569.1983.

2.4 Synthesis of 3,3′-((4-Nitrophenyl)methylene)bis(5-(benzyloxy)-1*H*-indole) (3dC)

This compound was synthesized using 4-nitrobenzaldehyde (0.075 g, 0.5 mmol), 5-(benzyloxy)-1*H*-indole (0.223 g, 1.0 mmol), and *Mo-catalyst* (0.023 g, 0.05 mmol). Yield: 0.276 g (95.8 %); mp 93–94 °C; IR (KBr; cm^{-1}) 3418, 1512, 1481, 1342, 1180; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.11 (d, $J = 8.8$ Hz, 2H, NH), 7.91 (s, 2H, ArH), 7.44 (d, $J = 8.8$ Hz, 2H, ArH), 7.39–7.27 (m, 12H, ArH), 6.97 (dd, $J = 8.8$, 2.2 Hz, 2H, ArH), 6.82 (d, $J = 2.4$ Hz, 2H, ArH), 6.63 (d, $J = 2.0$ Hz, 2H, ArH), 5.84 (s, 1H, methylene

CH), 5.01–4.95 (s, 4H, benzyl CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.0, 151.6, 146.4, 137.4, 131.9, 129.4, 128.4, 127.7, 127.4, 127.0, 124.4, 123.6, 117.5, 113.0, 112.0, 103.1, 70.7, 40.2; HRMS m/z calcd. for (M^+) $C_{37}H_{29}N_3O_4$ 579.2158; found 579.2183, and 602.2092 ($M + Na^+$).

2.5 Synthesis of 3,3′-((4-Nitrophenyl)methylene)bis(5-chloro-1*H*-indole) (3eC)

This compound was synthesized using 4-nitrobenzaldehyde (0.074 g, 0.5 mmol), 5-chloro-1*H*-indole (0.150 g, 1.0 mmol), and *Mo-catalyst* (0.023 g, 0.05 mmol). Yield: 0.202 g (93.5 %); mp 129–130 °C; IR (KBr; cm^{-1}) 3425, 1512, 1342 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.28–8.07 (m, 4H, NH and ArH), 7.47 (d, $J = 8.8$ Hz, 2H, ArH), 7.36–7.27 (m, 4H, ArH), 7.17 (dd, $J = 8.4$, 1.6 Hz, 2H, ArH), 6.70 (d, $J = 2.0$ Hz, 2H, ArH), 5.88 (s, 1H, methylene CH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.9, 146.7, 135.0, 129.4, 127.6, 125.4, 125.0, 123.8, 122.8, 118.8, 117.4, 112.4, 39.9; HRMS m/z calcd. for (M^+) $C_{23}H_{15}Cl_2N_3O_2$ 435.0541; found 435.0595.

3 Results and Discussion

Sugar derived molybdenum complexes are known since more than a decade, however their applications are scarce. The structure of *Mo-catalyst* has already been established using single crystal X-ray crystallography [28] and it has been used in two catalytic reactions [26, 27]. Inspired by these reports, which suggest the stability and usability of the complex as efficient catalyst; we have explored it's application in the synthesis of BIMs (Scheme 1). Literature is evident that the reaction of electron deficient aldehyde with electron rich indole derivatives affords the best yield of BIMs [29, 30] and following this logic, we set the trial reaction using *p*-nitrobenzaldehyde (0.5 mmol), indole (1 mmol) and *Mo-catalyst* (0.05 mmol) in methanol (3 mL) under reflux condition. The progress of reaction was monitored using thin layer chromatography. After 12 h of reflux, reaction mixture was cooled, filtered and filtrate was concentrated under reduced pressure. The product **3aC** was isolated in 87 % yield from the concentrated filtrate using column chromatography. After this initial success of catalytic reaction, we optimized the nature of solvent for maximum productivity and the results are presented in Table 1. Inspiring from the literature report on use of molten tetra-n-butyl ammonium bromide (TBAB) for BIMs synthesis [31], we performed this reaction using *Mo-catalyst* in TBAB and obtained 96 % yield of **3aC** after 10 min reaction time. Further, optimization of this reaction under solvent free condition also led to 96 % yield of **3aC** in 10 min reaction time. Few reports are available on BIMs synthesis using various catalyst under solvent free reaction condition [32, 33] but to the best of our knowledge, no report is available on molybdenum complex catalyzed such reaction under neat condition. Since we obtained the best yields in the presence of TBAB and solvent free condition, we preferred to perform the reactions under neat condition, as solvent free reactions are one of the requirements of the green methodology. After optimizing the solvent, we explored the amount of catalyst loading under neat condition for the same reaction system and the results are presented in Table 2. Under identical condition, no product formation was noticed in absence of catalyst from the model reaction, while best yield was obtained using 10 mol% of catalyst loading.

After optimizing the reaction conditions, indole and it's four derivatives (**1a–e**) were reacted with benzaldehyde and it's two derivatives (**2A–C**) to afford fifteen BIMs (**3aA–eC**) including four new ones (**3dA**, **3dB**, **3dC** and **3eC** mentioned in Scheme 1), whose characterization data is presented in this manuscript and spectra are deposited as

Scheme 1 Synthesis of BIMs using *Mo-catalyst*

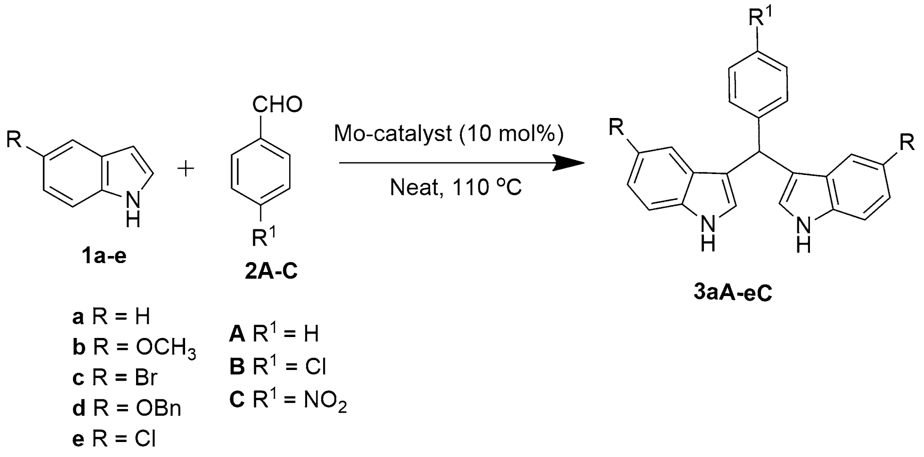

Table 1 Effect of solvent on the synthesis of BIMs

S. no	Solvent	Temperature	Time (h)	Yield (%)[a]
1	Water	Reflux	1	0
2	Methanol	Reflux	12	87
3	Ethanol	Reflux	12	69
4	Acetone	Reflux	24	85
5	Acetonitrile	Reflux	24	37
6	Chloroform	Reflux	24	54
7	Tetrahydrofuran	Reflux	24	46
8	Toluene	Reflux	24	26
9	TBAB	110 °C	1/6	96
10	TBAI	145 °C	1/6	92
11	Neat	110 °C	1/6	96

[a] Isolated yield

Table 2 Summary of catalytic loading study for the synthesis of BIMs

S. no.	Catalyst (mole%)[a]	Time (min)	Yield (%)[b]
1	0	10	0
2	2	10	<5
3	5	10	48
4	10	10	96

[a] Refer Fig. 1

[b] Isolated yield

supplementary information. The successful isolation of previously reported 11 compounds were confirmed by comparing their spectral data with the literature reports [19, 34–37]. All the reactions afforded good to excellent yields of BIMs (89–97 %) and the details are summarized in Table 3. The best yield was obtained from the reaction of electron deficient aldehyde **2C** with electron rich indole derivative **1b**. This finding is parallel to the established fact by various researchers that the reaction between electron deficient aldehyde and electron rich indole affords best yields in BIMs synthesis. Analogously, halogen substituted indoles (**1c** and **1e**) took longer reaction time, as the halogen group deactivates the indole ring via inductive effect [38].

Furthermore, we studied the recyclability of the *Mo-catalyst* in the synthesis of BIMs. For recycling, the reaction mixture of model reaction was extracted with ethyl acetate and the residue (catalyst) was reused directly for the new reaction. The catalyst was recycled five times (Fig. 2) and no appreciable change in catalytic activity was noticed. Under identical condition of reaction parameters, the isolated yields at the end of first and fifth cycles were recorded as 94 and 90 % respectively. UV–Visible spectra of pure and catalyst after first and fifth cycles were recorded in DMSO (supplementary information; Fig. S9) and compared. No appreciable changes in the spectral pattern were noticed however, slight shift in the λ_{max} values were observed for the recycled catalyst in compared to the pure one. This study clearly supports the stability and reliability of the *Mo-catalyst*.

Table 3 Synthesis of BIMs using *Mo-catalyst* under optimized condition

Entry	R	R^1	Time (h)	Product	Yield (%)
1	H	H	1/6	**3aA**	89
2	OCH_3	H	1/6	**3bA**	93
3	Br	H	1	**3cA**	91
4	OBn	H	1/6	**3dA**	91
5	Cl	H	1	**3eA**	90
6	H	Cl	1/6	**3aB**	92
7	OCH_3	Cl	1/6	**3bB**	95
8	Br	Cl	1	**3cB**	93
9	OBn	Cl	1/6	**3dB**	94
10	Cl	Cl	1	**3eB**	91
11	H	NO_2	1/6	**3aC**	95
12	OCH_3	NO_2	1/6	**3bC**	97
13	Br	NO_2	1	**3cC**	95
14	OBn	NO_2	1/6	**3dC**	96
15	Cl	NO_2	1	**3eC**	94

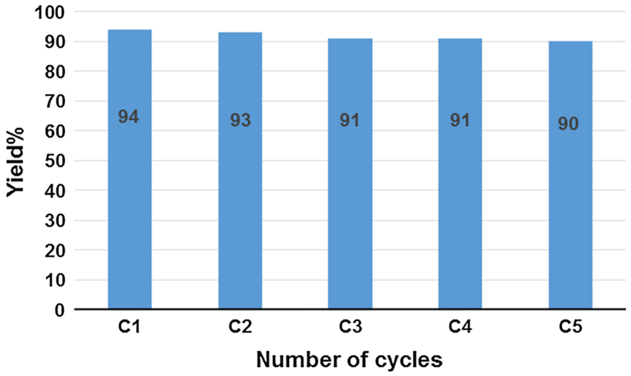

Fig. 2 Graphical representation of yields during catalytic recyclability of *Mo-catalyst*

4 Conclusions

4,6-*O*-ethylidene-*N*-(2-hydroxybenzylidene)-*β*-D-glucopyranosylamine derived cis-dioxo Mo(VI) complex has been proven to be an efficient catalyst for the selective synthesis of BIMs. A number of reaction conditions with respects to solvent, time and catalytic loading have been investigated and finally a series of BIMs were synthesized under solvent free condition in good to excellent yields. The catalyst has been successfully recycled five times without any appreciable loss in it's activity and proven to be stable and reliable. This is the first report on catalytic application of sugar derived molybdenum (VI) complex in the synthesis of BIMs. Here we are reporting a relatively greener process, where catalytic reaction has been performed under neat condition and catalyst is derived from natural occurring D-glucose molecule.

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