



An efficient and rapid synthesis of 3-hydroxy-3-alkyl-2-oxindoles via Zn-mediated barbier-type reaction under aqueous conditions

L RAJU CHOWHAN^{a,*}, MARRI SAMEER REDDY^b and NANDIGAMA SATISH KUMAR^a

^aCentre for Applied Chemistry, Central University of Gujarat, Gandhinagar, Gujarat 382 030, India

^bSchool of Chemical Sciences, Central University of Gujarat, Gandhinagar, Gujarat 382 030, India

E-mail: rchowhan@cug.ac.in

MS received 4 March 2017; revised 22 May 2017; accepted 10 June 2017

Abstract. A robust and rapid synthesis of 3-hydroxy-3-alkyl-2-oxindoles from isatins is described. This method introduces an ecofriendly, un-activated Zn dust, solid NH₄Cl and substrates under aqueous conditions, which has produced the product in moderate to good yields. Without using column chromatography, majority of the compounds were isolated in analytically pure form. The progress of the reaction could be visualized by naked eye.

Keywords. Allyl halides; barbier reaction; ecofriendly synthesis; isatin; oxindoles; green synthesis; water-mediated reaction.

1. Introduction

Organic reactions performed under aqueous conditions have attracted much attention in organic chemistry. These methods are greener, easy to handle and economically viable¹ making it as sustainable method which can be scaled up for industrial level applications. Many reactions including metal-catalyzed reactions for C-N,² C-C bond formation as well as catalytic asymmetric transformations³ and numerous other reactions have been successfully carried out under aqueous conditions with no or minimal amount of solvents. This information clearly proves the diverse utility of this methodology.

On the other hand, 3-hydroxy-3-alkyl-2-oxindoles were found to be important core motifs of many natural products and biologically important molecules (Figure 1).⁴ For example, TMC-95 acts as a proteomes inhibitor,⁵ Celogentins were used for treatment of liver and eye diseases,⁶ Convolutamydines possess anti-inflammatory activity⁷ and its artificial analogues were found to show anti-cancer⁸ and anti-convalescent activities.⁹ Welwitindolinones have shown multi-drug resistant activity.¹⁰ 3-(cyclopropylethynyl)-3-hydroxy-1,5-dimethylindolin-2-one has shown HIV reverse transcriptase inhibition activity and it is more active than the

drug Efavirenz which is an anti-HIV drug.¹¹ Interesting biological activities including antimicrobial,¹² antitumor,¹³ and oviposition-stimulant¹⁴ activities have been reported for brassinin and its analogues. There are a few reports in the literature for the synthesis of 3-hydroxy-3-alkyl-2-oxindoles.¹⁵ However, these methods involve the usage of toxic metals, costly and air sensitive catalysts and usage of volatile organic solvents. Based on these facts, it is necessary to develop a simple and eco-friendly protocol for the synthesis of 3-hydroxy-3-alkyl-2-oxindoles.

2. Experimental

Isatins, Ammonium chloride, alkyl halides were acquired from Sigma Aldrich and Merck, and used without further purification. N-substituted Isatins were synthesized as per literature¹⁶ and characterized by ¹H NMR to confirm the formation. Solvents used were acquired from Merck and SD Fine. Analytical thin layer chromatography was performed with the help of pre-coated silica gel plate (200 μm) which were acquired from Sigma Aldrich matrix gel on Aluminium with no fluorescent indicator. Zinc used was of laboratory grade reagent. Column chromatography was performed over silica gel of 60–120 mesh, both acquired from Rankem fine chemicals.

To a solution of isatins (1 mmol), zinc dust (5 mmol), alkyl halide (3 mmol) in THF was added saturated NH₄Cl

*For correspondence

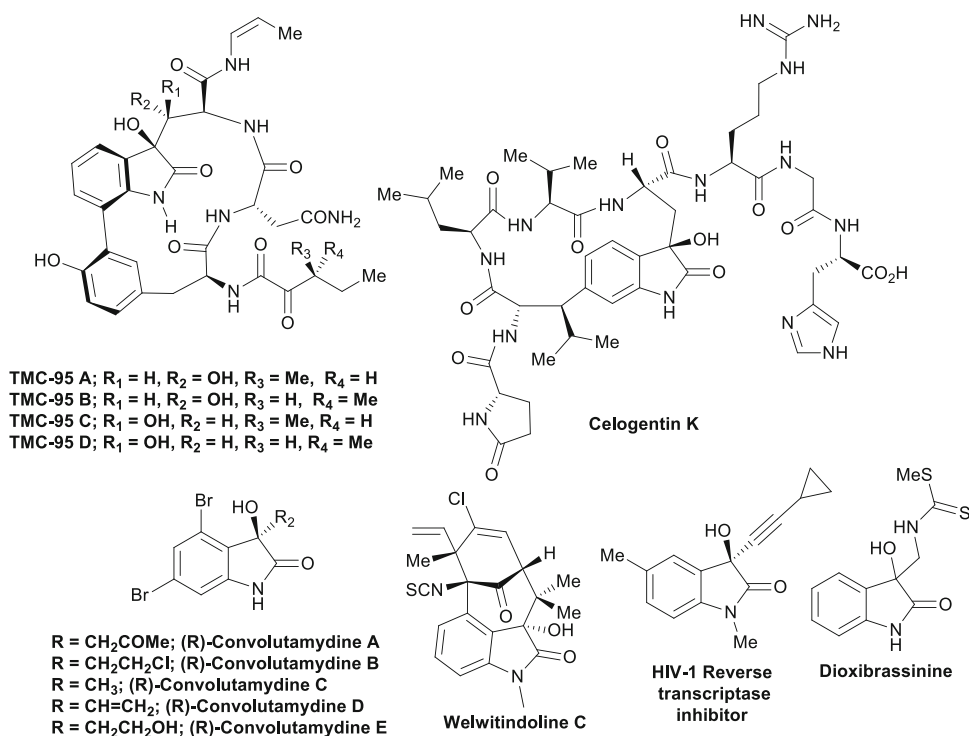


Figure 1. Natural products with 3-hydroxy-3-substituted-2-oxindoles core.

(37 mmol) and stirred at rt for 20 min. The reaction mixture was extracted with EtOAc (3×10 mL), the combined organic layer was washed with brine (5 mL) and dried over anhydrous Na_2SO_4 . Concentration in vacuum gave the corresponding 3-hydroxy-3-alkyl-2-oxindoles as white solid in pure form. All 3-benzylated products were purified with column chromatography by using hexanes and ethyl acetate.

3. Results and Discussion

Modified Barbier reaction protocol has gained much attention due to its operational simplicity and rapidness.¹⁷ Addition of organometallic to carbonyl compounds are known.¹⁸ However, these methods are

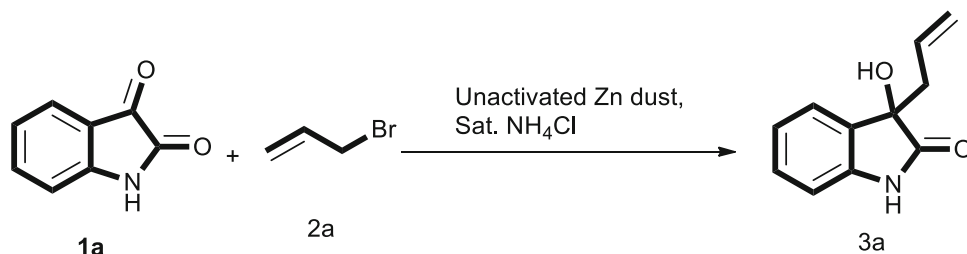
not one-pot reactions and involve the preparation of nucleophilic species separately under inert condition, followed by addition to carbonyl compound. Therefore, development of one-pot reaction under aqueous condition for addition of carbonyls are assumed to be important and will be useful in green chemistry perspective.

As a part of our ongoing research work on the synthesis of biologically active compounds,¹⁹ here we report a simple, mild and rapid method as an alternative to existing synthetic routes for the synthesis of 3-hydroxy-3-alkyl-2-oxindoles under aqueous conditions. We employed isatin **1a** and allyl bromide **2a** as model substrates for optimization of reaction con-

Table 1. Optimization study.

Entry	Allyl bromide (equivalent) ^a	Zinc (equivalent)	Time (min)	Yield (%) ^b
1	1	2	20	30
2	1	3	20	50
3	2	4	20	72
4	2	5	20	80
5	3	5	15	95
6	5	8	20	95

^aReaction conditions; all reactions were carried out at 1 mmol of Isatin and 37 equiv. of sat. NH_4Cl at rt. ^bIsolated yield.

**Scheme 1.** Barbier-type reaction with unactivated Zn dust.

ditions. Initially, we performed a reaction with isatin **1a** (1 equiv.), allyl bromide **2a** (1 equiv.) and Zn dust (2 equiv.) by stirring for 20 minutes (Table 1, entry 1) which formed the corresponding hydroxyoxindole in 30% yield, Scheme 1. Increase in the quantity of Zn increased the yield up to 50%. Further increase in the stoichiometric equivalents of allyl bromide and Zn dust, surprisingly increased the product yield up to 72% (entry 3, Table 1). Finally, we identified the best optimized reaction condition as isatin **1a** (1 equiv.), allyl bromide **2a** (3 equiv.), Zn dust (5 equiv.) and saturated NH_4Cl (37 equiv.) and stirring for 15 minutes at rt (entry 5, Table 1). The structure of the product was confirmed by using ^1H -NMR, ^{13}C -NMR and ESI-HRMS spectrometry studies.

We applied this protocol successfully to a variety of alkyl halides and isatins affording the desired product in good to excellent yields, as shown in Table 2. We used propargyl, benzyl and substituted allyl bromides (**2a–2g**) fruitfully with Isatin (**1a**) to prepare the corresponding hydroxyl oxindole derivatives (**3b–3o**), Scheme 2. The results are summarised in Table 2.

To increase the substrate scope, we have used 5-substituted (**1b**) and N-alkylated isatins (**1c**, **1d**). However, in the case where N-substituted isatins were employed as substrates, yield was lower compared with simple isatin (Table 2, **3k–3o**). We were delighted to find that many products were found to be pure enough (confirmed through NMR) after the workup and hence chromatographic purification was not necessary.

The limitation of this method was that it could not be extended to inactivated alkyl and aryl halides. Moreover, generation of nucleophile is not feasible under this condition. Allyl halide **2d** and **2f** afforded **3d** and **3f**, respectively, in 1:1 ratio of diastereomers, whereas the benzylic halide **2g** yielded **3g** in 1:2 diastereomeric ratio, Table 2. We observed no isomerisation of propargylic alcohols (**3b**, **3i**, **3l**) to the corresponding allenes.²⁰

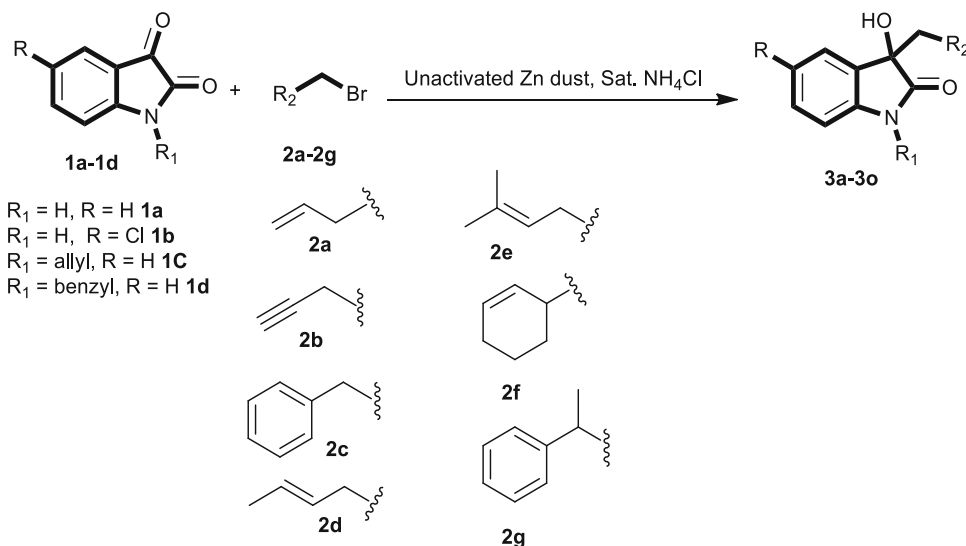
Table 2. Scope of substrates.

 3a , 95% ^b	 3b , 90% ^b	 3c , 89% ^b
 3d , 91% ^{b,c}	 3e , 98% ^b	 3f , 85% ^{b,c}
 3g , 70% ^{b,d}	 3h , 93% ^b	 3i , 76% ^b
 3j , 88% ^b	 3k , 71% ^b	 3l , 60% ^b
 3m , 58% ^b	 3n , 68% ^b	 3o , 70% ^b

^aReaction conditions: all reactions were carried out at 1 mmol of Isatin and saturated aqueous NH_4Cl at rt. ^bIsolated yield. ^c1:1 diastereomeric ratio. ^d1:2 diastereomeric ratio.

The progress of the reaction could be visualized by naked eye; as the reaction progresses, the colour of the reaction mixture turns into pale yellow from orange red.

We are interested to develop this protocol in gram scale. We performed the reaction between isatin (**1a**, 1.47 g), zinc dust (4 g), benzyl bromide (**2c**, 3 mL) and NH_4Cl (5 g) under optimized reaction conditions. After completion of the reaction, the product was purified by column chromatography (yield, 1.9 g) (Scheme 2).



Scheme 2. Reaction of Isatin with various alkyl halides.

4. Conclusions

In conclusion, a rapid and eco-friendly method for the synthesis of 3-Hydroxy-3-alkyl-2-Oxindoles was developed under aqueous conditions. Without using any previously activated zinc or solid support, the method has yielded the desired product in moderate to excellent yields. No isomerisation of propargylic alcohols to the corresponding allenes was observed. The method described here is simple, economical, and environmentally benign as it avoids purification in many cases. Efforts are being made to increase the scope of this method.

Supplementary Information (SI)

Characterization data and spectra for all the compounds are provided in the Supplementary Information, which is available at www.ias.ac.in/chemsci.

Acknowledgements

L. R. C thanks DST-SERB (SB/EMEQ-304/2014) for funding and M. S. R thanks UGC for Non-NET fellowship. Authors are grateful to Prof. S. A Bari Hon'ble Vice-Chancellor, CUG for his kind support and encouragement.

References

- (a) Abbat S, Dhaked D, Arfeen M and Bharatam P V 2015 Mechanism of the Paal-Knorr reaction: the importance of water mediated hemiacetal pathway *RSC Adv.* **5** 88353; (b) Zhou F and Li CJ 2014 The Barbier-Grignard-type arylation of aldehydes using unactivated aryl iodides in water *Nat. Commun.* **5** 4254; (c) Stavber G, Zupan M, Jereb M and Stavber S 2004 Selective and Effective Fluorination of Organic Compounds in Water Using Selectfluor F-TEDA-BF₄ *Org. Lett.* **6** 4973
- Fors B P, Krattiger P, Strieter E and Buchwald S L 2008 Water-Mediated Catalyst Preactivation: An Efficient Protocol for C-N Cross-Coupling Reactions *Org. Lett.* **10** 3505
- (a) Liu R, Dong C, Liang X, Wang X and Hu X 2005 Highly Efficient Catalytic Aerobic Oxidations of Benzylic Alcohols in Water *J. Org. Chem.* **70** 729; (b) Chen L and Chao-Jun Li 2004 A Remarkably Efficient Coupling of Acid Chlorides with Alkynes in Water *Org. Lett.* **6** 3151
- (a) Raghavan S, Ravikumar C and Ganapathy S 2016 Stereoselective Formal Synthesis of (+)- and (-)-Cyclophellitol, (-)-Conduritol-B and (-)-Conduramine-B Using a Sulfinyl Moiety for C-O Bond Formation and α -Chloro Sulfide for C-C bond formation *J. Org. Chem.* **81** 4252; (b) Raghavan S and Ganapathy S 2011 Modular, bidirectional synthesis of C13-C34 subunit of (-)-mucocin based on vicinal heterofunctionalization of a diene *Tetrahedron* **67** 7529; (c) Satyamaheshwar P 2009 3-Substituted-3-hydroxyl-2-oxindole, an emerging new scaffold for drug discovery with potential anticancer and other biological activities *Curr. Bioact. Compd.* **5** 20; (d) Raghavan S, Ganapathy S and Tony K A 2008 A formal convergent synthesis of (+)-trans-Solamin, *Tetrahedron Lett.* **49** 1601
- (a) Kohno J, Koguchi Y, Nishio M, Nakao K, Kuroda M, Shimizu R, Ohnuki T and Komatsubara S 2000 Structures of TMC-95A-D: Novel Proteasome Inhibitors from *Apiospora montagnei* Sacc. TC 1093 *J. Org. Chem.* **65** 990; (b) Brian K, Albrecht and Williams R M 2001 A concise, total synthesis of the TMC-95A/B proteasome inhibitors *PNAS* **101** 11949; (c) Inoue M, Sakazaki H, Furuyama H and Hirama M 2003 Total Synthesis of TMC-95A *Angew. Chem. Int. Ed.* **42** 2654
- (a) Hayakawa Y, Fujii H, Hase K, Ohnishi Y, Sakukawa R, Kadota S, Namba T and Saiki I 1998 Anti-metastatic and immunomodulating Properties of the Water Extract from *Celosia argentea* Seeds *Biol. Pharm. Bull.* **21** 1154;

- (b) Hase K, Kadota S, Basnet P, Takahashi T and Namba T 1996 Protective Effect of Celosian, an Acidic Polysaccharide, on Chemically and Immunologically Induced Liver Injuries *Biol. Pharm. Bull.* **19** 567; (b) Bing M, Banerjee B, Litvinov D N, He L and Castle S L 2010 Total Synthesis of the Antimitotic Bicyclic Peptide Celogentin C *J. Am. Chem. Soc.* **132** 1159; (c) Ma B, Litvinov D N, He L, Banerjee B and Castle S L 2009 Total Synthesis of Celogentin C *Angew. Chem. Int. Ed.* **48** 6104; (d) Kobayashi J, Suzuki H, Shimbo K, Takeya K and Morita H 2001 Celogentins A-C, New Antimitotic Bicyclic Peptides from the Seeds of *Celosia argentea* *J. Org. Chem.* **66** 6626; (e) Suzuki H, Morita H, Shirob M and Kobayashi J 2004 Celogentin K, a new cyclic peptide from the seeds of *Celosia argentea* and X-ray structure of moroidin *Tetrahedron* **60** 2489
7. (a) Luppi G, Monari M, Corrêa R J, Violante F A, Pinto A C, Kaptein B, Broxterman Q B, Garden S J and Tomasini C 2006 The first total synthesis of (R)-convolutamydine A *Tetrahedron* **62** 12017; (b) Nakamura S, Hara N, Nakashima H, Kubo K, Shibata N and Toru T 2008 Enantioselective Synthesis of (R)-Convolutamydine A with New N-Heteroarylsulfonylprolinamides *Chem. Eur. J.* **14** 8079
8. Prathima P S, Rajesh P, Rao V J, Kailash U S, Sridhar B and Rao M M 2014 On water expedient synthesis of 3-indolyl-3-hydroxy oxindole derivatives and their anticancer activity in vitro *Eur. J. Med. Chem.* **84** 155
9. Raj M, Veerasamy N and Singh V K 2010 Highly enantioselective synthesis of 3-cycloalkanone-3-hydroxy-2-oxindoles, potential anticonvulsants *Tetrahedron Lett.* **51** 2157
10. (a) Smith C D, Zilfou J T, Stratmann K, Patterson G M and Moore R E 1995 Welwitindolinone analogues that reverse P-glycoprotein-mediated multiple drug resistance *Mol. Pharmacol.* **47** 241; (b) Stratmann K, Moore R E, Bonjouklian R, Deeter J B, Patterson G M L, Shaffer S, Smith C D and Smitkat T A 1994 Welwitindolinones, Unusual Alkaloids from the Blue-Green Algae *Hapalosiphon welwitschii* and *Westiella intricata*. Relationship to Fischerindoles and Hapalindoles *J. Am. Chem. Soc.* **116** 9935
11. (a) Boechat N, Kover W B, Bongertz V, Bastos M M, Romeiro N C, Azevedo M L G and Wollinger W 2007 Design, Synthesis and Pharmacological Evaluation of HIV-1 Reverse Transcriptase Inhibition of New Indolin-2-Ones *Med. Chem.* **3** 533; (b) Dhara K, Kapat A, Ghosh T and Dash J 2016 Transition-Metal-Free Terminal Alkyne Addition to Isatins *Synthesis* **48** 4260
12. (a) Suchy' M, Kutschy P, Monde K, Goto G, Harada N, Takasugi M, Dzurilla M and Balentova' E 2001 Synthesis, Absolute Configuration, and Enantiomeric Enrichment of a Cruciferous Oxindole Phytoalexin, (S)-(-)-Spirobrassinin, and Its Oxazoline Analog *J. Org. Chem.* **66** 3940; (b) Pedras M S C, Okanga F I, Zaharia I L and Khan A Q 2000 Phytoalexins from crucifers: synthesis, biosynthesis, and biotransformation *Phytochemistry* **53** 161; (c) Gross D 1993 Phytoalexins of Brassicaceae *J. Plant. Dis. Prot.* **100** 433
13. (a) Mehta R G, Liu J, Constantinou A, Hawthorne M, Pezzuto J M, Moon R C and Moriarty R M 1994 Structure-activity relationships of brassinin in preventing the development of carcinogen-induced mammary lesions in organ culture *Anticancer Res.* **14** 1209; (b) Mehta R G, Liu J, Constantinou A, Thomas C F, Hawthorne M, You M, Gerhäuser C, Moon R C and Moriarty R M 1995 Cancer chemopreventive activity of brassinin, a phytoalexin from cabbage *Carcinogenesis* **16** 399
14. Baur E, Städler K, Monde K and Takasugi M 1998 Phytoalexins from Brassica (Cruciferae) as oviposition stimulants for the cabbage root fly, *Delia radicum* *Chemoecology* **8** 163
15. (a) Zhao L M, Zhang A L, Zhang J H, Gao H S and Zhou W 2016 Zinc-Mediated C-3 α Catalyzed Sakurai-Hosomi Allylation of Isatins and Isatin Ketoimines Using Allyltrimethylsilane *Org. Lett.* **13** 6398; (i) Li C J 1996 Aqueous Barbier-Grignard type reaction: Scope, mechanism, and synthetic applications *Tetrahedron* **52** 5643; (j) Chung L W, Chan T H and Wu Y D 2005 Theoretical Study of the Intrinsic Reactivities of Various Allylmetals toward Carbonyls and Water *Organometallics* **24** 1598; (k) Li C J and Chan T H 1991 Organometallic reactions; in aqueous media. 2. Convenient synthesis of methylenetetrahydrofurans *Organometallics* **10** 2548
16. Furdas S D, Srinivasaraghavan S S K, Sippl W and Jung M 2012 *Med. Chem. Comm.* **3** 305
17. Pétrier G C and Luche J L 1985 Allylzinc reagents additions in aqueous media *J. Org. Chem.* **50** 910
18. Zong H, Huang H, Liu J, Bian G and Song L 2012 Added-Metal-Free Catalytic Nucleophilic Addition of Grignard Reagents to Ketones *J. Org. Chem.* **77** 4645
19. Muthineni N, Kumar N S, Rao L C, Kumar V D, Misra S, Chowhan L R and Meshram H M 2016 An efficient four-component approach for the synthesis of novel 5-methyl-4-(2-(3-methyl-4-nitroisoxazol-5-yl)-1-arylethyl)-1H-pyrazol-3-ol derivatives and their anti-bacterial study *ChemistrySelect* **1** 4197
20. Alcaide B, Almendros P and Rodriguez-Acebes R 2006 Efficient Entry to Diversely Functionalized Spirocyclic Oxindoles from Isatins through Carbonyl-Addition/Cyclization Reaction Sequences *J. Org. Chem.* **71** 2346