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# Highly Regioselective Addition of Organozinc Reagents to 2-Oxo-1,2-dihydropyrimidine-5-carboxylates Activated by $BF_3{\cdot}OEt_2$: Synthesis of 2-Oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylates

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The incorporation of alkyl as well as phenyl groups at C-4, a key position of 2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylates, responsible for antagonist/agonist switching of the calcium channel blocking activity of these compounds, has been achieved by the addition of organozinc reagents to the corresponding 2-oxo-1,2-dihydropyrimidine-5-carboxylate derivatives catalysed by $BF_3OEt_2$.

## Introduction

The 2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylates **1** (Biginelli DHPMs)[1] represent one of the most actively investigated class of compounds due to their importance as potential calcium channel blockers[2] and have been known for more than a century.[3] Structurally decorated DHPMs are found in many pharmacologically potent compounds, specific examples include Sch575948 (**2**),[4] dehydrocrambine A[4] (**3**; inhibitors of HIV gp-120CD4), (*S*)-monastrol (**4**; mitotic kinesin Eg5 inhibitor),[5] (*S*)-[1]-771,668 (**5**; α1A-adrenoceptorantagonist),[6] (*R*)-SQ 32547 (**6**)[2a] and (*R*)-SQ 32926[2b] (**7**; antihypertensive agents; Figure 1). As a result of their diverse pharmacological profiles, synthetic investigations of DHPMs have received considerable attention by synthetic organic and medicinal chemists alike. The most important methodologies developed to prepare DHPMs rely on either a three-component reaction[3,7] (route a, Scheme 1) or on the functionalization of the precursor 2-oxo-1,2-dihydropyrimidine core (route b)[8] or the preformed DHPM core[8–13] (routes c, d[9] e,[10] f,[11] g[12] and h,[13] Scheme 1). More recently, the development of efficient chiral auxiliaries[2a,2b,12d–12g] or catalysts[14] has led to the asymmetric synthesis of DHPMs. Although three-component reactions (route a, Scheme 1) for the construction of libraries of DHPMs through solution,[7a–7e] solvent-free[7f] and solid-phase[7g–7l] strategies are suitable for high-throughput or combinatorial synthesis, the decoration of the preformed DHPM core by using the tools developed in our laboratory[8–11,12b,12d] have shown considerable poten-

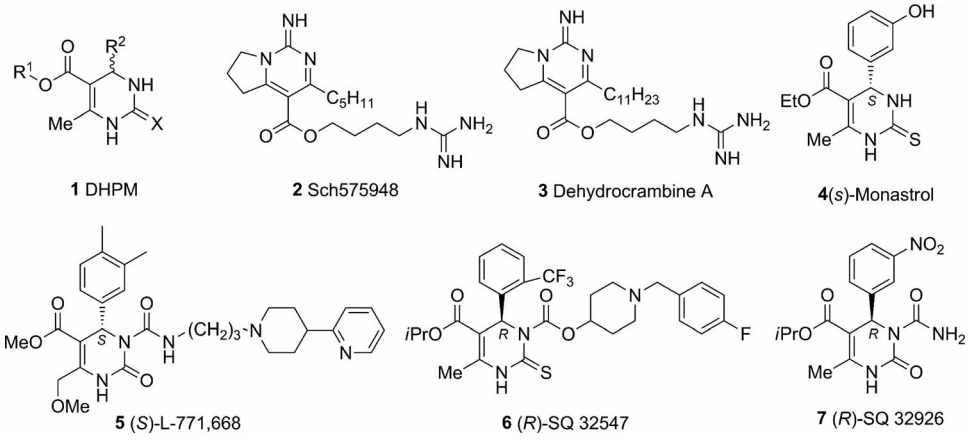


Figure 1. Biologically active DHPM derivatives.

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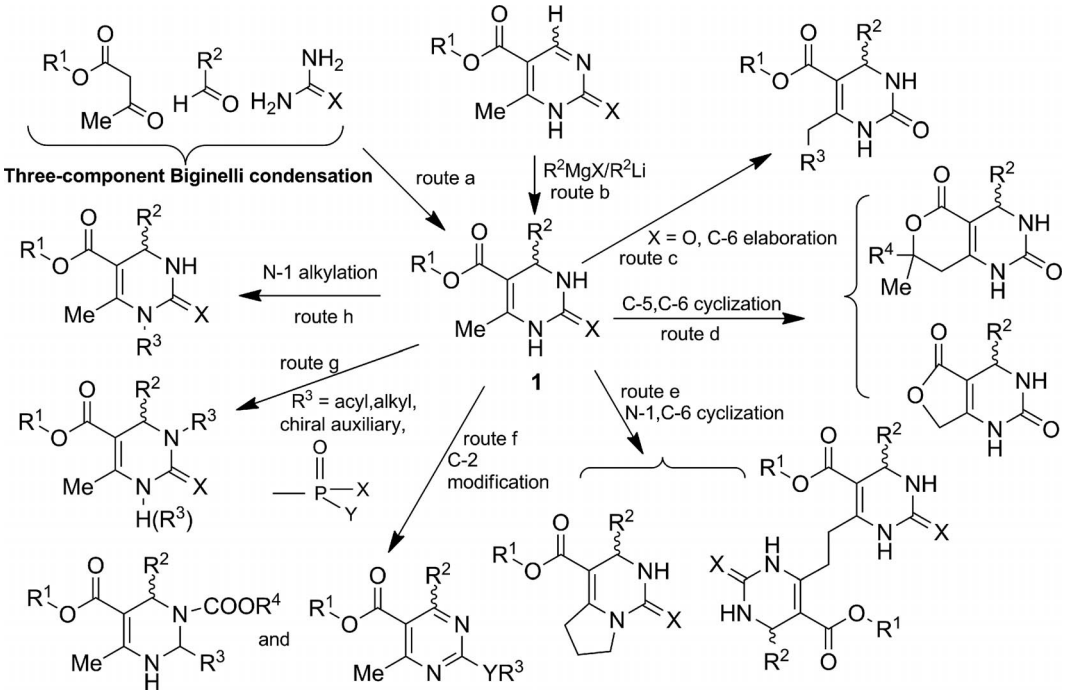



Scheme 1. Construction of DHPMs 1 by a hree-component reaction (route a) and functionalization of pyrimidines (routes b–h) to obtain DHPMs substituted at key diversity-orientated centres.

tial for appending tailor-made fragments at all possible (N-1, C-2, N-3, C-4, C-5 and C-6) diversity-oriented centres by using simple starting materials. By using these tools, we have previously achieved both racemic[7f,8] and diastereoselective[12d,12e] syntheses of DHPMs. In one of these studies, we achieved the regioselective addition of nucleophiles such as alkyl/heterocycloalkyllithium compounds, Grignard and phenyllithium reagents at the 4-position of 1,6-dimethyl-2-oxo-1,2-dihydropyrimidine-5-carboxylic esters.[8] Herein we report the regioselective addition of alkyl- as well as arylzinc reagents to 1,6-dimethyl- or 1-methyl-6-phenyl-2-oxo-1,2-dihydropyrimidine-5-carboxylates to obtain C-4-elaborated 2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylates with considerable ease. In addition, we describe theoretical studies supporting the formation of the products and the attendant regioselectivity of the process.

## Results and Discussion

The addition of organometallic reagents to the –C=N double bond of the 1,2-dihydropyrimidine core is a fundamentally important process from a biological point of view that provides convenient and versatile routes to a variety of 4-substituted DHPM derivatives. As the orientation of the C-4 group in the receptor serves as a molecular switch in determining the state-dependent affinity of the calcium channel, a significant role of the C-4 substituent in the switching of agonistic to antagonistic activity (depending upon the absolute configuration at C-4) of the receptor-bound conformation[15] of DHPM calcium channel blockers has been realized. From the view point of functional group tolerance around the DHPM core, the mild reactivity of organozinc reagents with an alkyl or aryl donor is advantageous if appropriate activation is possible. Activation of dialkylzinc can be achieved by transmetallation[16] or complexation with a variety of transition-metal salts as well as by Lewis acids.[17] Addition to imines is thermodynamically less favoured than addition to the carbonyl group, limited by the poor electrophilicity of the azomethine carbon atom (less polar C=N double bonds: C=N 0.9 D vs. C=O 2.3 D).[18] In spite of this, we have achieved the addition of a variety of organometallic reagents to the 1,2-dihydropyrimidine core without chemical activation. We believe that the ureido carbonyl group is able to stabilize the negative charge on the nitrogen atom resulting from the addition of organometallic reagents to the azomethine carbon atom and thus facilitated these additions. The atomic charges on the azomethine carbons and neighbouring atoms along with the IR stretching frequencies of the –C=N double bond determined by molecular orbital calculations at the HF/6-31G* level of theory (Gaussian 09),[19] are shown in Figure 2; the data unequivocally show the increased electrophilicity of the $BF_3OEt_2$-activated imine **13** relative to unactivated **8** and related structures **9**–**12**.

The approach we used in this work starts with the synthesis of 4-unsubstituted alkyl 1,6-dimethyl- or 1-methyl-6-phenyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylates **14a**–**d**,[20] which, upon further oxidation with ceric ammonium nitrate in acetone/water, were readily transformed into the corresponding methyl 1,6-dimethyl-2-oxo-1,2-dihydropyrimidine-5-carboxylate[21] (**15a**), ethyl 1,6-methyl-2-oxo-1,2-dihydropyrimidine-5-carboxylate (**15b**), isopropyl 1,6-methyl-2-oxo-1,2-dihydropyrimidine-5-carboxylate (**15c**) and ethyl 1-methyl-6-phenyl-2-oxo-1,2-dihydropyrim-

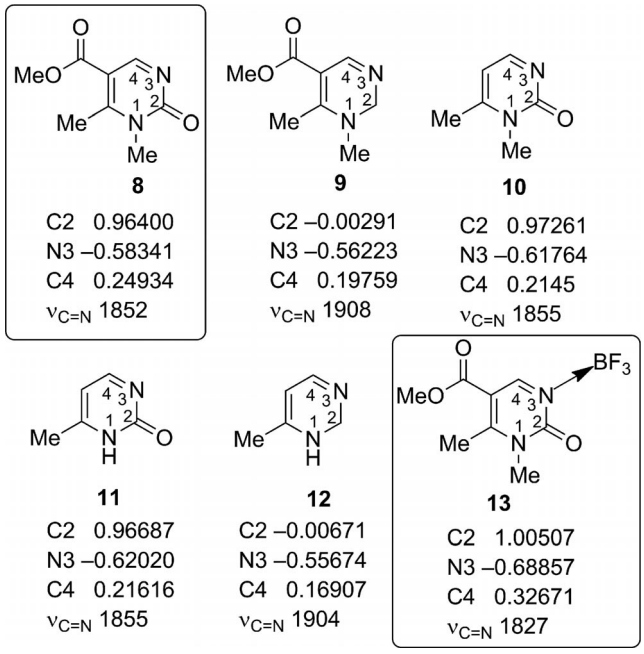



Figure 2. Structures of 2-oxo-1,2-dihydropyrimidine **8** and its analogues **9**–**13**, and the natural atomic charges on the azomethine carbon and other relevant atoms.

idine-5-carboxylate (**15d**), respectively (Scheme 2). Oxidation of **14** to **15** was also successfully achieved by us recently by using pyridinium chlorochromate (PCC).[22] The addition of freshly prepared organozinc reagents[23,24] to **15a**–**d** furnished exclusively the corresponding DHPM derivatives **16a**–**p** substituted at C-4 by an alkyl or phenyl substituent.

The formation of **16a**–**p** by the addition of carbon nucleophiles represents a smooth formation of those DHPMs that are otherwise not easily accessible through traditional methods employing aliphatic aldehydes because of their non-availability and operational difficulties. Furthermore, the addition of organolithium reagents to pyridines requires activation of the pyridine moiety as a 1-alkoxycarbonyl derivative,[25] and the regioselectivity of the reactions of 1-acylpyridinium salts with Grignard reagents[26] is additionally influenced by the structures of the Grignard reagent and the 1-acyl group. In the reaction protocol described herein, the addition of alkyl- or arylzinc reagents to **15a**–**d** (Table 1) proceeded regioselectively in a straight forward manner upon activation with the mild Lewis acid, $BF_3OEt_2$, in case of the former. All the products were characterized by IR, $^1H$ and $^{13}C$ NMR spectroscopy and MS analysis.

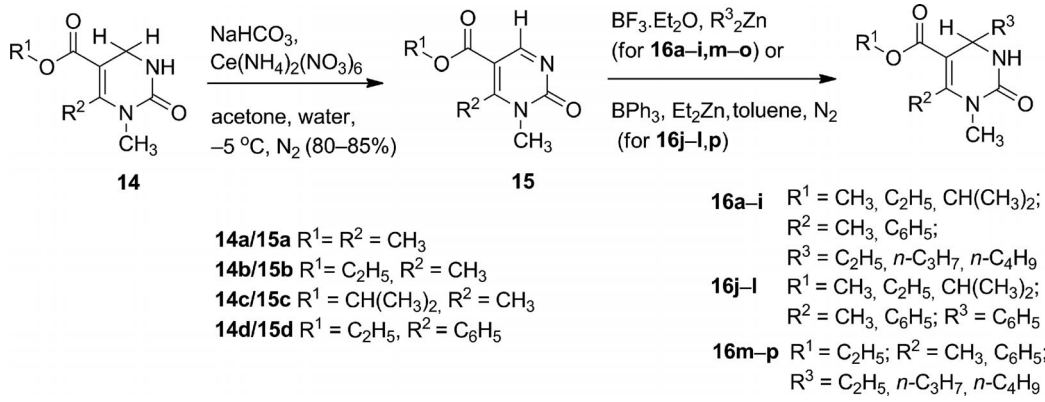
Table 1. Addition of dialkylzinc activated by $BF_3{\cdot}OEt_2$ or $Ph_3B{\cdot}Et_2Zn$ to 1,6-dimethyl or 1-methyl-6-phenyl-2-oxo-1,2-dihydropyrimidine-5-carboxylic esters (**15a**–**d**, Scheme 2).

| Product | $R^1$ | $R^2$ | $R^3$ | Yield [%][a,b] |
|---|---|---|---|---|
| **16a** | $C_2H_5$ | $CH_3$ | $C_2H_5$ | 70 |
| **16b** | $CH_3$ | $CH_3$ | $C_2H_5$ | 70 |
| **16c** | $CH(CH_3)_2$ | $CH_3$ | $C_2H_5$ | 68 |
| **16d** | $C_2H_5$ | $CH_3$ | *n*-$C_3H_7$ | 68 |
| **16e** | $CH_3$ | $CH_3$ | *n*-$C_3H_7$ | 68 |
| **16f** | $CH(CH_3)_2$ | $CH_3$ | *n*-$C_3H_7$ | 66 |
| **16g** | $C_2H_5$ | $CH_3$ | *n*-$C_4H_9$ | 70 |
| **16h** | $CH_3$ | $CH_3$ | *n*-$C_4H_9$ | 68 |
| **16i** | $CH(CH_3)_2$ | $CH_3$ | *n*-$C_4H_9$ | 68 |
| **16j** | $C_2H_5$ | $CH_3$ | $C_6H_5$ | 70 |
| **16k** | $CH_3$ | $CH_3$ | $C_6H_5$ | 68 |
| **16l** | $CH(CH_3)_2$ | $CH_3$ | $C_6H_5$ | 63 |
| **16m** | $C_2H_5$ | $C_6H_5$ | $C_2H_5$ | 80 |
| **16n** | $C_2H_5$ | $C_6H_5$ | *n*-$C_3H_7$ | 75 |
| **16o** | $C_2H_5$ | $C_6H_5$ | *n*-$C_4H_9$ | 78 |
| **16p** | $C_2H_5$ | $C_6H_5$ | $C_6H_5$ | 72 |

[a] Isolated yield. [b] Poor yields were obtained without $BF_3{\cdot}OEt_2$ as well as by using THF or DCM in place of toluene.

## Conclusions

A simple carbon–carbon bond-forming reaction at the key C-4 position of 1,6-dimethyl- or 1-methyl-6-phenyl-2-oxo-1,2-dihydropyrimidine-5-carboxylic esters with organozinc reagents in the presence of $BF_3OEt_2$ has been developed. Because of the tolerance of organozinc reagents to variations in substitution around the pyrimidine core and the regioselectivity of the reaction, this procedure provides an efficient route to C-4-elaborated 2-oxo-1,2,3,4-tetra-




Scheme 2. Synthesis of C-4-elaborated DHPMs by the addition of dialkylzinc activated by $BF_3{\cdot}OEt_2$ (1.0 equiv.) or diphenylzinc [generated in situ from $BPh_3$ (1.0 equiv.) and $Et_2Zn$ (3.0 equiv.)] to 1,6-dimethyl or 1-methyl-6-phenyl-2-oxo-1,2-dihydropyrimidine-5-carboxylic esters **15a**–**d**.

hydropyrimidines (DHPMs), which are useful therapeutic targets. An investigation of the asymmetric version of this reaction is underway.

## Experimental Section

**General:** All liquid reagents were dried/purified by using recommended drying agents and distilled before use. Triphenylborane for the preparation of diphenylzinc was bought from Sigma-Aldrich and used without purification. Toluene was dried (Na/benzophenone ketyl) and drawn with hypodermic glass syringes. $^1$H and $^{13}$C NMR spectra were recorded with a JEOL-FT NMR-AL spectrometer at 300 MHz or with a Bruker Avance spectrometer at 400 MHz with TMS as the internal standard using $CDCl_3$ and [$D_6$]DMSO as the deuteriated solvent. HRMS were recorded with a Bruker HRMS MICROTOF II spectrometer. IR spectra were recorded with a Perkin–Elmer FTIR-C92035 Fourier-transform spectrophotometer in the range 400–4000 cm$^{-1}$ in KBr medium. All reported yields are isolated yields. All alkylzinc regents (diethyl, di-*n*-propyl, di-*n*-butyl, diphenylzinc) were prepared freshly according to literature procedures[23,24] using a zinc/copper couple.[27] Silica gel (60–120 mesh) was employed for column chromatography with ethyl acetate/hexane mixtures as eluents.

**General Procedure for the Synthesis of 4-Alkyl-Substituted Alkyl 1,6-Dimethyl- or 1-Methyl-6-phenyl-2-oxo-1,2,3,4-tetrahydropyrimidin-5-carboxylates (16a–i,m–o):** A solution of $BF_3$·$Et_2O$ (0.1 mL, 1.0 mmol) was added to a stirred solution of **15** (0.1 g, 1 mmol) in dry toluene (30 mL) under an inert atmosphere at 0 °C. The reaction mixture was stirred at the same temperature for 30 min. Neat dialkylzinc (0.15 mL, 3 mmol) was added and the reaction allowed to warm to room temp. and stirred for 48 h. On completion of the reaction (TLC), it was quenched with saturated aqueous ammonium chloride solution and extracted with dichloromethane (2× 20 mL). Dichloromethane was removed under vacuum and the resulting crude product was purified by column chromatography using ethyl acetate/hexane mixtures as eluent to obtain pure **16a–i,m–o**.

**Ethyl 1,6-Dimethyl-4-ethyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (16a):** Yield 70%. White solid. $R_f$ = 0.4 (30% ethyl acetate/hexane). IR (KBr): $\tilde{\nu}_{max}$ = 1690, 1664, 2960, 3267 cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$, 25 °C): $\delta$ = 0.85 (t, $J$ = 7.48 Hz, 3 H, 4-$CH_3$), 1.29 (t, 3 H, ester-$CH_3$), 1.57–1.75 (m, 2 H, 4-$CH_2$), 2.30 (s, 3 H, 6-$CH_3$), 2.98 (s, 3 H, N-$CH_3$), 4.13–4.23 (m, 2 H, $CH_2$), 4.31 (t, $J$ = 4.7 Hz, 1 H, 4-H), 8.11 (br., 1 H, NH, $D_2O$ exchangeable) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$, 25 °C): $\delta$ = 8.1, 14.3, 18.3, 25.9, 33.3, 58.8, 59.7, 99.1, 148.1, 154.1, 166.1 ppm. HRMS: calcd. for $C_{11}O_3N_2H_{18}$ [M]$^+$ 226.1317; found [M + Na]$^+$ 249.1213.

**Methyl 1,6-Dimethyl-4-ethyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (16b):** Yield 70%. White solid. $R_f$ = 0.4 (30% ethyl acetate/hexane). IR (KBr): $\tilde{\nu}_{max}$ = 1682, 1625, 2941, 3275 cm$^{-1}$. $^1$H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta$ = 0.85 (t, $J$ = 7.5 Hz, 3 H, 4-$CH_3$), 1.56–1.77 (m, 2 H, 4-$CH_2$), 2.29 (s, 3 H, 6-$CH_3$), 2.93 (s, 3 H, N-$CH_3$), 4.06 (s, 3 H, $OCH_3$), 4.31 (t, $J$ = 4.8 Hz, 1 H, 4-H), 7.32 (br., 1 H, NH, $D_2O$ exchangeable) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$, 25 °C): $\delta$ = 8.1, 18.4, 29.6, 33.4, 50.9, 58.9, 99.2, 147.9, 153.2, 166.1 ppm. HRMS: calcd. for $C_{10}O_3N_2H_{16}$ [M]$^+$ 212.1161; found [M + Na]$^+$ 235.1058.

**Isopropyl 1,6-Dimethyl-4-ethyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (16c):** Yield 68%. White solid. $R_f$ = 0.4 (30% ethyl acetate/hexane). IR (KBr): $\tilde{\nu}_{max}$ = 1688, 1620, 2933, 3265 cm$^{-1}$. $^1$H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta$ = 0.78 (t, $J$ = 7.5 Hz, 3 H, 4-$CH_3$), 1.18 (d, $J$ = 2.4 Hz, 6 H, 2 $CH_3$), 1.55–1.60 (m, 2 H, 4-$CH_2$), 2.09 (s, 3 H, 6-$CH_3$), 2.91 (s, 3 H, N-$CH_3$), 4.22 (t, $J$ = 4.8 Hz, 1 H, 4-H), 4.93–5.04 (m,1 H, ester-CH), 7.34 (s, 1 H, NH, $D_2O$ exchangeable) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$, 25 °C): $\delta$ = 7.2, 17.5, 20.9, 21.0, 24.9, 32.3, 57.9, 66.1, 98.7, 146.3, 152.7, 164.5 ppm. HRMS: calcd. for $C_{12}O_3N_2H_{20}$ [M]$^+$ 240.1474; found [M + Na]$^+$ 263.1368.

**Ethyl 1,6-Dimethyl-4-*n*-propyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (16d):** Yield 68%. White solid. $R_f$ = 0.4 (30% ethyl acetate/hexane). IR (KBr): $\tilde{\nu}_{max}$ = 1683, 1621, 2966, 3288 cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$, 25 °C): $\delta$ = 0.86 (t, $J$ = 7.26 Hz, 3 H, 4-$CH_3$), 1.21–1.34 (m, 5 H, $OCH_3$, 4-$CH_2$), 1.51–1.64 (m, 2 H, 4-$CH_2$), 2.26 (s, 3 H, 6-$CH_3$), 2.96 (s, 3 H, N-$CH_3$), 4.10–4.20 (m, 2 H, $OCH_2$), 4.28 (t, $J$ = 4.9 Hz, 1 H, 4-H), 8.43 (br., 1 H, NH, $D_2O$ exchangeable) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$, 25 °C): $\delta$ = 14.1, 14.3, 17.3, 18.4, 33.5, 35.6, 57.9, 59.7, 100.0, 147.6, 153.8, 166.0 ppm. HRMS: calcd. for $C_{12}O_3N_2H_{20}$ [M]$^+$ 240.1474; found [M + Na]$^+$ 263.1370.

**Methyl 1,6-Dimethyl-4-*n*-propyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (16e):** Yield 68%. White solid. $R_f$ = 0.4 (30% ethyl acetate/hexane). IR (KBr): $\tilde{\nu}_{max}$ = 1693, 1655, 2943, 3279 cm$^{-1}$. $^1$H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta$ = 0.81 (t, $J$ = 7.24 Hz, 3 H, 4-$CH_3$), 1.14–1.27 (m, 2 H, 4-$CH_2$), 1.46–1.70 (m, 2 H, 4-$CH_2$), 2.21 (s, 3 H, 6-$CH_3$), 2.91 (s, 3 H, N-$CH_3$), 3.58 (s, 3 H, $OCH_3$), 4.23 (t, $J$ = 7.24 Hz, 1 H, 4-H), 8.08 (br., 1 H, NH, $D_2O$ exchangeable) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$, 25 °C): $\delta$ = 14.1, 17.2, 18.3, 33.5, 35.6, 50.9, 57.9, 99.7, 148.0, 153.9, 166.4 ppm. HRMS: calcd. for $C_{11}O_3N_2H_{18}$ [M]$^+$ 226.1317; found [M + Na]$^+$ 249.1215.

**Isopropyl 1,6-Dimethyl-4-*n*-propyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (16f):** Yield 66%. White solid. $R_f$ = 0.4 (30% ethyl acetate/hexane). IR (KBr): $\tilde{\nu}_{max}$ = 1686, 1659, 2931, 3269 cm$^{-1}$. $^1$H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta$ = 0.88 (t, $J$ = 7.28 Hz, 3 H, 4-$CH_3$), 1.20–1.31 (m, 10 H, 2 ester-$CH_3$, 2 4-$CH_2$), 2.20 (s, 3 H, 6-$CH_3$), 2.91 (s, 3 H, N-$CH_3$), 4.22–4.24 (m, 1 H, OCH), 4.98 (t, $J$ = 6.24 Hz, 1 H, 4-H), 8.88 (br., 1 H, NH, $D_2O$ exchangeable) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$ + [$D_6$]DMSO, 25 °C): $\delta$ = 14.0, 16.7, 17.4, 21.6, 32.8, 34.6, 35.3, 50.7, 56.9, 99.2, 147.9, 152.3 33.5, 167.1 ppm. HRMS: calcd. for $C_{13}O_3N_2H_{22}$ [M]$^+$ 254.1630; found [M + Na]$^+$ 277.1521.

**Ethyl 1,6-Dimethyl-4-*n*-butyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (16g):** Yield 70%. White solid. $R_f$ = 0.4 (30% ethyl acetate/hexane). IR (KBr): $\tilde{\nu}_{max}$ = 1694, 1645, 2945, 3282 cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$, 25 °C): $\delta$ = 0.93 (t, $J$ = 6.93 Hz, 3 H, 4-$CH_3$), 1.18–1.1.33 (m, 7 H, $OCH_3$, 2 4-$CH_2$), 1.54–1.70 (m, 2 H, 2 4-$CH_2$), 2.29 (s, 3 H, 6-$CH_3$), 2.99 (s, 3 H, N-$CH_3$), 4.13–4.23 (m, 2 H, $OCH_2$), 4.28 (t, $J$ = 5.12 Hz, 1 H, 4-H), 7.47 (br., 1 H, NH, $D_2O$ exchangeable) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$, 25 °C): $\delta$ = 13.0, 13.3, 17.5, 21.8, 25.1, 32.1, 32.5, 57.0, 58.8, 99.1, 146.4, 152.7, 165.0 ppm. HRMS: calcd. for $C_{13}O_3N_2H_{22}$ [M]$^+$ 254.1630; found [M + Na]$^+$ 277.1528.

**Methyl 1,6-Dimethyl-4-*n*-butyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (16h):** Yield 68%. White solid. $R_f$ = 0.4 (30% ethyl acetate/hexane). IR (KBr): $\tilde{\nu}_{max}$ = 1696, 1671, 2957, 3289 cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$, 25 °C): $\delta$ = 0.86 (t, $J$ = 6.92 Hz, 3 H, 4-$CH_3$), 1.17–1.32 (m, 4 H, 2 4-$CH_2$), 1.52–1.66 (m, 2 H, 2 4-$CH_2$), 2.28 (s, 3 H, 6-$CH_3$), 2.97 (s, 3 H, N-$CH_3$), 3.70 (s, 3 H, $OCH_3$), 4.30 (t, $J$ = 4.96 Hz, 1 H, 4-H), 7.96 (br., 1 H, NH, $D_2O$ exchangeable) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$, 25 °C): $\delta$ = 13.0, 17.4, 21.8, 24.9, 32.1, 32.5, 50.0, 57.0, 98.7, 147.0, 152.9, 165.4 ppm. HRMS: calcd. for $C_{12}O_3N_2H_{20}$ [M]$^+$ 240.1474; found [M + Na]$^+$ 263.1369.

**Isopropyl 1,6-Dimethyl-4-*n*-butyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (16i):** Yield 68%. White solid. $R_f$ = 0.4 (30% ethyl acetate/hexane). IR (KBr): $\tilde{\nu}_{max}$ = 1674, 1625, 2946, 3264 cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$, 25 °C): $\delta$ = 0.87 (t, $J$ = 6.92 Hz, 3 H, 4-$CH_3$), 1.20–1.33 (m, 10 H, 2 ester-$CH_3$, 2 4-$CH_2$), 1.54–1.68 (m, 2 H, 4-$CH_2$), 2.28 (s, 3 H, 6-$CH_3$), 2.99 (s, 3 H, N-$CH_3$), 4.28 (m, 1 H, OCH), 5.09 (t, $J$ = 6.1 Hz, 1 H, 4-H), 8.67 (br., 1 H, NH, $D_2O$ exchangeable) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$, 25 °C): $\delta$ = 14.0, 18.5, 21.9, 22.1, 22.8, 26.2, 33.1, 33.6, 58.1, 67.1, 100.5, 147.1, 153.7, 165.5 ppm. HRMS: calcd. for $C_{14}O_3N_2H_{24}$ [M]$^+$ 268.1787; found [M + Na]$^+$ 291.1681.

**Ethyl 1-Methyl-6-phenyl-4-ethyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (16m):** Yield 80%. White solid. $R_f$ = 0.5 (60% ethyl acetate/hexane). IR (KBr): $\tilde{\nu}_{max}$ = 1683, 1619, 1563, 3022, 3276 cm$^{-1}$. $^1$H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta$ = 0.89 (t, $J$ = 7.05 Hz, 3 H, 4-$CH_2CH_3$), 1.00 (t, $J$ = 7.5 Hz, 3 H, ester-$CH_3$), 1.76–1.87 (m, 2 H, 4-$CH_2CH_3$), 3.08 (s, 3 H, N-$CH_3$), 3.92 (q, $J$ = 7.05 Hz, 2 H, $OCH_2$), 4.42 (t, $J$ = 4.8 Hz, 1 H, 4-H), 6.40 (br., 1 H, NH, $D_2O$ exchangeable), 7.29–7.40 (m, 5 H, 6-$C_6H_5$) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$, 25 °C): $\delta$ = 8.1, 13.5, 26.0, 33.4, 59.3, 59.8, 100.3, 127.9, 128.1, 129.3, 135.2, 148.2, 152.8, 165.4 ppm. HRMS: calcd. for $C_{16}O_3N_2H_{20}$ [M]$^+$ 288.1474; found [M + H]$^+$ 289.1550.

**Ethyl 1-Methyl-6-phenyl-4-*n*-propyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (16n):** Yield 75%. White solid. $R_f$ = 0.5 (60% ethyl acetate/hexane). IR (KBr): $\tilde{\nu}_{max}$ = 1680, 1610, 1560, 3011, 3283 cm$^{-1}$. $^1$H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta$ = 0.87–0.96 (m, 6 H, 4-$CH_2CH_2CH_3$, ester-$CH_3$), 1.42–1.73 (m, 2 H, $CH_2$ in 4-$C_3H_7$), 1.75–1.78 (m, 2 H, $CH_2$ in 4-$C_3H_7$), 3.04 (s, 3 H, N-$CH_3$), 3.92 (q, $J$ = 6.9 Hz, 2 H, $OCH_2$), 4.41 (t, $J$ = 5.1 Hz, 1 H, 4-H), 6.33 (br., 1 H, NH, $D_2O$ exchangeable), 7.29–7.40 (m, 5 H, 6-$C_6H_5$) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$, 25 °C): $\delta$ = 13.5, 14.1, 17.4, 33.6, 33.7, 35.6, 58.5, 59.8, 101.2, 127.9, 128.0, 128.1, 129.4, 135.2, 147.9, 152.7, 165.4 ppm. HRMS: calcd. for $C_{17}O_3N_2H_{22}$ [M]$^+$ 302.1630; found [M + H]$^+$ 303.1711.

**Ethyl 1-Methyl-6-phenyl-4-*n*-butyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (16o):** Yield 78%. White solid. $R_f$ = 0.5 (60% ethyl acetate/hexane). IR (KBr): $\tilde{\nu}_{max}$ = 1672, 1633, 1581, 3032, 3272 cm$^{-1}$. $^1$H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta$ = 0.85–0.94 (m, 6 H, 4-$CH_2CH_2CH_2CH_3$, ester-$CH_3$), 1.33–1.46 (m, 4 H, 2 $CH_2$ in 4-$C_4H_9$), 1.73–1.81 (m, 2 H, $CH_2$ in 4-$C_4H_9$), 3.04 (s, 3 H, N-$CH_3$), 3.92 (q, $J$ = 6.7 Hz, 2 H, $OCH_2$), 4.42 (t, $J$ = 4.9 Hz, 1 H, 4-H), 6.34 (br., 1 H, NH, $D_2O$ exchangeable), 7.25–7.40 (m, 5 H, 6-$C_6H_5$) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$, 25 °C): $\delta$ = 13.5, 14.0, 22.8, 26.2, 33.0, 33.6, 58.5, 59.8, 101.0, 128.0, 128.1, 129.4, 135.2, 147.9, 152.7, 165.4 ppm. HRMS: calcd. for $C_{18}O_3N_2H_{24}$ [M]$^+$ 316.1787; found [M + H]$^+$ 317.1863.

**General Procedure for the Synthesis of 4-Phenyl-Substituted Alkyl 1,6-Dimethyl- or 1-Methyl-6-phenyl-2-oxo-1,2,3,4-tetrahydropyrimidin-5-carboxylates (16j–l,p):** Diethylzinc (0.1 mL, 3.0 mmol) was added dropwise under an inert atmosphere to a stirred solution of triphenylborane (0.12 g, 1.0 mmol) in dry toluene (15 mL) at ambient temperature. The resulting mixture was stirred for 30 min and then transferred through a syringe to a solution of **15a–d** (0.1 g, 1.0 mmol) in dry toluene under an inert atmosphere at 0 °C. The reaction mixture was stirred for 48 h. Upon completion of the reaction (TLC), it was quenched with a saturated aqueous ammonium chloride solution and extracted with dichloromethane (2× 20 mL). After removing dichloromethane under vacuum, the crude product was purified by column chromatography using ethyl acetate/hexane mixtures as eluent to obtain pure **16j–l,p**.

**Ethyl 1,6-Dimethyl-4-phenyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (16j):** Yield 70%. White solid. $R_f$ = 0.5 (60% ethyl acetate/hexane). IR (KBr): $\tilde{\nu}_{max}$ = 1695, 1616, 1579, 3014, 3269 cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$, 25 °C): $\delta$ = 1.86 (t, $J$ = 7.14 Hz, 3 H, $CH_3$), 2.51 (s, 3 H, 6-$CH_3$), 3.23 (s, 3 H, N-$CH_3$), 4.10 (q, $J$ = 7.12 Hz, 2 H, $OCH_2$), 5.38 (d, $J$ = 3.12 Hz, 1 H, 4-H), 5.59 (br., 1 H, NH, $D_2O$ exchangeable), 7.22–7.32 (m, 5 H, 4-$C_6H_5$) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$, 25 °C): $\delta$ = 14.1, 16.5, 30.3, 53.7, 60.1, 104.2, 126.2, 127.7, 128.6, 143.4, 149.4, 154.1, 166.1 ppm. HRMS: calcd. for $C_{15}O_3N_2H_{18}$ [M]$^+$ 274.1317; found [M + Na]$^+$ 297.1211.

**Methyl 1,6-Dimethyl-4-phenyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (16k):** Yield 68%. White solid. $R_f$ = 0.5 (60% ethyl acetate/hexane). IR (KBr): $\tilde{\nu}_{max}$ = 1683, 1628, 1540, 3031, 3275 cm$^{-1}$. $^1$H NMR (300 MHz, $CDCl_3$ + [$D_6$]DMSO, 25 °C): $\delta$ = 2.5 (s, 3 H, 6-$CH_3$), 3.16 (s, 3 H, N-$CH_3$), 3.61 (s, 3 H, $OCH_3$), 5.27 (d, $J$ = 3.84 Hz, 1 H, 4-H), 7.20–7.30 (m, 5 H, 4-$C_6H_5$), 7.74 (d, $J$ = 3.76 Hz, 1 H, NH, $D_2O$ exchangeable) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$ + [$D_6$]DMSO, 25 °C): $\delta$ = 16.0, 29.6, 50.7, 52.4, 102.8, 125.8, 126.9, 128, 143.4, 149.7, 153.4, 166.0 ppm. HRMS: calcd. for $C_{14}O_3N_2H_{16}$ [M]$^+$ 260.1161; found [M + Na]$^+$ 283.1064.

**Isopropyl 1,6-Dimethyl-4-phenyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (16l):** Yield 63%. White solid. $R_f$ = 0.5 (60% ethyl acetate/hexane). IR (KBr): $\tilde{\nu}_{max}$ = 1681, 1634, 1579, 3066, 3269 cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$, 25 °C): $\delta$ = 1.05 (d, $J$ = 6.24 Hz, 3 H, $CH_3$), 1.22 (d, $J$ = 6.24 Hz, 3 H, $CH_3$), 2.51 (s, 3 H, 6-$CH_3$), 3.23 (s, 3 H, N-$CH_3$), 4.94–5.00 (m, 1 H, OCH), 5.37 (d, $J$ = 2.92 Hz, 1 H, 4-H), 5.63 (br., 1 H, NH, $D_2O$ exchangeable), 7.22–7.31 (m, 5 H, 4-$C_6H_5$) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$, 25 °C): $\delta$ = 16.4, 21.6, 22.0, 30.2, 53.7, 67.5, 104.5, 126.2, 127.6, 128.5, 143.5, 149.0, 154.1, 165.6 ppm. HRMS: calcd. for $C_{16}O_3N_2H_{20}$ [M]$^+$ 288.1474; found [M + Na]$^+$ 311.1370.

**Ethyl 1-Methyl-4,6-diphenyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (16p):** Yield 72%. White solid. $R_f$ = 0.5 (60% ethyl acetate/hexane). IR (KBr): $\tilde{\nu}_{max}$ = 1685, 1611, 1550, 3014, 3269 cm$^{-1}$. $^1$H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta$ = 0.77 (t, $J$ = 7.2 Hz, 3 H, ester-$C_2H_5$), 2.81 (s, 3 H, N-$CH_3$), 3.73–3.83 (m, 2 H, $OCH_2$), 5.48–5.51 (m, 2 H, 4-H, NH, $D_2O$ exchangeable), 7.21–7.46 (m, 10 H, 4-$C_6H_5$, 6-$C_6H_5$) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$, 25 °C): $\delta$ = 13.4, 32.3, 54.3, 59.8, 105.4, 126.2, 127.3, 128.1, 128.4, 128.7, 134.8, 143.2, 150.3, 154.0, 165.2 ppm. HRMS: calcd. for $C_{20}O_3N_2H_{20}$ [M]$^+$ 336.1474; found [M + H]$^+$ 337.1558.

**Supporting Information** (see footnote on the first page of this article): Experimental procedure for the oxidation of **14a–d** to **15a–d**, $^1$H and $^{13}$C NMR spectra of compounds **16a–p**.

## Acknowledgments

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[1] a) K. Singh, K. Singh, in: *Advances in Heterocyclic Chemistry* (Ed.: A. R. Katritzky), Academic Press, USA, **2012**, vol. 105, p. 223–308; b) K. Singh, D. Arora, K. Singh, S. Singh, *Mini-Rev. Med. Chem.* **2009**, *9*, 95–106; c) C. O. Kappe, *Acc. Chem. Res.* **2000**, *33*, 879–888; d) C. O. Kappe, *Eur. J. Med. Chem.* **2000**, *35*, 1043–1052.

[2] a) G. C. Rovnyak, K. S. Atwal, A. Hedberg, S. D. Kimball, S. Moreland, J. Z. Gougoutas, B. C. O'Reilly, J. Schwartz, M. F. Malley, *J. Med. Chem.* **1992**, *35*, 3254–3263; b) K. S. Atwal, B. N. Swanson, S. E. Unger, D. M. Floyd, S. Moreland, A. Hedberg, B. C. O'Reilly, *J. Med. Chem.* **1991**, *34*, 806–811; c) K. S. Atwal, G. C. Rovnyak, S. D. Kimball, D. M. Floyd, S. Moreland, B. N. Swanson, J. Z. Gougoutas, J. Schwartz, K. M. Smillie, M. F. Malley, *J. Med. Chem.* **1990**, *33*, 2629–2635.

  

[3] P. Bignelli, *Gazz. Chim. Ital.* **1893**, *23*, 360–416.
[4] S.-W. Yang, T.-M. Chan, S. A. Pomponi, G. Chen, A. E. Wright, M. Patel, V. Gullo, B. Pramanik, M. J. Chu, *J. Antibiot.* **2003**, *56*, 970–972.
[5] a) S. DeBonis, J. P. Simorre, I. Crevel, L. Lebeau, D. A. Skoufias, A. Blangy, C. Ebel, P. Gans, R. Cross, D. D. Hackney, R. H. Wade, F. Kozielski, *Biochemistry* **2003**, *42*, 338–349; b) Z. Maliga, T. M. Kapoor, T. J. Mitchison, *Chem. Biol.* **2002**, *9*, 989–996; c) S. J. Haggarty, T. U. Mayer, D. T. Miyamoto, R. Fathi, R. W. King, T. J. Mitchison, S. L. Schreiber, *Chem. Biol.* **2000**, *7*, 275–286; d) T. U. Mayer, T. M. Kapoor, S. J. Haggarty, R. W. King, S. L. Schreiber, T. J. Mitchison, *Science* **1999**, *286*, 971–974.
[6] J. C. Barrow, P. G. Nantermet, H. G. Selnick, K. L. Glass, K. E. Rittle, K. F. Gilbert, T. G. Steele, C. F. Homnick, R. M. Freidinger, R. W. Ransom, P. Kling, D. Reiss, T. P. Broten, T. W. Schorn, R. S. L. Chang, S. S. O'Malley, T. V. Olah, J. D. Ellis, A. Barrish, K. Kassahun, P. Leppert, D. Nagarathnam, C. Forray, *J. Med. Chem.* **2000**, *43*, 2703–2718.
[7] a) A. Rajack, K. Yuvaraju, Ch. Praveen, Y. L. N. Murthy, *J. Mol. Catal. A* **2013**, *370*, 197–204; b) H. Kefayati, F. Asghari, R. Khanjanian, *J. Mol. Liq.* **2012**, *172*, 147–151; c) K. K. Pasunooti, H. Chai, C. N. Jensen, B. K. Gortiyala, S. Wang, *Tetrahedron Lett.* **2011**, *52*, 80–84; d) Q. Wang, W. Pei, *Synth. Commun.* **2010**, *40*, 1209–1215; e) S. Chitra, K. Pandiarajan, *Tetrahedron Lett.* **2009**, *50*, 2222–2224; f) K. Singh, D. Arora, S. Singh, *Tetrahedron Lett.* **2006**, *47*, 4205–4207; g) H. A. Stefani, C. B. Oliviera, R. B. Almeida, C. M. P. Pereira, R. C. Braga, R. Cella, V. C. Borges, L. Savegnago, C. W. Nogueira, *Eur. J. Med. Chem.* **2006**, *41*, 513–518; h) D. Dallinger, A. Stadler, C. O. Kappe, *Pure Appl. Chem.* **2004**, *76*, 1017–1024; i) A. Shaabani, A. Bazgir, F. Teimouri, *Tetrahedron Lett.* **2003**, *44*, 857–859; j) C. O. Kappe, *QSAR Comb. Sci.* **2003**, *22*, 630–645; k) C. O. Kappe, *Eur. J. Med. Chem.* **2000**, *35*, 1043–1052; l) P. Wipf, A. Cunningham, *Tetrahedron Lett.* **1995**, *36*, 7819–7822.
[8] a) K. Singh, D. Arora, D. Falkowski, Q. Liu, R. S. Moreland, *Eur. J. Org. Chem.* **2009**, 3258–3264; b) K. Singh, D. Arora, S. Singh, *Tetrahedron Lett.* **2007**, *48*, 1349–1352.
[9] K. Singh, S. Singh, A. Mahajan, *J. Org. Chem.* **2005**, *70*, 6114–6117.
[10] K. Singh, S. Singh, *Tetrahedron* **2008**, *64*, 11718–11723.
[11] a) K. Singh, H. Kaur, K. Chibale, J. Balzarini, S. Little, P. V. Bharatam, *Eur. J. Med. Chem.* **2012**, *52*, 82–97; b) K. Singh, K. Singh, B. Wan, S. Franzblau, K. Chibale, J. Balzarini, *Eur. J. Med. Chem.* **2011**, *46*, 2290–2294; c) K. Singh, D. Arora, J. Balzarini, *Tetrahedron* **2010**, *66*, 8175–8180.
[12] a) K. Singh, K. Singh, D. M. Trappanese, R. S. Moreland, *Eur. J. Med. Chem.* **2012**, *54*, 397–402; b) K. Singh, K. Singh, *Tetrahedron* **2009**, *65*, 10395–10399; c) K. Singh, S. Singh, *Tetrahedron Lett.* **2006**, *47*, 8143–8146; d) K. Singh, K. Singh, H. Kaur, *Tetrahedron* **2012**, *68*, 6169–6176; e) K. Singh, S. Singh, *Tetrahedron* **2009**, *65*, 4106–4112; f) P. A. Evans, J. Qin, J. E. Robinson, B. Bazin, *Angew. Chem.* **2007**, *119*, 7561; *Angew. Chem. Int. Ed.* **2007**, *46*, 7417–7419; g) A. Dondoni, A. Massi, A. Sabbatini, *Tetrahedron Lett.* **2002**, *43*, 5913–5916.
[13] K. Singh, D. Arora, E. Poremsky, J. Lowery, R. S. Moreland, *Eur. J. Med. Chem.* **2009**, *44*, 1997–2001.
[14] a) D.-Z. Xu, H. Li, Y. Wang, *Tetrahedron* **2012**, *68*, 7867–7872; b) F. Xu, D. Huang, X. Lin, Y. Wang, *Org. Biomol. Chem.* **2012**, *10*, 4467–4470; c) S. Saha, N. J. Moorthy, *J. Org. Chem.* **2011**, *76*, 396–402; d) Y.-Y. Wu, Z. Chai, X.-Y. Liu, G. Zhao, S.-W. Wang, *Eur. J. Org. Chem.* **2009**, 904–911; e) Y. Wang, H. Yang, J. Yu, Z. Miao, R. Chen, *Adv. Synth. Catal.* **2009**, *351*, 3057–3062; f) L.-Z. Gong, X.-H. Chen, X.-Y. Xu, *Chem. Eur. J.* **2007**, *13*, 8920–8926; g) X.-H. Chen, X.-Y. Xu, H. Liu, L.-F. Cun, L.-Z. Gong, *J. Am. Chem. Soc.* **2006**, *128*, 14802–14803; h) Y. Huang, F. Yang, C. Zhu, *J. Am. Chem. Soc.* **2005**, *127*, 16386–16387.
[15] G. C. Rovnyak, S. D. Kimball, B. Beyer, G. Cucinotta, J. D. DiMarco, J. Gougoutas, A. Hedberg, M. Malley, J. P. McCarthy, R. Zhang, S. Moreland, *J. Med. Chem.* **1995**, *38*, 119–129.
[16] a) J. Christoffers, G. Koripelly, A. Rosiak, M. Rossle, *Synthesis* **2007**, 1279–1300; b) F. Lopez, A. J. Minnaard, B. L. Feringa, *Acc. Chem. Res.* **2006**, *39*, 179–188; c) F. F. Kneisel, M. Dochnahl, P. Knochel, *Angew. Chem.* **2004**, *116*, 1032; *Angew. Chem. Int. Ed.* **2004**, *43*, 1017–1021; d) T. Soeta, K. Nagai, H. Fujihara, M. Kuriyama, K. Tomioka, *J. Org. Chem.* **2003**, *68*, 9723–9727; e) A. Alexakis, C. Benhaim, *Eur. J. Org. Chem.* **2002**, 3221–3236; f) A. Boudier, L. O. Bromm, M. Lotz, P. Knochel, *Angew. Chem.* **2000**, *112*, 4584; *Angew. Chem. Int. Ed.* **2000**, *39*, 4414–4435; g) P. Knochel, J. J. A. Perea, P. Jones, *Tetrahedron* **1998**, *54*, 8275–8319; h) M. Nakamura, E. Nakamura, *J. Synth. Org. Chem. Jpn.* **1998**, *56*, 632–644; i) P. Knochel, *Synlett* **1995**, 393–403; j) P. Knochel, R. D. Singer, *Chem. Rev.* **1993**, *93*, 2117–2188.
[17] a) T. Nishimura, Y. Yasuhara, T. Hayashi, *Org. Lett.* **2006**, *8*, 979–981; b) S. Basra, M. Fennie, M. Kozlowski, *Org. Lett.* **2006**, *8*, 2659–2661; c) J. R. Porter, J. F. Traverse, A. H. Hoveyda, M. L. Snapper, *J. Am. Chem. Soc.* **2001**, *123*, 984–985; d) J. R. Porter, J. F. Traverse, A. H. Hoveyda, M. L. Snapper, *J. Am. Chem. Soc.* **2001**, *123*, 10409–10410.
[18] a) K.-I. Yamada, K. Tomioka, *Chem. Rev.* **2008**, *108*, 2874–2886; b) R. Bloch, *Chem. Rev.* **1998**, *98*, 1407–1438.
[19] M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G. A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H. P. Hratchian, A. F. Izmaylov, J. Bloino, G. Zheng, J. L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, J. A. Montgomery Jr., J. E. Peralta, F. Ogliaro, M. Bearpark, J. J. Heyd, E. Brothers, K. N. Kudin, V. N. Staroverov, T. Keith, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, N. Rega, J. M. Millam, M. Klene, J. E. Knox, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, R. L. Martin, K. Morokuma, V. G. Zakrzewski, G. A. Voth, P. Salvador, J. J. Dannenberg, S. Dapprich, A. D. Daniels, O. Farkas, J. B. Foresman, J. V. Ortiz, J. Cioslowski, D. J. Fox, *Gaussian 09*, revision B.01, Gaussian, Inc., Wallingford, CT, **2010**.
[20] K. Singh, J. Singh, P. K. Deb, H. Singh, *Tetrahedron* **1999**, *55*, 12873–12880.
[21] P. Shanmugam, P. T. Perumal, *Tetrahedron* **2006**, *62*, 9726–9734.
[22] K. Singh, K. Singh, *Aust. J. Chem.* **2008**, *61*, 910–913.
[23] C. R. Noller, *Org. Synth.* **1943**, *Coll. Vol. II*, 184.
[24] C. Bolm, F. Schmidt, L. Zani, *Tetrahedron: Asymmetry* **2005**, *16*, 1367–1376.
[25] A. I. Meyers, T. Oppenlander, *J. Chem. Soc., Chem. Commun.* **1986**, 920–921.
[26] D. L. Comins, A. H. Abdullah, *J. Org. Chem.* **1982**, *47*, 4315–4319.
[27] R. D. Smith, H. E. Simmons, *Org. Synth., Coll.* **1973**, *5*, 855.

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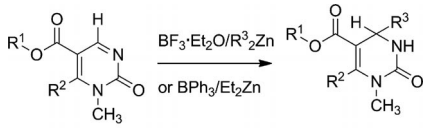
An efficacious diversification of the key C-4 position of 2-oxo-1,2-dihydropyrimidine-5-carboxylates has been achieved through the addition of organozinc reagents.




$R^1$ = alkyl; $R^2$ = $CH_3$, $C_6H_5$; $R^3$ = alkyl, $C_6H_5$

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Highly Regioselective Addition of Organozinc Reagents to 2-Oxo-1,2-dihydropyrimidine-5-carboxylates Activated by $BF_3$·$OEt_2$: Synthesis of 2-Oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylates

**Keywords:** Nitrogen heterocycles / Nucleobases / Zinc / Lewis acids / Imines

  