Tetrahedron Letters 53 (2012) 6091–6094

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

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

Oxidative C–H functionalization: a novel strategy for the acetoxylation/alkoxylation of arenes tethered to 3,4-dihydroisoquinolines

B. V. Subba Reddy *, N. Umadevi, G. Narasimhulu, J. S. Yadav

Natural Product Chemistry, CSIR–Indian Institute of Chemical Technology, Hyderabad 500 007, India

ARTICLE INFO

Article history:
Received 20 July 2012
Revised 28 August 2012
Accepted 29 August 2012
Available online 5 September 2012

Keywords:
1-Aryl-3,4-dihydroisoquinolines
Hypervalent iodine reagent
Acetoxylation
Alkoxylation
C–H activation

ABSTRACT

1-Aryl-3,4-dihydroisoquinolines undergo smooth acetoxylation/alkoxylation in the presence of 5 mol % $Pd(OAc)_2$ and a stoichiometric amount of $PhI(OAc)_2$ by means of C–H activation to produce the corresponding acetoxy- and alkoxy-1-aryl-3,4-dihydroisoquinoline derivatives respectively in good yields with high regioselectivity. It is a first example on oxidative functionalization of arenes tethered to dihydroisoquinoline moiety via the C–H activation.

Tetrahydroisoquinoline derivatives (Fig. 1)[1] are known to display a wide range of biological activities such as anticonvulsants and neuroprotective agents for the treatment of neurodegenerative diseases including ischemia, epilepsy, Alzheimer's, and Parkinson's disease.[2] They also exhibit antibacterial[3] and anti-HIV activities.[4] Furthermore, 1-aryl tetrahydroisoquinoline derivatives are the antagonists of AMPA, NMDA, and dopamine D_1 receptors which facilitate the glutamate and dopamine neurotransmission in the central nervous system.[5] Furthermore, solifenacin is a currently used drug for the treatment of overactive bladder.[6] In particular, 1-aryl-3,4-dihydroisoquinolines are the known inhibitors of *c*-Jun N-terminal kinases (JNK3) which are responsible for several diseases such as neurodegeneration, rheumatoid arthritis, inflammatory disorders, cancer, and diabetes.[7] In addition to this, 1-aryl-3,4-dihydroisoquinolines are known to inhibit the cell proliferation.[8] Consequently, there is a great demand for the generation of novel 1-aryl-3,4-dihydroisoquinoline libraries for biological evaluation.

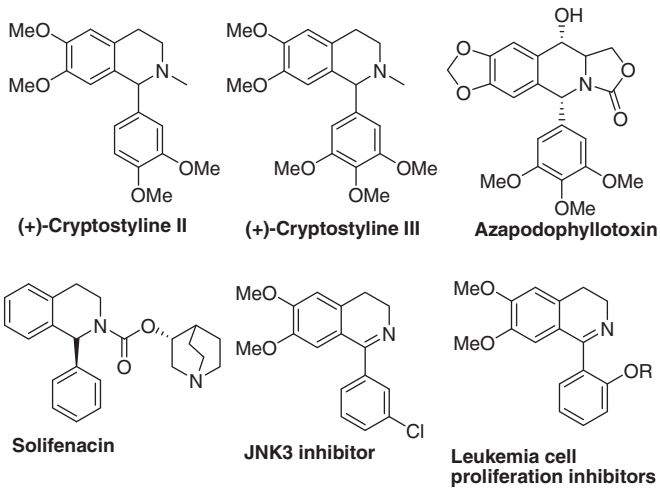
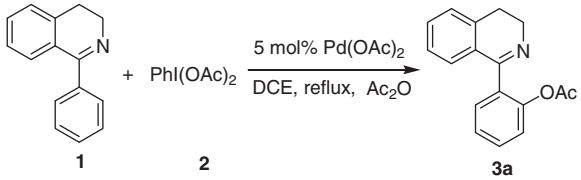


Figure 1. Examples of biologically active isoquinoline derivatives.

Recently, palladium catalyzed C–H bond activation has emerged as a powerful tool for the direct functionalization of unactivated C–H bonds.[9,10] However, the direct functionalization of substrates with similar C–H bonds tends to require a directing group.[11] As a result, the substrate directed C–H bond activation has received significant attention. In particular, the oxidation of aromatic C–H bonds is a challenging task in organic synthesis.[12] However, there have been no reports on the oxidative functionalization of 1-aryl-



Scheme 1. Acetoxylation of 1-phenyl-3,4-dihydroisoquinoline.

* Corresponding author. Fax: +91 40 27160512.
E-mail address: basireddy@iict.res.in (B.V. Subba Reddy).

0040-4039/$ - see front matter © 2012 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tetlet.2012.08.124

Table 1
$Pd(OAc)_2$-catalyzed acetoxylation/alkoxylation of 3,4-dihydroisoquinolines

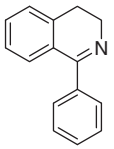
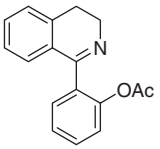
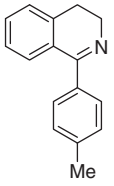
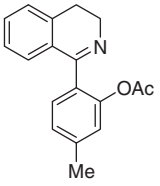
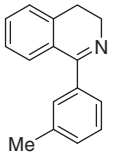
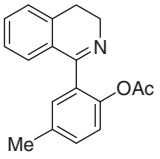
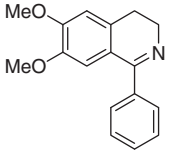
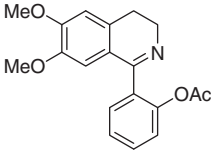
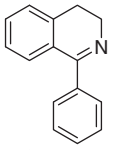
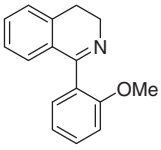
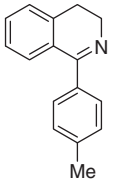
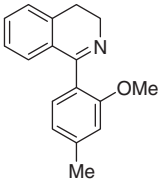
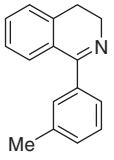
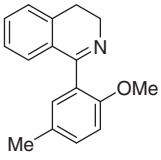
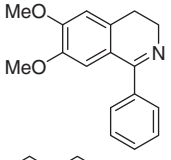
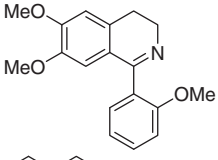
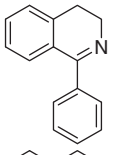
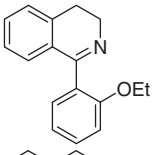
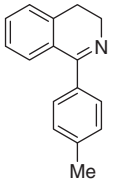
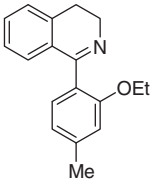
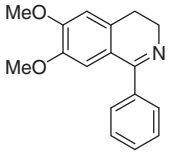
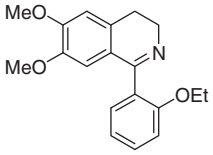
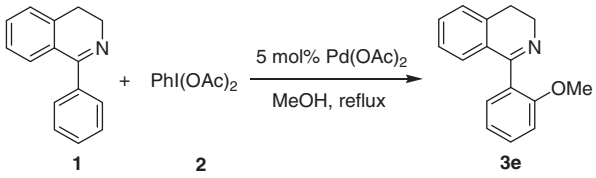
Entry	Dihydroisoquinoline (**1**)	Product (**3**)[a]		Time (h)	Yield[b] (%)
a			**3a**	3.0	82
b			**3b**	3.2	76
c			**3c**	3.4	74
d			**3d**	4.5	76
e			**3e**	3.0	76
f			**3f**	3.8	78
g			**3g**	4.0	75
h			**3h**	6.2	73
i			**3i**	3.0	72
j			**3j**	2.7	75

Table 1 (*continued*)

Entry	Dihydroisoquinoline (**1**)	Product (**3**)[a]		Time (h)	Yield[b] (%)
k			**3k**	6.2	73

[a] All products were characterized by NMR, IR, and mass spectrometry.
[b] Yield refers to pure products after chromatography.



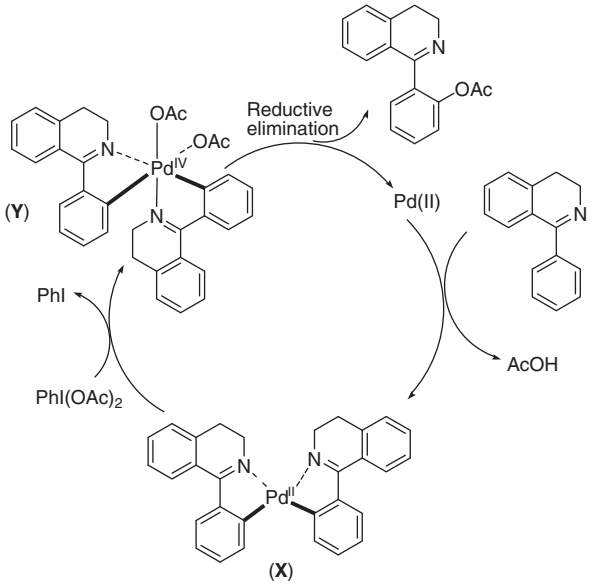
Scheme 2. Alkoxylation of 1-phenyl-3,4-dihydroisoquinoline.

3,4-dihydroisoquinolines by means of C–H activation involving *ortho*-chelating imino group.

In continuation of our interest on oxidative functionalization of arenes,[13] we herein report a novel strategy for the acetoxylation/alkoxylation of arenes by means of substrate-directed C–H activation. The starting materials, 1-aryl-3,4-dihydroisoquinolines were prepared by a known procedure.[14] Initially, we attempted the acetoxylation of 1-phenyl-3,4-dihydroisoquinoline using 5 mol % of $PhI(OAc)_2$ and 5 mol % $Pd(OAc)_2$ in the presence of stoichiometric amount of acetic anhydride at 80 °C. The desired acetoxy product was obtained in low yield (ca. 20%). The yield was notably increased from 20% to 82% by increasing the amount of $PhI(OAc)_2$ from 5 mol % to stoichiometric amount. Under the above conditions, the reaction proceeds smoothly in 1,2-dichloroethane at 80 °C and provides the 2-(3,4-dihydroisoquinolin-1-yl)phenyl acetate **3a** in 82% yield (Scheme 1).

In this C–H activation, $Pd(OAc)_2$ activates the aromatic C–H bond via dihydroisoquinoline directed oxidative insertion. Ac_2O acts as an acetoxylating agent. $PhI(OAc)_2$ acts as the terminal oxidant. The efficiency of other oxidants such as Fe_3O_4, Ag_2O, CuO, MnO_2, and 1,4-benzoquinone was tested for this reaction. To our surprise, the yields were far from satisfactory when the reactions were carried out with the above oxidants. Oxone was also found to be less effective for the acetoxylation of arenes. Thus $PhI(OAc)_2$ was found to be superior in terms of conversion. Next, the acetoxylation was carried out using various amounts of $Pd(OAc)_2$. Under optimized conditions, the acetoxylation typically requires acetic anhydride, 5 mol % $Pd(OAc)_2$, and a stoichiometric amount of $PhI(OAc)_2$ to achieve the products in good yields. Next we performed the acetoxylation at various temperatures in various solvents. The reaction proceeds well in 1,2-dichloroethane and nitromethane under reflux conditions. But the reaction was found to be sluggish in acetonitrile and tetrahydrofuran. As solvent, 1,2-dichloroethane gave the best results at 80 °C.

Under optimized conditions, various 1-aryl-3,4-dihydroisoquinolines such as *p*-methyl-1-phenyl- and *m*-methyl-1-phenyl- derivatives underwent smooth acetoxylation (Table 1, entries a–c). In the case of *m*-methyl substitution on the aromatic ring, the acetoxylation took place selectively at less sterically hindered *ortho*-position (Table 1, entry c). Furthermore, 6,7-dimethoxy-1-phenyl-3,4-dihydroisoquinoline also participated well in the acetoxylation (Table 1, entry d). Thus the acetoxylation of 1-aryl-3,4-dihydroisoquinolines was highly *ortho*-selective affording the acetoxylated products in good yields.



Scheme 3. A plausible reaction pathway.

Next, we extended this method for the alkoxylation of 1-aryl-3,4-dihydroisoquinolines. Accordingly, the treatment of 1-phenyl-3,4-dihydroisoquinoline (**1**) with a stoichiometric amount of $PhI(OAc)_2$ and 5 mol % $Pd(OAc)_2$ in refluxing methanol or ethanol gave the corresponding alkoxy products (**3e–k**) in good yields. Thus, alkoxylation of arenes was achieved by merely changing the solvent from 1,2-dichloroethane to methanol or ethanol (Scheme 2).

Interestingly, several 1-aryl-3,4-dihydroisoquinoline derivatives participated well in this oxidative functionalization. No acetoxylation was observed in the absence of either $Pd(OAc)_2$ or $PhI(OAc)_2$. The products were characterized by NMR, IR, and mass spectroscopy. The scope and generality of this process is illustrated with respect to various 1-aryl-3,4-dihydroisoquinoline derivatives and the results are presented in Table 1.[15]

Mechanistically, C–H bond activation proceeds likely via the formation of a highly reactive Pd^{II} intermediate (**X**) as shown in Scheme 3. By the addition of $PhI(OAc)_2$ to $(Ph\text{-}isoquin)_2Pd^{II}$ complex (**X**) generates the Pd^{IV} intermediate (**Y**). Reductive elimination via carboxylate dissociation from a 5-coordinate cationic Pd^{IV} intermediate (**Y**) facilitates the C–O bond formation.[11m] In this approach, 3,4-dihydroisoquinoline activates the unactivated C–H bond of aryl group through *ortho*-chelating imino group (Scheme 3).

In summary, we have developed a novel strategy for the acetoxylation/alkoxylation of 1-aryl-3,4-dihydroisoquinolines by means of C–H activation. This method is useful for the direct

acetoxylation and alkoxylation of arenes tethered to 3,4-dihydroisoquinoline via the substrate-directed oxidative functionalization.

Acknowledgements

NU thanks the UGC, GNL thanks the CSIR, New Delhi for the award of fellowships.

References and notes

1. (a) Chang, M.; Li, W.; Zhang, X. *Angew. Chem., Int. Ed.* **2011**, *50*, 10679; (b) Lee, K. M.; Kim, J. C.; Kang, P.; Lee, W. K.; Eumb, H.; Ha, J.-H. *Tetrahedron* **2012**, *68*, 883.
2. (a)*The Chemistry and Biology of Isoquinoline Alkaloids*; Phillipson, J. D., Roberts, M. F., Zenk, M. H., Eds.; Springer: Berlin, 1985; (b) Jack, D.; Williams, R. *Chem. Rev.* **2002**, *102*, 1669; (c) Bentley, K. W. *Nat. Prod. Rep.* **2006**, *23*, 444.
3. Tiwari, R. K.; Singh, D.; Singh, J.; Chhillar, A. K.; Chandra, R.; Verma, A. K. *Eur. J. Med. Chem.* **2006**, *41*, 40.
4. (a) Cheng, P.; Huang, N.; Jiang, Z. Y.; Zhang, Q.; Zheng, Y. T.; Chen, J. J.; Zhang, X. M.; Ma, Y. B. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 2475; (b) Chen, K. X.; Xie, H. Y.; Li, Z. G.; Gao, J. R. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 5381.
5. Gitto, R.; Barreca, M. L.; De Luca, L.; De Sarro, G.; Ferreri, G.; Quartarone, S.; Russo, E.; Constanti, A.; Chimirri, A. *J. Med. Chem.* **2003**, *46*, 197.
6. Naito, R.; Yonetoku, Y.; Okamoto, Y.; Toyoshima, A.; Ikeda, K.; Takeuchi, M. *J. Med. Chem.* **2005**, *48*, 6597.
7. Christopher, J. A.; Atkinson, F. L.; Bax, B. D.; Brown, M. J. B.; Champigny, A. C.; Chuang, T. T.; Jones, E. J.; Mosley, J. E.; Musgrave, J. R. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 2230.
8. Bermejo, A.; Andreu, I.; Suvire, F.; Leonce, S.; Caignard, D. H.; Renard, P.; Pierre, A.; Enriz, R. D.; Cortes, D.; Cabedo, N. *J. Med. Chem.* **2002**, *45*, 5058.
9. (a) Beccalli, E. M.; Broggini, G.; Martinelli, M.; Sottocornola, S. *Chem. Rev.* **2007**, *107*, 5318; (b) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174; (c) Giri, R.; Maugel, N. L.; Li, J. J.; Wang, D. H.; Breazzano, S. P.; Saunders, L. B.; Yu, J. Q. *J. Am. Chem. Soc.* **2007**, *129*, 3510; (d) Cai, G.; Fu, Y.; Li, Y.; Wan, X.; Shi, Z. *J. Am. Chem. Soc.* **2007**, *129*, 7666; (e) Shi, Z. J.; Li, B.; Wan, X.; Cheng, J.; Fang, Z.; Cao, B.; Qin, C.; Wang, Y. *Angew. Chem., Int. Ed.* **2007**, *46*, 5554; (f) Yu, W.-Y.; Sit, W. N.; Lai, K.-M.; Zhou, Z.; Chan, A. S. C. *J. Am. Chem. Soc.* **2008**, *130*, 3304; (g) Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2007**, *129*, 11904; (h) Yu, J. Q.; Giri, R.; Chen, X. *Org. Biomol. Chem.* **2006**, *4*, 4041.
10. (a) Chen, X.; Li, J. J.; Hao, X. S.; Goodhue, C. E.; Yu, J. Q. *J. Am. Chem. Soc.* **2006**, *128*, 78; (b) Chen, X.; Goodhue, C. E.; Yu, J. Q. *J. Am. Chem. Soc.* **2006**, *128*, 12634; (c) Zaitsev, V. G.; Shabashov, D.; Daugulis, O. *J. Am. Chem. Soc.* **2005**, *127*, 13154; (d) Daugulis, O.; Zaitsev, V. G. *Angew. Chem., Int. Ed.* **2005**, *44*, 4046; (e) Orito, K.; Horibata, A.; Nakamura, T.; Ushito, H.; Nagasaki, H.; Yuguchi, M.; Yamashita, S.; Tokuda, M. *J. Am. Chem. Soc.* **2004**, *126*, 14342; (f) Wakui, H.; Kawasaki, S.; Satoh, T.; Miura, M.; Nomura, M. *J. Am. Chem. Soc.* **2004**, *126*, 8658.
11. (a) Desai, L. V.; Ren, D. T.; Rosner, T. *Org. Lett.* **2010**, *12*, 1032; (b) Yoshikai, N.; Matsumoto, A.; Norinder, J.; Nakamura, E. *Angew. Chem., Int. Ed.* **2009**, *48*, 2925; (c) Zhao, X.; Yeung, C. S.; Dong, V. M. *J. Am. Chem. Soc.* **2010**, *132*, 5837; (d) Gu, S.; Chen, C.; Chen, W. *J. Org. Chem.* **2009**, *74*, 7203; (e) Thu, H. Y.; Yu, W. Y.; Che, C. M. *J. Am. Chem. Soc.* **2006**, *128*, 9048; (f) Wan, X.; Ma, Z.; Li, B.; Zhang, K.; Cao, S.; Zhang, S.; Shi, Z. *J. Am. Chem. Soc.* **2006**, *128*, 7416; (g) Tsang, W. C. P.; Zheng, N.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 14560; (h) Giri, R.; Liang, J.; Lei, J. G.; Li, J. J.; Wang, D. H.; Chen, X.; Naggar, I. C.; Guo, C.; Foxman, B. M.; Yu, J. Q. *Angew. Chem., Int. Ed.* **2005**, *44*, 7420; (i) Wasa, M.; Worrell, B. T.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2010**, *49*, 1275; (j) Chernyak, N.; Dudnik, A. S.; Huang, C.; Gevorgyan, V. J. *J. Am. Chem. Soc.* **2010**, *132*, 8270; (k) Huang, C.; Chattopadhyay, B.; Gevorgyan, V. J. *J. Am. Chem. Soc.* **2011**, *133*, 12406; (l) Wang, C.; Chen, H.; Wang, Z.; Chen, J.; Huang, Y. *Angew. Chem., Int. Ed.* **2012**, *51*, 7242; (m) Racowski, J. M.; Dick, A. R.; Sanford, M. S. *J. Am. Chem. Soc.* **2009**, *131*, 10974.
12. (a) Dick, A. R.; Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2004**, *126*, 2300; (b) Wang, G.-W.; Yuan, T.-T.; Wu, X.-L. *J. Org. Chem.* **2008**, *73*, 4717; (c) Wang, G.-W.; Yuan, T.-T. *J. Org. Chem.* **2010**, *75*, 476; (d) Stowers, K. J.; Sanford, M. S. *Org. Lett.* **2009**, *11*, 4584; (e) Desai, L. V.; Malik, H. A.; Sanford, M. S. *Org. Lett.* **2006**, *8*, 1141; (f) Kalyani, D.; Sanford, M. S. *Org. Lett.* **2005**, *7*, 4149.
13. (a) Reddy, B. V. S.; Reddy, L. R.; Corey, E. J. *Org. Lett.* **2006**, *8*, 3391; (b) Reddy, B. V. S.; Ramesh, K.; Yadav, J. S. *Synlett* **2011**, 169; (c) Reddy, B. V. S.; Revathi, G.; Reddy, A. S.; Yadav, J. S. *Synlett* **2011**, 2374; (d) Reddy, B. V. S.; Revathi, G.; Reddy, A. S.; Yadav, J. S. *Tetrahedron Lett.* **2011**, *52*, 5926; (e) Reddy, B. V. S.; Narasimhulu, G.; Umadevi, N.; Yadav, J. S. *Synlett* **2012**, 1364.
14. (a) Yang, C. H.; Tai, C. C.; Sun, I. W. *J. Mater. Chem.* **2004**, *14*, 947.
15. *Representative procedure for the acetoxylation of arenes*: A mixture of 1-aryl-3,4-dihydro-isoquinoline (1 mmol), iodobenzenediacetate (1.1 mmol), acetic anhydride (1.1 mmol) and $Pd(OAc)_2$ (5 mol %) in dichloroethane (4 mL) was stirred under reflux for a specified time (Table 1). After complete conversion, as indicated by TLC, the reaction mixture was diluted with water (10 mL) and extracted with dichloromethane (3×10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, concentrated in vacuo and purified by column chromatography on neutral alumina (ethyl acetate/hexane, 4:6) to afford the pure acetoxy aryl-3,4-dihydroisoquinoline. The products thus obtained were characterized by IR, NMR and mass spectroscopy.
3a. IR (neat): ν_{max} 3063, 2928, 2849, 1767, 1609, 1367, 1193, 1015, 748 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.73 (s, 3H), 2.80 (t, 2H, J = 6.8 Hz), 3.85 (t, 2H, J = 6.8 Hz), 7.01 (d, 1H, J = 7.5 Hz), 7.12–7.23 (m, 3H), 7.26–7.55 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.3, 25.8, 47.3, 118.1, 122.7, 125.9, 126.8, 127.1, 127.3, 128.5, 129.9, 130.4, 130.8, 137.4, 148.3, 165.1, 168.6; ESI-MS: m/z: 266 (M+H).
3b. IR (neat): ν_{max} 2975, 2932, 1735, 1603, 1457, 1374, 1270, 1109, 986, 753 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 1.72 (s, 3H), 2.34 (s, 3H), 2.76–2.85 (m, 2H), 3.79–3.90 (m, 2H), 6.96 (s, 1H), 7.14–7.24 (m, 2H), 7.36–7.43 (m, 2H), 7.67 (d, 2H, J = 7.6 Hz); ESI-MS: m/z: 280 (M+H).
3c. IR (neat): ν_{max} 2926, 1763, 1605, 1489, 1193, 1029, 825, 772 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.66 (s, 3H), 2.37 (s, 3H), 2.70–2.85 (m, 2H), 3.74–3.92 (m, 2H), 6.95–7.08 (m, 2H), 7.12–7.38 (m, 5H); ESI-MS: m/z: 280 (M+H), 318 (M+K).
3d. IR (neat): ν_{max} 2929, 2850, 1762, 1603, 1510, 1357, 1277, 1206, 1125, 1029, 949, 761 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.81 (s, 3H), 2.69–2.77 (m, 2H), 3.68 (s, 3H), 3.77–3.88 (m, 5H), 6.54 (s, 1H), 6.75 (s, 1H), 7.06 (d, 1H, J = 8.3 Hz), 7.13–7.17 (m, 1H), 7.27–7.37 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.3, 22.8, 41.5, 55.7, 55.8, 113.1, 123.1, 125.7, 128.2, 130.1, 131.8, 133, 133.7, 146.3, 148.8, 151.6, 169, 170.4; ESI-MS: m/z: 326 (M+H).
Representative procedure for the alkoxylation of arenes:
A mixture of 1-aryl-3,4-dihydroisoquinoline (1 mmol), iodobenzenediacetate (1.1 mmol), and $Pd(OAc)_2$ (5 mol %) in alcohol (4 mL) was stirred under reflux for a specified time (Table 1). After complete conversion, as indicated by TLC, the solvent was removed and the resulting residue was diluted with water (10 mL) and extracted with dichloromethane (3×10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, concentrated in vacuo and purified by column chromatography on neutral alumina (ethyl acetate/hexane, 4:6) to afford the pure alkoxy aryl-3,4-dihydroisoquinoline. The products thus obtained were characterized by IR, NMR, and mass spectroscopy.
3e. IR (KBr): ν_{max} 3016, 2925, 2851, 1741, 1608, 1573, 1458, 1430, 1238, 1022, 970, 750 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.85 (t, 2H, J = 6.8 Hz), 3.67 (s, 3H), 3.72–4.10 (m, 2H), 6.95 (t, 2H, J = 7.5 Hz), 7.03 (t, 1H, J = 7.5 Hz), 7.10–7.24 (m, 2H), 7.27–7.43 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 25.9, 47.5, 55.4, 110.9, 120.7, 126.5, 127.1, 128.6, 129.6, 130, 130.2, 130.3, 136.9, 157.1, 166.3; ESI-MS: m/z: 238 (M+H); HRMS calcd for $C_{16}H_{16}ON$: 238.1226, found: 238.1216.
3f. IR (KBr): ν_{max} 3008, 2946, 2892, 2841, 1607, 1566, 1458, 1404, 1278, 1170, 1032, 929, 814, 745 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.41 (s, 3H), 2.82 (t, 2H, J = 6.8 Hz), 3.65 (s, 3H), 3.67–4.01 (m, 2H), 6.70 (s, 1H), 6.81 (d, 1H, J = 7.5 Hz), 6.94 (d, 1H, J = 7.5 Hz), 7.06–7.32 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.6, 25.9, 47.5, 55.3, 111.7, 121.3, 125.7, 126.4, 1265.9, 127.1, 129.7, 129.9, 130.1, 136.9, 140.1, 157, 166.1; ESI-MS: m/z: 252 (M+H); HRMS calcd for $C_{17}H_{18}NO$: 252.1382, found: 252.1381.
3g. IR (neat): ν_{max} 2927, 1728, 1613, 1501, 1462, 1245, 1030, 745 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.32 (s, 3H), 2.75–2.93 (m, 2H), 3.65 (s, 3H), 3.67–4.02 (m, 2H), 6.79 (d, 1H, J = 9.0 Hz), 6.96 (d, 1H, J = 7.5 Hz), 7.06–7.21 (m, 4H), 7.30 (t, 1H, J = 7.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 25.8, 29.6, 47.4, 55.4, 110.9, 114.2, 120.7, 126.5, 127.1, 128.7, 129.6, 129.9, 130.1, 136.9, 144.1, 157.1, 166.2; ESI-MS: m/z: 252 (M+H).
3h. IR (neat): ν_{max} 2929, 2841, 1742, 1604, 1512, 1460, 1355, 1274, 1208, 1118, 1024, 945, 866, 756 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.66–2.88 (m, 2H), 3.54–4.03 (m, 11H), 6.51 (s, 1H), 6.73 (s, 1H), 6.95 (d, 1H, J = 8.3 Hz), 7.04 (t, 1H, J = 7.5 Hz), 7.32–7.43 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 25.6, 47.5, 55.4, 55.8, 55.9, 109.9, 110.8, 120.7, 122.6, 128.6, 130, 130.2, 130.7, 147.1, 150.6, 157, 165.5; LC–MS: m/z: 298 (M+H); HRMS calcd for $C_{18}H_{20}NO_3$: 298.1437, found: 298.1425.
3i. IR (neat): ν_{max} 3064, 2927, 2852, 1714, 1607, 1573, 1449, 1238, 1121, 1044, 927, 749 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.01 (t, 3H, J = 6.8 Hz), 2.70–2.95 (m, 2H), 3.54–4.25 (m, 4H), 6.91 (d, 1H, J = 8.3 Hz), 6.95–7.08 (m, 2H), 7.11–7.24 (m, 2H), 7.27–7.45 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.8, 25.9, 47.4, 63.7, 112.1, 120.7, 126.3, 126.8, 127, 129.9, 130, 130.1, 136.8, 156.5, 166.5; ESI-MS: m/z: 252 (M+H); HRMS calcd for $C_{17}H_{18}NO$: 250.1382, found: 252.1374.
3j. IR (KBr): ν_{max} 2926, 2846, 1706, 1604, 1511, 1384, 1250, 1165, 1113, 1028, 825, 751 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.00 (t, 3H, J = 6.8 Hz), 2.39 (s, 3H), 2.71–2.89 (m, 2H), 3.60–4.12 (m, 4H), 6.67 (s, 1H), 6.81 (d, 1H, J = 7.5 Hz), 6.96 (d, 1H, J = 7.5 Hz), 7.04–7.19 (m, 2H), 7.21–7.29 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.5, 55.4, 55.5, 58.6, 60.3, 111.5, 116.4, 117.4, 128.5, 129.5, 129.9, 132.5, 132.6, 137.6, 145.2, 152, 152.3, 168.5; ESI-MS: m/z: 266 (M+H).
3k. IR (KBr): ν_{max} 2925, 2853, 1742, 1604, 1512, 1453, 1355, 1273, 1210, 1118, 1038, 947, 756 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 1.07 (t, 3H, J = 6.6 Hz), 2.60–2.92 (m, 2H), 3.49–4.18 (m, 10H), 6.53 (s, 1H), 6.73 (s, 1H), 6.92 (d, 1H, J = 8.8 Hz), 7.03 (t, 1H, J = 7.7 Hz), 7.33–7.45 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 25.7, 47.4, 55.9, 56, 63.7, 109.8, 110.9, 112.1, 120.8, 122.8, 128.1, 130.1, 130.2, 130.7, 147.1, 150.6, 156.4, 165.9; ESI-MS: m/z: 312 (M+H); HRMS calcd for $C_{19}H_{22}O_3N$: 312.1594, found: 312.1579.