Tandem Hydroformylation/Biginelli Reaction

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I. General

All reactions were carried out under argon 5.0 (Südwest-Gas) atmospheres in dried glassware. Air and moisture sensitive liquids and solutions were transferred via syringe. All solvents were dried and distilled by standard procedures. Solutions were concentrated under reduced pressure by rotary evaporation. Chromatographic purification of products was accomplished on Merck silica gel Si 60® (200-400 mesh). Nuclear magnetic resonance spectra were acquired on BRUKER AMX 400, BRUKER DRX 500 and VARIAN Mercury 300 HFCP. Data for $^1$H NMR are reported as follows: chemical shift (δ in ppm), multiplicity (s, singlet; br s, broad singlet; d, doublet; t, triplet; q, quartet; m, multiplet), coupling constant (Hz), integration. Data for $^{13}$C NMR are reported in terms of chemical shift (δ in ppm), multiplicity and coupling constant (Hz). Elemental analyses were performed on an Elementar vario (Elementar Analysensysteme GmbH). Melting points were determined using a Dr. TOTTOLI apparatus (BÜCHI). IR Spectra were recorded with a Sicomb (9mm) probe of a ReactIR™ 45 by METTLER TOLEDO. The following substrates were purchased from commercial sources and distilled prior to use: 1-octene (ACROS), vinylcyclohexene (ACROS), 5-hexen-1-ol (VWR/MERCK), allylbenzene (AlfaAesar), 3,3-dimethylbutene (AlfaAesar).

The following substrates were prepared according to literature reported procedures:

$N$-Allyl-phthalimide$^1$

\[
\text{O} \quad \text{O} \\
\text{N} \quad \text{=}
\]

Acetic-acid-hex-5-enyl-ester$^2$

\[
\text{AcO} \quad \text{AcO} \\
\text{CH} \\
\]

Hex-5-enyloxymethylbenzene$^3$

\[
\text{BnO} \quad \text{BnO} \\
\text{CH} \\
\]

Phenylcarbamic-acid-hex-5-enyl-ester$^4$

\[
\text{OPh} \quad \text{OPh} \\
\text{CH} \\
\]

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Hex-5-en-1-yl benzoate\textsuperscript{5}

\[ \text{BzO} \]

\textit{N}-Methyl-\textit{N}-phenylpent-4-enamide\textsuperscript{6}

\[ \text{Ph} \quad \text{N} \quad \text{Me} \quad \text{O} \]

Methyl-undec-10-enoate\textsuperscript{7}

\[ \text{MeO} \quad \text{O} \]


\textsuperscript{*} based on the amount of alkene.
II. Experimental Details

General Experimental Procedure

All tandem reactions were performed in a Premex stainless steel autoclave Medimex (100 ml) containing a magnetic stirring bar (700 rpm). For hydroformylation/Biginelli experiments a synthesis gas mixture (Messer-Griesheim) was used (CO/H₂ = 1:1; carbon monoxide 3.7, hydrogen 4.3).

The optimized hydroformylation/Biginelli reactions were performed by charging an autoclave with [Rh(CO)₂acac] (2.60 mg, 10.0 μmol 0.25 mol%),* xantphos (57.9 mg 100 μmol, 2.5 mol%)* and urea (2, 132 mg, 2.2 mmol, 1.1 equiv.) as solids. Subsequently a solution of the alkene (4 mmol, 2 equiv.), ethyl-acetoacetate (3, 0.25 ml, 260 mg, 2 mmol, 1 equiv.) and HCl conc. (40 μl) in ethanol (4 ml) was prepared and then transferred into the autoclave via syringe. The autoclave was purged three times with syngas (CO/H₂, 1:1), pressurized at 20 bar and placed in a preheated aluminum block at 100 °C. The reactions were stopped after 24 h by cooling the autoclave in a water bath (18 °C), venting and purging with argon. To the crude reaction mixture 1,3,5-trimethoxybenzene (33.6 mg, 0.20 mmol, 0.1 equiv.) as internal standard was added and the suspension dissolved in CH₂Cl₂ (5 ml). After evaporation of the solvents the crude product was analyzed by NMR and purified via flash chromatography to yield the pure 3,4-dihydropyrimidin-2(IH)-ones as colorless solids or foams.
5-Ethoxycarbonyl-6-methyl-4-octyl-3,4-dihydropyrimidin-2(1H)-one (6a)

The general procedure was followed starting from 1-octene (623 μl, 449 mg, 4.00 mmol), [Rh(CO)\textsubscript{2}acac], xantphos, urea, ethyl-acetoacetate and HCl. Purification via flash chromatography (CH\textsubscript{2}Cl\textsubscript{2} to CH\textsubscript{2}Cl\textsubscript{2}/AcOEt = 1:1) furnished 5-Ethoxycarbonyl-6-methyl-4-octyl-3,4-dihydropyrimidin-2(1H)-one as a colorless solid (422 mg; 71% isolated yield).

Mp.: 137 °C
R\textsubscript{f} = 0.38 (DCM/EE 1:1).

\textsuperscript{1}H-NMR (400.131 MHz, DMSO)  
δ (ppm) = 0.84 (t, J=6.9 Hz, 3 H, H-14), 1.17 ppm (t, J=7.1 Hz, 3 H, Et-CH\textsubscript{3}), 1.14-1.31 (m, 12 H, H-8-13), 1.32-1.43 (m, 2 H, H-7), 2.14 (s, 3 H, H-6'), 2.96-4.13 (m, 3 H, Et-CH\textsubscript{2} & H-4), 7.28 (dd, J=2.1, 3.4 Hz, 1 H, H-3), 8.89 (d, J=1.6 Hz, 1 H, H-1).

\textsuperscript{13}C-NMR (101.620 MHz, DMSO)  
δ (ppm) = 13.88 (C-14), 14.16 (Et-CH\textsubscript{3}), 17.64 (C-6'), 22.03, 23.60, 28.54, 28.72, 28.27, 31.22 (1C respectively, C8-13), 36.64 (C-7), 49.99 (C-4), 58.96 (Et-CH\textsubscript{2}), 99.38 (C-5), 148.20 (C-6), 152.71 (C-2), 165.40 (C-5').

CHN  
Calc.: C 64.83 H 9.52 N 9.45  
Found.: C 64.85 H 9.63 N 9.38

HRMS for C\textsubscript{21}H\textsubscript{30}N\textsubscript{2}O\textsubscript{4}:  
(pos.APCI (MeOH), (M+H)+) Calc.: 297.21782; Found: 297.21820 (-1.3 ppm).
5-Ethoxycarbonyl-6-methyl-4-(3'-phenylpropyl)-3,4-dihydropyrimidin-2(1H)-one (6b)

The general procedure was followed starting from allylbenzene (531 μl, 473 mg, 4.00 mmol), [Rh(CO)2acac], xantphos, urea, ethyl-acetoacetate and HCl. Purification via flash chromatography (CH2Cl2 to CH2Cl2/AcOEt = 1:1) furnished 5-Ethoxycarbonyl-6-methyl-4-(3'-phenylpropyl)-3,4-dihydropyrimidin-2(1H)-one as a colorless solid (473 mg, 78% isolated yield).

Mp.: 167 °C

Rf = 0.21 (DCM/EE 4:1).

1H-NMR (400.131 MHz, DMSO)

δ (ppm) = 1.13 (t, J=7.1 Hz, 3 H, Et-CH3), 1.33 - 1.68 (m, 4 H, H-8,9), 2.14 (s, 3 H, H-6'), 2.51 - 2.60 (m, 2 H, H-7), 3.94 - 4.11 (m, 3 H, Et-CH2 & H-4), 7.10 - 7.20 (m, 3 H, Ar-H), 7.21 - 7.28 (m, 2 H, Ar-H), 7.33 (dd, J=3.5, 2.0 Hz, 1 H, H-3), 8.90 (d, J=1.8 Hz, 1 H, H-1).

13C-NMR (101.630 MHz, DMSO)

δ (ppm) = 14.17 (Et-CH3), 17.71 (C-6'), 25.92, 34.88 (1C respectively, C-8,9), 36.36 (C-7), 50.01 (C-4), 59.02 (Et-CH2), 99.32 (C-5), 125.62 (1 Ar-C), 128.18 (2 Ar-C), 128.25 (2 Ar-C), 142.9 (1-Ar-C), 148.32 (C-6), 152.71 (C-2), 165.39 (C-5').

CHN

Calc.: C 67.53 H 7.33 N 9.26

Found: C 67.85 H 7.50 N 9.00

HRMS for C21H30N2O4:

(pos.APCI (MeOH), (M+H)+) Calc.: 303.17087; Found: 303.17130 (-1.4 ppm).
4-[2'-(Cyclohex-3''-enyl)-ethyl]-5-ethoxycarbonyl-6-methyl-3,4-dihydropyrimidin-2(1H)-one (6c)

The **general procedure** was followed starting from vinylcyclohexene (521 μl, 432 mg, 4.00 mmol), [Rh(CO)₂acac], xantphos, urea, ethyl-acetoacetate and HCl. Purification via flash chromatography (CH₂Cl₂ to CH₂Cl₂/AcOEt = 2:1) furnished 4-[2'-(Cyclohex-3''-enyl)-ethyl]-5-ethoxycarbonyl-6-methyl-3,4-dihydropyrimidin-2(1H)-one as a colorless solid (440 mg; 75% isolated yield).

Mp.: 178-180 °C
\[ R_f = 0.17 \text{ (DCM/EE 4:1).} \]

**¹H-NMR (499.501 MHz, DMSO, 27 °C)** mixture of diastereomers
δ (ppm) = 1.05 – 1.32 (m, 3 H), 1.17 (t, \( J=7.1 \) Hz, 3 H, Et-CH₃), 1.38 - 1.47 (m, 3 H), 1.48 - 1.69 (m, 2 H), 1.96 (d, \( J=4.1 \) Hz, 2 H), 2.01 - 2.09 (m, 1 H), 2.15 (s, 3 H, H-6'), 3.97 - 4.13 (m, 2 H, Et-CH₂ & H-4), 5.60 (s, 2 H, H-12-13), 7.31 (bs, 1 H, H-3), 8.90 (bs, 1 H, H-1).

**¹³C-NMR (125.610 MHz, DMSO, 27 °C)**, mixture of diastereomers
δ (ppm) = 14.73 (Et-CH₃), 18.20 (C-6’), 25.08/25.14, 28.66/29.13, 30.90/31.03, 31.70/32.07, 32.99/33.08, 34.35/34.43 (6C, C7-11+14), 50.64/50.66 (C-4), 59.52 (Et-CH₂), 99.88/99.92 (C-5), 126.83/126.92 (C-13*), 127.22/127.27 (C-12*), 148.81 (C-6), 153.20 (C-2), 165.92 (C-5*).

*assignment commutable

**CHN**
Calc.: C 65.73 H 8.27 N 9.58
Found: C 65.82 H 8.11 N 9.44
HRMS for C\textsubscript{16}H\textsubscript{24}N\textsubscript{2}O\textsubscript{3}:

(pos.APCI (MeOH), (M+H)+) Calc.: 293.18652; Found: 293.18652 (0.4 ppm);
(neg.APCI (MeOH), (M-H)-) Calc.: 291.17060; Found: 291.17087 (0.4 ppm).

4-(3',3'-Dimethyl-butyl)-5-ethoxycarbonyl-6-methyl-3,4-dihydropyrimidin-2(1\textsubscript{H})-one (6d)

The **general procedure** was followed starting from 3,3-dimethylbutene (516 µl, 337 mg, 4.00 mmol), [Rh(CO)\textsubscript{2}acac], xantphos, urea, ethyl-acetoacetate and HCl. The reaction time was prolonged to 28 h. Purification via flash chromatography (CH\textsubscript{2}Cl\textsubscript{2} to CH\textsubscript{2}Cl\textsubscript{2}/AcOEt = 1:1) furnished 4-(3',3'-Dimethyl-butyl)-5-ethoxycarbonyl-6-methyl-3,4-dihydropyrimidin-2(1\textsubscript{H})-one as a colorless solid (350 mg; 65% isolated yield).

**Mp.**: 188 °C

**R\textsubscript{f}** = 0.15 (DCM/EE 4:1).

\textsuperscript{1}H-NMR (400.131 MHz, DMSO)

δ (ppm) = 0.81 (s, 9 H, \textit{t}Bu-CH\textsubscript{3}), 1.01 - 1.30 (m, 2 H, H-7), 1.17 (t, \textit{J}=7.1 Hz, 3 H, Et-CH\textsubscript{3}), 1.31-1.41 (m, 2 H, H-8), 2.15 (s, 3 H, H-6'), 3.91 - 4.21 (m, 3 H, Et-CH\textsubscript{2} & H-4), 7.26 (dd, \textit{J}=3.4, 2.1 Hz, 1 H, H-3), 8.87 (d, \textit{J}=1.6 Hz, 1 H, H-1).

\textsuperscript{13}C-NMR (101.630 MHz, DMSO)

δ (ppm) = 14.24 (Et-CH\textsubscript{3}), 17.68 (C-6'), 29.21 (3C-\textit{t}Bu), 29.76 (C-9), 31.89 (C-8), 37.90 (C-7), 50.89 (C-4), 58.94 (Et-CH\textsubscript{2}), 99.30 (C-5), 148.21 (C-6), 152.62 (C-2), 165.42 (C-5').

**CHN**

Calc.: C 62.66 H 9.01 N 10.44

Found: C 62.29 H 9.13 N 10.06
HRMS for C$_{21}$H$_{30}$N$_2$O$_4$:
(pos.APCI (MeOH), (M+H)$^+$) Calc.: 269.18652; Found: 269.18680 (-1.0 ppm).

5-Ethoxycarbonyl-4-(6'-hydroxy-hexyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one (6e)

\[
\begin{align*}
\text{C}_14\text{H}_{24}\text{N}_2\text{O}_4 \\
284.35 \text{ g/mol}
\end{align*}
\]

The general procedure was followed starting from 5-hexene-1-ol (480 µl, 401 mg, 4.00 mmol), [Rh(CO)$_2$acac], xantphos, urea, ethyl-acetoacetate and HCl. Purification via flash chromatography (CH$_2$Cl$_2$ to AcOEt) furnished 5-Ethoxycarbonyl-4-(6'-hydroxy-hexyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one (388; 68% isolated yield) as a colorless solid.

Mp.: 98-99 °C

$R_f$ = 0.13 (EE).

$^1$H-NMR (400.131 MHz, DMSO)

$\delta$ (ppm) = 1.17 (t, $J$=7.1 Hz, 3 H, Et-CH$_3$), 1.20 - 1.42 (m, 10 H, H-8-11, H-6'), 2.15 (s, 3 H, H-6'), 3.35 (dt, $J$=6.4, 6.4 Hz, 2 H, H-12), 3.97 - 4.13 (m, 3 H, Et-CH$_2$ & H-4), 4.30 (t, $J$=5.2 Hz, 1 H, OH), 7.28 (dd, $J$=3.5, 2.1 Hz, 1 H, H-3), 8.89 (d, $J$=1.8 Hz, 1 H, H-1).

$^{13}$C-NMR (101.630 MHz, DMSO)

$\delta$ (ppm) = 14.22 (Et-CH$_3$), 17.69 (C-6'), 23.76, 25.47, 28.71, 32.47 (1C respectively, C8-11), 36.72 (C-7), 50.05 (C-4), 59.02 (Et-CH$_2$), 60.69 (C-12), 99.43 (C-5), 148.22 (C-6), 152.75 (C-2), 165.44 (C-5').

CHN

Calc.: C 59.14  H 8.51  N 9.85

Found: C 59.17  H 58.28  N 9.67
HRMS for C\textsubscript{14}H\textsubscript{24}N\textsubscript{2}O\textsubscript{4}:
(pos.APCI (MeOH), (M+H\textsuperscript{+})) Calc.: 285.18143; Found: 285.18160 (-0.6 ppm);
(neg.APCI (MeOH), (M+Cl\textsuperscript{-})) Calc.: 319.14264; Found: 319.14210 (1.1 ppm).

4-(6'-Acetoxy-hexyl)-5-ethoxycarbonyl-6-methyl-3,4-dihydropyrimidin-2(1\textit{H})-one
(6f)

\[
\text{C}_{18}\text{H}_{26}\text{N}_{2}\text{O}_{5}
\]

326.39 g/mol

The general procedure was followed starting from Acetic-acid-hex-5-enyl-ester (469 mg,
4.00 mmol), [Rh(CO)\textsubscript{2}acac], xantphos, urea, ethyl-acetoacetate and HCl. Purification via flash
chromatography (CH\textsubscript{2}Cl\textsubscript{2} to CH\textsubscript{2}Cl\textsubscript{2}/AcOEt = 1:1) furnished
4-(6'-Acetoxy-hexyl)-5-ethoxycarbonyl-6-methyl-3,4-dihydropyrimidin-2(1\textit{H})-one as a colorless solid (365 mg; 57%
isolated yield).

\text{Mp.:} 77 \degree \text{C}

\text{R}_\text{f} = 0.1 \text{ (DCM/EE 4:1)}.

\textbf{\textit{\textsuperscript{1}H-NMR (400.131 MHz, DMSO)}}

\[\delta \text{ (ppm)} = 1.17 (t, J=7.1 \text{ Hz}, 3 \text{ H, Et-CH}_3), 1.19 - 1.43 (m, 8 \text{ H, H-8-11}), 1.45 - 1.59 (m, 2 \text{ H, H-7}), 1.98 (s, 3 \text{ H, Ac-CH}_3), 2.14 (s, 3 \text{ H, H-6'}), 3.96 (t, J=6.6 \text{ Hz}, 2 \text{ H, H-12}), 3.99 - 4.12 (m, 3 \text{ H, Et-CH}_2 \& H-4), 7.29 (dd, J=3.5, 2.2 \text{ Hz}, 1 \text{ H, H-3}), 8.89 (d, J=1.8 \text{ Hz}, 1 \text{ H, H-1}).\]

\textbf{\textit{\textsuperscript{13}C-NMR (101.630 MHz, DMSO)}}

\[\delta \text{ (ppm)} = 14.19 (\text{Et-CH}_3), 17.67 (\text{C-6'}), 20.68, 23.57, 25.32, 28.02, 28.35 (1 \text{C respectively, C8-11, Ac-CH}_3), 36.58 (\text{C-7}), 49.98 (\text{C-4}), 58.99 (\text{Et-CH}_2), 63.74 (\text{C-12}), 99.37 (\text{C-5}), 148.22 (\text{C-6}), 152.71 (\text{C-2}), 165.40 (\text{C-5'}), 170.34 (\text{Ac-C(=O)O}).\]

CHN
Calc.: C 58.88  H 8.03  N 8.58
Found: C 58.61  H 8.31  N 8.25

HRMS for C_{21}H_{30}N_{2}O_{4}:
(pos.APCI (MeOH), (M+H)^+) Calc.: 327.19200; Found: 327.19240 (-1.2 ppm).

4-(6'-Benzoyloxy-hexyl)-5-ethoxycarbonyl-6-methyl-3,4-dihydropyrimidin-2(1H)-one (6g)

The general procedure was followed starting from hex-5-en-1-yl benzoate (649 mg, 4.00 mmol), [Rh(CO)\textsubscript{2}acac], xantphos, urea, ethyl-acetoacetate and HCl. Purification via flash chromatography (CH\textsubscript{2}Cl\textsubscript{2} to CH\textsubscript{2}Cl\textsubscript{2}/AcOEt = 1:1) furnished 4-(6'-Benzoyloxy-hexyl)-5-ethoxycarbonyl-6-methyl-3,4-dihydropyrimidin-2(1H)-one as a colorless solid (376 mg; 52% isolated yield).

Mp.: 117-118 °C
R\textsubscript{f}= 0.18 (DCM/EE 4:1)

\textsuperscript{1}H-NMR (400.131 MHz, DMSO)
δ (ppm) = 1.16 (t, J=7.1 Hz, 3 H, Et-CH\textsubscript{3}), 1.21 - 1.47 (m, 8 H, H-8-11), 1.64 - 1.72 (m, 2 H, H-7), 2.15 (s, 3 H, H-6'), 3.94 - 4.12 (m, 3 H, Et-CH\textsubscript{2} & H-4), 4.25 (t, J=6.6 Hz, 2 H, H-12), 7.30 (dd, J=3.5, 2.1 Hz, 1 H, H-3), 7.48 - 7.55 (m, 2 H, Ar-H), 7.61 - 7.69 (m, 1 H, Ar-H), 7.91 - 7.98 (m, 2 H, Ar-H), 8.90 (d, J=1.9 Hz, 1 H, H-1).

\textsuperscript{13}C-NMR (101.630 MHz, DMSO)
δ (ppm) = 14.19 (Et-CH\textsubscript{3}), 17.69 (C-6'), 23.62, 25.44, 28.10, 28.38, (1C respectively, C8-11), 36.59 (C-7), 49.99 (C-4), 59.00 (Et-CH\textsubscript{2}), 64.64 (C-12), 99.40 (C-5), 128.73 (2C, Ar-C),
129.02 (2C, Ar-C), 129.85 (1C, Ar-C), 133.21 (1C, Ar-C), 148.24 (C-6), 152.72 (C-2), 165.41 (C-5'), 165.71 (C-Bz).

**HRMS** for C_{21}H_{28}N_{2}O_{5}:
(pos.APCI (MeOH), (M+H)^+) Calc.: 389.20765; Found: 389.20770 (-0.1 ppm);
(neg.APCI (MeOH), (M-H)^-) Calc.: 387.19200; Found: 387.19150 (1.3 ppm).

4-(6'-Benzyloxy-hexyl)-5-ethoxycarbonyl-6-methyl-3,4-dihydropyrimidin-2(1H)-one (6h)

The **general procedure** was followed starting from hex-5-enyloxymethylbenzene (593 mg, 4.00 mmol), [Rh(CO)_{2}acac], xantphos, urea, ethyl-acetoacetate and HCl. Purification via flash chromatography (CH_{2}Cl_{2} to CH_{2}Cl_{2}/AcOEt = 1:1) furnished 4-(6'-Benzyloxy-hexyl)-5-ethoxycarbonyl-6-methyl-3,4-dihydropyrimidin-2(1H)-one as a colorless solid (534 mg; 71% isolated yield).

**Mp.:** 88-90 °C  
**R_{f}=** 0.22 (DCM/EE 1:1)

**{^1}H-NMR (499.500 MHz, DMSO)**  
δ (ppm) = 1.16 (t, J=7.1 Hz, 3 H, Et-CH_{3}), 1.19 - 1.40 (m, 8 H, H-8-11), 1.45 - 1.54 (m, 2 H, H-7), 2.15 (s, 3 H, H-6'), 3.39 (t, J=6.6 Hz, 2 H, H-12), 3.96 - 4.11 (m, 3 H, Et-CH_{2} & H-4), 4.42 (s, 2 H, Bn-CH_{2}), 7.22 - 7.36 (m, 6 H, H-3, Ar-H), 8.91 (d, J=1.9 Hz, 1 H, H-1).

**{^{13}}C-NMR (125.610 MHz, DMSO)**  
δ (ppm) = 14.20 (Et-CH_{3}), 17.69 (C-6'), 23.66, 25.63, 28.55, 29.11 (1C respectively, C8-11), 36.64 (C-7), 50.02 (C-4), 59.00 (Et-CH_{2}), 69.55 (C-12), 71.75 (Bn-CH_{2}), 99.41 (C-5), 127.26
(1C, Ar-C), 127.34 (2C, Ar-C), 128.17 (2C, Ar-C), 138.72 (1C, Ar-C), 148.24 (C-6), 152.74 (C-2), 165.42 (C-5').

**CHN**
Calc.: C 67.35 H 8.07 N 7.48
Found: C 67.71 H 7.99 N 7.14

**HRMS** for C$_{21}$H$_{30}$N$_{2}$O$_{4}$:
(pos.APCI (MeOH), (M+H)$^+$) Calc.: 374.20798; Found: 374.20780 (0.5 ppm);
(neg.APCI (MeOH), (M-H)$^-$) Calc.: 372.19233; Found: 372.19270 (-1.0 ppm).

**5-Ethoxycarbonyl-4-(11'-methoxycarbonyl-undecyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one (6i)**

The general procedure was followed starting from Methyl-undec-10-enoate (793 mg, 4.00 mmol), [Rh(CO)$_2$acac], xantphos, urea, ethyl-acetoacetate and HCl. Purification via flash chromatography (CH$_2$Cl$_2$ to CH$_2$Cl$_2$/AcOEt = 1:1) furnished 5-Ethoxycarbonyl-4-(11'-methoxycarbonyl-undecyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one as a colorless solid (398 mg; 52% isolated yield).

**Mp.:** 110 °C

**R$_f$** = 0.23 (DCM/EE 1:1).

**$^1$H-NMR (400.131 MHz, DMSO)**

$\delta$ (ppm) = 1.13 - 1.44 (m, 16 H, H-8-15), 1.17 (t, $J$=7.1 Hz, 3 H, Et-CH$_3$), 1.45 - 1.53 (m, 2 H, H-7), 2.14 (s, 3 H, H-6'), 2.27 (t, $J$=7.5 Hz, 2 H, H-16), 3.56 (s, 3 H, OMe), 3.97 - 4.12 (m, 3 H, Et-CH$_2$ & H-4), 7.28 (dd, $J$=3.5, 2.1 Hz, 1 H, H-3), 8.89 (d, $J$=1.8 Hz, 1 H, H-1).

**$^{13}$C-NMR (101.630 MHz, DMSO)**
δ (ppm) = 14.20 (Et-CH$_3$), 17.67 (C-6'), 23.64, 24.41, 28.42, 28.64, 28.73, 28.83, 28.85, 28.91, 33.25 (1C respectively, C8-16), 36.66 (C-7), 50.02 (C-4), 51.02 (OMe), 58.99 (Et-CH$_2$), 99.40 (C-5), 148.22 (C-6), 152.72 (C-2), 165.44 (C-5'). 173.32 (C(=O)O).

**HRMS** for C$_{20}$H$_{34}$N$_2$O$_5$:  
(pos.APCI (MeOH), (M+H)$^+$) Calc.: 383.25460; Found: 383.25470 (-0.3 ppm);  
(neg.APCI (MeOH), (M-H)$^-$) Calc.: 381.23895; Found: 381.23940 (-1.2 ppm).

**5-Ethoxycarbonyl-6-methyl-4-(6'-N-phenylcarbamoylhexyl)-3,4-dihydropyrimidin-2(1H)-one (6j)**

\[
\begin{align*}
\text{C$_{21}$H$_{29}$N$_3$O$_5$} \\
\text{403.47 g/mol}
\end{align*}
\]

The **general procedure** was followed starting from Phenylcarbamic-acid-hex-5-enyl-ester (709 mg, 4.00 mmol), [Rh(CO)$_2$acac], xantphos, urea, ethyl-acetoacetate and HCl. Purification via flash chromatography (CH$_2$Cl$_2$ to CH$_2$Cl$_2$/AcOEt = 1:1) furnished 5-Ethoxycarbonyl-6-methyl-4-(6'-N-phenylcarbamoylhexyl)-3,4-dihydropyrimidin-2(1H)-one as a colorless foam (590 mg; 73% isolated yield).

R$_f$ = 0.12 (DCM/EE 4:1).

**$^1$H-NMR (400.131 MHz, DMSO)**

δ (ppm) = 1.17 (t, J=7.1 Hz, 3 H, 3 H, Et-CH$_3$), 1.20 - 1.43 (m, 8 H, H-8-11), 1.53 - 1.63 (m, 2 H, H-7), 2.15 (s, 3 H, H-6'), 3.97 - 4.12 (m, 5 H, Et-CH$_2$, H-4, H-12), 6.92 - 6.99 (m, 1 H, Ar-H), 7.21 - 7.27 (m, 2 H, Ar-H), 7.29 (dd, J=3.5, 2.1 Hz, 1 H, H-3), 7.41 - 7.47 (m, 2 H, Ar-H), 8.90 (d, J=1.9 Hz, 1 H, H-1), 9.54 (bs, 1 H, NH).

**$^{13}$C-NMR (101.630 MHz, DMSO)**

δ (ppm) = 14.21 (Et-CH$_3$), 17.69 (C-6'), 23.67, 25.36, 28.46, 28.50, (1C respectively, C8-11), 36.66 (C-7), 50.03 (C-4), 59.03 (Et-CH$_2$), 64.06 (C-12), 99.39 (C-5), 118.12 (1C, Ar-C), 118.12 (1C, Ar-C),
122.23 (2C, Ar-C), 128.66 (2C, Ar-C), 139.20 (1C, Ar-C), 148.24 (C-6), 152.73 (C-2), 153.58 (C-OC(=ON)), 165.43 (C-5').

**HRMS for C$_{21}$H$_{29}$N$_3$O$_5$:**
(pos.APCI (MeOH), (M+H)$^+$) Calc.: 404.21855; Found: 404.21860 (-0.1 ppm);
(neg.APCI (MeOH), (M-H)$^-$) Calc.: 438.17957; Found: 438.17900 (1.3 ppm).

**5-Ethoxycarbonyl-4-[5'-(N-methyl-N-phenylcarbamoyl)-pentyl]-6-methyl-3,4-dihydropyrimidin-2(1H)-one (6k)**

![Chemical structure of 6k](image.png)

C$_{20}$H$_{27}$N$_3$O$_4$
373.45 g/mol

The *general procedure* was followed starting from *N*-methyl-*N*-phenylpent-4-enamide (757 mg, 4.00 mmol), [Rh(CO)$_2$acac], xantphos, urea, ethyl-acetoacetate and HCl. Purification via flash chromatography (CH$_2$Cl$_2$ to AcOEt) furnished 5-Ethoxycarbonyl-4-[5'-(N-methyl-N-phenylcarbamoyl)-pentyl]-6-methyl-3,4-dihydropyrimidin-2(1H)-one as a colorless foam (488 mg; 65% isolated yield).

$R_f = 0.15$ (EE)

**$^1$H-NMR (400.131 MHz, DMSO)**
$\delta$ (ppm) = 0.96 - 1.31 (m, 4 H, H-8-9), 1.14 (t, $J$=7.1 Hz, 3 H, Et-CH$_3$), 1.89 - 2.03 (m, 2 H, H-7), 2.13 (s, 3 H, H-6'), 3.13 (s, 3 H, N-CH$_3$), 3.93 - 4.10 (m, 3 H, Et-CH$_2$, H-4), 7.19 - 7.48 (m, 6 H, Ar-H & H-3), 8.89 (d, $J$=1.8 Hz, 1 H, H-1).

**$^{13}$C-NMR (101.630 MHz, DMSO)**
$\delta$ (ppm) = 14.20 (Et-CH$_3$), 17.68 (C-6'), 23.35, 24.64, (1C respectively, C8-9), 33.14 (C-10), 36.51 (C-7, N-CH$_3$), 49.94 (C-4), 59.00 (Et-CH$_2$), 99.27 (C-5), 127.27 (2C, Ar-C), 129.58 (2C, Ar-C), 144.02 (2C, Ar-C), 148.23 (C-6), 152.66 (C-2), 165.43 (C-5'), 171.44 (C(=O)N).

**HRMS for C$_{20}$H$_{27}$N$_3$O$_4$:**

5-Ethoxycarbonyl-6-methyl-4-(3'-phthalimido-propyl)-3,4-dihydropyrimidin-2(1H)-one (6l)

\[
\begin{align*}
\text{C}_{19} \text{H}_{21} \text{N}_3 \text{O}_5 & \\
371.39 \text{g/mol}
\end{align*}
\]

The **general procedure** was followed starting from \(N\)-allyl-phthalimide (749 mg, 4.00 mmol), [Rh(CO)\(_2\)acac], xantphos, urea, ethyl-acetoacetate and HCl. Purification via flash chromatography (CH\(_2\)Cl\(_2\) to AcOEt) furnished 5-Ethoxycarbonyl-6-methyl-4-(3'-phthalimido-propyl)-3,4-dihydropyrimidin-2(1H)-one as a colorless solid (443 mg; 59% isolated yield).

**Mp.:** 195 °C  
**R\(_f\) = 0.08** (DCM/EE 2:1)

\(^1\)H-NMR (400.131 MHz, DMSO)

\(\delta\) (ppm) = 1.06 (t, \(J=7.1\) Hz, 3 H, Et-CH\(_3\)), 1.33 - 1.73 (m, 4 H, H-7,8), 2.13 (s, 3 H, H-6'), 3.46 - 3.61 (m, 2 H, Et-CH\(_2\)), 3.87 - 4.09 (m, 3 H, Et-CH\(_2\) & H-4), 7.26 (dd, \(J=3.4, 2.0\) Hz, 1 H, H-3), 7.77 - 7.88 (m, 4 H, Ar-H), 8.91 (d, \(J=1.8\) Hz, 1 H, H-1).

\(^{13}\)C-NMR (101.630 MHz, DMSO)

\(\delta\) (ppm) = 14.05 (Et-CH\(_3\)), 17.71 (C-6'), 23.02, 34.10 (1C respectively, C8-9), 37.37 (C-7), 50.03 (C-4), 58.96 (Et-CH\(_2\)), 98.62 (C-5), 122.99 (2C, ArC), 131.50 (2C, ArC), 134.40 (2C, ArC), 148.59 (C-6), 152.53 (C-2), 165.428 (C-5'), 167.89 (2C, PhC(=O)N).

**CHN**

Calc.: C 61.45  H 5.70  N 11.31  
Found: C 61.67  H 5.62  N 11.18
HRMS for C_{19}H_{21}N_{3}O_{5}:
(pos.APCI (MeOH), (M+H)^+) Calc.: 372.15595; Found: 372.15600 (-0.1 ppm);
(neg.APCI (MeOH), (M-H)^-) Calc.: 370.14030; Found: 370.13990 (1.1 ppm).

III. Optimization Experiments

Solvent Effects

Table 1:

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>c (mol/l)</th>
<th>yield\textsuperscript{a}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>EtOH</td>
<td>0.5</td>
<td>62%</td>
</tr>
<tr>
<td>2</td>
<td>DCM</td>
<td>0.5</td>
<td>15%</td>
</tr>
<tr>
<td>3</td>
<td>MeOH</td>
<td>0.5</td>
<td>31%</td>
</tr>
<tr>
<td>4</td>
<td>MeCN</td>
<td>0.5</td>
<td>43%</td>
</tr>
<tr>
<td>5</td>
<td>THF</td>
<td>0.5</td>
<td>32%</td>
</tr>
<tr>
<td>6</td>
<td>Dioxan</td>
<td>0.5</td>
<td>36%</td>
</tr>
<tr>
<td>7</td>
<td>EtOH\textsuperscript{c}</td>
<td>0.5</td>
<td>0%</td>
</tr>
<tr>
<td>8</td>
<td>EtOH</td>
<td>0.2</td>
<td>41%</td>
</tr>
<tr>
<td>9</td>
<td>EtOH</td>
<td>1</td>
<td>61%</td>
</tr>
</tbody>
</table>

Molar ratios aldehyde:urea:ketoester 1:1.1:1; *based on the amount of alkene; \textsuperscript{a}Determined by NMR via Integration against 0.1 eq 1,3,5-trimethoxybenzene as internal standard.
Reaction time

After optimizing the molar ratios we again tested different reaction times to see if there was a beneficial effect on the reaction rate. Results are depicted in table 2.

Table 2:

<table>
<thead>
<tr>
<th>Entry</th>
<th>t (h)</th>
<th>yield^a</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4</td>
<td>25%</td>
</tr>
<tr>
<td>2</td>
<td>16</td>
<td>68%</td>
</tr>
<tr>
<td>3</td>
<td>24</td>
<td>88%</td>
</tr>
</tbody>
</table>

Molar ratios aldehyde:urea:ketoester 2:1.1.1; *based on the amount of alkene; a) Determined by NMR via Integration against 0.1 eq 1,3,5-trimethoxybenzene as internal standard.
IV. Spectra

6a

$^1$H-NMR

$^{13}$C-NMR
IR (in DCM)

C_{16}H_{28}N_{2}O_{3}  
296.41 g/mol

6b

$^1$H-NMR
$^{13}$C-NMR

Chemical Shift (ppm)

IR:

Wavenumber (cm$^{-1}$)
6c

$^1$H-NMR

$^{13}$C-NMR

C$_{16}$H$_{24}$N$_2$O$_3$
292.37 g/mol
IR:

![IR spectrum graph]

\[ C_{16}H_{24}N_2O_3 \]
292.37 g/mol

6d

\[^1^H-NMR\]

![NMR spectrum graph]

\[ C_{14}H_{24}N_2O_3 \]
268.35 g/mol
$^1$H-NMR

$$C_{14}H_{24}N_2O_3$$
268.35 g/mol

IR:

$$C_{14}H_{24}N_2O_3$$
268.35 g/mol
$^{1}H$-NMR

$^{13}C$-NMR
IR:

\[ C_{14}H_{24}N_{2}O_{4} \]
\[ 284.35 \text{ g/mol} \]

6f

\[ ^1H-NMR \]

\[ C_{16}H_{26}N_{2}O_{5} \]
\[ 326.39 \text{ g/mol} \]
**13C-NMR**

![C-NMR Spectrum](image)

**IR:**

![IR Spectrum](image)
6g

$^1$H-NMR

C$_{21}$H$_{28}$N$_2$O$_5$
388.46 g/mol

$^{13}$C-NMR

C$_{21}$H$_{28}$N$_2$O$_5$
388.46 g/mol
IR:

![IR spectrum graph]

6h

$^1$H-NMR

![NMR spectrum graph]

C$_{21}$H$_{28}$N$_2$O$_5$
388.46 g/mol

C$_{21}$H$_{30}$N$_2$O$_4$
374.47 g/mol
\( ^{13}\text{C-NMR} \)

\[ \text{C}_{21}\text{H}_{30}\text{N}_{2}\text{O}_{4} \]

374.47 g/mol

\[ \text{IR} \]

\[ \text{C}_{21}\text{H}_{30}\text{N}_{2}\text{O}_{4} \]

374.47 g/mol
$6i$

$^1\text{H-NMR}$

$\text{C}_{20}\text{H}_{34}\text{N}_2\text{O}_5$

Mol. Wt.: 382.49

$^1\text{C-NMR}$

$\text{C}_{20}\text{H}_{34}\text{N}_2\text{O}_5$

Mol. Wt.: 382.49
IR:

\( \text{C}_{20}\text{H}_{34}\text{N}_{2}\text{O}_{5} \)
Mol. Wt.: 382.49

\( \text{C}_{21}\text{H}_{29}\text{N}_{3}\text{O}_{5} \)
403.47 g/mol

\( ^{1}H\)-NMR
\[ ^{13} \text{C-NMR} \]

\[ \text{C}_{21}\text{H}_{29}\text{N}_{3}\text{O}_{5} \]
\[ 403.47 \text{ g/mol} \]

IR:

\[ \text{C}_{21}\text{H}_{29}\text{N}_{3}\text{O}_{5} \]
\[ 403.47 \text{ g/mol} \]
6k

$^1$H-NMR

$^{13}$C-NMR
IR:

\[ C_{20}H_{27}N_{3}O_{4} \]
373,45 g/mol

\[ C_{19}H_{21}N_{3}O_{5} \]
371,39 g/mol

\[ \text{EtO} \]

\[ \text{H} \]

\[ \text{N} \]

\[ \text{O} \]

\[ \text{Ph} \]

\[ \text{NH} \]

\[ \text{C} \]

\[ \text{H} \]

\[ \text{N} \]

\[ \text{O} \]

\[ \text{EtO} \]

\[ \text{H} \]

\[ \text{N} \]

\[ \text{O} \]

\[ \text{C} \]

\[ \text{H} \]

\[ \text{N} \]

\[ \text{O} \]

\[ \text{EtO} \]

\[ \text{H} \]

\[ \text{N} \]

\[ \text{O} \]

\[ \text{C} \]

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\[ \text{N} \]

\[ \text{O} \]

\[ \text{EtO} \]

\[ \text{H} \]

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\[ \text{EtO} \]

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\[ \text{EtO} \]

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\[ \text{O} \]

\[ \text{EtO} \]

\[ \text{H} \]

\[ \text{N} \]

\[ \text{O} \]

\[ \text{C} \]

\[ \text{H} \]

\[ \text{N} \]

\[ \text{O} \]

\[ \text{EtO} \]

\[ \text{H} \]

\[ \text{N} \]

\[ \text{O} \]

\[ \text{C} \]

\[ \text{H} \]

\[ \text{N} \]

\[ \text{O} \]
$^{13}$C-NMR

\[
\begin{align*}
\text{C}_{19}\text{H}_{21}\text{N}_{3}\text{O}_{5} & \quad 371.39 \text{ g/mol} \\
\end{align*}
\]

IR:

\[
\begin{align*}
\text{C}_{19}\text{H}_{21}\text{N}_{3}\text{O}_{5} & \quad 371.39 \text{ g/mol} \\
\end{align*}
\]