Synthetic Studies on Novel 1,4-Dihydro-2-methylthio-4,4,6-trisubstituted Pyrimidine-5-carboxylic Acid Esters and Their Tautomers

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A mixture of alkyl 1,4-dihydro-2-methylthio-4,4,6-trisubstituted pyrimidine-5-carboxylate 1 and its tautomeric isomer, alkyl 1,6-dihydro-2-methylthio-4,6,6-trisubstituted pyrimidine-5-carboxylate 2 is synthesized by the Atwal–Biginelli cyclocondensation reaction of *S*-methylisothiourea hemisulfate salt 3 with 2-(*gem*-disubstituted)methylene-3-oxoesters 4 that can be accessed by the Lehnert procedure for the Knoevenagel-type condensation. The structures of the tautomeric products of the Atwal–Biginelli cyclocondensation reaction, 1 and 2, which are inseparable from each other, are determined unambiguously by ^{1}H-NMR spectroscopy at various temperatures and nuclear Overhauser enhancement spectroscopy (NOESY) experiment. Because these dihydropyrimidine products are otherwise inaccessible and thus hitherto unavailable, the synthetic methods established in this study will help to expand the molecular diversity of their related derivatives.

Key words Atwal–Biginelli reaction; 2-(*gem*-disubstituted methylene)-3-oxoester; tautomer; alkyl 1,4-dihydro-2-methylthio-4,4,6-trisubstituted pyrimidine-5-carboxylate; alkyl 1,6-dihydro-2-methylthio-4,6,6-trisubstituted pyrimidine-5-carboxylate

This article deals with a general approach to synthesizing alkyl 1,4-dihydro-2-methylthio-4,4,6-trisubstituted pyrimidine-5-carboxylate **1** and its tautomeric isomer, alkyl 1,6-dihydro-2-methylthio-4,6,6-trisubstituted pyrimidine-5-carboxylate **2**, which was achieved by applying the Atwal–Biginelli cyclocondensation reaction[1—3] of *S*-methylisothiourea hemisulfate salt **3** to 2-(*gem*-disubstituted)methylene-3-oxoesters **4** available by the Lehnert procedure[4,5] for the Knoevenagel-type condensation (Fig. 1). This synthetic study was conducted as part of our medicinal chemistry program to explore alkyl 3,4-dihydro-2-oxo-3,4,4,6-tetrasubstituted pyrimidine-5-carboxylates **5a** and their 2-thioxo congeners **5b** for novel therapeutic agents,[6] which was inspired by the two track records with the related 1,4-dihydro-4-monoaryl-6-methylpyrimidine derivatives that follow: (*R*)-SQ 32926 **6**,[7] a calcium channel blocker developed as an orally active antihypertensive agent, and monastrol **7**,[8—10] a possible anticancer agent that inhibits mitotic cell division by blocking the activity of kinesin Eg 5, a motor protein causing spindle bipolarity.

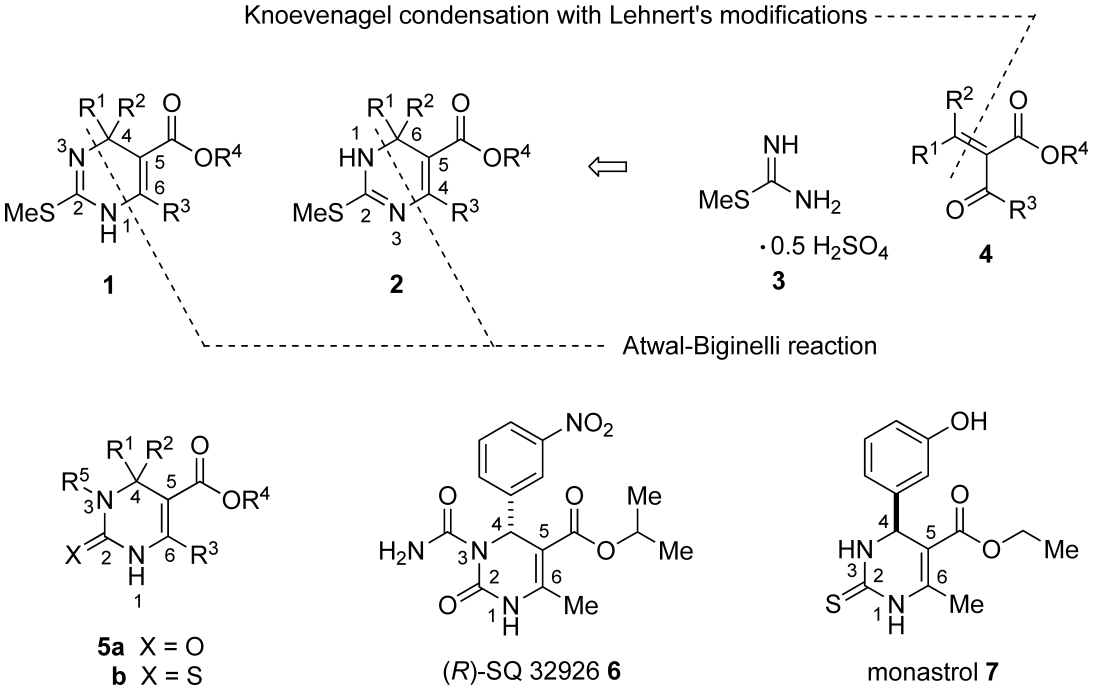

Fig. 1. Synthetic Approach to Alkyl 1,4-Dihydro-2-methylthio-4,4,6-trisubstituted Pyrimidine-5-carboxylate **1** and Its Tautomeric Isomer **2** and Structures of Related 2-Oxo and 2-Thioxo Analogs

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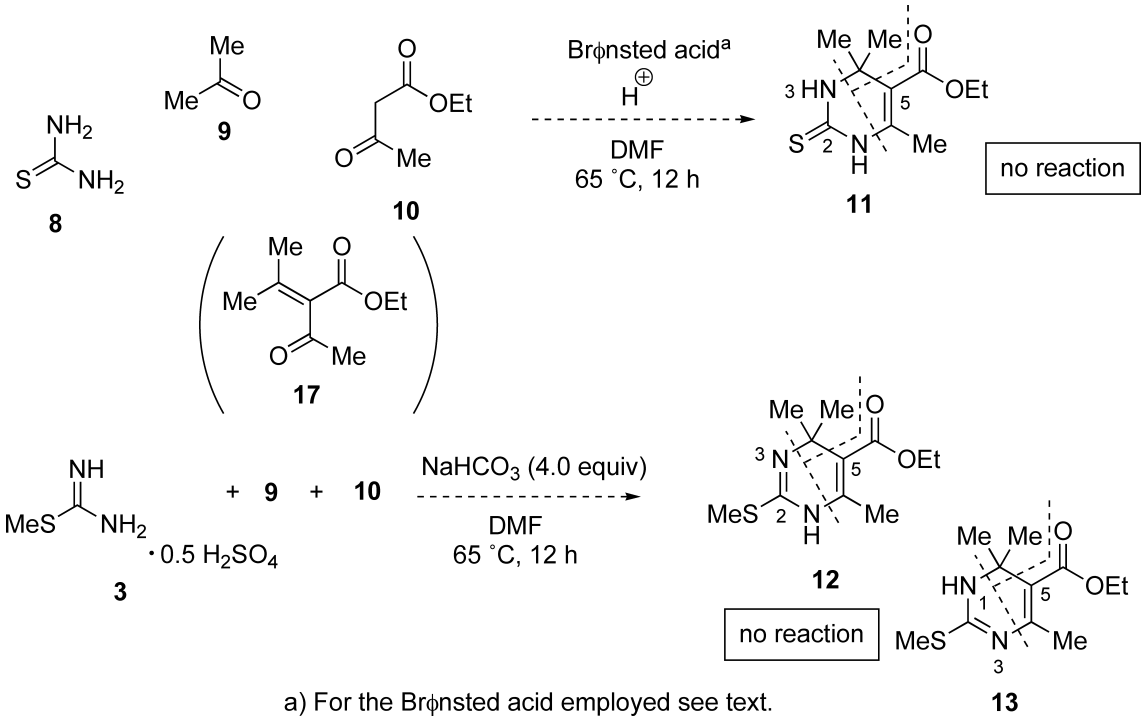


Chart 1. Three-Component Biginelli Reaction

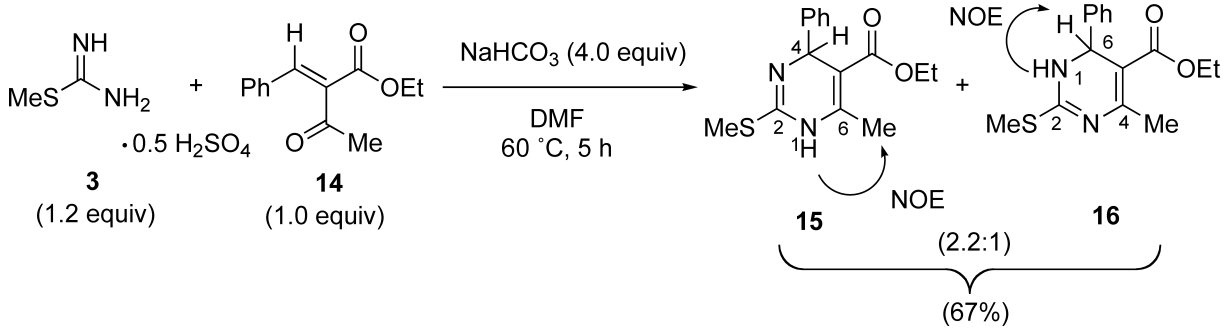


Chart 2. Typical Atwal–Biginelli Cyclocondensation Reaction to Afford Alkyl 1,4-Dihydro-2-methylthio-4,6-disubstituted Pyrimidine-5-carboxylate **15** and Its Tautomeric Isomer **16**

Results and Discussion

One of the ultimate synthetic targets being 3,4-dihydro-4,4,6-trisubstituted-2-thioxopyrimidine **5b** (R^5=H), a three-component Biginelli reaction was first attempted, in which ethyl acetoacetate (**10** 1.0 eq) was treated with thiourea **8** (1.2 eq) and acetone **9** (3—10 eq) in dimethylformamide (DMF) at 65 °C for 12 h in the presence of a Brønsted acid (1.0 eq), such as HCl, H_2SO_4, trifluoroacetic acid, 4-toluenesulfonic acid, or methanesulfonic acid (Chart 1).[11] However, no desired ethyl 3,4-dihydro-4,4,6-trimethyl-2-thioxopyrimidine-5-carboxylate **11** was produced, and the starting material **10** was recovered intact. Furthermore, no such three-component reaction took place to afford ethyl 1,4-dihydro-4,6,6-trimethyl-2-methylthiopyrimidine-5-carboxylate **12** or its 1,6-dihydro tautomer **13** when **9** (3—10 eq) and **10** (1.0 eq) were exposed to **3** (1.2 eq) instead of **8** in DMF in the presence of $NaHCO_3$ (4.0 eq) at 65 °C for 12 h.[12—14]

In contrast, when ethyl 2-benzylidene-3-oxobutanoate **14** [*E*/*Z* (1 : 3.0)],[15] a typical 2-(monosubstituted)methylene-3-oxoester prepared under the conventional Knoevenagel reaction conditions, was subjected to Atwal–Biginelli conditions [**3** (1.2 eq), $NaHCO_3$ (4.0 eq), DMF, 60 °C for 5 h], the cyclocondensation reaction proceeded uneventfully to provide ethyl 1,4-dihydro-2-methylthio-4,6-disubstituted pyrimidine-5-carboxylate **15** and its tautomeric isomer **16** as an inseparable mixture [**15**/**16** (2.2 : 1)] in a combined yield of 67% (Chart 2).[16,17] Structural assignments for **15** and **16** were made by the following nuclear Overhauser enhancement spectroscopy (NOESY) experiment. With the major component **15**, its 6-methyl protons exhibited a significant nuclear Overhauser effect (NOE) when the 1-NH proton was irradiated; hence, its structure was determined to be 1,4-dihydropyrimidine **15** as depicted in Chart 2. Irradiation of the 1-NH proton in the minor component **16** caused the NOE on the 6-proton, which led to its structure being determined to be 1,6-dihydropyrimidine **16**, a tautomeric isomer of **15** (Chart 2): for detail, see Experimental. Hence, it was envisioned that when prefabricated ethyl 3-oxo-2-(2-propylidene)-butanoate **17** was allowed to react with **8** and **3**, the cyclocondensation in question should proceed to give **11** and a mixture of **12** and **13**, respectively (Chart 1).

To test the above-mentioned proposition, **17** was required

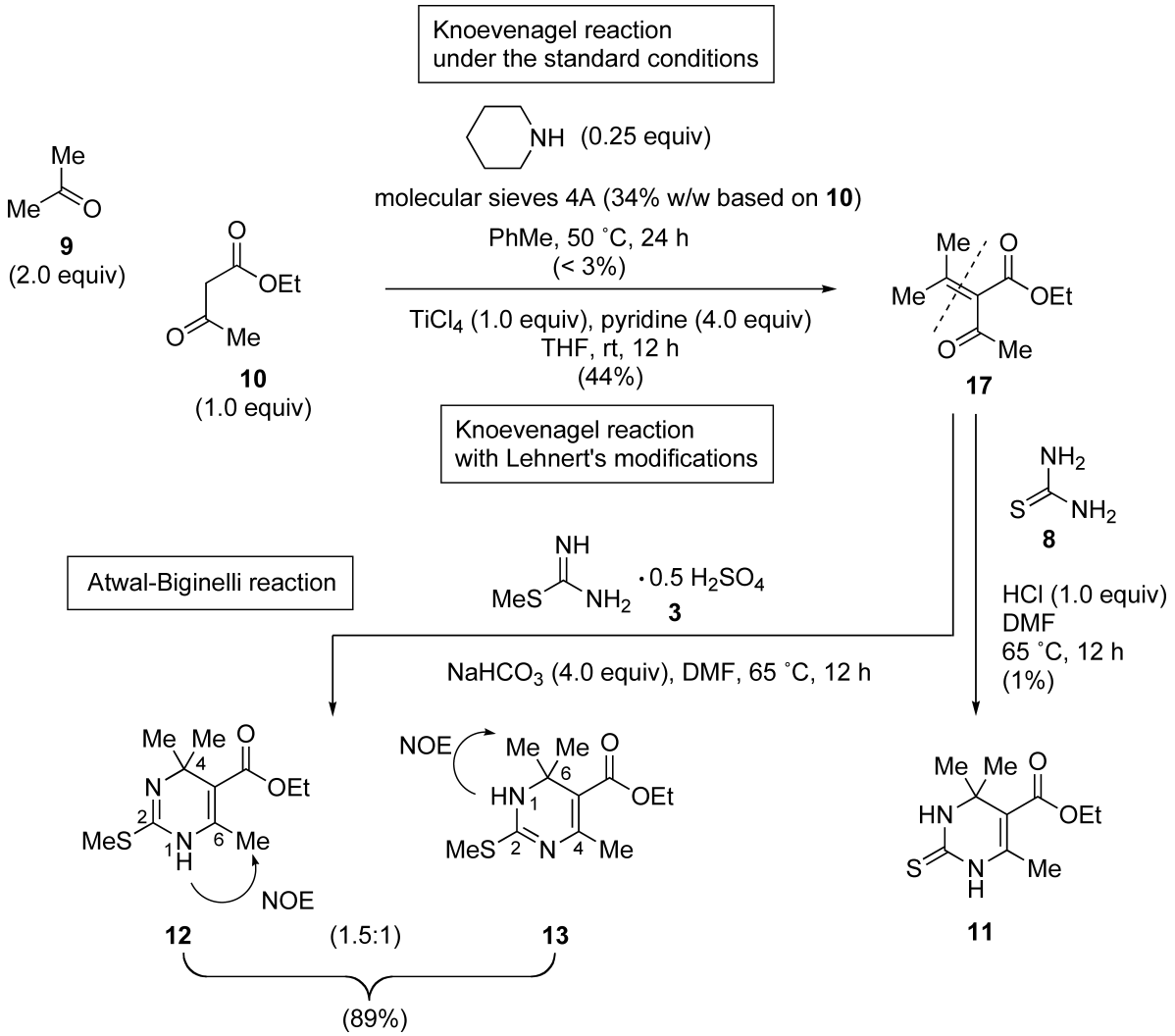


Chart 3. Synthesis of Ethyl 1,4-Dihydro-4,4,6-trimethyl-2-methylthiopyrimidine-5-carboxylate **12** and Its 1,6-Dihydro Tautomer **13**

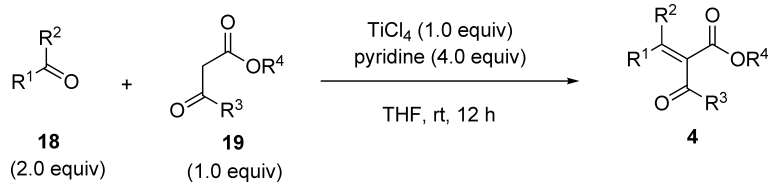
in sufficient quantity. To our disappointment, it was obtained in less than 3% yield when ethyl acetoacetate **10** (1.0 eq) and acetone **9** (2.0 eq) were subjected to the conventional Knoevenagel reaction conditions [piperidine (0.25 eq), molecular sieves 4A (34% w/w based on **10**), toluene, 50 °C, 24 h] (Chart 3).[18] However, literature search in parallel with failed experimentation led to identifying the Lehnert's report,[19—24] which was demonstrated to be the most effective means of preparing **17** by the Knoevenagel-type condensation: when **10** (1.0 eq) and **9** (2.0 eq) were treated with $TiCl_4$ (1.0 eq) in the presence of pyridine (4.0 eq) in tetrahydrofuran (THF) at room temperature for 12 h, **17** was obtained in 44% yield (Chart 3).[4,5]

Having secured **17** in quantity, we turned our attention towards the synthesis of **11** (Chart 3). When **17** was treated with thiourea **8** in the presence of HCl according to the typical procedures of the three-component Biginelli reaction, the expected 2-thione product **11** was obtained in a low yield of 1%. In contrast, the Atwal–Biginelli cyclocondensation reaction proceeded successfully with **17** and *S*-methylisothiourea hemisulfate salt **3** to afford 1,4-dihydro-4,4,6-trimethyl-2-methylthiopyrimidine-5-carboxylate **12** and its 1,6-dihydro tautomer **13** as an inseparable mixture [**12**/**13** (1.5 : 1)] in a combined yield of 89% (Chart 3). The structures of **12** and **13** were determined to be as depicted in Chart 3 by the NOESY experiment similar to that conducted with the tautomeric mixture of **15** and **16**: for detail, see Experimental.

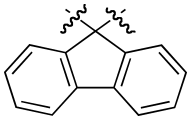
To see the concentration dependence of the tautomeric ratio of **12** to **13**, their combined concentration was changed from 1.1×10^{-2} to 8.8×10^{-2} M. The tautomeric ratio determined by ^{1}H-NMR at 25 °C remained unaffected at 1.5 : 1 throughout the concentrations varied. In contrast, the tautomeric ratio changed in a temperature-dependent manner. When the ^{1}H-NMR spectra were measured at temperatures increased from 25 to 105 °C, the ratio decreased from 1.5 : 1 to 1.3 : 1. When the mixture was cooled to 25 °C, the ratio was restored to the original value. Although the change in the composition was not large over the range of temperatures tested, it was such the temperature-dependent interconvertibility that corroborated the tautomeric relationship between **12** and **13**.

Now that the Knoevenagel-type condensation between the β-oxoester **10** and the ketone **9** had provided **17** in good yield under the Lehnert conditions,[4,5] we chose to apply those conditions to the synthesis of a range of 2-(*gem*-disubstituted)-methylene-3-oxoesters **4**. The Lehnert's procedures worked

Table 1. Synthesis of 2-(*gem*-Disubstituted)methylene-3-oxoesters **4** under Lehnert Conditions for the Knoevenagel-Type Reaction[a)]



18 (2.0 equiv) **19** (1.0 equiv) **4**

Entry		R^1	R^2	R^3	R^4	Yield (%)
1	**a**	Me	Me	Me	Me	47
2	**b**	Me	Me	Me	CH_2Ph	37
3	**c**	$-CH_2(CH_2)_3CH_2-$		Me	Et	17
4[b,c)]	**d**	Me	$Me(CH_2)_4$	Me	Et	16
5[b,c,d)]	**e**	$Me(CH_2)_2$	$Me(CH_2)_2$	Me	Et	11
6[b,d,e)]	**f**	Me	Me	Ph	Et	15
7[b,c,d)]	**g**	Ph	Et	Me	Et	7
8[b,d,f)]	**h**			Me	Et	7

a) General conditions: a mixture of **18** (80 mmol), **19** (40 mmol), $TiCl_4$ (40 mmol) and pyridine (160 mmol) in THF (40 ml) was stirred at room temperature for 12 h under an atmosphere of argon unless otherwise specified. *b*) For 24 h. *c*) **18** (1.0 eq) was used. *d*) $TiCl_4$ (2.0 eq) was used. *e*) **18** (3.0 eq) and pyridine (6.0 eq) were used at 40 °C. *f*) **18** (1.0 eq), **19** (1.5 eq), $TiCl_4$ (3.0 eq) and pyridine (6.0 eq) were used.

for the Knoevenagel-type condensation of the aliphatic ketones **18a**—**f** and the aromatic ketones **18g** and **h** to afford the expected products **4a**—**f**, as summarized in Table 1.

Lehnert reported that ketones could undergo the Knoevenagel-type condensation with dialkyl malonate in the presence of $TiCl_4$ and pyridine,[4)] with the use of 3-oxoester being limited to the condensation reaction with aldehydes.[5)] Thus, the experimental results in Table 1 are the first successful expansion of the Lehnert procedures to the Knoevenagel-type condensation between 3-oxoesters and ketones.

With a variety of 2-(*gem*-disubstituted)methylene-3-oxoesters **4** (**17**, **4a**—**h**) in hand, the stage was set for assembling 1,4-dihydro-2-methylthio-4,4,6-trisubstituted pyrimidine **1** and its 1,6-dihydro tautomeric isomer **2**, both of which had remained otherwise inaccessible. With all these substrates, **17** and **4a**—**h**, the Atwal–Biginelli cyclocondensation reaction [**3** (1.2 eq), $NaHCO_3$ (4.0 eq), DMF, 65 °C, 12 h)] proceeded uneventfully to give 1,4-dihydro-2-methylthio pyrimidine **1** and its 1,6-dihydro tautomer **2** in a fair to good yield, as listed in Table 2.

What is worth making comments with respect to the tabulated results are as follows. In addition to ethyl ester **17** (Chart 3), the methyl and benzyl esters **4a** and **4b**, respectively, were tolerated in the reaction, and the corresponding products **1a**/**2a** and **1b**/**2b** could be obtained without incident (entries 1, 2). Their alkylidene substituents being sterically demanding, **4c** and **4e** underwent olefin isomerization towards deconjunction under the basic conditions applied so that steric congestion can be relieved; however, when **3** was used in excess amounts, the cyclocondensation could compete with the isomerization to afford the respective products **1c**/**2c** and **1e**/**2e** in acceptable yields (entries 3, 5). When starting from ethyl 2-isopropylidene-3-phenyl-3-oxopropanoate **4f**, prepared from ethyl benzoylacetate **19f**, a phenyl group could be installed at the 6-position of **1f**/**2f** although **3** needed to be used in 3.0 eq to gain an acceptable yield (entry 6). A phenyl group could also be accommodated at the 4-position, as illustrated by **1g**/**2g** (entry 7). Furthermore, a fluorenylidene group could be appended to the dihydropyrimidine skeleton, as shown by **1h**/**2h** (entry 8).

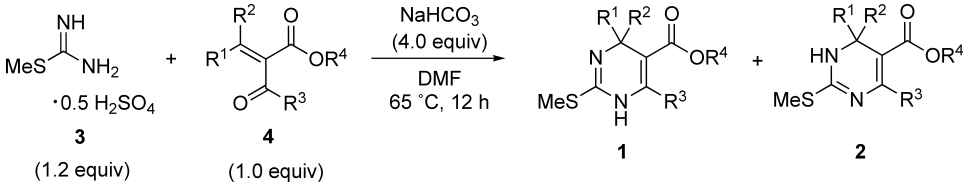
Conclusion

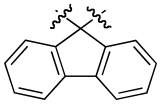
In summary, it was demonstrated that alkyl 1,4-dihydro-2-methylthio-4,4,6-trisubstituted pyrimidine-5-carboxylate **1** (**12**, **1a**—**h**) and its 1,6-dihydro tautomer **2** (**13**, **2a**—**h**) could be assembled by applying the Atwal–Biginelli cyclocondensation reaction to 2-(*gem*-disubstituted)methylene-3-oxoesters **4** (**17**, **4a**—**h**), which, in turn, was prepared from ketones, **9** and **18a**—**h**, and 3-oxoesters, **10** and **19a**—**h**, by resorting to the Lehnert conditions for the Knoevenagel-type condensation. In view of the fact that all the dihydropyrimidine derivatives reported in this article are new in spite of their existence as inseparable tautomeric mixtures, the synthetic procedures developed in our laboratory should help to expand the dihydropyrimidine-based molecular diversity, which would impact the drug discovery program.[6)]

Experimental

All melting points were determined with an AS ONE melting point apparatus ATM-02 without correction. IR spectra were measured on a JASCO FT/IR-6100. ^{1}H-NMR spectra were recorded on a Bruker AVANCE^{TM} III 600 (600 MHz) with tetramethylsilane (0 ppm) or dimethylsulfoxide (2.49 ppm) as an internal standard. ^{13}C-NMR spectra were recorded on a Bruker

Table 2. Synthesis of Alkyl 1,4-Dihydro-2-methylthio-4,4,6-trisubstituted Pyrimidine-5-carboxylate **1** and Its 1,6-Dihydro Tautomer **2** under Atwal–Biginelli Conditions[a)]



Entry		R^1	R^2	R^3	R^4	Yield[b)] (%)	**1**/**2**[c)]
1	**a**	Me	Me	Me	Me	84	1.5 : 1
2	**b**	Me	Me	Me	CH_2Ph	68	1.6 : 1
3[d)]	**c**	$-CH_2(CH_2)_3CH_2-$		Me	Et	63	8.4 : 1
4[e)]	**d**	Me	$Me(CH_2)_4$	Me	Et	80	1.7 : 1
5[d)]	**e**	$Me(CH_2)_2$	$Me(CH_2)_2$	Me	Et	63	1.8 : 1
6[d)]	**f**	Me	Me	Ph	Et	73	1 : 3.7
7[f)]	**g**	Ph	Et	Me	Et	63	3.0 : 1
8	**h**			Me	Et	40	6.0 : 1

a) General conditions: a mixture of **3** (0.6 mmol), **4** (0.5 mmol), $NaHCO_3$ (2.0 mmol) and DMF (1.0 ml) was stirred and heated at 65 °C for 12 h under an atmosphere of argon unless otherwise specified. *b*) A combined yield of **1** and **2**. *c*) Determined by ^{1}H-NMR spectroscopy featuring NOE experiment. *d*) **3** (3.0 eq) was used. *e*) With **4d** was used a (2.5 : 1) mixture of the *E*/*Z* isomers. *f*) With **4g** was used a single geometric isomer although its configuration was unidentified.

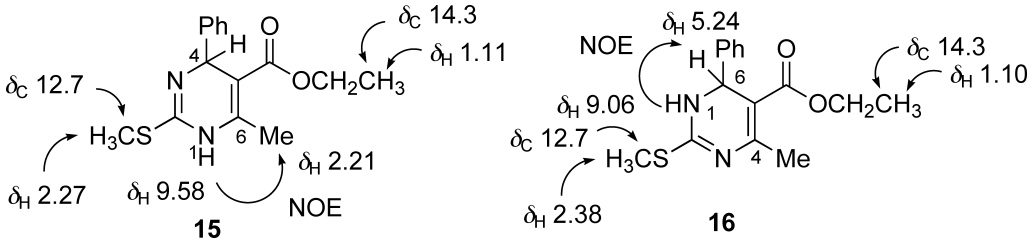


Fig. 2. NOE and HSQC Observed with **15** and **16**

AVANCE^{TM} III 600 (150 MHz) with chloroform (77.0 ppm) or dimethylsulfoxide (39.7 ppm) as an internal standard. Mass spectra were recorded on a JEOL JMS-700. High-resolution mass spectroscopy (HRMS) was performed using a JEOL JMS-700. Column chromatography was performed on silica gel 60 (nacalai tesque, 70—230 mesh) using the indicated solvents. TLC was performed using pre-coated silica gel 60 F_{254} plates (Merck KGaA) using the indicated solvents.

Ethyl 1,4-Dihydro-6-methyl-2-methylthio-4-phenyl Pyrimidine-5-carboxylate (15) and Ethyl 1,6-Dihydro-4-methyl-2-methylthio-6-phenyl Pyrimidine-5-carboxylate (16) Under an atmosphere of argon, a mixture of *S*-methylisothiourea hemisulfate (**3**; 84 mg, 0.6 mmol), **14** [109 mg, 0.5 mmol, *E*/*Z* (1 : 3.0)],[15] $NaHCO_3$ (168 mg, 2.0 mmol), and dry DMF (1.0 ml) was heated at 60 °C for 5 h. To the reaction mixture was added EtOAc (20 ml) followed by water (10 ml), and the organic layer was separated. The aqueous layer was extracted with EtOAc (20 ml×2), and the combined organic layer and extracts were washed with water, brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash column chromatography [*n*-hexane–EtOAc (2 : 1)] to give **15** and **16** as an inseparable mixture (97 mg, 0.33 mmol, 67%) in a ratio of 2.2 : 1 in favor of **15**. Colorless crystals. Melting point (mp) 168—171 °C (chloroform). ^{1}H-NMR [dimethyl sulfoxide (DMSO)-d_6] δ: 1.10 (0.94H, t, *J*=7.2 Hz, **16**), 1.11 (2.06H, t, *J*=7.2 Hz, **15**), 2.21 (2.06H, s, **15**), 2.26 (0.94H, s, **16**), 2.27 (2.06H, s, **15**), 2.38 (0.94H, s, **16**), 3.94—4.05 (2H, m, **15**+**16**), 5.24 (0.31H, d, *J*=3.0 Hz, **16**), 5.50 (0.69H, s, **15**), 7.15—7.35 (5H, m, **15**+**16**), 9.06 (0.31H, d, *J*=3.0 Hz, **16**), 9.58 (0.69H, s, **15**). Structural assignment was made unambiguously by NOESY experiment: With the major component, the significant NOE was observed between 1-NH proton (δ 9.58) and 6-methyl protons (δ 2.21) and as such, its structure was determined to be **15** (Fig. 2). With the minor component, the significant NOE was observed between 1-NH proton (δ 9.06) and 6-proton (δ 5.24) and as such, its structure was determined to be **16** (Fig. 2). ^{13}C-NMR (150 MHz, DMSO-d_6) δ: 12.7 (unresolved), 14.3 (unresolved), 17.7, 23.3, 53.3, 59.0, 59.2, 59.3, 98.4, 103.4, 126.4, 126.7, 126.8, 127.7, 128.3, 128.6, 145.0, 145.9, 146.2, 150.6, 155.2, 160.9, 166.36, 166.43. The unresolved signals, δ 12.7 and δ 14.3, were further analyzed by heteronuclear single-quantum coherence (HSQC) experiment, which revealed that the signal at δ_C 12.7 was due to the S-CH_3 of **15** and **16** because of its correlation to the signals at δ_H 2.27 (s, **15**) and δ_H 2.38 (s, **16**) and that δ_C 14.3 was due to the OCH_2CH_3 of **15** and **16** because of its correlation to attached to the signals δ_H 1.11 (t, **15**) and δ_H 1.10 (t, **16**) (Fig. 2). IR (KBr) cm^{-1}: 3320, 1657, 1470, 1281, 1155, 1109. Electron ionization (EI)-MS *m*/*z*: 290.1083 (Calcd for $C_{15}H_{18}N_2O_2S$: 290.1089). MS *m*/*z*: 290 (M^+), 261, 213, 185.

Ethyl 2-Acetyl-3-methylbut-2-enoate (17) According to the procedures reported by Lernert,[4,5] a solution of ethyl acetoacetate (**10**; 5.2 g, 40 mmol), acetone (**9**; 5.8 ml, 80 mmol), and pyridine (12.6 g, 160 mmol) in dry THF (15 ml) was added to an ice-cooled solution of $TiCl_4$ (4.4 ml, *d* 1.73, 40 mmol) in dry THF (25 ml) at 0 °C under an atmosphere of argon. The reaction mixture was stirred at room temperature for 12 h, and EtOAc (150 ml) and water (30 ml) were added. The organic layer was separated, and the aqueous layer was extracted with EtOAc (50 ml×2). The combined or-

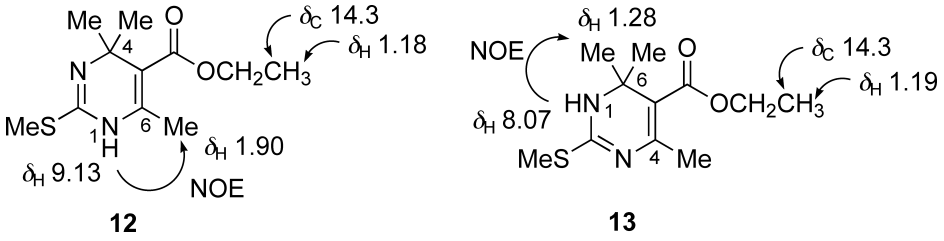


Fig. 3. NOE and HSQC Observed with **12** and **13**

ganic layer and extracts were washed with saturated $NaHCO_3$ aqueous solution, water, brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash column chromatography [*n*-hexane–EtOAc (20 : 1)] to give **17** (3.0 g, 17.6 mmol, 44%), the ^{1}H-NMR spectral data of which were identical to those reported ones.[25]

2-(*gem*-Disubstituted)methylene-3-oxoester (4a—h) The 2-(*gem*-disubstituted)methylene-3-oxoesters **4a**—**h**, were all assembled under the conditions similar to those described for the synthesis of **17**,[4,5] and below recorded are their isolated yield and their physicochemical and spectral data while the spectral data of **4c** (yield: 17%) and **4f** (yield: 15%) were identical to those reported ones.[25] Analysis and identification of the unresolved signal in the ^{13}C-NMR spectrum of **4h** were made based on HSQC experiment.

Methyl 2-Acetyl-3-methylbut-2-enoate (4a): Colorless oil. Yield: 47%. ^{1}H-NMR ($CDCl_3$) δ: 1.95 (3H, s), 2.11 (3H, s), 2.29 (3H, s), 3.77 (3H, s). ^{13}C-NMR ($CDCl_3$) δ: 22.9, 23.2, 30.6, 51.7, 131.8, 153.6, 166.0, 200.6. IR (neat) cm^{-1}: 2953, 1727, 1698, 1632, 1233. Chemical ionization (CI)-MS *m/z*: 156.1764 (Calcd for $C_8H_{12}O_3$: 156.0787). MS *m/z*: 156 (M^+), 125.

Benzyl 2-Acetyl-3-methylbut-2-enoate (4b): Colorless oil. Yield: 37%. ^{1}H-NMR ($CDCl_3$) δ: 1.95 (3H, s), 2.10 (3H, s), 2.23 (3H, s), 5.22 (2H, s), 7.30—7.42 (5H, m). ^{13}C-NMR ($CDCl_3$) δ: 23.0, 23.3, 30.7, 66.5, 128.2, 128.3, 128.5, 131.8, 135.3, 154.0, 165.4, 200.3. IR (neat) cm^{-1}: 1723, 1698, 1224, 1198. CI-MS *m/z*: 233.1189 (Calcd for $C_{14}H_{17}O_3$: 233.1177). MS *m/z*: 233 (M^++H), 125, 91.

Ethyl 2-Acetyl-3-methyloct-2-enoate (4d): Colorless oil. Yield: 16%. An inseparable (2.5 : 1) mixture of the *E*/*Z* isomers with theie structural assignment being impossible by the ordinary spectroscopic methods. ^{1}H-NMR ($CDCl_3$) δ: 0.89 (0.86H, t, *J*=7.2 Hz), 0.90 (2.14H, t, *J*=7.2 Hz), 1.25—1.37 (7H, m), 1.45—1.53 (2H, m), 1.95 (2.14H, s), 2.09 (0.86H, s), 2.18 (0.57H, t, *J*=7.8 Hz), 2.28 (2.14H, s), 2.29 (0.86H, s), 2.38 (1.43H, t, *J*=7.8 Hz), 4.23 (0.57H, q, *J*=7.2 Hz), 4.24 (1.43H, q, *J*=7.2 Hz). ^{13}C-NMR ($CDCl_3$) δ: 13.8, 13.9, 14.0, 20.5, 21.1, 22.3, 22.4, 27.65, 27.67, 30.5, 30.9, 31.75, 31.83, 36.5, 36.8, 60.6, 60.7, 131.86, 131.89, 157.1, 165.6, 166.0, 200.0, 200.7. IR (neat) cm^{-1}: 2958, 2933, 1725, 1703, 1626, 1227. EI-MS *m/z*: 226.1578 (Calcd for $C_{13}H_{22}O_3$: 226.1569). MS *m/z*: 226 (M^+), 151, 43.

Ethyl 2-Acetyl-3-propylhex-2-enoate (4e): Colorless oil. Yield: 11%. ^{1}H-NMR ($CDCl_3$) δ: 0.94 (3H, t, *J*=7.2 Hz), 0.96 (3H, t, *J*=7.2 Hz), 1.30 (3H, t, *J*=7.2 Hz), 1.45—1.55 (6H, m), 2.17 (2H, t, *J*=7.8 Hz), 2.28 (3H, s), 2.38 (2H, t, *J*=7.8 Hz), 4.23 (2H, q, *J*=7.2 Hz). ^{13}C-NMR ($CDCl_3$) δ: 14.1, 14.3, 14.4, 21.86, 21.93, 30.9, 35.7, 36.4, 60.7, 132.0, 160.8, 165.8, 200.5. IR (neat) cm^{-1}: 2964, 1724, 1698, 1615, 1205. CI-MS *m/z*: 227.1638 (Calcd for $C_{13}H_{23}O_3$: 227.1647). MS *m/z*: 227 (M^++H), 185, 153.

Ethyl 2-Acetyl-3-phenylpent-2-enoate (4g): Colorless oil. Yield: 7%. A single geometric isomer with its configuration being unidentified. ^{1}H-NMR ($CDCl_3$) δ: 1.01 (3H, t, *J*=7.2 Hz), 1.32 (3H, t, *J*=7.2 Hz), 1.83 (3H, s), 2.73 (2H, q, *J*=7.2 Hz), 4.28 (2H, t, *J*=7.2 Hz), 7.17—7.21 (2H, m), 7.35—7.40 (3H, m). ^{13}C-NMR ($CDCl_3$) δ: 12.4, 14.0, 29.5, 30.8, 61.0, 127.8, 128.5, 128.7, 133.7, 139.2, 157.3, 165.5, 201.5. IR (neat) cm^{-1}: 2979, 1723, 1703, 1233, 1204. EI-MS *m/z*: 246.1255 (Calcd for $C_{15}H_{18}O_3$: 246.1256). MS *m/z*: 246 (M^+), 200, 134, 105, 77.

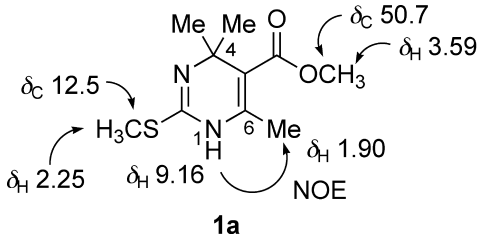
Ethyl 2-Fluoren-9-ylidene-3-oxobutanoate (4h): Yellow crystals. Yield: 7%. mp 62—63 °C (*n*-hexane). ^{1}H-NMR ($CDCl_3$) δ: 1.40 (3H, t, *J*=7.2 Hz), 2.62 (3H, s), 4.44 (2H, q, *J*=7.2 Hz), 7.19 (1H, dt, *J*=1.2, 7.8 Hz), 7.23 (1H, dt, *J*=1.2, 7.8 Hz), 7.38 (1H, dt, *J*=1.2, 7.8 Hz), 7.39 (1H, dt, *J*=1.2, 7.8 Hz), 7.49 (1H, d, *J*=7.8 Hz), 7.631 (1H, d, *J*=7.8 Hz), 7.632 (1H, d, *J*=7.8 Hz), 7.83 (1H, d, *J*=7.8 Hz). ^{13}C-NMR ($CDCl_3$) δ: 14.0, 31.1, 62.2, 119.7, 119.9, 125.4, 125.7, 127.6, 127.7, 130.6 (unresolved), 131.8, 135.45, 135.50, 140.1, 141.4, 141.5, 165.2, 201.2. The unresolved signal, δ 130.6 was further analyzed by HSQC experiment, which revealed that its correlation to the signals at δ_H 7.38 (dt) and δ_H 7.39 (dt). IR (KBr) cm^{-1}: 1721, 1688, 1584, 1226, 1210. EI-MS *m/z*: 292.1092 (Calcd for $C_{19}H_{16}O_3$: 292.1100). MS *m/z*: 292 (M^+), 263, 205, 176.

Ethyl 1,4-Dihydro-4,4,6-trimethyl-2-methylthio Pyrimidine-5-carboxylate (12) and Ethyl 1,6-Dihydro-4,6,6-trimethyl-2-methylthio Pyrimidine-5-carboxylate (13) Under an atmosphere of argon, a mixture of *S*-methylisothiourea hemisulfate (**3**; 84 mg, 0.6 mmol), **17** (85 mg, 0.5 mmol), and $NaHCO_3$ (168 mg, 2.0 mmol) in dry DMF (1.0 ml) was heated at 65 °C for 12 h. To the reaction mixture was added EtOAc (20 ml) followed by water (10 ml), and the organic layer was separated. The aqueous layer was extracted with EtOAc (20 ml×2), and the combined organic layer and extracts were washed with water, brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash column chromatography [*n*-hexane–EtOAc (4 : 1)] to give **12** and **13** as an inseparable mixture (108 mg, 0.45 mmol, 89%) in a ratio of 1.5 : 1 in favor of **12**. Colorless crystals. mp 93—94 °C (*n*-hexane–EtOAc). ^{1}H-NMR (DMSO-d_6) δ: 1.18 (1.8H, t, *J*=7.2 Hz, **12**), 1.19 (1.2H, t, *J*=7.2 Hz, **13**), 1.26 (3.6H, s, **12**), 1.28 (2.4H, s, **13**), 1.90 (1.8H, s, **12**), 1.94 (1.2H, s, **13**), 2.24 (1.8H, s, **12**), 2.32 (1.2H, s, **13**), 4.05 (1.2H, q, *J*=7.2 Hz, **12**), 4.07 (0.8H, q, *J*=7.2 Hz, **13**), 8.07 (0.4H, s, **13**), 9.13 (0.6H, s, **12**). Structural assignment was made unambiguously by NOESY experiment: With the major component, the significant NOE was observed between 1-NH proton (δ 9.13) and 6-methyl protons (δ 1.90) and as such, its structure was determined to be **12** (Fig. 3). With the minor component, the significant NOE was observed between 1-NH (δ 8.07) and 6,6-dimethyl protons (δ 1.28) and as such, its structure was determined to be **13** (Fig. 3). ^{13}C-NMR (DMSO-d_6) δ: 12.4, 12.5, 14.3 (unresolved), 17.8, 23.2, 29.1, 31.0, 53.3, 55.8, 59.27, 59.33, 105.0, 110.2, 141.7, 147.4, 150.2, 159.7, 167.0, 167.2. The unresolved signal, δ 14.3, was further analyzed by HSQC experiment, which revealed that the signal at δ_C 14.3 was due to the OCH_2CH_3 of **12** and **13** because of its correlation to the signals at δ_H 1.18 (t, **12**) and δ_H 1.19 (S, **13**) (Fig. 3). IR (KBr) cm^{-1}: 3154, 2929, 1698, 1643, 1609, 1485, 1311, 1171. EI-MS *m/z*: 242.1088 (Calcd for $C_{11}H_{18}N_2O_2S$: 242.1089). MS *m/z*: 242 (M^+), 227, 199.

1,4-Dihydro-2-methylthio-4,4,6-trisubstituted Pyrimidine-5-carboxylates and 1,4-Dihydro-2-methylthio-4,6,6-trisubstituted Pyrimidine-5-carboxylates (1a—h/2a—h) A tautomeric mixture of **1a**—**h**/**2a**—**h** were synthesized according to the same procedures as described for the synthesis of the mixture of **12** and **13**; below listed are their isolated yield and their physicochemical and spectral data for **1a**—**h**/**2a**—**h**. Analysis and identification of the unresolved signals in the ^{13}C-NMR spectra of **1a**—**b**/**2a**—**b**, **1d**—**e**/**2d**—**e** and **1g**/**2g** were made based on HSQC experiment.

Methyl 1,4-Dihydro-4,4,6-trimethyl-2-methylthio Pyrimidine-5-carboxylate (1a) and Methyl 1,6-Dihydro-4,6,6-trimethyl-2-methylthio Pyrimidine-5-carboxylate (2a): Colorless crystals. Yield: 84%. **1a**/**2a**= 1.5 : 1. mp 85—86 °C (*n*-hexane). ^{1}H-NMR (DMSO-d_6) δ: 1.26 (3.6H, s, **1a**), 1.28 (2.4H, s, **2a**), 1.90 (1.8H, s, **1a**), 1.95 (1.2H, s, **2a**), 2.25 (1.8H, s, **1a**), 2.33 (1.2H, s, **2a**), 3.59 (1.8H, s, **1a**), 3.60 (1.2H, s, **2a**), 8.10 (0.4H, s, **2a**), 9.16 (0.6H, s, **1a**). Exact structural assignment was made using NOESY experiment: With the major component, the significant NOE was observed between 1-NH proton (δ 9.16) and 6-methyl protons (δ 1.90) and as such, its structure was determined to be **1a** (Fig. 4). With the minor component, the significant NOE was observed between 1-NH (δ 8.10) and 6,6-dimethyl protons (δ 1.28) and as such, its structure was determined to be **2a** (Fig. 4). ^{13}C-NMR (DMSO-d_6) δ: 12.5 (unresolved), 17.8, 23.3, 29.1, 31.0, 50.7 (unresolved), 53.3, 55.8, 104.8, 110.0, 142.0, 147.3, 150.5, 159.9, 167.7. The unresolved signals, δ 12.5 and δ 50.7, were further analyzed by HSQC experiment, which revealed that the signal at δ_C 12.5 was due to the S-CH_3 of **1a** and **2a** because of its correlation to the signals at δ_H 2.25 (s, **1a**) and δ_H 2.33 (s, **2a**) and that δ_C 50.7 was due to the OCH_3 of **1a** and **2a** because of its correlation to attached to the signals δ_H 3.59 (s, **1a**) and δ_H 3.60 (s, **2a**) (Fig. 4). IR (KBr) cm^{-1}: 2929, 1708, 1649, 1609, 1486, 1316, 1173. EI-MS *m/z*: 228.0939 (Calcd for $C_{10}H_{16}N_2O_2S$: 228.0933). MS *m/z*: 228 (M^+), 213, 181.

Benzyl 1,4-Dihydro-4,4,6-trimethyl-2-methylthio Pyrimidine-5-car-



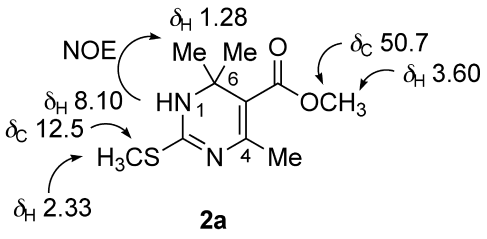
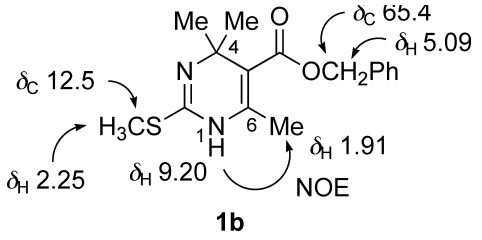


Fig. 4. NOE and HSQC Observed with **1a** and **2a**



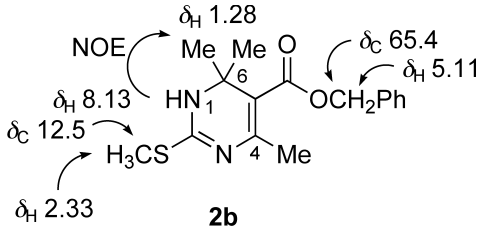


Fig. 5. NOE and HSQC Observed with **1b** and **2b**

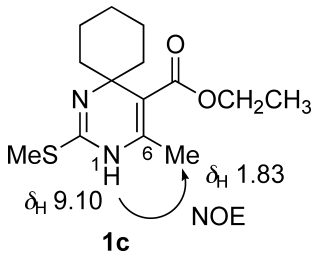


Fig. 6. NOE Observed with **1c**

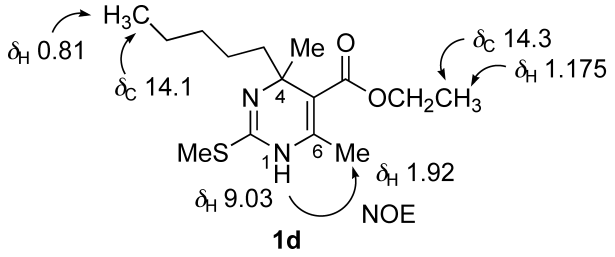
boxylate (1b) and Benzyl 1,6-Dihydro-4,6,6-trimethyl-2-methylthio Pyrimidine-5-carboxylate (2b): Colorless oil. Yield: 68%. **1b**/**2b**=1.6 : 1. ^{1}H-NMR (DMSO-d_6) δ: 1.27 (3.69H, s, **1b**), 1.28 (2.31H, s, **2b**), 1.91 (1.85H, s, **1b**), 1.96 (1.15H, s, **2b**), 2.25 (1.85H, s, **1b**), 2.33 (1.15H, s, **2b**), 5.09 (1.23H, s, **1b**), 5.11 (0.77H, s, **2b**), 7.28—7.41 (5H, m, **1b**+**2b**), 8.13 (0.38H, s, **2b**), 9.20 (0.62H, s, **1b**). Exact structural assignment was made using NOESY experiment: with the major component, the significant NOE was observed between 1-NH proton (δ 9.20) and 6-methyl protons (δ 1.91) and as such, its structure was determined to be **1b** (Fig. 5). With the minor component, the significant NOE was observed between 1-NH (δ 8.13) and 6,6-dimethyl protons (δ 1.28) and as such, its structure was determined to be **2b** (Fig. 5). ^{13}C-NMR (DMSO-d_6) δ: 12.5 (unresolved), 18.0, 23.4, 29.2, 31.1, 53.4, 55.9, 65.4 (unresolved), 104.6, 109.9, 128.2, 128.4, 128.7, 136.6, 142.6, 147.4, 151.1, 160.1, 167.0, 167.1. The unresolved signals, δ 12.5 and δ 65.4, were further analyzed by HSQC experiment, which revealed that the signal at δ_C 12.5 was due to the S-CH_3 of **1b** and **2b** because of its correlation to the signals at δ_H 2.25 (s, **1b**) and δ_H 2.33 (s, **2b**) and that δ_C 65.4 was due to the OCH_2Ph of **1b** and **2b** because of its correlation to attached to the signals δ_H 5.09 (s, **1b**) and δ_H 5.11 (s, **2b**) (Fig. 5). IR (neat) cm^{-1}: 3322, 1685, 1522, 1489, 1313, 1131. EI-MS *m*/*z*: 304.1249 (Calcd for $C_{16}H_{20}N_2O_2S$: 304.1245). MS *m*/*z*: 304 (M^+), 289, 91.

Ethyl 4-Methyl-2-methylthio-1,3-diazaspiro[5,5]undeca-2,5-diene 5-Carboxylate (1c) and Ethyl 4-Methyl-2-methylthio-1,3-diazaspiro[5,5] undeca-2,4-diene 5-Carboxylate (2c): Colorless crystals. Yield: 63%. **1c**/**2c**=8.4:1. mp 111—112 °C (*n*-hexane). ^{1}H-NMR (DMSO-d_6) δ: 1.10—1.90 (13.32H, m, **1c**+**2c**), 1.83 (2.68H, s, **1c**), 2.31 (2.68H, s, **1c**), 2.32 (0.32H, s, **2c**), 4.06 (1.79H, q, *J*=7.2 Hz, **1c**), 4.09 (0.21H, q, *J*=7.2 Hz, **2c**), 7.75 (0.11H, s, **2c**), 9.10 (0.89H, s, **1c**). Exact structural assignment was made using NOESY experiment: with the major component, the significant NOE was observed between 1-NH proton (δ 9.10) and 6-methyl protons (δ 1.83) and as such, its structure was determined to be **1c** (Fig. 6). ^{13}C-NMR (DMSO-d_6) δ: 12.6, 12.8, 14.3, 17.5, 19.8, 21.0, 22.3, 25.0, 25.9, 34.4, 36.9, 54.9, 57.6, 59.4, 59.6, 106.1, 112.0, 140.3, 146.9, 147.2, 159.4, 167.5. IR (KBr) cm^{-1}: 3293, 2944, 2922, 1686, 1656, 1618, 1482, 1141. EI-MS *m*/*z*: 282.1408 (Calcd for $C_{14}H_{22}N_2O_2S$: 282.1402). MS *m*/*z*: 282 (M^+), 239, 209, 154.

Ethyl 1,4-Dihydro-4,6-dimethyl-2-methylthio-4-pentyl Pyrimidine-5-carboxylate (1d) and Ethyl 1,6-Dihydro-4,6-dimethyl-2-methylthio-6-pentyl Pyrimidine-5-carboxylate (2d): Colorless oil. Yield: 80%. **1d**/**2d**=1.7 : 1. ^{1}H-NMR (DMSO-d_6) δ: 0.81 (1.89H, t, *J*=7.2 Hz, **1d**), 0.82 (1.11H, t, *J*=7.2 Hz, **2d**), 1.00—1.38 (7H, m, **1d**+**2d**), 1.175 (1.89H, t, *J*=7.2 Hz, **1d**), 1.178 (1.11H, t, *J*=7.2 Hz, **2d**), 1.22 (1.89H, s, **1d**), 1.25 (1.11H, s, **2d**), 1.82—1.94 (1H, m, **1d**+**2d**), 1.92 (1.89H, s, **1d**), 1.97 (1.11H, s, **2d**), 2.24 (1.89H, s, **1d**), 2.32 (1.11H, s, **2d**), 4.00—4.09 (2H, m, **1d**+**2d**), 7.93 (0.37H, s, **2d**), 9.03 (0.63H, s, **1d**). Exact structural assignment was made using NOESY experiment: with the major component, the significant NOE was observed between 1-NH proton (δ 9.03) and 6-methyl protons (δ 1.92) and as such, its structure was determined to be **1d** (Fig. 7). With the minor component, the significant NOE was observed between 1-NH (δ 7.93) and 6-methyl protons (δ 1.25) and as such, its structure was determined to be **2d** (Fig. 7). ^{13}C-NMR (DMSO-d_6) δ: 12.4, 12.5, 14.1 (unresolved), 14.3 (unresolved), 17.9, 22.3, 23.5, 24.2, 24.7, 29.6, 30.9, 31.7, 31.8, 40.9, 42.5, 56.9, 59.1, 59.2, 59.3, 102.9, 107.8, 142.8, 147.3, 151.5, 160.0, 167.2, 167.4. The unresolved signals, δ 14.1 and δ 14.3, were further analyzed by HSQC experiment, which revealed that the signal at δ_C 14.1 was due to the $CH_2CH_2CH_2CH_2CH_3$ of **1d** and **2d** because of its correlation to the signals at δ_H 0.81 (t, **1d**) and δ_H 0.82 (t, **2d**) and that δ_C 14.3 was due to the OCH_2CH_3 of **1d** and **2d** because of its correlation to attached to the signals δ_H 1.175 (t, **1d**) and δ_H 1.178 (t, **2d**) (Fig. 7). IR (neat) cm^{-1}: 3313, 2927, 1674, 1487, 1138. EI-MS *m*/*z*: 298.1720 (Calcd for $C_{15}H_{26}N_2O_2S$: 298.1715). MS *m*/*z*: 298 (M^+), 227, 199.

Ethyl 1,4-Dihydro-6-methyl-2-methylthio-4,4-dipropyl Pyrimidine-5-carboxylate (1e) and Ethyl 1,6-Dihydro-4-methyl-2-methylthio-6,6-dipropyl Pyrimidine-5-carboxylate (2e): Colorless oil. Yield: 63%. **1e**/**2e**=1.8 : 1. ^{1}H-NMR (DMSO-d_6) δ: 0.79 (3.86H, t, *J*=7.2 Hz, **1e**), 0.82 (2.14H, t, *J*=7.2 Hz, **2e**), 1.09—1.34 (9H, m, **1e**+**2e**), 1.75—1.87 (2H, m, **1e**+**2e**), 1.93 (1.93H, s, **1e**), 1.99 (1.07H, s, **2e**), 2.24 (1.93H, s, **1e**), 2.31 (1.07H, s, **2e**), 4.04 (1.29H, q, *J*=7.2 Hz, **1e**), 4.05 (0.71H, q, *J*=7.2 Hz, **2e**), 7.77 (0.36H, s, **2e**), 8.90 (0.64H, s, **1e**). Exact structural assignment was made using NOESY experiment: with the major component, the significant NOE was observed between 1-NH proton (δ 8.90) and 6-methyl protons (δ 1.93) and as such, its structure was determined to be **1e** (Fig. 8). With the minor component, the significant NOE was observed between 1-NH (δ 7.77) and 6-methylene protons (δ 1.75—1.87) and as such, its structure was determined to be **2e** (Fig. 8). ^{13}C-NMR (DMSO-d_6) δ: 12.2, 12.3, 14.3, 14.4, 14.6 (unresolved), 17.8, 18.01, 18.03, 23.8, 44.1, 45.3, 59.06, 59.13, 60.7, 63.0, 100.4, 105.0, 143.7, 147.2, 152.8, 160.3, 167.4, 167.5. The unresolved signal, δ 14.6, was further analyzed by HSQC experiment, which revealed that the signal at δ_C 14.6 was due to the $CH_2CH_2CH_3$ of **1e** and **2e** because of its correlation to the signals at δ_H 0.79 (t, **1e**) and δ_H 0.82 (t, **2e**) (Fig. 8). IR (neat) cm^{-1}: 2958, 1689, 1668, 1658, 1499, 1279, 1139. EI-MS *m*/*z*: 298.1714 (Calcd for $C_{15}H_{26}N_2O_2S$: 298.1715). MS *m*/*z*: 298 (M^+), 255, 227.

Ethyl 1,4-Dihydro-4,4-dimethyl-2-methylthio-6-phenyl Pyrimidine-5-carboxylate (1f) and Ethyl 1,6-Dihydro-6,6-dimethyl-2-methylthio-4-phenyl Pyrimidine-5-carboxylate (2f): Colorless crystals. Yield: 73%. **1f**/**2f**=1 : 3.7. mp 132—134 °C (*n*-hexane–EtOAc). ^{1}H-NMR (DMSO-d_6) δ: 0.67 (0.64H, t, *J*=7.2 Hz, **1f**), 0.77 (2.36H, t, *J*=7.2 Hz, **2f**), 1.33 (1.28H, s,



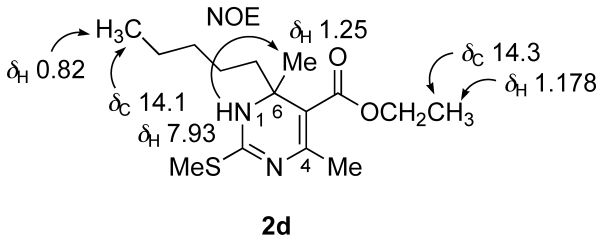


Fig. 7. NOE and HSQC Observed with **1d** and **2d**

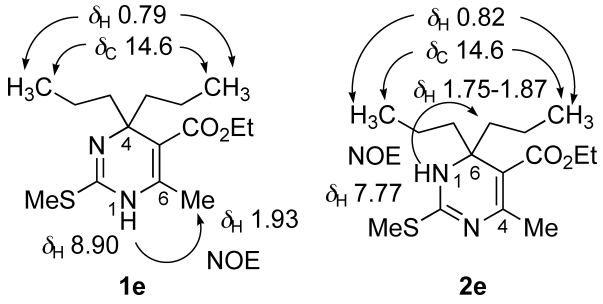


Fig. 8. NOE and HSQC Observed with **1e** and **2e**

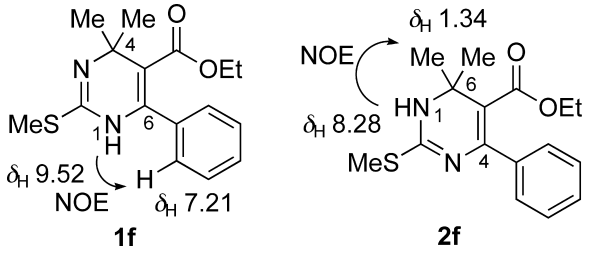
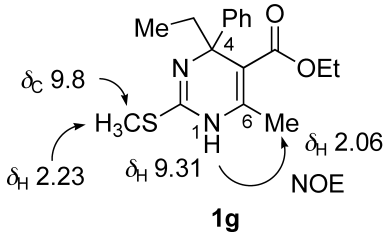


Fig. 9. NOE Observed with **1f** and **2f**



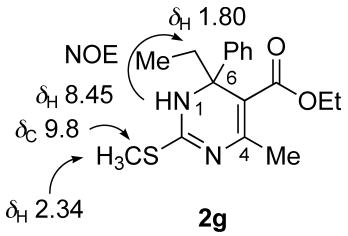


Fig. 10. NOE and HSQC Observed with **1g** and **2g**

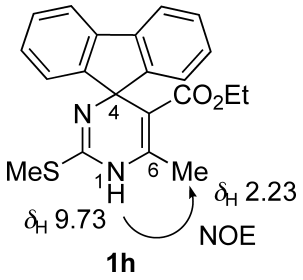


Fig. 11. NOE Observed with **1h**

1f), 1.34 (4.72H, s, **2f**), 2.29 (0.64H, s, **1f**), 2.38 (2.36H, s, **2f**), 3.70 (0.43H, q, J=7.2 Hz, **1f**), 3.79 (1.57H, q, J=7.2 Hz, **2f**), 7.21 (0.43H, dd, J=1.8, 7.8 Hz, **1f**), 7.25—7.34 (3.93H, m, **2f**), 7.35—7.45 (0.64H, m, **1f**), 8.28 (0.79H, s, **2f**), 9.52 (0.21H, s, **1f**). Exact structural assignment was made using NOESY experiment: with the major component, the significant NOE was observed between 1-NH proton (δ 8.28) and 6,6-methyl protons (δ 1.34) and as such, its structure was determined to be **2f** (Fig. 9). With the minor component, the significant NOE was observed between 1-NH (δ 9.52) and 6-phenyl protons (δ 7.21) and as such, its structure was determined to be **1f** (Fig. 9). ^{13}C-NMR (DMSO-d_6) δ: 12.7, 12.8, 13.46, 13.53, 28.6, 30.2, 53.2, 55.8, 59.3, 59.6, 107.0, 110.9, 127.7, 127.9, 128.0, 128.2, 128.3, 129.1, 135.3, 140.8, 141.4, 147.8, 148.9, 159.7, 167.5, 167.9. IR (KBr) cm^{-1}: 2976, 1702, 1535, 1499, 1326, 1194, 1051. EI-MS (EI) m/z: 304.1250 (Calcd for $C_{16}H_{20}N_2O_2S$: 304.1245). MS (EI) m/z: 304 (M^+), 289, 261.

Ethyl 4-Ethyl-1,4-dihydro-6-methyl-2-methylthio-4-phenyl Pyrimidine-5-carboxylate (1g) and Ethyl 6-Ethyl-1,6-dihydro-4-methyl-2-methylthio-6-phenyl Pyrimidine-5-carboxylate (2g): Colorless crystals. Yield: 63%. **1g**/**2g**=3.0 : 1. mp 149—150 °C (*n*-hexane–EtOAc). ^{1}H-NMR (DMSO-d_6) δ: 0.80 (2.25H, t, J=7.2 Hz, **1g**), 0.90 (0.75H, t, J=7.2 Hz, **2g**), 0.94 (2.25H, t, J=7.2 Hz, **1g**), 0.95 (0.75H, t, J=7.2 Hz, **2g**), 1.80 (0.25H, dq, J=13.8, 7.2 Hz, **2g**), 1.87 (0.75H, dq, J=7.2, 13.2 Hz, **1g**), 2.06 (2.25H, s, **1g**), 2.13 (0.75H, s, **2g**), 2.23 (2.25H, s, **1g**), 2.34 (0.75H, s, **2g**), 2.36—2.47 (1H, m, **1g**+**2g**), 3.79—3.92 (2H, m, **1g**+**2g**), 7.11 (0.75H, t, J=7.2 Hz, **1g**), 7.19 (0.25H, t, J=7.2 Hz, **2g**), 7.23 (1.5H, t, J=7.2 Hz, **1g**), 7.30 (0.5H, t, J=7.2 Hz, **2g**), 7.31 (1.5H, d, J=7.2 Hz, **1g**), 7.37 (0.5H, d, J=7.2 Hz, **2g**), 8.45 (0.25H, s, **2g**), 9.31 (0.75H, s, **1g**). Exact structural assignment was made using NOESY experiment: with the major component, the significant NOE was observed between 1-NH proton (δ 9.31) and 6-methyl protons (δ 2.06) and as such, its structure was determined to be **1g** (Fig. 10). With the minor component, the significant NOE was observed between 1-NH (δ 8.45) and 6-methylene protons (δ 1.80) and as such, its structure was determined to be **2g** (Fig. 10). ^{13}C-NMR (DMSO-d_6) δ: 9.8 (unresolved), 12.4, 12.5, 13.95, 13.98, 18.10, 24.0, 31.3, 32.9, 59.0, 59.1, 62.2, 64.9, 101.0, 105.6, 125.8, 126.4, 126.7, 126.8, 127.5, 127.9, 144.3, 147.9, 149.0, 150.3, 153.5, 159.8, 166.95, 167.0. The unresolved signal, δ 9.8, was further analyzed by HSQC experiment, which revealed that the signal at δ_C 9.8 was due to the S-CH$_3$ of **1g** and **2g** because of its correlation to the signals at δ_H 2.23 (s, **1g**) and δ_H 2.34 (s, **2g**) (Fig. 10). IR (KBr) cm^{-1}: 3264, 2969, 1664, 1583, 1530, 1462, 1314, 1073. EI-MS m/z: 318.1401 (Calcd for $C_{17}H_{22}N_2O_2S$: 318.1400). MS m/z: 318 (M^+), 289, 261.

Ethyl 6-Methyl-2-methylthio Spiro[9′*H*-fluorene-9′,4-1,4-dihydropyrimidine] 5-Carboxylate (1h) and Ethyl 4-Methyl-2-methylthio Spiro[9′*H*-fluorene-9′,6-1,6-dihydropyrimidine] 5-Carboxylate (2h): Yellow amorphous solid. Yield: 40%. **1h**/**2h**=6.0 : 1. mp 57—63 °C. ^{1}H-NMR (DMSO-d_6) δ: 0.35 (2.57H, t, J=7.2 Hz, **1h**), 0.36 (0.43H, t, J=7.2 Hz, **2h**), 2.02 (2.57H, s, **1h**), 2.23 (2.57H, s, **1h**), 2.27 (0.43H, s, **2h**), 2.40 (0.43H, s, **2h**), 3.30 (1.71H, q, J=7.2 Hz, **1h**), 3.33 (0.29H, q, J=7.2 Hz, **2h**), 7.19—7.26 (3.42H, m, **1h**), 7.26—7.29 (0.29H, m, **2h**), 7.30 (1.71H, dt, J=1.2, 7.2 Hz, **1h**), 7.36 (0.29H, dt, J=1.2, 7.2 Hz, **2h**), 7.40 (0.29H, d, J=7.8 Hz, **2h**), 7.71 (1.71H, d, J=7.2 Hz, **1h**), 7.74 (0.29H, d, J=7.2 Hz, **2h**), 8.75 (0.14H, s, **2h**), 9.73 (0.86H, s, **1h**). Exact structural assignment was made using NOESY experiment: with the major component, the significant NOE was observed between 1-NH proton (δ 9.73) and 6-methyl protons (δ 2.23) and as such, its structure was determined to be **1h** (Fig. 11). ^{13}C-NMR

(DMSO-d_6) δ: 12.4, 12.7, 13.0, 13.1, 18.1, 24.0, 58.4, 58.5, 65.7, 69.4, 99.5, 105.0, 119.7, 120.0, 124.1, 124.3, 127.7, 127.9, 128.3, 128.8, 139.3, 139.5, 146.6, 150.0, 152.3, 155.0, 155.2, 161.0, 165.8, 165.9. IR ($CHCl_3$) cm^{-1}: 3298, 1676, 1648, 1483, 1165, 1106. EI-MS *m*/*z*: 364.1249 (Calcd for $C_{21}H_{20}N_2O_2S$: 364.1245). MS *m*/*z*: 364 (M^+), 291.

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