A Facile One-pot Synthesis of Novel Substituted 1,2,3,4-Tetrahydropyrimidines

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A facile one-pot synthesis of 5-benzoyl-6-methylthio-1,2,3,4-tetrahydropyrimidines in good yields is reported.

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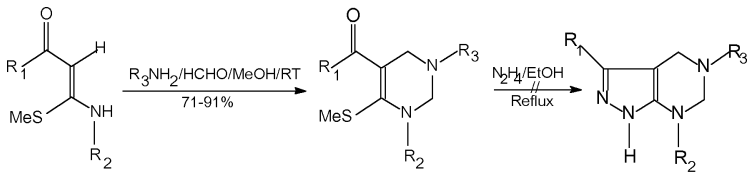
A few 5-nitro-1,2,3,4-tetrahydropyrimidines [1,2] are known and their derivatives are reported [3-8] to act as potential pesticides and insecticides. However, to the best of our knowledge, 5-aroyl-6-methylthio-1,2,3,4-tetrahydropyrimidines are unknown in the literature and hence their biological activities remain unexplored. Prompted by the above observations we undertook the present investigation because of our interest in the synthetic applications [9-12] of 3-(aryl/benzyl)amino-3-methylthio-1-arylprop-2-en-1-one (**1**) and also in the construction [13] of tetrahydropyrimidine rings using formaldehyde and primary amines. The results of our study are reported herein.

Thus, when a mixture of **1a**, formaldehyde and *p*-anisidine (1:2:1) was stirred at room temperature in methanol, work-up of the reaction mixture yielded a white solid in 74% yield, which was characterized as 1-benzyl-3-(4-methoxyphenyl)-5-benzoyl-6-methylthio-1,2,3,4-tetrahydropyrimidine (**2a**). The reaction was found to be general with other alkyl, aralkyl and arylamines and with corresponding **1b-d** to give the respective **2b-h** in 71-91% overall yields. The structures of the tetrahydropyrimidines were established on the basis of spectral and analytical data. Thus, the infrared spectra of **2a-h** showed strong peaks around 1550 and 1610 cm^{-1} due to highly delocalized double bonds and carbonyl group stretching frequencies of enaminone functionalities. Their ^1H nmr spectra exhibited a singlet due to methylene protons at C-2, between δ = 4.16-4.94 while the methylene protons at C-4 appeared as singlets between δ = 3.50-4.30. The benzylic methylene protons in **2a-c** gave singlets in the range of 3.60-4.53 ppm. In case of **2b**, two overlapping singlets due to two methylene group protons were observed at 3.59 ppm. The singlets due to the protons of methylthio group appeared between δ = 1.66-1.73 in case of **2c-h**, while in **2a** and **2b** they appeared at 2.00 and 2.01 ppm respectively. The tetrahydropyrimidines **2a-h** were found to be stable and could be crystallized from methanol. The synthesis of other tetrahydropyrimidines and studies of their biological properties are in progress.

Attempted synthesis of tetrahydropyrimidine annulated pyrazoles **3** by reacting **2a** with hydrazinehydrate was not successful and resulted in the formation of only intractable reaction mixtures. This is probably due to the cleavage of the fragile tetrahydropyrimidine ring in the presence of this nucleophilic agent under experimental conditions.

Scheme



1 **2** **3**

1	R_1	R_2
a	C_6H_5	$C_6H_5CH_2$
b	4-MeC_6H_4	$C_6H_5CH_2$
c	4-$MeOC_6H_4$	C_6H_5
d	4-ClC_6H_4	C_6H_5

2, 3	R_1	R_2	R_3
a	C_6H_5	$C_6H_5CH_2$	4-$MeOC_6H_4$
b	4-MeC_6H_4	$C_6H_5CH_2$	$C_6H_5CH_2$
c	4-$MeOC_6H_4$	C_6H_5	$C_6H_5CH_2$
d	4-ClC_6H_4	C_6H_5	4-ClC_6H_4
e	4-ClC_6H_4	C_6H_5	4-MeC_6H_4
f	4-ClC_6H_4	C_6H_5	4-$MeOC_6H_4$
g	4-ClC_6H_4	C_6H_5	C_2H_5
h	4-ClC_6H_4	C_6H_5	CH_3

EXPERIMENTAL

Melting points were determined on Thomas Hoover apparatus and are uncorrected. The reaction progress was monitored by tlc on silica gel. The infrared spectra of the products were recorded on Perkin Elmer 983 spectrophotometer and ^{1}H nmr spectra on Varian EM-390 spectrometer using TMS as internal standard. Mass spectra were recorded on Jeol D-300 mass spectrometer, while the ^{13}C nmr spectra were obtained on a Brucker ACF-300 spectrometer. The starting materials, **1a-d,** were prepared by the reported procedure [14].

1-Aralkyl/aryl-3-alkyl/aralkyl/aryl-5-benzoyl-6-methylthio-1,2,3,4-tetrahydropyrimidines (**2a-h**).

General Procedure.

A mixture of primary amine (1 mmol) and formaldehyde (2 mmol, 40% solution) in 2 mL methanol was stirred at room temperature for 5 minutes. To this was added a solution of N, S-acetal **1** (1 mmol) in 4-5 mL methanol and the resulting mixture was stirred at room temperature. A precipitate was observed after 5-10 minutes. After completion of the reaction (2-6 hours, monitored by tlc), the reaction mixture was cooled in ice and the precipitate was filtered, washed with cold methanol (3x1 mL) and dried to give analytically pure **2a-h**. These compounds were recrystallized from methanol.

1-Benzyl-3-(4-methoxyphenyl)-5-benzoyl-6-methylthio-1,2,3,4-tetrahydropyrimidine (**2a**).

This compound was obtained as a white solid in 74% yield, mp 131-132 °C; ir (KBr): 1605, 1594, 1574, 1538, 1505 cm^{-1} ; ^{1}H nmr ($CDCl_3$): δ 2.00 (s, 3H), 3.70 (s, 3H), 3.96 (s, 2H), 4.30 (s, 2H), 4.53 (s, 2H), 6.70-7.00 (m, 4H), 7.20-8.00 (m, 10H); ^{13}C nmr ($CDCl_3$): δ 16.41, 50.79, 54.93, 55.58, 67.50, 114.62, 117.85, 118.94, 127.55, 128.00, 128.62, 128.84, 131.39, 137.79, 140.97, 142.18, 152.51, 153.91, 195.90.

Anal. Calcd. for $C_{26}H_{26}N_2O_2S$ (430.56): C, 72.53; H, 6.09; N, 6.51. Found: C, 72.27; H, 6.15; N, 6.62.

1,3-Dibenzyl-5-(4-methylbenzoyl)-6-methylthio-1,2,3,4-tetrahydropyrimidine (**2b**).

This compound was obtained as a white solid in 85% yield, mp 130 °C; ir (KBr): 1627, 1601, 1558, 1491 cm^{-1}; ^{1}H nmr ($CDCl_3$): δ 2.01 (s, 3H), 2.40 (s, 3H), 3.48 (s, 2H), 3.59 (2s, each, 2H), 4.45 (s, 2H), 7.04-7.71 (m, 14H); ^{13}C nmr ($CDCl_3$): δ 16.37, 21.57, 54.70, 54.79, 58.08, 67.80, 96.02, 118.96, 127.08, 127.17, 127.83, 128.24, 128.35, 128.52, 128.79, 137.68, 137.85, 137.96, 141.66, 149.74, 195.27.

Anal. Calcd. for $C_{27}H_{28}N_2OS$ (428.59): C, 75.66; H, 6.58; N, 6.54. Found: C, 75.89; H, 6.50; N, 6.41.

1-Phenyl-3-benzyl-5-(4-methoxybenzoyl)-6-methylthio-1,2,3,4-tetrahydropyrimidine (**2c**).

This compound was obtained as a white solid in 77% yield, mp 128-129 °C; ir (KBr): 1615, 1592, 1541, 1496 cm^{-1} ; ^{1}H nmr (CCl_4): δ 1.70 (s, 3H), 3.60 (s, 2H), 3.70 (s, 2H), 3.80 (s, 3H), 4.16 (s, 2H), 6.66-7.86 (m, 14H); ms: m/z 431 (M^++1, 10%), 430 (M^+, 13.8%), 385 (27.4%), 91 (100%).

Anal. Calcd. for $C_{26}H_{26}N_2O_2S$ (430.56): C, 72.53; H, 6.09; N, 6.51. Found: C, 72.81; H, 5.98; N, 6.60.

1-Phenyl-3-(4-chlorophenyl)-5-(4-chlorobenzoyl)-6-methylthio-1,2,3,4-tetrhydropyrimidine (**2d**).

This compound was obtained as a white solid in 83% yield, mp 181-182 °C; ir (KBr): 1616, 1591, 1547, 1489 cm^{-1}; ^{1}H nmr (CCl_4): δ 1.72 (s, 3H), 4.25 (s, 2H), 4.93 (s, 2H), 6.50-8.20 (m, 13H).

Anal. Calcd. for $C_{24}H_{20}Cl_2N_2OS$ (455.40): C, 63.29; H, 4.43; N, 6.15. Found: C, 63.06; H, 4.31; N, 5.99.

1-Phenyl-3-(4-methylphenyl)-5-(4-chlorobenzoyl)-6-methylthio-1,2,3,4-tetrahydropyrimidine (**2e**).

This compound was obtained as a white solid in 81% yield, mp 162-163 °C; ir (KBr): 1616, 1585, 1549, 1515, 1486 cm^{-1}; ^{1}H nmr (CCl_4): δ 1.73 (s, 3H), 2.23 (s, 3H), 4.26 (s, 2H), 4.94 (s, 2H), 6.60-8.25 (m, 13H).

Anal. Calcd. for $C_{25}H_{23}ClN_2OS$ (434.98): C, 69.03; H, 5.33; N, 6.44. Found: C, 69.31; H, 5.26; N, 6.39.

1-Phenyl-3-(4-methoxyphenyl)-5-(4-chlorobenzoyl)-6-methylthio-1,2,3,4-tetrahydropyrimidine (**2f**).

This compound was obtained as a bright yellow solid in 91% yield, mp 170-172 °C; ir (KBr): 1593, 1562, 1524, 1511 cm^{-1}; ^{1}H nmr (CCl_4): δ 1.72 (s, 3H), 3.70 (s, 3H), 4.14 (s, 2H), 4.84 (s, 2H), 6.60-6.80 (m, 4H), 6.90-8.10 (m, 9H); ms: m/z 452 (M^++2, 4.6%), 451 (M^++1, 5.6%), 450 (M^+, 11.9%), 403 (28%), 268 (76.4%), 139 (100%).

Anal. Calcd. for $C_{25}H_{23}ClN_2O_2S$ (450.98): C, 66.58; H, 5.14; N, 6.21. Found: C, 66.25; H, 5.23; N, 6.30.

1-Phenyl-3-ethyl-5-(4-chlorobenzoyl)-6-methythio-1,2,3,4-tetrahydropyrimidine (**2g**).

This compound was obtained as an off-white solid in 80% yield, mp 129 °C; ir (KBr): 1608, 1587, 1532, 1487 cm^{-1}; ^{1}H nmr (CCl_4): δ 1.00 (t, 3H), 1.66 (s, 3H), 2.60 (q, 2H), 3.60 (s, 2H), 4.25 (s, 2H), 7.00-8.02 (m, 9H); ms: m/z 374 (M^++2, 0.5%), 373 (M^++1, 1.3%), 372 (M^+, 5.2%), 267 (100%), 139 (85.6%).

Anal. Calcd. for $C_{20}H_{21}ClN_2OS$ (372.91): C, 64.42; H, 5.67; N, 7.51. Found: C, 64.70; H, 5.65; N, 7.64.

1-Phenyl-3-methyl-5-(4-chlorobenzoyl)-6-methythio-1,2,3,4-tetrahydropyrimidine (**2h**).

This compound was obtained as an off-white solid in 71% yield, mp 126-127 °C; ir (KBr): 1608, 1587, 1533, 1488 cm^{-1}; ^{1}H nmr (CCl_4): δ 1.66 (s, 3H), 2.36 (s, 3H), 3.50 (s, 2H), 4.20 (s, 2H), 7.00-8.00 (m, 9H); ^{13}C nmr ($CDCl_3$): δ 15.07, 41.59, 55.39, 75.05, 117.98, 125.32, 125.81, 128.28, 128.93, 129.82, 137.42, 139.48, 146.16, 146.93, 194.93.

Anal. Calcd. for $C_{19}H_{19}ClN_2OS$ (358.89): C, 63.59; H, 5.34, N, 7.80. Found: C, 63.72; H, 5.40; N, 7.71.

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