Facile aza-Michael additions of uracil derivatives to acrylates

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24 Aza-Michael adducts were synthesised in moderate to excellent yields by the addition of 5-substituted uracils to acrylates with ethylamine as a catalyst. Many of the adducts were obtained in almost quantitive yield without column chromatography. The procedure provideded an efficient approach to the synthesis of N-1 uracil adducts using acrylates as acceptors. The structures of the compounds were determined by ^{1}H NMR, ^{13}C NMR, mass spectra and X-ray crystallography analyses. The uracil unit is present in DNA and related natural products and has a broad spectrum of biological activity.

Keywords: uracil derivatives, acrylates, aza-Michael addition, crystal structure

Uracil and its derivatives are of interest because the uracil unit is present in DNA and related natural products.[1,2] Uracils are privileged structures in drug discovery and display a broad spectrum of biological activity.[3–5] For example, 5-nitrouracil and its derivatives exhibit antiviral effects because they are inhibitors of thymidylate synthetase.[5] 5-Fluorouracil and its derivatives are widely used for the treatment of cancers[6–8] and 1-cyanomethyl 5-halogenouracils were active against P-388/s, FM-3A/s and U-937/s cell lines.[9] Recently, several methods for the modification of uracil and its derivatives have been developed.[10–13] The functionalisations of uracil derivatives at the N-1 or N-3 position are of importance. The Michael-type addition (in this case aza-Michael reaction) is one of the most common strategies for the synthsis of N-alkylated uracils and their precursors and it is also one of the convenient synthetic approaches towards the formation of an exocyclic C–N bond.[14–18]

Continuing our research interest on the modification of uracil and its 5-substituted derivatives at the N-1 position,[19] we now report the study of the Michael-type addition of uracil anions to acceptors possessing activated double bonds, *e.g.*, acrylic esters. As shown in Scheme 1, N-1 monoadducts could be prepared when uracil or 5-substituted uracils are used as Michael donors, and reacted with acrylic esters in the presence of triethylamine. In addition, the common methods of purification by column chromatography and recrystallisation were not necessary for many of examples.

Results and discussion

Initially, we selected a trial reaction using 1: 1.2 M ratio of 5-fluorouracil (**1b**) and methyl acrylate (**2a**), 0.1 mmol triethylamine as a catalyst in order to optimise the solvent, and the temperature range from room temperature to 60 °C, DMF gave the best result. The reaction proceeded smoothly in DMF to give **3b** in 95% yield (Table 1, entry 8). We subsequently screened the temperature, from 60 °C to 100 °C, and found that the yield stabilised at 95% in DMF after 60 °C. Unlike the aza-Michael addition of aromatic amines to α,β-unsaturated ketones which proceeded without any catalyst or solvent, [17] no adduct was formed in this reaction without a catalyst. The yield increased significantly when triethylamine was added in (entries 9 and 10). We then changed the catalyst to K_2CO_3 or ammonia instead of triethylamine. The yield improved from 50% to 80% when the reaction carried out from 40 °C to 100 °C in DMF.

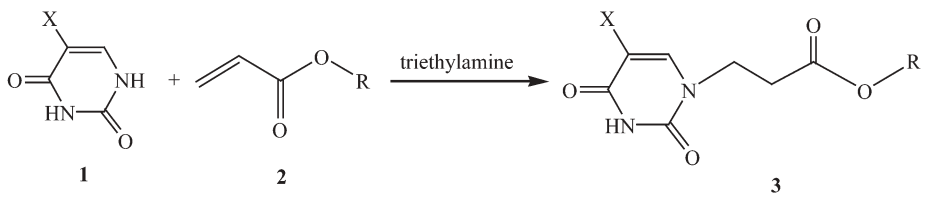
Using the optimal condition, we then investigated the reaction of uracil and other 5-substituted uracils. As seen from Table 2, the reaction offered moderate to excellent yields. Among the 5-substituted uracils selected, those bearing the chloro-(**1c**), bromo-(**1d**), iodo-(**1e**), methyl-(**1h**) substituent reacted with methyl acrylate (**2a**) to give the corresponding pure products without column chromatography or recrystallisation. Similar results were obtained when ethyl acrylate(**2b**) or butyl acrylate(**2c**) was used as a substrate. However, when 5-nitrouracil (**1g**) was utilised, the corresponding adducts were obtained in lower yields maybe because of the poor nucleophilicity of the substrate.

All the adducts were characterised by ^{1}H NMR,^{13}C NMR and MS. In order to confirm the structure of compound **3**, the crystal structure of **3e** as a representative example was determined by X-ray crystallography. An ORTEP view of the molecule together with the atom numbering is shown in Fig. 1, the crystal data and structure refinement is shown in Table 3.

In conclusion, 24 aza-Michael adducts have been synthesised from uracil or 5-substituted uracil derivatives and acrylates, the crystal structure of **3e** was determined by X-ray diffraction analysis. The biological activity of the above adducts is being investigation in our laboratory.

Experimental

All chemicals were purchased from Aladdin chemical companies. The progress of the reactions was detected by TLC using silica gel GF 254 plates. Melting points were recorded on a Digital Melting Point Appatatus WRS-1B and are uncorrected. ^{1}H NMR (500 MHz) and ^{13}C



X= H, F, Cl, Br, I, CH_2OH, NO_2, CH_3

R= Me, Et, n-Butyl

Scheme 1

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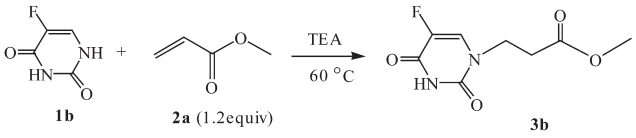
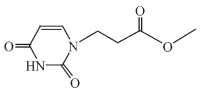
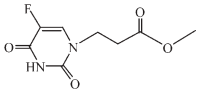
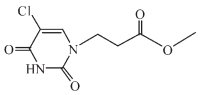
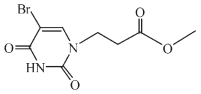
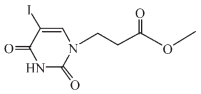
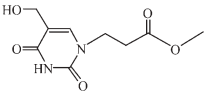
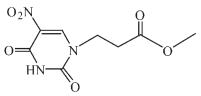
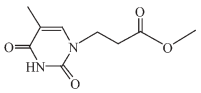
Table 1 Optimisation of aza–Michael reaction of **1b** with **2a**



1b **2a** (1.2equiv) **3b**

Entry	Solvent	Yield/%
1	Ethyl acetate	48
2	CH_3CN	67
3	THF	61
4	Toluene	22
5	1,4-dioxane	44
6	Acetone	34
7	Ethanol	56
8	DMF	95
9	H_2O	65
10	Solvent free	50

Table 2 Aza-Michael addition of 5-substituted uracils to methyl acrylate in DMF at 60 °C

Entry	Substituted uracils	Product		Yield /%
1	Uracil	**3a**		86
2	5-Fluorouracil	**3b**		95
3	5-Chlorouracil	**3c**		93
4	5-Bromouracil	**3d**		97
5	5-Iodouracil	**3e**		92
6	5-Hydroxymethyluracil	**3f**		88
7	5-Nitrouracil	**3g**		71
8	5-Methyluracil	**3h**		95

The corresponding ethyl and butyl esters are described in the experimental section.

NMR (125 MHz) analyses were recorded on a Bruker AVANCE 500 spectrometer in DMSO-d_6 with TMS as internal standard. Elemental analyses were using a Carlo-Erba 1112 elemental analyser. Mass spectra were obtained on a DECAX-30000 LCQ DecaXP Plus instrument. The crystallographic data were collected on a Bruker Smart-Apex CCD diffractometer.

Synthesis of compound **3***; general procedure*

Uracil or 5-substituted uracil (10 mmol), acrylic ester (12 mmol), triethylamine (0.1 mmol) and DMF 20 mL were added into a flask and stirred at 60 °C for 2–4 hours with TLC detection. The solid **3** was obtained after distillation of the DMF, and removal of excessive acrylic ester with ethyl acetate or ether under reduced pressure.

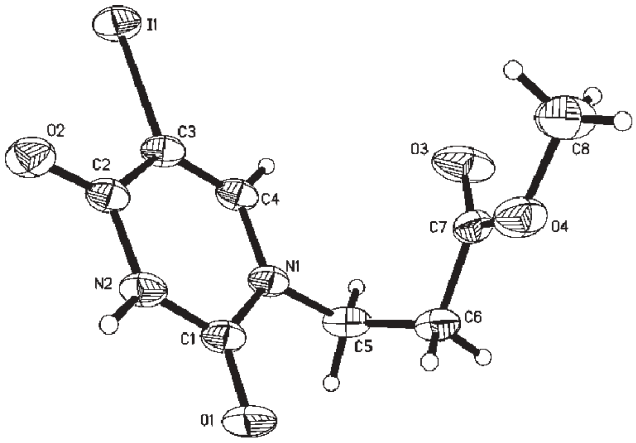


Fig. 1 The molecular structure of **3e**.

Table 3 Crystal data and structure refinement for **3e**

Empirical formula	$C_8\ H_9\ I\ N_2\ O_4$
Formula weight	324.07
Temperature	298(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
space group	P 21/c
Volume	1099.7(2) Å
Z	4
Calculated density	1.957 Mg m^{-3}
Unit cell dimensions	a = 11.1572(12) Å, b = 8.1666(9) Å c = 12.0789(14) Å α = 90 °, β = 92.300(2) °, γ = 90°
μ(mm^{-1})	2.909
F(000)	624
Index ranges	$-13 \leq h \leq 13$ $-9 \leq k \leq 9$ $-14 \leq l \leq 14$
wR^2	0.1316
Goodness-of-fit on F^2	1.043

3-(2,4-Dioxo-3,4-dihydro-2H- pyrimidin-1-yl)-propionic acid methyl ester (**3a**): Yield 86%, m.p. 133.2–134.9 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.25 (s, 1H), 7.63 (d, 1H, J = 7.5 Hz), 5.54 (d, 1H, J = 7.5 Hz), 3.89 (t, 2H, J = 7.0 Hz), 3.61 (s, 3H), 2.70 (t, 2H, J = 7.0 Hz); ^{13}C NMR (125 MHz, DMSO-d_6) δ 171.4, 163.9, 151.0, 146.2, 100.9, 51.7, 44.2, 32.7. ESI-MS *m/z*: 199 $[M+H]^+$. Anal. Calcd for $C_8H_{10}N_2O_4$: C, 48.48; H, 5.09; N, 14.14. Found: C, 48.42; H, 5.03; N, 14.22%.

3-(5-Fluoro-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-propionic acid methyl ester (**3b**): Yield 95%, m.p. 153.3–153.8 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.78 (s, 1H), 8.05 (d, 1H, J_{FH} = 7.0 Hz), 3.86 (t, 2H, J = 7.0 Hz), 3.61 (s, 3H), 2.72 (t, 2H, J = 7.0 Hz); ^{13}C NMR (125 MHz, DMSO-d_6) δ 171.4, 157.6 (d, $^2J_{CF}$ = 25.5 Hz), 149.7, 139.5 (d, $^1J_{CF}$ = 227.1 Hz), 130.7 (d, $^2J_{CF}$ = 33.3 Hz), 51.7, 44.3, 32.4. ESI-MS *m/z*: 217 $[M+H]^+$. Anal. Calcd for $C_8H_9FN_2O_4$: C, 44.45; H, 4.20; N, 12.96. Found: C, 44.62; H, 4.14; N, 13.01%.

3-(5-Chloro-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-propionic acid methyl ester (**3c**): Yield 95%; m.p. 157.1–158.4 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.79 (s, 1H), 8.10 (s, 1H), 3.90 (t, 2H, J = 7.0 Hz), 3.58 (s, 3H), 2.72 (t, 2H, J = 7.0 Hz); ^{13}C NMR (125 MHz, DMSO-d_6) δ 171.4, 159.7, 150.2, 143.5, 106.0, 51.7, 44.5, 32.4. ESI-MS *m/z*: 233 $[M+H]^+$. Anal. Calcd for $C_8H_9ClN_2O_4$: C, 41.31; H, 3.90; N, 12.04. Found: C, 41.40; H, 3.96; N, 11.93%.

3-(5-Bromo-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-propionic acid methyl ester (**3d**): Yield 97%; m.p. 163.3–164.9 °C ; ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.77 (s, 1H), 8.19 (s, 1H), 3.92 (t, 2H, J = 7.0 Hz), 3.60 (s, 3H), 2.73 (t, 2H, J = 7.0 Hz); ^{13}C NMR (125 MHz,

DMSO-d_6) δ 171.4, 159.8, 150.4, 145.9, 94.5, 51.7, 44.4, 32.5. ESI-MS *m/z*: 277 $[M+H]^+$. Anal. Calcd for $C_8H_9BrN_2O_4$: C, 34.68; H, 3.27; N, 10.11. Found: C, 34.45; H, 3.21; N, 10.17%.

3-(5-Iodo-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-propionic acid methyl ester (**3e**): Yield 92%; m.p. 185.6–187.3 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.61 (s, 1H), 8.15 (s, 1H), 3.90 (t, 2H, J = 7.0 Hz), 3.59 (s, 3H), 2.70 (t, 2H, J = 7.0 Hz); ^{13}C NMR (125 MHz, DMSO-d_6) δ 171.3, 161.2, 150.7, 150.5, 67.9, 51.7, 44.2, 32.5. ESI-MS *m/z*: 325 $[M+H]^+$. Anal. Calcd for $C_8H_9IN_2O_4$: C, 29.65; H, 2.80; N, 8.64. Found: C, 29.50; H, 2.85; N, 8.56%.

3-(5-Hydroxymethyl-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-propionic acid methyl ester (**3f**): Yield 88%; m.p. 136.7–139.5 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.28 (s, 1H), 7.53 (s, 1H), 4.96 (t, 1H, J = 5.0 Hz), 4.13 (d, 2H, J = 5.0 Hz), 3.92 (t, 2H, J = 7.0 Hz), 3.61 (s, 3H), 2.70 (t, 2H, J = 7.0 Hz); ^{13}C NMR (125 MHz, DMSO-d_6) δ 171.4, 163.4, 150.9, 150.5, 142.3, 113.4, 56.0, 51.7, 44.2, 32.9. ESI-MS *m/z*: 229 $[M+H]^+$. Anal. Calcd for $C_9H_{12}N_2O_5$: C, 47.37; H, 5.30; N, 12.28. Found: C, 47.54; H, 5.38; N, 12.22%.

3-(5-Nitro-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-propionic acid methyl ester (**3g**): Yield 71%; m.p. 151.8–153.3 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.03 (s, 1H), 9.26 (s, 1H), 4.08 (t, 2H, J = 7.0 Hz), 3.61 (s, 3H), 2.79 (t, 2H, J = 7.0 Hz); ^{13}C NMR (125 MHz, DMSO-d_6) δ 171.3, 155.2, 151.5, 149.4, 124.8, 51.8, 45.5, 32.1. ESI-MS *m/z*: 244 $[M+H]^+$. Anal. Calcd for $C_8H_9N_3O_6$: C, 39.51; H, 3.73; N, 17.28. Found: C, 39.34; H, 3.77; N, 17.35%.

3-(5-Methyl-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-propionic acid methyl ester (**3h**): Yield 95%; m.p. 126.7–127.5 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.23 (s, 1H), 7.51 (s, 1H), 3.86 (t, 2H, J = 7.0 Hz), 3.61 (s, 3H), 2.70 (t, 2H, J = 7.0 Hz), 1.75 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 171.4, 164.4, 151.0, 141.8, 108.4, 51.7, 43.9, 32.8, 12.1. ESI-MS *m/z*: 213 $[M+H]^+$. Anal. Calcd for $C_9H_{12}N_2O_4$: C, 50.94; H, 5.70; N, 13.20. Found: C, 50.75; H, 5.64; N, 13.28%.

3-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-propionic acid ethyl ester (**3i**): Yield 83%, m.p. 101.3–101.6 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.24 (s, 1H), 7.63 (d, 1H, J = 8.0 Hz), 5.54 (d, 1H, J = 8.0 Hz), 4.06 (q, 2H, J = 7.0 Hz), 3.89 (t, 2H, J = 7.0 Hz), 2.68 (d, 2H, J = 7.0 Hz), 1.17 (t, 3H, J = 7.0 Hz); ^{13}C NMR (125 MHz, DMSO-d_6) δ 170.9, 163.9, 151.0, 146.2, 100.8, 60.4, 44.2, 32.9, 14.1. ESI-MS *m/z*: 213 $[M+H]^+$. Anal. Calcd for $C_9H_{12}N_2O_4$: C, 50.94; H, 5.70; N, 13.20. Found: C, 50.80; H, 5.65; N, 13.23%.

3-(5-Fluoro-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-propionic acid ethyl ester (**3j**): Yield 93%, m.p. 133.5–134.0 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.78 (s, 1H), 8.06 (d, 1H, J_{FH} = 7.0 Hz), 4.07 (dq, 2H, J = 7.0, 1.5 Hz), 3.86 (t, 2H, J = 7.0 Hz), 2.70 (t, 2H, J = 7.0 Hz), 1.18 (dt, 3H, J = 7.0, 1.5 Hz); ^{13}C NMR (125 MHz, DMSO-d_6) δ 170.8, 157.6 (d, $^2J_{CF}$ = 25.6 Hz), 149.7, 139.5 (d, $^1J_{CF}$ = 227.1 Hz), 130.7 (d, $^2J_{CF}$ = 33.4 Hz), 60.4, 44.3, 32.7, 14.1. ESI-MS *m/z*: 231 $[M+H]^+$. Anal. Calcd for $C_9H_{11}FN_2O_4$: C, 46.96; H, 4.82; N, 12.17. Found: C, 46.80; H, 4.85; N, 12.25%.

3-(5-Chloro-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-propionic acid ethyl ester (**3k**): Yield 96%, m.p. 159.6–160.0 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.80 (s, 1H), 8.12 (s, 1H), 4.07 (q, 2H, J = 7.0 Hz), 3.91 (t, 2H, J = 7.0 Hz), 2.71 (t, 2H, J = 7.0 Hz), 1.18 (t, 3H, J = 7.0 Hz); ^{13}C NMR (125 MHz, DMSO-d_6) δ 170.8, 159.7, 150.2, 143.6, 106.0, 60.4, 44.5, 32.7, 14.1. ESI-MS *m/z*: 247 $[M+H]^+$. Anal. Calcd for $C_9H_{11}ClN_2O_4$: C, 43.83; H, 4.50; N, 11.36. Found: C, 43.67; H, 4.55; N, 11.42%.

3-(5-Bromo-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-propionic acid ethyl ester (**3l**): Yield 99%, m.p. 160.1–160.6 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.77 (s, 1H), 8.19 (s, 1H), 4.07 (q, 2H, J = 7.0 Hz), 3.92 (t, 2H, J = 7.0 Hz), 2.71 (t, 2H, J = 7.0 Hz), 1.18 (t, 3H, J = 7.0 Hz); ^{13}C NMR (125 MHz, DMSO-d_6) δ 170.8, 159.8, 150.4, 146.0, 94.4, 60.4, 44.5, 32.7, 14.2. ESI-MS *m/z*: 291 $[M+H]^+$. Anal. Calcd for $C_9H_{11}BrN_2O_4$: C, 37.13; H, 3.81; N, 9.62. Found: C, 37.35; H, 3.85; N, 9.58%.

3-(5-Iodo-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-propionic acid ethyl ester (**3m**): Yield 91%; m.p. 153.5–155.0 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.64 (s, 1H), 8.17 (s, 1H), 4.06 (q, 2H, J = 7.0 Hz), 3.92 (t, 2H, J = 7.0 Hz), 2.70 (t, 2H, J = 7.0 Hz), 1.18 (t, 3H, J = 7.0 Hz); ^{13}C NMR (125 MHz, DMSO-d_6) δ 170.8, 161.2, 150.7, 150.5, 67.8, 60.4, 44.3, 32.8, 14.2. ESI-MS *m/z*: 339 $[M+H]^+$. Anal. Calcd for $C_9H_{11}IN_2O_4$: C, 31.97; H, 3.28; N, 8.29. Found: C, 31.92; H, 3.25; N, 8.48%.

3-(5-hydroxymethyl-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-propionic acid ethyl ester (**3n**): Yield 85%; m.p. 124.1–124.5 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.28 (s, 1H), 7.52 (s, 1H), 4.95 (t, 1H, J = 5.0 Hz), 4.13 (d, 2H, J = 5.0 Hz), 4.06 (q, 2H, J = 7.0 Hz), 3.91 (t, 2H, J = 6.5 Hz), 2.67 (t, 2H, J = 6.5 Hz), 1.17 (t, 3H, J = 7.0 Hz); ^{13}C NMR (125 MHz, DMSO-d_6) δ 170.9, 163.3, 150.9, 142.3, 113.4, 60.4, 56.0, 44.2, 33.1, 14.1. ESI-MS *m/z*: 243 $[M+H]^+$. Anal. Calcd for $C_{10}H_{14}N_2O_5$: C, 49.58; H, 5.83; N, 11.56. Found: C, 49.65; H, 5.86; N, 11.69%.

3-(5-Nitro-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-propionic acid ethyl ester (**3o**): Yield 79%; m.p. 162.5–163.7 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.03 (s, 1H), 9.26 (s, 1H), 4.09 (d, 2H, J = 6.5 Hz), 4.06 (q, 2H, J = 7.0 Hz), 2.76 (t, 2H, J = 6.5 Hz), 1.18 (t, 3H, J = 7.0 Hz); ^{13}C NMR (125 MHz, DMSO-d_6) δ 170.8, 155.2, 151.5, 149.4, 124.8, 60.5, 45.5, 32.4, 14.1. ESI-MS *m/z*: 258 $[M+H]^+$. Anal. Calcd for $C_9H_{11}N_3O_6$: C, 42.03; H, 4.31; N, 16.34. Found: C, 42.35; H, 4.26; N, 16.23%.

3-(5-Methyl-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-propionic acid ethyl ester (**3p**): Yield 99%; m.p. 154.6–155.1 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.23 (s, 1H), 7.51 (s, 1H), 4.07 (q, 2H, J = 7.0 Hz), 3.87 (t, 2H, J = 7.0 Hz), 2.68 (t, 2H, J = 7.0 Hz), 1.75 (s, 3H), 1.17 (t, 3H, J = 7.0 Hz); ^{13}C NMR (125 MHz, DMSO-d_6) δ 170.9, 164.4, 151.0, 141.9, 108.4, 60.3, 44.0, 33.0, 14.1, 12.0. ESI-MS *m/z*: 227 $[M+H]^+$. Anal. Calcd for $C_{10}H_{14}N_2O_4$: C, 53.09; H, 6.24; N, 12.38. Found: C, 53.23; H, 6.16; N, 12.30%.

3-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-propionic acid butyl ester (**3q**): Yield 87%, m.p. 77.0–77.9 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.25 (s, 1H), 7.62 (d, 1H, J = 8.0 Hz), 5.54 (dd, 1H, J = 8.0, 2.0 Hz), 4.02 (t, 2H, J = 6.5 Hz), 3.90 (t, 2H, J = 6.5Hz), 2.70 (t, 2H, J = 6.5 Hz), 1.56–1.51 (m, 2H), 1.34–1.27 (m, 2H), 0.88 (t, 3H, J = 7.5 Hz); ^{13}C NMR (125 MHz, DMSO-d_6) δ 171.0, 163.9, 151.0, 146.1, 100.8, 64.1, 44.2, 32.9, 30.3, 18.7, 13.6. ESI-MS *m/z*: 241 $[M+H]^+$. Anal. Calcd for $C_{11}H_{16}N_2O_4$: C, 54.99; H, 6.71; N, 11.66. Found: C, 54.83; H, 6.65; N, 11.74%.

3-(5-Fluoro-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-propionic acid butyl ester (**3r**): Yield 90%, m.p. 71.9–72.3 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.78 (s, 1H), 8.05 (d, 1H, J_{FH} = 6.5 Hz), 4.03 (t, 2H, J = 7.0 Hz), 3.86 (t, 2H, J = 6.5 Hz), 2.71 (t, 2H, J = 6.5 Hz), 1.57–1.51 (m, 2H), 1.34–1.27 (m, 2H), 0.88 (t, 3H, J = 7.0 Hz); ^{13}C NMR (125 MHz, DMSO-d_6) δ 170.9, 157.6 (d, $^2J_{CF}$ = 25.6 Hz), 149.6, 139.5 (d, $^1J_{CF}$ = 227.1 Hz), 130.6 (d, $^2J_{CF}$ = 33.3 Hz), 64.1, 44.3, 32.6, 30.3, 18.7, 13.6. ESI-MS *m/z*: 259 $[M+H]^+$. Anal. Calcd for $C_{11}H_{15}FN_2O_4$: C, 51.16; H, 5.85; N, 10.85. Found: C, 51.03; H, 5.92; N, 10.98%.

3-(5-Chloro-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-propionic acid butyl ester (**3s**): Yield 95%, m.p. 93.9–95.2 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.81 (s, 1H), 8.12 (s, 1H), 4.03 (t, 2H, J = 6.5 Hz), 3.91 (t, 2H, J = 7.0 Hz), 2.72 (t, 2H, J = 7.0 Hz), 1.56–1.51 (m, 2H), 1.34–1.27 (m, 2H), 0.88 (t, 3H, J = 6.5 Hz); ^{13}C NMR (125 MHz, DMSO-d_6) δ 170.9, 159.6, 150.2, 143.5, 106.0, 64.1, 44.5, 32.7, 30.3, 18.7, 13.7. ESI-MS *m/z*: 275 $[M+H]^+$. Anal. Calcd for $C_{11}H_{15}ClN_2O_4$: C, 48.10; H, 5.50; N, 10.20. Found: C, 48.32; H, 5.54; N, 10.13%.

3-(5-Bromo-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-propionic acid butyl ester (**3t**): Yield 98%, m.p. 122.4–122.8 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.77 (s, 1H), 8.18 (s, 1H), 4.02 (t, 2H, J = 6.5 Hz), 3.92 (t, 2H, J = 6.5 Hz), 2.72 (t, 2H, J = 6.5 Hz), 1.56–1.51 (m, 2H), 1.34–1.27 (m, 2H), 0.88 (t, 3H, J = 6.5 Hz); ^{13}C NMR (125 MHz, DMSO-d_6) δ 170.9, 159.8, 150.4, 145.9, 94.5, 64.1, 44.5, 32.7, 30.3, 18.7, 13.7. ESI-MS *m/z*: 319 $[M+H]^+$. Anal. Calcd for $C_{11}H_{15}BrN_2O_4$: C, 41.40; H, 4.74; N, 8.78. Found: C, 41.64; H, 4.69; N, 8.65%.

3-(5-Iodo-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-propionic acid butyl ester (**3u**): Yield 90%, m.p. 142.9–143.3 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.63 (s, 1H), 8.15 (s, 1H), 4.02 (t, 2H, J = 7.0 Hz), 3.91 (t, 2H, J = 6.5 Hz), 2.70 (t, 2H, J = 6.5 Hz), 1.56–1.51 (m, 2H), 1.34–1.28 (m, 2H), 0.88 (t, 3H, J = 7.0 Hz); ^{13}C NMR (125 MHz, DMSO-d_6) δ 170.9, 159.8, 150.4, 145.9, 94.5, 64.1, 44.5, 32.7, 30.3, 18.7, 13.7. ESI-MS *m/z*: 367 $[M+H]^+$. Anal. Calcd for $C_{11}H_{15}IN_2O_4$: C, 36.08; H, 4.13; N, 7.65. Found: C, 36.24; H, 4.19; N, 7.82%.

3-(5-hydroxymethyl-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-propionic acid butyl ester (**3v**): Yield 85%; m.p. 94.9–95.4 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.28 (s, 1H), 7.52 (s, 1H), 4.95 (t, 1H, J = 5.0 Hz), 4.13 (d, 2H, J = 5.0 Hz), 4.02 (t, 2H, J = 7.0 Hz), 3.91 (t, 2H, J = 7.0 Hz), 2.69 (t, 2H, J = 7.0 Hz), 1.56–1.51 (m, 2H), 1.34–1.26 (m, 2H), 0.87 (t, 3H, J = 7.0 Hz); ^{13}C NMR (125 MHz, DMSO-d_6)

δ 170.9, 163.3, 150.9, 142.2, 113.4, 64.1, 56.0, 44.3, 33.1, 30.3, 18.7, 13.7. ESI-MS *m/z*: 271 $[M+H]^+$. Anal. Calcd for $C_{12}H_{18}N_2O_5$: C, 53.33; H, 6.71; N, 10.36. Found: C, 53.62; H, 6.78; N, 10.51%.

3-(5-Nitro-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-propionic acid butyl ester (**3w**): Yield 75%; m.p. 155.5–156.5 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.04 (s, 1H), 9.26 (s, 1H), 4.09 (t, 2H, J = 6.5 Hz), 4.03 (t, 2H, J = 6.5 Hz), 2.78 (t, 2H, J = 6.5 Hz), 1.57–1.52 (m, 2H), 1.35–1.27 (m, 2H), 0.88 (t, 3H, J = 7.5 Hz); ^{13}C NMR (125 MHz, DMSO-d_6) δ 170.9, 155.2, 151.5, 149.4, 124.8, 64.2, 45.6, 32.4, 30.3, 18.8, 13.7. ESI-MS *m/z*: 286 $[M+H]^+$. Anal. Calcd for $C_{11}H_{15}N_3O_6$: C, 46.32; H, 5.30; N, 14.73. Found: C, 46.50; H, 5.36; N, 14.82%.

3-(5-Methyl-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-propionic acid butyl ester (**3x**): Yield 94%; m.p. 90.5–90.9 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.23 (s, 1H), 7.50 (s, 1H), 4.02 (t, 2H, J = 6.5 Hz), 3.87 (t, 2H, J = 7.0 Hz), 2.69 (t, 2H, J = 7.0 Hz), 1.75 (s, 3H), 1.56–1.50 (m, 2H), 1.34–1.26 (m, 2H), 0.87 (t, 3H, J = 7.0 Hz); ^{13}C NMR (125 MHz, DMSO-d_6) δ 170.9, 164.4, 150.9, 141.9, 108.4, 64.0, 44.0, 33.0, 30.3, 18.7, 13.6, 12.0. ESI-MS *m/z*: 255 $[M+H]^+$. Anal. Calcd for $C_{12}H_{18}N_2O_4$: C, 56.68; H, 7.13; N, 11.02. Found: C, 56.87; H, 7.10; N, 11.08%.

Crystal data (see Table 3).
Compound (**3e**): $C_8H_9IN_2O_4$, M 324.07, T 298(2) K; monoclinic; space group, P 21/c; a=11.1572(12); b=8.1666(9); c=12.0789(14) Å. V 1099.7(2) Å^3. Dc (Z 4) 1.957 g cm^{-3}, F(000) 624, μ 2.909 mm^{-1}, R^1 = 0.0323, wR^2 = 0.1316.

Crystal structure determination and refinement
A single crystal having dimension of 0.32 × 0.25 × 0.21 mm was mounted on a glass fiber. All measurements were made on a Bruker Smart Apex diffractometer with graphite monochromated Mo Kα (λ = 0.71073 Å) radiation with an ω-scan technique. The data were collected at 298(2) K to maximum θ value of 25.19°. Determination of the crystal class, orientation matrix, and cell dimensions were performed according to the established procedures. Lorentz polarisation and absorption corrections were applied. Absorption corrections were applied by fitting a pseudoellipsoid to the ψ-scan data of selected strong reflections over a range of 2θ angles. The structure was solved by direct method and expanded using Fourier techniques. Most of the non-hydrogen atoms in the crystal structure were located with the direct methods, and subsequent Fourier syntheses were used to derive the remaining non-hydrogen atoms. All of non-hydrogen atoms were refined anisotropically, and all of the hydrogen atoms were held stationary and included in the final stage of full-matrix least-squares refinement based on F^2 using the SHELXS-97 and SHELXL-97 programs.

The CIF file has been deposited with the Cambridge Crystallographic Data Centre. Supplementary data are available from the CCDC, on request, quoting the deposition number 838253. NMR spectra of the compounds are available directly from the correspondent.

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