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New approaches to polysubstituted pyrroles and pyrrolinones from α-cyanomethyl-β-ketoesters

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Abstract—In this present paper, we report the efficient, regioselective one-pot synthesis of 5-alkoxy and 5-alkylsulfanylpyrrole-3-carboxylates in high yields via the zinc perchlorate-catalyzed addition of alcohols and thiols to the nitrile carbon of α-cyanomethyl-β-ketoesters followed by annulation. The addition–annulation process is undertaken in aqueous solution to give 4,5-dihydro-5-oxo-1*H*-pyrrole-3-carboxylates (pyrrolinones) in good yields. These 4,5-dihydro-5-oxo-1*H*-pyrrole-3-carboxylates are also obtained by the hydrolysis of 5-alkoxypyrrole-3-carboxylates.

1. Introduction

Pyrroles are an important class of heterocyclic compounds and are widely used in synthetic organic chemistry and material science.[1,2] Pyrroles are often seen as building blocks in naturally occurring and biologically active compounds. Alkoxy and alkylsulfanyl substituted pyrrole carboxylates and their hydrolysis product pyrrolinones (4,5-dihydro-5-oxo-1*H*-pyrrole-3-carboxylates) are versatile 4-carbon synthons,[3] show interesting biological properties and have been used as precursors for currently known drugs.[4] Because of their multifunctional nature, these heterocycles can take part in several stereoselective transformations, such as conjugate additions,[5] cycloadditions,[6] acyliminium ion chemistry,[7] and allylic substitutions.[8]

Alkoxy and alkylsulfanyl substituted pyrrole carboxylates are not readily available through general pyrrole ring-formation methods. Many excellent methodologies have been developed for constructing pyrrole rings, although relatively few examples have been reported for the preparation of simple alkoxy and alkylsulfanyl substituted pyrrole carboxylate and substituted pyrrolinones.[9]

As we have described in our previous papers, the condensation reaction of α-cyanomethyl-β-dicarbonyl compounds with amines catalyzed by *p*-TsOH affords the corresponding enamines in good yields. Base catalyzed cyclization via the addition of an amine moiety to the carbon–nitrogen triple bond of nitrile in turn furnished 2-aminopyrroles in high yields. We recently discovered that when α-cyanomethyl-β-ketoesters were allowed to react with amine in the presence of $Zn(ClO_4)_2$, in addition to the CN triple bond of **1** and subsequent to cyclocondensation, 2-aminopyrroles were afforded.[10] We have found that perchlorate salts are effective catalysts for the activation of the C═O bond and CN triple bond.

The addition of heteroatom nucleophiles to CN triple bonds of nitriles is one of the most attractive transformations of nitriles.[11] The reported methods are limited, however, because of the low reactivity of nitriles. The development of a catalytic method, which proceeds under neutral and mild conditions, is desired. To continue our investigations, which are directed toward the synthesis of substituted pyrroles and related compounds,[12] we were especially interested in carrying out the addition–annulation reaction to α-cyanomethyl-β-ketoesters with oxygen and sulfur nucleophiles in order to discover if thiols or alcohols can give alkoxy and alkylsulfanyl substituted pyrrole carboxylate and their hydrolysis products pyrrolinones (4,5-dihydro-5-oxo-1*H*-pyrrole-3-carboxylates).

Herein, we report the zinc perchlorate-catalyzed selective one-pot synthesis of substituted 5-alkoxypyrrole-3-carboxylates and pyrrolinone carboxylates from α-cyanomethyl-β-ketoesters and alcohols.

2. Results and discussion

As shown in Scheme 1, α-cyanomethyl-β-dicarbonyl compounds **1a–e** were synthesized by the alkylation of

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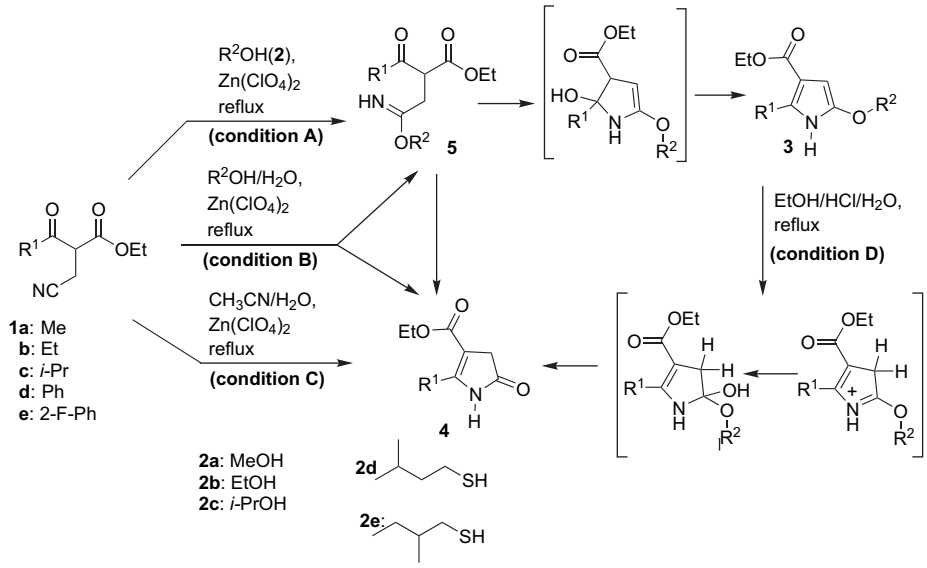


Scheme 1.

commercially available β-dicarbonyl compounds with bromoacetonitrile (using either NaH/THF or DBU/benzene) in 71–80% yields (Scheme 1) according to the literature procedure.[10]

In an initial reaction α-cyanomethyl-β-ketoester **1d** and 5 mol % of $Zn(ClO_4)_2$ were heated to reflux in methanol with the reaction being monitored by TLC. Three different products were isolated after work-up and chromatographic separation. The isolated products were identified as an addition product **5a** (minor product), pyrrole derivative **3d**, and pyrrolinone derivative **4d** (as the major products) (Scheme 1).

When this reaction is carried out in anhydrous methanol with 5 mol % of $Zn(ClO_4)_2$ the pyrrole derivative **3d** was isolated in 91% yield after chromatography (Scheme 1, condition A). Using these conditions, various α-cyanomethyl-β-ketoesters derived from commercially available β-ketoesters and different alcohols were prepared as shown in Table 1. The 5-alkoxypyrrole-3-carboxylates were thus obtained in good to high yields. Using dichloroethane as a solvent (contains 10% methanol), **3d** was also furnished in 82% yield with a long reaction time (12 h).

The addition–annulation process is also carried out with two representative thiols, and the corresponding 5-alkylsulfanyl-pyrrole-3-carboxylates obtained in 79–80% yields (Table 1, entries 16 and 17); for these reaction, dichloroethane was used as the solvent.

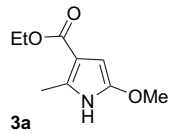
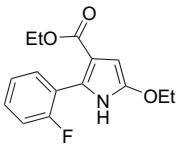
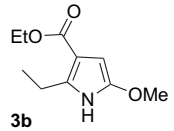
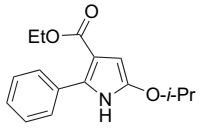
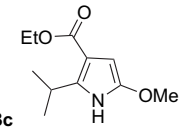
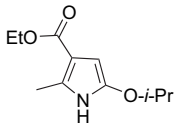
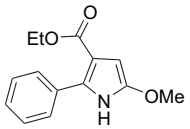
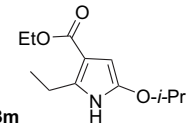
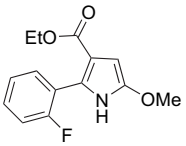
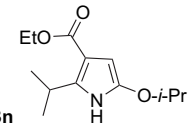
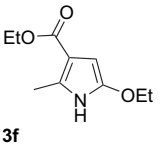
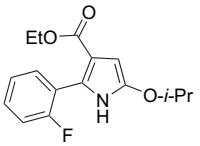
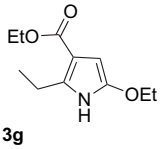
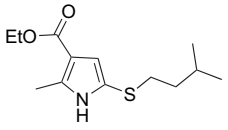
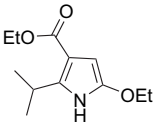
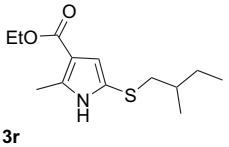
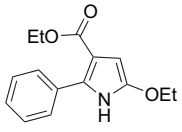
As shown in Table 1, the use of isopropanol decreased the yields to 70–78% (Table 1, entries 11–15) and pyrrolinones **4a–e** (Table 2) were also isolated as side products. We suggest that the presence of a small amount of water in isopropanol is the reason for the diminished yields and the formation of pyrrolinones. Thus, when a few drops of water were added to the reaction medium, pyrrole/pyrrolinone mixture **3l**:**4a** was obtained in a 2:1 ratio. After this result, the addition–annulation reaction was carried out with **1a** in a MeOH/water (2:1) mixture at reflux in the presence of $Zn(ClO_4)_2$ (Scheme 1, condition B). At the start of the reaction, only the formation of pyrrole **3a** was observed, subsequently the formation of pyrrolinone **4a** in increasing amount along with the disappearance of pyrrole **3a** was observed. The only product isolated from the reaction was identified as pyrrolinone **4a** in 95% yield. The formation of pyrrolinone must proceed via the formation of pyrrole **3a** and then undergo hydrolysis with water, as well as by the direct addition of water to nitrile C followed by heteroannulation. As shown in Table 2, different pyrrolinones can be synthesized according to this procedure in high yields.

In order to shed light on the formation of pyrrolinone, the typical pyrrole formation reaction with **1a** was carried out in a CH_3CN/water mixture (5:1) in the presence of $Zn(ClO_4)_2$ (condition C). TLC monitoring of these mixtures showed that ketoesters **1** were completely converted into pyrrolinones (Scheme 1, condition C). The results of this conversion with various ketoesters are summarized in Table 2. In the non-catalytic case, ketoester **1a** was refluxed with methanol for several hours in the absence of $Zn(ClO_4)_2$, and only a trace amount of **3a** was detected by GC–MS.

As shown in Scheme 1 (condition D), the heating of pyrroles in an HCl/water/alcohol mixture (ethanol/2 N HCl; 20 mL/L) furnished the corresponding pyrrolinones in 82–85% yields.

The mechanism of pyrrole formation starting from α-cyanomethyl-β-ketoesters and anhydrous alcohols was investigated systematically. To demonstrate that alcohol attack at the nitrile is the initial step, the isolation of the corresponding iminoesters was carried out for selected examples as shown in Table 3. The reactions were stopped when an isolable amount of iminoesters was formed according to TLC monitoring (1–2 h). After work-up and chromatographic separation, the corresponding iminoesters **5a–d** were isolated in 12–15% yields. The second step was carried out

Table 1. Pyrroles synthesized by using condition A (Scheme 1)

Entry	1	2	Pyrrole 3	Yield (%)	Time (h)	Entry	1	2	Pyrrole 3	Yield (%)	Time (h)
1	**a**	**a**	 **3a**	93	6	10	**e**	**b**	 **3j**	80	5
2	**b**	**a**	 **3b**	90	6	11	**d**	**c**	 **3k**	78	6
3	**c**	**a**	 **3c**	89	6	12	**a**	**c**	 **3l**	75	5
4	**d**	**a**	 **3d**[a]	91	7	13	**b**	**c**	 **3m**	77	5
5	**e**	**a**	 **3e**	82	7	14	**c**	**c**	 **3n**	73	5
6	**a**	**b**	 **3f**	86	6	15	**e**	**c**	 **3o**	70	7
7	**b**	**b**	 **3g**	88	5	16[b]	**a**	**d**	 **3p**	79	5
8	**c**	**b**	 **3h**	79	6	17[b]	**a**	**e**	 **3r**	80	6
9	**d**	**b**	 **3i**	82	5						

[a] When using dichloroethane as a solvent (contains 10% methanol), **3d** was also furnished in 82% yield with a long reaction time (12 h).
[b] DCE was used as solvent.

with **5a** in methanol and $Zn(ClO_4)_2$, and the annulation product **3d** obtained in 74% yield.

In all of the cases, the products were readily separable by flash column chromatography, and the products are obtained in nearly pure form. In some cases, the pyrrolinones could be directly obtained from the crude product via crystallization.

The present reaction can be rationalized by assuming that the anhydrous conditions, attack of an external alcohol on the complex substrate form an iminoester complex. However, if the alcohol is used when wet, attack of water on the formed iminoester and direct attack on the complex afford a carboximide complex, the precursor of pyrrolinones (Scheme 1).

Table 2. Pyrrolinones synthesized using conditions B and C

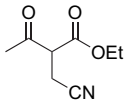
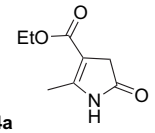
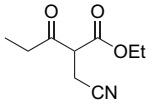
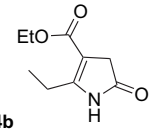
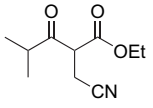
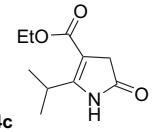
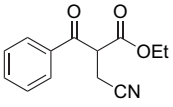
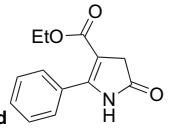
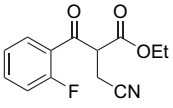
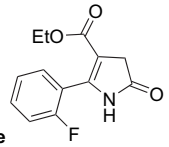
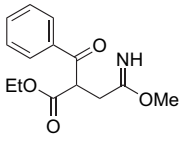
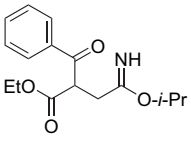
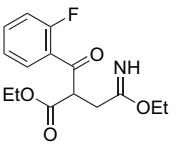
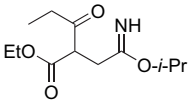
Entry	Ketoester **1**	Pyrolinone **4**	Condition B		Condition C	
			Yield (%)	Time (h)	Yield (%)	Time (h)
1		 **4a**	95	2	93	4
2		 **4b**	94	3	91	3
3		 **4c**	89	3	92	4
4		 **4d**	95	2	90	4
5		 **4e**	87	3	89	4

Table 3. Iminoesters synthesized

Entry	Ketoester **1**	Alcohol **2**	Iminoester **5**	Yield (%)	Time (h)
1	**1d**	**2a**	 **5a**	12	2
2	**1d**	**2c**	 **5b**	15	1
3	**1e**	**2b**	 **5c**	13	2
4	**1b**	**2c**	 **5d**	12	1

3. Conclusions

Typically, when α-cyanomethyl-β-ketoesters were allowed to react with alcohols, thiols, and water in the presence of $Zn(ClO_4)_2$, addition to the CN triple bond of **1** and subsequent to cyclocondensation occurred, and afforded 5-alkoxy-, 5-alkylsulfanylpyrroles, and pyrrolinones. Starting from α-cyanomethyl-β-ketoesters and alcohols in the presence of $Zn(ClO_4)_2$, the 5-alkoxypyrrole-3-carboxylate can be synthesized under water free conditions in 70–93% yields. The same reaction was carried out in water–alcohol or in water, which furnished the pyrrolinones in 87–95% yields. The pyrrolinones can also be synthesized from pyrroles in 82–85% yields with EtOH/HCl.

This method opens an entry for the selective synthesis of 5-alkoxypyrroles and pyrrolinones, depending on the reaction conditions.

4. Experimental section

4.1. General

^1H and ^{13}C NMR spectra were obtained on Bruker Avance 300 MHz, DPX 400 spectrometers. All resonances are referenced to residual solvent signals. Elemental analyses: Leco CHNS 932 Analysator. IR spectra were obtained on Bruker IFS 66/s. Column chromatography was conducted on silica gel 60 (40–63 μm). TLC was carried out on aluminum sheets pre-coated with silica gel $60F_{254}$ (Merck), and the spots were visualized with UV light (λ=254 nm). Commercially available $Zn(ClO_4)_2$ was used.

4.1.1. The general procedure for the synthesis of pyrroles (3a–o) (condition A). β-Ketoester (1 mmol) was dissolved in alcohol (5 mL) together with a catalytic amount of $Zn(ClO_4)_2$ (5 mol %). The reaction was refluxed for 5–6 h and monitored by TLC. The reaction mixture was then extracted with ethyl acetate (50 mL). The organic extract was dried over $MgSO_4$ and the solvent evaporated under

reduced pressure. The crude product was then purified by column chromatography.

4.1.1.1. Ethyl 5-methoxy-2-methyl-1*H*-pyrrole-3-carboxylate 3a. Yield: 170 mg, 93%, white solid (mp=106–107 °C), R_f (20% EtOAc/hexane), IR ($CHCl_3$): 3947, 3293, 3286, 2986, 2369, 2309, 1722, 1439 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.99 (1H, br s, N*H*), 5.47 (1H, d, J=3.0 Hz, C*H*), 4.20 (2H, q, J=7.1 Hz, OCH_2Me), 3.71 (3H, s, O*Me*), 2.35 (3H, s, *Me*), 1.20 (3H, t, J=7.1 Hz, CH_2*Me*); ^{13}C NMR (100 MHz, $CDCl_3$): 165.8, 146.4, 127.8, 109.5, 83.1, 59.3, 57.4, 14.5, 12.7; Anal. Calcd for $C_9H_{13}NO_3$ (183.2): C, 59.00; H, 7.15; N, 7.65. Found: C, 58.88; H, 7.24; N, 7.44.

4.1.1.2. Ethyl 2-ethyl-5-methoxy-1*H*-pyrrole-3-carboxylate 3b. Yield: 177 mg, 90%, white solid (mp=70–71 °C), R_f (20% EtOAc/hexane) 0.70, IR ($CHCl_3$): 3940, 3293, 3285, 2978, 2312, 1732, 1456 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.63 (1H, br s, N*H*), 5.44 (1H, d, J=2.9 Hz, C*H*), 4.17 (2H, q, J=7.0 Hz, OCH_2Me), 3.70 (3H, s, O*Me*), 2.82 (2H, q, J=7.5 Hz, CH_2Me), 1.26 (3H, t, J=7.0 Hz, OCH$_2$*Me*), 1.13 (3H, t, J=7.5 Hz, CH_2*Me*); ^{13}C NMR (100 MHz, $CDCl_3$): 165.1, 146.3, 133.3, 106.5, 83.3, 59.1, 57.5, 20.1, 14.5, 13.6; Anal. Calcd for $C_{10}H_{15}NO_3$ (197.23): C, 60.90; H, 7.67; N, 7.10. Found: C, 60.81; H, 7.55; N, 6.88.

4.1.1.3. Ethyl 2-isopropyl-5-methoxy-1*H*-pyrrole-3-carboxylate 3c. Yield: 187 mg, 89%, white solid (mp=121–122 °C), R_f (20% EtOAc/hexane) 0.67, IR ($CHCl_3$): 3945, 3423, 3189, 3055, 2982, 2930, 2326, 1692, 1495 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.81 (1H, br s, N*H*), 5.47 (1H, d, J=2.9 Hz, C*H*), 4.19 (2H, q, J=7.1 Hz, OCH_2Me), 3.71 (3H, s, O*Me*), 3.65 (1H, m, C*H*Me$_2$), 1.26 (3H, t, J=7.1 Hz, CH_2*Me*), 1.15 (6H, d, J=7.0 Hz, CH*Me*$_2$); ^{13}C NMR (100 MHz, $CDCl_3$): 165.2, 146.3, 137.7, 107.9, 83.1, 59.3, 57.5, 25.6, 22.0, 14.5; Anal. Calcd for $C_{11}H_{17}NO_3$ (211.26): C, 62.54; H, 8.11; N, 6.63. Found: C, 62.42; H, 8.23; N, 6.48.

4.1.1.4. Ethyl 5-methoxy-2-phenyl-1*H*-pyrrole-3-carboxylate 3d. Yield: 228 mg, 91%, white solid (mp=129–131 °C), R_f (20% EtOAc/hexane) 0.81, IR ($CHCl_3$): 3944, 3432, 3190, 3032, 2985, 2306, 1722, 1426 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.77 (1H, br s, N*H*), 7.21–7.51 (5H, m, *Ph*), 5.65 (1H, d, J=2.9 Hz, C*H*), 4.13 (2H, q, J=7.1 Hz, OCH_2Me), 3.78 (3H, s, O*Me*), 1.19 (3H, t, J=7.1 Hz, OCH$_2$*Me*); ^{13}C NMR (100 MHz, $CDCl_3$): 168.3, 147.8, 133.3, 129.0, 128.7, 128.0, 127.7, 110.5, 85.8, 59.3, 32.8, 14.3; Anal. Calcd for $C_{14}H_{15}NO_3$ (245.27): C, 68.56; H, 6.16; N, 5.71. Found: C, 68.48; H, 6.12; N, 5.58.

4.1.1.5. Ethyl 2-(2-fluorophenyl)-5-methoxy-1*H*-pyrrole-3-carboxylate 3e. Yield: 215 mg, 82%, white solid (mp=122–123 °C), R_f (20% EtOAc/hexane) 0.78, IR ($CHCl_3$): 3966, 3701, 3433, 3055, 2988, 2370, 1684, 1595 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 8.06 (1H, br s, N*H*), 6.99–7.52 (4H, m, *Ph*), 5.73 (1H, d, J=2.9 Hz, C*H*), 4.11 (2H, q, J=7.1 Hz, OCH_2Me), 3.77 (3H, s, O*Me*), 1.10 (3H, t, J=7.1 Hz, OCH$_2$*Me*); ^{13}C NMR (100 MHz, $CDCl_3$): 164.6, 160.9 (d, J=245 Hz), 148.1, 132.0, 129.6 (d, J=8.7 Hz), 123.6 (d, J=3 Hz), 122.0, 119.7 (d, J=13 Hz), 115.6 (d, J=22 Hz), 112.4, 85.6, 59.7, 57.6, 14.1; Anal. Calcd for $C_{14}H_{14}FNO_3$ (263.26): C, 63.87; H, 5.36; N, 5.32. Found: C, 63.71; H, 5.28; N, 5.12.

4.1.1.6. Ethyl 5-ethoxy-2-methyl-1*H*-pyrrole-3-carboxylate 3f. Yield: 169 mg, 86%, white solid (mp=114–115 °C), R_f (20% EtOAc/hexane) 0.69, IR ($CHCl_3$): 3932, 3290, 3294, 2982, 2366, 2334, 1732, 1421 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.91 (1H, br s, N*H*), 5.45 (1H, d, J=2.9 Hz, C*H*), 4.18 (2H, q, J=7.1 Hz, OCH_2Me), 3.95 (2H, q, J=7.1 Hz, CH_2Me), 2.35 (3H, s, *Me*), 1.21 (3H, t, J=7.1 Hz, CH_2*Me*), 1.20 (3H, t, J=7.1 Hz, OCH$_2$*Me*); ^{13}C NMR (100 MHz, $CDCl_3$): 165.8, 145.3, 127.5, 109.5, 83.9, 66.2, 59.2, 57.4, 14.5, 12.7; Anal. Calcd for $C_{10}H_{15}NO_3$ (197.23): C, 60.90; H, 7.67; N, 7.10. Found: C, 60.72; H, 7.58; N, 6.81.

4.1.1.7. Ethyl 5-ethoxy-2-ethyl-1*H*-pyrrole-3-carboxylate 3g. Yield: 185 mg, 88%, white solid (mp=115–116 °C), R_f (20% EtOAc/hexane) 0.65, IR ($CHCl_3$): 3944, 3687, 3190, 3049, 2984, 2312, 1691, 1426 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.61 (1H, br s, N*H*), 5.41 (1H, d, J=3.1 Hz, C*H*), 4.11 (2H, q, J=7.1 Hz, OCH_2Me), 4.06 (2H, q, J=7.2 Hz, OCH_2Me), 2.81 (2H, q, J=7.5 Hz, CH_2Me), 1.25 (3H, t, J=7.2 Hz, OCH$_2$*Me*), 1.15 (3H, t, J=7.5 Hz, CH_2*Me*), 1.02 (3H, t, J=7.1 Hz, OCH$_2$*Me*); ^{13}C NMR (100 MHz, $CDCl_3$): 165.0, 145.1, 133.0, 108.7, 84.0, 65.8, 58.9, 20.0, 14.6, 14.5, 13.5; Anal. Calcd for $C_{11}H_{17}NO_3$ (211.26): C, 62.54; H, 8.11; N, 6.63. Found: C, 62.43; H, 8.04; N, 6.49.

4.1.1.8. Ethyl 5-ethoxy-2-isopropyl-1*H*-pyrrole-3-carboxylate 3h. Yield: 177 mg, 79%, white solid (mp=101–103 °C), R_f (20% EtOAc/hexane) 0.67, IR ($CHCl_3$): 3947, 3809, 3291, 3043, 2986, 2301, 1733, 1495 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.74 (1H, br s, N*H*), 5.44 (1H, d, J=2.4 Hz, C*H*), 4.17 (2H, q, J=7.1 Hz, OCH_2Me), 3.93 (2H, q, J=7.1 Hz, OCH_2Me), 3.65 (1H, m, C*H*Me$_2$), 1.29 (3H, t, J=7.1 Hz, OCH$_2$*Me*), 1.25 (3H, t, J=7.1 Hz, OCH$_2$*Me*), 1.13 (6H, d, J=6.9 Hz, CH*Me*$_2$); ^{13}C NMR (100 MHz, $CDCl_3$): 165.4, 145.2, 137.4, 107.9, 83.7, 66.1, 59.2, 25.5, 22.0, 14.7, 14.5; Anal. Calcd for $C_{12}H_{19}NO_3$ (225.28): C, 63.98; H, 8.50; N, 6.22. Found: C, 63.86; H, 8.45; N, 6.11.

4.1.1.9. Ethyl 5-ethoxy-2-phenyl-1*H*-pyrrole-3-carboxylate 3i. Yield: 212 mg, 82%, white solid (mp=129–131 °C), R_f (20% EtOAc/hexane) 0.62, IR ($CHCl_3$): 3939, 3295, 3045, 2982, 2369, 1702, 1593 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.88 (1H, br s, N*H*), 7.22–7.51 (5H, m, *Ph*), 5.68 (1H, d, J=2.9 Hz, C*H*), 4.15 (2H, q, J=7.0 Hz, OCH_2Me), 4.03 (2H, q, J=7.1 Hz, OCH_2Me), 1.34 (3H, t, J=7.0 Hz, OCH$_2$*Me*), 1.21 (3H, t, J=7.1 Hz, OCH$_2$*Me*); ^{13}C NMR (100 MHz, $CDCl_3$): 164.9, 147.0, 132.0, 128.8, 128.6, 128.0, 127.7, 110.3, 86.4, 66.4, 59.6, 14.6, 14.2; Anal. Calcd for $C_{15}H_{17}NO_3$ (259.3): C, 69.48; H, 6.61; N, 5.40. Found: C, 69.32; H, 6.59; N, 5.11.

4.1.1.10. Ethyl 5-ethoxy-2-(2-fluorophenyl)-1*H*-pyrrole-3-carboxylate 3j. Yield: 221 mg, 80%, white solid (mp=104–105 °C), R_f (20% EtOAc/hexane) 0.71, IR ($CHCl_3$): 3945, 3693, 3416, 3189, 3053, 2985, 1691,

1421 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 8.05 (1H, br s, N*H*), 7.01–7.56 (4H, m, *Ph*), 5.71 (1H, d, *J*=2.9 Hz, C*H*), 4.12 (2H, q, *J*=7.1 Hz, OCH_2Me), 4.10 (2H, q, *J*=7.0 Hz, OCH_2Me), 1.32 (3H, t, *J*=7.0 Hz, OCH$_2$*Me*), 1.16 (3H, t, *J*=7.1 Hz, OCH$_2$*Me*); ^{13}C NMR (100 MHz, $CDCl_3$): 164.7, 160.9 (d, *J*=245 Hz), 147.1, 132.0, 129.4 (d, *J*=8.8 Hz), 123.6, 122.4, 121.8, 119.6 (d, *J*=13 Hz), 115.4 (d, *J*=22 Hz), 86.3, 66.5, 59.6, 14.6, 14.1; Anal. Calcd for $C_{15}H_{16}FNO_3$ (277.29): C, 64.97; H, 5.82; N, 5.05. Found: C, 64.82; H, 5.71; N, 5.21.

4.1.1.11. Ethyl 5-isopropoxy-2-phenyl-1*H*-pyrrole-3-carboxylate 3k. Yield: 201 mg, 78%, colorless oil, R_f (20% EtOAc/hexane) 0.74, IR (neat): 3939, 3422, 3295, 3193, 3045, 2982, 2369, 1702, 1593 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.77 (1H, br s, N*H*), 7.25–7.57 (5H, m, *Ph*), 5.68 (1H, d, *J*=2.9 Hz, C*H*), 4.43 (1H, m, C*H*Me$_2$), 4.19 (2H, q, *J*=7.1 Hz, OCH_2Me), 1.37 (6H, d, *J*=6.1 Hz, CH*Me*$_2$), 1.25 (3H, t, *J*=7.1 Hz, OCH$_2$*Me*); ^{13}C NMR (100 MHz, $CDCl_3$): 164.4, 145.6, 132.0, 128.7, 128.6, 128.4, 127.8, 110.4, 87.6, 73.7, 59.2, 21.9, 14.2; Anal. Calcd for $C_{16}H_{19}NO_3$ (273.3): C, 70.31; H, 7.01; N, 5.12. Found: C, 70.15; H, 6.88; N, 4.89.

4.1.1.12. Ethyl 5-isopropoxy-2-methyl-1*H*-pyrrole-3-carboxylate 3l. Yield: 140 mg, 75%, white solid (mp=121–122 °C), R_f (20% EtOAc/hexane) 0.62, IR ($CHCl_3$): 3934, 3273, 3279, 2977, 2356, 2322, 1735, 1423 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.63 (1H, br s, N*H*), 5.45 (1H, d, *J*=2.8 Hz, C*H*), 4.27 (1H, m, C*H*Me$_2$), 4.16 (2H, q, *J*=7.1 Hz, OCH_2Me), 2.35 (3H, s, *Me*), 1.25 (3H, t, *J*=7.1 Hz, OCH$_2$*Me*), 1.23 (6H, d, *J*=6.1 Hz, CH*Me*$_2$); ^{13}C NMR (100 MHz, $CDCl_3$): 165.7, 144.0, 127.2, 109.7, 85.6, 74.0, 59.2, 21.9, 14.5, 12.8; Anal. Calcd for $C_{11}H_{17}NO_3$ (211.26): C, 62.54; H, 8.11; N, 6.63. Found: C, 62.33; H, 8.01; N, 6.42.

4.1.1.13. Ethyl 2-ethyl-5-isopropoxy-1*H*-pyrrole-3-carboxylate 3m. Yield: 173 mg, 77%, yellow oil, R_f (20% EtOAc/hexane) 0.71, IR (neat): 3941, 3682, 3429, 3293, 3043, 2990, 2332, 1692, 1426 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.76 (1H, br s, N*H*), 5.49 (1H, d, *J*=3.0 Hz, C*H*), 4.25 (1H, m, C*H*Me$_2$), 4.18 (2H, q, *J*=7.0 Hz, OCH_2Me), 2.82 (2H, q, *J*=7.5 Hz, CH_2Me), 1.26 (3H, t, *J*=7.0 Hz, CH$_2$*Me*), 1.25 (6H, d, *J*=6.2 Hz, CH*Me*$_2$), 1.12 (3H, t, *J*=7.5 Hz, OCH$_2$*Me*); ^{13}C NMR (100 MHz, $CDCl_3$): 164.4, 143.0, 132.1, 107.6, 84.1, 72.7, 60.0, 49.7, 20.8, 13.4, 12.4; Anal. Calcd for $C_{12}H_{19}NO_3$ (225.28): C, 63.98; H, 8.50; N, 6.22. Found: C, 63.69; H, 8.45; N, 6.08.

4.1.1.14. Ethyl 5-isopropoxy-2-isopropyl-1*H*-pyrrole-3-carboxylate 3n. Yield: 174 mg, 73%, yellow oil, R_f (20% EtOAc/hexane) 0.86, IR (neat): 3945, 3426, 3193, 3055, 2984, 2300, 1722, 1427 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.74 (1H, br s, N*H*), 5.46 (1H, d, *J*=3.0 Hz, C*H*), 4.23 (1H, m, OC*H*Me$_2$), 4.11 (2H, q, *J*=7.1 Hz, OCH_2Me), 3.65 (1H, m, C*H*Me$_2$), 1.25 (6H, d, *J*=7.0 Hz, OCH*Me*$_2$), 1.24 (3H, t, *J*=7.1 Hz, OCH$_2$*Me*), 1.15 (6H, d, *J*=6.2 Hz, CH*Me*$_2$); ^{13}C NMR (100 MHz, $CDCl_3$): 165.7, 146.3, 137.7, 107.9, 83.1, 74.2, 59.6, 22.0, 21.9, 14.5, 14.2; Anal. Calcd for $C_{13}H_{21}NO_3$ (239.31): C, 65.25; H, 8.84; N, 5.85. Found: C, 65.12; H, 8.71; N, 5.71.

4.1.1.15. Ethyl 2-(2-fluorophenyl)-5-isopropoxy-1*H*-pyrrole-3-carboxylate 3o. Yield: 202 mg, 70%, white solid (mp=116–117 °C), R_f (20% EtOAc/hexane) 0.76, IR ($CHCl_3$): 3899, 3690, 3425, 3143, 2979, 2369, 2326, 1682, 1495 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.85 (1H, br s, N*H*), 7.02–7.56 (4H, m, *Ph*), 5.72 (1H, d, *J*=2.9 Hz, C*H*), 4.35 (1H, m, OC*H*Me$_2$), 4.12 (2H, q, *J*=7.1 Hz, OCH_2Me), 1.30 (6H, d, *J*=6.0 Hz, OCH*Me*$_2$), 1.15 (3H, t, *J*=7.1 Hz, OCH$_2$*Me*); ^{13}C NMR (100 MHz, $CDCl_3$): 160.9 (d, *J*=246 Hz), 164.2, 145.8, 132.0, 129.5 (d, *J*=8.5 Hz), 123.4 (d, *J*=3 Hz), 121.4, 119.6, 115.3 (d, *J*=22 Hz), 112.4, 87.6, 73.8, 59.3, 21.9, 14.2; Anal. Calcd for $C_{16}H_{18}FNO_3$ (291.32): C, 65.97; H, 6.23; N, 4.81. Found: C, 65.82; H, 6.11; N, 4.71.

4.1.2. The general procedure for the synthesis of pyrroles (3p, 3r). β-Ketoester (1 mmol) was dissolved in dichloromethane (5 mL). The corresponding thiol (2 mmol) along with a catalytic amount of $Zn(ClO_4)_2$ (5 mol %) was added to the stirred mixture. The reaction was then refluxed for 5–6 h and monitored by TLC. The reaction mixture was extracted with ethyl acetate (50 mL). The organic extract was dried over $MgSO_4$ and the solvent evaporated under reduced pressure. The crude product was then purified by column chromatography.

4.1.2.1. Ethyl 5-(isopentylthio)-2-methyl-1*H*-pyrrole-3-carboxylate 3p. Yield: 196 mg, 79%, white solid (129–131 °C), R_f (20% EtOAc/hexane) 0.64, IR ($CHCl_3$): 3956, 3293, 3286, 3041, 2986, 2303, 2316, 1721, 1439 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 8.17 (1H, br s, N*H*), 6.44 (1H, s, C*H*), 4.30 (2H, q, *J*=7.0 Hz, OCH_2Me), 2.76 (2H, t, *J*=7.6 Hz, SCH_2CH$_2$), 2.49 (3H, s, *Me*), 1.71 (1H, m, C*H*Me$_2$), 1.52 (2H, m, CH$_2$CH_2CH$_2$), 1.39 (3H, t, *J*=7.0 Hz, OCH$_2$*Me*), 0.91 (6H, d, *J*=6.5 Hz, CH*Me*$_2$); ^{13}C NMR (100 MHz, $CDCl_3$): 164.6, 136.1, 117.6, 116.1, 111.9, 59.2, 37.7, 32.1, 27.4, 22.3, 14.4, 14.0; Anal. Calcd for $C_{13}H_{21}NO_2S$ (249.24): C, 61.14; H, 8.29; N, 5.48. Found: C, 61.03; H, 8.17; N, 5.22.

4.1.2.2. Ethyl 5-(2-methylbutylthio)-2-methyl-1*H*-pyrrole-3-carboxylate 3r. Yield: 199 mg, 80%, white solid (127–129 °C), R_f (20% EtOAc/hexane) 0.62, IR ($CHCl_3$): 3951, 3299, 3289, 3045, 2996, 2308, 2320, 1722, 1443 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 8.32 (1H, br s, N*H*), 6.39 (1H, s, C*H*), 4.20 (2H, q, *J*=7.0 Hz, OCH_2Me), 2.52–2.71 (2H, m, SCH$_2$CH), 2.44 (3H, s, *Me*), 1.46–1.62 (2H, m, CHCH_2CH$_3$), 1.30 (3H, t, *J*=7.0 Hz, OCH$_2$*Me*), 1.16 (1H, m, C*H*Me), 0.93 (3H, d, *J*=10.5 Hz, CH*Me*), 0.82 (3H, t, *J*=7.0 Hz, CH$_2$*Me*); ^{13}C NMR (100 MHz, $CDCl_3$): 163.8, 135.3, 117.0, 114.9, 110.8, 58.3, 40.4, 33.2, 27.9, 18.1, 13.5, 13.0, 10.3; Anal. Calcd for $C_{13}H_{21}NO_2S$ (249.24): C, 61.14; H, 8.29; N, 5.48. Found: C, 61.19; H, 8.44; N, 5.31.

4.1.3. The general procedure for the synthesis of pyrrolinones (4a–e) (condition B). The corresponding β-ketoester (1 mmol) together with a catalytic amount of $Zn(ClO_4)_2$ (5 mol %) was dissolved in a water/isopropanol mixture (10 mL/4 mL). The reaction was refluxed for 6–7 h and was monitored with TLC. The reaction mixture was then extracted with ethyl acetate (50 mL). The organic extract was dried over $MgSO_4$ and the solvent evaporated under

reduced pressure. The crude product was then purified by column chromatography.

4.1.3.1. Ethyl 4,5-dihydro-2-methyl-5-oxo-1*H*-pyrrole-3-carboxylate 4a. Yield: 160 mg, 95%, white solid (mp=124–125 °C), R_f (20% EtOAc/hexane) 0.10, IR ($CHCl_3$): 3691, 3416, 3297, 2984, 2306, 2326, 1691, 1426 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 8.91 (1H, br s, N*H*), 4.15 (2H, q, *J*=7.1 Hz, OCH_2Me), 3.23 (2H, d, *J*=2.1 Hz, CH_2), 2.21 (3H, s, *Me*), 1.23 (3H, t, *J*=7.1 Hz, OCH$_2$*Me*); ^{13}C NMR (100 MHz, $CDCl_3$): 178.5, 164.1, 151.7, 104.4, 59.8, 37.5, 14.4, 13.4; Anal. Calcd for $C_8H_{11}NO_3$ (169.18): C, 56.80; H, 6.55; N, 8.28. Found: C, 56.64; H, 6.43; N, 8.15.

4.1.3.2. Ethyl 2-ethyl-4,5-dihydro-5-oxo-1*H*-pyrrole-3-carboxylate 4b. Yield: 172 mg, 94%, white solid (mp=99–100 °C), R_f (20% EtOAc/hexane) 0.18, IR ($CHCl_3$): 3692, 3434, 3295, 2984, 2326, 2326, 1726, 1474 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 9.07 (1H, br s, N*H*), 4.13 (2H, q, *J*=7.1 Hz, OCH_2Me), 3.32 (2H, s, CH_2), 2.78 (2H, q, *J*=7.6 Hz, CH_2Me), 1.22 (3H, t, *J*=7.1 Hz, OCH$_2$*Me*), 1.13 (3H, t, *J*=7.6 Hz, CH$_2$*Me*); ^{13}C NMR (100 MHz, $CDCl_3$): 178.9, 163.5, 157.2, 103.3, 59.5, 37.6, 20.4, 14.4, 11.6; Anal. Calcd for $C_9H_{13}NO_3$ (183.2): C, 59.0; H, 7.15; N, 7.65. Found: C, 58.74; H, 7.12; N, 7.59.

4.1.3.3. Ethyl 4,5-dihydro-2-isopropyl-5-oxo-1*H*-pyrrole-3-carboxylate 4c. Yield: 175 mg, 89%, white solid (mp=128–129 °C), R_f (20% EtOAc/hexane) 0.11, IR ($CHCl_3$): 3657, 3425, 3191, 3053, 2983, 1723, 1593 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 9.62 (1H, br s, N*H*), 4.18 (2H, q, *J*=7.0 Hz, OCH_2Me), 3.90 (1H, m, C*H*Me$_2$), 3.27 (2H, s, CH_2), 1.29 (3H, t, *J*=7.0 Hz, OCH$_2$*Me*), 1.20 (6H, d, *J*=7.0 Hz, CH*Me*$_2$); ^{13}C NMR (100 MHz, $CDCl_3$): 178.9, 163.4, 161.2, 102.1, 59.5, 37.6, 25.7, 20.0, 14.4; Anal. Calcd for $C_{10}H_{15}NO_3$ (197.23): C, 60.90; H, 7.67; N, 7.10. Found: C, 60.79; H, 7.62; N, 6.88.

4.1.3.4. Ethyl 4,5-dihydro-5-oxo-2-phenyl-1*H*-pyrrole-3-carboxylate 4d. Yield: 210 mg, 95%, white solid (mp=173–174 °C), R_f (20% EtOAc/hexane) 0.14, IR ($CHCl_3$): 3660, 3426, 3198, 3053, 2987, 2361, 1701, 1438 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 8.62 (1H, br s, N*H*), 7.35–7.56 (5H, m, *Ph*), 4.05 (2H, q, *J*=7.1 Hz, OCH_2Me), 3.41 (2H, s, CH_2), 1.14 (3H, t, *J*=7.1 Hz, OCH$_2$*Me*); ^{13}C NMR (100 MHz, $CDCl_3$): 178.6, 163.4, 152.3, 130.4, 129.4, 128.7, 128.1, 104.2, 60.0, 39.2, 14.9; Anal. Calcd for $C_{13}H_{13}NO_3$ (231.25): C, 67.52; H, 5.67; N, 6.06. Found: C, 67.49; H, 5.62; N, 5.81.

4.1.3.5. Ethyl 2-(2-fluorophenyl)-4,5-dihydro-5-oxo-1*H*-pyrrole-3-carboxylate 4e. Yield: 221 mg, 87%, white solid (mp=116 °C), R_f (20% EtOAc/hexane) 0.11, IR ($CHCl_3$): 3653, 3194, 3045, 2987, 2303, 1689, 1498 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 8.76 (1H, br s, N*H*), 7.11–7.51 (4H, m, *Ph*), 4.09 (2H, q, *J*=7.1 Hz, OCH_2Me), 3.44 (2H, s, CH_2), 1.15 (3H, t, *J*=7.1 Hz, OCH$_2$*Me*); ^{13}C NMR (100 MHz, $CDCl_3$): 176.8, 162.3 (d, *J*=246 Hz), 145.1, 132.0 (d, *J*=8.6 Hz), 130.6, 123.7, 115.8 (d, *J*=21 Hz), 107.0, 59.8, 37.9, 13.9; Anal. Calcd for $C_{13}H_{12}FNO_3$ (249.24): C, 62.65; H, 4.85; N, 5.62. Found: C, 62.76; H, 4.81; N, 5.56.

4.1.4. The general procedure for the synthesis of pyrrolinones (condition C) (4a–e). The required β-ketoester (1 mmol) together with a catalytic amount of $Zn(ClO_4)_2$ (5 mol %) was dissolved in a water/acetonitrile mixture (10 mL/2.0 mL). The reaction was refluxed for 3–4 h and was monitored with TLC. The reaction mixture was extracted with ethyl acetate (50 mL). The organic extract was dried over $MgSO_4$ and the solvent evaporated under reduced pressure. The crude product was then purified by column chromatography.

4.1.4.1. 3-(Ethoxycarbonyl)-4-oxo-4-phenylbutanoxylimidic acid methyl ester 5a. Yield: 26 mg, 12%, yellow oil, R_f (20% EtOAc/hexane) 0.78, IR (neat): 3866, 3538, 3197, 2990, 1745, 1419 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.45–8.01 (5H, m, *Ph*), 4.80 (1H, t, *J*=7.1 Hz, C*H*CH$_2$), 4.12 (2H, q, *J*=7.1 Hz, OCH_2Me), 3.69 (3H, s, *Me*), 3.02 (2H, m, CH_2CH), 1.15 (3H, t, *J*=7.1 Hz, OCH$_2$*Me*); ^{13}C NMR (100 MHz, $CDCl_3$): 193.4, 171.3, 168.2, 135.9, 133.2, 128.7, 128.4, 61.4, 51.7, 49.4, 32.7, 13.8; Anal. Calcd for $C_{14}H_{17}NO_4$ (263.29): C, 63.87; H, 6.51; N, 5.32. Found: C, 63.81; H, 6.64; N, 5.19.

4.1.4.2. 3-(Ethoxycarbonyl)-4-oxo-4-phenylbutanoxylimidic acid isopropyl ester 5b. Yield: 43 mg, 15%, yellow oil, R_f (20% EtOAc/hexane) 0.80, IR (neat): 3856, 3532, 3195, 2985, 1722, 1412 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.44–8.02 (5H, m, *Ph*), 5.13 (1H, m, C*H*Me$_2$), 4.81 (1H, t, *J*=7.1 Hz, C*H*CH$_2$), 4.14 (2H, q, *J*=7.1 Hz, OCH_2Me), 2.98 (2H, m, CHCH_2), 1.21 (6H, d, *J*=6.2 Hz, CH*Me*$_2$), 1.16 (3H, t, *J*=7.1 Hz, OCH$_2$*Me*); ^{13}C NMR (100 MHz, $CDCl_3$): 128.4, 193.5, 170.3, 168.3, 136.0, 133.2, 128.7, 68.1, 61.3, 49.5, 33.4, 21.6, 13.8; Anal. Calcd for $C_{16}H_{21}NO_4$ (291.34): C, 65.96; H, 7.27; N, 4.81. Found: C, 65.93; H, 7.31; N, 4.71.

4.1.4.3. 3-(Ethoxycarbonyl)-4-(2-fluorophenyl)-4-oxobutanoxylimidic acid ethyl ester 5c. Yield: 31 mg, 13%, yellow oil, R_f (20% EtOAc/hexane) 0.76, IR (neat): 3866, 3552, 3192, 2982, 1752, 1432 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.12–7.91 (4H, m, *Ph*), 4.68 (1H, t, *J*=5.7 Hz, C*H*CH$_2$), 4.14 (2H, q, *J*=7.2 Hz, OCH_2Me), 4.13 (2H, q, *J*=7.1 Hz, OCH_2Me), 2.87–3.11 (2H, m, CHCH_2), 1.29 (3H, t, *J*=7.1 Hz, OCH$_2$*Me*), 1.16 (3H, t, *J*=7.2 Hz, OCH$_2$*Me*); ^{13}C NMR (100 MHz, $CDCl_3$): 191.7, 170.7, 168.5, 161.5 (d, *J*=253 Hz), 134.7, 131.2, 125.0, 124.4, 116.5 (d, *J*=23 Hz), 61.3, 60.7, 53.4, 32.8, 14.1, 13.8; Anal. Calcd for $C_{15}H_{18}FNO_4$ (295.31): C, 61.01; H, 6.14; N, 4.74. Found: C, 61.12; H, 6.25; N, 4.61.

4.1.4.4. 3-(Ethoxycarbonyl)-4-oxohexanoxylimidic acid isopropyl ester 5d. Yield: 35 mg, 12%, yellow oil, R_f (20% EtOAc/hexane) 0.68, IR (neat): 3846, 3539, 3198, 2991, 1744, 1418 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 4.93 (1H, m, *Ph*), 4.13 (2H, q, *J*=7.1 Hz, OCH_2Me), 3.89 (1H, m, C*H*Me$_2$), 2.90 (2H, m, CH_2Me), 2.58 (2H, m, CHCH_2), 1.22 (3H, t, *J*=7.1 Hz, OCH$_2$*Me*), 1.14 (6H, d, *J*=6.2 Hz, CH*Me*$_2$), 1.02 (3H, t, *J*=7.2 Hz, CH$_2$*Me*); ^{13}C NMR (100 MHz, $CDCl_3$): 204.7, 170.8, 168.6, 68.5, 61.7, 53.7, 36.1, 32.8, 21.7, 14.0, 7.6; Anal. Calcd for $C_{12}H_{21}NO_4$ (243.3): C, 59.24; H, 8.70; N, 5.79. Found: C, 59.31; H, 8.55; N, 5.66.

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