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Expeditious Microwave-Assisted Synthesis of 5-Alkoxyoxazoles from α-Triflyloxy Esters and Nitriles

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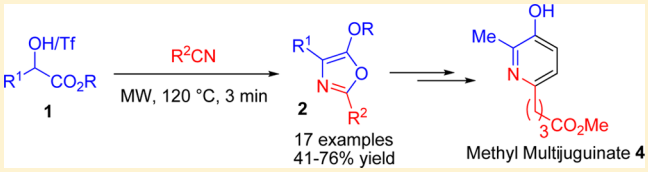
Supporting Information

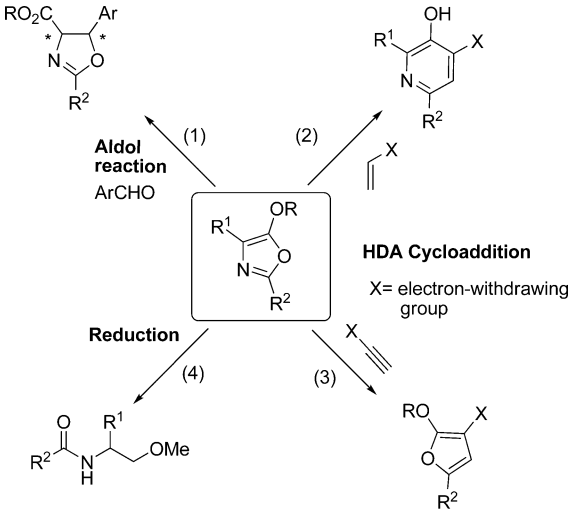
ABSTRACT: A rapid and general access to diversely substituted 5-alkoxyoxazoles **2** (i.e., R^1, R^2 = alkyl, phenyl) from easily accessible α-triflyloxy/hydroxy esters **1** and nitriles with good yields (41−76%) is reported. The versatility of the cyclization is shown for a range of substrates with high selectivity toward triflates over mesylates and proved to be compatible with sensitive functional groups. As an illustration of this transformation, the first synthesis of the recently isolated hydroxypyridine methyl multijuguinate **4** was achieved in four steps through a hetero Diels−Alder reaction of the 5-alkoxyoxazole and acrylic acid, followed by a protodecarboxylation reaction.



INTRODUCTION

5-Alkoxyoxazoles are an important class of heterocycles that are key intermediates in the synthesis of natural compounds[1] and aldol partners in the asymmetric preparation of α-amino-β-hydroxy acid derivatives (Scheme 1, eq 1).[2] 5-Alkoxyoxazoles have also proven to be valuable heterodienes in both pyridine[3] and furan[4] frameworks construction via the Diels−Alder strategy involving electron deficient alkenes and alkynes respectively (Scheme 1, eqs 2 and 3). Recently, functionalized amino alcohol derivatives were readily accessed from 5-alkoxyoxazoles (Scheme 1, eq 4).[5]

Scheme 1. Reactions Involving 5-Alkoxyoxazoles as Key Precursors



Although several methods of preparation of 5-alkyloxazoles exist,[6] few strategies for the formation of their 5-alkoxy derivatives are reported in the literature. Indeed, electron-rich oxazoles such as 5-alkoxyoxazoles are usually more sensitive to both acidic and thermal conditions rendering their formation/isolation often difficult. They are traditionally generated by cyclodehydration of 2-acylamino acid esters, with reaction times varying from one to several hours, depending of the substrate considered.[7] Recent methods include metal-catalyzed decomposition of α-diazo esters in the presence of nitriles,[8] acylation of isocyano esters,[9] and the Ritter reaction of α-oxo tosylates with nitriles.[10,11] However, number of these methods require specific groups at the C-4 position of the heterocycle such as a silyle,[8b] an aromatic,[10] or an electron-withdrawing group.[8a] As part of our ongoing research on the 3-hydroxypyridine ring synthesis,[3e] we were interested in developing a rapid and versatile access to diversely substituted 5-alkoxyoxazole derivatives at both C-2 and C-4 positions. Since long reaction time, scope limitation may be a restriction of these methods, we wish to report an efficient and general access to both 4-alkyl/phenyl-5-alkoxyoxazoles from the corresponding α-triflyloxy or α-hydroxy esters and nitriles. Application of these intermediates in the first synthesis of the recently isolated methyl multijuguinate from the leaves of *Senna multijuga* is described.

RESULTS AND DISCUSSION

Our attention focused on a strategy recently developed by Taylor, based on a Ritter reaction of α-oxo tosylates with nitriles to generate 4-aromatic substituted oxazole derivatives.[10] Indeed, the easy access to both starting materials renders this process very convenient and attractive. However, our efforts to

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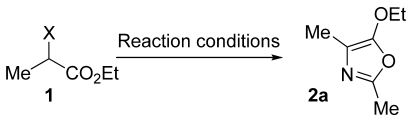
extend this strategy to the synthesis of *4-aliphatic*-5-alkoxyoxazoles using the reported reaction conditions (TMS-OTf, DCE, 80 °C, 20 h), using for instance the ethyl O-[(*p*-methylphenyl)sulfonyl]-2-hydroxypropanoate **1a** as a substrate to screen optimized conditions, failed (Table 1, entry 1). No trace of the desired product **2a** was observed. The substrate was recovered unchanged.

Table 1. Optimization of the Reaction Conditions for 5-Alkoxyoxazoles Synthesis



entry	substrate (X)	reaction conditions	yield[a] (%)
1	**1a** (OTs)	TMSOTf (2.5 equiv) CH_3CN/DCE, 80 °C, 20 h	0
2	**1a** (OTs)	TMSOTf (1.75 equiv) CH_3CN, MW, 120 °C, 3 min	0
3	**1b** (I)	TMSOTf (1.75 equiv) CH_3CN, MW, 120 °C, 3 min	0
4	**1c** (OTf)	TMSOTf (0.1 equiv) CH_3CN, MW, 120 °C, 3 min	63

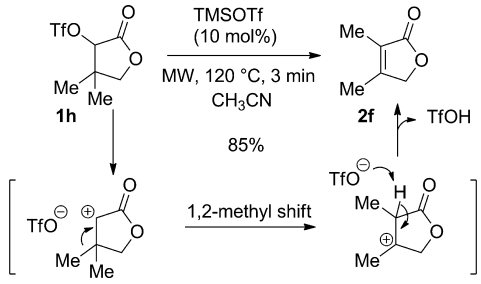
[a]Isolated yield.

Moreover, the reaction performed in acetonitrile at higher temperature under microwave conditions (i.e., 120 °C, 3 min) did not provide the desired 2,2-dimethyl-5-ethoxyoxazole **2a** (entry 2). Thus, attempts to run the reaction with the iodo derivative **1b**, bearing a better leaving group than compound **1a**, also proved unsuccessful (entry 3). The expected oxazole product **2a** was not observed, and the substrate was recovered unchanged. Pleasingly, the *α*-triflyloxy ester derivative **1c** was found to be a suitable substrate, under microwave conditions (10 mol % TMS-OTf, 120 °C, 3 min), affording the 2,4-dimethyl-5-ethoxyoxazole **2a** in satisfying 63% isolated yield (entry 4). This encouraging result demonstrated that a poorly nucleophilic species such as acetonitrile was able to react with aliphatic triflate. Indeed, the presence of cation-stabilizing substituents in *α*-position of the leaving group was no longer a requisite for this reaction, as recently reported.[10] These new conditions considerably widen the scope of this chemistry. It should also be stressed that the expected elimination reaction leading to the corresponding *α*,*β*-unsaturated ester was not significantly observed with all the following substrates tested (<10% when observed).

To explore the scope and limitation of this methodology, a range of *α*-triflyloxy esters were prepared and tested in the presence of acetonitrile, using previously optimized reaction conditions (i.e., MW, 120 °C, 3 min, TMS-OTf 10 mol %). The results obtained are summarized in Table 2.

α-Triflyloxy esters bearing an aliphatic group at position R^1 led to the corresponding alkoxyoxazoles **2a** and **b** in useful yield (63%, entries 1 and 2). The bulky *sec*-butyl substituent afforded the oxazole **2c** in a lower yield of 42%, along with 13% of elimination product (*E*)-ethyl 4-methylpent-2-enoate (entry 3). To our satisfaction, the diester **1f** afforded the oxazole **2d** in a good 75% yield. Remarkably, the challenging derivative **1g** reacted chemoselectively with the triflate moiety in the presence of the mesylate group to afford **2e** in 54% yield. However, the cyclization reaction with particularly hindered cyclic triflate derivative **1h** did not occur but formed the dimethylfuranone **2f** in 85% yield via a 1,2-methyl shift, through a plausible reaction scenario depicted in Scheme 2.[12]

Scheme 2. Possible Reaction Mechanism To Form 2f



Finally, 4-phenyl-5-alkoxyoxazoles **2g**–**i** were directly obtained from their corresponding *α*-hydroxy esters **1i**–**k** in good yields (58–76%, entries 7–9), probably due to facile formation of the highly reactive *α*-oxo carbocation species.[13] In this case, 1.75 equiv of TMS-OTf was required to complete the reaction, probably due to a side reaction between the oxazole and the Lewis acid used in the reaction. Nevertheless, in the presence of the *α*-triflyloxy esters, the triflic acid generated in the course of the reaction would be trapped by the oxazoles formed instead of the TMS-OTf that could be used in a catalytic amount.

Next, the scope of the reaction was examined with various volatile and nonvolatile nitriles, and the results are summarized in Table 3. The amount of nitrile required for the reaction was reduced to 5 equiv, allowing their facile chromatographic purification, without noticeable loss in yields. Aliphatic nitriles afforded oxazole derivatives **2j**–**m** in 50–64% yields. The bulky trimethylacetonitrile gave the corresponding oxazole **2n** in 46% yield. The reaction proved to be compatible with an aromatic nitrile such as benzonitrile affording **2o** in 60% yield. Pleasingly, nitriles bearing functional groups such as esters or sensitive alkyl chlorides, led to formation of oxazoles **2p**–**r** in acceptable yields (41–61%).

With these results in hand, we next evaluated the possibility of using this strategy to prepare naturally occurring methyl multijuguinate **4**. This 3-hydroxypyridine alkaloid displays a moderate AChE inhibitory activity, was very recently isolated from the leaves of *Senna multijuga* with an extraction yield of 0.001%.[14] An alternative synthetic route to prepare this compound would be beneficial to further explore the biological activities of other analogs.

Although it is generally accepted that hetero-Diels–Alder (HDA) reactions between 5-ethoxyoxazoles and electron-poor dienophiles afford an efficient avenue to 3-hydroxypyridine cores, this method remains greatly underexplored to access natural products. Indeed, the electron-withdrawing group on the olefinic partner required to promote the cycloaddition step, is often undesirable on the final pyridine ring system. Also, we reasoned that acrylic acid may be a suitable cycloaddition partner for both reasons: (1) it is an excellent dienophile toward 5-alkoxyoxazoles in HDA reactions (neither thermal nor catalytic[3e] activation is required); (2) the carboxylic acid group thus generated on the pyridine core would benefit from the presence of an *ortho*-hydroxy substituent,[15] known to facilitate the protodecarboxylation reaction. Consequently, the methyl multijuguinate **4** would be accessible using the hetero-Diels–Alder reaction as key step, between conveniently substituted

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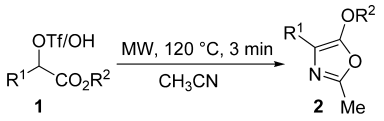
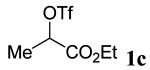
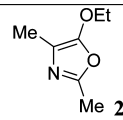
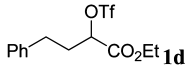
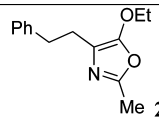
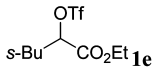
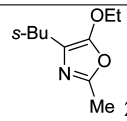
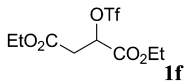
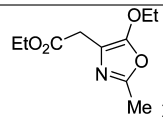
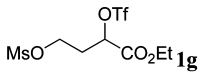
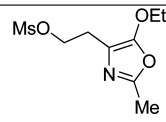
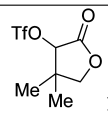
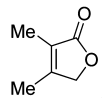
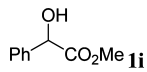
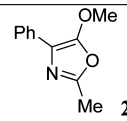
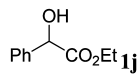
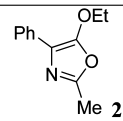
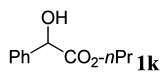
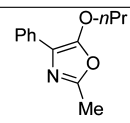
Table 2. Scope of the Reaction with a Range of α-Triflyloxy/hydroxy Esters[a]



entry	substrate	product	yield (%)[b]
1	 **1c**	 **2a**	63
2	 **1d**	 **2b**	63
3	 **1e**	 **2c**	42 (13)[c]
4	 **1f**	 **2d**	75
5	 **1g**	 **2e**	54
6	 **1h**	 **2f**	85
7	 **1i**	 **2g**	76[d]
8	 **1j**	 **2h**	70[d]
9	 **1k**	 **2i**	58[d]

[a]A solution of α-triflyloxy esters **1** (0.9 mmol) and TMS-OTf (0.09 mmol, 0.1 equiv) in acetonitrile (2.4 mL) in a microwave vial was heated for 3 min at 120 °C under microwave conditions (P_{max} = 100 W). [b]Isolated yield. [c]Isolated yield of the elimination product. [d]TMS-OTf (1.57 mmol, 1.75 equiv).

alkoxyoxazole **2q** and dienophile, followed by a final protodecarboxylation reaction to remove the undesired carboxyl group. First, the 5-ethoxyoxazole **2o** was conveniently prepared in 52% yield from ethyl-O-trifluoromethanesulfonyl-2-hydroxypropanoate **1a** and readily accessible methyl 4-cyanobutyrate, under previously optimized conditions (MW, 120 °C, 3 min). Pleasingly, cycloaddition of **2o** with acrylic acid afforded the hydroxypyridine **3** in 73% isolated yield. Next, efforts to protodecarboxylate **3** under conventional methods ($Pd(O_2CCF_3)_2$/DMF,[16] Cu/quinoline[17] or Ag_2CO_3/DMSO[18]) were unfruitful. Satisfyingly, the protodecarboxylation was effectively promoted in good 80% yield, in the presence of 10 mol % of AgOAc in NMP, at 220 °C within only 10 min, under microwave irradiation.[19] It should be stressed that in our case, addition of a mild base such as K_2CO_3 did not increase the yield as observed by Gooβen, but resulted in partial decomposition of the reaction mixture probably due to the presence of a base-sensitive ester group.[20] Consequently, the methyl multijuguinate **4** was obtained in four steps in 29% overall yield from commercially available ethyl lactate (Scheme 3).

CONCLUSION

In conclusion, we reported a rapid access to 2,4-alkyl/phenyl-5-alkoxyoxazoles from easily available α-hydroxy esters and nitriles, under microwave conditions. Optimization of the

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Scheme 3. Synthesis of the Methyl Multijuguinate 4

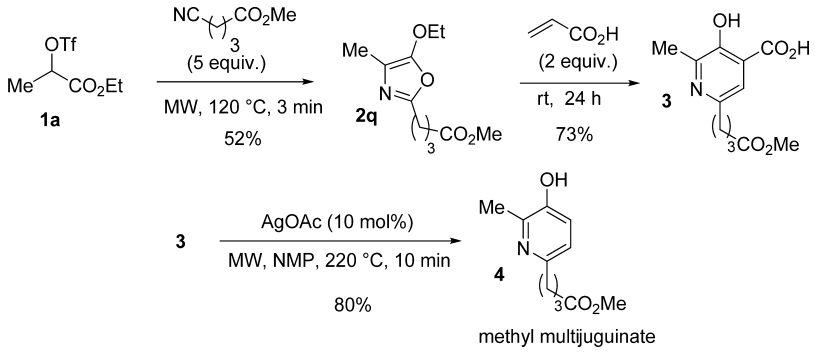
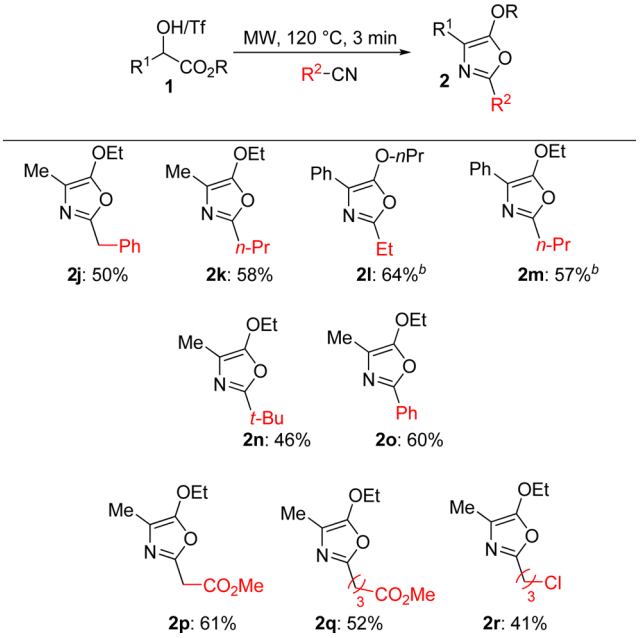


Table 3. Scope of the Reaction with Various Nitrile Derivatives[a]



[a]A solution of α-triflyloxy esters (0.9 mmol), TMS-OTf (0.09 mmol, 0.1 equiv), and nitriles (4.5 mmol, 5 equiv) in a microwave vial was heated for 3 min at 120 °C under microwave conditions (P_{max} = 100 W). [b]TMS-OTf (1.57 mmol, 1.75 equiv).

reaction conditions allowed us to considerably widen the scope of this reaction, which was found to be compatible with sensitive functional groups and allowed the first synthesis of the methyl multijuguinate within four steps from commercially available compounds in 29% overall yield (extraction yield of 0.001%). The use of acrylic acid as ethylene equivalent in the Kondrat'eva HDA is unprecedented, and should open up new opportunities for the synthesis of natural 3-hydroxypyridine alkaloids that are currently being investigated in our laboratory.

EXPERIMENTAL SECTION

General Information. All solvents were dried following standard procedures (CH_2Cl_2 and CH_3CN: distillated over CaH_2; DMF, NMP and MeOH: dried over 3A MS). Acrylic acid was distilled prior to use. Commercially available reagents were used without further purification. Column chromatography purifications were performed on Merck silica gel (40−63 μm). Thin-layer chromatography (TLC) was carried out on Merck DC Kieselgel 60 F-254 aluminum sheets. HRMS were obtained using the electrospray ionization (ESI) technique and a time-of-flight (TOF) analyzer. ^{1}H and ^{13}C NMR chemical shifts are expressed in parts per million (ppm) from $CDCl_3$ (δ_H= 7.26, δ_C = 77.00), DMSO-d_6 (δ_H= 2.50, δ_C = 39.43), MeOD-d_4 (δ_H= 3.31, δ_C = 49.05). Semipreparative HPLC were performed on a column Varian Kromasil C18, 10 μm, 21.2 × 250 mm. Microwave reactions were performed using a CEM Focused Microwave Synthesis System apparatus, Model Discover. The machine consists of a continuous focused microwave power delivery system with operator selectable power output from 0 to 300 W. All the reactions were performed in special 10 mL glass vessels under an atmosphere of argon. Reaction mixture temperatures were measured during microwave heating with an IR surface sensor located in the base of the Discover. The temperature fixed to 120 °C was maintained for 3 min. (i.e., hold time: time the system maintains the control parameters) and was usually reached within one minute (i.e., run time: maximum run time for the method for situations where the control point is not reached)

Nitrile derivatives were commercially available, except the methyl 4-cyanobutyrate **B**. α-Triflyloxy esters **1d**[21] and **1h**,[22] were prepared according to known procedures.

Methyl 4-Cyanobutyrate B. Step 1, ethyl 4-cyanobutyrate **A**:[23] A solution of ethyl 4-bromobutyrate (2 mL, 13.9 mmol) and potassium cyanide (4.54 g, 69.9 mmol, 5 equiv) in DMF (15 mL) was heated at 80 °C for 12 h. Water (60 mL) was added to the cooled solution and the solution extracted with EtOAc (2 × 50 mL). The combined organic phase was washed with satd aq NH_4Cl (40 mL) and brine (20 mL) and dried over $MgSO_4$. The crude product was purified by chromatography on silica gel (20% EtOAc/Pentane) to give the product **A** as a colorless oil (10.35 mmol, 1.460 g, 74%). The ^{1}H NMR spectrum was in accordance with literature data: ^{1}H (200 MHz, $CDCl_3$) δ 4.15 (q, J = 7.2 Hz, 2H), 2.52−2.43 (m, 4H), 2.05−1.91 (m, 2H), 1.27 (t, J = 7.2 Hz, 3H).

Step 2: methyl 4-cyanobutyrate **B**: To a stirred solution of ethyl 4-cyanobutyrate (300 mg, 2.13 mmol) in dry MeOH at 0 °C was added K_2CO_3 solid (340 mg, 2.46 mmol, 1.15 equiv). After 12 h of stirring at room temperature, the reagent mixture was concentrated, diluted in water, and extracted with EtOAc (2×). The combined organic phase was washed with satd aq NH_4Cl (40 mL) and brine (20 mL), dried over $MgSO_4$, and concentrated under reduced pressure to afford **B** (110 mg, 0.87 mmol, 41%) as a colorless oil: IR (neat) 2962, 2247, 1732, 1439, 1224, 1201, 1164; ^{1}H (200 MHz, $CDCl_3$) δ 3.70 (s, 3H), 2.54−2.43 (m, 4H), 1.99 (quint, J = 6.8 Hz, 2H); ^{13}C (75 MHz, $CDCl_3$) δ 172.3, 119.0, 51.7, 32.0, 20.6, 16.4. Anal. Calcd for $C_6H_9NO_2$: C, 56.68; H, 7.13; N, 11.02. Found: C, 56.22; H, 7.14; N, 11.21.

Ethyl 2-[[(Trifluoromethyl)sulfonyl]oxy]propanoate 1c.[24] To a solution of ethyl lactate (635 mg, 5.38 mmol) in dry CH_2Cl_2 (5 mL) were added dropwise and successfully 2,6-lutidine (0.75 mL, 6.45 mmol, 1.2 equiv) and trifluoromethanesulfonic anhydride (1.0 mL, 5.9 mmol, 1.1 equiv) at 0 °C under inert atmosphere. The mixture was then stirred at the same temperature for 1.5 h and monitored by TLC for consumption of starting material. The solution was washed by water, dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was finally purified by chromatography on silica gel (100% CH_2Cl_2) to give the product as an orange oil (5.22 mmol,

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1.306 g, 97%). ^{1}H NMR spectrum was in accordance with literature data.

Ethyl 4-Methyl-2-[[(trifluoromethyl)sulfonyl]oxy]pentanoate 1e. The triflate was prepared according to the procedure described above using ethyl 2-hydroxy 4-methylpentanoate (600 mg, 3.75 mmol), 2,6-lutidine (0.52 mL, 4.50 mmol, 1.2 equiv) and trifluoromethanesulfonic anhydride (0.69 mL, 4.13 mmol, 1.1 equiv) in dry CH_2Cl_2 (3 mL). The crude product was purified by chromatography on silica gel (100% CH_2Cl_2, R_f = 0.8) to give the product as an orange oil (3.34 mmol, 976 mg, 89%): IR (neat) 2968, 1764, 1417, 1197, 1143; ^{1}H (200 MHz, $CDCl_3$) δ 5.17−5.11 (m, 1H), 4.30 (q, J = 7.2 Hz, 2H), 2.01−1.92 (m, 1H), 1.88−1.70 (m, 2H), 1.33 (t, J = 7.2 Hz, 3H), 0.99 (d, J = 6.0 Hz, 6H); ^{13}C (75 MHz, $CDCl_3$) δ 167.6, 118.6 (q, J = 317.3 Hz), 82.6, 62.7, 40.7, 24.1, 22.8, 21.0, 13.9. Anal. Calcd for $C_9H_{15}F_3O_5S$: C, 36.98; H, 5.16; S, 10.97. Found: C, 36.97; H, 5.16; S, 10.79.

Diethyl 2-[[(Trifluoromethyl)sulfonyl]oxy]succinate 1f. The triflate was prepared according to the procedure described above, using the diethyl 2-hydroxysuccinate (500 mg, 2.63 mmol), 2,6-lutidine (0.37 mL, 3.16 mmol, 1.2 equiv), and trifluoromethanesulfonic anhydride (0.49 mL, 2.89 mmol, 1.1 equiv) in dry CH_2Cl_2 (5 mL). The crude product was purified by chromatography on silica gel (100% CH_2Cl_2, R_f = 0.8) to give the product as an orange oil (2.48 mmol, 800 mg, 95%): IR (neat) 2985, 1739, 1419, 1201, 1140, 1021; ^{1}H (200 MHz, $CDCl_3$) δ 5.48 (t, J = 5.8 Hz, 1H), 4.33 (q, J = 7.2 Hz, 2H), 4.22 (q, J = 7.2 Hz, 2H), 3.04 (d, J = 6.0 Hz, 2H), 1.34 (t, J = 7.2 Hz, 3H), 1.28 (t, J = 7.2 Hz, 3H); ^{13}C (75 MHz, $CDCl_3$) δ 167.6, 166.1, 118.4 (q, J = 317.6 Hz), 78.9, 63.2, 61.8, 36.9, 14.0, 13.8; HRMS (ESI+) calcd for $C_9H_{14}F_3O_7S$ 323.0401, found 323.0407.

Ethyl 4-[(Methylsulfonyl)oxy]-2-[[(trifluoromethyl)sulfonyl]-oxy]butanoate 1g. The triflate was prepared according to the procedure described above, using ethyl 2-hydroxy 4-[(methylsulfonyl)-oxy]butanoate[25] (231 mg, 1.02 mmol, 1 equiv), 2,6-lutidine (0.12 mL, 1.22 mmol, 1.2 equiv), and trifluoromethanesulfonic anhydride (0.19 mL, 4.13 mmol, 1.12 equiv) in dry CH_2Cl_2 (4 mL). The crude product was purified by chromatography on silica gel (100% CH_2Cl_2, R_f = 0.7) to give the product as an orange oil (0.72 mmol, 257 mg, 70%): IR (neat) 2987, 2951, 1754, 1413, 1360, 1205, 1174, 1138; ^{1}H (200 MHz, CDCl3) δ 5.29 (dd, J = 7.2 Hz, J = 4.6 Hz, 1H), 4.48−4.28 (m, 4H), 3.05 (s, 3H), 2.54−2.43 (m, 2H), 1.35 (t, J = 7.2 Hz, 3H); ^{13}C (50 MHz, $CDCl_3$) δ 166.3, 118.4 (q, J = 317.4 Hz), 79.5, 63.8, 63.1, 37.1, 31.5, 13.7; HRMS (ESI+) calcd for $C_8H_{13}F_3O_8NaS_2$ 380.9902, found 380.9906.

General Procedure for the Synthesis of the 5-Alkoxyoxazoles 2a−r. To the corresponding triflate (0.9 mmol) was added acetonitrile (2.40 mL) or a functionalized nitrile (4.5 mmol, 5 equiv) under inert atmosphere in a microwave vial, equipped with a magnetic stirrer bar. Then, trimethylsilyl trifluoromethanesulfonate (16 μL, 0.09 mmol, 0.1 equiv) was added. The vial was sealed and the reaction was performed in a microwave during 3 min (holding time) at 120 °C with a maximum power of 100 W. The solution was quenched with satd aq $NaHCO_3$ (10 mL) and extracted with CH_2Cl_2 or AcOEt (2 × 15 mL). The organic phases were washed with brine (5 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was finally purified by chromatography on silica gel to give the desired product. For aromatic α-hydroxy esters (0.9 mmol), the same procedure was used. However, the quantity of trimethylsilyl trifluoromethanesulfonate was increased (0.29 mL, 1.58 mmol, 1.75 equiv).

2,4-Dimethyl-5-ethoxy-1,3-oxazole 2a:[1b] 0.57 mmol, 80 mg, 63%. ^{1}H NMR spectrum is in accordance with literature: ^{1}H (200 MHz, $CDCl_3$) δ 4.10 (q, J = 7.0 Hz, 2H), 2.30 (s, 3H), 1.99 (s, 3H), 1.34 (t, J = 7.0 Hz, 3H).

5-Ethoxy-2-methyl-4-phenethyl-1,3-oxazole 2b: 0.56 mmol, 130 mg, 63%; 100% CH_2Cl_2, R_f = 0.1; yellow oil; IR (neat) 3029, 2975, 2929, 1667, 1583, 1452, 1378, 1267, 1016; ^{1}H (200 MHz, $CDCl_3$) δ 7.31−7.17 (m, 5H), 3.87 (q, J = 7.0 Hz, 2H), 2.94−2.87 (m, 2H), 2.68−2.60 (m, 2H), 2.34 (s, 3H), 1.24 (t, J = 7.0 Hz, 3H); ^{13}C (75 MHz, $CDCl_3$) δ 153.9, 152.4, 141.9, 128.6, 128.3, 125.9, 116.1, 70.5, 34.9, 26.9, 15.0, 14.4; HRMS (ESI+) calcd for $C_{14}H_{18}NO_2$ 232.1338, found 232.1336.

2-Methyl-4-*sec*-butyl-5-ethoxy-1,3-oxazole 2c: 0.38 mmol, 69 mg, 42%; 100% CH_2Cl_2, R_f = 0.7; yellow oil; IR (neat) 2954, 2928, 1667, 1587, 1371, 1256, 1191, 1021; ^{1}H (300 MHz, $CDCl_3$) δ 4.10 (q, J = 7.2 Hz, 2H), 2.31 (s, 3H), 2.20 (d, J = 6.9 Hz, 2H), 1.97−1.88 (m, 1H), 1.35 (t, J = 7.2 Hz, 2H), 0.91 (d, J = 4.2 Hz, 6H); ^{13}C (75 MHz, $CDCl_3$) δ 154.2, 152.1, 116.0, 70.3, 33.7, 27.8, 22.4, 15.1, 14.3; HRMS (ESI+) calcd for $C_{10}H_{18}NO_2$ 184.1338, found 184.1336.

Ethyl 2-(5-ethoxy-2-methyloxazol-4-yl)acetate 2d: 0.68 mmol, 144 mg, 75%; 80% cyclohexane/20% AcOEt, R_f = 0.1; yellow oil; IR (neat) 2980, 1735, 1679, 1584, 1377, 1257, 1181, 1151, 1019; ^{1}H (200 MHz, $CDCl_3$) δ 4.23−4.11 (m, 4H), 3.40 (s, 2H), 2.33 (s, 3H), 1.36 (td, J = 7.2 Hz, J = 0.8 Hz, 3H), 1.26 (td, J = 7.2 Hz, J = 0.8 Hz, 3H); ^{13}C (75 MHz, $CDCl_3$) δ 170.4, 154.8, 152.4, 109.9, 70.3, 60.8, 30.7, 14.8, 14.2, 14.1; HRMS (ESI+) calcd for $C_{10}H_{16}NO_4$ 214.1079, found 214.1083.

2-(5-Ethoxy-2-methyloxazol-4-yl)ethyl methanesulfonate 2e: 0.38 mmol, 94 mg, 54%, 80% cyclohexane/20% AcOEt, R_f = 0.3; yellow oil; IR (neat) 2990, 2933, 1674, 1737, 1674, 1350, 1268, 1169; ^{1}H (300 MHz, $CDCl_3$) δ 4.41 (t, J = 6.9 Hz, 2H), 4.15 (q, J = 7.2 Hz, 2H), 2.98 (s, 3H), 2.81 (t, J = 6.9 Hz, 2H), 2.31 (s, 3H), 1.36 (t, J = 7.2 Hz, 3H); ^{13}C (75 MHz, $CDCl_3$) δ 154.7, 152.6, 111.0, 70.4, 68.1, 37.2, 25.0, 14.9, 14.2; HRMS (ESI+) calcd for $C_9H_{16}NO_5S$ 250.0749, found 250.0759.

3,4-Dimethyl-2(5*H*)-furanone 2f:[26] 0.77 mmol, 86 mg, 85%, 100% CH_2Cl_2, R_f = 0.2. ^{1}H NMR spectrum is in accordance with literature: ^{1}H (200 MHz, $CDCl_3$) δ 4.61 (q, J = 1.0 Hz, 2H), 2.01 (d, J = 1.0 Hz, 3H), 1.81 (q, J = 1.0 Hz, 3H).

2-Methyl-4-phenyl-5-methoxy-1,3-oxazole 2g:[10] 0.69 mmol, 130 mg, 76%; yellow oil. ^{1}H NMR spectrum is in accordance with literature: ^{1}H (200 MHz, $CDCl_3$) δ 7.77 (d, J = 7.6 Hz, 2H), 7.37 (t, J = 7.4 Hz, 2H), 7.21 (t, J = 7.4 Hz, 1H), 4.03 (s, 3H), 2.42 (s, 3H).

2-Methyl-4-phenyl-5-ethoxy-1,3-oxazole 2h:[27] 0.64 mmol, 129 mg, 70%; yellow oil. ^{1}H NMR spectrum is in accordance with literature: ^{1}H (300 MHz, $CDCl_3$) δ 7.79 (d, J = 7.2 Hz, 2H), 7.37 (t, J = 7.5 Hz, 2H), 7.21 (t, J = 7.5 Hz, 1H), 4.30 (q, J = 7.2 Hz, 2H), 2.41 (s, 3H), 1.45 (t, J = 7.2 Hz, 3H).

2-Methyl-4-phenyl-5-n-propyloxy-1,3-oxazole 2i: 0.53 mmol, 114 mg, 58%; yellow oil; IR (neat) 2974, 1643, 1365, 1201; ^{1}H (300 MHz, $CDCl_3$) δ 7.79 (d, J = 8.4 Hz, 2H), 7.37 (t, J = 7.5 Hz, 2H), 7.20 (t, J = 7.2 Hz, 1H), 4.19 (t, J = 6.6 Hz, 2 Hz), 2.41 (s, 3H), 1.83 (hex, J = 7.2 Hz, 2H), 1.05 (t, J = 7.2 Hz, 3H); ^{13}C (75 MHz, $CDCl_3$) δ 153.6, 151.7, 131.4, 128.2, 125.9, 124.6, 114.7, 75.1, 22.6, 14.0, 10.1; HRMS (ESI+) calcd for $C_{13}H_{16}NO_2$ 218.1176, found 218.1175.

2-Benzyl-4-methyl-5-ethoxy-1,3-oxazole 2j: 0.45 mmol, 98 mg, 50%, 100% CH_2Cl_2, R_f = 0.4; yellow oil; IR (neat) 2984, 2937, 1661, 1322, 1234, 1015; ^{1}H (300 MHz, $CDCl_3$) δ 7.34−7.21 (m, 5H), 4.08 (q, J = 7.1 Hz, 2H), 3.94 (s, 2H), 2.00 (s, 3H), 1.31 (t, J = 7.1 Hz, 3H); ^{13}C (75 MHz, $CDCl_3$) δ 153.9, 153.6, 135.8, 128.6, 128.6, 126.9, 112.7, 70.2, 35.1, 14.9, 10.0; HRMS (ESI+) calcd for $C_{13}H_{16}NO_2$ 218.1181, found 218.1180.

2-*n*-Propyl-4-methyl-5-ethoxy-1,3-oxazole 2k: 0.52 mmol, 88 mg, 58%, 100% CH_2Cl_2, R_f = 0.2; yellow oil; IR (neat) 2965, 1741, 1675, 1576, 1223; ^{1}H (300 MHz, $CDCl_3$) δ 4.10 (q, J = 7.2 Hz, 2H), 2.57 (t, J = 7.5 Hz, 2H), 2.00 (s, 3H), 1.71 (quint, J = 7.5 Hz, 2H), 1.34 (t, J = 7.2 Hz, 3H), 0.97 (t, J = 7.5 Hz, 2H); ^{13}C (75 MHz, $CDCl_3$) δ 155.4, 153.2, 112.1, 70.0, 30.2, 20.1, 14.7, 13.4, 9.7; HRMS (ESI+) calcd for $C_9H_{16}NO_2$ 170.1181, found 170.1175.

2-Ethyl-4-phenyl-5-ethoxy-1,3-oxazole 2l: 0.58 mmol, 134 mg, 64%; yellow oil; IR (neat) 2969, 1741, 1642, 1449, 1361; ^{1}H (300 MHz, $CDCl_3$) δ 7.80 (d, J = 7.2 Hz, 2H), 7.37 (t, J = 7.5 Hz, 2H), 7.20 (t, J = 7.2 Hz, 1H), 4.20 (t, J = 6.6 Hz, 2H), 2.74 (q, J = 7.5 Hz, 2H), 1.83 (m, J = 7.5 Hz, 2H), 1.34 (t, J = 7.8 Hz, 3H), 1.05 (t, J = 7.2 Hz, 3H); ^{13}C (75 MHz, $CDCl_3$) δ 156.1, 153.5, 131.6, 128.3, 125.9, 124.7, 114.6, 75.0, 22.7, 21.9, 11.1, 10.2; HRMS (ESI+) calcd for $C_{14}H_{18}NO_2$ 232.1338, found: 232.1330.

2-*n*-Propyl-4-phenyl-5-ethoxy-1,3-oxazole 2m: 0.51 mmol, 118 mg, 57%; yellow oil; IR (neat) 2968, 1642, 1604, 1449, 1379, 1352, 1192; ^{1}H (300 MHz, $CDCl_3$) δ 7.81 (d, J = 7.2 Hz, 2H), 7.37 (t,

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J = 7.5 Hz, 2H), 7.20 (t, J = 7.2 Hz, 1H), 4.30 (q, J = 6.9 Hz, 2H), 2.68 (t, J = 7.5 Hz, 2H), 1.79 (m, J = 7.2 Hz, 2H), 1.44 (t, J = 6.9 Hz, 3H), 1.01 (t, J = 7.5 Hz, 3H); ^{13}C (75 MHz, $CDCl_3$) δ 155.3, 153.2, 131.5, 128.2, 125.9, 124.7, 114.9, 69.3, 30.2, 20.3, 14.9, 13.5; HRMS (ESI+) calcd for $C_{14}H_{18}NO_2$ 232.1338, found 232.1331.

2-*tert*-Butyl-4-methyl-5-ethoxy-1,3-oxazole 2n: 0.41 mmol, 76 mg, 46%, 100% CH_2Cl_2, R_f = 0.3; yellow oil; IR (neat) 2974, 2937, 1682, 1562, 1307, 1228, 1171, 1082, 1020; ^{1}H (300 MHz, $CDCl_3$) δ 4.11 (q, J = 7.2 Hz, 2H), 2.01 (s, 3H), 1.37 (t, J = 7.2 Hz, 3H), 1.32 (s, 9H); ^{13}C (75 MHz, $CDCl_3$) δ 161.8, 153.3, 112.0, 70.2, 33.6, 28.4, 15.0, 10.1; HRMS (ESI+) calcd for $C_{10}H_{18}NO_2$ 184.1338, found 184.1335.

2-Phenyl-4-methyl-5-ethoxy-1,3-oxazole 2o:[28] 0.54 mmol, 109 mg, 60%, 50% pentane/50% CH_2Cl_2, R_f = 0.3; yellow oil. ^{1}H NMR spectrum is in accordance with literature: ^{1}H (300 MHz, $CDCl_3$) δ 7.93−7.90 (m, 2H), 7.45−7.37 (m, 3H), 4.24 (q, J = 7.2 Hz, 2H), 2.12 (s, 3H), 1.41 (t, J = 7.2 Hz, 3H).

Methyl 2-(5-ethoxy-4-methyloxazol-2-yl)acetate 2p: 0.55 mmol, 110 mg, 61%, 100% CH_2Cl_2, R_f = 0.2; yellow oil; IR (neat) 2984, 2958, 1744, 1671, 1583, 1223, 1202, 1166, 1098, 1010; ^{1}H (300 MHz, $CDCl_3$) δ 4.14 (q, J = 7.1 Hz, 2H), 3.74 (s, 3H), 3.69 (s, 2H), 2.02 (s, 3H), 1.35 (t, J = 7.1 Hz, 3H); ^{13}C (75 MHz, $CDCl_3$) δ 168.1, 154.3, 147.8, 113.1, 70.2, 52.4, 34.6, 14.8, 9.8; HRMS (ESI+) calcd for $C_9H_{14}NO_4$ 200.0923, found 200.0923.

Methyl 4-(5-ethoxy-4-methyloxazol-2-yl)butanoate 2q: 0.46 mmol, 104 mg, 52%, 100% CH_2Cl_2, R_f = 0.1; colorless oil; IR (neat) 2987, 1737, 1674, 1576, 1221; ^{1}H (300 MHz, $CDCl_3$) δ 4.10 (q, J = 7.2 Hz, 2H), 3.66 (s, 3H), 2.66 (t, J = 7.2 Hz, 2H), 2.40 (t, J = 7.2 Hz, 2H), 2.04 (quint, J = 7.2 Hz, 2H), 1.99 (s, 3H), 1.34 (t, J = 7.2 Hz, 3H); ^{13}C (75 MHz, $CDCl_3$) δ 173.1, 154.3, 153.4, 112.3, 70.0, 51.3, 32.8, 27.5, 21.8, 14.8, 9.8; HRMS (ESI+) calcd for $C_{11}H_{18}NO_4$ 228.1236, found 228.1232.

2-(3-Chloropropyl)-5-ethoxy-4-methyloxazole 2r: 0.38 mmol, 77 mg, 41%, 100% CH_2Cl_2, R_f = 0.4; orange oil; IR (neat) 2977, 2924, 1676, 1578, 1224, 1085, 1017; ^{1}H (300 MHz, $CDCl_3$) δ 4.11 (q, J = 7.1 Hz, 2H), 3.62 (t, J = 6.3 Hz, 2H), 2.79 (t, J = 7.3 Hz, 2H), 2.19 (tt, J = 7.2 Hz, J = 6.4 Hz, 2H), 2.00 (s, 3H), 1.35 (t, J = 7.1 Hz, 3H); ^{13}C (75 MHz, $CDCl_3$) δ 154.1, 153.7, 112.6, 70.3, 43.9, 29.5, 25.6, 15.0, 10.0; HRMS (ESI+) calcd for $C_9H_{15}ClNO_2$ 204.0789, found 204.0787.

3-Hydroxy-6-(4-methoxy-4-oxobutyl)-2-methylisonicotinic Acid 3. To a stirred solution of the oxazole **2q** (1.08 g, 4.75 mmol) at 0 °C in a 1 mL round-bottom flask under argon atmosphere was added the acrylic acid freshly distilled (651 μL, 9.50 mmol, 2 equiv). The reagent mixture was stirred for 24 h at room temperature. The precipitate obtained was washed several times with small portions of Et_2O, precipitate concentrated to afford **3** (875 mg, 3.46 mmol, 73%) as a white solid: mp 248−250 °C; IR (neat) 2511, 1726, 1611, 1411, 1261; ^{1}H (300 MHz, DMSO-d_6) δ 7.64 (s, 1H), 3.56 (s, 3H), 2.79 (t, J = 7.5 Hz, 2H), 2.47 (s, 3H), 2.35 (t, J = 7.5 Hz, 2H), 1.89 (quint, J = 7.5 Hz, 2H); ^{13}C (50 MHz, DMSO-d_6) δ 172.7, 167.9, 157.9, 144.9, 141.1, 127.0, 122.0, 51.1, 32.2, 31.6, 24.3, 15.0. Anal. Calcd for $C_{12}H_{15}NO_5$: C, 56.91; H, 5.97; N, 5.53. Found: C, 56.57; H, 5.97; N, 5.47.

Methyl Multijuguinate 4. The carboxylic acid B (50 mg, 0.2 mmol) was dissolved in dry NMP (1.5 mL) in an oven-dried 10 mL microwave vial. Then AgOAc (3.3 mg, 0.02 mmol, 0.1 equiv), dried for 1 h under reduced pressure, was added, and argon was bubbled through the solution for 15 min. The reaction vessel was sealed and the reaction mixture was heated by microwave irradiation at 220 °C for 10 min with a fixed hold time. After cooling, the reaction mixture was directly purified by semipreparative RP-HPLC (solvent system: 0.1% aq TFA 100% (5 min) followed by linear gradient from 100% to 95% of 0.1% aq TFA/CH_3CN (10 min), then 95% of 0.1% aq TFA/CH_3CN (5 min), followed by a linear gradient from 95% to 75% of 0.1% aq TFA/CH_3CN (20 min); solvent flow 20 mL/min; t_R = 28.70−34.15 min). The product-containing fractions were lyophilized to afford the pure pyridinium trifluoroacetate. The residue was dissolved in EtOAC (10 mL) and a satd aq $NaHCO_3$ (5 mL). The aqueous layer was separated and extracted with EtOAc (2 × 20 mL).The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo to afford the methyl multijuguinate **4** (33 mg, 0.16 mmol, 80%) as white solid: mp 120−122 °C; IR (neat) 2963, 1729, 1437, 1278; ^{1}H (300 MHz, MeOD-d_4) δ 7.06 (d, J = 8.1 Hz, 1H), 6.92 (d, J = 8.1 Hz, 1H), 3.63 (s, 3H), 2.66 (t, J = 7.5 Hz, 2H), 2.38 (s, 3H), 2.32 (t, J = 7.5 Hz, 2H), 1.92 (quint, J = 7.5 Hz, 2H); ^{13}C (75 MHz, MeOD-d_4) δ 175.5, 151.6, 151.5, 146.9, 123.8, 122.5, 52.0, 36.7, 34.1, 26.7, 18.3.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

NMR spectra for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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