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An improved procedure for the lateral lithiation of ethyl 4-acetyl-5-methyl-3-isoxazolyl carboxylate☆

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Abstract—Ethyl 4-acetyl-5-methyl-3-isoxazolyl carboxylate was smoothly lithiated at the 5-methyl position, when the 4-acetyl group was protected with a 5,5-dimethyl-1,3-dioxanyl group. The lithio anion was quenched with a variety of electrophiles such as alkyl halides, aldehydes, TMSCl, and Me_3SnCl in good to excellent yields. The lithiation of the unprotected compound and the 4-acetyl group protected as 1,3-dioxolanyl both failed. The effects of different bases have been investigated and the addition of LiCl significantly increased yields. Based on variable temperature NMR studies the 5,5-dimethyl-1,3-dioxanyl group appears to occupy a single chair conformation which may facilitate lateral metalation. This represents a facile entry into 5-functionalized 3-isoxazolyl carboxylic acid derivatives as prodrugs for the AMPA glutamate neurotransmitters of the central nervous system.

1. Introduction

Analogues of α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA, **1**), an ionotropic glutamate receptor agonist, may be of significant medicinal value since excitatory imbalance of these receptors is thought to be the primary culprit in neurological disorders including epilepsy, cerebral ischemia, Parkinson's, Huntington's, and Alzheimer's diseases.[2] 2-Amino-3-(3-carboxyl-5-methyl-4-isoxazolyl)-propionic acid, ACPA (**2**) has been identified as a promising lead in the search for potential drug candidates (Fig. 1).[3a,b] In a recent review[1a] Krogsgaard–Larsen indicated that the C-5 substituted AMPA analogues APPA (**3**) and ATPA (**4**) exhibit subunit specific binding to glutamate receptors. It is theorized that the receptor subunits contain a lipophilic pocket capable of accommodating groups up to a certain size and this is supported by the single crystal X-ray of a glutamate receptor bound with the AMPA ligand.[3c,d] In addition, lipophilic groups could facilitate passage through the blood brain barrier, a prerequisite for neurological drug candidates. To this end we have developed an efficient method for the lateral lithiation of ethyl 4-[1-(5,5-dimethyl-1,3-dioxanyl)]-ethyl-5-methyl-3-isoxazolyl carboxylate, (**8**) to serve as a precursor in the pursuit of AMPA analogues.

In structure activity relationship studies of 4-isoxazolyl-1,4-dihydropyridines, we previously reported lateral lithiation of 4-oxazolinyl-isoxazoles as a facile entry to functionally complex isoxazoles.[4] In the development of AMPA analogues, different starting materials were usually required to produce the desired 5-functionalized isoxazoles through

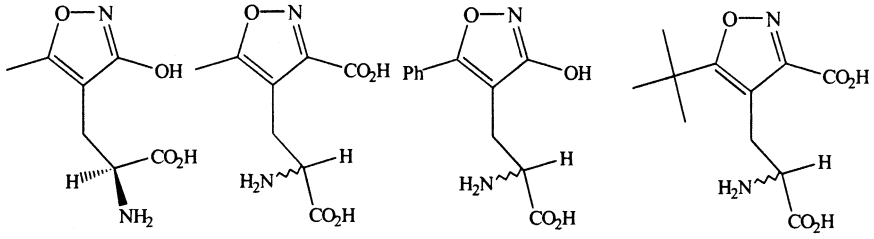

Figure 1.

☆ See Ref. 1b.

Keywords: isoxazole; lateral lithiation; AMPA.

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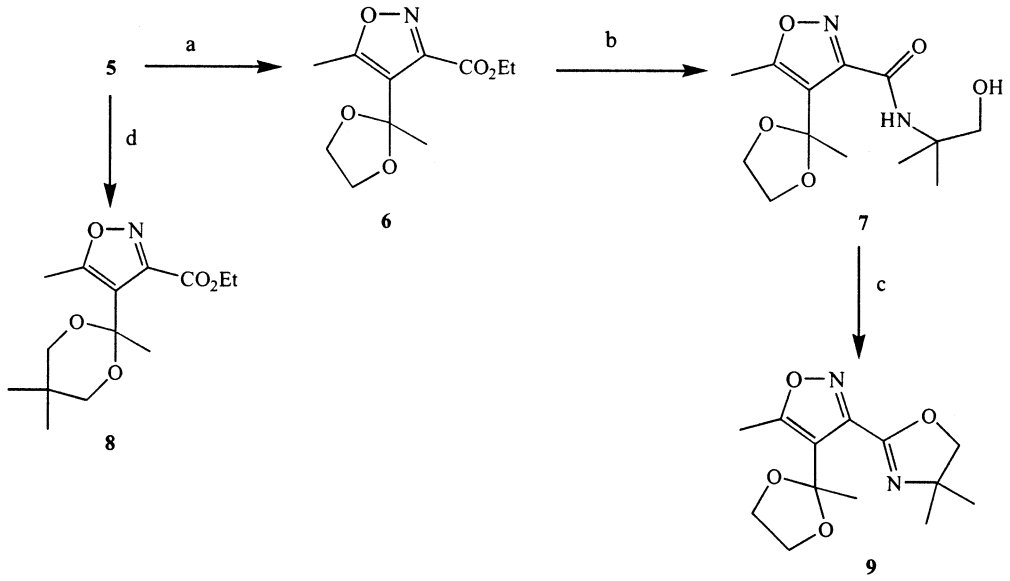


Figure 2. (a) $(CH_2OH)_2$, TsOH–H_2O, C_6H_6, 86%. (b) 2-amino-2-methyl-1-propanol, nBuLi, 1% $SmCl_3$, CH_2Cl_2, 96%. (c) Ph_3P, CCl_4, NEt_3, CH_3CN, 82%. (d) 2,2-dimethyl-1,3-propanediol, TsOH–H_2O, C_6H_6, 97%.

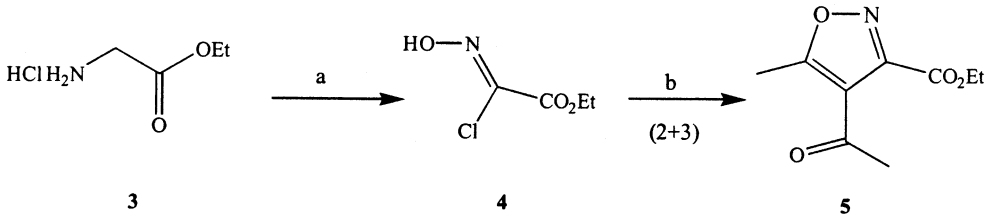


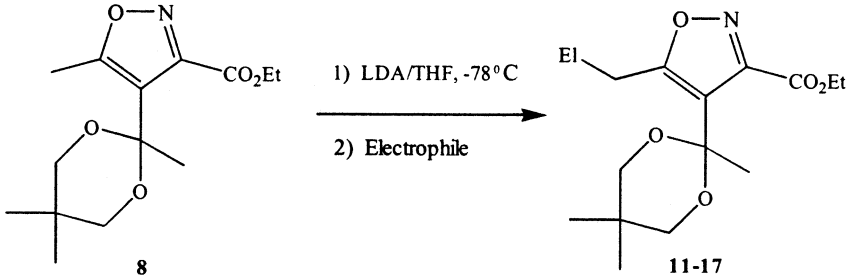
Figure 3. (a) 2 equiv. HCl, 2 equiv. $NaNO_2$, −5°C, 54%. (b) 2,4-pentanedione, NaOEt/EtOH, 83%.

2+3 cycloadditions.[3,6] The use of the 5,5-dimethyl-1,3-dioxanyl as a successful protecting group in previous studies made it a promising candidate for the lithiation of (**5**) (Fig. 2).[5]

2. Results

The starting material (**5**) was prepared with a 2+3 cycloaddition of ethyl chloroximidoacetate (**4**)[7] and 2,4-pentanedione by a modified method (Fig. 3).[8] Lateral lithiation of both (**5**) and the 1,3-dioxolanyl protected (**6**) resulted in a mixture of unidentified decomposition products. Further protection of the 3-ethoxycarbonyl in (**6**) as 4′,4′-dimethyl-2-oxazolinyl group was expected to facilitate the lateral lithiation. Indeed, lateral lithiation of (**9**) gave the desired product, but only in low yield along with a mixture of decomposition products again. Using the 5,5-dimethyl-

Table 1. Lateral lithiation of **8** with LDA/electrophiles



Entry	Electrophile	Product	Yield (%)
1	MeI	**11** (Me)	81
2	BnBr	**12** (Bn)	72
3	Acetone	**13** [$C(OH)Me_2$]	68
4	TMSCl	**14** ($SiMe_3$)	66
5	Me_3SnCl	**15** ($SnMe_3$)	42
6	MeSSMe	**16** (SMe)	61
7	PhNCO	**17** (CONHPh)	68

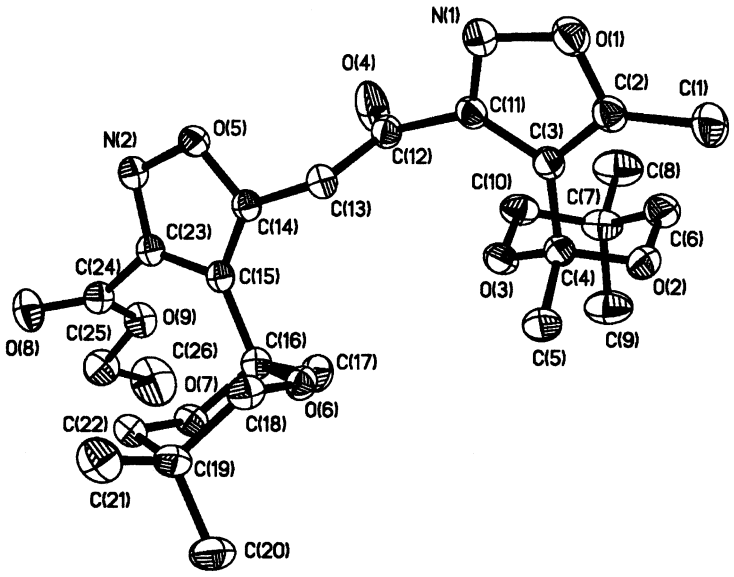


Figure 4. ORTEP plot for isoxazole dimer **23** the primary reaction byproduct (at 30% probability, H atoms omitted for clarity).

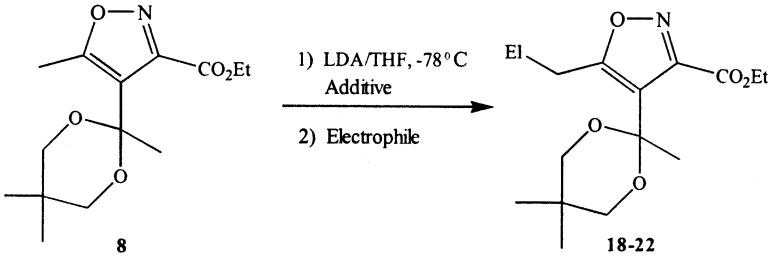
1,3-dioxanyl protecting group on (**5**) gave compound (**8**). Lateral lithiation of (**8**) with LDA followed by electrophilic quenching produced the results as shown in Table 1. The primary lithiation byproduct (**23**) was isolated and an X-ray crystal structure obtained (Fig. 4). Significantly, both dioxanyl rings of (**23**) adopt the isoxazole-axial conformation observed for the starting material (**8**).[9] Intermolecular condensation of one C-3 ester produces this ketone dimer (**23**) however, this side reaction can be supressed by running the reaction at −100°C with slow addition of the electrophiles, as this reaction is observed to be highly exothermic. Although the use of other bases was attempted (i.e. *t*BuLi, LiHMDS, NaHMDS), LDA provided the optimum results to date.

On a multigram scale the reaction should be run at −100°C to maintain reported yields. When LiCl (6 equiv.) was added the yields were improved for aldehyde addition as shown in Table 2. HMPA (as a cation-complexing agent) dramatically lowered the yield to less than 10% (entry 3). Intermediate amounts of LiCl worked well for the ethyl bromide example.

3. Discussion

Several reactions generally compete with lateral lithiation of the 5-methyl in the isoxazoles.[10] Strong bases are also known to produce single electron transfer reactions, which lead to the cleavage of the oxygen nitrogen bond in isoxazole ring.[11] The corresponding acid of (**5**) is not stable due to decarboxylation of the conjugated vinylogous

Table 2. Lateral lithiation of **8** in the presence of an additive



Entry	Electrophile	Additive	Product (%)
1	PhCHO	None	**18** (72)
2	PhCHO	6 equiv. LiCl	**18** (95)
3	PhCHO	20% HMPA	**18** (<10)
4	*p*-ClC_6H_4CHO	None	**19** (67)
5	*p*-ClC_6H_4CHO	6 equiv. LiCl	**19** (83)
6	Me_2CHCH_2CHO	6 equiv. LiCl	**20** (79)
7	*trans*-Cinnamaldehyde	6 equiv. LiCl	**21** (82)
8	EtBr	None	**22** (65)
9	EtBr	1.5 equiv. LiCl	**22** (83)
10	EtBr	6 equiv. LiCl	**22** (0)

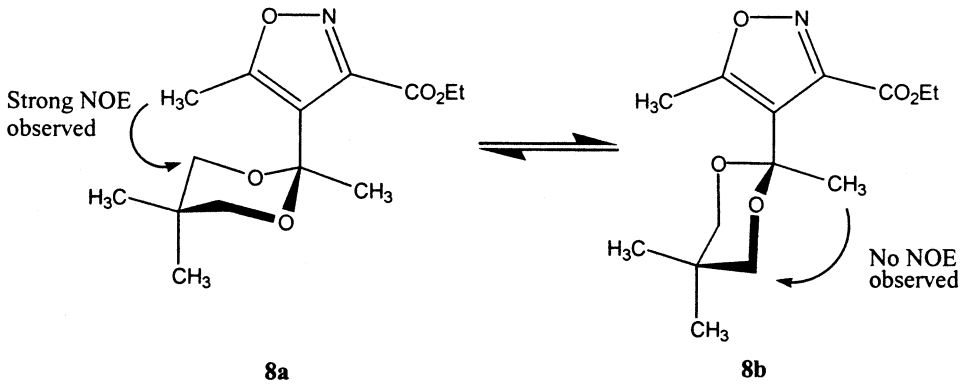


Figure 5. In the solid state only **8a** was observed by X-ray crystallography and NMR data indicates that this may predominate in solution as well.

β-hetero-carboxylic acid system, which produced 2-acetyl-3-oxobutyronitrile (**10**). The low yield of lateral lithiation for (**9**) might also be attributed to β-elimination of the 1,3-dioxolanyl group.[12]

We reasoned that the 5,5-dimethyl-1,3-dioxanyl protecting group would be a better choice due to its dimethyl group prohibiting a possible β-elimination. The oxygen atoms of the dioxoanyl as potential electron donors would likely favor the lateral lithiation process. X-Ray crystallography reveals that the dioxanyl ring of (**8**) adopts a single chair conformation (**8a**) with the isoxazole axial to it (Fig. 5).[9] To determine the behavior of (**8**) in solution, solid state ^{13}C NMR, variable temperature ^{13}C NMR, ^{1}H NMR, and ROESY were performed. The striking similarity of the ^{13}C NMR recorded in the solid state, where it is known that the dioxanyl ring is in a single chair conformation (**8a**), with the solution phase ^{13}C NMR recorded at −100°C, supports the idea that (**8**) exists as a single conformer in solution at low temperature.

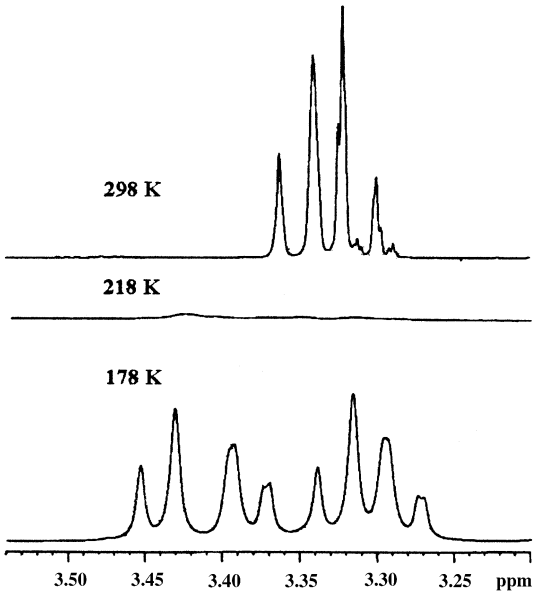


Figure 6. Variable temperature ^{1}H NMR of **8** shows a reduction in free rotation at −100°C between the isoxazole and dioxanyl rings making the dioxanyl methylene protons nonequivalent with the coalescence point at −55°C.

In d8-THF at room temperature, the methylene protons of the dioxanyl ring give a single AB quartet and in the ^{13}C NMR, the methylene carbons are equivalent giving a single signal at 72.3 ppm. Upon cooling, the methylene AB quartet coalesces at −55°C and subsequently splits into two AB quartets at −100°C (Fig. 6). The coalescence point at −55°C correlates well with the literature inversion barrier of 5,5-dimethyl dioxane[13] (10.5 Kcal mol^{-1}), but could result from either chair to chair interconversion or restricted rotation between the isoxazole and dioxane rings. The ROESY spectrum at −100°C shows that the C-5 methyl of the isoxazole strongly correlates with only one pair of the dioxanyl methylene protons (Fig. 7), suggesting restricted rotation of the isoxazole ring. At −100°C the methylene carbons of the dioxane ring also split into two signals (69.7, 70.3 ppm) in the ^{13}C NMR similarly indicating a lack of free rotation between the isoxazole and dioxane rings.

The lack of any NOE coupling between the dioxanyl C-2 methyl group and dioxanyl methylenes also suggests a single chair conformer is present, since the second chair (**8b**) places these groups in close proximity. In addition, if the nonequivalence at low temperature were a product of two conformers of the dioxane ring, we would expect four carbon signals for the 5,5-dimethyl group of the dioxane ring in the low temperature ^{13}C NMR, but observe only two. The NMR data strongly suggests (**8**) is locked in a single chair conformer (**8a**) which places the C-5 methyl group of the isoxazole in close proximity to a dioxanyl oxygen atom which may facilitate the metalation process.

There is significant evidence from previous studies of 1,3-dioxane to indicate that compound (**8**) would be expected to adopt a favored chair conformation with the isoxazole axial. Because of puckering at the C-2 end of the dioxane ring and short C–O bond lengths, an aliphatic axial substituent is much closer to the methylene protons producing an unfavorable 1,3 diaxial interaction with bulky aliphatic groups.[14] Secondly, polar groups including electron deficient aromatic rings,[14b] commonly favor the axial position in 1,3-dioxane rings due to the anomeric effect.[14,15] These factors taken together explain why that conformer (**8a**) is observed at low temperature in solution.

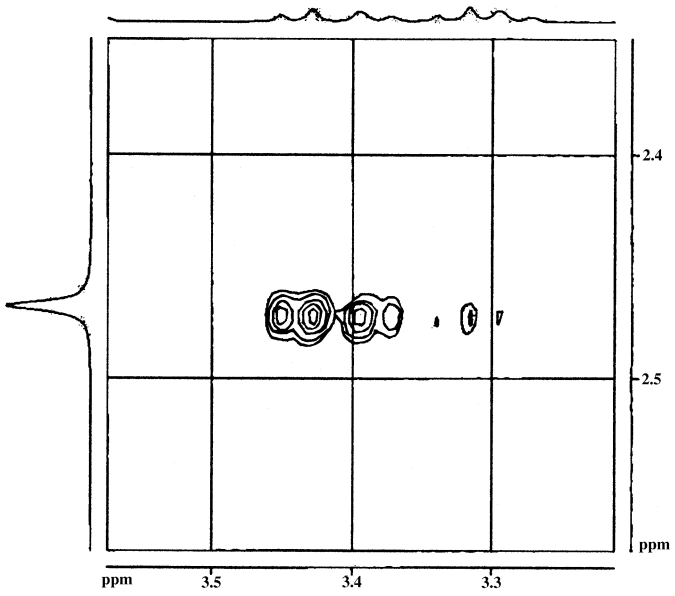


Figure 7. Low temperature ROESY of **8** shows a strong coupling between only one dioxanyl methylene and the C-5 methyl group of the isoxazole due to restricted rotation between the isoxazole and dioxane rings.

4. Conclusion

In summary, lateral lithiation of ethyl 4-acetyl-5-methyl-3-isoxazolyl carboxylate was conducted smoothly with 5,5-dimethyl-1,3-dioxanyl as a protective group. This might be explained by heteroatom facilitation and proximity directing effects via an axial isoxazolyl conformer which is observed in solution by NMR. At low temperature the C-3 ester adopts a conformation wherein it is shielded by the dioxanyl ring like an umbrella. Above the coalescence temperature, the ester swings out with a large sweep volume making it more vulnerable to intermolecular condensation. The implication of this conformation dynamic for potential asymmetric synthesis has not escaped our attention, and is currently being pursued. The lateral lithiation of ethyl 4-acetyl-5-methyl-3-isoxazolyl carboxylate represents a good method for the development 4,5-functionalized 3-isoxazolyl carboxylic acid derivatives of AMPA and will allow for the establishment of a systematic structure activity relationship, which will be reported in due course.

5. Experimental

5.1. General

All reactions were performed under inert atmosphere. THF and diisopropylamine were dried over sodium/benzophenone and distilled prior to use. *n*-Butyllithium was titrated using standard methods.[16] Melting points are uncorrected.

5.2. NMR

The ^{1}H- and ^{13}C NMR high-resolution and solid-state spectra were obtained with a Bruker DRX500 spectrometer. The signal assignments were performed on the basis of a series of 2D experiments with *z*-gradient selection: $^{1}H-^{1}H$ DQF COSY, $^{1}H-^{13}C$ HMQC, and $^{1}H-^{13}C$ HMBC.[17] The low-temperature NOE experiments were performed in the rotating frame (2D ROESY) with a mixing time of 250 ms.[17] The solid-state ^{13}C spectra were obtained under cross-polarization magic angle spinning (CP/MAS) conditions with a Bruker 5 mm CP/MAS probe. The spinning rates were 8 and 14.5 kHz. These spectra were referenced to the external secondary standard (solid adamantane, 38.6 and 28.8 ppm from TMS).

5.2.1. 3-Isoxazolecarboxylic acid 5-methyl-4-(2-methyl-1,3-dioxolan-2-yl)-ethyl ester (6). Ethylene glycol (3.2 g, 43.0 mmol), **5** (8.5 g, 43.0 mmol), and *p*-toluenesulfonic acid monohydrate (0.41 g, 2.1 mmol) in benzene (175 mL) was refluxed for 6 h with a Dean–Stark trap, the reaction was then cooled to room temperature and saturated $NaHCO_3$ solution was added. The mixture was separated, and the aqueous phase was extracted with EtOAc. The combined organic layers were washed with brine and dried (Na_2SO_4). Filtration, evaporation and Kugelrohr distillation produced **6** as a yellowish oil, 112–124°C/0.4 mm Hg, yield 94%. ^{1}H NMR δ 1.40 (t, J=7.18 Hz, 3H), 1.75 (s, 3H), 2.52 (s, 3H), 3.77 (m, 2H), 4.02 (m, 2H), 4.40 (q, J=7.18 Hz, 2H). ^{13}C NMR δ 166.9, 160.9, 155.0, 116.9, 104.6, 64.3, 61.8, 26.1, 13.6, 11.3. IR (KBr) 1740 cm^{-1}. EIMS *m/z*: 241 (M^{+}), 225. HRCIMS *m/z* Calcd for $C_{11}H_{15}NO_5$ (M+1): 241.0950. Found 241.0946.

5.2.2. *N*-(2-Hydroxy-1,1-dimethyl)-5-methyl-4-(2-methyl-1,3-dioxolan-2-yl)-3-isoxazolecarboxamide (7). Anhydrous $SmCl_3$ (156.7 mg, 0.61 mmol) was placed in a 500 mL round bottom flask that was charged with dry CH_2Cl_2, 2-methyl-2-amino-1-propanol (67.1 mmol) and the reaction was stirred under nitrogen for 15 min to form a milky suspension. The flask was cooled in an ice-water bath, *n*BuLi (34.7 mL, 64.1 mmol, 1.85 M) was added dropwise through a syringe, the mixture was stirred for 15 min at this temperature, then was allowed to warm to room temperature and brought to reflux. The ketal **6** (14.71 g, 61 mmol) was added with a syringe and refluxed for 1 h. The reaction

mixture was cooled to room temperature, filtered and washed with CH_2Cl_2, the filtrate was washed with brine, dried (Na_2SO_4), filtered and evaporated. Kugelrohr distillation produced 16.81 g **7** as a yellow oil, bp 108°C/0.11 mm Hg, yield 97%. ^{1}H NMR δ 7.09 (br, 1H, NH), 4.18 (t, 2H, J=8 Hz, CH_2) 4.04 (m, 2H, CH_2), 3.86 (m, 2H, CH_2), 3.70 (t, 1H, J=8 Hz, OH), 2.50 (s, 3H, CH_3), 1.76 (s, 3H, CH_3), 1.39 (s, 6H, CH_3). ^{13}C NMR δ 167.5, 160.3, 157.4, 116.4, 105.5, 69.3, 64.6, 56.8, 26.8, 24.4, 12.1. EIMS m/z: 284 (M^+), 252. HRCIMS m/z Calcd for $C_{13}H_{20}N_2O_5$ (M+1): 285.1450. Found 285.1439.

5.2.3. 3-(4,5-Dihydro-4,4-dimethyl-1,3-dioxolan-2-yl)-isoxazole (9). Compound **7** (16.81g, 59.0 mmol), Ph_3P (20.0 g, 76.3 mmol) and abs. MeCN were placed in a round bottom flask, stirred under nitrogen to form clear solution. The flask was cooled with an ice-water bath, 12.0 mL CCl_4 was added over 3 h, and stirred for another hour, NEt_3 (17.0 mL) was added over 2 h, the reaction was allowed to warm to room temperature over 12 h. The reaction mixture was filtered and concentrated. Two Kugelrohr distillations produced 12.86 g **9** as yellowish oil, 90°C/0.08 mm Hg, yield 82%. ^{1}H NMR δ 3.99 (s, 2H), 3.83–3.89 (m, 2H), 3.55–3.62 (m, 2H), 2.35 (s, 3H), 1.58 (s, 3H), 1.24 (s, 6H). ^{13}C NMR δ 166.8, 154.4, 152.2, 117.0, 104.6, 79.2, 67.8, 64.0, 27.5, 26.1, 11.3. IR: 1713 cm^{-1}. EIMS m/z: 267 [$(M+1)^+$], 251. HRCIMS m/z Calcd for $C_{13}H_{15}N_2O_4$ (M+1): 267.1344. Found: 267.1351.

5.2.4. 3-Isoxazolecarboxylic acid 5-methyl-4-(2,5,5-trimethyl-1,3-dioxan-2-yl)-ethyl ester (8). The procedure for the preparation of compound **6** was used. Kugelrohr distillation produced **8**, as a colorless solid and was recrystallized with hexane, bp 93°C/0.05 mm Hg, mp 80–82°C, yield: 96%. ^{1}H NMR d8-THF δ 0.66 (s, 3H, dioxCH_{3a}, 1.21 (s, 3H, dioxCH_{3b}, 1.38 (t, J=7.20 Hz, 3H, esterCH_3), 1.65 (s, 3H, dioxCH_{3c}, 2.47 (s, 3H, isoxCH_3), 3.36 (q, J=10.93 Hz, 4H, dioxCH_2), 4.39 (q, J=7.20 Hz, 2H, esterCH_2). ^{13}C NMR d8-THF δ 11.1 (isoxCH_3), 14.0 (esterCH_3), 21.7 (dioxCH_{3a}, 22.6 (dioxCH_{3b}, 29.8 (dioxCH_{3c}, 30.1 (dioxC5), 62.4 (esterCH_2), 72.3 (dioxCH_2), 96.8 (dioxC2), 114.0 (isoxC-4), 156.4 (isoxC-3), 161.6 (esterCO), 167.6 (isoxC-5). ^{13}C NMR (solid state) 11.9, 14.9, 21.5, 22.7, 30.2, 31.9, 63.6, 71.7, 96.9, 114.8, 157.3, 163.0, 169.3; IR: 1735 cm^{-1}. EIMS m/z: 284 [$(M+1)^+$], 268. Anal. Calcd For $C_{14}H_{21}NO_5$: C, 59.35; H, 7.39; N, 4.94. Found: C, 59.35; H, 7.40; N, 4.90.

5.3. General procedure for lateral lithiation

To a solution of diisopropylamine (0.29 mL) in THF under nitrogen at 0~5°C was added nBuLi in hexane (2.1 mmol). The solution was stirred for 10 min and then cannulated into a solution of **8** (566.6 mg, 2.0 mmol) in 15 mL of THF under nitrogen that was already cooled to −78°C. The mixture was stirred for 10 min. An electrophile (2.1 mmol) solution in 5 mL of THF under nitrogen was cannulated again into this mixture in 5 min (if the electrophile was a liquid, it was added with a syringe). The reaction mixture was allowed to warm to room temperature in 6 h. Saturated NH_4Cl solution was added and the solution was concentrated under reduced pressure to remove THF. The aqueous-oil mixture was extracted with EtOAc. The extract was washed with brine, and dried (Na_2SO_4), evaporated under reduced pressure, the residue was purified by Chromatotron (hexane–EtOAc) to afford the desired product as following **11**–**22**.

5.3.1. 3-Isoxazolecarboxylic acid 5-ethyl-4-(2,5,5-trimethyl-1,3-dioxan-2-yl)-ethyl ester (11). Kugelrohr distillation at 110°C/0.06 mm Hg, colorless solid, mp 59–61°C, yield 81%. ^{1}H NMR δ 0.66 (s, 3H), 1.21 (s, 3H), 1.32 (t, J=7.70 Hz, 3H), 1.38 (t, J=7.18 Hz, 3H), 1.66 (s, 3H), 2.87 (q, J=7.70 Hz, 2H), 3.37 (s, 4H), 4.40 (q, J=7.18 Hz, 2H). ^{13}C NMR δ 11.7, 14.0, 19.4, 21.8, 22.5, 29.8, 30.1, 62.4, 71.9, 96.2, 113.0, 156.4, 161.9, 171.9. MS m/z: 298 [$(M+1)^+$], 282. HRCIMS m/z Calcd for $C_{15}H_{23}NO_5$ (M+1): 298.1654. Found 298.1659.

5.3.2. 3-Isoxazolecarboxylic acid 5-(2-phenylethyl)-4-(2,5,5-trimethyl-1,3-dioxan-2-yl)-ethyl ester (12). Yield 72%, colorless solid, mp 59.5–60.5°C. ^{1}H NMR δ 0.57 (s, 3H), 1.15 (s, 3H), 1.36 (t, J=7.18 Hz, 3H), 1.42 (s, 3H), 3.03–3.31 (m, 8H), 4.57 (q, J=7.18 Hz, 2H), 7.12–7.30 (m, 5H). ^{13}C NMR δ 14.0, 21.8, 22.5, 28.1, 29.7, 29.9, 33.4, 62.5, 71.8, 96.2, 114.5, 126.6, 128.5, 128.7, 140.1, 156.4, 161.8, 169.8. Calcd for $C_{21}H_{27}NO_5$: C, 67.43; H, 7.29; N, 3.74. Found: C, 67.43, H, 7.29; N, 3.68.

5.3.3. 3-Isoxazolecarboxylic acid 5-[(2,2-hydroxymethyl)propyl]-4-(2,5,5-trimethyl-1,3-dioxan-2-yl)-ethyl ester (13). Yield 68%, colorless solid, mp 103–104°C. ^{1}H NMR δ 0.69 (s, 3H), 1.18 (s, 3H), 1.33 (s, 6H), 1.38 (t, J=7.18 Hz, 3H), 1.73 (s, 3H), 2.26 (s, 1H), 3.07 (s, 2H), 3.36 (q, J=10.77, 7.18 Hz, 4H), 4.40 (q, J=7.18 Hz, 2H). ^{13}C NMR δ 13.9, 21.8, 22.3, 29.3, 29.9, 39.4, 62.4, 70.8, 71.6, 96.3, 115.9, 156.3, 161.7, 167.9. MS m/z: 326, 197. Calcd for $C_{17}H_{27}NO_6$: C, 59.81; H, 7.97; N, 4.10. Found: C, 60.01; H, 7.91; N, 4.26.

5.3.4. 3-Isoxazolecarboxylic acid 4-(2,5,5-trimethyl-1,3-dioxan-2-yl)-5-[(trimethylsilyl) methyl]-ethyl ester (14). Yield 66%, colorless crystals, mp 87–8°C. ^{1}H NMR δ 0.10 (s, 9H), 0.51 (s, 3H), 1.10 (s, 3H), 1.24 (t, J=7.18 Hz, 3H), 1.52 (s, 3H), 2.21 (s, 2H), 3.21 (2, 4H), 4.25 (q, J=7.18 Hz, 2H). ^{13}C NMR δ 0.0, 14.9, 17.1, 22.7, 23.4, 30.7, 30.9, 63.2, 72.6, 97.2, 112.5, 157.3, 162.9, 171.8. EIMS m/z: 340 [$(M-15)^+$]. Calcd for $C_{17}H_{29}NO_5Si$: C, 57.44; H, 8.22; N, 3.94. Found: C, 57.73; H, 8.28; N, 3.91.

5.3.5. 3-Isoxazolecarboxylic acid 4-(2,5,5-trimethyl-1,3-dioxan-2-yl)-5-[(trimethylstannyl) methyl]-ethyl ester (15). Yield 42%, colorless solid, mp 90–92°C. ^{1}H NMR δ 0.16 (s, 9H), 0.60 (s, 3H), 1.14 (s, 3H), 1.32 (t, J=7.18 Hz, 3H), 1.57 (s, 3H), 2.41 (d, 2.82 Hz, 2H), 3.30 (s, 3H), 4.34 (q, J=7.18 Hz, 2H). ^{13}C NMR δ 2.4, 9.2, 13.9, 21.8, 22.5, 29.7, 62.3, 71.7, 96.3, 109.4, 156.4, 162.0, 173.3. EIMS m/z: 447 [$(M+1)^{+1}$], 165. HRCIMS m/z Calcd for $C_{17}H_{29}NO_5Sn$: 447.1068. Found 447.0991.

5.3.6. 3-Isoxazolecarboxylic acid 5-[(methylthio)methyl]-4-(2,5,5-trimethyl-1,3-dioxan-2-yl)-ethyl ester (16). Yield 61%, colorless solid, mp 67–68°C. ^{1}H NMR δ 0.66 (s, 3H), 1.19 (s, 3H), 1.38 (t, J=7.18 Hz, 3H), 1.69 (s, 3H), 2.26 (s, 3H), 3.38 (s, 4H), 3.82 (s, 2H), 4.40 (q, J=7.18 Hz, 2H). ^{13}C NMR δ 14.0, 16.8, 21.8, 22.4, 27.3, 29.7, 29.8, 62.6, 72.0,

Table 3.

Identification code	bt194	
Empirical formula	$C_{26}H_{36}N_2O_9$	
Formula weight	520.57	
Temperature	203(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	*P*-1	
Unit cell dimensions	a=8.844(6) Å	α=106.142(10)°
	b=12.451(8) Å	β=91.139(11)°
	c=13.869(9) Å	γ=100.541(10)°
Volume	1438.3(16) Å^3	
Z	2	
Density (calculated)	1.202 mg m^{-3}	
Absorption coefficient	0.091 mm^{-1}	
F(000)	556	
Crystal size	0.56×0.32×0.17 mm^3	
Crystal color and habit	Colorless needle	
Diffractometer	Siemens SMART 1000	
Theta range for data collection	1.96–25.00°	
Index ranges	$-10 <= h <= 10$, $-14 <= k <= 14$, $-16 <= l <= 16$	
Reflections collected	15365	
Independent reflections	5062 [R(int)=0.0265]	
Completeness to theta=25.00°	99.8%	
Absorption correction[a]	Empirical	
Max. and min. transmission	0.9847 and 0.9509	
Solution method	XS, Bruker SHELXTL v. 5.10	
Refinement method	Full-matrix least-squares on F^2	
Data/restraints/parameters	5062/0/342	
Goodness-of-fit on F^2	1.033	
Final R indices [$I > 2$sigma(I)]	$R1$=0.0427, $wR2$=0.1065	
R indices (all dat(a)	$R1$=0.0638, $wR2$=0.1153	
Largest diff. peak and hole	0.190 and −0.153 e.Å^{-3}	

[a] SADABS: an empirical absorption program by G. M. Sheldrick, Bruker AXS, Madison, WI, 1999.

96.2, 114.1, 156.4, 161.5, 168.3. EIMS *m/z*: 329 (M^+, 40), 170 (100). Calcd for $C_{15}H_{23}NO_5S$: C, 54.69; H, 7.04; N, 4.25. Found: C, 55.26; H, 7.07; N, 4.20.

5.3.7. 3-Isoxazolecarboxylic acid 5-[2-oxo-2-(phenylamino)ethyl]-4-(2,5,5-trimethyl-1,3-dioxan-2-yl)-ethyl ester (17). Yield 68%. colorless solid, mp 147–148°C. ^{1}H NMR δ 0.64 (s, 3H), 1.15 (s, 3H), 1.37 (t, J=7.18 Hz, 3H), 1.70 (s, 3H), 3.35 (s, 3H), 3.96 (s, 2H), 4.40 (q, J=7.18 Hz, 2H), 7.10(t, 1H), 7.29 (t, 2H), 7.48 (d, 2H), 8.26 (s, 2H). ^{13}C NMR δ 13.9, 21.9, 22.4, 29.2, 29.8, 35.2, 62.7, 71.8, 96.2, 116.7, 120.1, 124.8, 129.0, 137.3, 156.4, 161.5, 163.9. EIMS *m/z*: 402 (M^+), 93. Calcd for $C_{21}H_{26}N_2O_6$: C, 62.67; H, 6.51; N, 6.96. Found: C, 62.43; H, 6.44; N, 6.83.

5.3.8. 3-Isoxazolecarboxylic acid 5-[(2,2-hydroxyphenyl) ethyl]-4-(2,5,5-trimethyl-1,3-dioxan-2-yl)-ethyl ester (18). Yield 95%, yellowish oil. ^{1}H NMR δ 0.60 (s, 3H), 1.15 (s, 3H), 1.35 (t, J=7.18 Hz, 3H), 1.46 (s, 3H), 2.62 d, J= 3.59 Hz, 1H), 3.12–3.40 (m, 6H), 4.36 (q, J=7.18 Hz, 2H), 5.21 (m, 1H), 7.25–7.35 (m, 5H). ^{13}C NMR δ 13.8, 21.7, 22.3, 29.4, 29.6, 35.9, 62.4, 71.6, 71.8, 96.0, 115.3, 125.5, 128.0, 128.5, 143.0, 156.2, 161.5, 167.6. Calcd For $C_{21}H_{27}NO_6$: C, 64.77; H, 6.99; N, 3.60. Found: C, 64.47; H, 6.98; N, 3.42.

5.3.9. 3-Isoxazolecarboxylic acid 5-[(2,2-hydroxy-4-chlorophenyl) ethyl]-4-(2,5,5-trimethyl-1,3-dioxan-2-yl)-ethyl ester (19). Yield 83%. colorless solid, mp 86–88°C, ^{1}H NMR δ 0.63 (s, 3H), 1.16 (s, 3H), 1.37 (t, J=7.18 Hz, 3H), 1.54 (s, 3H), 2.36 (d, J=3.59 Hz, 1H), 3.14–3.18 (m, 6H), 4.39 (q, J=7.18 Hz, 2H), 5.22 (m, 1H), 7.32 (s, 4H). ^{13}C NMR δ 14.0, 21.9, 22.47, 29.5, 29.8, 36.0, 62.6, 71.5, 71.7, 96.2, 115.8, 127.0, 128.9, 133.9, 141.5, 156.5, 161.7, 167.3. EIMS *m/z*: 408 [$(M-15)^+$], 197. Calcd for $C_{21}H_{26}NO_6Cl$: C, 59.50; H, 6.18; N, 3.30. Found: C, 59.56; H, 6.14; N, 3.22.

5.3.10. 3-Isoxazolecarboxylic acid 5-[(2,4-hydroxymethyl) pentyl]-4-(2,5,5-trimethyl-1,3-dioxan-2-yl)-ethyl ester (20). Yield 79%, colorless oil. ^{1}H NMR δ 0.67 (s, 3H), 0.92 (d, J=3.33 Hz, 3H), 0.95 (d, J=3.33 Hz, 3H), 1.19 (s, 3H), 1.38 (t, J=7.18 Hz, 3H), 1.25–1.51 (m, 2H), 1.60–1.80 (m, 1H), 1.98 (m, 1H), 2. 99 (m, 2H), 3.35 (s, 4H), 4.15 (br, 1H), 4.40 (q, J=7.18 Hz, 2H). ^{13}C NMR δ 14. 0, 21.9, 22.5, 23.3, 24.6, 29.8, 34.6, 46.6, 62.5, 67.9, 71.8, 96.3, 115.3, 156.5, 160.1, 168.6. EIMS *m/z*: 354 [$(M-15)^{+1}$], 197. Calcd for $C_{19}H_{31}NO_6$: C, 61.42; H, 8.47; N, 3.77. Found: C, 61.42; H, 8.27; N, 3.72.

5.3.11. 3-Isoxazolecarboxylic acid 5-[(1,3-phenylhydroxy) *trans*-butene]-4-(2,5,5-trimethyl-1,3-dioxan-2-yl)-ethyl ester (21). Yield 82%, yellowish oil. ^{1}H NMR δ 0.62 (s, 3H), 1.18 (s, 3H), 1.36 (t, J=7.18 Hz, 3H), 1.68 (s, 3H), 2.35 (d, 3.84 Hz, 1H), 3.07–3.34 (m, 2H), 3.37 (s, 4H), 4.38 (q, J=7.18 Hz, 2H), 4.80 (br, 1H), 6.24 (dd, J=6.67, 9.23 Hz, 1H), 6.64 (dd, J=1.02, 14.88 Hz, 1H), 7.20–7.39 (m, 5H). ^{13}C NMR δ 14.0, 21.8, 22.5, 29.9, 34.2, 62.5, 70.7, 71.8, 96.3, 115.6, 126.6, 128.1, 128.7, 130.5, 131.4, 156.4, 161.6, 167.7. CIMS *m/z*: 444 [$(M+29)^+$], 416 [$(M+H)^+$], 197. HRCIMS *m/z* Calcd for $C_{23}H_{29}NO_6$: 419.1995. Found 419.1989.

5.3.12. 3-Isoxazolecarboxylic acid 5-propyl-4-(2,5,5-trimethyl-1,3-dioxan-2-yl)-ethyl ester (22). Yield 83%, colorless solid, mp 76–78°C. ^{1}H NMR δ 0.65 (s, 3H), 0.99 (t, J=7.44 Hz, 3H), 1.20 (s, 3H), 1.37 (t, 7.18 Hz, 3H), 1.66 (s, 3H), 1.75 (hexa, J=7.44 Hz, 2H), 2.81 (t, J=7.44 Hz, 2H), 3.35 (s, 4H), 4.38 (q, J=7.18 Hz, 2H). ^{13}C NMR δ 14.0, 20.8, 21.8, 22.5, 27.8, 29.8, 30.1, 62.4, 71.9, 96.2, 113.6, 156.1, 162.0, 171.0. Calcd for $C_{16}H_{25}NO_5$: C, 61.72; H, 8.09; N, 4.50. Found: C, 61.64; H, 7.98; N, 4.53.

5.3.13. Isoxazole dimer (23). Typical yield of byproduct at −78°C is 15–33% on a multigram scale, colorless solid, mp 47–48°C. ^{1}H NMR δ 0.62 (s, 3H), 0.68 (s, 3H), 1.11 (s, 3H), 1.15 (s, 3H), 1.24 (t, J=7.18 Hz, 3H), 1.35 (s, 3H), 1.39 (s, 3H), 2.48 (s, 3H), 3.33 (m, 8H), 4.36 (q, J=7.18 Hz, 2H), 4.53 (s, 2H); ^{13}C NMR δ 12.1, 13.7, 21.4, 21.5, 21.8, 22.2, 28.3, 28.6, 28.7, 28.7, 61.4, 69.7, 70.3, 112.1, 155.4, 155.7, 160.8, 166.8, 166.9; EIMS *m/z*: 505 (M−15), 419, 331, 259, 194;

Crystal data and structure refinement for isoxazole dimer (**23**). See Table 3.

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