J. Chem. Sci. (2020)132:92
https://doi.org/10.1007/s12039-020-01791-4

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

SUJIT HEGADE[a], YUVRAJ JADHAV[a], SANJAY CHAVAN[b], GANPATRAO MULIK[c] and GAUTAM GAIKWAD[a,*]

[a]Department of Chemistry, Shrimant Babasaheb Deshmukh Mahavidyalaya (affiliated to Shivaji University, Kolhapur), Atpadi Dist-Sangli, Maharashtra 415301, India
[b]Department of Chemistry, Shivaji University, Kolhapur, Maharashtra, India
[c]Department of Chemistry, Balwant College (affiliated to Shivaji University, Kolhapur), Vita Dist-Sangli, Maharashtra, India
E-mail: gaikwadga@rediffmail.com

MS received 9 January 2020; revised 27 March 2020; accepted 30 March 2020

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 heterocycles[8]. 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 K_2CO_3 or Cs_2CO_3 (1.2 equiv) in DMF[13] (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 $CuCO_3/Cs_2CO_3$ (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

*For correspondence

Electronic supplementary material: The online version of this article (https://doi.org/10.1007/s12039-020-01791-4) contains supplementary material, which is available to authorized users.

Published online: 01 August 2020

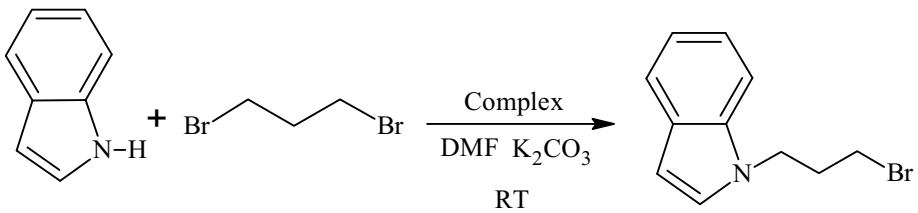
all the complexes worked as efficient catalyst. N-alkylation of heterocycles with 1,3-dibromopropane in 1:1 coupling ratio is easier with higher yields as compared with N-alkylation in 2:1 coupling ratio.

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% yield (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 1,3-dibromopropane 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.

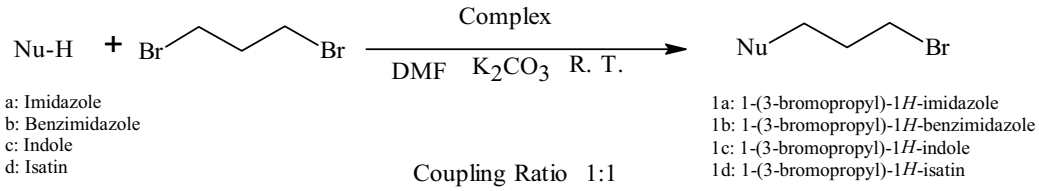


(Scheme 1)

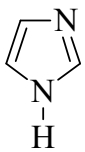
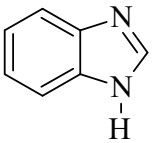
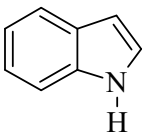
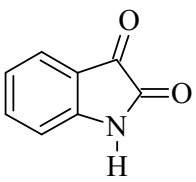
Entry	Complex		Time (h)	Yield %
1		–	48	0
2	C-1	$[Co(L)_2Cl_2]$	**36**	**76**
3	C-2	$[Ni(L)_2Cl_2]$	36	62
4	C-3	$[Cu(L)_2Cl_2]$	36	41
5	C-4	$[Zn(L)_2Cl_2]$	36	56
6	C-5	$[Co(L)(Phen)Cl_2]$	33	73
7	C-6	$[Ni(L)(Phen)Cl_2]$	33	77
8	C-7	$[Cu(L)(Phen)Cl_2]$	**33**	**88**
9	C-8	$[Zn(L)(Phen)Cl_2]$	33	80
10	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 K_2CO_3, Solvent DMF R.T.: room temperature.

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

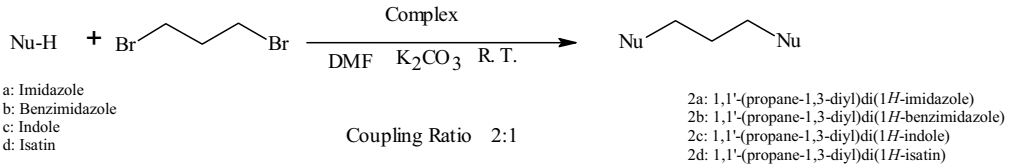


(Scheme-2)

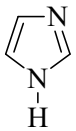
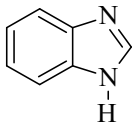
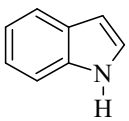
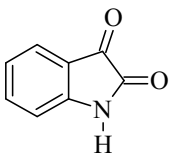
Entry	Heterocycles	Complex	Product	Time (h)	Yield (%)
1		$[Co(L)_2Cl_2]$	1a	36	76
2		$[Cu(L)(Phen)Cl_2]$		33	73
3		$[Ni(L)(PPh_3)_2Cl_2]$		30	**78**
4		$[Co(L)_2Cl_2]$	1b	36	62
5		$[Cu(L)(Phen)Cl_2]$		33	77
6		$[Ni(L)(PPh_3)_2Cl_2]$		30	**79**
7		$[Co(L)_2Cl_2]$	1c	36	41
8		$[Cu(L)(Phen)Cl_2]$		33	88
9		$[Ni(L)(PPh_3)_2Cl_2]$		30	**92**
10		$[Co(L)_2Cl_2]$	1d	36	56
11		$[Cu(L)(Phen)Cl_2]$		33	80
12		$[Ni(L)(PPh_3)_2Cl_2]$		30	**83**

Reaction conditions: Coupling of heterocycles (1 mmol) with 1,3-dibromopropane (1 mmol) (1:1), Base K_2CO_3, Solvent DMF R.T.: Room temperature.

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



(Scheme 3)

Entry	Heterocycles	Complex	Product	Time (h)	Yield (%)
1		$[Co(L)_2Cl_2]$	2a	36.5	43
2		$[Cu(L)(Phen)Cl_2]$		33.5	57
3		$[Ni(L)(PPh_3)_2Cl_2]$		30.5	**63**
4		$[Co(L)_2Cl_2]$	2b	36.5	48
5		$[Cu(L)(Phen)Cl_2]$		33.5	62
6		$[Ni(L)(PPh_3)_2Cl_2]$		30.5	**74**
7		$[Co(L)_2Cl_2]$	2c	36.5	53
8		$[Cu(L)(Phen)Cl_2]$		33.5	69
9		$[Ni(L)(PPh_3)_2Cl_2]$		30.5	**75**
10		$[Co(L)_2Cl_2]$	2d	36.5	56
11		$[Cu(L)(Phen)Cl_2]$		33.5	68
12		$[Ni(L)(PPh_3)_2Cl_2]$		30.5	**78**

Reaction conditions: Coupling of heterocycles (2 mmol) with 1,3-dibromopropane (1 mmol), (2:1), Base K_2CO_3, Solvent DMF R.T.: Room temperature.

system- monoclinic, Cell parameters: a = 9.597 Å, b =19.455 Å, c= 11.287 Å; a = γ= 90°, β= 112.52° and unit cell volume V = 1946.32 Å3 (XRD) (Figure 1) and high catalytic Surface area (a_sBET = 3.9369 M^2 g^{-1} total pore volume (P/Po=0.990) = 0.02006 cm^3 g^{-1} and Mean pore diameter = 20.381 nm (BET) (Figure 2). The correlation between electronic and geometrical properties of $[Ni(L)(PPh_3)_2Cl_2]$ is measured with X band EPR spectrum at 100 K in the solid-state (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.

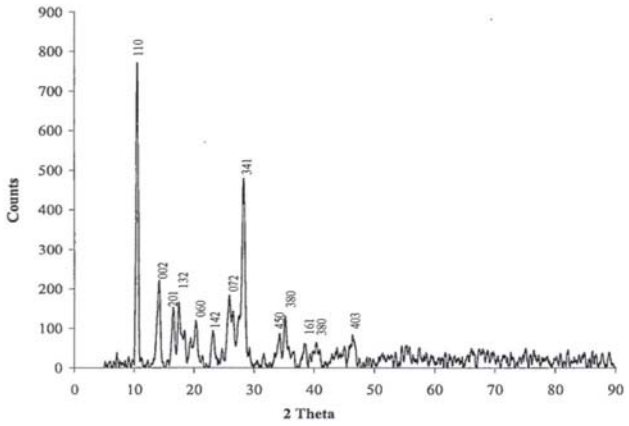


Figure 1. X-ray powder diffractogram complex $[Cu(L)(phen)Cl_2]$.

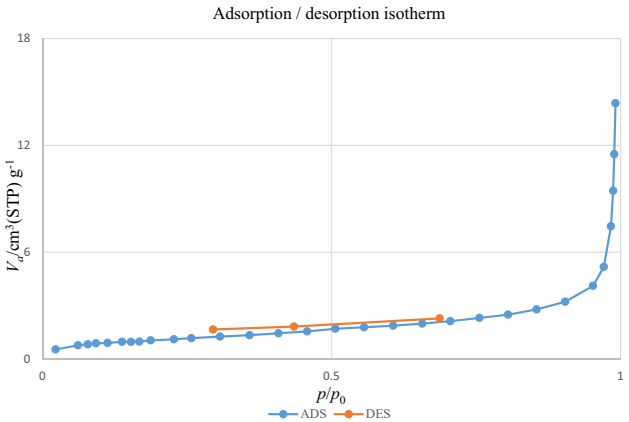


Figure 2. BET curve of complex $[Ni(L)(PPh_3)_2Cl_2]$.

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% $[C_{11}H_{12}NBr]$

^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.70–6.56(Ar-H), δ 2.80 (2H, t), δ 2.85 (2H, m), δ 2.90 (2H, t). ^{13}C 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% $[C_{19}H_{18}N_2]$

^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.66–6.85 (Ar-H), δ 2.62 (2H, t), δ 2.78 (2H, m), δ 2.83 (2H, t).

^{13}C 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 1,3-dibromopropane 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 $[Ni(L)(PPh_3)_2Cl_2]$ complex is more suitable for these

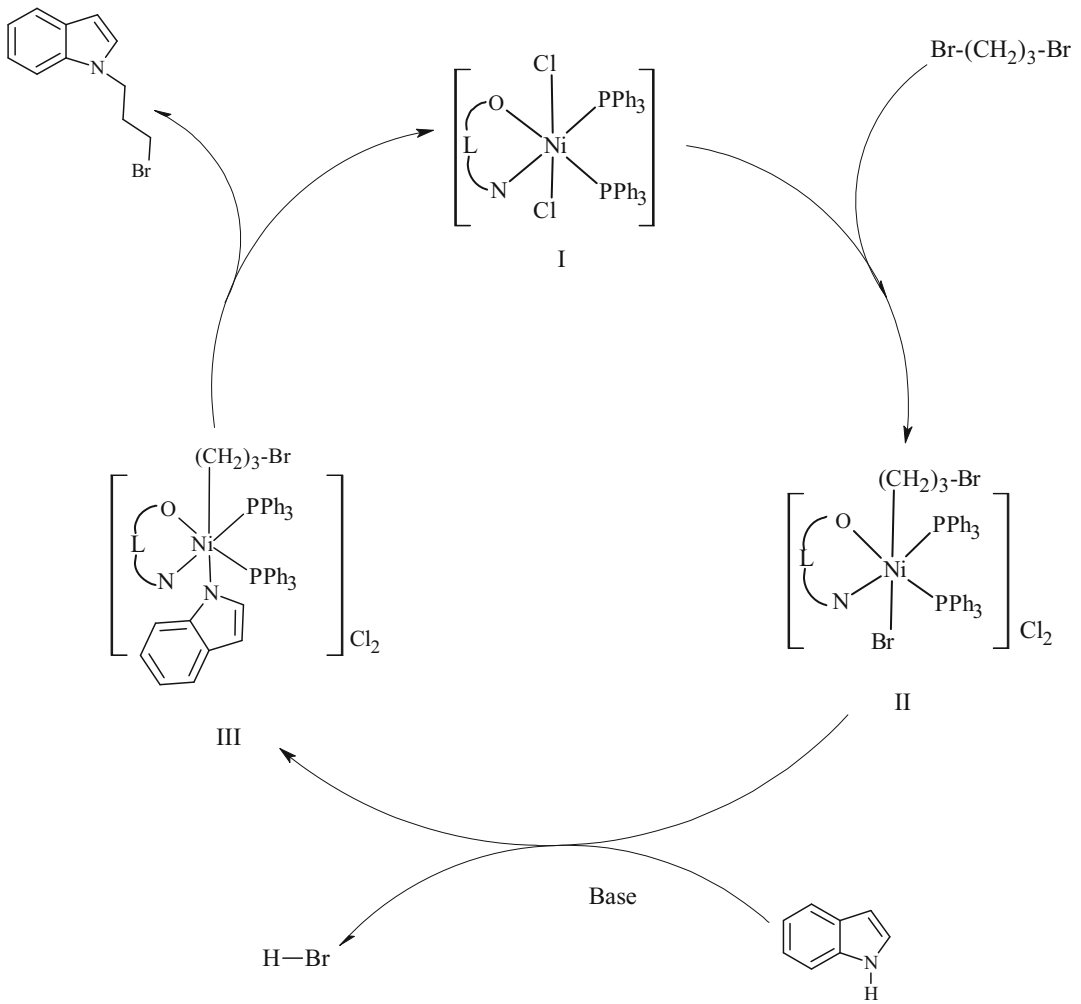


Figure 3. Probable mechanism for N-alkylation of indole with 1,3-dibromopropane catalyzed by Ni(II) PPh_3 complex.

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.

Acknowledgement

Author S S Hegade is thankful to the University Grant Commission, New Delhi, for financial assistance [F1-17.1/2016-17/RGNF-2015-17-SC-MAH-13603]. We also acknowledge Department of Chemistry, Shrimant Babasaheb Deshmukh Mahavidyalaya Atpadi; Department of Chemistry, Balwant College Vita for providing laboratory facilities. We also acknowledge Department of Chemistry, Shivaji University Kolhapur, for providing UV, IR, NMR, TGA-DSC, BET, ESR XRD and Mass facilities.

References

1. Lopez A P, Avandano C and Menendez J C 2008 Heterocyclic compounds with indole and Carbazole Systems *J. Org. Chem.* **61** 5865
2. Silva J and Garden S J 2001 The chemistry of isatin *J. Braz. Chem. Soc.***12** 273
3. Jarrahpour A and Khalili D, Synthesis of benzylisatin 2007 Cytotoxic and anticancer activities of isatin and its derivatives: a comprehensive review *Tetrahedron Lett.* **48** 7140
4. Giles P R, Rogers-Evans M and Knight 2003 Organic synthesis at high pressures *J. Org. Process Res. Dev*. **7** 22
5. Girard M and Hamel P J 2000 The preparation of monomethylaniline *Org. Chem*. **65** 3123
6. Normant H and Cuvigny T 2009 Synthesis, antibacterial, antifungal and antiviral activity evaluation of some new bis-Schiff bases of isatin *Bull. Soc. Chim. Fr*. **4** 186
7. Fink D M 2004 The chemistry of isatins and their derivatives *Synlett* **11** 239

8. Garden S J, Torres J C, Da Silva and Pinto L E 2008 Isatin – a link between natriuretic peptides and monoamines *Synth. Commun*. ***28*** 1679
9. Lotter A N, Pathak P R, Sello T S, Fernandes M A, Otterlo W L and deKonig C B 2011 The chemistry of isatins: a review *Tetrahedron* **63** 2263
10. Vine K L, Locke J M, Ranson M, Pyne S G and Bremner J B 2012 Biological activities of isatin and its derivatives. *J. Med. Chem*. **50** 5109
11. Torisawa Y and Minamikawa J I 2009 Biochemical and pharmacological characterization of isatin and its derivatives: from structure to activity *Bioorg. Med. Chem. Lett*. **11** 829
12. James S L, Adams C J, Bolm C and Braga D 2012 Isolation and structure elucidation of 6-(30- methyl-buten-20-yl) isatin, an unusual metabolite from Streptomyces albus. *Chem. Soc. Rev*. **41** 413
13. Margetic D 2005 Prenisatin (5-(3-methyl-2- butenyl)indole-2,3-dione): an antifungal isatin derivative from Chaetomium globosum *Chem. Ind.* **54** 351
14. Glasovac Z, Troselj P and Jusinski I 2013 Isatin – a link between natriuretic peptides and monoamines *Synlett* **24** 2540
15. Margetic D and Warrener R N 2014 The chemistry of isatins: a review *J. Heterocycl. Chem.* **51** 1369
16. Strukil V, Margetić D and Igrc M D 2012 Synthesis, antibacterial, antifungal and antiviral activity evaluation of some new bis-Schiff bases of isatin and their derivatives. *Chem. Commun.* **48** 9705
17. Đud M, Magdysyuk O V and Margetic D V 2016 Design and synthesis of anticonvulsants from a combined phthalimide-GABA-anilide and hydrazone pharmacophore *Green Chem.* **18** 2666
18. Gudasi K B, Patil S A, Vadavi R S and Shenoy R V 2005 Five-coordinate cobalt(II), nickel(II) and zinc(II) complexes derived from 2-pyridine-2-yl-3-(pyridine-2-carboxylideneamino)-1,2-dihydroquinazolin-4(3H)-one. The crystal structure of the cobalt(II) complex *Trans. Metal Chem*. **31** 586
19. Gaikwad G A, Hegade S S and Mulik G N 2016 Schiff base transition metal complexes catalyzed N-arylation of heterocycles under mild conditions *Adv. Org. Chem. Lett*. **3** 18
20. Hegade S S, Gaikwad G A and Mulik G N 2018 N-Arylation of heterocycles by mixed ligand transition metal complexes under mild conditions *Indian J. Chem.* **57** 1304
21. Zhen-Feng C, Li M, Li-Min L, Yan-Cheng L, Yan P, Xue H, Hong-Hong W, Hua- Gang, L and Hong L 2011 Synthesis of mixed ligand transition metal complexes *J. Inorg. Biochem*. **105** 171
22. Brondani D J, Magalhaes D R, Farias M P, Souza F R, Barbosa F F and Leite 2013 N-alkylation of heterocycles *Org. Chem*. **65** 313