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DOI: 10.1039/C4OB02224F

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ARTICLE

Synthesis of 4-substituted oxazolo[4,5-*c*]quinolines by direct reaction at C-4 position of oxazole

Cite this: DOI: 10.1039/xoxxoooooox

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Received ooth January 2012,
Accepted ooth January 2012

DOI: 10.1039/xoxxoooooox

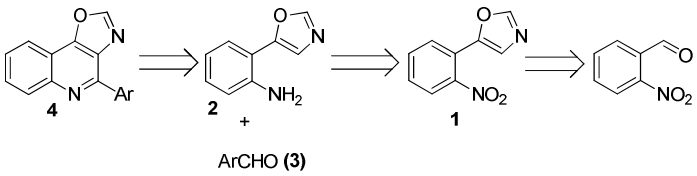
www.rsc.org/

A facile synthesis of 4-aryl substituted oxazolo[4,5-*c*]quinolines has been described via modified Pictet-Spengler method and using $Cu(TFA)_2$ as a catalyst. The developed methodology directly functionalizes C-4 position of oxazoles without the aid of any prefunctionalization, in presence of more reactive C-2 position in good yields. The versatility of the established method has been demonstrated by its application in the synthesis of 4-substituted oxazolo-[1, 8]naphthyridine ring systems.

Introduction

Oxazoles and fused-oxazoles are found in many bioactive natural products.[1] These heterocycles play an important role in medicinal chemistry as anti-tubercular, antibacterial, TRPV1 antagonist and DNA intercalating agents.[2-5] Substituted oxazoles have also been used as fluorescent organic materials.[6] These properties of oxazole derivatives have made them an attractive target for synthetic chemists.

Recently, we have reported the synthesis pyrrolo-quinoline compounds as anti-tubercular and selective metal sensors based on modified Pictet-Spengler approach.[7] In continuation of our studies on fused-heterocycles, synthesis of 4-substituted oxazolo[4,5-*c*]quinolines was conceived to further explore their properties. Only few papers pertaining to the synthesis of substituted oxazolo[4,5-*c*]quinoline are reported in the literature.[8] Moreover, these methods are based only on the formation of the oxazole ring in the final step of the sequence, leading to oxazolo[4,5-*c*]quinoline skeleton. However, for our work, we were interested in synthesizing fused-oxazoles with diverse substitution at position 4. Based on our previous experience,[7a] we envisaged the application of modified Pictet-Spengler approach would be appropriate to access 4-substituted oxazolo[4,5-*c*]quinoline **4**. A reterosynthetic analysis of our target structure is depicted in Scheme 1. The oxazolo-quinoline ring **4** can be assembled from oxazole **2** upon C-4 functionalization of the oxazole ring. Intermediate **2** can be synthesized from 2-nitrobenzaldehyde (**1**) in two steps using van Leusen oxazole synthesis.[13]



Scheme 1: Retrosynthetic analysis of 4-substituted oxazolo[4,5-*c*]quinolines

While designing this synthesis we were aware of the synthetic challenge posed by the functionalization of oxazole at C-4 position in presence of more reactive C-2 position. Most literature examples related to C-4 functionalization of oxazole ring are initiated by lithiation, followed by reaction with suitable electrophiles. If both C-2 and C-4 positions are available, lithiation happens at oxazole C-2 position selectively with subsequent equilibration to ring opened lithium enolate.[9] It is the ambident nucleophilicity of ring opened lithium enolate which results in reaction with electrophiles to give C-4 substituted oxazoles at low temperatures. When both C-2 and C-5 positions are blocked, lithiation happens directly on C-4 position.[10] Other known methods for functionalization of C-4 position includes Heck, Negishi, Stille, Sonagashira and Suzuki couplings, which also require prior activation of the aforementioned site.[11] Antilla *et.al*. has reported functionalization of C-4 position *via* C-H activation using $Pd(OAc)_2$ as catalyst.[12] However, in their work the C-4 functionalization was carried out when more reactive C-2 and C-5

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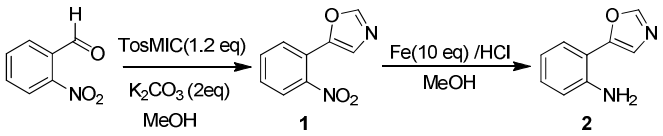
positions were blocked. To the best of our information no method has been reported in the literature demonstrating direct functionalization of C-4 position without aid of any supporting step, when more reactive C-2 position is also available in the molecule. For our work, lithiation or other methods for C-4 activation did not appeared to be viable as side reactions are likely to happen. Therefore we sought to device a methodology to functionalize C-4 position of oxazole leading to fused oxazolo-quinoline ring system (**4**). Herein, we wish to report the synthesis of 4-substituted oxazolo[4,5-*c*]quinolines by direct functionalization of C-4 position of the oxazole ring.

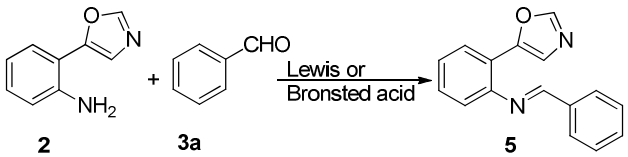
Results and discussions

The synthesis of target molecules **4** commenced with a general synthesis of amino oxazole **2** (Scheme-2). *o*-Nitrobenzaldehyde was converted to 5-(2-nitrophenyl)oxazole **1** in the presence of TosMIC and potassium carbonate in methanol using literature procedure.[13] Subsequently, a Fe mediated reduction of the nitro functionality was carried out to obtain compound **2**.[7a]



Scheme 2: Synthesis of 2-(oxazol-5-yl)aniline (**2**)

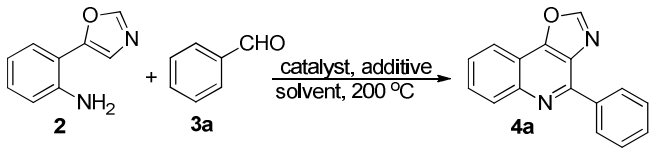
Having accomplished the synthesis of 2-(oxazol-5-yl)aniline **2**, we set out to explore the condensation-cyclization reaction of **2** with various aldehydes, as outlined in the retrosynthetic analysis (Scheme 1). Taking a cue from Pictet-Spengler, initial attempts were carried out in presence of acids (Lewis and Bronsted acids), using 2-(oxazol-5-yl)aniline (**2**) and benzaldehyde (**3a**) as the model reactants. Preliminary investigations were carried out with acetic acid / trifluoroacetic acid / $ZnCl_2$ / $FeCl_3$ / $BF_3.OEt_2$. Inspired from our previous experience with 2-(1*H*-pyrrol-3-yl)aniline,[7a] at first, the reactions were carried out in ethanol as a solvent at 80 ^oC, except for $BF_3.OEt_2$, which was used in solvent THF. However, only the formation aldimine **5** was observed under these conditions (Scheme 3). No further cyclization of imine at C-4 position of oxazole was observed. These results reflect the low reactivity of C-4 position of oxazole towards the desired cyclization. Despite increasing the reaction temperature to 140 ^oC (in xylene), further cyclization of **5** could not be achieved.



Scheme 3: Proposed synthesis of 4-substituted oxazolo[4,5-*c*]quinolines using various Lewis and bronsted acids

Subsequently, we expanded our search of a Lewis acid suitable to catalyse the formation of the oxazolo-quinoline ring. As shown in Table 1, a number of potential transition metal catalysts were screened for the desired transformation to take place. The reaction temperatures were usually kept high due to low reactivity of C-4 position. The reactions were initiated at 150 ^oC using hexamethyl phosphoramide (HMPA) as solvent and monitored by TLC. Failure to see any conversion from aldimine to the desired compound prompted us to increase the temperature further to 200 ^oC. Gratifyingly, the increase in temperature did result in the formation of desired product in case of $Cu(TFA)_2$, $Cu(acac)_2$ and $Cu(OAc)_2$. The best yields were obtained using $Cu(TFA)_2$. Because the role of nitrobenzene is also well documented as an oxidizing agent in Skraup synthesis of quinoline,[14] we thought its use might lead to improved yields of **4**. Additional solvents, such as ethylene glycol and nitrobenzene were screened for further improvement in the yields. Indeed, better yields of **4** were obtained in nitrobenzene compared to HMPA (Table 1, Entry 11). Furthermore, additives such as 1, 10-phenanthroline known to facilitate reactions catalyzed by $Cu(TFA)_2$ were utilized.[15] The reactions were then carried out in the presence of $Cu(TFA)_2$ with 1, 10-phenathroline as additive in various combinations (Table 1, entries 13-16). Thus, after a thorough screening, best results were obtained with the use of 30 mol% of both $Cu(TFA)_2$ and 1, 10-phenathroline in nitrobenzene at 200 ^oC.

Table 1: Screening of catalysts for synthesis of quinoline ring



Entry	Catalyst (mol %)/ Additive(mol%)	Solvent	Yield
1	$Cu(TFA)_2$ (20)	HMPA	25
2	$Pd(OAc)_2$ (20)	HMPA	0
3	$Pd(TFA)_2$ (20)	HMPA	0
4	$Yb(OTf)_3$ (20)	HMPA	0
5	$Cu(acac)_2$ (20)	HMPA	22
6	CuI (20)	HMPA	0
7	$Cu(OAc)_2$ (20)	HMPA	10
8	$Fe(acac)_2$ (20)	HMPA	0
9	$Cu(TFA)_2$ (10)	HMPA	7
10	$Cu(TFA)_2$ (20)	ethylene glycol	4
11	$Cu(TFA)_2$ (20)	nitrobenzene	38
12	$Cu(TFA)_2$ (30)	nitrobenzene	46
13	$Cu(TFA)_2$ (20)/1,10 phenanthroline (20)	nitrobenzene	48
14	$Cu(TFA)_2$ (30)/ 1,10 phenanthroline (30)	nitrobenzene	61
15	$Cu(TFA)_2$ (40)/ 1,10 phenanthroline (40)	nitrobenzene	42
16	$Cu(TFA)_2$ (30)/ 1,10 phenanthroline (30)	nitrobenzene	46

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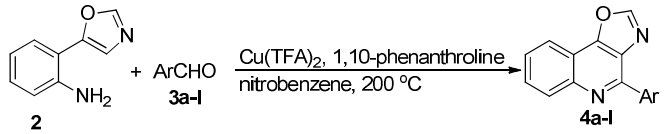
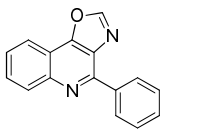
After having the optimized conditions for the formation of oxazolo[4,5-*c*]quinoline in hand, we set out to demonstrate the substrate scope of the newly developed methodology. As listed in Table 2, wide array of aromatic aldehydes were examined in the synthesis of oxazolo-quinoline **4a-l**. In general, aldehydes possessing electron donating groups (such as -OMe, -OH) resulted in good yields of the corresponding fused-oxazole products. On the other hand, substrates with electron-withdrawing substitutions (e.g. CF_3, -NO_2) yielded the cyclized products in moderate yields. Interestingly, the yields in the cases of halo-substituted reactants were found to be effected by the electronegativity of the halogens. Improved yield was obtained using bromobenzaldehyde, whereas, the yield was compromised in the case of fluorobenzaldehyde. Remarkably, the use of thiophenecarboxaldehyde in place of benzaldehyde also resulted in the corresponding quinoline substituted product **4d** in moderate yields under the optimized conditions. Reactions were also attempted with aliphatic aldehydes but no product formation was observed.

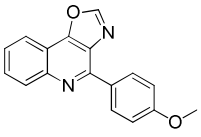
Table 2: Synthesis of various 4-substituted oxazolo[4,5-*c*]quinolines[a]



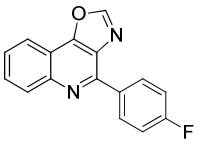
2 4a-l



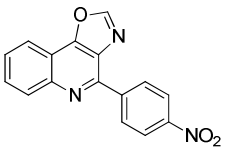
4a (61%)



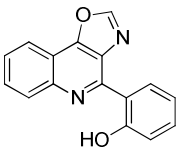
4e (70%)



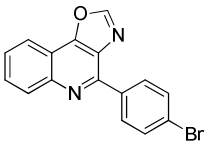
4i (44%)



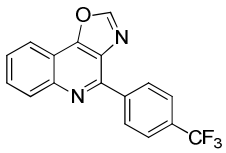
4b (41%)



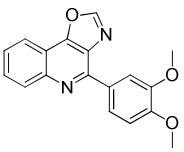
4f (77%)



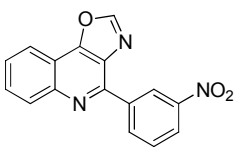
4j (61%)



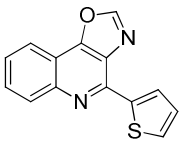
4c (43%)



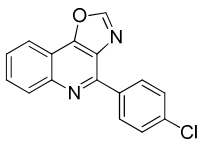
4g (60%)



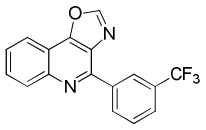
4k (46%)



4d (42%)



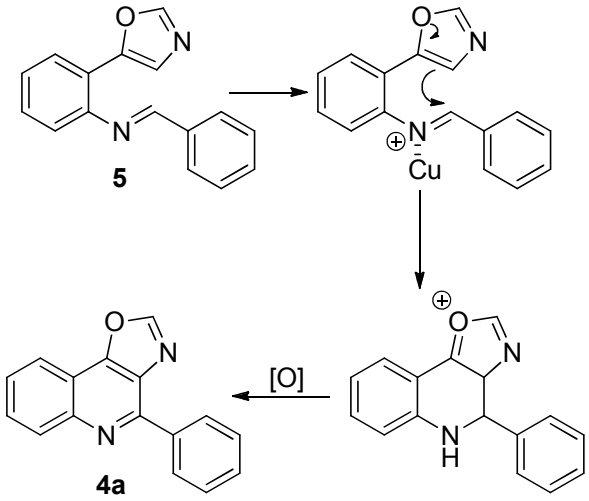
4h (55%)



4l (40%)

[a]Reaction condition: 1.25 mmol of **2**, 1.25 mmol of aldehyde, $Cu(OCOCF_3)_2$(30 mol%), 1,10-phenathroline(30 mol%) and nitrobenzene(1ml).

Based on the above observations a plausible mechanism for the formation of oxazolo[3,2-*c*]quinoline systems is proposed (Scheme-4). It is assumed that $Cu(TFA)_2$ forms complex with the imine nitrogen which is followed by attack of oxazole C-4 on imine carbon. The resulting cyclic intermediate then undergoes aromatization to a more stable fused oxazolo-quinoline system. Higher yields of **4** with electron rich aldehydes further support the proposed mechanism. However, given the low reactivity of oxazole C-4 position there is also a possibility of involvement of C-H activation. A detailed investigation is required in future to fully understand the mechanism involved.



Scheme 4: Initial attempt to synthesize 4-substituted oxazolo[4,5-*c*]quinolines using various Lewis and bronsted acids

Next, in order to further demonstrate the synthetic utility of the developed methodology we attempted the synthesis of fused oxazolo-[1,8]-naphthyridine system. We began with the conversion of commercially available 2-amino-3-formylpyridine to 3-(oxazol-5-yl)pyridine-2-amine **(6)** by reaction under basic condition with TosMIC. To our delight, the amine **6** reacted with aromatic aldehydes analogous to 2-(oxazol-5-yl)aniline (**2**), resulting in the formation of 4-aryl substituted oxazolo[4,5-*c*][1,8]naphthyridine (7a-d; Table 3) in good yields.

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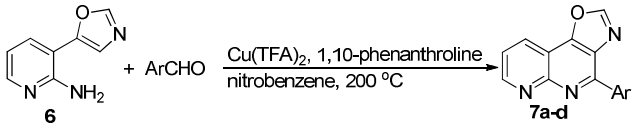
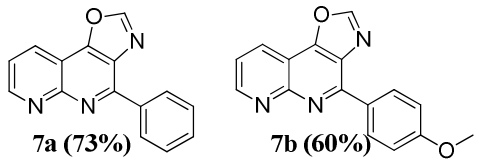
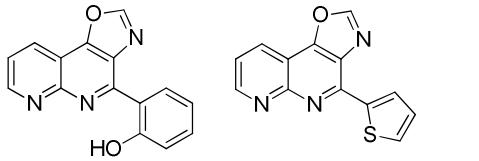
Table 3: Synthesis of various 4-aryl substituted oxazolo[4,5-*c*][1,8]naphthyridines[a]







[a]Reaction condition: 1.25 mmol of **6**, 1.25 mmol of aldehyde, $Cu(OCOCF_3)_2$(30 mol%), 1,10-phenathroline(30 mol%) and nitrobenzene(1ml).

Conclusions

In conclusion, we have developed a $Cu(TFA)_2$-catalyzed synthesis of substituted oxazolo[4,5-*c*]quinoline from 2-(oxazol-5-yl)aniline with various aldehydes via modified Pictet-Spengler reaction. In the course of this synthesis we have also demonstrated, for the first time, a method that does not require any prefunctionalization of unreactive C-4 position of oxazole. The developed methodology is amenable to a wide range of functional groups and allows the formation of fused oxazolo-quinoline/oxazolo-1,8-naphthyridine systems in good to moderate yields. Since many natural products containing oxazole are C-4 substituted, the method developed in this paper will open up the possibility of synthesizing these molecules without aid of any additional activation or prefunctionalization step.

Experimental

All starting materials were purchased from Spectrochem, SRL, Aldrich, and Sd Fine(India) and used directly without further purification. Solvents were dried using standard methods and distilled before use. Melting points were recorded on a Stuart SMP 30 melting point apparatus and are uncorrected. ^{1}H NMR (300 MHz) and ^{13}C (75 MHz) spectra were recorded in $CDCl_3$ and DMSO using $(CH_3)_4Si$ as internal standard. IR spectra were recorded as KBr plates on Jasco FT/IR-4200 instrument. High resolution mass spectra were obtained at the Department of Chemistry, Dalhousie University, Canada, by Mr. Xiao Feng.

General procedure for the preparation of 4-substituted oxazolo[4, 5-*c*]quinolones/[1, 8]naphthyridines

2-(oxazol-5-yl)aniline or 3-(oxazol-5-yl)pyridin-2-amine (1.25 mmol), aldehyde(1.25 mmol), $Cu(OCOCF_3)_2$(30 mol%), 1,10-phenathroline(30 mol%) and nitrobenzene(1ml) were added in a 25 ml round bottam flask under nitrogen atmosphere. The reaction mixture was heated at 200 ^{0}C for 8h and then cooled to room temperature. The reaction mixture was diluted with EtOAc (5mL) adsorbed on silica gel and purified by a column chromatography on silica gel using hexane/ethyl acetate or hexane/Et_2O as the eluent to give the corresponding product.

4-Phenyloxazolo[4,5-*c*]quinoline (4a): Yield: 61%. Light yellow solid, m.p. 134-138 ^{o}C; R_f 0.5 [hexane-Et_2O (9:1)]; ν_{max} (KBr)/cm^{-1} 3068, 1507, 1049; ^{1}H NMR (300 MHz, DMSO) δ 7.58 (d, *J* = 7.4 Hz, 3H), 7.72 (d, *J* = 6.6 Hz, 1H), 7.80 (d, *J* = 7.2 Hz, 1H), 8.20 (d, *J* = 5.5 Hz, 2H), 8.69 (d, *J* = 5.6 Hz, 2H), 9.09 (d, *J* = 3.7 Hz, 1H); ^{13}C NMR (75 MHz, DMSO) δ 115.62, 120.60, 127.93, 128.99, 129.47, 130.04, 130.63, 131.86, 136.80, 145.38, 149.85, 152.20, 154.23; HRMS-ESI (m/z): Calcd for $C_{16}H_{11}N_2O$ $[M+H]^+$ 247.0871, found 247.0865.

4-(4-Nitrophenyl)oxazolo[4,5-*c*]quinoline (4b): Yield: 41%. Yellow solid, m.p. 184-186 ^{o}C; R_f 0.5 [hexane-EtOAc (8:2)]; ν_{max} (KBr)/cm^{-1} 3067, 1515, 1350, 1065; ^{1}H NMR (300 MHz, DMSO) δ 7.84 (t, *J* = 7.4 Hz, 1H), 7.92 (t, *J* = 7.7 Hz, 1H), 8.32 (t, *J* = 7.9 Hz, 2H), 8.48 (d, *J* = 8.7 Hz, 2H), 8.99 (d, *J* = 8.6 Hz, 2H), 9.22 (s, 1H); ^{13}C NMR (75 MHz, DMSO) δ 115.96, 120.79, 124.24, 128.95, 130.33, 130.42, 130.51, 132.18, 142.51, 145.31, 147.21, 148.60, 152.51, 154.79; HRMS-ESI (m/z): Calcd for $C_{16}H_{10}N_3O_3$ $[M+H]^+$ 292.0722, found 292.0704.

4-(4-(Trifluoromethyl)phenyl)oxazolo[4,5-*c*]quinoline (4c): Yield: 43%. Light yellow solid, m.p. 122-126 ^{o}C; R_f 0.5 [hexane-Et_2O (8:2)]; ^{1}H NMR (300 MHz, DMSO) δ 7.89 – 7.64 (m, 2H), 7.93 (d, *J* = 7.5 Hz, 2H), 8.21 (d, *J* = 6.0 Hz, 2H), 8.85 (d, *J* = 7.4 Hz, 2H), δ 9.12 (s, 1H); ^{13}C NMR (75 MHz, DMSO) δ 115.83, 120.69, 125.85, 125.88, 125.93, 128.58, 129.97, 130.20, 130.32, 131.98, 140.38, 145.26, 147.96, 152.37, 154.57; HRMS-ESI (m/z): Calcd for $C_{17}H_{10}F_3N_2O$ $[M+H]^+$ 315.0745, found 315.0733.

4-(Thiophen-2-yl)oxazolo[4,5-*c*]quinoline (4d): Yield: 42%. Light brown solid, m.p. 178-182 ^{o}C; R_f 0.4 [hexane-EtOAc (9:1)]; ν_{max} (KBr)/cm^{-1} 3090, 1521, 1053; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28 (t, *J* = 4.2 Hz, 1H), 7.62 (dd, *J* = 15.2, 6.4 Hz, 2H), 7.76 (t, *J* = 7.3 Hz, 1H), 8.18 (d, *J* = 8.0 Hz, 1H), 8.26 (d, *J* = 8.0 Hz, 1H), 8.33 (s, 1H), 8.69 (d, *J* = 2.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 115.65, 120.18, 126.83, 128.52, 129.53, 129.58, 131.02, 141.65, 145.81, 146.20, 151.64, 152.21; HRMS-ESI (m/z): Calcd for $C_{14}H_9N_2OS$ $[M+H]^+$ 253.0436, found 253.0428.

4-(4-Methoxyphenyl)oxazolo[4,5-*c*]quinoline (4e): Yield: 70%. Light yellow solid, m.p. 108 ^{o}C. R_f 0.45 [hexane-EtOAc (9:1)]; ν_{max} (KBr)/cm^{-1} 2934, 1507, 1030; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.93 (s, 2H), 7.12 (d, *J* = 8.7 Hz, 1H), 7.64 (t, *J* = 7.5 Hz, 1H), 7.78 (t, *J* = 7.7 Hz, 1H), 8.21 (d, *J* = 8.1 Hz, 1H), 8.30 (d, *J* = 9.8 Hz, 1H), 8.74 (d, *J* = 8.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.42, 114.05, 115.55, 120.16, 126.68, 129.37, 129.57, 129.87, 131.00, 131.67,

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145.90, 150.67, 151.28, 152.45, 161.31; HRMS-ESI (m/z): Calcd for $C_{17}H_{13}N_2O_2$ $[M+H]^+$ 277.0977, found 277.0976.

2-(Oxazolo[4,5-*c*]quinolin-4-yl)phenol (4f): Yield: 77%. Yellow solid, m.p. 164-168 °C; R_f 0.5 [hexane-EtOAc(7:3)]; ν_{max} (KBr)/cm^{-1} 3123, 2701, 1513, 1302; ^{1}H NMR (300 MHz, DMSO) δ 6.96 (t, *J* = 7.7 Hz, 2H), 7.38 (t, *J* = 7.5 Hz, 1H), 7.69 (t, *J* = 7.5 Hz, 1H), 7.79 (t, *J* = 7.5 Hz, 1H), 8.05 (d, *J* = 8.3 Hz, 1H), 8.15 (d, *J* = 8.0 Hz, 1H), 9.12 (s, 1H), 9.20 (d, *J* = 7.9 Hz, 1H), 14.91 (s, 1H); ^{13}C NMR (75 MHz, DMSO) δ 115.19, 118.10, 118.16, 119.03, 120.69, 127.71, 128.23, 130.87, 131.31, 132.99, 142.20, 151.65, 152.42, 154.38, 160.98; HRMS-ESI (m/z): Calcd for $C_{16}H_{11}N_2O_2$ $[M+H]^+$ 263.0821, found 263.0809.

4-(3,4-Dimethoxyphenyl)oxazolo[4,5-*c*]quinoline (4g): Yield: 60%. Light brown solid, m.p. 138 °C; R_f 0.5[hexane-EtOAc (8:2)]; ν_{max} (KBr)/cm^{-1} 3070, 3007, 1591, 1512, 1268, 1146; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.00 (s,3H), 4.09 (s,3H), 7.08 (d, *J* = 8.5 Hz, 1H), 7.64 (t, *J* = 7.5 Hz, 1H), 7.78 (t, *J* = 7.7 Hz, 1H), 8.20 (d, *J* = 8.1 Hz, 1H), 8.31 (t, *J* = 4.1 Hz, 2H), 8.48 (d, *J* = 8.4 Hz, 1H), 8.37 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.9, 56.0, 110.8, 111.7, 115.5, 120.1, 123.1, 126.7, 129.3, 129.8, 131.7, 145.8, 149.0, 150.4, 150.8, 151.2, 152.4; HRMS-ESI (m/z): Calcd for $C_{18}H_{15}N_2O_3$ $[M+H]^+$ 307.1083, found 307.1072.

4-(4-Chlorophenyl)oxazolo[4,5-*c*]quinoline (4h): Yield: 55%. Light yellow solid, m.p. 182 °C; R_f 0.5[hexane-EtOAc (9:1)]; ν_{max} (KBr)/cm^{-1} 2925, 1509, 1181, 1065; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55 (d, *J* = 8.5 Hz, 2H), 7.65 (t, *J* = 7.5 Hz, 1H), 7.78 (t, *J* = 7.7 Hz, 1H), 8.19 (d, *J* = 8.1 Hz, 1H), 8.27 (d, *J* = 10.1 Hz, 2H), 8.70 (d, *J* = 8.5 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 115.74, 120.17, 127.26, 128.81, 129.51, 130.09, 130.68, 131.72, 135.26, 136.26, 145.76, 149.46, 151.42, 152.49; HRMS-ESI (m/z): Calcd for $C_{16}H_{10}ClN_2O$ $[M+H]^+$ 281.0482, found 281.0467.

4-(4-Fluorophenyl)oxazolo[4,5-*c*]quinoline (4i): Yield: 44% . Light yellow solid, m.p. 158-162 °C; R_f 0.6 [hexane-Et_2O (9:1)]; ν_{max} (KBr)/cm^{-1} 3076, 1507, 1228, 1067; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27 (d, *J* = 17.2 Hz, 2H), 7.65 (t, *J* = 7.5 Hz, 1H), 7.78 (t, *J* = 7.7 Hz, 1H), 8.19 (d, *J* = 8.1 Hz, 1H), 8.28 (d, *J* = 8.5 Hz, 2H), 8.80 – 8.71 (m, 2H);^{13}C NMR (75 MHz, $CDCl_3$) δ 115.47, 115.65, 115.76, 120.17, 127.13, 129.51, 129.97, 131.42, 131.54, 131.66, 132.93, 132.97, 145.72, 149.70, 151.44, 152.50, 162.50, 165.82; HRMS-ESI (m/z): Calcd for $C_{16}H_{10}FN_2O$ $[M+H]^+$, 265.0777 found 265.0781.

4-(4-Bromophenyl)oxazolo[4,5-*c*]quinoline (4j): Yield: 61%. Light yellow solid, m.p. 170-175 °C; R_f 0.5[hexane-EtOAc(9:1)]; ν_{max} (KBr)/cm^{-1} 2928, 1514,1064; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.66 (d, *J* = 7.2 Hz, 1H), 7.71 (d, *J* = 8.5 Hz, 1H), 7.79 (t, *J* = 7.7 Hz, 1H), 8.21 (d, *J* = 8.1 Hz, 1H), 8.29 (d, *J* = 9.3 Hz, 1H), 8.65 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 115.79, 120.20, 124.84, 127.31, 129.55, 130.11, 130.94, 131.75, 131.78, 135.70, 145.78, 149.56, 151.45, 152.54; HRMS-ESI (m/z): Calcd for $C_{16}H_{10}BrN_2O$ $[M+H]^+$ 324.9977, found 324.9973.

4-(3-Nitrophenyl)oxazolo[4,5-*c*]quinoline (4k): Yield: 46%. Light yellow solid, m.p. 200-202 °C; R_f 0.6[hexane-EtOAc(7:3)]; ν_{max} (KBr)/cm^{-1} 2926, 1524, 1347,1064; ^{1}H NMR (300 MHz, DMSO) δ 7.75 (t, *J* = 7.4 Hz, 1H), 7.83 (t, *J* = 7.8 Hz, 2H), 8.22 – 8.12 (m, 2H), 8.33 (d, *J* = 8.0 Hz, 1H), 9.06 (d, *J* = 7.7 Hz, 1H), 9.12 (s, 1H), 9.46 (s, 1H);^{13}C NMR (75 MHz, DMSO) δ 115.93, 120.77, 123.68, 125.20, 128.73, 130.20, 130.47, 130.80, 131.87, 135.29, 138.08, 145.20, 148.58, 152.48, 152.50, 152.52, 154.77; HRMS-ESI (m/z): Calcd for $C_{16}H_{10}N_3O_3$ $[M+H]^+$ 292.0722, found 292.0728.

4-(3-(Trifluoromethyl)phenyl)oxazolo[4,5-*c*]quinoline (4l): Yield: 40%. Light yellow solid, m.p. 118-120 °C; R_f 0.5[hexane-Et_2O(9:1)]; ν_{max} (KBr)/cm^{-1} 3117, 2972, 1515, 1320, 1123; ^{1}H NMR (300 MHz, DMSO) δ 7.80 (tt, *J* = 19.3, 7.5 Hz, 5H), 8.19 (d, *J* = 8.2 Hz, 2H), 8.94 (d, *J* = 7.6 Hz, 1H), 9.01 (s, 1H), 9.10 (s, 1H);^{13}C NMR (75 MHz, DMSO) δ 115.75, 120.61, 125.53, 125.58, 125.62, 127.05, 127.08, 127.11, 128.42, 129.61, 130.03, 130.12, 130.23, 131.75, 132.98, 137.50, 145.16, 147.59, 152.31, 154.52; HRMS-ESI (m/z): Calcd for $C_{17}H_{10}F_3N_2O$ $[M+H]^+$ 315.0745, found 315.0747.

4-Phenyloxazolo[4,5-*c*][1,8]naphthyridine (7a): Yield: 73%. Light yellow solid, m.p. 168-170°C; R_f 0.5[hexane-EtOAc(5:5)]; ν_{max} (KBr)/cm^{-1} 2923, 2854, 1488, 1273, 1059; ^{1}H NMR (300 MHz, DMSO) δ 7.60 (s, 3H). 7.78 – 7.70 (m, 1H), 8.72 (t, *J* = 5.9 Hz, 3H), 9.14 (s, 1H), 9.19 (d, *J* = 5.3 Hz, 1H);^{13}C NMR (75 MHz, DMSO) δ 110.83, 123.15, 129.15, 129.76, 130.51, 131.25, 132.37, 132.38, 136.48, 152.03, 152.44, 153.40, 153.77, 155.35; HRMS-ESI (m/z): Calcd for $C_{15}H_{10}N_3O$ $[M+H]^+$ 248.0824, found 248.0812.

4-(4-Methoxyphenyl)oxazolo[4,5-*c*][1,8]naphthyridine (7b): Yield: 60%. Yellow solid, m.p. 156-157 °C. R_f 0.5[hexane-EtOAc(4:6)]; ν_{max} (KBr)/cm^{-1} 2924, 1565, 1459, 1127; ^{1}H NMR (300 MHz, DMSO) δ 3.87 (s, 3H), 7.15 (d, *J* = 8.2 Hz, 3H), 7.67 (s, 1H), 8.19 (d, *J* = 8.1 Hz, 1H), 8.88 – 8.58 (m, 2H), 9.19 – 8.99 (m, 1H); ^{13}C NMR (75 MHz, DMSO) δ 55.33, 110.02, 114.06, 122.13, 128.55, 129.88, 130.95, 131.47, 151.19, 151.79, 153.01, 153.07, 154.61, 161.42; HRMS-ESI (m/z): Calcd for $C_{16}H_{12}N_3O_2$ $[M+H]^+$ 278.0930, found 278.0918.

2-(Oxazolo[4,5-*c*][1,8]naphthyridin-4-yl)phenol (7c): Yield: 61%. Yellow solid, m.p. 170 °C; R_f 0.5[hexane-EtOAc (4:6)]; ν_{max} (KBr)/cm^{-1} 3092, 2931, 1502, 1263; ^{1}H NMR (300 MHz, DMSO) δ 7.00 (t, *J* = 6.6 Hz, 2H), 7.43 (t, *J* = 7.5 Hz, 1H), 7.75 (dd, *J* = 7.8, 4.2 Hz, 1H), 8.69 (d, *J* = 8.1 Hz, 1H), 9.08 (d, *J* = 3.4 Hz, 1H), 9.24 (d, *J* = 9.2 Hz, 2H), 15.25 (s, 1H); ^{13}C NMR (75 MHz, DMSO) δ 110.56, 117.71, 118.46, 119.17, 123.52, 130.53, 131.39, 131.57, 133.77, 150.69, 152.62, 153.46, 154.22, 155.46, 161.59; HRMS-ESI (m/z): Calcd for $C_{15}H_{10}N_3O_2$ $[M+H]^+$ 264.0773, found 264.0761.

4-(Thiophen-2-yl)oxazolo[4,5-*c*][1,8]naphthyridine (7d): Yield: 55%. Yellow solid, m.p. 154-158 °C; R_f 0.5[hexane-EtOAc (6:4)]; ν_{max} (KBr)/cm^{-1} 2925, 1498, 1278, 1065; ^{1}H NMR (300 MHz, DMSO) δ 7.36 – 7.30 (m, 1H), 7.70 (dd, *J* = 8.0, 4.3 Hz, 1H), 7.92 (d, *J* = 4.9 Hz, 1H), 8.72 – 8.59 (m, 3H), 9.10 – 9.06 (m, 1H), 9.20 (s, 1H); ^{13}C NMR (75 MHz, DMSO) δ 110.83, 122.76, 129.47, 130.51, 130.84, 132.18, 132.33, 141.47, 147.63, 152.10, 153.48, 153.72, 155.76; HRMS-ESI

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DOI: 10.1039/C4OB02224F
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(m/z): Calcd for $C_{13}H_8N_3OS$ $[M+H]^+$ 254.0388, found 254.0383.

Acknowledgements

M.A. thanks University Grants Commission (India) for SRF. A.B. thanks Department of Science and Technology, Government of India for the fast-track grant.

Notes and references

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