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Graphical Abstract`

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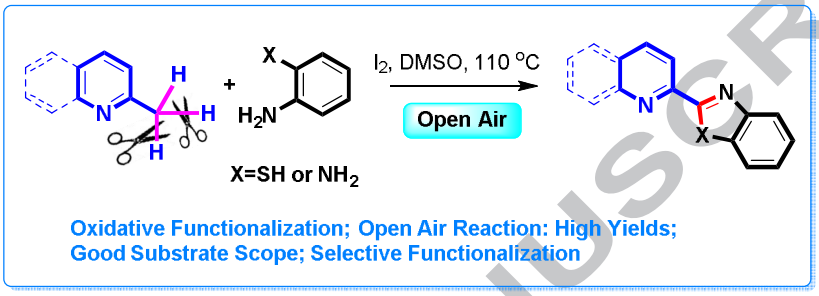

Oxidative Functionalization; Open Air Reaction: High Yields; Good Substrate Scope; Selective Functionalization

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Oxidative C_{sp3}-H Functionalization of 2-Methylazaarenes: A Practical Synthesis of 2-Azaarenyl-benzimidazoles and benzothiazoles

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ABSTRACT

Oxidative C_{sp3}-H functionalization of 2-Methylazaarenes using I_2-DMSO in open flask has been described first time for the synthesis of 2-azaarenyl benzimidazoles and 2-azaarenyl benzothiazoles. Generally, methyl group of 2-methylazaarenes serves as a carbon nucleophile and in this work the methyl group served as electrophilic carbon (Umpolung!) and condensed with o-Phenylenediamine and 2-Aminothiophenol to furnish the corresponding benzimidazoles and benzothiazoles in high yields with good substrate scope and functional group tolerance.

Quinolines are one of the most extensively studied structural motiffs for the drug discovery and hence it is considered as a "privileged structure".[1] Owing to its potential structural features and medicinal importance it is always in high demand to generate quinoline based "new chemical entities" (NCE) to fulfil the pharmaceutical needs. Among the several synthetic methods developed, C_{sp3}-H functionalization of 2-methylazaarenes become more challenging and intriguing technique for the synthetic chemists owing to the large scope of versatile products.[2-4] In most of these methods, methyl group of 2-methylazaarene served as a carbon nucleophile and was added to a suitable electrophile (Figure 1, equation 1).[2] In this context we had contributed three seminal publications for the synthesis of azaarenyl based heterocycles through a C-H functionalization of 2-methylazaarenes.[3] Nevertheless, a limited number of reports are available where the polarity of the methyl group of 2-methylazaarene has been reversed from nucleophilic carbon to electrophilic carbon (probably "umppolung" type) as depicted in the Figure 1, equation 2.[4]

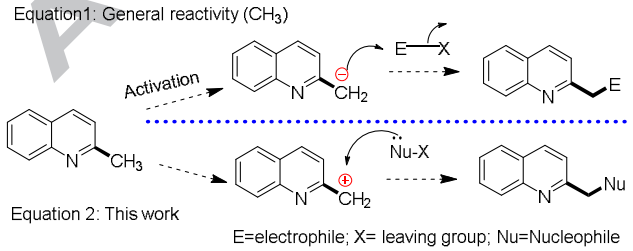
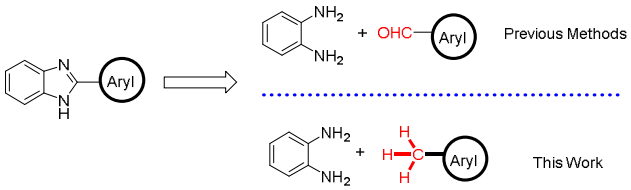


Figure 1. Different modes of C_{sp3}-H functionalization of 2-methylquinoline

For example Li et al reported a copper promoted (CuI, $Cu(OAc)_2$, DMSO, DTBP) oxidative C-H amination for the synthesis of imidazoquinolines,[4a] Yin et al reported another copper catalysed process (CuCl, Ph_2PO_2H, PhCl) for the synthesis of azaarenyl-quinazolinones.[4b] and an iodine catalyzed oxidative benzylic C-H amination of azaarenes for the synthesis of quinazolinones was also reported by Yang et al.[4c]



Scheme 1. Retrosynthetic plan for the 2-aryl (azaarenyl here) benzimidazoles

Benzimidazoles are known to be potential building blocks for the development of medicinally important molecules and especially substituted benzimidazoles have found diverse applications as therapeutic agents, including antiulcers, antihypertensives, antivirals, antifungals, anticancers, and antihistaminics.[5] Most of the synthetic methods will consider a o-Phenylenediamine and aryl aldehyde as starting materials[6] (Scheme 1). Looking at the biological importance of benzimidazoles and quinolones we designed a new synthetic strategy for the hybrid molecule which comprises of these two important scaffolds. When looked into the literature we found that this kind of molecules are known as selective A1 adenosine receptor antagonists with stimulant activity on human colon motility[7] and metal chelating agents to show oligimerization reactivity.[8] Indeed, these methods also involved the condensation of quinaldinaldehyde with diamine

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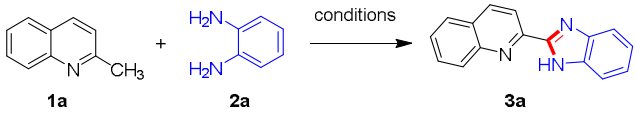
using oxone,[10c] $NaHSO_3$,[10a] Condensation of quinoline-2-carboxylic acid with diamine was reported with PPA[7]. Iron sulfide mediated benzimidazole synthesis was reported with quinaldine.[10b] In continuation of our research interest towards the C-H functionzalization of 2-methyl azaarenes herein we report a iodine catalyzed double oxidative functionalization/condensation cascade for the synthesis of benzimidazol-2-ylazaarenes and benzothiozol-2-ylazaarenes.

Table 1. Optimization of reaction conditions for the synthesis of 2-(1H-benzimidazol-2-yl)quinoline (**3a**) from **1a** and **2a.**[a]



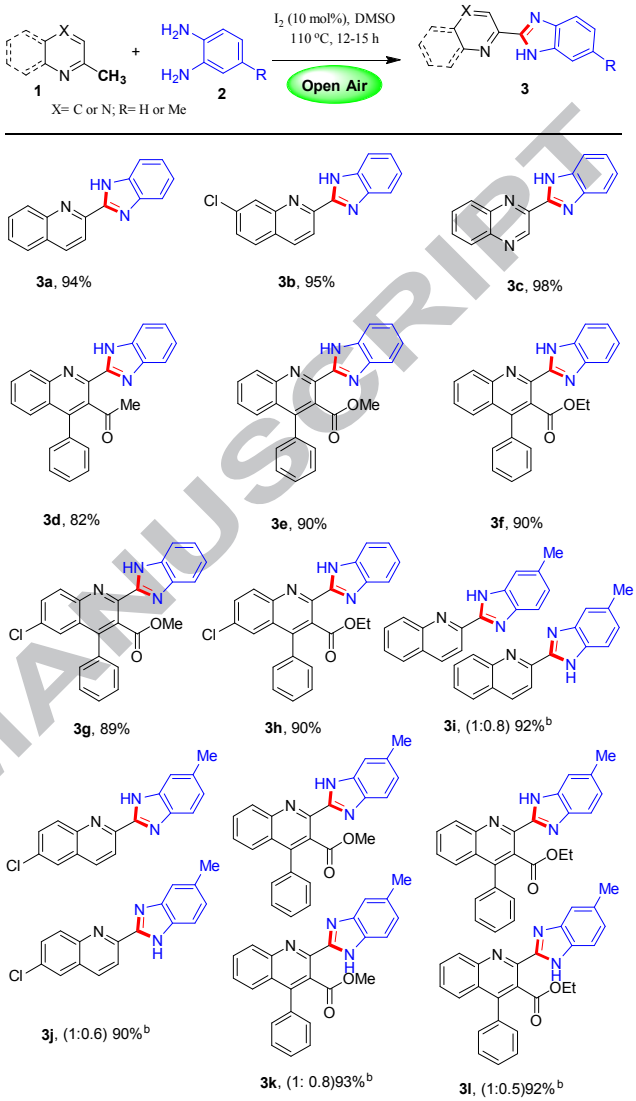
Entry	Reaction conditions[a]	Yield (%)[b]
1	I_2 (100 mol%), NMO (100 mol%)	45
2	I_2 (100 mol%), TBHP (100 mol%)	80
3	I_2 (100 mol%), H_2O_2 (100 mol%)	15
4	I_2 (100 mol%), TEMPO (100 mol%)	35
5	I_2 (100 mol%), Open air	90
6	I_2 (50 mol%), Open air	90
7	I_2 (20 mol%), Open air	93
8	I_2 (10 mol%), Open air	94
9	Open air	no reaction

[a]. **1a** (0.67 mmol.), **2a** (0.84 mmol) in DMSO (0.6 mL) at 110 °C for over night. [b]. Isolated yields reported. NMO:N-Methylmorpholine-N-oxide; TBHP: tert-butyl hydrogenperoxide; TEMPO: 2,2,6,6-tetramenthyl-1-peperidinyloxy.

Inspired by I_2-DMSO catalysed oxidation of active methyl groups,[9] we commenced our initial experiment by treating 2-methylquinoline **1a** (159 mg, 1.2 equiv.) and orthophenylenediamine **2a** (100 mg, 1 equiv.) with molecular iodine (1 equiv.), NMO (1 equiv.) in 0.6 mL DMSO at 110 °C for overnight. Gratifyngly benzimidazol-2ylquinoline **3a** was isolated in 45% (Table 1, entry 1) and confirmed by the spectral data and matched with reported one.[10.] Experiments with other oxidants such as TBHP (entry 2), H_2O_2 (entry 3) and TEMPO (entry 4) could not furnished the satisfactory yield of **3a**. Interestingly the reaction in the open air gave very good yield (90%) of **3a** in the absence of external oxidating agents (Table 1, entry 5). Efforts to minimize the iodine loadings were successful and 10 mol% of I_2 in open air gave excellent yield (94%) of **3a** (entries 6-8, Table 1) and it is worth to mention here that the reaction could not initiated in the absence of iodine (entry 9).

Having established the efficient conditions for the synthesis of **3a** from **1a** and **2a**, we decided to check the scope of our protocol for a large variety of 2-methylazaarenes and the results are summarized in the Table 2. 2-Methyl-7-chloroquinaldine and 2-methyl quinoxaline showed similar reactivity towards **2a** and yielded the respective benzimidazoles **3b** and **3c** in nearly quantitative yields. 2-Methyl, 3-acyl, 4-phenyl quinoline (fully substituted) underwent a smooth chemoselective oxidation (2-methyl verses methyl ketone) to furnish the benzimidazole **3d** in 82% after 12 h. The reaction profile was not found clean enough (on TLC) when left for long time (24 h), probably methyl group of acyl moiety started reacting after longer reaction times. Other fully substituted 2-mentyl quinolines also reacted well to produce the respective condensed products **3e**, **3f** and **3g** in excellent yields (Table 2). In case of 4-methylbenzene-1,2-diamine (**2b**), the reaction proceeded with equal ease however it resulted a mixture of regioisomers **3i**-**3l** in good yields.[11]

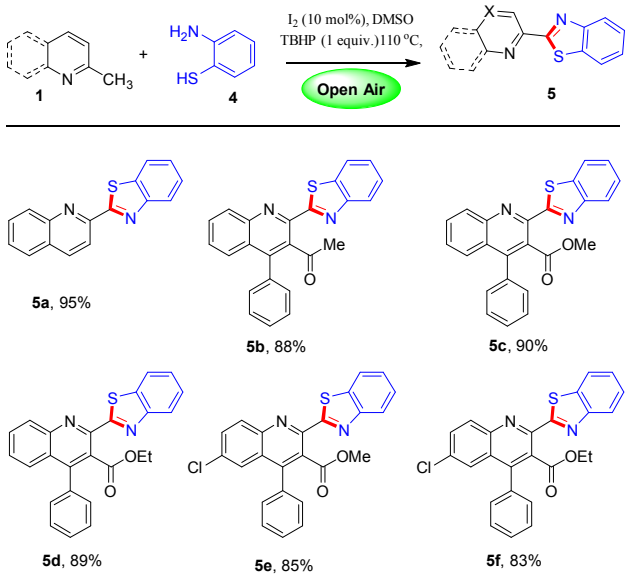
Table 2. Substrate scope in the I_2-DMSO promoted oxidative functionalization of 2-methylazaarenes in the open flask reaction.[a]



[a]. Reaction conditions: **1** (1.0 equiv.), **2** (1.2 equiv.) in DMSO (0.6 mL) at 110 °C for over night. Isolated yields reported. [b]. the regioisomeric ratio was determined by ^{1}H NMR spectra and combined yields are reported.

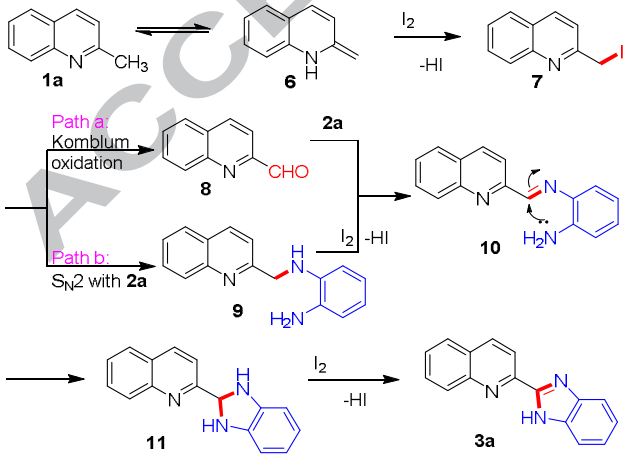
Encouraged by the successful demonstration of cascade oxidative C-H functionalization and bezimidazole formation (Table 2), we were interested to look at the synthesis of a similar bioisosteric heterocyclic compound, benzothiazol-2-ylquinoline **5a** by simply replacing orthophenylenediamine with 2-aminobenzenethiol. When the reaction was performed with 2-methylquinoline **1a** and 2-aminobenzenethiol **4** under standard conditions the expected product **5a** was found in <10% yield. Addition of oxidatng agents such as NMO and TEMPO could increase the yields of **5a** upto 35%. Neverthless addition of TBHP increased the yield of **3a** to almost quantitative (95%). This reaction proceeded with same ease with other substituted 2-methylazaarenes to result the benzothiazoles **5b**-**5f** in excellent yields as depicted in the Table 3.

Table 3. Substrate scope in the I_2-DMSO promoted oxidative functionalization of 2-methylazaarenes for the synthesis benzothiazol-2-ylazaarenes.[a]



[a]. Reaction conditions: **1** (1.0 equiv.), **4** (1.2 equiv.) in DMSO (0.6 mL) at 110 °C for over night. Isolated yields reported.

A plausible mechanism for the cascade C_{sp3}-H functionalization of 2-methylazaarenes and condensation to furnish the benzimidazol-2ylquinolines has been described in the Scheme 2.[12] There exists an equilibrium between quinaldine **1a** and its enamine **6** which then reacts with I_2 to produce the methyl iodide **7**. Iodide **7** will undergo a Komblum oxidation[13] to yield the respective aldehyde **8** which further makes an imine **10**.[14] Alternatively iodide **7** can undergo a nucleophilic substitution reaction (S_N2) with **2a** to furnish the amine **9** which further yields imine **10**. An intramolecular azacyclisation of **10** followed by HI elimination furnish the benzimidazole **3a**. Among the two paths proposed, path a seems to be more predominant as the aldehyde **8** was isolated and confirmed. Though internmediate **9** was not isolated, path b can not be ruled out.[4c] Since at 110 °C, the reaction may be very fast in furnishing the intermediate **9** and an intramolecular cyclisation aromatization is the driving force to form **3a**.



Scheme 2. Plausible mechanism for the I_2-DMSO mediated 2-azaarenyl benzimidazole

In summary, we are successful in demonstrating a simple and open-flask oxidative functionalization (promoted by I_2-DMSO) of 2-methylazaarene to furnish 2-azaarenyl benzimidazoles and benzothiazoles for the first time. The broad substrate scope, functional group tolerance, high yields and open air conditions made this protocol more potential.

All the compounds were characterized by ^{1}H NMR, ^{13}C NMR, Mass and IR.[15]

Acknowledgements

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References

1. (a) Solomn VR, Lee H. *Curr. Med. Chem.* 2011;18:1488; (b) Kumar S, Bawa S, Gupta H. *Mini. Rev. Med. Chem.* 2009;9:1648; (c) Eswaran S, Adhikari A V, Shetty N S. *Eur. J. Med. Chem.* 2009;44: 4637.
2. (a) Muthukumar A, Sekar G, *Org. Biomol. Chem.* 2017;15:691; (b) Mallepalli R, Vennam D K R, Perali R S. *Tetrahedron Lett*. 2016;57: 4541; (c) Jamal Z, Teo Y-C, *RSC Adv.* 2015;5:26949; (d) Hao S.-H, Zhang X.-Y, Dong D-Q, Wang Z-L. *Chinese Chem. Lett.* 2015;26:599; (e) Kumar A, Dutt S, Ratnakar. *Green Chem.* 2015;17: 848; (f) Pi D, Jiang K, Zhou H, Sui Y, Uozumi Y, Zou K. *RSC Adv.* 2014;4:57875; (g) Khorshidi A, Shariati S. *ChemXpress* 2014;4:305; (h) Kumari K, Allam BK, Singh KN. *RSC Adv.* 2014;4:19789; (i) Mulla S A R, Pathan MY, Chavan SS. *RSC Adv.* 2013;3:20281; (j) Raghu M, Rajasekhar M, Chandra OB, Suresh RC, Subba BV. *Tetrahedron Lett.* 2013;54:3503; (k) Vuppalapati, S. V. N.; Lee, Y. R. *Tetrahedron* 2012;68:8286; (l) Niu R, Xiao J, Liang T, Li X. *Org. Lett*. 2012;14:676; (m) Andreassen EJ, Bakke JM. *J. Heterocyclic Chem.* 2006;43:49.
3. (a) Yaragorla S, Dada R, Singh G. *Synlett* 2016;27:912; (b) Yaragorla S, Singh G, Dada R. *Tetrahedron Lett.* 2016;57:591; (c) Yaragorla S, Singh G, Dada R. *Tetrahedron Lett*. 2015;56:5924.
4. (a) Li Z, Wu S-S, Luo Z-G, Liu W-K, Feng C-T, Ma S-T. *J. Org. Chem.* 2016;81:4386; (b) Li Q, Huang Y, Chen T, Zhou Y, Xu Q, Yin S-F, Han L-B. *Org. Lett.* 2014;16:3672; (c) Yang L, Shi X, Hu B-Q, Wang L-X. *Aisan J. Org. Chem.* 2016;5:494 (d) Liu M, Chen T, Zhou Y, Yin S-F. Catal. Sci. Technol. 2016, 6, 5792.
5. (a) Erhardt P W. *J. Med. Chem.* 1987;30:231; (b) Tomczuk BE, Taylor CR Jr. Moses L M, Sutherland D B, Lo Y S, Johnson D N, Kinnier WB, Kilpatrick BF. *J. Med. Chem.* 1991;34:2993; (c) Spasov AA, Yozhitsa IN, Bugaeva LI, Anisimova VA. *Pharm. Chem. J.* 1999;33:232; (d) Preston, PN. *Chem. Heterocycl. Compd.* 1980;40:531; (e) Zimmer C, Wahnert U. *Prog. Biophys. Mol. Biol.* 1986;47:31; (f) Gravatt GL, Baguley BC, Wilson WR. Denny WA. *J. Med. Chem.* 1994;37:4338; (g) Soderlind K-J, Gorodetsky B, Singh AK, Bachur N, Miller GG, Lown JW. *Anti-Cancer Drug Des.* 1999; 14:19; (h) Roth T, Morningstar ML, Boyer PL, Hughes SH, Buckheit RW, Michejda CJ. *J. Med. Chem.* 1997;40:4199.
6. For synthesis see the recent reviews: (a) Alaqeel S I. *J. Saudi. Chem. Soc.* 2016, doi.org/10.1016/j.jscs.2016.08.001; (b) Panda S S, Malik R, Jain S C. *Curr. Org. Chem.* 2012;16:1905
7. Cosimelli B, Taliani S, Greco G, Novellino E, Sala A, Severi E, Settimo F-D, Motta C-L, Pugliesi I, Antonioli L, Fornai M, Colucci R, Blandizzi C, Daniele S, Trincavelli M, Martini C. *Chem. Med. Chem.* 2011;6:1910.
8. (a) Zhang M, Zhang S, Hao P, Jie S, Sun W-H, Li P, Lu X. *Eur. J. Inorg. Chem.* 2007; 3816; (b) Martin D, Rouffet M, Cohen SM. *Inor. Chem.* 2010;49:10226; (c) Wei X, Jiang Y, Cui X, Li Y, Wang H, Qi X. *J. Coordination Chem.* 2015;68:3825.
9. (a) Wu X, Gao Q, Geng X, Zhang J, Wu Y-D, W A-X. *Org. Lett.* 2016;18:2507; (b) Rao NN, Reddy MR, Ramakrishna K, Meshram HM. *Helvetica Chimica Acta* 2014;97:744; (c) Reddy MR, Rao NN, Ramakrishna K, Meshram, HM. *Tetrahedron Lett.* 2014;55:1898; (d)

Zhu Y-P, Liu M-C, Jia F-C, Yuan J-J, Gao Q, Lian M,Wu A. Org. Lett. 2012;14:3392.

10. (a) Hu J, Li J, Qi J, Chen J. *New J. Chem.* 2015;39:843; (b) Nguyen T B, Ermolenko L, Al-Mourabit A. *J. Am. Chem. Soc.* 2013;135:118; (c) Tynebor R, Millings E. *Synthetic Commun*. 2013;43:1902; (c) Hati S, Dutta PK, Dutta S, Munshi P, Sen S. *Org. Lett*. 2016;18:3090.
11. The ratios of the regioisomers is determined based on the ^{1}HNMR spectra.
12. Mechanism proposed based on the previous report. See ref-4c. However intermediate **8** was isolated and confirmed.
13. Kornblum N, Jones W J, Anderson G J. *J. Am. Chem. Soc.* 1959;81: 4113.
14. Aldehyde **8** was isolated and characterized.
15. *General experimental procedure for the synthesis Benzimidazol-2ylquinolines **3**:* A mixture of o-Phenylenediamine **2a** (0.84 mmol), 2-methylazaarene (0.67 mmol) and Iodine (10 mol%) were heated in DMSO (0.6 mL) in open flask at 110 ^{o}C for overnight. After completion of the reaction (monitored by TLC), reaction mixture was diluted with 10 mL aqueous saturated solution of sodium thiosulphate and extracted with dichloromethane (3x15 mL). Combined organic layers were washed with brine solution, dried over anhydrous Na_2SO_4, solvent was removed under reduced pressure and the resultant crude product was purified by silica gel column chromatography using hexane and ethyl acetate (10:1) as eluents to obtain the desired product 3. *General experimental procedure for the synthesis Benzothiazol-2ylquinolines **5**:* A mixture of 2-aminobenzenethiol **4** (0.84 mmol), 2-methylazaarene (0.67 mmol), Iodine (10 mol%) and TBHP (2 equiv.) were heated in DMSO (0.6 mL) in open flask at 110 ^{o}C for overnight. After completion of the reaction (monitored by TLC), reaction mixture was diluted with 10 mL aqueous saturated solution of sodium thiosulphate and extracted with dichloromethane (3x15 mL). Combined organic layers were washed with brine solution, dried over anhydrous Na_2SO_4, solvent was removed under reduced pressure and the resultant crude product was purified by silica gel column chromatography using hexane and ethyl acetate (10:1) as eluents to obtain the desired product 5. Spectral data of selected compounds: *2-(1H-benzo[d]imidazol-2-yl)quinoline* **(3a):**[8c] Yield: 94%; mp 227-229 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.60 (d, *J* = 8.5 Hz, 1H), 8.35 (d, *J* = 8.5 Hz, 1H), 8.13 (d, *J* = 8.5 Hz, 1H), 7.90 (d, *J* = 8 Hz, 2H), 7.78 – 7.75 (m, 1H), 7.62 – 7.59 (m, 1H), 7.46 (s, 1H), 7.34 – 7.32 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 150.9, 148.2, 147.5, 144.5, 137.4, 134.0, 130.2, 129.1, 128.6, 127.9, 127.3, 124.3, 122.8, 120.3, 119.1, 111.3; HRMS (ESI) m/z calcd. for $C_{16}H_{11}N_3$[M+] 245.0953; found 245.0956.; *2-(quinolin-2-yl)benzo[d]thiazole* **(5a):** Yellow solid; mp 198-299 ^{o}C; Yield: 95%; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.39 (d, *J* = 8.5 Hz, 1H), 8.20 (d, *J* = 9 Hz, 1H), 8.10 (d, *J* = 8.5 Hz, 1H), 8.04 (d, *J* = 8 Hz, 1H), 7.89 (d, *J* = 8 Hz, 1H), 7.77 (d, *J* = 8.5 Hz, 1H), 7.67 – 7.35 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 169.9, 154.3, 151.3, 147.9, 137.0, 130.1, 129.8, 129.7, 129.0, 127.7, 127.6, 126.3, 125.9, 123.8, 122.0, 118.3; IR (KBr): 2930, 2853, 2432, 1590, 1421, 1248 cm^{-1}; Mass (m/z): 263.0640; *ethyl 2-(benzo[d]thiazol-2-yl)-4-phenylquinoline-3-carboxylate* **(5d):** Yield: 89%; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.01 (s, 1H), 8.00 – 7.80 (m, 2H), 7.63 – 7.61 (m, 1H), 7.57 – 7.55 (m, 1H), 7.54 – 7.50 (m, 4H), 7.49 – 7.44 (m, 4H), 4.28 (q, *J* = 7 Hz, 2H), 1.16 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 168.0, 167.4, 154.1, 147.4, 147.3, 146.5, 136.3, 134.6, 130.7, 129.8, 128.7, 128.2, 127.3, 126.7 (2C), 126.0 (2C), 125.6, 124.1, 121.8, 61.5, 13.8; IR (KBr): 2945, 2820, 1708, 1590, 1418 cm^{-1}; Mass (m/z): 411.1158.; *ethyl 2-(benzo[d]thiazol-2-yl)-6-chloro-4-phenylquinoline-3-carboxylate* **(5f):** Yield: 83%; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.10 (s, 1H), 7.80 (d, *J* = 8 Hz, 1H), 7.74 - 7.71 (m, 1H), 7.57 – 7.55 (m, 5H), 7.46 – 7.44 (m, 2H), 7.35 – 7.32 (m, 1H), 7.30 -7.27 (m, 1H), 4.33 (q, *J* = 14.5 Hz, 2H), 1.17 (t, *J* = 7 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 167.1, 148.9, 146.6, 145.5, 144.5, 143.9, 133.9, 133.8, 133.5, 131.7, 130.9, 129.5, 129.0, 128.4, 127.7, 127.1, 125.5, 124.5, 122.5. 121.0, 111.1, 61.9, 13.7; IR (KBr): 2980, 2850, 2420, 1698, 1530, 1434, 1205 cm^{-1}; HRMS (ESI) m/z calcd. for $C_{25}H_{17}ClN_2O_2S$ [M+] 444.1356; found 444.1359.

Highlights of the Work

- Oxidative C_{sp3}-H Functionalization of 2-Methylazaarenes using Iodine as catalyst
- First Report for the Synthesis of Benzimidazol-2-ylquinolines and Benzothiazol-2-ylquinolines using this Concept
- Open Air Reaction
- Functional Group Tolerance (-COMe, -CO_2Me, -CO_2Et, -Cl)
- High Yields and broad Substrate Scope