RSC Advances



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Cite this: RSC Adv., 2024, 14, 13306

Mono and di *ortho*-C–H acetoxylation of 2aryloxyquinoline-3-carbaldehydes[†]

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Received 19th February 2024 Accepted 8th April 2024

DOI: 10.1039/d4ra01289e

rsc.li/rsc-advances

2-Aryloxyquinolines are well known for various biological activities. In this report, we have developed a novel protocol for introducing an acetoxy functional group on the aryl sp² carbon of 2-aryloxyquinoline-3-carbaldehyde using a palladium catalyst for the first time. Interestingly, this C-H acetoxylation reaction is highly chemo- and site-selective. By modifying the reaction conditions, mono or di *ortho*-C-H acetoxylation products have been synthesized selectively with good yields and with good functional group tolerance.

Quinoline-based compounds are an important class of *N*heterocyclics with a diverse range of biological activities. In the class of quinolines, 2-aryloxyquinolines have gained a lot of interest as they contain important pharmacophores which are frequently useful in many biologically active compounds.¹ Because of the significance of these molecules, many research groups have made efforts to develop more efficient methods for their synthesis.² Moreover, these 2-aryloxyquinoline molecules have antiasthmatic, antiviral, antifungal, antiprotozoal, anthelmintic, cardiotonic, and local anesthetic properties³ (Fig. 1).

Over the last two decades, tremendous progress has been made in transition-metal-catalyzed C-H activation reactions.⁴ In general, the construction of a C-C bond and C-hetero atom bond by activating the inert C-H bonds of arenes has gained a lot of interest in both academic research and industry. In that direction, the construction of a C-O bond via the C-H activation reaction is challenging due to low reactivity and regioselectivity. Using the directing group (DG) strategy, a number of C-O bondforming reactions have been reported in recent years.⁵ Among the various C-O bond-forming reactions, the acetoxylation of aromatic compounds is important. Furthermore, acetoxylation of aromatic compounds is essential since they can be easily converted into phenolic derivatives which are an integral part of many natural products and biologically active molecules. Also, aromatic C-H acetoxylation and hydroxylation reactions are complementary reactions to each other for the incorporation of an acetoxy or hydroxyl group into the product. Towards this end, Sanford and her co-workers developed a regio- and

chemoselective method for the acetoxylation of the 2-aryl pyridine $C(sp^2)$ -H bond using pyridine as the DG *via* a palladium catalyst for the first time. Later, various DGs were successfully utilized for selective $C(sp^2)$ -H acetoxylation by using various transition metal catalysts⁶ (Scheme 1).

Among nitrogen-directing-group-assisted C–H activation reactions, pyridine, oxime, and imine groups are very much utilized as chelating groups. However, the nitrogen of the quinoline-moiety-directed C–H activation has not been explored much in the literature and quinolines are most commonly



Fig. 1 Structures of bioactive aryloxyquinoline derivatives



Scheme 1 Metal-catalyzed C-H acetoxylation.

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[†] Electronic supplementary information (ESI) available. See DOI: https://doi.org/10.1039/d4ra01289e

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found in various natural products, alkaloids, and pharmacologically active scaffolds. Due to the importance of quinolones, quinolone-containing molecules, such as 2-aryloxyquinoline can be easily transformed into a variety of new scaffolds and this will be helpful in finding new or active pharmaceutical ingredients (APIs) as well as in improving the biological activity of existing drug molecules. Moreover, from the point of view of the C-H activation reaction, functionalization of the C-H bond in the presence of another reactive functional group such as aldehyde is not known and is highly challenging due to the competitive reaction associated with the aldehyde functional group. Further, the aldehyde group will be very useful in latestage modifications and for the creation of new pharmacophores through various functional group transformations. In continuation of our interest in C-H activation,7 herein we disclose a novel site-selective ortho-C-H activation reaction for the introduction of an acetoxyl group on aryl ether derivatives. To execute our idea, we chose 2-aryloxyquinolines (1a) as the model substrate. Interestingly, we optimized the reaction conditions for both the mono- and di-acetoxylation of 2-aryloxyquinolines with moderate to good yields.

In order to execute our idea, we prepared 2-aryloxyquinoline-3-carbaldehyde (1a) and treated it with PhI(OAc)₂ in the presence of Pd(OAc)₂ as a catalyst and AcOH as a solvent at 110 °C for 6 hours (see Table 1, entry 1). Interestingly, the reaction produced the desired mono-acetoxylated product 2a in 30% yield. In order to increase the yield of mono-acetoxylated product, we increased the reaction time from 6 h to 9 h, which yielded the mono-acetoxylated product in moderate yield (45%) (see Table 1, entry 2). To improve the yield further, we carried out the reaction with increased time *i.e.*, from 9 h to

Table 1 Optimisation of reaction conditions ^a									
۲۵ الم		Pd(OAc)₂ Phi(OAc)₂ cOH, 110 °C	CHO NO 2a CH ₁	Aco OAc 3a CH ₃					

Entry	Pd(OAc) ₂ (mol%)	PhI(OAc) ₂ (equiv.)	Time (h)	Yield ^{b} (2a %)	Yield ^b (3a %)
	-	4.5	<i>c</i>	20	0
1	5	1.5	6	30	0
2	5	1.5	9	45	0
3	5	1.5	12	62	13
4	10	1.5	12	85	10
5	5	3.0	6	40	32
6	5	3.0	9	50	45
7	5	3.0	12	18	62
8	10	3.0	9	40	50
9	10	3.0	12	25	70
10	5	3.5	12	21	66
11	10	3.5	12	15	78
12	10	3.5	15	14	76

 $[^]a$ Reaction conditions: 1a (0.3 mmol), catalyst (5–10 mol%), oxidant (1.5–3.5 equiv.), AcOH (2 mL), 110 $^{\rm o}{\rm C},$ 6–15 h. b Isolated yields.

12 h. Interestingly, in this case, we observed the formation of mono-acetoxylated product **2a** in 62% yield and di-acetoxylated product **3a** in 13% yield (see Table 1, entry 3). However, the best result was obtained when we carried out the reaction with increased catalyst loading from 5 mol% to 10 mol%, which produced the expected mono-acetoxylated product **2a** in 85% yield and di-acetoxylated product **3a** in 10% yield (see Table 1, entry 4). We also observed that decreasing the load of the catalyst and even increasing the equivalents of PhI(OAc)₂ did not provide **2a** with better yield (see Table 1, eEntries 5 and 6). Hence the standardized conditions for the mono-acetoxylated product are Pd(OAc)₂ 10 mol%, PhI(OAc)₂ (1.5 equiv.) at 110 ° C for 12 hours.

Then we focussed our attention on improving the yield of diacetoxylation product. Accordingly, we treated **2a** with 5 mol% of Pd(OAc)₂ and 3 equiv. of PhI(OAc)₂ at 110 °C for 12 h, which produced mono-acetoxylated product **2a** in 18% yield and the di-acetoxylated product in 62% yield. Then we carried out the reaction by increasing Pd(OAc)₂ loading from 5 mol% to 10 mol% and 3 equiv. of PhI(OAc)₂ at 110 °C for 9 h, which produced **2a** in 40% yield and the desired di-acetoxylated product **3a** in 50% yield (see Table 1, entry 8). The same reaction was carried out with 10 mol% of Pd(OAc)₂ and 3 equiv. of PhI(OAc)₂ at 110 °C for 12 h, which produced monoacetoxylated product **2a** in 25% yield while the di-acetoxylated product **3a** was formed in 70% yield (see Table 1, entry 9).

Decreasing the $Pd(OAc)_2$ loading from 10 mol% to 5 mol% and increasing the equivalents of $PhI(OAc)_2$ from 3 equiv. to 3.5 equiv. at 110 °C for 12 h also produced mono-acetoxylated product **2a** in 21% yield and di-acetoxylated product **3a** in 66% yield (see Table 1, entry 10). Finally, the best result was obtained when we carried out the reaction with 10 mol% of $Pd(OAc)_2$ and 3.5 equiv. of $PhI(OAc)_2$ at 110 °C for 12 h, which provided the desired di-acetoxylated product **3a** in 78% yield and mono-acetoxylated product **2a** in 15% yield (see Table 1, entry 11). Further increasing the reaction time of the same reaction from 12 h to 15 h did not improve the yield of **3a** (see Table 1, entry 12).

With the standardized conditions for the formation of mono-acetoxylated product 2a in hand, we focussed on studying the scope of the *ortho*-C–H mono-acetoxylation reaction with a wide range of substrates. Initially, we tuned the quinoline ring with different electron-donating and electron-withdrawing groups. In all cases, we observed the formation of mono-acetoxylated products (2a–f) in good yields (60–85%). Later, we changed the substitution on the aryloxy ring, which provided the desired mono-acetoxylated products (2g–j) in good yields (51–65%) (Table 2). It is important to note that the C–H functionalization reaction provided the desired product without any interference from aldehyde functional groups.

After studying the scope of the mono-acetoxylation reaction, we focussed our attention on the scope of the di-acetoxylated product **3**. Accordingly, we investigated the scope of the di-acetoxylation reaction with electron-donating groups (EDG) and electron-withdrawing groups (EWG) on the quinoline part. Both EDG and EWG consisting of substrates (**1**) were

Table 2Mono ortho-C-H acetoxylation of 2-aryloxyquinoline-3-
carbaldehydes a



 a Reaction conditions: 1a (0.3 mmol), Pd(OAc)_2 (10 mol%), PhI(OAc)_2 (1.5 equiv.), AcOH (2 mL), 110 °C, 12 h.

Table 3 Di C–H acetoxylation of 2-arylocyquinoline-3-carbaldehyde^a



 a Reaction conditions: 1a (0.3 mmol), Pd(OAc)_2 (10 mol%), PhI(OAc)_2 (3.5 equiv.), AcOH (2 mL), 110 °C, 12 h.

compatible and provided the desired di-acetoxylated products in good yields (52–78%) (Table 3).

Subsequently, we conducted a competitive experiment between *p*-methyl and *p*-chloro derivatives (**1a and i**), which produced the *p*-methyl *ortho* acetoxylated product (**2a**) in 65% yield and the *p*-chloro *ortho* acetoxylated product (**2i**) in 17% yield. This reaction clearly indicates that the electron-donating group on the aryloxy ring facilitated the reaction compared to the electron-withdrawing group (Scheme 2).

To understand further which functional group (the quinoline nitrogen or aldehyde group) acts as a directing group, we prepared substrate 4, where we kept the reactive site containing the aryloxy group at the 4th position of the quinoline moiety,



Scheme 2 Competition reaction.

which in turn increased the distance and changed the positions between the nitrogen atom and the reactive site containing the aryloxy moiety. Accordingly, we carried out a couple of control experiments with 4-(*p*-tolyloxy)quinoline-3-carbaldehyde (4) under the standard reaction conditions, which did not provide the expected product (5). This indicates that the close proximity of the quinoline nitrogen to the reactive site of the aryloxy moiety is essential for the reaction. Therefore, the quinoline nitrogen acts as a directing group, not the aldehyde group. Next, we prepared 3-formyl-2-(*p*-tolyloxy)quinoline 1-oxide (6), in this substrate we converted the quinoline nitrogen into N-oxide to understand the importance of iminium nitrogen. Accordingly, substrate 6 under the optimized conditions for the *ortho*-C-H acetoxylation reaction did not lead to the expected C-H



Scheme 3 Control experiments.



Scheme 4 Plausible mechanism for the formation of acetoxylated 2aryloxyquinoline-3-carbaldehyde (2).

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activation product (7). This clearly indicates that the quinoline nitrogen acts as the DG and not the N-oxide group (Scheme 3).

The proposed mechanism for the *ortho*-C-H acetoxylation reaction is depicted in Scheme 4. The catalytic reaction proceeds *via* preferential coordination of the *N* atom of compound **1** with Pd(OAc)₂ to generate intermediate **A**. In the next step, intermediate **A** undergoes C-H activation and forms palladacycle **B** by the liberation of AcOH. Subsequently, palladacycle **B** transforms to complex C *via* oxidative addition using PhI(OAc)₂. Finally, desired product **2a** is obtained from complex C *via* reductive elimination. The catalytic cycle is completed by the regeneration of the Pd(π) species, as shown in Scheme 4.

Conclusions

We have developed a novel and efficient protocol for the synthesis of mono- and di-acetoxylated 2-aryloxyquinoline-3carbaldehydes using a palladium catalyst for the first time. A variety of mono- and di-acetoxylated 2-aryloxyquinoline-3carbaldehydes were synthesized in very good yields with excellent site selectivity. Various functional groups on the aryl rings as well as the more reactive aldehyde functional group were well tolerated in this reaction. Keeping the aldehyde functional group intact in the reaction will help in further useful transformations. Additionally, the incorporation of acetoxy groups on 2-aryloxyquinoline-3-carbaldehydes is useful for making a variety of phenolic scaffolds.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

We thank DST-SERB for the Financial support (Ref. No. CRG/ 2023/007946). T. T. R. thanks CSIR, New Delhi, for a direct Senior Research Fellowship (D-SRF) and O. S. A. thanks University of Lagos Tetfund IBR (CRC/TETFUND/No.2018/016) for providing fellowship. We thank Pondicherry University for ESI-HRMS and NMR facilities.

Notes and references

- (a) J. L. McCormick, T. C. McKee, J. H. Cardellina and M. R. Boyd, J. Nat. Prod., 1996, 59, 469-471; (b) I. S. Chen, H. F. Chen, M. J. Cheng, Y. L. Chang, C. M. Teng, I. Tsutomu, J. J. Chen and I. L. Tsai, J. Nat. Prod., 2001, 64, 1143-1147; (c) M. E. Wall, M. C. Wani, C. E. Cook, K. H. Palmer, A. T. McPhail and G. A. Sim, J. Am. Chem. Soc., 1966, 88, 3888-3890; (d) A. Marella, O. P. Tanwar, R. Saha, M. R. Ali, S. Srivastava, M. Akhter, M. Shaquiquzzaman and M. M. Alam, Saudi Pharm. J., 2013, 21, 1-12.
- 2 X. Yang, G. Zhou and W. Y. Wong, *Chem. Soc. Rev.*, 2015, 44, 8484–8575.
- 3 (a) M. P. LaMontagne, P. Blumbergs and D. C. Smith, J. Med. Chem., 1989, 32, 1728–1732; (b) S. T. Hazeldine, L. Polin,

J. Kushner, K. White, N. M. Bouregeois, B. Crantz, E. Palomino, T. H. Corbett and J. P. Horwitz, J. Med. Chem., 2002, 45, 3130-3137; (c) S. T. Hazeldine, L. Polin, J. Kushner, K. White, T. H. Corbett and J. P. Horwitz, Bioorg. Med. Chem., 2006, 14, 2462 - 2467;(d)Upadhayaya, G. M. Kulkarni, N. R. Vasireddy, R. S. K. Vandavasi, S. S. Dixit, V. Sharma and J. J. Chattopadhyaya, Bioorg. Med. Chem., 2009, 17, 4681-4692; (e) U. J. Ries, H. W. M. Priepke, N. H. Hauel, E. E. J. Haaksma, J. M. Stassen, W. Wienen and H. Nar, Bioorg. Med. Chem. Lett., 2003, 13, 2291-2295; (f) D. G. Batt, J. J. Petraitis, S. R. Sherk, R. A. Copeland, R. L. Dowling, T. L. Taylor, E. A. Jones, R. L. Magolda and B. D. Jaffee, Bioorg. Med. Chem. Lett., 1998, 8, 1745-1750; (g) F. Caijo, P. Mosset, R. Grée, V. Audinot-Bouchez, J. Boutin, P. Renard, D. H. Caignard and C. Dacquet, Bioorg. Med. Chem. Lett., 2005, 15, 4421-4426; (h) D. Mabire, S. Coupa, C. Adelinet, A. Poncelet, Y. Simonnet, M. Venet, R. Wouters, A. S. J. Lesage, L. V. Van Beijsterveldt and F. Bischoff, J. Med. Chem., 2005, 48, 2134-2153.

- 4 (a) R. Giri, B. F. Shi, K. M. Engle, N. Maugel and J. Q. Yu, Chem. Soc. Rev., 2009, 38, 3242-3272; (b) D. A. Colby, R. G. Bergman and J. A. Ellman, Chem. Rev., 2010, 110, 624-655; (c) J. Le Bras and J. Muzart, Chem. Rev., 2011, 111, 1170-1214; (d) T. Gensch, M. N. Hopkinson, F. Glorius and J. Wencel-Delord, Chem. Soc. Rev., 2016, 45, 2900-2936; (e) H. M. L. Davies and D. Morton, ACS Cent. Sci., 2017, 3, 936-943; (f) Z. Dong, Z. Ren, S. J. Thompson, Y. Xu and G. Dong, Chem. Rev., 2017, 117, 9333-9403; (g) X. S. Xue, P. Ji, B. Zhou and J. P. Cheng, Chem. Rev., 2017, 117, 8622-8648; (h) P. Gandeepan and L. Ackermann, Chem, 2018, 4, 199-222; (i) S. K. Sinha, S. Guin, S. Maiti, J. P. Biswas, S. Porey and D. Maiti, Chem. Rev., 2022, 122, 5682-5841; (j) A. Banerjee, A. Bera, S. K. Santra, S. Guin and B. K. Patel, RSC Adv., 2014, 4, 8558-8566; (k) A. Mandal, S. Dana, D. Chowdhury and M. Baidya, Chem.-Asian J., 2019, 14, 4074; (l) S. B. Jadhav, S. Maurya, N. Navaneetha and R. Chegondi, Chem. Commun., 2021, 57, 13598-13601; (m) S. Basak, T. Paul, S. Mandal, P. Karjee, M. V. Nanjegowda and T. Punniyamurthy, Synthesis, 2023, 55, 3454-3469; (n) S. M. Patel, P. Paradakshini, M. Bakthadoss and D. S. Sharada, Org. Lett., 2021, 23, 257-261; (o) A. Murugan, K. R. Gorantla, B. S. Mallik and D. S. Sharada, Org. Biomol. Chem., 2018, 16, 5113-5118.
- 5 (a) I. B. Krylov, V. A. Vil' and A. O. Terent'ev, Beilstein J. Org. Chem., 2015, 11, 92–146; (b) B. Liu and B. F. Shi, Tetrahedron Lett., 2015, 56, 15–22; (c) S. Moghimi, M. Mahdavi, A. Shafiee and A. Foroumadi, Eur. J. Org Chem., 2016, 3282; (d) Y. F. Liang and N. Jiao, Acc. Chem. Res., 2017, 50, 1640–1653; (e) F. Yang, H. Zhang, X. Liu, B. Wang and L. Ackermann, Chin. J. Org. Chem., 2019, 39, 59; (f) X. Wang, H. Wang, C. Zhou, L. Yang, L. Fu and G. Li, Chem. Commun., 2022, 58, 4993–4996.
- 6 (a) A. R. Dick, K. L. Hull and M. S. Sanford, J. Am. Chem. Soc., 2004, 126, 2300–2301; (b) Z. Ren, J. E. Schulz and G. Dong, Org. Lett., 2015, 17, 2696–2699; (c) T. Okada, K. Nobushige, T. Satoh and M. Miura, Org. Lett., 2016, 18, 1150–1153; (d)

Q. Zhang, X. Xie, J. Peng, F. Chen, J. Ma, C. Li, H. Liu, D. Wang and J. Wang, Org. Lett., 2021, 23, 4699–4704; (e) L. V. Desai,
K. J. Stowers and M. S. Sanford, J. Am. Chem. Soc., 2008, 130, 13285–13293; (f) S. Gu, C. Chen and W. Chen, J. Org. Chem., 2009, 74, 7203–7206; (g) L. Wang, L. Pan, Y. Huang,
Q. Chen and M. He, Eur. J. Org Chem., 2016, 3113–3118; (h)
I. Urruzuno, P. A. Sampedro and A. Correa, Eur. J. Org Chem., 2023, e202201489; (i) Z. Peng, Z. Yu, T. Li, N. Li,
Y. Wang, L. Song and C. Jiang, Organometallics, 2017, 36, 2826–2831.

7 (a) M. Bakthadoss and P. V. Kumar, *Adv. Synth. Catal.*, 2018, 36, 2650–2658; (b) M. Bakthadoss, T. T. Reddy, V. Agarwal and D. S. Sharada, *Chem. Commun.*, 2022, 58, 1406–1409; (c)

M. Bakthadoss, T. T. Reddy and D. S. Sharada, *RSC Adv.*, 2020, **10**, 31570–31574; (*d*) M. Bakthadoss, P. V. Kumar, R. Kumar, M. Surendar and D. S. Sharada, *New J. Chem.*, 2019, **43**, 14190–14195; (*e*) M. Bakthadoss, P. V. Kumar, R. Kumar and V. Agarwal, *Org. Biomol. Chem.*, 2019, **17**, 4465–4469; (*f*) M. Bakthadoss, T. T. Reddy and D. S. Sharada, *RSC Adv.*, 2020, **10**, 31570–31574; (*g*) M. Bakthadoss, P. V. Kumar and T. T. Reddy, *Eur. J. Org Chem.*, 2017, 4439; (*h*) M. Bakthadoss and T. T. Reddy, *Chem. Sci.*, 2023, **14**, 5880–5886; (*i*) M. Bakthadoss, M. A. Hussain and T. T. Reddy, *Chem. Commun.*, 2023, **59**, 5249–5252; (*j*) S. Arepally, V. N. Babu, M. Bakhadoss and D. S. Sharada, *Org. Lett.*, 2017, **19**, 5014–5017.