Tandem Retro-Michael Addition–Claisen Rearrangement–Intramolecular Cyclization: One-Pot Synthesis of Densely Functionalized Ethyl Dihydropyrimidine-4-carboxylates from Simple Building Blocks

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Received 19 November 2007

Abstract: Pyrolysis of suitably functionalized oxadiazoline diesters in refluxing xylenes provided ethyl 1,2-disubstituted 5-hydroxy-6-oxo-1,6-dihydropyrimidine-4-carboxylates in moderate to good yields. Under thermal conditions, the oxadiazoline esters undergo a sequence of complex molecular reorganizations, namely retro-Michael addition, Claisen rearrangement, and cyclization, to produce the desired pyrimidinones.

Key words: retro-Michael addition, Claisen rearrangement, intramolecular cyclization, 1,6-dihydropyrimidine-4-carboxylates

Pyrimidines and pyrimidinones are a very important class of diazine heterocycles and are constituents of many biologically active compounds.[1] 5-Hydroxy-6-oxo-1,6-dihydropyrimidine-4-carboxylic acid esters **1** and **2** (Figure 1) are a newly emerging group of densely functionalized pyrimidine derivatives. Recently, these compounds have received increased attention because of their ability to coordinate metal ions, a property that confers promising biological properties.[2,3]

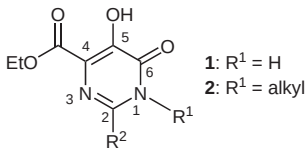
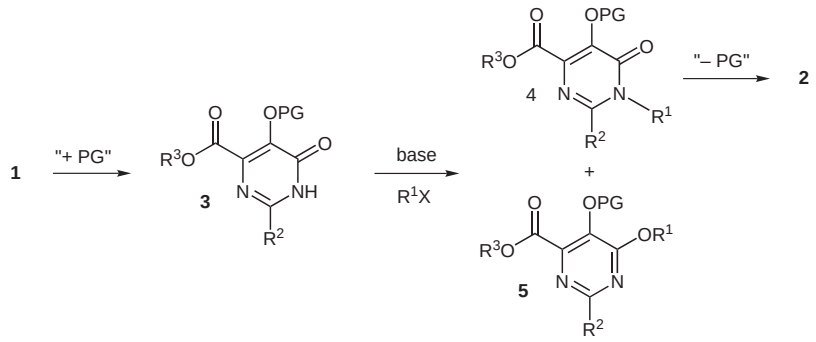


Figure 1 Ethyl-5-hydroxy-6-oxo-1,6-dihydropyrimidine-4-carboxylates

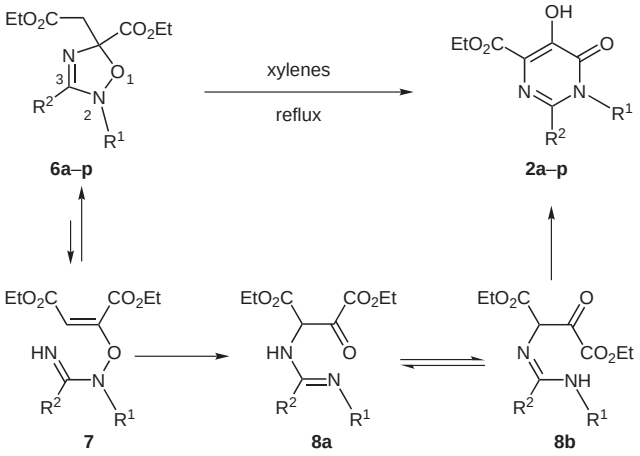
During the course of our drug discovery efforts, we sought access to several pyrimidinone carboxylic acid esters **2**. In the literature, these compounds have typically been prepared from **1** by a three-step sequence involving protection–alkylation–deprotection, as summarized in Scheme 1.[2,3a] Frequently, the alkylation step was nonchemoselective and produces, in addition to desired N-alkylated pyrimidinone **4**, the unwanted O-alkylated pyrimidine **5** often as a major product. Although this procedure is reliable, it requires several steps and suffers from poor chemoselectivity and low overall yield. Consequently, we sought to develop a short and versatile synthetic approach to pyrimidinone carboxylic acid esters **2**. In this paper, we describe a one-pot synthetic protocol for the preparation of **2** from readily accessible oxadiazolines **6**.

We envisaged that under the pyrolytic conditions, oxadiazoline **6** would undergo ring opening via a retro-Michael reaction to afford **7** (Scheme 2), a transient intermediate that could undergo a thermal Claisen rearrangement to provide the keto diester **8**. Intramolecular cyclization of **8** would furnish the desired pyrimidinone **2**. Although, the Claisen rearrangement followed by cyclization of unsubstituted amidoxime **7**, in which $R^1 = H$ is known,[4] we were concerned about the fate of this transformation when the hydrogen atom is replaced by a sterically more demanding alkyl group.[5]

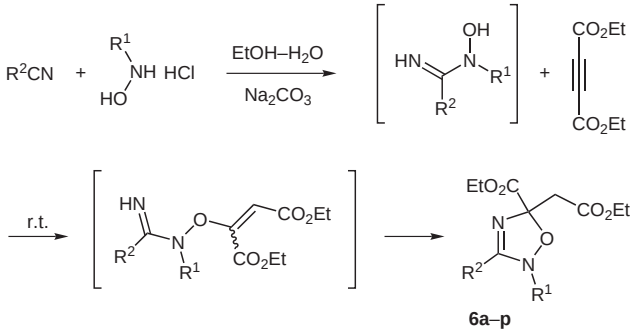


Scheme 1 Current approach to *N*-alkylpyrimidinones **2**

SYNLETT 2008, No. 4, pp 0547–0550
Advanced online publication: 12.02.2008
DOI: 10.1055/s-2008-1032088; Art ID: S08907ST



Scheme 2 Proposed mechanism



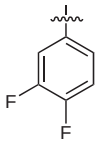
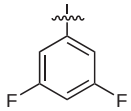
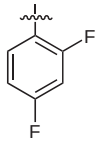
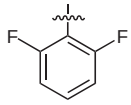
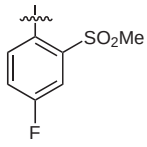
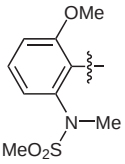
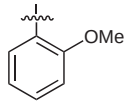
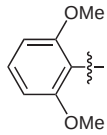
Scheme 3 Synthesis of oxadiazolines

The required 1,2,4-oxadiazoline diesters **6** were prepared using appropriate nitrile, *N*-alkylhydroxylamine and diethyl acetylenedicarboxylate (DEAD) according to the literature procedure (Scheme 3).[6] The pyrolytic reaction was examined in several solvents and we quickly found that the reaction does not take place in refluxing toluene. However, we were gratified that the transformation occurred as anticipated in refluxing xylenes and, moreover, the reaction proceeds more rapidly at higher temperatures. For example, the conversion of oxadiazolines into pyrimidinones was two- to threefold faster at 180 °C in 1,3,5-trimethylbenzene than in boiling xylenes (bp 140–145 °C). However, in xylenes the reactions were generally cleaner and provided better yields of the desired products.

The thermal rearrangement of oxadiazoline diesters **6** with a variety of N2-substituents, including methyl, benzyl, isopropyl, and cyclohexyl, and C3-substituents, including aryls and alkyls, were investigated and the results are summarized in Table 1. This conversion proceeded uneventfully with diverse C3-aryl groups, providing the desired pyrimidinones in good yields (entries 1–9). Both electron-donating and electron-withdrawing substituents on the C3-aryl ring are well tolerated.

Interestingly, oxadiazolines with an unsubstituted C3-phenyl and C3-phenyl incorporating *meta* and *para* substitution took significantly longer to rearrange to products (entries 1–3) than oxadiazolines incorporating *ortho* substitution (entries 4–9). This difference in rate may, in part, arise from the presence of the *ortho* substituent, which

Table 1 Ethyl 1,2-Disubstituted 5-Hydroxy-6-oxo-1,6-dihydropyrimidine-4-carboxylates

Entry	Product	R^1	R^2	Time (h)	Yield (%)[a]
1	**2a**	Me	Ph	20	58
2	**2b**	Me		15	53
3	**2c**	Me		12	57
4	**2d**	Me		3	69
5	**2e**	Me		1.5	60
6	**2f**	Me		6	47
7	**2g**	Me		2	56
8	**2h**	Me		3	43
9	**2i**	Me		2	62
10	**2j**	Me	Bn	5	51
11	**2k**	Bn	Me	20	41
12	**2l**	*i*-Pr	Me	24	7
13	**2m**	*i*-Pr	Bn	24	trace[b]
14	**2n**	Cy	Bn	24	trace[b]
15	**2o**	Me	*i*-Pr	24	38
16	**2p**	Me	*c*-C_5H_9	15	35

[a] Isolated yields.
[b] Observed by LCMS.

will restrict rotation and orient the phenyl moiety orthogonally to the plane of the amidine C–N bond. This arrangement may minimize steric interactions in the transition state for the Claisen rearrangement and/or intramolecular cyclization steps that, in turn, results in the faster reaction rate.

Oxadiazolines incorporating a variety of C3-alkyl substituents are converted into pyrimidinones in low to moderate yields (entries 10, 11, 15, and 16). However, substrates with bulky N2-substituents, such as isopropyl and cyclohexyl groups, failed to furnish the desired products in acceptable yield (entries 12–14). This may be due to the bulky N2-substituents making this nitrogen less accessible for nucleophilic attack. Conversely, oxadiazolines with bulky C3-alkyl groups readily participate in this transformation, providing the desired products in moderate yields, as captured by entries 15 and 16.

In summary, we have described a simple and convenient route to the synthesis of ethyl dihydropyrimidine-4-carboxylates from readily available 2,4-oxadiazoline diesters **6**. This methodology works well with a variety of substrates and furnishes densely functionalized pyrimidinones in moderate to good yields. One of the important advantages of this protocol is that, in most cases, the products are obtained without resort to chromatographic purification either by crystallization or by simple acid–base extraction from the crude reaction mixture.[7,8]

Acknowledgment

We thank Drs. Nicholas A. Meanwell and Michael A. Walker for their support of this work.

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(7) **Representative Procedures**
Method A: A solution of **6e** (2.68 g, 7.52 mmol) in xylenes (50 mL) was heated at reflux for 1.5 h and cooled to r.t. The precipitate was filtered and dried to give **2e** as an off-white solid (1.4 g, 60% yield).
Method B: A solution of **6j** (9.77 g, 29.22 mmol) in xylenes (100 mL) was heated at reflux for 5 h and cooled. Then, the reaction mixture was diluted with EtOAc (100 mL) and extracted with 0.5 M Na_2CO_3 (3 × 30 mL). The combined aqueous layers were acidified with concd HCl and extracted with CH_2Cl_2 (4 × 50 mL). The combined CH_2Cl_2 layers were dried (Na_2SO_4), filtered, and concentrated to give a brown solid which was triturated with Et_2O and filtered to afford **2j** as a light-brown powder (4.32 g, 51%).

(8) **Analytical Data for New Compounds**
Compound **2a**: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 10.76 (1 H, s), 7.49–7.46 (5 H, m), 4.48 (2 H, q, *J* = 7.0 Hz), 3.45 (3 H, s), 1.41 (3 H, t, *J* = 7.0 Hz). HRMS: *m/z* calcd for $C_{14}H_{15}N_2O_4$ [M + H]: 275.1032; found: 275.1042. Anal. Calcd for $C_{14}H_{14}N_2O_4$: C, 61.30; H, 5.14; N, 10.21. Found: C, 61.31; H, 5.10; N, 10.21.
Compound **2b**: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 10.63 (1 H, s), 7.39–7.23 (3 H, m), 4.49 (2 H, q, *J* = 7.0 Hz), 3.47 (3 H, s), 1.42 (3 H, t, *J* = 7.0 Hz). HRMS : *m/z* calcd for $C_{14}H_{13}F_2N_2O_4$ [M + H]: 311.0844; found: 311.0832. Anal. Calcd for $C_{14}H_{14}N_2O_4$: C, 54.19; H, 3.89; N, 9.03. Found: C, 54.21; H, 3.85; N, 8.85.
Compound **2c**: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 10.85 (1 H, s),), 7.06–7.01 (2 H, m), 6.98–6.94 (1 H, m), 4.50 (2 H, q, *J* = 7.0 Hz), 3.47 (3 H, s), 1.42 (3 H, t, *J* = 7.0 Hz). HRMS: *m/z* calcd for $C_{14}H_{13}F_2N_2O_4$ [M + H]: 311.0843; found: 311.0836. Anal. Calcd for $C_{14}H_{14}N_2O_4$: C, 54.19; H, 3.89; N, 9.03. Found: C, 54.15; H, 3.79; N, 9.15.
Compound **2d**: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 10.81 (1 H, s), 7.51–7.46 (1 H, m), 7.04 (2 H, td, *J* = 8.2, 1.8 Hz), 6.95–6.91 (1 H, m), 4.49 (2 H, q, *J* = 7.0 Hz), 3.42 (3 H, s), 1.41 (3 H, t, *J* = 7.0 Hz). HRMS: *m/z* calcd for $C_{14}H_{13}F_2N_2O_4$ [M + H]: 311.0843; found: 311.0828. Anal. Calcd for $C_{14}H_{14}N_2O_4$: C, 54.19; H, 3.89; N, 9.03. Found: C, 54.21; H, 3.65; N, 8.94.
Compound **2e**: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 10.96 (1 H, s), 7.50–7.45 (1 H, m), 7.04 (2 H, t, *J* = 7.3 Hz), 4.51 (2 H, q, *J* = 7.0 Hz), 3.41 (3 H, s), 1.41 (3 H, t, *J* = 7.0 Hz). HRMS: *m/z* calcd for $C_{14}H_{13}F_2N_2O_4$ [M + H]: 311.0843; found: 311.0837. Anal. Calcd for $C_{14}H_{14}N_2O_4$: C, 54.19; H, 3.89; N, 9.03. Found: C, 54.10; H, 3.77; N, 9.00.
Compound **2f**: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 10.57 (1 H, s), 7.90 (1 H, dd, *J* = 7.93, 2.44 Hz), 7.49–7.42 (2 H, m), 4.54–4.47 (1 H, m), 4.41–4.34 (1 H, m), 3.31 (3 H, s), 3.30 (3 H, s), 1.35 (3 H, t, *J* = 7.02 Hz). ESI-HRMS: *m/z* calcd for $C_{15}H_{16}FN_2O_6S$ [M + H]: 371.0713; found: 371.0724.
Compound **2g**: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 10.65 (1 H, s), 7.57–7.52 (1 H, m), 7.28 (1 H, d, *J* = 7.9 Hz), 7.22 (1 H, t, *J* = 8.9 Hz), 4.55–4.49 (1 H, m), 4.40–4.33 (1 H, m), 3.46 (3 H, s), 3.30 (3 H, s), 2.90 (3 H, s), 1.37 (3 H, t, *J* = 7.0 Hz). ESI-HRMS: *m/z* calcd for $C_{16}H_{19}FN_3O_6S$ [M + H]: 400.0979; found: 400.0979.
Compound **2h**: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 10.76 (1 H, s), 7.45 (1 H, td, *J* = 7.3, 1.53 Hz), 7.34 (1 H, d, *J* = 7.3 Hz), 7.06 (1 H, t, *J* = 7.3 Hz), 6.94 (1 H, d, *J* = 8.6 Hz), 4.55–4.41 (2 H, m), 3.79 (3 H, s), 3.34 (3 H, s), 1.40 (3 H, t, *J* = 7.0 Hz). HRMS: *m/z* calcd for $C_{15}H_{15}N_2O_5$ [M + H]: 303.0981; found: 303.0980.
Compound **2i**: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 10.83 (1 H, s), 7.35 (1 H, t, *J* = 8.5 Hz), 6.59 (2 H, d, *J* = 8.5 Hz), 4.50 (2 H, q, *J* = 7.0 Hz), 3.75 (6 H, s), 3.28 (3 H, s), 1.39 (3 H, t, *J* = 7.0 Hz). HRMS: *m/z* calcd for $C_{16}H_{19}N_2O_6$ [M + H]: 335.1243; found: 335.1240.
Compound **2j**: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 10.64 (1 H, s), 7.33–7.14 (5 H, m), 4.53 (2 H, q, *J* = 7.0 Hz), 4.17 (2 H, s), 3.41 (3 H, s), 1.46 (3 H, t, *J* = 7.0 Hz). ^{13}C NMR (125

MHz, $CDCl_3$): δ = 169.5, 158.9, 149.8, 149.0, 134.7, 129.2, 128.2, 127.5, 124.7, 63.1, 42.3, 32.0, 14.3. HRMS: calcd for $C_{15}H_{17}N_2O_4$ [M + H]: 289.1188; found: 289.1186. Anal. Calcd for $C_{15}H_{16}N_2O_4$: C, 62.49; H, 5.59; N, 9.71. Found: C, 62.44; H, 5.79; N, 9.60.

Compound **2k**: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 10.88 (1 H, s), 7.31–7.24 (3 H, m), 7.14 (2 H, d, *J* = 7.3 Hz), 5.29 (2 H, s), 4.47 (2 H, q, *J* = 7.0 Hz), 2.43 (3 H, s), 1.41 (3 H, t, *J* = 7.0 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 169.1, 158.7, 149.5, 148.9, 134.6, 129.1, 128.2, 126.8, 124.7, 63.2, 48.2, 31.7, 22.6, 14.2. HRMS: *m/z* calcd for $C_{15}H_{17}N_2O_4$ [M + H]: 289.1188. Found: 289.1176.

Compound **2l**: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.89 (1 H, br s), 4.60–4.49 (1 H, m), 4.47 (2 H, q, *J* = 7.0 Hz), 2.57 (3 H, s), 1.63 (6 H, d, *J* = 6.7 Hz), 1.42 (3 H, t, *J* = 7.0 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 168.6, 158.7, 149.4, 149.0, 123.5, 77.7, 63.1, 22.9, 19.1, 14.1. HRMS: *m/z* calcd for $C_{11}H_{17}N_2O_4$ [M + H]: 241.1188; found: 241.1191.

Compound **2o**: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 10.39 (1 H, s), 4.44 (2 H, q, *J* = 7.0 Hz), 3.61 (3 H, s), 3.05 (1 H, qt, *J* = 6.7 Hz), 1.43 (3 H, t, *J* = 7.0 Hz), 1.30 (6 H, d, *J* = 6.7 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 169.5, 159.1, 155.2, 148.0, 124.9, 62.4, 32.0, 30.9, 20.7, 14.1. HRMS: *m/z* calcd for $C_{11}H_{17}N_2O_4$ [M + H]: 241.1188; found: 241.1186. Anal. Calcd for $C_{11}H_{16}N_2O_4$: C, 54.99; H, 6.71; N, 11.66. Found: C, 55.01; H, 6.82; N, 11.68.

Compound **2p**: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 10.36 (1 H, s), 4.43 (2 H, q, *J* = 7.0 Hz), 3.60 (3 H, s), 3.13 (1 H, qt, *J* = 7.9 Hz), 2.01–1.94 (4 H, m), 1.86–1.78 (2 H, m), 1.69–1.61 (2 H, m), 1.42 (3 H, t, *J* = 7.0 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 169.6, 159.2, 154.1, 148.0, 124.6, 62.5, 43.1, 31.3, 31.1, 25.7, 14.2. HRMS: *m/z* calcd for $C_{13}H_{19}N_2O_4$ [M + H]: 267.1345; found: 267.1337. Anal. Calcd for $C_{13}H_{18}N_2O_4$: C, 58.63; H, 6.81; N, 10.52. Found: C, 58.63; H, 6.72; N, 10.49.

Compound **6b**: yield 75%. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.61–7.57 (1 H, m), 7.51–7.47 (1 H, m), 7.26–7.21 (1 H, m), 4.35–4.10 (4 H, m), 3.40 (1 H, d, J_{AB} = 16.5 Hz), 3.17 (3 H, s), 3.02 (1 H, d, J_{AB} = 16.5 Hz), 1.32 (3 H, t, *J* = 7.0 Hz), 1.24 (3 H, t, *J* = 7.0 Hz). HRMS: *m/z* calcd for $C_{16}H_{19}N_2O_5F_2$ [M + H]: 357.1262; found: 357.1273. Anal. Calcd for $C_{16}H_{18}N_2O_5F_2$: C, 53.93; H, 5.09; N, 7.86. Found: C, 53.82; H, 4.90; N, 8.13.

Compound **6c**: yield 72%. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.29–7.25 (2 H, m), 6.99–6.95 (1 H, m), 4.35–4.12 (4 H, m), 3.40 (1 H, d, J_{AB} = 16.5 Hz), 3.18 (3 H, s), 3.04 (1 H, d, J_{AB} = 16.5 Hz), 1.32 (3 H, t, *J* = 7.0 Hz), 1.25 (3 H, t, *J* = 7.0 Hz). HRMS: *m/z* calcd for $C_{16}H_{19}N_2O_5F_2$ [M + H]: 357.1262; found: 357.1262. Anal. Calcd for $C_{16}H_{18}N_2O_5F_2$: C, 53.93; H, 5.09; N, 7.86. Found: C, 53.90; H, 4.84; N, 7.81.

Compound **6d**: yield 60%. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.73 (1 H, dd, *J* = 14.5, 8.1 Hz), 6.96 (1 H, td, *J* = 8.5, 2.4 Hz), 6.91 (1 H, td, *J* = 8.2, 2.5 Hz), 4.36–4.10 (4 H, m), 3.40 (1 H, d, J_{AB} = 16.5 Hz), 3.11 (3 H, s), 3.07 (1 H, d, J_{AB} = 16.5 Hz), 1.32 (3 H, t, *J* = 7.0 Hz), 1.25 (3 H, t, *J* = 7.0 Hz). HRMS: *m/z* calcd for $C_{16}H_{19}N_2O_5F_2$ [M + H]: 357.1262; found: 357.1253. Anal. Calcd for $C_{16}H_{18}N_2O_5F_2$: C, 53.93; H, 5.09; N, 7.86. Found: C, 53.91; H, 5.01; N, 7.75.

Compound **6f**: yield 64%. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.89 (1 H, dd, *J* = 8.1, 2.6 Hz), 7.62 (1 H, dd, *J* = 8.4, 5.04 Hz), 7.40 (1 H, td, *J* = 8.2, 2.4 Hz), 4.35–4.26 (2 H, m), 4.19–4.13 (2 H, m), 3.40 (3 H, s), 3.38 (1 H, d, J_{AB} = 16.2 Hz), 3.15 (1 H, d, J_{AB} = 16.2 Hz), 3.02 (3 H, s), 1.36–1.30 (3 H, m), 1.27–1.23 (3 H, m). HRMS: *m/z* calcd for $C_{17}H_{22}FN_2O_7S$: 417.1132; found: 417.1116.

Compound **6g**: yield 56%. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.52–7.48 (1 H, m), 7.31 (1 H, d, *J* = 8.2 Hz), 7.18 (1 H, t, *J* = 8.6 Hz), 4.35–4.25 (2 H, m), 4.18 (2 H, q, *J* = 7.0 Hz), 3.40 (1 H, d, J_{AB} = 16.5 Hz), 3.21 (3 H, s), 3.09 (1 H, d, J_{AB} = 16.5 Hz), 3.09 (3 H, s), 3.07 (3 H, s), 1.33 (3 H, t, *J* = 7.0 Hz), 1.26 (3 H, t, *J* = 7.0 Hz). HRMS: *m/z* calcd for $C_{18}H_{25}FN_3O_7S$: 446.1397; found: 446.1383.

Compound **6i**: yield 86%. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.32–4.19 (2 H, m), 4.14 (2 H, q, *J* = 7.0 Hz), 3.72–3.67 (1 H, m), 3.23 (1 H, d, J_{AB} = 15.9 Hz), 2.88 (1 H, d, J_{AB} = 15.9 Hz), 1.98 (3 H, s), 1.30 (3 H, t, *J* = 7.0 Hz), 1.25–1.20 (9 H, m). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 168.9, 168.4, 162.5, 102.9, 61.9, 60.9, 53.2, 42.9, 19.2, 19.0, 14.21, 14.16, 13.0. HRMS: *m/z* calcd for $C_{13}H_{23}N_2O_5$ [M + H]: 287.1607; found: 287.1606.