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$Cu(OTf)_2$-triggered benzotriazole ring cleavage (BtRC) approach for the synthesis of 2-aryl/alkyl benzoxazoles from *N*-acylbenzotriazoles

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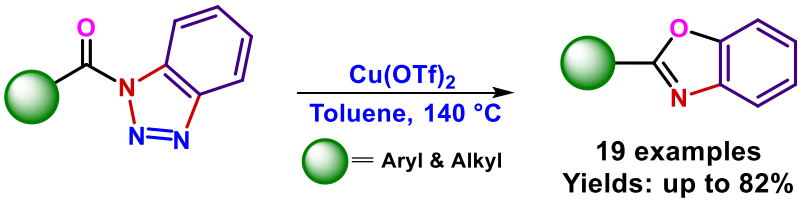
Received 08-24-2024 **Accepted** 11-19-2024 **Published on line** 11-24-2024

Abstract

$Cu(OTf)_2$ is introduced as a novel reagent for the benzotriazole ring cleavage (BtRC) of *N*-acylbenzotriazoles (RCOBt), followed by cyclization to the corresponding benzoxazoles. This method exhibits unprecedented efficiency, achieving high yields across a broad substrate scope, including aryl and alkyl derivatives, and is scalable from milligram to gram quantities.



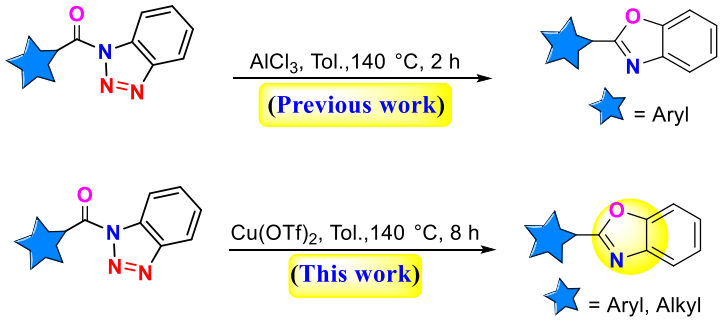
Keywords: benzotriazole, benzoxazole, cyclization, ring cleavage

Introduction

Benzotriazole is among the most versatile and widely used synthetic auxiliaries in organic chemistry. It activates attached groups through various mechanisms, including proton activation, cation stabilization, functioning as a good leaving group, and serving as a precursor for anions or radicals. Over the past four decades, benzotriazole-based methodologies have enabled efficient and cost-effective syntheses of diverse molecular targets, including biologically and medicinally significant compounds.[1-3]

Benzo-fused azoles are a notable class of compounds that can be synthesized using the Benzotriazole Ring Cleavage (BtRC) approach. This method employs mechanisms such as the Dimroth rearrangement, thermolysis, photolysis, reagent-supported ring opening, or radical pathways.[4-20] Among these, benzoxazoles are particularly significant due to their extensive biological activities, pharmaceutical relevance, and industrial as well as analytical applications.[21-28] Benzoxazoles serve as the structural core of numerous natural products and synthetic compounds with remarkable biological properties. These include HIV reverse transcriptase inhibitors (*e.g.*, L-697,661), anti-mycobacterial agents (*e.g.*, pseudopteroxazole, UK-1, AJI9561), estrogen receptor-β agonists (*e.g.*, ERB-041), anticancer agents (*e.g.*, NSC-693638), and selective peroxisome proliferator-activated receptor γ antagonists (*e.g.*, JTP-426467). A prominent example is Tafamidis meglumine, a SCRIPPS/Pfizer-developed transthyretin amyloid inhibitor and FDA-approved drug for the treatment of neurodegenerative disorders.[29,30]

In our previous work, we explored the use of BtRC methodology for synthesizing 2-arylbenzoxazoles from *N*-acylbenzotriazoles using $AlCl_3$ as the ring-cleaving agent.[31] While this protocol achieved good yields for aryl-substituted substrates, it was ineffective for benzotriazoles with aliphatic substitutions. To address this limitation, we sought a reagent capable of synthesizing both 2-aryl- and 2-alkylbenzoxazoles from *N*-acyl-benzotriazoles with comparable efficiency and yields. Herein, we present the results of this endeavour, representing a significant advancement of our earlier work.

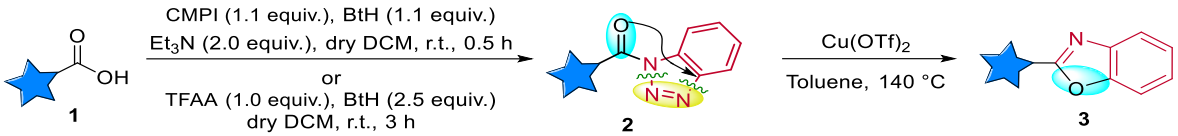


Scheme 1. Comparison of Benzotriazole ring cleavage (BtRC) processes.

Results and Discussion

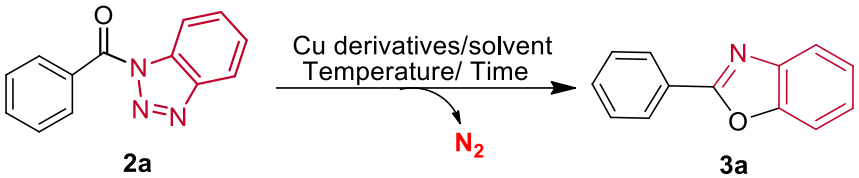
With the motive to find a suitable reagent for the synthesis of both 2-aryl- and 2-alkylbenzoxazole from corresponding *N*-acylbenzotriazoles by ring cleavage strategy, our approach began with the synthesis of our starting material, *i.e.*, *N*-acylbenzotriazoles **2** from corresponding carboxylic acids **1** by reaction with 1*H*-benzotriazole employing two standard protocols, *i.e.*, in presence of either CMPI/Et_3N or TFAA.[32,33] On the basis of previous reports suggesting the use of $Cu(OTf)_2$ as suitable reagent for Diels Alder, Friedel–Crafts

reaction and in nitriles mediated synthesis of benzoxazole[34-37] work resulting *N*-acylbenzotriazoles **2** were subjected to ring cleavage, by employing 1 equiv. of $Cu(OTf)_2$ at 140 °C which produced benzoxazole derivative **3** (Scheme 2).



Scheme 2. Schematic of investigation to obtain benzoxazole **3**.

Table 1. Optimization with (1*H*-benzo[*d*][1,2,3]triazol-1-yl)(phenyl)methanone



Entry[a]	Reagent (equiv.)	Time (h)	Solvent	Temp (°C)	Yield[b] (%)
1	CuO (1)	12	Toluene	140	0
2	CuI (1)	12	Toluene	140	0
3	CuBr (1)	12	Toluene	140	0
4	CuCl (1)	12	Toluene	140	0
5	$Cu(OAc)_2$ (1)	12	Toluene	140	0
6	Cu (1)	12	Toluene	140	0
7	$Cu(OTf)_2$ (1)	12	Toluene	140	75
8	$Cu(OTf)_2$ (0.6)	12	Toluene	140	76
9	$Cu(OTf)_2$ (0.4)	12	Toluene	140	76
10	$Cu(OTf)_2$ (0.2)	12	Toluene	140	56
11	$Cu(OTf)_2$ (0.4)	12	Benzene	140	63
12	$Cu(OTf)_2$ (0.4)	12	DMF	140	0
13	$Cu(OTf)_2$ (0.4)	12	DCM	45	0
14	$Cu(OTf)_2$ (0.4)	12	THF	70	0
15	$Cu(OTf)_2$ (0.4)	12	NMP	140	0
16	$Cu(OTf)_2$ (0.4)	12	Diphenyl ether	140	20
17	$Cu(OTf)_2$ (0.4)	12	DMSO	140	0
18	$Cu(OTf)_2$ (0.4)	12	Toluene	120	10
19	$Cu(OTf)_2$ (0.4)	12	Toluene	100	0
20	$Cu(OTf)_2$ (0.4)	2	Toluene	140	40
21	$Cu(OTf)_2$ (0.4)	4	Toluene	140	50
22	$Cu(OTf)_2$ (0.4)	8	Toluene	140	76

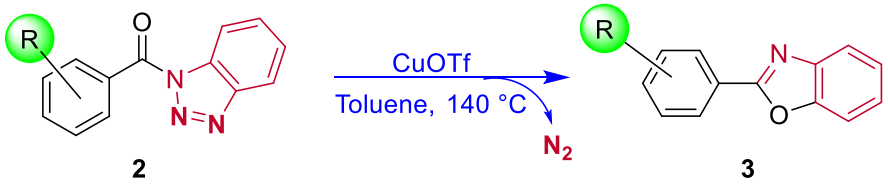
[a] Reaction carried out at higher temperature in a sealed tube under argon. [b] Yields reported after column chromatography (SiO_2).

For optimization of the reaction with respect to reagent, solvent, and temperature, a series of reactions were carried out by taking compound **2a** as starting material and varying the Cu-reagents, solvents and temperature to afford benzoxazole **3a** (Table 1).

In our experimental results, high boiling point aprotic non-polar solvents, such as, toluene and benzene, were most suitable for the reaction (Table 1, entries 7-11). The reaction gave best yields at 140 °C (Table 1, entry 17), but hardly proceeded at temperatures below 120 °C (Table1, entries 18 & 19). Among various copper compounds only $Cu(OTf)_2$ could assist the reaction (Table 1, entries 1-6) and only 0.4 equivalent of $Cu(OTf)_2$ produced a maximum yield (76%) in anhydrous toluene under inert atmosphere condition in 8 h reaction time.

The optimized reaction conditions were applied for the BtRC reaction of a wide range of aryl/alkyl group containing *N*-acylbenzotriazoles to produce corresponding 2-aryl/alkyl benzoxazoles in good yields (Table 2).

Table 2. Synthesis of benzoxazoles **3** from corresponding *N*-acylbenzotriazoles **2**



2 **3**

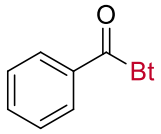
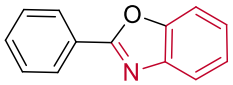
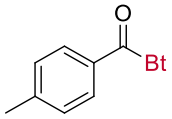
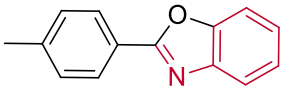
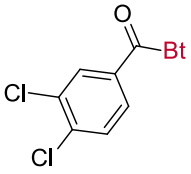
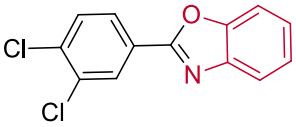
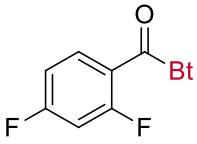
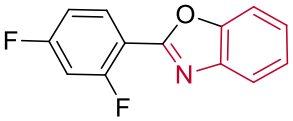
Entry	Acylbenzotriazole (2)	Benzoxazole (3)	Yield[a]
1	 **2a**	 **3a**	76
2	 **2b**	 **3b**	79
3	 **2c**	 **3c**	61
4	 **2d**	 **3d**	53

Table 2. Continued

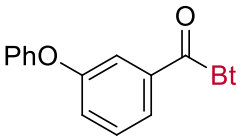
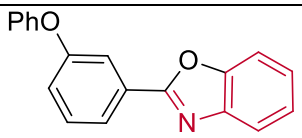
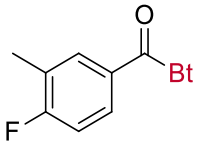
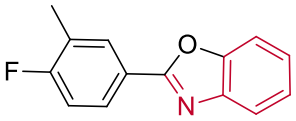
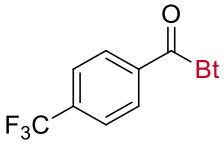
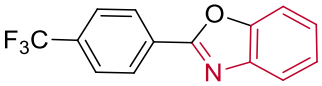
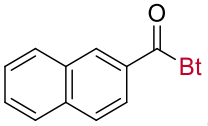
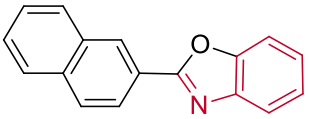
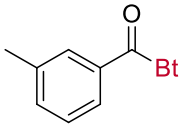
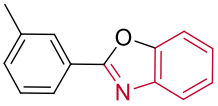
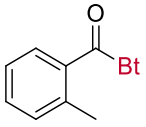
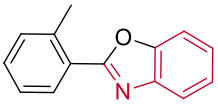
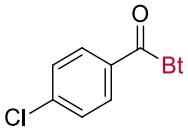
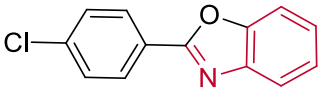
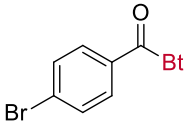
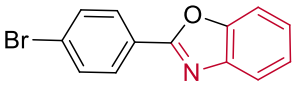
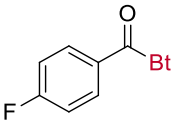
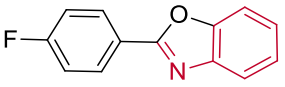
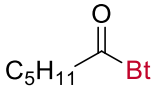
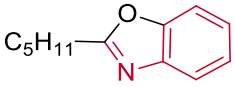
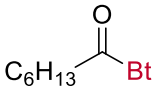
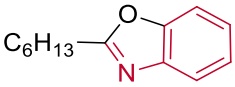
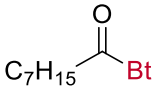
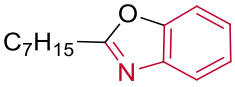
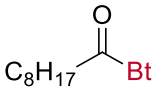
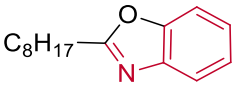
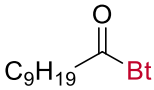
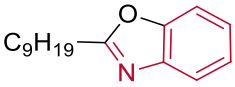
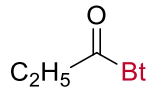
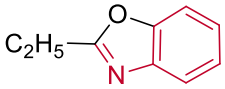
Entry	Acylbenzotriazole (2)	Benzoxazole (3)	Yield[a]
5	 **2e**	 **3e**	63
6	 **2f**	 **3f**	57
7	 **2g**	 **3g**	41
8	 **2h**	 **3h**	81
9	 **2i**	 **3i**	80
10	 **2j**	 **3j**	82
1 1	 **2k**	 **3k**	63
12	 **2l**	 **3l**	65
13	 **2m**	 **3m**	45

Table 2. Continued

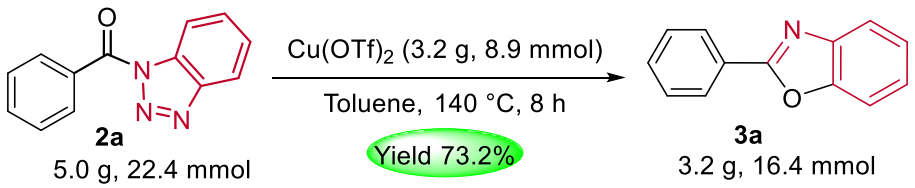
Entry	Acylbenzotriazole (2)	Benzoxazole (3)	Yield[a]
14	 **2n**	 **3n**	70
15	 **2o**	 **3o**	74
16	 **2p**	 **3p**	75
17	 **2q**	 **3q**	79
18	 **2r**	 **3r**	82
19	 **2s**	 **3s**	54

[a] Molar ratios: $Cu(OTf)_2$ (0.4 equiv.); Yield reported after purification by column chromatography (SiO_2).

The reaction produced average to good yields (45-82%) of benzoxazoles **3** from the respective acylbenzotriazoles **2** (Table 2). Considerable variation in the product yields was found by varying the substitution on the aryl ring of the substrates. In the presence of an electron donor group on any position of the aryl substituent, an increase in reaction yield was noticed (Table 2, entries 2, 9 & 10). Also, with the decreasing distance of the methyl group from the acyl group, the yield of product increased. Introduction of an electron withdrawing group on the aryl substituent decreased the yield and as the number of the electron withdrawing groups on the ring increased, the product yield further decreased (Table 2, entries 3-7 & 11-13). In case of alkyl group containing *N*-acylbenzotriazoles increasing the length of alkyl group increased the product yield also (Table 2, entries 14-18). These results suggest that the product formation is supported by the increased electron density around the acyl group of the substrate of the reaction.

BtRC-mediated cyclization reaction in gram scale

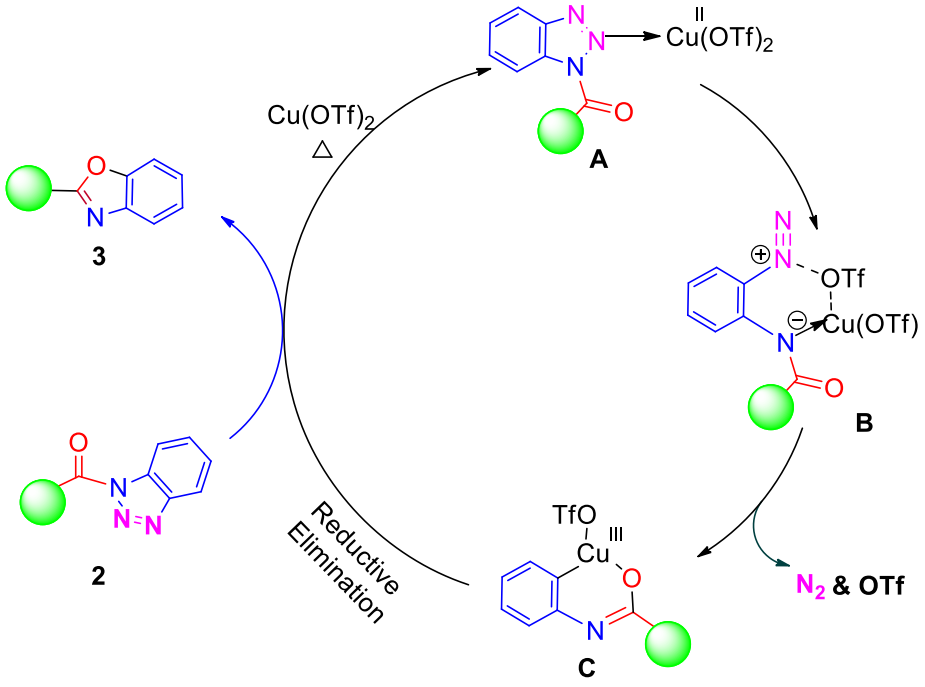
A gram scale reaction was carried out applying the optimized reaction conditions with 5 g of starting material **2a**. To our delight, the course and the yield of the reaction did not vary by scaling-up the quantity and the final product **3a** was produced 73.2% yield (Scheme 3).



Scheme 3. Synthesis of **3a** in gram scale *via* BtRC approach using $Cu(OTf)_2$.

Mechanistic consideration

In a plausible mechanistic sequence of the reaction, $Cu(OTf)_2$ attacks the *N*-acylbenzotriazoles **2** and activates ring-opening process of benzotriazole at N1–N2 bond by formation of benzotriazole–$Cu(OTf)_2$ complex **A**. Complex **A** converts into intermediate **B** by stabilization through the formation of an arenediazonium triflate species. This intermediate **B** releases N_2 and OTf group to form intermediate **C**, which on reductive elimination gives our desired product **3** (Scheme 4).[38]



Scheme 4. Proposed mechanism for benzotriazole ring cleavage using $Cu(OTf)_2$.

Conclusions

We have introduced $Cu(OTf)_2$ as a reliable reagent for the convenient one-step high yielding synthesis of 2-benzoxazoles from *N*-acylbenzotriazoles *via* benzotriazole ring cleavage (BtRC). The reaction was equally compatible for aryl-, as well as alkyl-substituted substrates and probably followed a cationic mechanism. This is also the first report of the use of BtRC reaction for the synthesis of 2-alkyl-substituted benzoxazoles. This synthetic route was successfully employed for milligram to gram scale reactions and achieved high yields of product.

Experimental Section

General. All the reactions were performed under an argon atmosphere in anhydrous solvents. Glassware's were dried in oven 100 °C one hour prior to use. All reagents and solvents were of pure analytical grade. Thin layer chromatography (TLC) was done using 60 F_{254} Silica gel pre-coated aluminum plates and visualized under UV lamp (λ_{max} 254 nm). ^{1}H, and ^{13}C NMR spectra were recorded in $CDCl_3$ solvent at 400 and 100 MHz, respectively. Chemical shifts are reported in ppm (δ) downfield from TMS as internal standard; *J* values in Hz.

Procedure for the synthesis of benzoxazole and their characterization data. A stirring solution of compound **2a** (1.0 mmol) in toluene was added with $Cu(OTf)_2$ (0.4 mmol) under inert atmosphere. The reaction was stirred under heating at 140 °C. After completion of the reaction (monitored by TLC), the reaction mixture was concentrated in vacuo, extracted with CH_2Cl_2, water, and brine solutions. After drying over anhydrous Na_2SO_4, the organic layer was concentrated in vacuo. Purification using flash column chromatography afforded benzoxazole derivative.

2-Phenylbenzo[*d*]oxazole (3a).[39] Crystalline, yield 76%; R_f 0.6 (10% ethyl acetate/n-hexane); mp 103-104 °C; lit. mp 101-102 °C; MS: *m/z* 196 $[M+H]^+$; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.28-8.25 (m, 2H), 7.79-7.76 (m, 1H), 7.60-7.57 (m, 1H), 7.54-7.50 (m, 3H), 7.38-7.34 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.0, 150.8, 142.1, 131.5, 128.9, 127.6, 127.2, 125.1, 124.6, 120.0, 110.6.

2-(*p*-Tolyl)benzo[*d*]oxazole (3b).[39] Colourless solid, yield 79%; R_f 0.6 (10% ethyl acetate/n-hexane); mp 114-118 °C; lit. mp 116-118 °C; MS: *m/z* 210 $[M+H]^+$; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.10-8.04 (m, 2H), 7.79-7.75 (m,1H), 7.60-7.56 (m, 1H), 7.43-7.40 (m, 1H), 7.37-7.33 (m, 3H), 2.40 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.3, 150.7, 142.2, 142.0, 129.6, 127.6, 124.9, 124.5, 124.4, 119.8, 110.5, 21.6.

2-(3,4-Dichlorophenyl)benzo[*d*]oxazole (3c).[40] Crystalline, yield 61%; R_f 0.5 (2% ethyl acetate/n-hexane); mp 142-144 °C; lit. mp 142-144 °C; MS: *m/z* 263.99 $[M+H]^+$; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.34 (d, *J* 1.6, 1H), 8.08-8.05 (dd, *J* 2.0, 6.4, 1H), 7.78-7.75 (m, 1H), 7.60-7.57 (m, 2H), 7.40-7.35 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.6, 150.6, 141.7, 135.7, 133.3, 130.91, 129.1, 126.8, 126.3, 125.6, 124.1, 120.1, 110.6.

2-(2,4-Fluorophenyl)benzo[*d*]oxazole (3d).[41] Crystalline, yield 53%; R_f 0.5 (10% ethyl acetate/n-hexane); mp 120-122 °C; MS: *m/z* 232.05 $[M+H]^+$; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.27-8.21 (m, 1H), 7.83-7.79 (m, 1H), 7.79-7.58 (m, 1H), 7.40-7.35 (m, 2H), 7.07-6.99 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.6 (dd, *J* 260.0, 11.1), 161.3 (dd, *J* 260.0, 12.0), 158.5 (d, *J* 6.0), 150.2, 141.5, 131.7 (dd, *J* 10.0, 2.0), 125.4, 124.6, 120.2, 112.1 (dd, *J* 21.0, 3.0), 110.5, 105.3 (t, *J* 25.0).

2-(3-Phenoxyphenyl)benzo[*d*]oxazole (3e).[42] Colourless Crystalline, yield 63%; R_f 0.6 (10% ethyl acetate/n-hexane); mp 83-84 °C; lit. mp 82-83 °C, MS: *m/z* 288.10 $[M+H]^+$; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.01 (d, *J* 7.6, 1H), 7.89 (s, 1H), 7.77-7.75 (m, 1H), 7.58-7.55 (m, 1H), 7.49 (t, *J* 8.0, 1H), 7.40-7.33 (m, 4H), 7.20-7.14 (m, 2H), 7.08 (d, *J* 8.0, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.5, 157.9, 156.8, 150.8, 142.1, 130.4, 130.0, 128.9, 125.4, 124.7, 123.8, 122.4, 122.0, 120.1, 119.2, 117.7, 110.0.

2-(4-Fluoro-3-methylphenyl)benzo[*d*]oxazole (3f).[43] Colourless Crystalline, yield 57%; R_f 0.6 (3% ethyl acetate/n-hexane);MS: *m/z* 228.08 $[M+H]^+$, ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.94 (d, *J* 8.0, 1H), 7.89 (d, *J* 10.4, 1H), 7.78-7.74 (m, 1H), 7.60-7.56 (m, 1H), 7.38-7.32 (m, 3H), 2.36 (d, *J* 1.2, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.6, 162.1, 162.1, 160.2, 150.7, 142.1, 132.1, 132.0, 129.1, 128.9, 126.6, 126.6, 125.3, 124.7, 123.1, 123.1, 120.1, 114.3, 114.0, 110.6, 14.8, 14.8.

2-[4-(Trifluoromethyl)phenyl]benzo[*d*]oxazole (3g).[44] Crystalline, yield 41%; R_f 0.7 (10% ethyl acetate/n-hexane); mp 141-142 °C; lit. mp 141-143 °C; MS: *m/z* 264.06 $[M+H]^+$; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.38 (d, *J*

8.0, 2H), 7.82-7.78 (m, 3H), 7.63-7.60 (m, 1H), 7.43-7.37 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.6, 151.0, 142.0, 133.3-132.9 (m), 130.5, 128.0, 126.1 (m), 125.9, 125.2, 125.1, 122.5, 120.5, 110.9.

2-(Naphthalen-2-yl)benzo[*d*]oxazole (3h).[45] Crystalline, yield 81%; R_f 0.7 (10% ethyl acetate/n-hexane);mp 116-118 °C; lit. mp 116-120 °C; MS: *m/z* 246.09 $[M+H]^+$; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.79 (s, 1H), 8.32 (dd, *J* 1.4, 7.2Hz, 1H), 8.00-7.97 (m, 2H), 7.91-7.89 (m, 1H), 7.82-7.79 (m, 1H), 7.64-7.40 (m, 3H) and 7.39-7.36 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.1, 150.8, 142.2, 134.7, 132.9, 128.9, 128.7, 128.1, 127.9, 127.8, 126.9, 125.2, 124.6, 124.3, 123.9, 120.0, 110.6.

2-(*m*-Tolyl)benzo[*d*]oxazole (3i).[39] Crystalline, yield 80%; R_f 0.7 (10% ethyl acetate/n-hexane); mp 83-85 °C; lit. mp 82-83 °C; MS: *m/z* 210.09 $[M+H]^+$; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.13 (s, 1H), 8.08 (d, *J* 7.6 Hz, 1H), 7.82-7.78 (m, 1H), 7.63-7.59 (m, 1H), 7.44 (t, *J* 7.6 Hz, 1H), 7.40-7.36 (m, 3H) and 2.49 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.1, 150.6, 141.9, 138.5, 132.25, 128.6, 128.0, 127.0, 126.8, 124.9, 124.4, 119.8, 110.4, 21.2.

2-(*o*-Tolyl)benzo[*d*]oxazole (3j).[39] Crystalline, yield 82%; R_f 0.7 (10% ethyl acetate/n-hexane); mp 56-58 °C; lit. mp 54-55 °C; MS: *m/z* 210.09 $[M+H]^+$; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.18 (m, 1H), 7.81(m, 1H), 7.61 (m, 1H), 7.59-7.31 (m, 5H) and 2.81 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.5, 150.4, 142.2, 138.9, 131.9, 131.0, 130.0, 126.3, 126.2, 125.1, 124.5, 120.2, 110.6, 22.3.

2-(4-Chlorophenyl)benzo[*d*]oxazole (3k).[39] Colourless crystals, yield 63%; R_f 0.6 (2% ethyl acetate/n-hexane); mp 150-151 °C; lit. mp 148-150 °C; MS: *m/z* 230.03 $[M+H]^+$; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.22 (d, *J* 8.4, 2H), 7.81-7.77 (m, 1H), 7.62-7.58 (m, 1H), 7.53 (d, *J* 8.4, 2H), 7.41-7.37 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.0, 150.7, 142.0, 137.7, 129.2, 128.8, 125.6, 125.3, 124.7, 120.1, 110.6.

2-(4-Bromophenyl)benzo[*d*]oxazole (3l).[40] Colourless solid, yield 65%; R_f 0.6 (10 % ethyl acetate/n-hexane); mp 158-160 °C; lit. mp 158-159 °C; MS: *m/z* 273.98 $[M+H]^+$; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.12 (d, *J* 8.4Hz, 2H), 7.78-7.76 (m, 1H), 7.67 (d, *J* 8.4Hz, 2H), 7.59-7.57 (m, 1H), 7.38-7.35 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.3, 150.9, 142.1, 132.4, 129.1, 126.3, 126.2, 125.5, 124.9, 120.2, 110.7.

2-(4-Fluorophenyl)benzo[*d*]oxazole (3m).[39] Colourless solid, yield 45%; R_f 0.5 (10% ethyl acetate/n-hexane); mp 103-104 °C; lit. mp 104-105 °C; MS: *m/z* 214.06 $[M+H]^+$; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.28-8.24 (m, 2H), 7.77-7.75 (m, 1H), 7.59-7.57 (m, 1H), 7.38-7.35 (m, 2H), 7.22 (t, *J* 8.4Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.1, 163.6, 162.2, 150.8, 142.1, 129.9 (d, *J* 9.0), 125.2, 124.7, 123.5, (d, *J* 3.0), 120.0, 116.2 (d, *J* 23.0), 110.6.

2-Pentylbenzo[*d*]oxazole (3n).[46] Colourless liquid, yield 70%; R_f 0.7 (2% ethyl acetate/n-hexane); MS: *m/z* 190.12 $[M+H]^+$; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.68-7.65 (m, 1H), 7.49-7.46 (m, 1H), 7.30-7.27 (m, 2H), 2.92 (t, *J* 7.6Hz, 2H), 1.89 (quin, *J* 7.2, 2H), 1.45-1.33 (m, 4H) and 0.91 (t, *J* 7.2, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.3, 150.7, 141.3, 124.3, 124.0, 119.4, 110.2, 31.3, 28.6, 26.45, 22.2, 13.8.

2-Hexylbenzo[*d*]oxazole (3o).[47] Colourless liquid, yield 74%; R_f 0.7 (10% ethyl acetate/n-hexane); MS: *m/z* 204.13 $[M+H]^+$; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.69-7.65 (m, 1H), 7.48-7.45 (m, 1H), 7.30-7.27 (m, 2H), 2.93 (t, *J* 7.6, 2H), 1.88 (quin, *J* 7.6, 2H), 1.44-1.39 (m, 2H), 1.35-1.31 (m, 4H) and 0.88 (t, *J* 6.8, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.4, 150.4, 141.2, 124.3, 124.0, 119.4, 110.2, 31.5, 31.3, 28.6, 26.7, 22.4, 14.0.

2-Heptylbenzo[*d*]oxazole (3p).[48] Colourless liquid, yield 75%; R_f 0.7 (10% ethyl acetate/n-hexane); MS: *m/z* 218.15 $[M+H]^+$; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.67-7.66 (m, 1H), 7.49-7.46 (m, 1H), 7.31-7.27 (m, 2H), 2.92 (t, *J* 7.6, 2H), 1.88 (quin, *J* 7.2, 2H), 1.45-1.11 (m, 8H) and 0.88 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.4, 150.8, 141.3, 124.4, 124.0, 119.5, 110.2, 31.6, 29.2, 29.1, 28.9, 26.8, 22.6, 14.1.

2-Octylbenzo[*d*]oxazole (3q).[49] Colourless liquid, yield 79%; R_f 0.7 (10% ethyl acetate/n-hexane); MS: *m/z* 232.16 $[M+H]^+$; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.68-7.66 (m, 1H), 7.48-7.46 (m, 1H), 7.30-7.28 (m, 2H), 2.92 (t, *J* 7.6, 2H), 1.88 (quin, *J* 7.2, 2H), 1.58-1.26 (m, 10H) and 0.88-0.83 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.5, 150.8, 141.4, 124.4, 124.1, 119.6, 110.3, 31.9, 29.3, 29.2, 28.7, 26.8, 22.7, 14.2.

2-Nonylbenzo[*d*]oxazole (3r).[46] Colourless liquid, yield 82%; R_f 0.7 (10 % ethyl acetate/n-hexane); MS: *m/z* 232.16 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$): δ 7.69-7.66 (m, 1H), 7.49-7.46 (m, 1H), 7.32-7.28 (m, 2H), 2.93 (t, *J* 7.6, 2H), 1.88 (quin, *J* 7.6, 2H), 1.45-1.26 (m, 12H) and 0.87 (t, *J* 6.4, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.4, 150.8, 141.5, 124.4, 124.1, 119.6, 110.3, 31.9, 29.4, 29.3, 29.3, 29.2, 28.7, 26.8, 22.7, 14.1.

2-Ethylbenzo[*d*]oxazole (3s).[40] Colourless liquid, yield 54%; R_f 0.5 (10% ethyl acetate/n-hexane); MS: *m/z* 148.07 $[M+H]^+$; ^1H NMR 7.69-7.66 (m, 1H), 7.48-7.45 (m, 1H), 7.31-7.26 (m, 2H), 2.99-2.93 (qt, J_1 7.56, J_2 7.6, 2H), 1.45 (t, *J* 7.56, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.0, 150.7, 141.2, 124.3, 123.9, 119.4, 110.1, 22.0, 10.8.

Acknowledgements

The authors are sincerely thankful to BBD University, Lucknow, Uttar Pradesh-226028, India for providing lab facility for experiments and CIRC, Jubilant Biosys Ltd, Greater Noida, Uttar Pradesh-201310, India, for providing spectroscopic studies of the developed molecules.

Supplementary Material

Characterization data 2-aryl/alkyl benzoxazoles (for all the developed 2-aryl/alkyl benzoxazoles) including copies of $^1H/^{13}C$ NMR spectra associated with this paper can be found in the online version.

References

1. Katritzky, A. R.; Lan, X.; Yang, J. Z.; Denisko, O. V. *Chem. Rev.* **1998**, *98*, 409-548. http://dx.doi.org/10.1021/cr941170v
2. Katritzky, A. R.; Rachwal, S. *Chem. Rev.* **2010**, *110*, 1564-1610. http://dx.doi.org/10.1021/cr900204u
3. Kale, R. R.; Prasad, V.; Mohapatra, P. P.; Tiwari, V. K. *Monatsh. Chem.* **2010**, *141,* 1159-1182. http://dx.doi.org/10.1007/s00706-010-0378-1
4. Kumar, D.; Mishra, A.; Mishra, B. B.; Bhattacharya, S.; Tiwari, V. K. *J. Org. Chem.* **2013**, *78,* 899-909. https://doi.org/10.1021/jo3021049
5. Kumar, D.; Mishra, B. B.; Tiwari, V. K. *J. Org. Chem.* **2014**, *79,* 251-266. https://doi.org/10.1021/jo4024107
6. Kumar, D.; Singh, A. S.; Tiwari, V. K. *RSC Adv.* **2015**, *5*, 31584-31593. https://doi.org/10.1039/C5RA01545F
7. Katritzky, A. R.; Yang, B.; Jiang, J.; Steel, P. J. *J. Org. Chem.* **1995**, *60,* 246-249. https://doi.org/10.1021/jo00106a041
8. Katritzky, A. R.; Zhang, G.; Jiang, J.; Steel, P. J. *J. Org. Chem.* **1995**, *60,* 7625-7630. https://doi.org/10.1021/jo00128a040
9. Nakamura, I.; Nemoto, T.; Shiraiwa, N.; Terada, M. *Org. Lett.* **2009**, *11,* 1055-1058. https://doi.org/10.1021/ol900113f
10. Katritzky, A. R.; Huang, T. B.; Denisko, O. V.; Steel, P. J. *J. Org. Chem.* **2002**, *67,* 3118-3119.

https://doi.org/10.1021/jo011028b
11. Kumar, A.; Ahmed, Q. N. *Eur. J. Org. Chem.* **2017**, *19*, 2751-2756. https://doi.org/10.1002/ejoc.201700357
12. Singh, A. S.; Kumar, D.; Mishra, N.; Tiwari, V. K. *RSC Adv.* **2016**, *6,* 84512-84522. https://doi.org/10.1039/C6RA14131E
13. Singh, A. S.; Singh, M.; Mishra, N.; Mishra, S.; Agrahari, A. K.; Tiwari, V. K. *ChemistrySelect* **2017**, *2*, 154-159. https://doi.org/10.1002/slct.201601116
14. Mico, X. I.; Ziegler, T.; Subramanian, L. R. *Angew. Chem., Int. Ed.* **2004**, *43*, 1400-1403. https://doi.org/10.1002/anie.200352782
15. Uhde, M.; Ziegler, T. *Synth. Commun.* **2010**, *40*, 3046-3057. https://doi.org/10.1080/00397910903353754
16. Katritzky, A. R.; Ji, F. B.; Fan, W. Q.; Gallos, J. K.; Greenhill, J. V.; King, R. W.; Steel, P. J. *J. Org. Chem*. **1992**, *57*, 190-195. https://doi.org/10.1021/jo00027a036
17. Habraken, C. L.; Erkelens, C.; Mellema, J. R.; Cohen-Fernandes, P. *J. Org. Chem.* **1984**, *49*, 2197-2200. https://doi.org/10.1021/jo00186a024
18. Katritzky, A. R.; Yang, B. *J. Org. Chem.* **1998**, *63*, 1467-1472. https://doi.org/10.1021/jo9715229
19. Kim, T.; Kim, K. *Tetrahedron Lett*. **2010**, *51*, 868-871. https://doi.org/10.1016/j.tetlet.2009.12.030
20. Katritzky, A. R.; Du, W.; Matskawa, Y.; Ghiviriga, I.; Denisenko, S. N. *J. Heterocycl. Chem.* **1999**, *36*, 927-932. https://doi.org/10.1002/jhet.5570360417
21. Rodriguez, A. D.; Ramirez, C.; Rodriguez, I. I.; Gonzalez, E. *Org. Lett.* **1999**, *1*, 527-530. https://doi.org/10.1021/ol9907116
22. Davidson, J. P.; Corey, E. J. *J. Am. Chem. Soc.* **2003**, *125*, 13486-13489. https://doi.org/10.1021/ja0378916
23. Ueki, M.; Ueno, K.; Miyadoh, S.; Abe, K.; Shibata, K.; Taniguchi, M.; Oi, S. *J. Antibiot.* **1993**, *46*, 1089-1094. https://doi.org/10.7164/antibiotics.46.1089
24. Sato, S.; Kajiura, T.; Noguchi, M.; Takehana, K.; Kobayashi, T.; Tsuji, T. *J. Antibiot.* **2001**, *54*, 102-104. https://doi.org/10.7164/antibiotics.54.102.
25. Grobler, J. A.; Dornadula, G.; Rice, M. R.; Simcoe, A. L.; Hazuda, D. J.; Miller, M. D. *J. Biol. Chem.* **2007**, *282*, 8005-8010. https://doi.org/10.1074/jbc.M608274200.
26. Leventhal, L.; Brandt, M. R.; Cummons, T. A.; Piesla, M. J.; Rogers, K. E.; Harris, H. A. *Eur. J. Pharmacol.* **2006**, *553*, 146-148. https://doi.org/10.1016/j.ejphar.2006.09.033
27. Nishiu, J.; Ito, M.; Ishida, Y.; Kakutani, M.; Shibata, T.; Matsushita, M.; Shindo, M. *Diabetes, Obes. Metab.* **2006**, *8*, 508-516. https://doi.org/10.1111/j.1463-1326.2005.00536.x
28. Easmon, J.;Pürstinger, G.; Thies, K.-S.; Heinisch,G.; Hofmann, J. *J. Med. Chem.* **2006**, *49*, 6343-6350. https://doi.org/10.1021/jm060232u
29. Bulawa, C. E.; Connelly, S.; DeVit, M.; Wang, L.; Weigel, C.; Fleming, J.; Packman, J.; Powers, E. T.; Wiseman, R. L.; Foss, T. R.; Wilson, I. A.; Kelly, J. W.; Labaudiniere, R. *Proc. Natl. Acad. Sci.* **2012**, *109*, 9629-9634. https://doi.org/10.1073/pnas.1121005109

30. Razavi, H.; Palaninathan, S. K. Powers, E. T.; Wiseman, R. L.; Purkey, H. E.; Mohamadmohaideen, N. N.; Deechongkit, S.; Chiang, K. P.; Dendle, M. T. A.; Sacchettini, J. C.; Kelly, J. W. *Angew. Chem., Int. Ed.* **2003**, *42*, 2758-2761. https://doi.org/10.1002/anie.200351179.
31. Singh, A. S.; Mishra, N.; Kumar, D.; Tiwari, V. K. *ACS Omega* **2017**, *2*, 5044-5051. https://doi.org/10.1021/acsomega.7b00965
32. Pandey, R. K.; Prajapati, R.; Gupta, M.; Rajput, C. S.; Pathak, A.; Singh, A. S. *Arkivoc* **2022**, *ix*, 133-146. https://doi.org/10.24820/ark.5550190.p011.762
33. Pandey, R. K.; Gupta, M.; Rajput, C. S.; Singh, A. S. *Arkivoc* **2023**, *vii,* 202312042. https://doi.org/10.24820/ark.5550190.p012.042
34. Zhang, Y.; Chen, L.; Lu, T. *Adv. Synth. Catal.* **2011**, *353*, 1055-1060. https://doi.org/10.1002/adsc.201000966
35. Wu, J.; Wang, D.; Wu, F.; Wan, B. *J. Org. Chem.* **2013**, *78*, 5611–5617. https://doi.org/10.1021/jo400747d
36. Tan, H.; Pan, C.-x.; Xu, Y.-l.; Wang, H.-s.; Pan, Y.-m. *J. Chem. Res*. **2012**, *36*, 370-373. https://doi.org/10.3184/174751912X13360692916944
37. Evans, D. A.; Miller, S. J.; Lectka, T.; Matt, P. *J. Am. Chem. Soc.* **1999**, *121*, 7559-7573. https://doi.org/10.1021/ja991190k
38. Wang, Y.; Wu, Y.; Li, Y.; Tang, Y. *Chem. Sci.* **2017**, *8*, 3852-3857. https://doi.org/10.1039/C7SC00367F
39. Wu, F.; Zhang, J.; Wei, Q.; Liu, P.; Xie, J.; Jiang, H.; Dai, B. *Org. Biomol. Chem.* **2014**, *12*, 9696-9701. https://doi.org/10.1039/C4OB02068E
40. Evindar, G.; Batey, R. A. *J. Org. Chem.* **2006**, *71*, 1802–1808. https://doi.org/10.1021/jo051927q
41. Yang, K.; Wang, P.; Zhang, C.; Kadi, A. A.; Fun, H.-K.; Zhang, Y.; Lu, H. *Eur. J. Org. Chem.* ***2014****, 34,* 7586–7589. https://doi.org/10.1002/ejoc.201403234
42. Ueda, S.; Nagasawa, H. *J. Org. Chem.* **2009**, *74*, 4272-4277. https://doi.org/10.1021/jo900513z
43. Li, Y.; Yu, X.; Wang, Y.; Fu, H.; Zheng, X.; Chen, H.; Li, R. *Organometallics* **2018**, *37*, 979–988. https://doi.org/10.1021/acs.organomet.8b00005
44. Wang, J.-M.; Jiang, X.; Tang, T.; Zhu, Y.-M.; Shen, J.-K. *Heterocycles* **2014**, *89*, 1441–1453. https://doi.org/10.3987/COM-14-12996
45. Mishra, N.; Singh, A. S.; Agrahari, A. K.; Singh, S. K.; Singh, M.; Tiwari, V. K. *ACS Comb. Sci.* **2019**, *21*, 389–399. https://doi.org/10.1021/acscombsci.9b00004
46. Saha, P.; Ramana, T.; Purkait, N.; Ali, M. A.; Paul, R.; Punniyamurthy, T. *J. Org. Chem.* **2009**, *74*, 8719–8725. https://doi.org/10.1021/jo901813g
47. Shimada, T.; Yamamoto. Y. *J. Am. Chem. Soc.* **2003**, *125*, 6646-6647. https://doi.org/10.1021/ja034105o
48. Zhao, S.; Chen, Y.; Song, Y.-F. *Appl. Catal., A* **2014***, 475,* 140–146. https://doi.org/10.1016/j.apcata.2014.01.017

49. Marsden, S. P.; Steer, J. T.; Orlek, B. S. *Tetrahedron* **2009***, 65,* 5503–5512*.* https://doi.org/10.1016/j.tet.2009.03.105