XtalFluor-E: An Efficient Reagent for Synthesis of Oxazolines from Carboxylic Acids and *O*-Silylated Amino Alcohols

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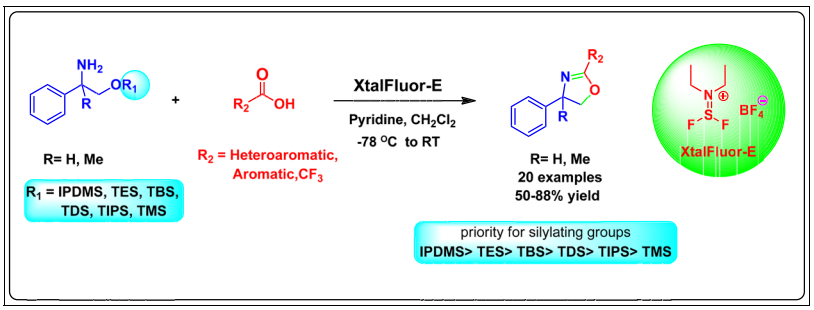

An efficient protocol has been developed for the synthesis of 2-oxazolines from carboxylic acids and silylated amino alcohols. The advantage of this method was demonstrated by preparing *O*-silylated amino alcohols. The reaction proceeds *via in situ* desilylation of *O*-silylated amide followed by cyclization. Studies on silyl deprotection were carried out to explain yield for 2-oxazolines.

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INTRODUCTION

Oxazolines are the most common heterocyclic compounds in many natural products like disorazole and hennoxazole. They are valuable synthetic intermediates 1a, b, as IndPHOX ligands for asymmetric synthesis 1c, d, and also act as protecting groups. For more than a century now, oxazoline rings are the best surrogate to carboxylic acid [2]. 2-Oxazoline, containing natural products, are also known to reduce chronic neurodegenerative diseases [3]. Thus, the oxadiazole moieties are versatile in synthetic utility, that is, synthetic intermediates, ligand scaffolds, chiral auxiliaries, and also chiral catalysts [4,5]. Because of the importance of oxazolines and oxadiazole scaffolds in biological applications like cytotoxic, antitumor, antibacterial, antidepressant, and anti-Alzheimer activities [6,7], many researchers are interested to work on methodologies to simplify the conditions, cost, and time. Some of the molecules such as allosamidin, trehazolin (insecticides), rilmenidine (antihypertensive), A289099 (tubulin polymerize inhibitor), and bistamide E (Fig. 1) are known to be biologically active due to an oxazoline fragment 7i, j. Ever since oxazolidine-containing natural products have shown promising medicinal value, chiral synthesis of 2-oxazolines is the research frontier in discovery as well as medicinal chemistry [8]. A common route to oxazolines is the reaction of an acid chloride with β-amino alcohol; the corresponding hydroxyamide is then treated with thionyl chloride and cyclized with the base *via* inversion of the configuration. Several milder approaches have been developed for the cyclization of the β-hydroxyamide, including the use of (diethylamino)sulfur trifluoride, Mitsunobu conditions, and PPh_3–CCl_4 [9]. Cyclization of β-hydroxyamide with PPh_3–CCl_4 allows the direct synthesis of oxazolines from carboxylic acids [10]. These methods exhibit less tolerance towards functionalization and causes epimerization [11].

A number of synthetic methods are reported for the synthesis of functionalized oxazoline derivatives from carboxylic acids, aldehydes, nitriles, esters, olefins, carbonyl compounds, and β-hydroxyamides. Pirrung and Tumey described the synthesis of oxazolines using polymer-bound tosyl chloride [12]. The commercially available fluorinating agents DAST and XtalFluor-E were used recently for cyclodehydration of β-hydroxyamides in good yields and without epimerization of α-position [13,14]. Later, Murai et al. reported the synthesis of oxazoline from aldehydes and amino alcohols by using 1,4-Diazabicyclo [2.2.2] octane-DABCO and N-Chlorosuccinimide-NCS [15]. Chaudhry et al. reported the synthesis of oxazolines from aldehydes and 1,2-hydroxyalkyl azides using Lewis acid BF_3–OEt_2 followed by polymer-bonded tosyl hydrazine [16]. Crosignani and Swinnen reported a one-pot protocol using Mukaiyama reagent followed by polymer-bound tosyl chloride [17]. Hazra and his team reported the synthesis of oxazoline derivatives by the reaction of alkenes with NBS in the presence of nitriles and Cu $(OTf)_2$/Zn $(OTf)_2$ [18]. Gratia et al. reported the synthesis of oxazolines by the reaction

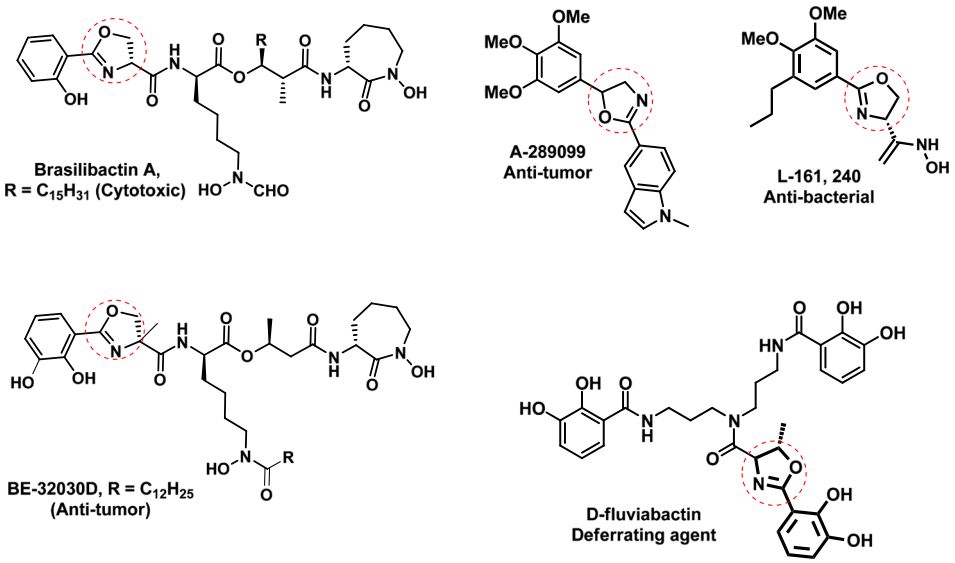


Figure 1. Examples of 2-oxazoline containing molecules. [Color figure can be viewed at wileyonlinelibrary.com]

of amides and alkenes in the presence of NIS and propionitriles [19].

Orliac and coworkers reported the synthesis of amide by using XtalFluor-E [20]. This group utilized XtalFluor-E as a coupling reagent for optically active substrates without epimerization. Phillips et al. reported the synthesis of oxazolines from β-hydroxyamides using Deoxo-Fluor and DAST [21]. Recently, Brandstatter and coworkers reported the synthesis of 2-oxazolines from silylated protected β-hydroxyamides using XtalFluor-E *via in situ* desilylation followed by cyclodehydration [22]. But there are hardly any reports towards the synthesis of oxazoline derivatives using *O*-silylated amino alcohols. As a part of our continuing research interest in methodologies [23], herein, we report the synthesis of substituted 2-oxazoline derivatives using *O*-silylated amino alcohols and carboxylic acids using XtalFluor-E under standard conditions (Scheme 1).

RESULTS AND DISCUSSION

The scope of 2-oxazoline synthesis was demonstrated here by taking carboxylic acid **2** and β-hydroxy amino alcohol **1** with tosyl chloride and triethylamine as a base in tetrahydrofuran solvent. We observed the formation of the desired product (**3**) in ~10% yield along with side product (**4**) in 80% yield (Table 1, entry 1). Use of different sulfonyl chlorides like pentafluorosulfonyl chloride and 4-nitrobenzene sulfonyl chloride did not alter the yield of the product (Table 1, entries 2 and 3). Then, we switched the coupling reagent by using fluorinating agents like DAST, XtalFluor-E, and Deoxo-Fluor to observe the formation of product **3** in 20 to 25% yield. In these conditions, we observed ester **4** as a side product formed *via* esterification of intermediate **IV** and acid in the presence of triethylamine (Table 1, entries 4–6). In order to increase the formation of desired product **3**, we carried out the reaction of acid (**2**) with trimethylsilyl (TMS)-protected and triethylsilyl (TES)-protected β-hydroxyl amino alcohols (**1**) using XtalFluor-E as reagent and triethylamine as a base at −78°C in tetrahydrofuran solvent (Table 1, entries 7 and 8). Unfortunately, TMS protection was unstable with XtalFluor-E and resulted in ~25% yield, whereas TES-protected β-hydroxyl amino alcohol gave 60% yield towards the product formation **3**. Screening of different solvents such as CH_2Cl_2, $CHCl_3$, 1,4-dioxane, and 1,2-Dichloroethane-DCE resulted in improved yield with dichloromethane facilitating easy workup (Table 1, entry 9). In order to improve the yield of the reaction, various

Scheme 1. One-pot synthesis of 2-oxazolines from carboxylic acids and amino alcohols. [Color figure can be viewed at wileyonlinelibrary.com]

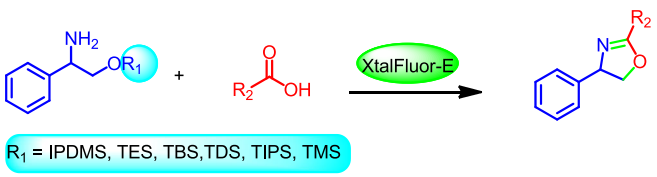
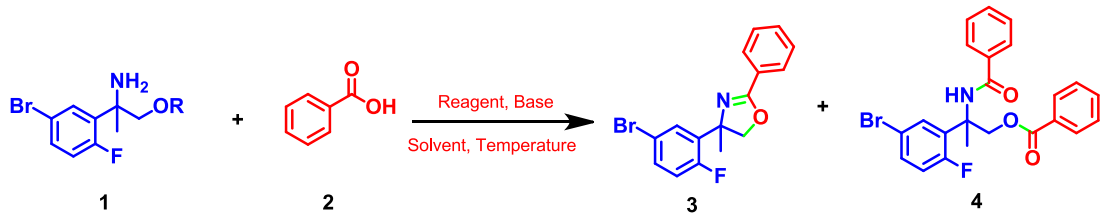


Table 1

Optimization of reaction conditions for the synthesis of oxazoline



S. No.	R	Reagent	Solvent	Temperature	Base	**3** (%)
1	H	Tosyl	THF	0°C	TEA	10
2	H	Nosyl	THF	0°C	TEA	15
3	H	Pentafluoro	THF	0°C	TEA	17
4	H	DAST	THF	−78°C to r.t.	TEA	20
5	H	XtalFluor-E	THF	78°C to r.t.	TEA	25
6	H	Deoxo-Fluor	THF	−78°C to r.t.	TEA	20
7	TMS	XtalFluor-E	THF	78°C to r.t.	TEA	25
8	TES	XtalFluor-E	THF	−78°C to r.t.	TEA	60
9	TES	XtalFluor-E	CH_2Cl_2	−78°C to r.t.	TEA	70
10	TES	XtalFluor-E	$CHCl_3$	−78°C to r.t.	TEA	65
11	TES	XtalFluor-E	1,4-Dioxane	−78°C to r.t.	TEA	60
12	TES	XtalFluor-E	DCE	−78°C to r.t.	TEA	53
13	TES	XtalFluor-E	CH_2Cl_2	−78°C to r.t.	DIPEA	60
14	TES	XtalFluor-E	CH_2Cl_2	−78°C to r.t.	2,6-Lutidine	65
15	**TES**	**XtalFluor-E**	**CH_2Cl_2**	**−78°C to r.t.**	**Pyridine**	**80**
16	**IPDMS**	**XtalFluor-E**	**CH_2Cl_2**	**−78°C to r.t.**	**Pyridine**	**85**
17	TBS	XtalFluor-E	CH_2Cl_2	78°C to r.t.	Pyridine	50
18	TDS	XtalFluor-E	CH_2Cl_2	78°C to r.t.	Pyridine	40
19	TIPS	XtalFluor-E	CH_2Cl_2	78°C to r.t.	Pyridine	30
20	TBDPS	XtalFluor-E	CH_2Cl_2	78°C to r.t.	Pyridine	30

All reactions were performed with 0.144 mmol of **1** compound, 0.144 mmol of acid **2**, 0.432 mmol of base, and 0.312 mmol of XtalFluor-E at −78°C to room temperature.
The best entries during the optimization studies are emphasized in bold.
TES, triethylsilyl; THF, tetrahydrofuran; TMS, trimethylsilyl.

bases like *N*,*N*-diisopropyl ethylamine, 2,6-lutidine, and pyridine were screened (Table 1, entries 13, 14, and 15). Among these, pyridine gave a good yield of 80% in CH_2Cl_2 solvent using XtalFluor-E at −78°C to ambient temperature. We even observed an increase in yield to 85% on changing the silyl-protecting group from TES to isopropyldimethylsilyl-IPDMS (Table 1, entry 15 vs 16). Then, we envisioned to study the rate of reaction by changing various silyl-protecting groups such as t-Butyldimethylsilyl-TBS, Thexyldimethylsilyl-TDS, Triisopropylsilyl-TIPS, and t-Butyldiphenylsilyl-TBDPS (Table 1, entries 17–20). Silyl-protecting groups like TBS,

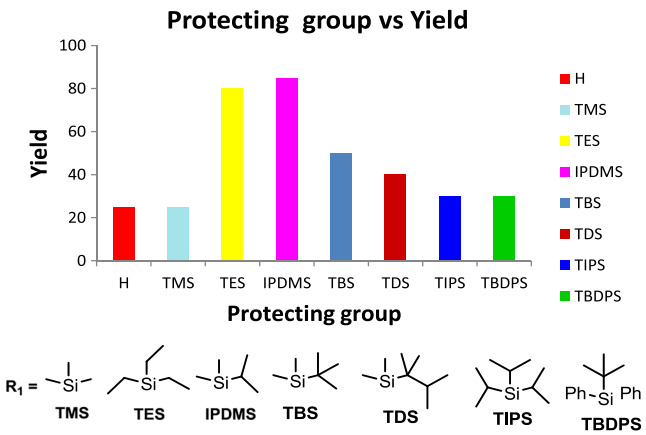
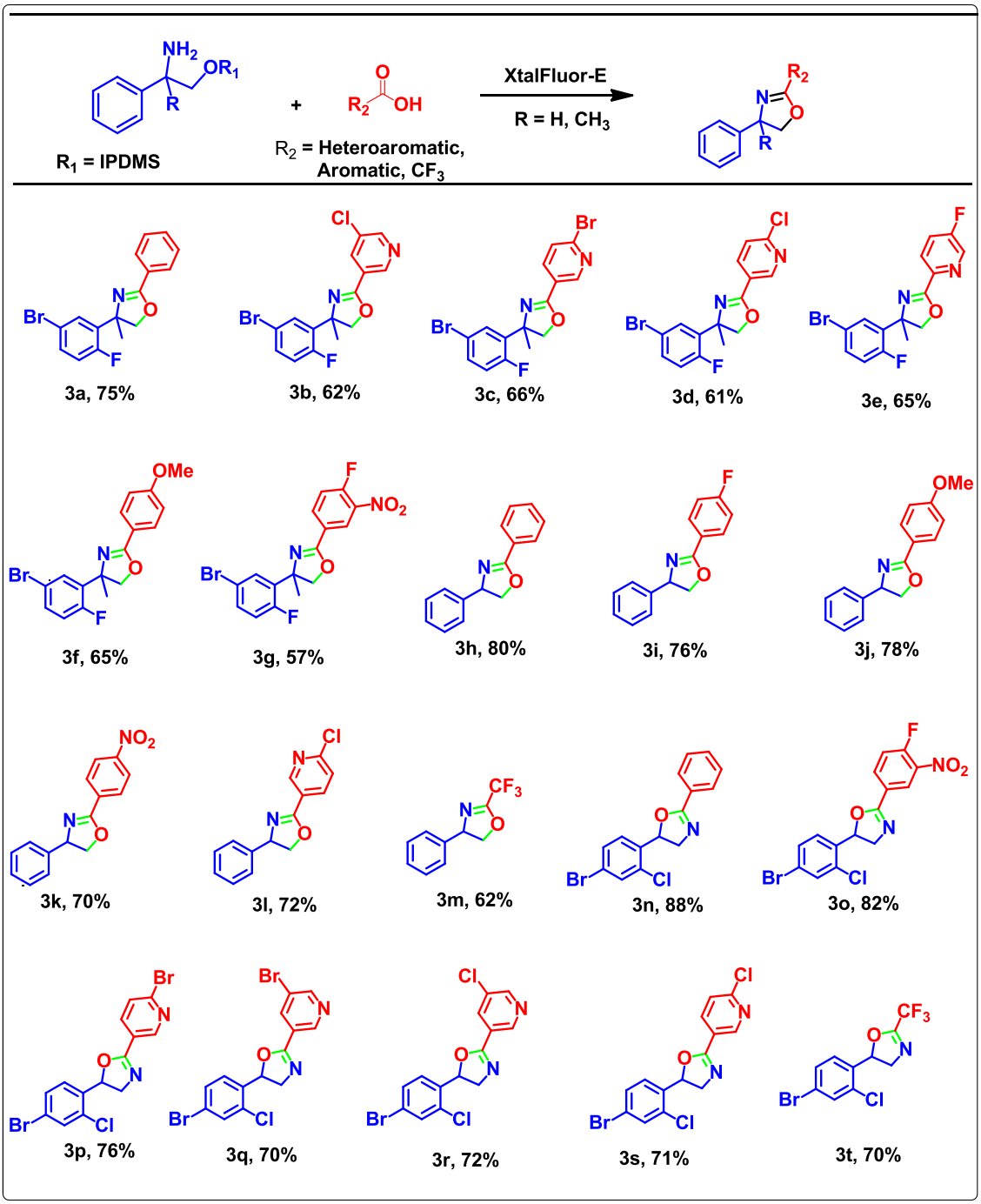


Figure 2. Comparative analysis between % of yield versus protecting group. [Color figure can be viewed at wileyonlinelibrary.com]

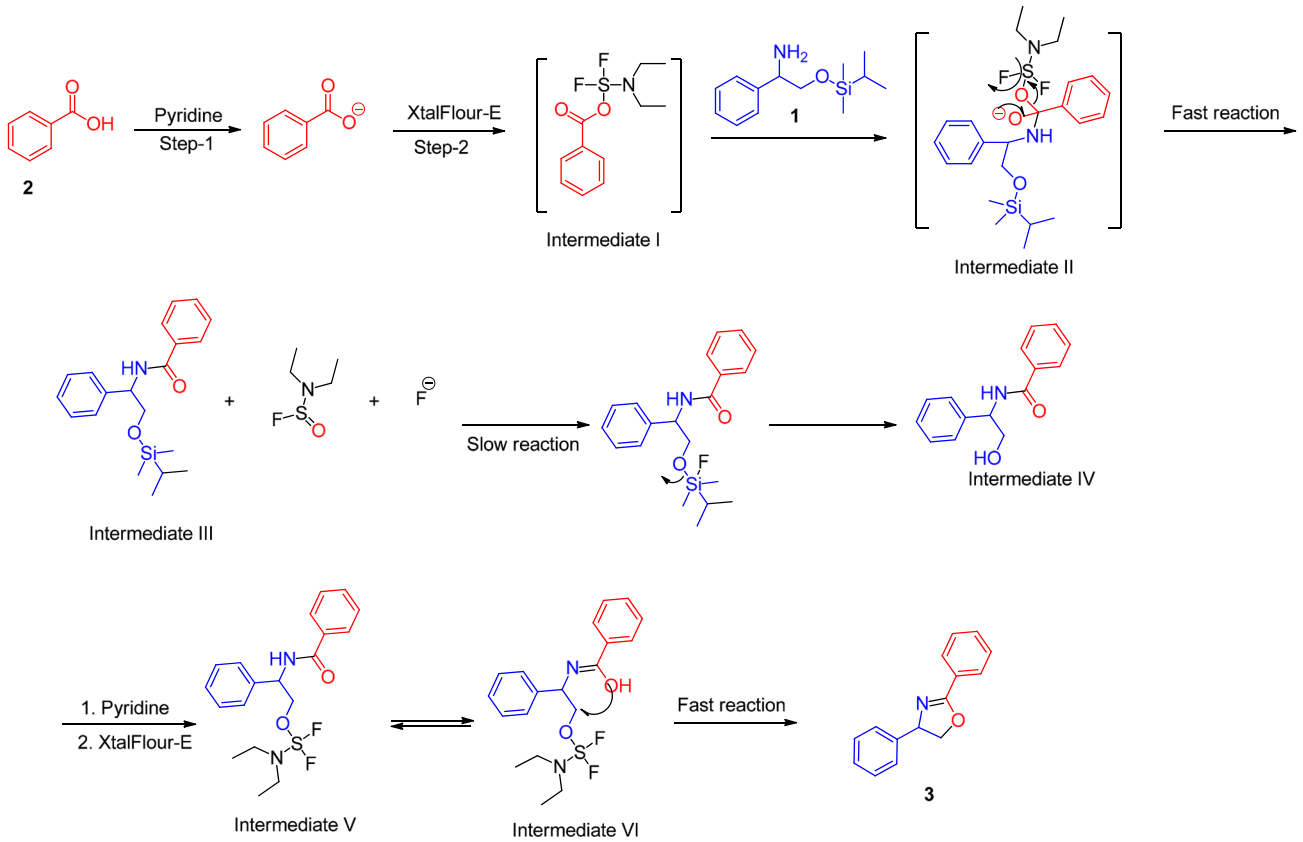
TDS, TIPS, and TBDPS decreased the yield for the formation of product **3** due to steric hindrance. Compounds containing bulky protecting groups could not undergo complete deprotection and remain as a major starting material. From the preceding observations, we concluded that the yields were proportional to the rate of silyl deprotection (Fig. 2). The order of silyl group deprotection from the reaction is IPDMS > TES > TBS > TDS > TIPS > TMS.

On the basis of optimized conditions, we synthesized different aryl 2-oxazolines using different acids with IPDMS protected amino alcohols (Scheme 2). Benzoic acid and its derivatives gave excellent yields with optimized conditions of XtalFluor-E (2.2 eq). On the

Scheme 2. Scope of different benzoic acids and different *O*-silylated amino alcohols towards the synthesis of 2-oxazoline derivatives. [Color figure can be viewed at wileyonlinelibrary.com]



Scheme 3. Proposed mechanism. [Color figure can be viewed at wileyonlinelibrary.com]



other hand, the heteroaromatic acids gave moderate to good yields towards the oxazoline formation. The 2-fluoro-5-bromo-substituted amino alcohols on reaction with different acids gave 2-oxazoline derivatives (**3a**–**3g**) in moderate to good yields (57–75%). Similarly, simple phenyl amino alcohols on reaction with various acids gave 2-oxazoline derivatives (**3h**–**3m**) in good yields. Disubstituted derivatives such as 2-chloro, 4-bromo-substituted amino alcohols also gave good yields towards the formation of oxazoline derivatives (**3n**–**3t**).

All synthesized compounds were confirmed by liquid chromatography-mass spectrometry (LC-MS), ^{1}H NMR, and ^{13}C NMR. A possible mechanism for the synthesis of 2-oxazoline derivatives is shown in Scheme 3. XtalFluor-E is attacked by nucleophilic oxygen of aromatic acid **2** to give intermediate **I**. Nucleophilic attack by nitrogen of amine (i.e., silyl protected amino alcohol) **1** at carbonyl carbon of intermediate **I** generate intermediate **II**. Rearrangement followed by elimination of fluoride ion gives intermediate **III**. Nucleophilic attack of the small fluoride anion leads to a pentavalent silicon centre. The formation of the strong Si–F bond is the driving force for a fast cleavage of O–Si bond. The deprotection of the silyl group *via* fluoride ion from intermediate **III** gives intermediate **IV**, which further reacts with XtalFluor-E followed by cyclization to give compound **3**.

CONCLUSION

In summary, we have reported the new protocol for the synthesis of 2-aryl oxazoline derivatives from aromatic acids and *O*-silylated amino alcohols using XtalFluor-E reagent in excellent yields with a broad range of carboxylic acids, including aromatic, heteroaromatic, aliphatic, and 1°, 2°, and 3° amino alcohols using a slight excess (2.2 equiv.) of the XtalFluor-E. The reaction occurs *via in situ* formation of β- hydroxy silylated amide followed by the deprotection of the silyl group and then successive cyclization using XtalFluor-E.

EXPERIMENTAL PROCEDURE

2-Bromo-5-[4-(5-bromo-2-fluoro-phenyl)-4-methyl-4,5-dihydro-oxazol-2-yl]-pyridine (3c). To a solution of 2-(5-bromo-2-fluoro-phenyl)-1-((isopropyldimethyl-silyl) oxy) propan-2-amine (0.144 mmol, 1.0 equiv) in dry

dichloromethane (3 mL) was added XtalFluor-E (0.316 mmol, 2.2 equiv) followed by the addition of 6-bromonicotinic acid (0.144 mmol, 1.0 equiv) at −78°C. The reaction mixture was slowly warmed to room temperature and stirred for 2 h at room temperature. The reaction mixture was quenched with saturated sodium bicarbonate solution at 0°C and extracted by dichloromethane (3 × 20 mL). The combined organic layers were dried over sodium sulfate and concentrated. The crude product was purified by column chromatography using 20–50% ethyl acetate in hexane as eluent gave pure compounds.

4-(5-Bromo-2-fluoro-phenyl)-4-methyl-2-phenyl-4,5-dihydro-oxazole (3a). White solid. Yield: 36 mg, 75%; ^{1}H NMR (400 MHz, chloroform-*d*): δ 8.08–8.05 (m, 2H), 7.98–7.96 (m, 1H), 7.54–7.52 (m, 1H), 7.49–7.45 (m, 2H), 7.39–7.35 (m, 1H), 6.98–6.94 (m, 1H), 4.65 (dd, *J* = 8.4, 2.8 Hz, 1H), 4.41 (dd, *J* = 8.8, 2.0 Hz, 1H), 1.67 (s, 3H); ^{13}C NMR (100 MHz, chloroform-*d*): δ 163.08, 159.75, 157.32, 136.58, 131.97, 131.51, 130.84, 128.52, 127.61, 127.07, 117.58, 117.35, 117.05, 79.04, 71.14, 28.74; LC-MS: *m*/*z* calculated for $C_{16}H_{13}BrFNO$: 333.02; observed mass 334.2, 336.2 (M + 1, M + 3).

3-[4-(5-Bromo-2-fluoro-phenyl)-4-methyl-4,5-dihydro-oxazol-2-yl]-5-chloro-pyridine (3b). Off white solid. Yield: 33 mg, 62%; ^{1}H NMR (300 MHz, chloroform-*d*): δ 8.71–8.70 (m, 1H), 8.13–8.10 (m, 1H), 7.97–7.94 (m, 1H), 7.83–7.79 (m, 1H), 7.39–7.34 (m, 1H), 6.98–6.92 (m, 1H), 4.74 (dd, *J* = 9.0, 3.6 Hz, 1H), 4.47 (d, *J* = 8.9 1.9 Hz, 1H), 1.67 (s, 3H); ^{13}C NMR (100 MHz, chloroform-*d*): δ 161.87, 161.12, 159.64, 157.21, 142.80, 138.59, 135.96, 131.67, 130.69, 125.88, 123.51, 117.63, 117.10, 79.62, 71.66, 28.79; LC-MS: *m*/*z* calculated for $C_{15}H_{11}BrClFN_2O$: 368.0; observed mass 369.0, 371.0 (M + 1, M + 3).

2-Bromo-5-[4-(5-bromo-2-fluoro-phenyl)-4-methyl-4,5-dihydro-oxazol-2-yl]-pyridine (3c). Off white solid. Yield: 36 mg, 66%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.89 (s, 1H), 8.26–8.23 (m, 1H), 7.82–7.78 (m, 2H), 7.56–7.52 (m, 1H), 7.27–7.22 (m, 1H), 4.73 (dd, *J* = 8.8, 2.8 Hz, 1H), 4.43 (dd, *J* = 8.8, 2.0 Hz, 1H), 1.56 (s, 3H); ^{13}C NMR (100 MHz, chloroform-*d*): δ 160.43, 159.65, 157.22, 150.05, 145.37, 138.15, 135.84, 131.68, 130.60, 127.95, 123.04, 117.47, 117.09, 79.29, 71.44, 28.73; LC-MS: *m*/*z* calculated for $C_{15}H_{11}Br_2FN_2O$: 411.92; observed mass 413.0, 415.5, 417.0 (M + 1, M + 3, M + 5).

5-[4-(5-Bromo-2-fluoro-phenyl)-4-methyl-4,5-dihydro-oxazol-2-yl]-2-chloro-pyridine (3d). White solid. Yield: 32 mg, 61%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.94 (s, 1H), 8.39–8.37 (m, 1H), 7.82–7.80 (m, 1H), 7.69 (d, *J* = 8.24 Hz, 1H), 7.57–7.54 (m, 1H), 7.29–7.24 (m, 1H), 4.74 (dd, *J* = 8.8 Hz, 1H), 4.45 (dd, *J* = 8.8 Hz, 1H), 1.57 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6): 162.54, 160.34, 136.89, 132.40, 130.30, 129.17, 127.44, 119.02, 116.81, 78.68, 71.04, 29.62; LC-MS: *m*/*z* calculated for $C_{15}H_{11}BrClFN_2O$: 367.97; observed mass 369.0, 371.0 (M + 1, M + 3).

2-[4-(5-Bromo-2-fluoro-phenyl)-4-methyl-4,5-dihydro-oxazol-2-yl]-5-fluoro-pyridine (3e). White solid. Yield: 33 mg, 65%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.72 (s, 1H), 8.25–8.22 (m, 1H), 7.92–7.87 (m, 1H), 7.81–7.80 (m, 1H), 7.57–7.54 (m, 1H), 7.29–7.24 (m, 1H), 4.74 (dd, *J* = 8.6 Hz, 1H), 4.44 (dd, *J* = 8.4 Hz, 1H), 1.57 (s, 3H); LC-MS: *m*/*z* calculated for $C_{15}H_{11}BrF_2N_2O$: 352.0; observed mass 353.2, 355.2 (M + 1, M + 3).

4-(5-Bromo-2-fluoro-phenyl)-2-(5-methoxypyridin-2-yl)-4-methyl-4,5-dihydrooxazole (3f). White solid. Yield: 34 mg, 65%; ^{1}H NMR (300 MHz, chloroform-*d*): δ 8.08 (m, 2H), 8.00 (d, *J* = 7.8 Hz, 1H), 7.60–7.48 (m, 2H), 7.26–7.21 (m, 1H), 6.86–6.83 (m, 1H), 4.98 (dd, *J* = 8.6 Hz, 1H), 4.52 (dd, *J* = 8.58 Hz, 1H), 3.87 (s, 3H), 1.66 (s, 3H); LC-MS: *m*/*z* calculated for $C_{16}H_{14}BrFN_2O_2$: 364.02; observed mass 365.0, 367.0 (M + 1, M + 3).

4-(5-Bromo-2-fluoro-phenyl)-2-(4-fluoro-3-nitrophenyl)-4-methyl-4,5-dihydro-oxazole (3g). White solid. Yield: 32 mg, 57%; ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.61–8.57 (m, 1H), 8.37–8.33 (m, 1H), 7.82–7.71 (m, 2H), 7.58–7.53 (m, 1H), 7.29–7.23 (m, 1H), 4.77 (dd, *J* = 9.0 2.7 Hz, 1H), 4.47 (dd, *J* = 8.8, 1.5 Hz, 1H), 1.57 (s, 3H); LC-MS: *m*/*z* calculated for $C_{16}H_{11}BrF_2N_2O_3$: 396.02; observed mass 397.0, 399.0 (M + 1, M + 3).

2,4-Diphenyl-4,5-dihydrooxazole (3h). White solid. Yield: 30 mg, 80%; ^{1}H NMR (400 MHz, chloroform-*d*): δ 8.04 (d, *J* = 7.2 Hz, 1H), 7.53–7.51 (m, 1H), 7.50–7.43 (m, 2H), 7.38–7.35 (m, 2H), 7.32–7.28 (m, 3H), 5.39 (dd, *J* = 8.0, 1.2 Hz, 1H), 4.80 (dd, *J* = 8.4, 0.8 Hz, 1H), 4.28 (t, *J* = 6.8 Hz, 1H); ^{13}C NMR (125 MHz, chloroform-*d*): δ 164.77, 142.41 131.58, 128.79, 128.42, 127.66, 126.79, 74.92, 70.15; LC-MS: *m*/*z* calculated for $C_{15}H_{13}NO$: 223.10; observed mass 224.0 (M + 1).

2-(4-Fluoro-phenyl)-4-phenyl-4,5-dihydrooxazole (3i). White solid. Yield: 38 mg, 76%; ^{1}H NMR (400 MHz, chloroform-*d*): δ 8.07–8.03 (m, 2H), 7.38–7.31 (m, 2H), 7.30–7.27 (m, 3H), 7.14–7.09 (m, 2H), 5.38 (dd, *J* = 6.8, 1.2 Hz, 1H), 4.80 (dd, *J* = 6.8, 1.6 Hz, 1H), 4.28 (t, *J* = 6.8 Hz, 1H); ^{13}C NMR (125 MHz, chloroform-*d*): δ 165.98, 163.89, 163.25, 140.99, 130.64, 128.97, 128.50, 125.86, 124.02, 115.76, 81.37, 63.28; LC-MS: *m*/*z* calculated for $C_{15}H_{12}FNO$: 241.09; observed mass 242.0 (M + 1).

2-(4-Methoxyphenyl)-4-phenyl-4,5-dihydrooxazole (3j). White solid. Yield: 41 mg, 78%; ^{1}H NMR (400 MHz, chloroform-*d*): δ 7.99 (dt, *J* = 8.0, 4.0, 2.0 Hz, 2H), 7.37–7.31 (m, 2H), 7.30–7.26 (m, 3H), 6.96–6.93 (m, 2H), 5.35 (dd, *J* = 8.0, 0.8 Hz, 1H), 4.77 (dd, *J* = 8.0, 6.8 Hz, 1H), 4.24 (t, *J* = 6.8, Hz, 1H), 3.85 (s, 3H); ^{13}C NMR (125 MHz, chloroform-*d*): δ 164.57, 162.28,

142.65, 130.25, 128.76, 127.60, 126.80, 120.04, 113.76, 74.83, 70.09, 55.40; LC-MS: *m/z* calculated for $C_{16}H_{15}NO_2$: 253.11; observed mass 254.0 (M + 1).

2-(4-Nitrophenyl)-4-phenyl-4,5-dihydrooxazole (3k). White solid. Yield: 39 mg, 70%; ^{1}H NMR (400 MHz, chloroform-*d*): δ 8.27 (d, *J* = 7.2 Hz, 2H), 8.20 (d, *J* = 6.8 Hz, 2H), 7.39–7.36 (m, 2H), 7.32–7.29 (m, 3H), 5.44 (dd, *J* = 8.0, 7.2 Hz, 1H), 4.86 (dd, *J* = 8.0, 6.8 Hz, 1H), 4.34 (t, *J* = 6.8 Hz, 1H); ^{13}C NMR (125 MHz, chloroform-*d*): δ 162.95, 149.60, 141.65, 133.43, 129.57, 128.97, 127.99, 126.78, 123.65, 75.38, 70.47; LC-MS: *m/z* calculated for $C_{15}H_{12}N_2O_3$: 268.08; observed mass 269.0 (M + 1).

2-(6-Chloropyridin-3-yl)-4-phenyl-4,5-dihydrooxazole (3l). White solid. Yield: 39 mg, 72%; ^{1}H NMR (400 MHz, chloroform-*d*): δ 8.99 (s, 1H), 8.26 (dd, *J* = 6.8, 2.0 Hz, 1H), 7.40–7.35 (m, 3H), 7.31–7.27 (m, 3H), 5.39 (dd, *J* = 8.4 6.8 Hz, 1H), 4.82 (dd, *J* = 8.4, 6.8 Hz, 1H), 4.30 (t, *J* = 6.4 Hz, 1H); ^{13}C NMR (125 MHz, chloroform-*d*): δ 161.97, 154.33, 149.82 141.68, 138.53, 129.98, 127.99, 126.77, 124.20, 122.82, 75.21, 70.30; LC-MS: *m/z* calculated for $C_{14}H_{11}ClN_2O$: 258.06; observed mass 259.0 (M + 1).

4-Phenyl-2-(trifluoromethyl)-4,5-dihydrooxazole (3m). White solid. Yield: 28 mg, 62%; ^{1}H NMR (400 MHz, chloroform-*d*): δ 7.41–7.38 (m, 2H), 7.36–7.32 (m, 1H), 7.26–7.24 (m, 2H), 5.43–5.39 (m, 1H), 4.89 (dd, *J* = 8.4, 6.8 Hz, 1H), 4.40 (t, *J* = 6.8 Hz, 1H); LC-MS: *m/z* calculated for $C_{10}H_8F_3NO$: 215.06; observed mass 217.0 (M + 2). ^{19}F NMR (368 MHz, DMSO-d_6): δ 61.21.

5-(4-Bromo-2-chlorophenyl)-2-(4-fluoro-3-nitrophenyl)-4,5-dihydrooxazole (3o). White solid. Yield: 46 mg, 82%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.47 (s, 1H), 8.26–8.22 (m, 2H), 7.68 (m, 1H), 7.54 (d, *J* = 5.2 Hz, 1H), 7.36 (dd, *J* = 5.6, 1.6 Hz, 1H), 5.85 (t, *J* = 8.0 Hz, 1H), 4.50 (t, *J* = 9.2 Hz, 1H), 3.95 (t, *J* = 8.4 Hz, 1H); LC-MS: *m/z* calculated for $C_{15}H_9BrClFN_2O_3$: 398.00; observed mass 399.0, 401.0 (M + 1, M + 3).

5-(4-Bromo-2-chlorophenyl)-2-(6-bromopyridin-3-yl)-4,5-dihydrooxazole (3p). White solid. Yield 44 mg, 76%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.34 (d, *J* = 2.0 Hz, 1H), 8.28–8.23 (m, 3H), 7.66 (dd, *J* = 8.0, 2.0 Hz, 1H), 7.38 (dd, *J* = 6.0, 2.4 Hz, 1H), 5.97 (t, *J* = 8.0 Hz, 1H), 4.55 (t, *J* = 8.8 Hz, 1H), 4.06 (dd, *J* = 9.2, 8.0 Hz, 1H); LC-MS: *m/z* calculated for $C_{14}H_9Br_2ClN_2O$: 413.88; observed mass 415.0, 417.0, 418.0 (M + 1, M + 3, M + 4).

5-(4-Bromo-2-chlorophenyl)-2-(6-bromopyridin-3-yl)-4,5-dihydrooxazole (3q). White solid. Yield: 42 mg, 70%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.59 (d, *J* = 2.4 Hz, 1H), 8.29 (m, 1H), 8.24 (m, 1H), 8.09 (dd, *J* = 8.0, 2.8, 1H), 7.63 (d, *J* = 8.0 Hz, 1H), 7.37 (dd, *J* = 6.0, 2.4 Hz, 1H), 5.87 (t, *J* = 8.4, 1H), 4.47 (t, *J* = 8.8 Hz, 1H), 4.04 (t, *J* = 8.8 Hz, 1H); LC-MS: *m/z* calculated for $C_{14}H_9Br_2ClN_2O$: 413.88; observed mass 415.0, 417.0, 418.0 (M + 1, M + 3, M + 4).

5-(4-Bromo-2-chlorophenyl)-2-(5-chloropyridin-3-yl)-4,5-dihydrooxazole (3r). White solid. Yield 38 mg, 72%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.27 (s, 1H), 8.22 (d, *J* = 6.0 Hz, 1H), 7.96–7.94 (m, 2H), 7.69 (d, *J* = 8.4 Hz, 1H), 7.34–7.32 (m, 1H), 5.90 (t, *J* = 8.0 Hz, 1H), 4.51 (t, *J* = 8.8 Hz, 1H), 3.98 (t, *J* = 8.8 Hz, 1H); LC-MS: *m/z* calculated for $C_{14}H_9BrCl_2N_2O$: 370.0; observed mass 371.0, 373.0 (M + 1, M + 3).

5-(4-Bromo-2-chlorophenyl)-2-(6-chloropyridin-3-yl)-4,5-dihydrooxazole (3s). White solid. Yield: 38 mg, 72%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.27–8.23 (d, 2H), 8.07 (s, 1H), 7.87–7.80 (m, 2H), 7.36 (dd, *J* = 6.0, 2.0 Hz, 1H), 5.89 (t, *J* = 8.4 Hz, 1H), 4.47 (t, *J* = 8.8 Hz, 1H), 3.98 (t, *J* = 8.8 Hz, 1H); LC-MS: *m/z* calculated for $C_{14}H_9BrCl_2N_2O$: 370.0; observed mass 371.0, 373.0 (M + 1, M + 3).

5-(4-Bromo-2-chlorophenyl)-2-(trifluoromethyl)-4,5-dihydrooxazole (3t). White solid. Yield: 32 mg, 70%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.87–7.80 (m, 2H), 7.54 (t, *J* = 9.2 Hz, 1H), 5.87 (t, *J* = 8.8 Hz, 1H), 3.95 (t, *J* = 8.8 Hz, 1H), 3.47 (t, *J* = 8.4 Hz, 1H); LC-MS: *m/z* calculated for $C_{10}H_6BrClF_3NO$: 326.93; observed mass 328.0, 330.0 (M + 1, M + 3).

2-Benzamido-2-(5-bromo-2-fluoro-phenyl)propyl benzoate (5). White solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.03 (dd, *J* = 1.2, 8.4 Hz, 2H), 7.80 (dd, *J* = , 8.4,1.2 Hz, 2H), 7.63–7.60 (m, 2H), 7.59–7.57 (m, 6H), 6.94 (dd, *J* = 8.8, 12.0 Hz, 1H), 4.97 (d, *J* = 11.2 Hz, 1H), 4.63 (d, *J* = 11.2 Hz, 1H), 1.58 (s, 3H); LC-MS: *m/z* calculated for $C_{23}H_{19}BrFNO_3$: 455.05; observed mass 456.2, 458.2 (M + 1, M + 3).

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