REGULAR ARTICLE



Catalytic assay of Schiff base Co(II), Ni(II), Cu(II) and Zn(II) complexes for N-alkylation of heterocycles with 1,3-dibromopropane

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Abstract. N-alkylation of heterocycles with 1,3-dibromopropane using Schiff base Co(II), Ni(II), Cu(II) and Zn(II) transition metal complexes as a catalyst was studied in 1:1 and 2:1 coupling ratios under mild conditions. It was observed that all the complexes worked as efficient catalyst with product yield 78–92% for coupling ratio 1:1 and product yield 63–78% for coupling ratio 2:1. N-alkylation of heterocycles with 1,3-dibromopropane in 1:1 coupling ratio is easier with higher yields as compared with N-alkylation in 2:1 coupling ratio.

Keywords. Schiff base; transition metal complexes; N-alkylation of heterocycles; 1,3-dibromopropane.

1. Introduction

The improvement of environmentally benign organic reactions is a rising area of interest. The reduction impact of chemical reactions on the environment could be accomplished by the minimization of unemployed produced in the process, the employment of the supplementary efficient reagents and catalysts and by the application of microwave.¹ N-alkylation of isatin reduces the liability of the isatin nucleus towards bases, while maintaining its typical reactivity. Thus, N-substituted isatins have been frequently used as intermediates and synthetic precursors for the preparation of a wide variety of heterocyclic compounds.^{2, 3} N-Alkylated indole and pyrrole produced by regioselective synthesis belong to an extremely attractive domain in heterocyclic chemistry as a result of their unusual bioactivities. One possible way of accomplishing the N-alkylation is by using a stoichiometric amount of a strong base. The established methods of accomplishing this include the use of alkali sodium hydroxide in DMF,⁴ NaH or KH in DMF,⁵ HMPA,⁶ Cs_2CO_3 in DMPU and phase-transfer catalytic conditions.⁷

A variety of methods have been demonstrated for the N-alkylation of different heterocycles⁸. Some of the more general methods include the use of sodium hydride in DMF (25–80 °C),⁹ THF (20 °C to rt),¹⁰ as well as calcium hydride (CaH^{2, 4}0–50 °C),¹¹ conditions which have been found suitable for derivatives with electron-withdrawing substituents on the aromatic nucleus.¹² Another general protocol involves the use of K₂CO₃ or Cs₂CO₃ (1.2 equiv) in DMF¹³ (rt to 80 °C) in the presence of KI (0.2 equiv).¹⁴ The susceptibility of 5-nitroisatin to undergo nucleophilic cleavage of the amide bond under basic conditions,^{15,16} for *N*-alkylation employing a mild base combination of CuCO₃/Cs₂CO₃ (1:2) in anhydrous DMF (50–70 °C).¹⁷

In the present work, we report N-alkylation of heterocycles with 1,3-dibromopropane using Schiff base Co(II), Ni(II), Cu(II) and Zn(II) transition metal complexes under mild conditions. It was observed that

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all the complexes worked as efficient catalyst. N-alkylation of heterocycles with 1,3-dibromopropane in 1:1 coupling ratio is easier with higher yields as compared with N-alkylation in 2:1 coupling ratio.

2. Result and Discussion

The catalytic study of Schiff base transition metal complexes C-1 to C-12 is studied for N-alkylation of indole with 1,3-dibromopropane. We have synthesized three series of Schiff base transition metal complexes C-1 to C-4, C-5 to C-8, C-9 to C-12. These complexes are screened for N-alkylation of indole with 1,3-dibromopropane under mild conditions. It is observed that all the Schiff base transition metal complexes worked as efficient catalyst for N-alkylation of indole with 1,3-dibromopropane with 41-92% vield (Scheme 1, Table 1). Complex C-1 from first series gave better yield 76% (Table 1 entry 2), complex C-6 from second series gave better yield 88% (Table 1 entry 8) and complex C-11 from third series gave better yield 92% (Table 1 entry 11). We have screened different heterocycles such as imidazole. benzimidazole, indole and isatin with 1,3-dibromopropane in 1:1 coupling ratio (Scheme 2, Table 2). Using best performer from each series complexes C-1, C-6 and C-11 gave better yields. Complex C-1 shows 41-76% yield (Table 2 entries 1, 4, 7, 10) complex C-6 shows 73–88% yield (Table 2 entries 2, 5, 8, 11) and complex C-11 shows 78-92% yield (Table 2 entries 3, 6, 9, 12). Especially complex C-10 gave better yield 92% (Table 2 entry 9). The reaction time required for this reaction is 30 h. It requires less reaction time as compared to other reactions. Similarly these three selected complexes C-1, C-7 and C-10 were screened for N-alkylation of heterocycles such as imidazole, benzimidazole, indole and isatin with 1,3dibromopropane in 2:1 coupling ratio (Scheme-3, Table 3). Complex C-1 shows 43–56% yield (Table 3) entries 1,4,7,10) complex C-7 shows 57-69% yield (Table 3 entries 2,5,8,11), and complex C-10 shows 63–78% yield (Table 3 entries 3,6,9,12). Especially complex C-10 gave better product yield 78% having less reaction time 30.5 h (Table 3 entries 9).

Finally it is concluded that complex $[Ni(L)(PPh_3)_2Cl_2]$ shows comparatively higher yields. It is because of high thermal stability with Crystal

 Table 1.
 Screening of complexes for N-alkylation of indole with 1,3-dibromopropane.



(Scheme 1)

Entry	Complex		Time (h)	Yield %	
1		_	48	0	
2	C-1	$[Co(L)_2Cl_2]$	36	76	
3	C-2	$[Ni(L)_2Cl_2]$	36	62	
4	C-3	$[Cu(L)_2Cl_2]$	36	41	
5	C-4	$[Zn(L)_2Cl_2]$	36	56	
6	C-5	$[Co(L)(Phen)Cl_2]$	33	73	
7	C-6	$[Ni(L)(Phen)Cl_2]$	33	77	
8	C-7	$[Cu(L)(Phen)Cl_2]$	33	88	
9	C-8	$[Zn(L)(Phen)Cl_2]$	33	80	
10	C-9	$[Co(L)(PPh_3)_2Cl_2]$	30	78	
11	C-10	$[Ni(L)(PPh_3)_2Cl_2]$	30	92	
12	C-11	$[Cu(L)(PPh_3)_2Cl_2]$	30	79	
13	C-12	$[Zn(L)(PPh_3)_2Cl_2]$	30	83	

Reaction conditions: Coupling of heterocycles (1 mmol) with 1,3-dibromopropane (1 mmol), Base K₂CO₃, Solvent DMF R.T.: room temperature.

Table 2. N-alkylation of heterocycles with 1,3-dibromopropane coupling ratio 1:1.



(Scheme-2)

Entry	Heterocycles	Complex	Product	Time (h)	Yield (%)
1		[Co(L)2Cl2]		36	76
2		[Cu(L)(Phen)Cl ₂]	1a	33	73
3	Ĥ	[Ni(L)(PPh ₃) ₂ Cl ₂]		30	78
4	N	[Co(L)2Cl2]		36	62
5		[Cu(L)(Phen)Cl ₂]	1b	33	77
6		[Ni(L)(PPh ₃) ₂ Cl ₂]		30	79
7		[Co(L)2Cl2]		36	41
8		[Cu(L)(Phen)Cl ₂]	1c	33	88
9		[Ni(L)(PPh ₃) ₂ Cl ₂]		30	92
10		$[Co(L)_2Cl_2]$		36	56
11		[Cu(L)(Phen)Cl ₂]	1d	33	80
12		[Ni(L)(PPh ₃) ₂ Cl ₂]		30	83

Reaction conditions: Coupling of heterocycles (1 mmol) with 1,3-dibromopropane (1 mmol) (1:1), Base K₂CO₃, Solvent DMF R.T.: Room temperature.

Nu-H a: Imidazoi b: Benzimi c: Indole d: Isatin	+ Br Br	DMF K ₂ CO ₃ R.T. Coupling Ratio 2:1 (Scheme 3)	Nu Na 2a: 1,1'-(propan 2b: 1,1'-(propan 2c: 1,1'-(propan 2d: 1,1'-(propan	1 e-1,3-diyl)di(1 <i>H</i> -imi e-1,3-diyl)di(1 <i>H</i> -ben e-1,3-diyl)di(1 <i>H</i> -isat e-1,3-diyl)di(1 <i>H</i> -isat	dazole) zimidazole) ole) in)
Entry	Heterocycles	Complex	Product	Time (h)	Yield (%)
1	//_N	$[Co(L)_2Cl_2]$		36.5	43
2	N	[Cu(L)(Phen)Cl ₂]	2a	33.5	57
3	Н	[Ni(L)(PPh ₃) ₂ Cl ₂]		30.5	63
4	N	[Co(L)2Cl2]		36.5	48
5	N	[Cu(L)(Phen)Cl ₂]	2b	33.5	62
6	Н	[Ni(L)(PPh3)2Cl2]		30.5	74
7		[Co(L)2Cl2]		36.5	53
8		[Cu(L)(Phen)Cl ₂]	2c	33.5	69
9		[Ni(L)(PPh ₃) ₂ Cl ₂]		30.5	75
10		[Co(L)2Cl2]		36.5	56
11		[Cu(L)(Phen)Cl ₂]	2d	33.5	68
12		[Ni(L)(PPh ₃) ₂ Cl ₂]		30.5	78

Table 3. N-alkylation of heterocycles with 1,3-dibromopropane coupling ratio 2:1.

Reaction conditions: Coupling of heterocycles (2 mmol) with 1,3-dibromopropane (1 mmol), (2:1), Base K₂CO₃, Solvent DMF R.T.: Room temperature.

system- monoclinic, Cell parameters: a = 9.597 Å, b = 19.455 Å, c = 11.287 Å; $a = \gamma = 90^{\circ}$, $\beta = 112.52^{\circ}$ and unit cell volume V = 1946.32 Å3 (XRD) (Figure 1) and high catalytic Surface area ($a_sBET = 3.9369 \text{ M}^2 \text{ g}^{-1}$ total pore volume (P/Po=0.990) = 0.02006 cm³ g⁻¹ and Mean pore diameter = 20.381 nm (BET) (Figure 2). The correlation between electronic and

geometrical properties of [Ni (L)(PPh₃)₂Cl₂] is measured with X band EPR spectrum at 100 K in the solidstate (EPR). Hence complex C-10 gave better product yield in both coupling ratio 1.1 (92%) as well as coupling ratio 2:1 (75%) as compared to other complexes. Introduction of one alkyl group is much easier compared with double alkylation.



Figure 1. X-ray powder diffractogram complex $[Cu(L)(phen)Cl_2]$.



Figure 2. BET curve of complex [Ni(L)(PPh₃)₂Cl₂].

3. Experimental Section

3.1 Synthesis of Schiff base and their transition metal complexes

The Schiff base 2-Phenyl, 3-benzylamino, 1, 2-dihydroquinazoli-4(3H)-one (PBADQ) is synthesized by modified reported method.¹⁸ Schiff base and their transition metal Co(II), Ni(II), Cu(II) and Zn(II) complexes C-1 to C-12 were synthesized by modified reported method.^{19–21}

3.2 General procedure for N-alkylation of heterocycles with 1,3-dibromopropane

The general procedure for the N-alkylation of heterocycles was as follows.²² Heterocycle (1 mmol) was dissolved in 5 ml anhydrous DMF. Then complex (0.05 mmol) and K_2CO_3 was added to the solution at room temperature. Shortly afterwards (20 min), 1,3-dibromopropane (1 mmol) was added in portions to the reaction mixture. The reaction was stirred at room temperature. The inorganic salt was removed by filtration and rinsed twice with dichloromethane. The solution was poured into water and extracted with dichloromethane (2 x 25 ml). The combined organic layers were washed with brine, dried over anhydrous sodium sulphate, filtered, and concentrated in vacuo resulting in the formation of the product in 92 % yield with coupling ratio 1:1 and product yield 78 % with coupling ratio 2:1. N-alkylation of heterocycles with 1,3-dibromopropane having 1:1 coupling proportion (Scheme-2) is easier than 2:1 coupling proportion (Scheme-3).

1-(3-bromopropyl)-1H-indole (1c)Yield 92% [C₁₁H₁₂NBr]

¹H NMR (CDCl₃, 300 MHz) δ 7.70–6.56(Ar-H), δ 2.80 (2H, t), δ 2.85 (2H, m), δ 2.90 (2H, t). ¹³C NMR: 163.2, 136.3, 128.7, 125.3, 124.5, 123.1, 120.2, 110.4, 104.4, 38.8, 32.7 ppm. MS (ES): *m/z*= 238 [M] +.

1, 1-(propane-1, 3-diyl) di(1H-indole) (2c)

Yield 75% [C₁₉H₁₈N₂]

¹H NMR (CDCl₃, 300 MHz) δ 7.66–6.85 (Ar-H), δ 2.62 (2H, t), δ 2.78 (2H, m), δ 2.83 (2H, t).

¹³C NMR: 186.3, 176.8, 169.4, 166.5, 163.4, 159.7, 156.2, 136.8, 131.1, 123.3, 122.5, 121.1, 120.5, 109.4, 107.9, 100.9, 99.5, 40.4, 36.8 ppm.

MS (ES): *m*/*z*= 273 [M] +.

4. Probable mechanism of N-alkylation of indole with 1,3-dibromopropane

The possible mechanism for the N-alkylation of indole with 1,3-dibromopropane is illustrated. Initially 1,3dibromopropane is oxidatively added to Nickel (II) complex i.e. compound (I) to give compound (II). The secondary heterocycle indole coordinate to Nickel center to form compound (III) and compound (III) again activate in presence of base with removal of hydrogen bromide. Finally chlorine ions from outer sphere transferred to inner sphere with formation of N-Alkylated product (N-(3-bromopropyl) indole) and generate the corresponding complex catalyst (Figure 3).

5. Conclusion

The catalytic role of complexes 1-12 were tested for N-alkylation of different heterocycles with 1,3-dibromopropane. It was observed that all the complexes worked as the efficient catalysts. Especially [Ni(L)(PPh₃)₂Cl₂] complex is more suitable for these



Figure 3. Probable mechanism for N-alkylation of indole with 1,3-dibromopropane catalyzed by Ni(II) PPh₃ complex.

reactions. The mild catalytic reaction conditions, easy synthesis of Schiff base complexes, very simplicity in experiment and broad substrate scope are the features of this catalytic method. Further catalytic applications of these Schiff base transition metal complexes for these organic reactions are currently going on in our chemical laboratory.

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