Tetrahedron Letters 53 (2012) 6901–6904

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Cesium carbonate mediated synthesis of 3-(α-hydroxyaryl)indoles

Rasokkiyam Elayaraja [a], R. Joel Karunakaran [b,*]

[a] Research and Development Centre, Orchid Chemicals and Pharmaceuticals Ltd, Sholinganallur, Chennai 600119, India
[b] Associate Professor, Department of Chemistry, Madras Christian College, Tambaram, Chennai 600059, India

ARTICLE INFO

Article history:
Received 17 June 2012
Revised 30 September 2012
Accepted 1 October 2012
Available online 12 October 2012

Keywords:
Cs_2CO_3
Indole
Aldehydes
3-(α-Hydroxyaryl)indoles

ABSTRACT

A series of 3-(α-hydroxyaryl)indoles have been synthesized by the reaction of aromatic aldehydes with indoles, catalyzed by cesium carbonate in DMF medium. The reactivity of the various alkali metal carbonates is discussed. The stability of 3-(α-hydroxyaryl)indoles is also discussed.

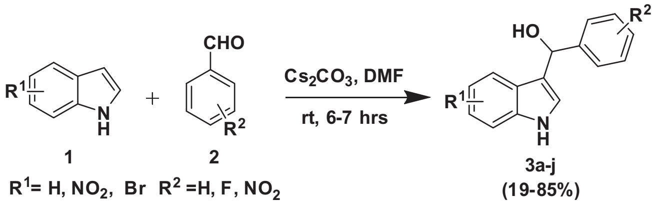
3-(α-Hydroxyaryl)indoles are unstable toward both acids and bases, due to their tendency to undergo dehydration to form stable vinylogous iminium intermediates. This iminium species generated in situ triggers several chemical transformations.[1] 3-(α-Hydroxyaryl)indoles can be used in the preparation of unsymmetrical bis(indolyl)alkanes,[2,3] as a starting material for getting prochiral compound[4b] and one pot synthesis of β-indolylketones.[4a] Apart from these, a few selected heteroaromatic substituted 3-(α-hydroxyaryl)indoles[5] (**3d**) were reduced[6] to their respective 3-(aryl)methylindoles that are useful in the preparation of indole alkaloids,[7] pyridiocarbazoles,[8] and 4-skatylpiperidines.[9,10]

There are two major issues associated with the preparation of 3-(α-hydroxyaryl)indoles, namely, the stability during the isolation and their reactivity after formation in the reaction medium. As per the previous reports, 3-(α-hydroxyaryl)indoles are unstable in organic solvents, and they are degraded during isolation,[4a,b] and the isolated compound needs to be stored at a lower temperature in an inert gas atmosphere. The other major issue is the formation of bis(indolyl)methanes during the reaction, which turned out to be the major product. The plausible reason for its formation is due to the formation of vinylogous iminium ion by losing a water molecule, which can react with another molecule of indole to form the bis(indolyl)methanes.[11]

Owing to these problems, the number of methods for the preparation of 3-(α-hydroxyaryl)indoles is scarce. The existing method for making 3-(α-hydroxyaryl)indoles is by the reaction of indole-3-carboxaldehyde with the corresponding aryl-magnesium halides. An alternative synthetic procedure is the base (NaOH) catalyzed reaction of indoles with aldehydes in methanol or ethanol medium.[4a,6]

On the other hand Cs_2CO_3 is a powerful versatile inorganic base used in many organic reactions. Cs_2CO_3 has unique properties such as compatibility with a broad range of functional groups, and replacing sodium and potassium based compounds.[12] Recently cesium substituted heteropolyacids catalyzed synthesis of bis(3-indolyl)phenylmethanes was reported.[13] Additionally several indolyl derivatives are prepared[14] successfully with the use of Cs_2CO_3. In this preliminary work, we report a novel method,[15] which is free from the formation of bisindolylmethane for the preparation of 3-(α-hydroxyaryl)indoles (Scheme 1). To the best of our knowledge this may be the first report, which exclusively deals with the synthesis and stability of 3-(α-hydroxyaryl)indoles.

In order to obtain a maximum yield, the mole ratio and catalyst loading have been studied. Except cesium carbonate none of the other reagents has a considerable impact on the yield. The yield variations with respect to the cesium carbonate are tabulated (Table 1) and the result shows that 1.0 mole of Cs_2CO_3 gives better yield. The optimal reaction time for maximum yield is determined



Scheme 1. General scheme for the preparation of 3-(α-hydroxyaryl)indoles.

---

* Corresponding author. Tel.: +91 9444350863; fax: +91 4422394352.
E-mail address: rjkmcc@yahoo.com (R. Joel Karunakaran).

0040-4039/$ - see front matter © 2012 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tetlet.2012.10.002

Table 1
Yield variation with different mole ratios of Cs_2CO_3 with respect to aldehyde

Products	Yield[a] (%)			
	0.15 mole (%)	0.50 mole (%)	1.0 mole (%)	1.2 mole (%)
3b	27	45	71	72
3c	25	42	69	69

[a] Isolated yield in percentage.

as 6–7 h. If the reaction time is extended, the reaction leads to many uncharacterized compounds in the case of nitro benzaldehyde.

A number of substituted indoles and aldehydes have been chosen for this study (Table 2). In all the reactions studied, the formation of bis(indolyl)methane formation was not observed. It was also found that the yield of the product is largely controlled by the nature of the functional group present in the benzaldehyde, rather than substituents in the indole moiety. Generally, aldehydes with

Table 2
Reaction of various indoles with different aldehydes in the presence of Cs_2CO_3

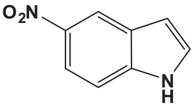
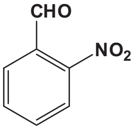
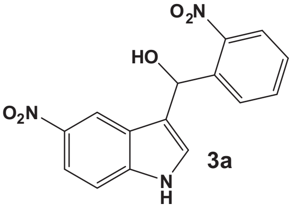
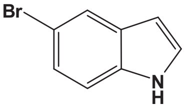
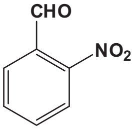
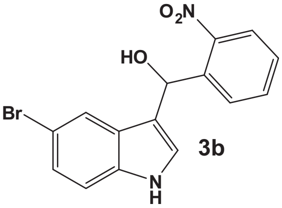
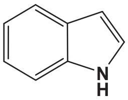
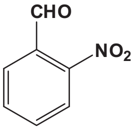
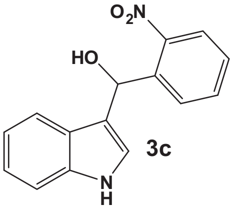
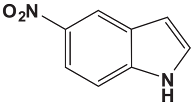
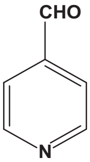
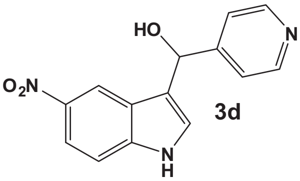
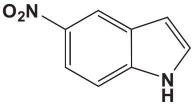
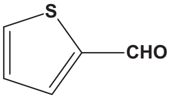
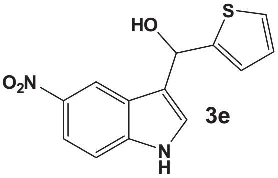
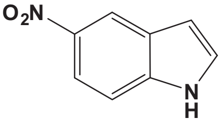
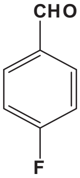
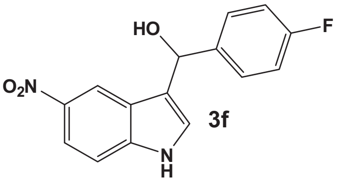
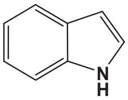
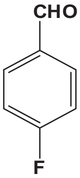
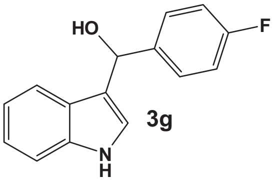
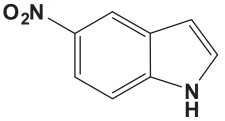
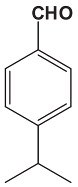
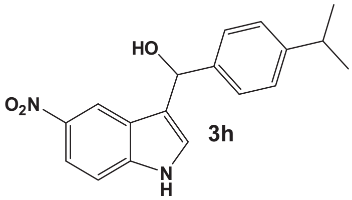
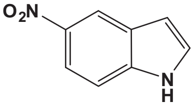
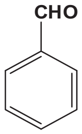
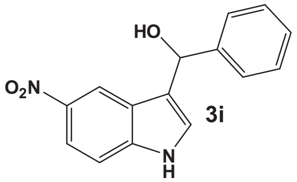
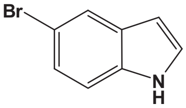
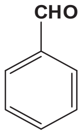
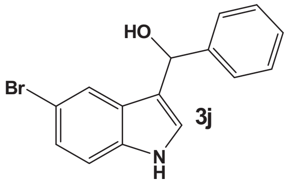
Entry	Indole	Aldehyde*	Products	Yield[a] (%)
1			 3a	85
2			 3b	71
3			 3c	69
4			 3d	47
5			 3e	40
6			 3f	40
7			 3g	35

Table 2 (*continued*)

Entry	Indole	Aldehyde[*]	Products	Yield[a] (%)
8			 **3h**	30
9			 **3i**	30
10			 **3j**	19

[*] All reactions were carried out with minimum 1 g scale.

[a] Isolated yield in percentage.

Table 3
Yield variation and time duration with different alkali metal carbonates

Entry	Products	Bases	Time	Isolated yield (%)
1	**3a**	Cs_2CO_3	6–7 h	85
2	**3b**	Cs_2CO_3	6–7 h	71
3	**3c**	Cs_2CO_3	6–7 h	69
4	**3a**	K_2CO_3	4 days	80
5	**3b**	K_2CO_3	4 days	65
6	**3c**	K_2CO_3	4 days	60
7	**3a**	Li_2CO_3/Na_2CO_3	4 days	—
8	**3b**	Li_2CO_3/Na_2CO_3	4 days	—
9	**3c**	Li_2CO_3/Na_2CO_3	4 days	—

electron withdrawing groups afforded good yields (Table 2, entries 1, 2, 3), while those with electron releasing substituents gave moderate yield. It has also been observed that the isolation procedure for all the substrates is tedious except in the case of compounds with an electron withdrawing group .(Table 2, entries 1, 2, 3) From this study it is also noted that this method is not suitable for substituted phenolic aldehydes and benzoic acid aldehydes.

To study the reaction details, we have carried out a few of the reactions (Table 2, entries 1, 2, 3) with different solvents and different inorganic bases. The effect of solvent on reaction was evaluated along with DMF, which revealed that the progress of reaction was very slow in acetonitrile and acetone and produced lower yields. In water medium the yield was almost similar to that of DMF medium; however it took nearly 20 h for the maximum conversion.

Among the bases studied, Li_2CO_3 and Na_2CO_3 were found to be unreactive under these conditions. The reaction with K_2CO_3 progressed very slow and took 4 days for completion. The product yield and the time duration are summarized in Table 3.

The substituents present in the aldehyde play a vital role in the product stability. During purification by column chromatography, it was observed that the isolation of products containing electron withdrawing groups was easy and also the products after isolation were found to be stable.

In summary, we have developed a new effective methodology for the preparation of 3-(α-hydroxyaryl)indoles with moderate to good yields which can be employed on a wide range of substrates. This method not only deals with the preparation of 3-(α-hydroxyaryl)indoles but also explores the stability.

Acknowledgements

We are grateful to Orchid Chemicals and Pharmaceuticals Ltd, R&D centre, Sholinganallur and Department of Chemistry, Madras Christian College for providing facilities to carry out this research work. We thank the reviewers for their valuable comments and suggestions.

References and notes

1. For selected examples on transformations involving vinylogous iminium intermediates see: (a) Kogan, N. A.; Kulbitskii, G. N. *Chem. Heterocycl. Compd.* **1978**, *14*, 46–48; (b) Palmieri, A.; Petrini, M. *J. Org. Chem.* **2007**, *72*, 1863–1866; (c) Cozzi, P. G.; Benfatti, F.; Zoli, L. *Angew. Chem., Int. Ed.* **2009**, *48*, 1313–1316; (d) Guo, Q.; Peng, Y.; Zhang, J.; Song, L.; Feng, Z.; Gong, L. *Org. Lett.* **2009**, *11*, 4620–4623; (e) Jing, L.; Wei, J.; Zhou, L.; Huang, Z.; Li, Z.; Wu, D.; Xiang, H.; Zhou, X. *Chem. Eur. J.* **2010**, *16*, 10955–10958; (f) Shaikh, R. R.; Mazzanti, A.; Petrini, M.; Bartoli, G.; Melchiorre, P. *Angew. Chem., Int. Ed.* **2008**, *47*, 8707–8710; (g) Ballini, R.; Palmieri, A.; Petrini, M.; Shaikha, R. *Adv. Synth. Catal.* **2008**, *350*, 129–134; (h) Li, Y.; Shi, F.; He, Q.; You, S. *Org. Lett.* **2009**, *11*, 3182–3185; (i) Zheng, B.; Ding, C.; Hou, X.; Dai, L. *Org. Lett.* **2010**, *12*, 1688–1691.
2. Zeng, X.; Ji, S.; Yiwang, S. *Tetrahedron* **2005**, *61*, 10235–10241.
3. Bandgar, B. P.; Abasaheb; Patil, V.; Kamble, V. T. *ARKIVOC* **2007**, 252–259.
4. (a) Shen, Z.; Ji, S.; Wang, S.; Zeng, X. *Tetrahedron* **2005**, *61*, 10552–10558; (b) Wang, D.; Tang, J.; Zhou, Y.; Chen, M.; Yu, C.; Duan, Y.; Jiang, G. *Chem. Sci.* **2011**, *2*, 803–806.
5. *Spectroscopic data for selected compounds.* (5-Nitro-1H-indol-3-yl)(pyridine-4-yl)methanol 4, ^{1}H NMR (DMSO-d_6) δ 6.09 (d, J = 4.0 Hz, –OH); 6.14(d, J = 4.0 Hz, 1H); 7.46(s, 1H); 7.48(m, 2H); 7.53(d, J = 8.9 Hz, 1H); 7.98(d, J = 8.9 Hz, 1H); 8.52(m, 3H); 11.75(br s, NH); ^{13}C NMR (DMSO-d_6) δ 67.1, 112.1, 116.6, 116.7, 120.9, 121.3, 124.8, 127.0, 139.8, 140.3, 149.5, 153.7 ppm; MS (EI): calcd mass for $C_{14}H_{11}N_3O_3$ is 269.29, found: 267.9 $(M^+-1)^-$.
6. Zhou, P.; Li, Y.; Meagher, K. L.; Mewshaw, R. G.; Harrison, B. L. *Tetrahedron Lett.* **2001**, *42*, 7333–7335.
7. (a) Bosch, J.; Mauleon, D.; Feliz, M.; Granados, R. *J. Org. Chem.* **1983**, *48*, 4836–4841; (b) Bosch, J.; Feliz, M.; Bennasar, M. *Tetrahedron* **1984**, *40*, 1419–1424.
8. Kametani, T.; Suzuki, T.; Takahashi, K.; Ichikawa, Y.; Fukumoto, K. *J. Chem. Soc., Perkin Trans. 1* **1975**, 413–415.
9. Gray, A. P. *J. Org. Chem.* **1958**, *23*, 1453–1454.
10. DeGraw, J. L.; Kennedy, J. G.; Skinner, W. A. *J. Heterocycl. Chem.* **1966**, *3*, 67–69.

11. (a) Deb, M. L.; Bhuyan, P. J. *Tetrahedron Lett.* **2006**, *47*, 1441–1443; (b) Gibbs, T. J. K.; Tomkinson, N. C. O. *Org. Biomol. Chem.* **2005**, *3*, 4043–4045; Mo, L.-P.; Zhang, Z.-H. *Synth. Commun.* **2005**, *35*, 1997–2004.
12. (a) Hofmann, H. *Chem. Ind. Dig.* **1993**, *6*, 113–117. and references therein; (b) Hofmann, H. *Spec. Chem.* **1993**, *13*, 59. 62–63, 65; (c) Blum, Z. *Acta Chem. Scand.* **1989**, *43*, 248–250.
13. Rafiee, E.; Zolfagharifr, Z.; Joshashani, M.; Eavani, S. *Appl. Catal. A* **2009**, *365*, 287–291.
14. Some selected examples. Deprotection of N-tosylated indoles using Cs_2CO_3 (a) Bajwa, J. S.; Chen, G.; Prasad, K.; Repic, O.; Blocklock, T. J. *Tetrahedron Lett.* **2006**, *47*, 6425–6427; Cs_2CO_3 promoted N-alkylation of indoles (b) Fink, D. M. *Synlett* **2004**, 2394–2396.
15. *General procedure for the synthesis of 3-(α-hydroxyaryl)indoles*: A mixture of benzaldehyde, indole, and Cs_2CO_3 with a mole ratio of 1:1.2:1 was stirred in 10 volumes of DMF for 6–7 h, and then diluted with 20 mL of water and extracted with 25 mL of ethyl acetate. The organic layer was washed with 20 mL of water and evaporated under reduced pressure. The residue thus obtained was purified by column chromatography on silica gel and was eluted with dichloromethane–methanol mixture to provide the corresponding 3-(α-hydroxyaryl)indoles.