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An efficacious protocol for C-4 substituted 3,4-dihydropyrimidinones. Synthesis and calcium channel binding studies

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Abstract

Ethyl 1,2-dihydro-1,6-dimethyl/6-methyl-2-oxopyrimidine-5-carboxylates react with C-nucleophiles as well as anion of enantiopure chiral auxiliary (1*R*,2*S*,5*R*)-(–)-methyl (*S*)-*p*-toluenesulfonate to afford C-4 substituted and enantiopure congeners of medicinally potent Biginelli dihydropyrimidinones. The calcium channel blocking activity of some of the compounds was evaluated and compared with nifedipine for their ability to relax a membrane depolarization induced contraction.

Keywords

Biginelli reaction; lithiation; regioselective addition; chiral sulfoxide; vascular smooth muscles

Introduction

The scaffold decoration of bioactive molecules represents one of the most vibrant research areas in organic chemistry and has a rich history within the realm of fragment-based drug design. The Biginelli 3,4-dihydropyrimidin-2(1*H*)-ones (DHPMs) are known for more than a century.^[1] These compounds and their appropriately functionalized derivatives have interesting pharmacological profiles such as antihypertensive agent **1–2**,^[2] mitotic kinesin inhibitors **3**,^[3] α_1 -adrenergic receptor antagonists **4**,^[4] and hepatitis B virus replication inhibitors.^[5]

The synthesis and scaffold decoration of DHPM core has played important role in the total synthesis of polycyclic guanidine containing marine alkaloids such as batzelladine A.^[6] These are also common moieties in some of the most bioactive natural products including dehydrocrambine A **5** and Sch575948 **6**^[7] which are inhibitor of HIV gp-120-CD4 interaction. Due to their diverse pharmacological profile, synthetic investigations on DHPMs have received extensive attention by both synthetic organic chemists as well as

medicinal chemists. Synthetic approaches to DHPMs can be divided into two major strategies.

While the Multi (three) component reactions (Figure 1) for the construction of Biginelli libraries *via* solution as well as solid phase strategies are amenable to a high throughput or combinatorial format, the post-Biginelli condensation scaffold decoration tools are prized for appending tailor-made fragments at all possible (N-1, C-2, N-3, C-4, C-5 and C-6) diversity oriented centres^[8] from simple starting materials. Using the latter tools, we have previously described, both racemic as well as diastereoselective methods for DHPM synthesis.^[9]

In a preliminary communication,^[10] we recently reported realization of a nucleophilic addition sequence for regioselective incorporation of substituents at C-4 position of DHPMs, and herein, we provide a full account of our development of this process and its further extension to asymmetric synthesis. In addition, we describe highly regioselective addition reactions of a number of Grignard reagents to synthesize DHPM derivatives, which in fact, are formed with greater efficiency. Finally we report calcium channel blocking studies of selected compounds to further extend the existing understanding on structure-activity relationships.

Results and Discussion

The current understanding of calcium channel modulation (antagonist *vs* agonist activity) of DHPM derivatives, like 1,4-dihydropyridine drugs such as nifedipine, points to the nature (size, polarity etc.) of the substituent at C-4 as well as the absolute configuration at C-4 position.^[11] Different enantiomers of some DHPMs are found to possess opposing biological effects.^[11] While the approach to C-4 elaborated DHPMs using 3-component Biginelli condensation and its variants thus far has been mainly through the use of aldehydes,^[12] the C-4 addition method proved to be a highly useful and dependable method

with the added advantage that it proceeds with remarkably high regio- as well as chemoselectivity and does not require any chemical activation.

The synthetic route of the current approach starts with the synthesis of C-4 unsubstituted ethyl 1,2,3,4-tetrahydro-1,6-dimethyl-2-oxopyrimidine-5-carboxylate **7a** and ethyl 1,2,3,4-tetrahydro-6-methyl-2-oxopyrimidine-5-carboxylate **7b** for which we have relied on using formyl equivalent: 1,3-oxazinane derivative^[13] rather than direct use of formaldehyde. **7a,b** on further oxidation with nitric acid^[14] readily transformed to ethyl 1,2-dihydro-1,6-dimethyl-2-oxopyrimidine-5-carboxylate **8a** and ethyl 1,2-dihydro-6-methyl-2-oxopyrimidine-5-carboxylate **8b** (Scheme 1). Oxidation of **7** to **8** has also been successfully achieved by us, recently using pyridinium chlorochromate (PCC).^[15] The addition of stabilized carbanions, aryllithium and heterocyclic anions on **8a** and **8b** furnished exclusively C-4 elaborated DHPM derivatives and made available those DHPMs which are otherwise not accessible through traditional methods employing aldehydes owing to their non-availability and operational difficulties with aliphatic counterparts. Therefore the reactions in the present case represent addition of only carbon nucleophiles. Further, whereas the addition reactions of pyridines with aryl lithium^[16] reagents required activation of pyridine as 1-alkoxycarbonyl derivative, the regioselectivity of the reactions of 1-acylpyridinium salts with Grignard reagents^[17], was additionally influenced by the structures of the Grignard reagent and the 1-acyl group. However, the addition reactions of pyrimidin-2(1*H*)-ones **7** with carbon nucleophiles proceeded regioselectively without activation of the pyrimidinone substrates.

Addition of carbon nucleophiles to pyrimidine-2(1*H*)-ones **8**. Formation of C-4 elaborated DHPM derivatives

Treatment of appropriate DHPM derivative **8a/8b** with intense yellow coloured dianions of ethyl/methyl acetoacetate,^[18] generated using NaH and *n*-BuLi (2.5 equiv. each), in sequence, in anhydrous THF at low temperature (Table 1), under a blanket of nitrogen gas, after extractive workup (*vide experimental*) furnished C-4 substituted **9** and **10** depicting a clean addition of carbanion at C-4 position. No other product arising from addition at C-5 ester or any other position was detected pointing to the observed high regio- and chemoselectivity of the transformation. Likewise reactions of the anions of acetone,^[19] acetonitrile,^[19] acetophenone,^[19] methyl phenyl sulfone,^[20] thiophene^[21] and furan,^[22] generated using standard methods furnished corresponding C-4 elaborated DHPM derivatives in a synthetically useful manner. Only in the reactions of thiophene and furan, products of ester displacement were detected (¹H NMR spectrum) only in traces. Similar of phenyl lithium^[23] proceeded with complete regioselectivity to furnish C-4 substituted DHPM derivative **9g**. All the products were characterized by IR, ¹H NMR, ¹³C NMR, MS and elemental analysis.

Addition of Grignard reagents to pyrimidine-2(1*H*)-ones **8**. Formation of DHPM derivatives bearing aliphatic chains at C-4

While the DHPM derivatives listed in Table 1, particularly entries 6–13, were designed to evaluate their calcium channel blocking properties, entries 1–5 served probing the effect of aliphatic functionalized chains at C-4 on the calcium channel blocking activity. The importance of appending alkyl chains at C-4 position can also be gauged from the fact that naturally occurring marine alkaloids such as **5** and **6** have long aliphatic chains (C₅ and C₁₁, respectively) appended at C-4. To append such chains through the use of aliphatic aldehydes, under acid catalyzed conditions of traditional Biginelli condensation reaction are prone to side reactions of aldehydes owing to their vulnerability.^[8b] Herein we describe a useful protocol for appending long aliphatic chains by the use of above methodology using Grignard reagents^[24] as nucleophiles and the examples mentioned in Table 2 (entries 7, 9)

demonstrate a useful protocol for appending long chains at C-4, a synthetic sequence of considerable importance in connection with the total synthesis of **5/6** and their analogues.

Treatment of **8a** and **8b** with freshly prepared Grignard reagents^[24] of aliphatic alkyl groups with carbon chain lengths varying from C₁₋₅, C₁₀ and C₁₁ at -78 °C under the atmosphere of nitrogen gas furnished the corresponding DHPMs (Table 2, entries **1-9**) in good yields. Similar reaction with allyl magnesium bromide furnished C-4 addition product **12i** in 65% yield after column chromatography. The reaction of phenylmagnesium bromide with **8b** leading to the exclusive formation of **12j** was very facile as no side product was detected.

Addition of monoanion of *R* (+)-Methyl *p*-tolyl sulfoxide to **8b**. Synthesis of (*R*)- and (*S*)-enantiomers

Access to diastereomerically/enantiomerically pure DHPM derivatives utilizing the tools of asymmetric synthesis is of general current interest and has been a formidable task. The literature records on the use of resolution methods employing fractional crystallization of the diastereomeric salts^[25] or through the use of chiral aldehydes.^[26] Appending chiral auxiliaries especially at N-3 position to resolve diastereomers of DHPMs has also been found useful to enantiomerically enriched DHPM derivatives after removal of the chiral auxiliary.^[27] Analytical separation through the use of designer chiral stationary phases in chiral HPLC has allowed useful and efficient separation of enantiomers.^[28] Biocatalytic as well as chemical catalytic methods employing proteases,^[29] Lewis acids in the presence of chiral ligands,^[30] enantioselective organocatalytic Biginelli reaction^[31a,b,c,d] or cinchona alkaloid-catalyzed Mannich reaction,^[31e,f,g] have also been advantageously employed.

Chiral sulfoxides have been used in numerous enantioselective transformations of synthetic and biological interest.^[32] To further expand the scope of the C-4 elaboration methodology, we sought to employ chiral sulfoxides for the enantioselective synthesis of DHPMs.^[33] Lithiation of enantiomerically pure *R* (+)-methyl *p*-tolyl sulfoxide **13** was achieved with LDA using standard method. Addition of this anion to **8b** resulted in the smooth formation of diastereomeric mixture comprising of **14** {[α _D²⁵ +10 (methanol, *c* = 0.2)} and **15** {[α _D²⁵ +185 (methanol, *c* = 0.2)} in the ratio of 80:20, determined from the ¹H NMR spectrum of the crude reaction mixture (Scheme 2). The major diastereomer **14** separated out from the hot methanol solution and was recrystallized to obtain analytically pure sample. The remaining mixture was resolved by column chromatography to obtain additional **14** and the minor diastereomer **15**.

The assignment of the absolute configuration at C-4 position of a series of DHPM derivatives has been based on the combination of enantioselective HPLC and circular dichroism (CD) spectroscopy,^[28b] through correlation with DHPM derivatives of known configuration. A correlation of specific optical rotation has also been used for predicting the configuration at C-4 bearing aryl substituents at C-4.^[30a] Since the chiral auxiliary used in this reaction has (*R*)-configuration at the sulfur atom, the two diastereomers **14** and **15** have been assigned, (*R*) and (*S*) configuration, respectively at C-4. The assignment of absolute configuration of the major diastereomer **14** was unambiguously attested from the single crystal x-ray structure determination (Figure 2).

Desulfurisation of the major diastereomer **14** using Raney Ni in methanol led to corresponding optically active (*S*) enantiomer **16** {[α _D²⁵ -205.00 (methanol, *c* = 0.2)} The purity of **16** has also been attested by recording ¹H NMR in the presence of chiral shift reagent europium tris[3-heptafluoropropylhydroxymethylene]-(+)-camphorate] (Eu(hfc)₃). Similarly, desulfurisation of the minor diastereomer **15** with Raney Ni furnished (*R*) enantiomer **17** {[α _D²⁵ +160 (methanol, *c* = 0.2)}. The C-4 (*S*) configuration of the major

enantiomer was also corroborated with the CD spectra (Figure 3) of **16** with that of a 4-methyl DHPM of known absolute configuration.^[34]

Further, in view of the exceptional stabilization influence of the sulfoxide sulfur to the carbanions, synthesis of a number of derivatives of **14** could be envisaged.

Biological results and discussion

Some of the newly synthesized compounds were screened for their calcium channel blocking activity based on their ability to relax a membrane depolarization induced contraction of vascular smooth muscle. Swine carotid arteries were obtained from a local slaughterhouse and transported to the laboratory in an ice-cold physiological salt solution (PSS) buffered (pH 7.4) with 3-[N-morpholino] propane sulfonic acid (MOPS). The PSS contained, in mM: 140 NaCl, 4.7 KCl, 1.2 MgSO₄, 1.6 CaCl₂, 1.2 Na₂HPO₄, MOPS, 5 D-glucose, and 0.02 Na₂-ethylenediaminetetraacetic acid (EDTA). Arteries were cleaned of connective tissue, and then dissected free of both intima and adventitia leaving a thin medial layer for experimentation. Intact medial strips of swine carotid artery (7 × 0.7 mm) were suspended between a Grass FT.03 force transducer and a stationary clip in water jacketed organ baths. The strips were equilibrated in PSS at 37° C, pH 7.4 and bubbled with 100% O₂ for 90 – 120 min. A passive force of ~2 g was applied to all tissues. This passive force sets the muscle at a length that approximates L₀, the length at which maximal active force is generated. During the equilibration period, tissues were maximally contracted with 110 mM KCl (equimolar substitution for NaCl) several times until similar levels of force were attained.

The equilibrated vascular strips were contracted with 110 mM KCl containing PSS, allowed to achieve a stable level of force and then subjected to the cumulative addition of calcium channel blocker (1 μM – 30 mM) or DMSO as a vehicle control. Data are presented (Figure 4) as a percent of the initial maximal response to 110 mM KCl at each dose of compound.

The calcium channel blockers were compared against nifedipine for their ability to relax a membrane depolarization induced contraction which is almost exclusively dependent on the influx of extracellular calcium.^[35] The novel compounds and nifedipine were tested across a concentration range of 1 μM to 30 mM. Nifedipine completely relaxed the KCl-induced contraction with an IC₅₀ in the 10 μM range. In contrast these compounds maximally relaxed the KCl- induced contractions by only 40% with IC₅₀s ranging from 100–300 μM (Figure 4).

Conclusions

In summary, inspired by the biological potential of a number of dihydropyrimidinone based natural products, we have developed method for highly regio- and chemoselective synthesis of C-4 elaborated DHPMs. This approach allows incorporation of aliphatic, aromatic as well as heterocyclic substituents with possibility of further synthetic transformations on the C-4 substituents. Also this approach was extended to synthesize both enantiomers of DHPM through the use of optically pure sulfoxide carbanion. Finally DHPMs with substitutional variation at C-4 were tested for their ability to relax a membrane depolarization induced contraction which is almost exclusively dependent on the influx of extracellular calcium. Long aliphatic chains appended at C-4 don't seem to be particularly useful for calcium channel blocking activity in so far as their comparison with C-4 aryl derivatives of DHPMs is concerned.

There is considerable variability in the magnitude of the specific rotation of the minor enantiomer, which can presumably be attributed to purity.

Experimental Section

Freshly prepared *n*-butyl lithium (2.0 N in hexanes), phenyllithium, LDA, and Grignard reagents were employed. Tetrahydrofuran and diethyl ether were dried (Na-benzophenone ketyl) under nitrogen and drawn with hypodermic glass syringes. All liquid reagents were dried/purified following recommended drying agents and/or distilled over 4 Å molecular sieves. Reactions were run under a blanket of dry nitrogen gas in a single necked RBF, sealed with rubber septum (Aldrich). The reagents were introduced through hypodermic syringes and/or cannula. The low temperature was achieved by using slush of liquid nitrogen with appropriate solvent or alternatively using dry ice. Pre-coated aluminium TLC plates (60 F₂₅₄, 0.2 mm) were used for TLC monitoring of the reactions. The compounds were purified using flash chromatography using silica gel (60–120 mesh) and mixtures of ethyl acetate/hexane as eluent.

Melting points were determined by open capillaries and are uncorrected. ¹H and ¹³C NMR spectra were recorded on JEOL FT-NMR AL-300MHz spectrometer using TMS as an internal standard. The mass spectra were recorded on Esquire 3000-00037 mass spectrometer. The elemental analysis was done on Thermo Flash EA 112. Analyses indicated by the symbols of the elements were within ±0.4% of the theoretical values. The optical rotation was recorded on Atago (AP-100), digital polarimeter at 25 °C. The CD spectra were recorded on Applied Photophysics Chirascan Circular Dichroism Spectrometer with Stop Flow.

Typical procedure for the synthesis of 8a–b

Method A—To a stirred aqueous solution of nitric acid (40% v/v, 6.5 mL), maintained at 0 °C, powdered DHPM **7a** or **7b** (4.0 mmol) was added, portion-wise during 5–10 minutes. The reaction was stirred for an additional 5 minutes at the same low temperature, after which the mixture was allowed to warm to room temperature during 30 minutes. The mixture was poured onto crushed ice (10 g) and neutralized to pH 7.0 using solid potassium carbonate. The resulting aqueous solution was subsequently extracted with dichloromethane (3 × 30 mL), the organic layer dried over anhydrous sodium sulfate and evaporated to dryness under reduced pressure. The residual product was purified by recrystallization from ethanol to obtain appropriate **8**.

Method B—Alternatively, a solution of DHPM **7** (1.97 mmol) in DCM was stirred with PCC (5.90 mmol) (Aldrich) till the reaction was found to be completed (16–25 h, TLC). The reaction mixture filtered over a Celite bed to remove any suspension and the residue obtained after removal of the solvent was flash chromatographed to obtain corresponding pyrimidinone **8**.

Ethyl 1,2-dihydro-1,6-dimethyl-2-oxopyrimidine-5-carboxylate (8a)—Creamy solid. *R*_f = 0.5 (70% ethyl acetate/hexane). Yield = 80%. M.p. 212 °C (dichloromethane). IR (KBr): ν_{max} 1680, 1690 cm⁻¹. ¹H NMR (300 MHz, CDCl₃, 25 °C): δ = 1.37 (t, 3H, *J* = 7.2 Hz), 2.71 (s, 3H), 3.61 (s, 3H), 4.33 (q, 2H, *J* = 7.2 Hz), 8.39 (s, 1H) ppm. ¹³C NMR (75 MHz, CDCl₃, 25 °C): δ = 14.2, 26.1, 39.1, 61.2, 108.1, 152.6, 155.0, 163.1 and 176.6 ppm. C₉H₁₂N₂O₃: calcd. C, 55.10; H, 6.12; N, 14.28; found: C, 54.75; H, 6.01; N, 14.14. MS: *m/z* 219 (M+23).

Ethyl 1,2-dihydro-6-methyl-2-oxopyrimidine-5-carboxylate (8b)—Creamy solid. *R*_f = 0.5 (80% ethyl acetate/hexane). Yield = 75%. M.p. 210 °C (methanol). IR (KBr): ν_{max} 1675, 1680 cm⁻¹. ¹H NMR (300 MHz, DMSO-*d*₆, 25 °C): δ = 1.23 (t, 3H, *J* = 7.2 Hz), 2.49 (s, 3H), 4.18 (q, 2H, *J* = 7.2 Hz), 8.69 (s, 1H) ppm. ¹³C NMR (75 MHz, CDCl₃ and DMSO,

25 °C): = 14.0, 20.8, 60.4, 106.2, 152.6, 155.5, 163.5 and 165.0 ppm. C₈H₁₀N₂O₃: calcd. C, 52.74; H, 5.53; N, 15.38; found: C, 52.45; H, 5.42; N, 15.14. MS: *m/z* 205 (M+23).

Addition of carbon nucleophiles to pyrimidine-2(1*H*)-ones **8**. Formation of DHPM derivatives **9** and **10**. Typical procedure for the synthesis of **9a**

A solution of ethyl acetoacetate (6.37 mmol) in anhydrous THF (10 mL) under the blanket of dry nitrogen gas was cooled to 0 °C and treated with NaH (6.37 mmol). After the cessation of hydrogen gas, freshly prepared *n*-BuLi (2.0 N solution in hexanes) (6.37 mmol) was introduced through hypodermic syringe, at the same temperature and the reaction continued to stir at ambient temperature for additional half an hour whereupon an intense yellow coloured anion formed. The dianion suspension was cooled to –78 °C and quenched by the addition of **8a** (2.5 mmol) dissolved in THF (20 mL) with the help of cannula. The progress of the reaction was monitored with thin layer chromatography (TLC). After completion of reaction, it was quenched with cold saturated aqueous solution of NH₄Cl at low temperature. The organic phase was washed with brine and extracted with ethyl acetate. The extract was dried over anhydrous sodium sulfate and the mixture was concentrated under reduced pressure. The corresponding product **9a** was isolated in 73% yield after column chromatography using silica gel (60–120 mesh) and mixtures of ethyl acetate and hexane as eluent.

For the synthesis of various **9** and **10** (Table 1) appropriate **8a** and **8b** (Table 1) was similarly treated with anions of various carbon acids [read: carbon acid (equivalents of base used) product]: ethyl acetoacetate (2.0) **10a**; methyl acetoacetate (2.0) **10b**; acetone (2.5) **9b**; acetonitrile (1.5) **10c**; acetophenone (2.5) **9c**; methyl phenyl sulfone (2.5) **9d**; methyl phenyl sulfone (2.0) **10d**; thiophene (2.5) **9e**; thiophene (2.5) **10e**; furan (2.5) **9f**; furan (2.5) **10f** and PhLi (2.5 mmol) was used for **9g**.

Addition of Grignard reagents to pyrimidine-2(1*H*)-ones **8**. Formation of DHPM derivatives **11** and **12**. Typical procedure for the synthesis of **11a**

Grignard reagent^[24] (6.37 mmol) prepared using activated magnesium metal (6.37 mmol) and iodomethane (6.37 mmol) in anhydrous ether was transferred to a solution of **8a** (2.55 mmol) in anhydrous THF maintained at –78 °C under nitrogen atmosphere. Extractive work up from ethyl acetate and column chromatography furnished product **11a** in 92% yield. Similar reaction of **8** with other Grignard reagents (Table 2) furnished corresponding products **12a–j**.

Addition of monoanion of *R* (+)-Methyl *p*-tolyl sulfoxide to **8b**. Synthesis of DHPM diastereomers **14** and **15**

R (+)-Methyl *p*-tolyl sulfoxide was prepared from (1*R*,2*S*,5*R*)-(–)-menthyl (*S*)-*p*-toluenesulfinate following the procedure of Solladie.^[33] To a solution of diisopropylamine (8.35 mmol) in THF (2 mL), *n*-BuLi (8.25 mmol) was added dropwise at –78 °C, under a nitrogen atmosphere. The solution was allowed to warm to 0 °C and stirred for an additional 10 min. The solution was cooled to –78 °C and pre-cooled THF (25 mL at –78 °C) was added with stirring. *R* (+)-Methyl *p*-tolyl sulfoxide (5.50 mmol) dissolved in THF (10 mL) was then introduced via hypodermic syringe and the solution stirred for additional 10 min. to ensure complete deprotonation to monoanion. A solution of **8b** (2.75 mmol) dissolved in THF (20 mL) was introduced with the help of cannula. Reaction was warmed to room temperature and stirring was continued to complete the reaction (TLC), after which a saturated aqueous solution of NH₄Cl was introduced. The reaction was extracted with ethyl acetate (3 × 25 mL) treated in sequence with brine. The extracts were dried over anhydrous

Na₂SO₄ and the mixture concentrated under reduced pressure. The diastereomers **14** and **15** were resolved by crystallization (methanol) of the column chromatographed mixture.

(4R,SR)- Ethyl 1,2,3,4-tetrahydro-6-methyl-2-oxo-4-(p-tolylsulfonfylmethyl)pyrimidine-5-carboxylate (major diastereomer) (14)—White solid. *R_f* = 0.5 (45% ethyl acetate/hexane). Yield = 70%. M.p. 216–219 °C (methanol). IR (KBr): $\nu_{\max}$ 1676, 1706 cm⁻¹. ¹H NMR (300 MHz, CDCl₃, 25 °C): δ = 1.29 (t, 3H, *J* = 7.2 Hz), 2.25 (s, 3H), 2.41 (s, 3H), 2.87–3.18 (AB part of ABX, 2H, *J*_{AX} = 13.2 Hz, *J*_{BX} = 3.6 Hz), 4.14–4.24 (m, 2H), 5.03 (dd, 1H, *J*_(AX+BX) = 9.0 Hz), 6.18 (s, NH, exchanged with D₂O), 7.29–7.54 (m, 4H), 7.67 (br, 1H, NH, exchanged with D₂O) ppm. ¹³C NMR (75 MHz, CDCl₃ and DMSO-*d*₆, 25 °C): δ = 14.1, 18.5, 21.2, 49.2, 59.9, 62.7, 97.8, 123.7, 129.9, 140.6, 141.6, 149.1, 152.7 and 165.1 ppm. C₁₆H₂₀SN₂O₄: calcd. C, 57.14; H, 5.95; N, 8.33; S, 9.52; found: C, 57.15; H, 6.00; N, 8.50; S, 9.38. MS: *m/z* 359 (M+23). {[δ]_D²⁵ = +10 (methanol, *c* = 0.2)}

(4S,SR)- Ethyl 1,2,3,4-tetrahydro-6-methyl-2-oxo-4-(p-tolylsulfonfylmethyl)pyrimidine-5-carboxylate (minor diastereomer) (15)—White solid. *R_f* = 0.5 (45% ethyl acetate/hexane). Yield = 20%. M.p. = 180–181 °C (methanol). ¹H NMR (300 MHz, CDCl₃, 25 °C): δ = 1.07 (t, 3H, *J* = 7.2 Hz), 2.27 (s, 3H), 2.43 (s, 3H), 2.71–3.34 (AB part of ABX, 2H, *J*_{AX} = 13.2 Hz, *J*_{BX} = 3.6 Hz), 3.88–4.03 (m, 2H), 4.84 (dd, 1H, *J*_(AX+BX) = 9.6 Hz), 6.27 (s, NH, exchanged with D₂O), 7.35–7.53 (m, 4H), 7.67 (br, 1H, NH, exchanged with D₂O) ppm. ¹³C NMR (75 MHz, CDCl₃, 25 °C): δ = 14.2, 18.6, 21.3, 47.5, 59.8, 97.9, 124.1, 130.0, 139.2, 141.5, 149.5, 153.4 and 164.7 ppm. C₁₆H₂₀SN₂O₄: calcd. C, 57.14; H, 5.95; N, 8.33; S, 9.52; found: C, 57.20; H, 6.92; N, 8.28; S, 9.56. MS: *m/z* 359 (M+23). {[δ]_D²⁵ = +185 (methanol, *c* = 0.2)}

Reductive desulfurization of **14** and **15**. Synthesis of enantiomeric DHPMs **16** and **17**

A solution of compound **14** or **15** (0.14 mmol) in dry methanol (50 mL) was treated with excess of Raney-Ni (2 g) at 0 °C temperature. Whereas complete desulfurization of **14** required stirring at r.t. followed by overnight reflux, the desulfurization of **15** completed at 0 °C. After completion (TLC), reactions were filtered through a bed of celite and the solvent was removed under reduced pressure. The crude product was purified by crystallization in methanol.

(4S)-Ethyl 1,2,3,4-tetrahydro-4,6-dimethyl-2-oxopyrimidine-5-carboxylate (16)—White solid. *R_f* = 0.5 (60% ethyl acetate/hexane). Yield = 51%. M.p. 206–210 °C (methanol). ¹H NMR (300 MHz, CDCl₃, 25 °C): δ = 1.25–1.31 (m, 6H), 2.28 (s, 3H), 4.15–4.23 (m, 2H), 4.41–4.44 (m, 1H), 5.25 (br, 1H, NH, exchanged with D₂O), 7.14 (br, 1H, NH, exchanged with D₂O) ppm. ¹³C NMR (75 MHz, CDCl₃ and DMSO-*d*₆, 25 °C): δ = 13.7, 17.6, 22.9, 46.4, 59.0, 101.2, 146.5, 153.7 and 165.4 ppm. C₉H₁₄N₂O₃: calcd. C, 54.53; H, 7.12; N, 14.13; found: C, 54.65; H, 7.14; N, 14.20. MS: *m/z* 221 (M+23). {[δ]_D²⁵ = –205.00 (methanol, *c* = 0.2)}

(4R)-Ethyl 1,2,3,4-tetrahydro-4,6-dimethyl-2-oxopyrimidine-5-carboxylate (17)—White solid. *R_f* = 0.5 (60% ethyl acetate/hexane). Yield = 45%. M.p. 195–198 °C (methanol). ¹H NMR (300 MHz, CDCl₃, 25 °C): δ = 1.25–1.31 (m, 6H), 2.28 (s, 3H), 4.15–4.23 (m, 2H), 4.40–4.44 (m, 1H), 5.08 (br, 1H, NH, exchanged with D₂O), 6.57 (br, 1H, NH, exchanged with D₂O) ppm. ¹³C NMR (75 MHz, CDCl₃, 25 °C): δ = 14.3, 18.5, 23.6, 47.5, 59.8, 102.6, 146.1, 154.2 and 165.7 ppm. C₉H₁₄N₂O₃: calcd. C, 54.53; H, 7.12; N, 14.13; found: C, 54.41; H, 7.06; N, 14.05. MS: *m/z* 221 (M+23). {[δ]_D²⁵ = +160 (methanol, *c* = 0.2)}

X-ray Analysis

CCDC-628121 (for **14**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Supplementary Material

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Figure 1. Multi-step (*route a*) construction of functionalized 3,4-dihydropyrimidin-2(1*H*)-one derivatives and post Biginelli condensation scaffold decoration pathway (*route b*).

Figure 2.
X-ray crystal structure of **14**.

Figure 3.
Experimental CD spectra of **16** and **17**.

Figure 4.

Medial strips from the swine carotid artery were contracted with 110 mM KCl-PSS and then subjected to the cumulative addition of calcium channel blocker to determine their potential for relaxation. Nifedipine and **17** novel calcium channel blockers were tested.

Scheme 1.
Synthetic strategy for C-4 elaborated DHPMs **9**.

Scheme 2.

Addition of monoanion of *R*(+)-Methyl *p*-tolyl sulfoxide to **8b**.

Table 1

Addition of carbon nucleophiles to pyrimidine-2(1*H*)-ones **8**. Formation of C-4 substituted DHPM derivatives **9**

Entry	Nu substrate	Reaction conditions ^[a]	Product 9/10 R ²	Yield [%] ^[b]
1	MeCOCH ₂ COOEt	−78 °C/NaH/ <i>n</i> -BuLi/THF	9a ^[c] CH ₂ COCH ₂ COOEt	73
2	MeCOCH ₂ COOEt	−78 °C/NaH/ <i>n</i> -BuLi/THF	10a CH ₂ COCH ₂ COOEt	57
3	MeCOCH ₂ COOMe	−78 °C/NaH/ <i>n</i> -BuLi/THF	10b CH ₂ COCH ₂ COOMe	35
4	MeCOMe	−78°C/LDA/THF	9b CH ₂ COMe	75
5	MeCN	−78°C/LDA/THF	10c CH ₂ CN	50
6	PhCOMe	−78°C/LDA/THF	9c CH ₂ COPh	96
7	PhSO ₂ Me	−78 °C/ <i>n</i> -BuLi/THF	9d CH ₂ SO ₂ Ph	77
8	PhSO ₂ Me	−78 °C/ <i>n</i> -BuLi/THF	10d CH ₂ SO ₂ Ph	52
9	Thiophene	−40 °C/ <i>n</i> -BuLi/THF	9e (C ₄ H ₃ S-2yl)	80
10	Thiophene ^[d]	−40 °C/ <i>n</i> -BuLi/THF	10e (C ₄ H ₃ S-2yl)	40
11	Furan	−40 °C/ <i>n</i> -BuLi/THF	9f (C ₄ H ₃ O-2yl)	81
12	Furan ^[d]	−40 °C/ <i>n</i> -BuLi/THF	10f (C ₄ H ₃ O-2yl)	35
13	PhLi ^[e]	−78 °C/THF	9g Ph	78

^[a]Equivalents of the base used are mentioned in the experimental section

^[b]Isolated yields

^[c]Mixture of keto-enol tautomers (¹H NMR)

^[d]Traces of products of ester displacement^{9a} were detected (see supporting information)

^[e]Freshly prepared from bromobenzene and lithium.

Table 2

Addition of Grignard reagents to pyrimidine-2(1*H*)-ones **8**. Formation of C-4 substituted DHPM derivatives **11/12**

Entry	$R^2\text{MgX}$ [equiv.]/ ^[a]	Product 11/12 R^2	Yield [%]/ ^[b]
1	MeMgI [2.5]	11a Me	92
2	MeMgI [1.0]	12a Me	51
3	EtMgBr [1.0]	12b Et	88
4	<i>n</i> -PrMgBr [1.0]	12c <i>n</i> -Pr	85
5	<i>n</i> -BuMgBr [1.0]	12d <i>n</i> -Bu	79
6	<i>s</i> -BuMgBr [1.0]	12e <i>s</i> -Bu	77
7	<i>n</i> -C ₅ H ₁₁ MgBr [1.0]	12f <i>n</i> -C ₅ H ₁₁	90
8	<i>n</i> -C ₁₀ H ₂₁ MgBr [1.0]	12g <i>n</i> -C ₁₀ H ₂₁	85
9	<i>n</i> -C ₁₁ H ₂₃ MgBr [1.0]	12h <i>n</i> -C ₁₁ H ₂₃	80
10	AllyMgBr [1.0]	12i Allyl	65
11	PhMgBr [2.5]	12j Ph	45

^[a]Freshly prepared reagent was used

^[b]Isolated yields.