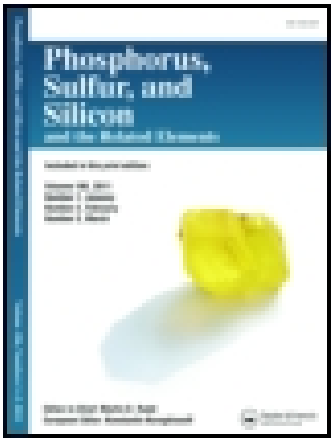

Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/gpss20

Addition of Organolithium and Grignard Reagents to Pyrimidine-2(1H)-thione: Easy Access to 4-Substituted 3,4-Dihydropyrimidine-2(1H)-thiones

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Published online: 22 Jul 2009.

To cite this article: Jacek G. Sośnicki (2009) Addition of Organolithium and Grignard Reagents to Pyrimidine-2(1H)-thione: Easy Access to 4-Substituted 3,4-Dihydropyrimidine-2(1H)-thiones, Phosphorus, Sulfur, and Silicon and the Related Elements, 184:8, 1946-1957, DOI: 10.1080/10426500903110066

To link to this article: http://dx.doi.org/10.1080/10426500903110066

Phosphorus, Sulfur, and Silicon, 184:1946–1957, 2009

ISSN: 1042-6507 print / 1563-5325 online
DOI: 10.1080/10426500903110066

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Addition of Organolithium and Grignard Reagents to Pyrimidine-2(1*H*)-thione: Easy Access to 4-Substituted 3,4-Dihydropyrimidine-2(1*H*)-thiones

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Organolithium and Grignard reagents are added to pyrimidine-2(1H)-thione, yielding 4-substituted 3,4-dihydropyrimidine-2-(1H)-thiones. Since the synthetic procedure can be performed on a multigram scale, and since pyrimidine-2(1H)-thione as well as the majority of organometallic reagents are readily available, the process described provides an easy access and complementary to other methods to 4-substituted 3,4-dihydropyrimidine-2-(1H)-thiones.

Keywords 3,4-Dihydropyrimidine-2(1*H*)-thiones; Grignard reagents; nucleophilic addition; organolithium reagents; pyrimidine-2(1*H*)-thione

INTRODUCTION

In the last two decades, 3,4-dihydropyrimidine-2(1*H*)-thiones were recognized as valuable pharmacophores, which show a wide range of pharmacological activities,[1] including calcium channel modulation activity (e.g., **1**, SQ 32547, Figure 1)[2] and anticancer activity (monastrol, **2**, Figure 1),[3] as well as novel low molecular weight molecules with high cell permeability[4] and biological activities of other type.[5–7]

A large majority of 3,4-dihydropyrimidine-2(1*H*)-thione derivatives were synthesized according to the three-component protocol developed by Biginelli in 1893 (Scheme 1).[8] To the present date, a number of improvements have been introduced in order to enhance the efficiency of this reaction,[9,10] including an enantioselective approach.[11–13] However, due to limited application to the aromatic or unsaturated aldehydes,

Received 13 December 2007; accepted 12 August 2008.

Dedicated to Professor Marian Mikołajczyk, CBMiM PAN in Łódź, Poland, on the occasion of his 70th birthday.

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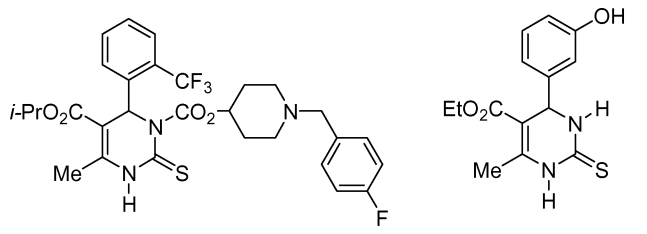


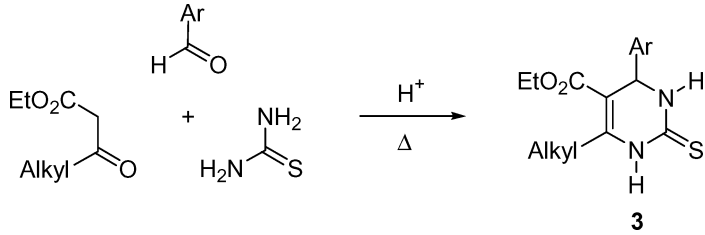
FIGURE 1 Biologically active representatives of the 3,4-dihydropyrimidine-2(1*H*)-thione family.

the Biginelli reaction suffers from the lack of the attachment of the optional substituent at C-4.

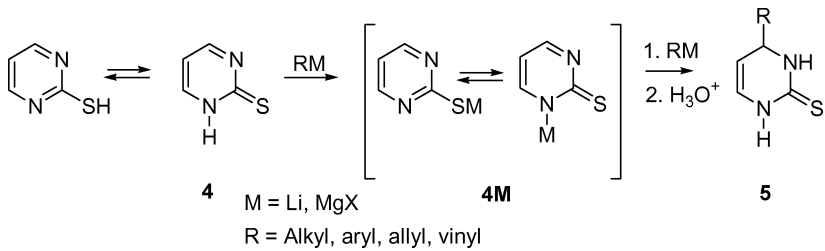
Another method of synthesizing 3,4-dihydropyrimidine-2(1*H*)-thiones involves the condensation reaction between functionalized amines with either 4-isothiocyanato-2-pentanone or 3-isothiocyanatobutanal.[5–7,14] The synthesis of 3,4-dihydropyrimidine-2(1*H*)-thiones by the reaction of derivatives of pyrimidine-2(1*H*)-thiones with organometallic nucleophiles has been given less attention; it has been limited only to *N*-substituted 4,6-dimethyl species.[15]

Exploring the concept of the use of simple precursors in the synthesis of functionalized piperidine-2(1*H*)-(thio)ones, we have recently reported that organolithium reagents can be added to pyridine-2(1*H*)-thione (commercially available as 2-mercaptopyridine) yielding 4- or 6-substituted dihydropyridine-2-thiones,[16,17] while standard Grignard reagents were insufficiently reactive in these reactions.

Taking into account a more pronounced electron deficiency in the pyrimidine than in the pyridine ring,[18] we investigated the reaction of organometallic reagents with pyrimidine-2(1*H*)-thione (commercially available as 2-mercaptopyrimidine). We anticipated that addition of the organometallic reagents to pyrimidine-2(1*H*)-thione would take place



SCHEME 1 Biginelli aryl-3,4-dihydropyrimidine-2(1*H*)-thiones synthesis.



SCHEME 2 Synthesis of 4-substituted 3,4-dihydropyrimidine-2(1*H*)-thiones **5**.

much easier than to pyridine-2(1*H*)-thione, and that the preparation of 3,4-dihydropyrimidine-2(1*H*)-thione could be achieved also using Grignard reagents. In order to check the scope and the limitations of the addition and to demonstrate the possibilities of introducing a substituent at C-4, a variety of alkyl, aryl, allyl, and vinyl organolithium compounds as well as Grignard reagents were tested in these reactions.

RESULTS AND DISCUSSION

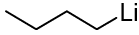
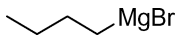
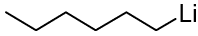
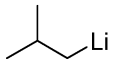
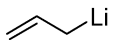
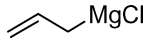
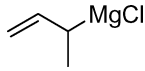
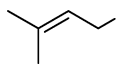
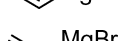
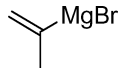
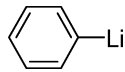
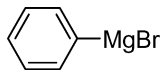
As expected, pyrimidine-2(1*H*)-thione **4** affords 4-substituted 3,4-dihydropyrimidine-2(1*H*)-thiones (**5**) from the reactions with both organolithium and Grignard reagents. The results and conditions of the reactions are presented in Table I. An amount of 2–3 equivalents of the organometallic reagent with respect to **4** was required in order to obtain product **5** in optimum yields. The first equivalent of RM converted **4** into the metallated salt **4M**, and the second one induced addition (Scheme 2, Table I).

In general, the reactions were performed at 0°C in THF or in DEE as solvents. However, in some cases the reaction was initiated at a low temperature, which was subsequently raised. All 4-substituted 3,4-dihydropyrimidine-2(1*H*)-thiones were obtained in good yields and on a multigram scale. In the case of 1-methyl-2-propenylmagnesium chloride, the addition afforded an inseparable 70:30 mixture of two diastereomers (Table I).

It should be emphasized that the products did not require labor-consuming purification. The protocol applied, sufficient to obtain the product in pure state, consisted of an extraction using ethyl acetate, simple filtration of the solution through the pad of Celite under reduced pressure, and subsequent crystallization of the white solid.

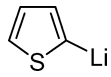
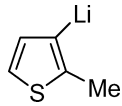
As far as the reactivity of the organometallic reagents is concerned, it should be noted that the organometallic compounds used showed

TABLE I Reaction Conditions and Yields of 5 Obtained by the Addition Reaction of 4 with Organolithium and Grignard Reagents

5	RM	Solvent[d]	Temp. [°C]	Reaction Time [min]	Equivalents RM	Yields [%]
a		THF/DEE	0	15	3	80
a		THF	0	15	3	30
b		THF/hexane	0	15	3	84
b		THF	0	30	3	31
c		DEE/hexane	0	15	3	99
d	 [a]	DEE/pentane	−78 −78 to −40	15 15	3	98
e		DEE/pentane	−78 −78 to r.t.	20 30	2.5	92
f	 [b]	THF/pentane	−78 to r.t.	30	2.1	75
f		THF	0	30	2.2	99
g		THF	0	15	2.2	78[e]
h	 [c]	THF	0 0 to r.t.	60 15	2.5	96
i	 [a]	DEE/pentane	−78 −78 to r.t.	30 30	2.5	80
j		THF	0	30	2.5	96
k		THF	0	30	2.6	63
l		DBE/DEE	−78 to −20	30	2.1	95
l		DEE/THF	0	30	2.5	40

(*Continued on next page*)

TABLE I Reaction Conditions and Yields of 5 Obtained by the Addition Reaction of 4 with Organolithium and Grignard Reagents (*Continued*)

5	RM	Solvent[d]	Temp. [°C]	Reaction Time [min]	Equivalents RM	Yields [%]
m		THF	−78 to 0	30	2.1	70
n		THF/pentane	−30 −30 to r.t.	60 15	2.2	55

[a]RLi obtained by the reaction of RX (X = I, **5d**, X = Br, **5i**) with 2 equiv. of *t*-BuLi.[19]

[b]Allyllithium prepared from AllylBu$_3$Sn (see the Experimental section).

[c]1,1-Dimethylallyl substituent is present in the product.

[d]THF – tetrahydrofuran; DEE – diethylether; DBE – dibuthylether.

[e]Obtained as 70:30 mixture of diastereomers.

different reactivity regarding the addition to pyrimidine-2(1*H*)-thione. Alkyl and aryl organolithium nucleophiles were more effective than the corresponding Grignard reagents, thus the majority of products **5** with alkyl and aryl substituents were prepared using organolithium compounds, both commercially available and prepared according to known methods. On the other hand, allyl- and vinylmagnesium reagents are very reactive and afford products in good or very good yield; this applies particularly to allylmagnesium reagents. Since preparation of allyllithium reagents often requires expensive and toxic starting materials (e.g., organotin derivatives), the use of allyl Grignard reagents seemed to be a good alternative for these reactions.

The structures of all products **5** were determined on the basis of 1D NMR (^{1}H, ^{13}C, ^{13}C-DEPT) and 2D NMR (^{1}H, ^{1}H COSY, ^{13}C, ^{1}H HETCOR) spectroscopy, IR spectroscopy, mass spectrometry, and elemental analysis. ^{1}H NMR spectroscopy showed the characteristic signals of CH-4, appearing in the region of 3.7–5.4 ppm as a broad singlet or as a broad multiplet. The signals of =CH-5 and =CH-6 are present at 4.8–5.1 ppm and near 6.0 ppm, respectively. Analysis of the multiplets showed that in all cases =CH-5 and =CH-6 protons are coupled and that the value of coupling constant (*J*) is about 8.0 Hz.

In summary, we have described an efficient access to 4-substituted derivatives of 3,4-dihydropyrimidine-2(1*H*)-thione obtained by the reaction between organolithium and/or Grignard reagents with

unsubstituted pyrimidine-2(1*H*)-thione. Due to complementary reactivity of both reactants, alkyl, aryl, allyl and vinyl substituents were introduced at C-4. Since this synthetic procedure can be performed on a multigram scale, and since pyrimidine-2(1*H*)-thione **4** and most of organometallic reagents used are readily available, the process described provides a new and easy way to obtain 4-substituted 3,4-dihydropyrimidine-2-(1*H*)-thione derivatives, which complements other methods.

EXPERIMENTAL

Melting points were determined on a Boetius hot stage apparatus. ^{1}H and ^{13}C NMR spectroscopic measurements were performed with a Bruker DPX 400 spectrometer equipped with a 5 mm ^{1}H/BB–inverse probehead, operating at 400.13 and 100.62 MHz, respectively. TMS was used as internal reference. Two-dimensional spectra were acquired using standard Bruker software. Mass spectra (70 eV) were recorded with an HP 6890 (Hewlett-Packard) GC-MS spectrometer equipped with a mass detector HP 5973. Elemental analyses were performed with EuroEA 3000 series, EuroVector CHNS-O Elemental Analyzer.

Starting Compounds

Pyrimidine-2(1*H*)-thione **4**, butyllithium (2.5 M in hexane), *tert*-butyllithium (1.7 M in pentane), phenyllithium (2.0 M in Bu_2O), hexyllithium (2.3 M in hexane), 2-thienyllithium (1.0 M in THF), allylmagnesium chloride (2.0 M in THF), and 1-methyl-2-propenylmagnesium chloride (0.5 M in THF) were purchased from Aldrich. Methyllithium (1.6 M in Et_2O) was purchased from Acros Organics. Isobutyllithium was prepared from appropriate iodoalkane and 2.0 eq of *tert*-butyllithium.[19] The same procedure was applied for the synthesis of cyclopentenyllithum; however here 1-bromocyclopentene was used. 3,3-Dimethylallylmagnesium bromide was prepared as described earlier.[20] 3-(2-Methylthienyl)lithium was obtained by treatment of 2-methylthiophene with butyllithium in equimolar ratio at -30°C in THF and stirred over 1 h. Allyllithium reagents were prepared by stirring the appropriate allyltributyltin compound (1.0 eq) with 1.0 eq of butyllithium at r.t. for 30 min. All reagents were prepared under argon prior to use. Solvents (THF and DEE) were purified over sodium in argon atmosphere according to a standard procedure prior to use.

Preparation of 3,4-Dihydropyrimidine-2(1*H*)-thiones: General Procedure

To a cooled and stirred solution of 0.029 mol of pyrimidine-2(1*H*)-thione (**4**) in dry solvent (50–70 mL) (see Table I), a portion of 0.059–0.088 mol of RM solution (see Table I) was added via syringe over 3 min under argon. The mixture was stirred at the temperature and for the period specified in Table I. After quenching with aqueous saturated NH_4Cl (15 mL), the water layer was extracted with ethyl acetate (2 × 150 mL) and the combined organic layers were dried over $MgSO_4$. Filtration through a 1 cm pad of Celite followed by concentration of the filtrate in vacuo and crystallization from the appropriate solvent yielded **4** as white solid in all cases.

4-Methyl-3,4-dihydropyrimidine-2(1H)-thione (5a)

White solid, mp 137–139°C from *n*-hexane:ethyl acetate; ^{1}H NMR (400.13 MHz, $CDCl_3$): δ =1.32 (d, J = 6.4 Hz, 3H, CH_3), 4.23 (br s, 1H, CH-4), 4.85 (d, J = 7.7 Hz, 1H, =CH-5), 5.96 (dd, J = 7.2, 4.8 Hz, 1H, =CH-6), 7.44 (br s, 1H, NH), 8.54 (br s, 1H, NH);^{13}C NMR (100.63 MHz, $CDCl_3$): δ = 24.5 (CH_3), 48.0 (CH-4), 105.1 (=CH-5), 122.1 (=CH-6), 174.6 (C-2); MS (EI, 70 eV) m/z: 128 (100), 113 (94), 79 (14), 68 (15), 60 (7), 41 (9); IR (KBr pellet, cm^{-1}):ν_{max} = 3204, 2968, 2928, 1674, 1584, 1504, 1436, 1302, 1220, 1192, 736, 638; Anal. Calcd. for $C_5H_8N_2S$: C 46.84; H 6.29; N 21.85; S 25.01; Found: C 46.85; H 6.33; N 21.79; S 24.90.

4-Butyl-3,4-dihydropyrimidine-2(1H)-thione (5b)

White solid, mp 91–93°C from *n*-hexane:ethyl acetate; ^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 0.91 (t, J = 7.1 Hz, 3H, CH_3), 1.27–1.43 (m, 4H, CH_2), 1.54–1.64 (m, 2H, CH_2), 4.09–4.15 (m, 1H, CH-4), 4.86 (d of quintets, J = 7.9, 1.6 Hz, 1H, =CH-5), 5.99 (ddd, J = 7.9, 4.6, 1.0 Hz, 1H, =CH-6), 7.22 (br s, 1H, NH), 8.46 (br s, 1H, NH); ^{13}C NMR (100.63 MHz, $CDCl_3$): δ = 14.0 (CH_3), 22.5 (CH_2), 26.1 (CH_2), 37.8 (CH_2), 52.3 (CH-4), 103.7 (=CH-5), 122.6 (=CH-6), 175.0 (C-2); MS (EI, 70 eV) m/z: 170 ($M^{+\cdot}$, 32), 126 (3), 113 (100), 79 (9); IR (KBr pellet, cm^{-1}):ν_{max} = 3192, 2956, 2928, 1570, 1498, 1312, 1218, 1180, 754, 650; Anal. Calcd. for $C_8H_{14}N_2S$: C 56.43; H 8.29; N 16.45; S 18.83: Found: C 56.36; H 8.35; N 16.44; S 18.91.

4-Hexyl-3,4-dihydropyrimidine-2(1H)-thione (5c)

White solid, mp 94–96°C from *n*-hexane:ethyl acetate; ^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 0.88 (t, J = 7.0 Hz, 3H, CH_3), 1.25–1.42 (m, 8H, CH_2), 1.53–1.61 (m, 2H, CH_2), 4.08–4.15 (m, 1H, CH-4), 4.86 (d

of quintets, $J = 8.0$, 1.6 Hz, 1H, =CH-5), 5.98 (ddd, $J = 8.0$, 4.5, 0.8 Hz, 1H, =CH-6), 7.04 (br s, 1H, NH), 8.27 (br s, 1H, NH); ^{13}C NMR (100.63 MHz, $CDCl_3$): $\delta = 14.1$ (CH_3), 22.6 (CH_2), 24.0 (CH_2), 29.0 (CH_2), 31.7 (CH_2), 38.2 (CH_2), 52.3 (CH-4), 103.7 (=CH-5), 122.6 (=CH-6), 175.2 (C-2); MS (EI, 70 eV) m/z: 198 (30), 113 (100), 79 (6), 41 (4); IR (KBr pellet, cm^{-1}) :$\nu_{max} = 3196$, 2960, 2856, 1678, 1570, 1498, 1380, 1316, 1216, 1178, 754; Anal. Calcd. for $C_{10}H_{18}N_2S$: C 60.56; H 9.15; N 14.12; S 16.17; Found: C 60.61; H 9.18; N 14.03; S 16.22.

4-Isobutyl-3,4-dihydropyrimidine-2(1H)-thione (5d)

White solid, mp 160–163°C from EtOH; ^{1}H NMR (400.13 MHz, $CDCl_3$): $\delta = 0.92$ (d, $J = 6.6$ Hz, 6H, CH_3), 1.42 (quintet, $J = 6.8$ Hz, 1H, C<u>H</u>H), 1.56 (quintet, $J = 6.8$ Hz, 1H, CH<u>H</u>), 1.79 (septet, $J = 6.7$ Hz, 1H, CH), 4.12 (br s, 1H, CH-4), 4.89 (br d, $J = 7.9$ Hz, 1H, =CH-5), 5.97 (dd, $J = 7.9$, 4.6, Hz, 1H, =CH-6), 6.85 (br s, 1H, NH), 8.07 (br s, 1H, NH); ^{13}C NMR (100.63 MHz, $CDCl_3$): $\delta = 22.3$ (CH_3 or CH), 22.8 (CH_3 or CH), 23.3 (CH_3 or CH), 47.4 (CH_2), 50.5 (CH-4), 104.2 (=CH-5), 122.4 (=CH-6), 175.3 (C-2); MS (EI, 70 eV) m/z: 170 (34), 113 (100), 79 (10); IR (KBr pellet, cm^{-1}):$\nu_{max} = 3208$ br, 2956, 1676, 1572, 1492, 1464, 1384, 1302, 1214, 1168, 756, 648; Anal. Calcd. for $C_8H_{14}N_2S$: C 56.43; H 8.29; N 16.45; S 18.83; Found: C 56.38; H 8.22; N 16.53; S 18.90.

4-tert-Butyl-3,4-dihydropyrimidine-2(1H)-thione (5e)

White solid, mp 245–246°C from EtOH; ^{1}H NMR (400.13 MHz, $CDCl_3$): $\delta = 0.93$ (s, 9H, CH_3), 3.67–3.71 (m, 1H, CH-4), 4.94 (d of quintets, $J = 8.1$, 2.0 Hz, 1H, =CH-5), 6.07 (ddd, $J = 8.1$, 4.6, 0.7 Hz, 1H, =CH-6), 6.52 (br s, 1H, NH), 7.61 (br s, 1H, NH); ^{13}C NMR (100.63 MHz, $CDCl_3$): $\delta = 24.6$ (CH_3), 37.2 (<u>C</u>(CH_3)$_3$), 62.0 (CH-4), 101.1 (=CH-5), 123.4 (=CH-6), 176.1 (C-2); MS (EI, 70 eV) m/z: 170 ($M^{+\cdot}$, 27), 113 (100), 79 (10); IR (KBr pellet, cm^{-1}): $\nu_{max} = 3212$, 2964, 1678, 1566, 1490, 1304, 1218, 1182; Anal. Calcd. for $C_8H_{14}N_2S$: C 56.43; H 8.29; N 16.45; S 18.83; Found: C 56.51; H 8.19; N 16.39; S 18.91.

4-Allyl-3,4-dihydropyrimidine-2(1H)-thione (5f)

White solid, mp 100–102°C from *n*-hexane:ethyl acetate; ^{1}H NMR (400.13 MHz, $CDCl_3$): $\delta = 2.27$–2.43 (m, 2H, CH_2), 4.14–4.20 (m, 1H, CH-4), 4.87 (d of quintets, $J = 8.0$. 1.6 Hz, 1H, =CH-5), 5.15 (m, 2H, =CH_2), 5.69–5.81 (m, 1H, =CH), 6.00 (ddd, $J = 8.0$, 4.7, 1.3 Hz, 1H, =CH-6), 7.16 (br s, 1H, NH), 8.51 (br s, 1H, NH); ^{13}C NMR (100.63 MHz, $CDCl_3$): $\delta = 42.6$ (CH_2), 51.6 (CH-4), 103.1 (=CH-5), 119.8 (=CH_2), 122.9 (=CH-6), 132.0 (=CH), 175.1 (C-2); MS (EI, 70 eV) m/z: 154 (6), 113 (100), 79 (14); IR (KBr pellet, cm^{-1}): $\nu_{max} = 3212$, 1676, 1568, 1496,

1314, 1216, 1178, 912, 740; Anal. Calcd. for $C_7H_{10}N_2S$: C 54.51; H 6.54; N 18.16; S 20.79; Found: C 54.45; H 6.62; N 18.15; S 20.69.

4-(1-Methylallyl)-3,4-dihydropyrimidine-2(1H)-thione (5g)

White solid. Crystallization from *n*-hexane:ethyl acetate enriched the quantity of the major isomer from 70:30 to 80:20; NMR data of the major isomer were obtained from the spectra of 80:20 diastereomer mixture. ^{1}H NMR (400.13 MHz, $CDCl_3$): $\delta = 1.07$ (d, $J = 6.9$ Hz, 3H, CH_3), 2.29–2.39 (m, 1H, 4-CH), 4.08–4.13 (m, 1H, CH-4), 4.85 (dm, $J =$ 8.1 Hz, 1H, =CH-5), 5.17 (dt, $J = 17.2$, 1.3 Hz, 1H, =C<u>H</u>H), 5.21 (dt, $J = 10.6$, 1.3 Hz, 1H, =CH<u>H</u>), 5.78 (ddd, $J = 17.2$, 10.6, 6.6 Hz, 1H, =CH), 6.04 (ddd, $J = 8.1$, 4.6, 1.3 Hz, 1H, =CH-6), 6.61 (br s, 1H, NH), 8.00 (br s, 1H, NH); ^{13}C NMR (100.63 MHz, $CDCl_3$): $\delta = 13.1$ (CH_3), 43.9 (CH-4), 56.4 (CH-4), 101.9 (=CH-5), 117.3 (=CH_2), 123.5 (=CH-6), 138.2 (=CH), 175.9 (C-2); MS (EI, 70 eV) m/z: 168 ($M^{+\cdot}$, 2), 113 (100), 79 (11); IR (KBr pellet, cm^{-1}): $\nu_{max} =$ 3208 br, 2972, 1678, 1568, 1492, 1216, 1180, 916, 752. Anal. Calcd. for $C_8H_{12}N_2S$: C, 57.11; H, 7.19; N, 16.65; S, 19.06; Found: C, 57.03; H, 7.16; N, 16.74; S, 18.99.

4-(1,1-Dimethylallyl)-3,4-dihydropyrimidine-2(1H)-thione (5h)

White solid, mp 227–229°C from EtOH; ^{1}H NMR (400.13 MHz, $CDCl_3$): $\delta = 1.01$ (s, 3H, CH_3), 1.04 (s, 3H, CH_3), 3.78–3.82 (m, 1H, CH-4), 4.91 (d of quintets, $J = 8.1$, 1.8 Hz, 1H, =CH-5), 5.14 (d, $J =$ 17.4 Hz, 1H, =C<u>H</u>H), 5.19 (d, $J = 10.8$ Hz, 1H, =CH<u>H</u>), 5.71 (dd, $J =$ 17.4, 10.8 Hz, 1H, =CH), 6.08 (ddd, $J = 8.1$, 4.6, 1.3 Hz, 1H, =CH-6), 6.52 (br s, 1H, NH-3), 7.95 (br s, 1H, NH-1); ^{13}C NMR (100.63 MHz, $CDCl_3$): $\delta = 20.4$ (CH_3), 22.3 (CH_3), 43.3 (4<u>C</u>(CH_3)$_2$), 60.2 (CH-4), 100.2 (=CH-5), 115.3 (=CH_2), 123.8 (=CH-6), 143.1 (=CH), 175.8 (C-2); MS (EI, 70 eV) m/z: 182 ($M^{+\cdot}$, 1), 113 (100), 79 (9); IR (KBr pellet, cm^{-1}): $\nu_{max} =$ 3208 br, 2928, 1678, 1566, 1498, 1308, 1218, 1184, 916. Anal. Calcd. for $C_9H_{14}N_2S$: C 59.30; H 7.74; N 15.37; S 17.59; Found: C 59.39; H 7.69; N 15.40; S 17.63.

4-Cyclopent-1-enyl-3,4-dihydropyrimidine-2(1H)-thione (5i)

White solid, mp 166–168°C from EtOH; ^{1}H NMR (400.13 MHz, $CDCl_3$): $\delta = 1.92$ (quintet, $J = 7.5$ Hz, 2H, CH_2), 2.27–2.42 (m, 4H, CH_2), 4.74 (br s, 1H, CH-4), 4.87 (dm, $J = 7.8$ Hz, 1H, =CH-5), 5.62 (br s, 1H, =CH), 6.02 (ddd, $J = 7.9$, 4.8, 1.3 Hz, 1H, =CH-6), 6.93 (br s, 1H, NH), 8.35 (br s, 1H, NH); ^{13}C NMR (100.63 MHz, $CDCl_3$): $\delta = 23.2$ (CH_2), 30.7 (CH_2), 32.2 (CH_2), 52.7 (CH-4), 102.4 (CH-5), 122.6 (=CH-6), 127.6 (=CH), 144.3 (=C), 175.1 (C-2); MS (EI, 70eV) m/z: 180 (M^+, 100), 151 (12), 120 (11), 93 (24); IR (KBr pellet, cm^{-1}): $\nu_{max} =$ 3188 br.,

2988, 2940, 2844, 1676, 1580, 1492, 1284, 1216, 1180, 740, 628; Anal. Calcd. for $C_9H_{12}N_2S$: C, 59.96; H, 6.71; N, 15.54; S, 17.79; Found: C, 60.02; H, 6.82; N, 15.64; S, 17.66.

4-Vinyl-3,4-dihydropyrimidine-2(1H)-thione (5j)

White solid, mp 155–157°C from *n*-hexane:ethyl acetate; ^{1}H NMR (400.13 MHz, $CDCl_3$): $\delta = 4.58$ (br s, 1H, CH-4), 4.89 (dm, $J = 7.9$ Hz, 1H, =CH-5), 5.18 (dt, $J = 10.0$, 0.7 Hz, 1H, =C<u>H</u>H), 5.22 (dt, $J = 17.1$, 0.9 Hz, 1H, =CH<u>H</u>), 5.85 (ddd, $J = 17.1$, 10.0, 7.1 Hz, 1H, =CH), 6.00 (ddd, $J = 7.9$, 4.8, 1.5 Hz, 1H, =CH-6), 6.66 (br s, 1H, NH), 7.90 (br s, 1H, NH); ^{13}C NMR (100.63 MHz, $CDCl_3$): $\delta = 55.0$ (CH-4), 102.5 (=CH-5), 116.6 (=CH_2), 122.4 (=CH-6), 137.7 (=CH), 175.3 (C-2); MS (EI, 70 eV) m/z: 140 (100), 113 (44), 80 (32), 53 (8); IR (KBr pellet, cm^{-1}): $\nu_{max} =$ 3192 br, 2988, 1678, 1580, 1498, 1220, 1180, 984, 932, 736, 640; Anal. Calcd. for $C_6H_8N_2S$: C, 51.40; H, 5.75; N, 19.98; S, 22.87; Found: C, 51.44; H, 5.77; N, 20.06; S, 22.94.

4-Isopropenyl-3,4-dihydropyrimidine-2(1H)-thione (5k)

White solid, mp 136–138°C from *n*-hexane:ethyl acetate; ^{1}H NMR (400.13 MHz, $CDCl_3$): $\delta = 1.80$ (s, 3H, CH_3), 4.57 (br s, 1H, CH-4), 4.84 (d of quintets, $J = 7.8$, 1.7 Hz, 1H, =CH-5), 4.86 (s, 1H, =C<u>H</u>H), 4.92 (s, 1H, =CH<u>H</u>), 6.04 (ddd, $J = 7.8$, 4.7, 1.0 Hz, 1H, =CH-6), 7.07 (br s, 1H, NH), 8.54 (br s, 1H, NH); ^{13}C NMR (100.63 MHz, $CDCl_3$): $\delta =$ 17.4 (CH_3), 58.4 (CH-4), 102.4 (=CH-5), 112.9 (=CH_2), 122.9 (=CH-6), 145.0 (=C), 175.0 (C-2); MS (EI, 70 eV) m/z: 154 (79), 139 (4), 113 (100), 94 (19), 79 (14); IR (KBr pellet, cm^{-1}): $\nu_{max} = 3200$, 2984, 1676, 1566, 1492, 1438, 1214, 1176, 912, 762; Anal. Calcd. for $C_7H_{10}N_2S$: C 54.51; H 6.54; N 18.16; S 20.79; Found: C 54.46; H 6.47; N 18.21; S 20.80.

4-Phenyl-3,4-dihydro-pyrimidine-2(1H)-thione (5l)

White solid, mp 185–186°C from *n*-hexane:ethyl acetate; ^{1}H NMR (400.13 MHz, $CDCl_3$): $\delta = 4.98$ (d of quintets, $J = 8.0$, 1.5 Hz, 1H, =CH-5), 5.13–5.16 (m, 1H, CH-4), 6.07 (ddd, $J = 8.0$, 4.7, 1.5 Hz, 1H, =CH-6), 6.91 (br s, 1H, NH), 7.31–7.42 (m, 5H, C_6H_5), 8.15 (br s, 1H, NH); ^{13}C NMR (100.63 MHz, $CDCl_3$): $\delta = 56.6$ (CH-4), 103.8 (=CH-5), 121.9 (=CH-6), 126.9 (C_6H_5), 128.6 (C_6H_5), 129.1 (C_6H_5), 142.3 (C_6H_5), 174.4 (C-2); MS (EI, 70eV) m/z: 190 (100, $M^{+\cdot}$), 189 (45), 130 (68), 115 (9), 113 (38), 103 (15), 77 (19); IR (KBr pellet, cm^{-1}): $\nu_{max} = 3160$, 2976, 1674, 1566, 1490, 1284, 1210, 1174, 764, 698; Anal. Calcd. for $C_{10}H_{10}N_2S$: C 63.13; H 5.30; N 14.72; S 16.85; Found: C 63.20; H 5.27; N 14.81; S 16.79.

4-Thiophen-2-yl-3,4-dihydropyrimidine-2(1H)-thione (5m)

White solid, mp 181–183°C from EtOH; ^{1}H NMR (400.13 MHz, $CDCl_3$): $\delta = 5.09$ (d of quintets, $J = 7.9$, 1.6 Hz, 1H, =CH-5), 5.26–5.45 (m, 1H, CH-4), 6.12 (ddd, $J = 7.9$, 4.8, 1.5 Hz, 1H, =CH-6), 6.82 (br s, 1H, NH), 6.99 (dd, $J = 5.0$, 3.6 Hz, 1H, CH-4_{arom}), 7.01 (dd, $J = 3.6$, 1.2 Hz, 1H, CH-3_{arom}), 7.33 (dd, $J = 5.0$, 1.2 Hz, 1H, CH-5_{arom}), 7.79 (br s, 1H, NH); ^{13}C NMR (100.63 MHz, $CDCl_3$): $\delta = 51.4$ (CH-4), 103.1 (=CH-5), 122.5 (=CH-6), 125.3 (C_4H_3S), 126.6 (C_4H_3S), 127.1 (C_4H_3S), 146.1 (C_4H_3S), 174.5 (C-2); MS (EI, 70 eV) m/z: 196 ($M^{+\cdot}$, 100), 195 (29), 163 (9), 153 (7), 136 (80), 109 (10); IR (KBr pellet, cm^{-1}): $\nu_{max} =$ 3160 br, 2976, 1672, 1566, 1490, 1220, 1176, 996, 758. Anal. Calcd. for $C_8H_8N_2S_2$: C 48.95; H 4.11; N 14.27; S 32.67; Found: C 49.00; H 4.09; N 14.31; S 32.78.

4-(2-Methylthiophen-3-yl)-3,4-dihydropyrimidine-2(1H)-thione (5n)

White solid, mp 195–198°C from EtOH; ^{1}H NMR (400.13 MHz, $CDCl_3$): $\delta = 2.46$ (d, $J = 0.9$ Hz, 3H, CH_3), 5.06 (d of quintets, $J = 7.9$, 1.7 Hz, 1H, =CH-5), 5.31–5.34 (m, 1H, CH-4), 6.09 (ddd, $J = 7.9$, 4.8, 1.4 Hz, 1H, =CH-6), 6.63 (d of quartets, $J = 6.6$, 1.0 Hz, 1H, CH-4_{arom}), 6.77 (d, $J = 3.4$ Hz, 1H, CH-5_{arom}), 6.82 (br s, 1H, NH), 7.87 (br s, 1H, NH); ^{13}C NMR (100.63 MHz, $CDCl_3$): $\delta = 15.5$ (CH_3), 51.6 (CH-4), 103.2 (=CH-5), 122.4 (=CH-6), 125.0 (C_5H_5S), 126.1 (C_5H_5S), 141.5 (C_5H_5S), 143.7 (C_5H_5S), 174.3 (C-2); MS (EI, 70 eV) m/z: 210 (100), 209 (24), 195 (5), 177 (10), 167 (5), 150 (77), 136 (12), 118 (12); IR (KBr pellet, cm^{-1}): $\nu_{max} = 3188$ br, 2984, 1678, 1578, 1494, 1276, 1222, 1178, 800, 772, 732. Anal. Calcd. for $C_9H_{10}N_2S_2$:C 51.40; H 4.79; N 13.32; S 30.49; Found: C 51.38; H 4.85; N 13.33; S 30.60.

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