Synthesis of (pyrimidin-4-yloxy)- and (pyrimidin-3-yl)acetyl azides and their rearrangement to carbamates and ureas

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Abstract

On nitrosation of (pyrimidin-4-yloxy)- and (pyrimidin-3-yl)acetohydrazides **2**, **3** with sodium nitrite in diluted hydrochloric acid at 0-5 °C the corresponding (pyrimidinyl)acetyl azides **5**, **6** were prepared. Azides **5**, **6** undergo Curtius rearrangement in the reactions with alcohols, phenols, arylamines or water to give carbamates **7**-**9**, **11**-**14** or ureas **15**-**21**.

Keywords: (Pyrimidinyl)acetyl azide, (pyrimidinyl)methylcarbamate, (pyrimidinyl)methylurea, nitrosation, Curtius rearrangement

Introduction

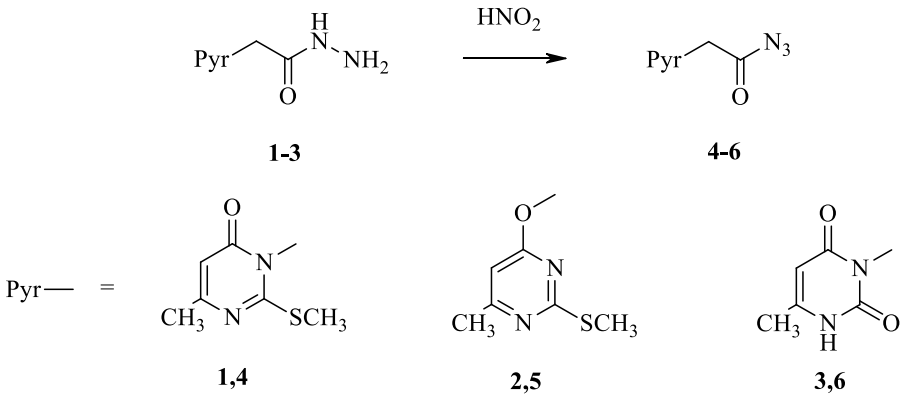
In recent years naturally occurring and synthetic heterocyclic compounds are of interest in pharmaceutical and pesticide research.[1] Pyrimidines, in particular, cover the considerable position among compounds exhibiting diverse biological activities.[2-6] On the other hand, compounds with the linkage of carbamate or urea are citied to show cytotoxic,[7-12] antimicrobial and insecticidal[13] or fatty acid amide hydrolase inhibitory[14] activity. There are some recent examples of biologically active pyrimidine-based carbamates and ureas.[15-19]

Carbamates and ureas are frequently synthesized from acyl azides *via* Curtius rearrangement.[13,20] A number of methods for the synthesis of acyl azides have been reported. Acyl azides are commonly prepared from carboxylic acid and ethyl chloroformate *via* mixed anhydrides and sodium azide or by the reaction of acyl chlorides with trimethylsilyl azide.[21] A. R. Katritzsky *et al.* recently reported a simple and safe synthesis of acyl azides from the corresponding N-acyl benzotriazoles and sodium azide.[22] Acyl azides can also be prepared from hydrazides by nitrozation with sodium nitrite in acidic media.[13,20,23] This approach is a convenient one, especially for readily accessible hydrazides. Hydrazide nitrosation to give acyl azides is applied for a large-scale synthesis.[24]

Continuing our interest in the synthesis of compounds with potential biological activity,[6,25] herein we report the synthesis of new pyrimidine-based acetyl azides and their rearrangement reactions to form carbamates and ureas.

Results and Discussion

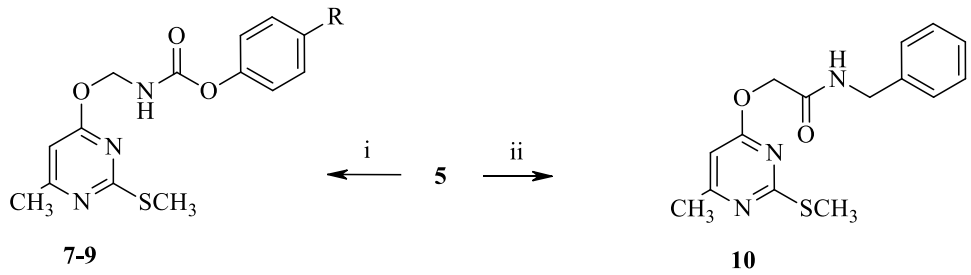
Previously we reported the synthesis of acetyl azide **4** by nitrosation of hydrazide **1** in a 50% acetic acid or diluted hydrochloric acid.[26] Performing this reaction in acetic acid the yield of azide **4** was higher, when in a diluted hydrochloric acid together with the azide **4** formation some azide **6** was obtained. In this work azides **5**, **6** were successfully prepared under treatment of acetohydrazides **2**, **3** with sodium nitrite at 0-5 °C in a diluted hydrochloric acid solution (Scheme 1).



Scheme 1

Compounds **5**, **6** were sufficiently pure to be used for further rearrangement reactions. The IR spectra of acyl azides **5**, **6** display strong absorption bands characteristic for azide stretching vibrations at 2158 and 2150 cm^{-1}, respectively.

Acyl azides undergo thermal rearrangement in an inert solvents to give isocyanates (Curtius rearrangement), which on reaction with alcohols or amines lead to the formation of carbamates and ureas.[21] Azide **5** being heated at reflux in benzene with phenols gave carbamates **7-9** (Scheme 2).



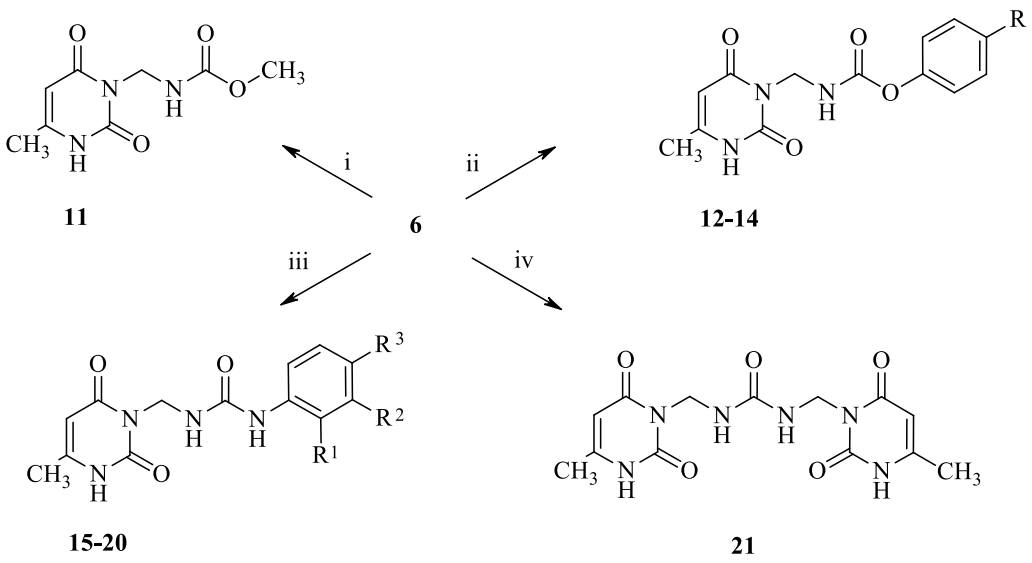
7-9 **10**

R = H (**7**), Cl (**8**), F (**9**).
i: 4-R-C_6H_4-OH, dry C_6H_6; ii: $C_6H_5CH_2NH_2$, dry C_6H_6.

Scheme 2

Analytically pure carbamates **7-9** after recrystallization from 2-propanol were isolated in 43-59% yields. The reaction of azide **5** and benzylamine to form the corresponding urea was unsuccessful, amide **10** was isolated instead. Heating of azide **5** at reflux in benzene for 4 h to rearrange to isocyanate, then addition of benzylamine and further heating for 1 h gave a complex mixture of unidentified products. By adding azide **5** and benzylamine at one go and immediate heating in benzene for 1 h resulted in amide **10** formation in 67% yield. The ^{1}H NMR spectra of carbamates **7-9** show characteristic dublets at 5.50 and 5.51 ppm for OCH_2 group protons and triplets for NH protons (broad singlet for comp. **8**) in the region of 6.53-6.56 ppm. In the ^{1}H NMR of amide **10** singlet at 4.95 ppm for OCH_2 group protons, dublet at 4.56 ppm for CH_2 benzyl protons and broad singlet at 6.60 ppm due to NH proton were observed.

In contrast to azide **5**, reactions of azide **6** with nucleophiles proceeded smoothly and yields of products were higher (Scheme 3).



R = H (**12**), Cl (**13**), F (**14**); $R^1 = R^2 = R^3 = H$ (**15**); $R^1 = CH_3$, $R^2 = R^3 = H$ (**16**); $R^1 = R^2 = H$, $R^3 = OCH_3$ (**17**); $R^1 = R^2 = H$, $R^3 = F$ (**18**); $R^1 = R^3 = Cl$, $R^2 = H$ (**19**); $R^1 = R^3 = H$, $R^2 = CF_3$ (**20**).

i: abs. CH_3OH; ii: R–C$_6$H$_4$–OH, dry dioxane; iii: R^3–C$_6$H$_3$(R^2,R^1)–NH_2, dry dioxane; iv: H_2O, dioxane.

Scheme 3

Thus, azide **6** under heating at reflux for 5 h in methanol gave carbamate **11** in 56% yield. For reactions with phenols dry solvents, benzene and dioxane, were used. In benzene azide **6** did not show any reaction with phenols, likely because of poor solubility. In dioxane on heating at reflux for 5 h azide **6** with phenols furnished carbamates **12-14** in 63-74% yields. In the ^{1}H NMR spectra of **11-14** the characteristic doublets for NCH_2 group protons were observed at 5.09 and 5.18 ppm along with the broad singlets in the region of 7.49 and 8.17-8.25 ppm. due to NH protons.

Heating at reflux of acyl azide **6** and arylamines in dioxane for 1 h produced ureas **15-20** in 57-88% yields, while heating at reflux for 4 h of azide **6** in the presence of water gave disubstituted urea **21**. In the ^{1}H NMR spectra of ureas **15-20** characteristic dublets for NCH_2 group protons resonate at 5.22-5.25 ppm and the nearby NH proton shifts appear as triplets in the region of 6.78-7.86 ppm (for comp. **15** and **16** these peaks overlap with signals of aromatic protons). Besides the well-distinctive sharp one-proton peaks due to the NH group next to aromatic ring are observed downfield at 7.94-9.13 ppm. The symmetrical urea **21** spectrum shows a dublet at 5.10 ppm for NCH_2 group protons and neighboring NH proton as a triplet at 6.96 ppm indicating magnetic equivalency of protons in both halves of the molecule.

The newly synthesized compounds were tested for antiproliferative activity *in vitro*. Compounds 7-**21** were inactive.

In conclusion, nitrosation of (pyrimidinyl)acetohydrazides is convenient and simple method for the synthesis of (pyrimidin-4-yloxy)- and (pyrimidin-3-yl)acetyl azides. Both of azides are suitable synthons for the new carbamate and urea synthesis.

Experimental Section

General. Melting points were determined in open capillaries and are uncorrected. NMR spectra were recorded on a Unity Varian INOVA spectrometer at 300 MHz for ^{1}H and 75 MHz for ^{13}C. Chemical shifts (δ) are reported in ppm relative to TMS. The IR spectra were recorded on a Spectrum BX FT-IR (Perkin-Elmer, Sweden) as potassium bromide pellets. The reactions and purity of compounds was controlled by tlc on Silica gel 60 F_{254} plates (MERCK, Germany). Elemental analyses were performed at the Microanalytical Laboratory of the Department of Organic Chemistry of Vilnius University. All solvents were dried and distilled before use.
(6-Methyl-2-methylthiopyrimidin-4-yloxy)acetohydrazide **2** and (6-methyl-2,4-dioxo-1,2-dihydropyrimidin-3(4*H*)-yl)acetohydrazide **3** were synthesized as reported in references[27,28].

General procedure for the synthesis of acetyl azides (5) and (6)
To a cooled to 0-5 °C temperature suspension of hydrazide **2** or **3** (5 mmol), water (15 mL) and conc. hydrochloric acid (4 mL), a solution of sodium nitrite (1.73 g, 25 mmol) in water (10 mL) was added dropwise under stirring. The reaction mixture was stirred at this temperature for 1 h, the precipitate was collected by filtration (for compound **5** the reaction mixture was neutralized with sodium hydrogen carbonate before filtration), washed with cold water and dried over sodium sulphate in vacuum.
(6-Methyl-2-methylthiopyrimidin-4-yloxy)acetyl azide (3). Yield 0.88 g (74%), mp 56-58 °C; IR, ν, cm^{-1}: 1706 (C=O), 2158 (N_3); ^{1}H NMR ($CDCl_3$), δ, ppm: 2.42 (s, 3H, CH_3), 2.51 (s, 3H, SCH_3), 4.93 (s, 2H, OCH_2), 6.40 (s, 1H, CH); ^{13}C NMR ($CDCl_3$), δ, ppm: 14.2, 24.1, 64.5, 102.1, 168.0, 169.0, 171.6, 175.8. Anal. Calcd. for $C_8H_9N_5O_2S$: C, 40.16; H, 3.79; N, 29.27. Found: C, 40.52; H, 3.79; N, 29.43.
(6-Methyl-2,4-dioxo-1,2-dihydropyrimidin-3(4*H*)-yl)acetyl azide (6). Yield 0.74 g (71%), mp 135-137 °C (ref.[26] mp 135-137 °C); IR, ν, cm^{-1}: 1634, 1716, 1741 (C=O), 2150 (N_3); ^{1}H NMR (DMSO-d_6), δ, ppm: 2.09 (s, 3H, CH_3), 4.57 (s, 2H, NCH_2), 5.56 (s, 1H, CH), 11.40 (s, 1H, NH); ^{13}C NMR (DMSO-d_6), δ, ppm: 18.9, 43.5, 98.5, 151.7, 153.1, 162.8, 176.3. Anal. Calcd. for $C_7H_7N_5O_3$: C, 40.20; H, 3.37; N, 33.48. Found: C, 40.53; H, 3.57; N, 33.62.

General procedure for the synthesis of carbamates (7-9) and (12-14)
To a solution of azide **5** (0.24 g, 1 mmol) in dry benzene (3 mL) or azide **6** (0.21 g, 1 mmol) in dry dioxane (3 mL) the corresponding phenol (1 mmol) was added. The reaction mixture was heated at reflux for 5 h, then the solvent was removed under reduced pressure. The residue was

worked up with diethyl ether to give a solid, which was collected by filtration and crystallized from the appropriate solvent.

Phenyl (6-methyl-2-methylthiopyrimidin-4-yloxy)methylcarbamate (7). Yield 0.18 g (59%), mp 134-135 °C (2-propanol); IR, ν, cm^{-1}: 1744 (C=O), 3229 (NH); ^{1}H NMR ($CDCl_3$), δ, ppm: 2.27 (s, 3H, CH_3), 2.59 (s, 3H, SCH_3), 5.50 (d, *J* = 6.9 Hz, 2H, OCH_2), 6.10 (s, 1H, CH) 6.53 (t, *J* = 6.9 Hz, 1H, NH), 7.15 (d, *J* = 7.8 Hz, 2H, ArH), 7.18-7.26 (m, 1H, ArH), 7.34-7.40 (m, 2H, ArH); ^{13}C NMR ($CDCl_3$), δ, ppm: 15.5, 24.1, 52.1, 108.0, 121.8, 125.9, 129.6, 150.9, 154.4, 161.5, 163.5, 163.9. Anal. Calcd. for $C_{14}H_{15}N_3O_3S$: C, 55.07; H, 4.95; N, 13.76. Found: C, 55.40; H, 5.09; N, 13.92.

4-Chlorophenyl (6-methyl-2-methylthiopyrimidin-4-yloxy)methylcarbamate (8). Yield 0.16 g (48%), mp 141-142 °C (2-propanol); IR, ν, cm^{-1}: 1737 (C=O), 3191 (NH); ^{1}H NMR ($CDCl_3$), δ, ppm: 2.27 (s, 3H, CH_3), 2.59 (s, 3H, SCH_3), 5.50 (d, *J* = 6.6 Hz, 2H, OCH_2), 6.10 (s, 1H, CH) 6.56 (br s, 1H, NH), 7.10 (d, *J* = 8.4 Hz, 2H, ArH), 7.33 (d, *J* = 8.4 Hz, 2H, ArH); ^{13}C NMR ($CDCl_3$), δ, ppm: 15.5, 24.1, 52.1, 108.0, 123.1, 129.6, 131.2, 149.4, 154.0, 163.5, 164.0. Anal. Calcd. for $C_{14}H_{14}ClN_3O_3S$: C, 49.49; H, 4.15; N, 12.37. Found: C, 49.21; H, 3.96; N, 12.21.

4-Fluorophenyl (6-methyl-2-methylthiopyrimidin-4-yloxy)methylcarbamate (9). Yield 0.14 g (43%), mp 148-149 °C (2-propanol); IR, ν, cm^{-1}: 1737 (C=O), 3234 (NH); ^{1}H NMR ($CDCl_3$), δ, ppm: 2.27 (s, 3H, CH_3), 2.59 (s, 3H, SCH_3), 5.51 (d, *J* = 6.9 Hz, 2H, OCH_2), 6.10 (s, 1H, CH) 6.53 (t, *J* = 6.9 Hz, 1H, NH), 7.0-7.17 (m, 4H, ArH); ^{13}C NMR ($CDCl_3$), δ, ppm: 15.5, 24.1, 52.1, 108.0, 116.0, 116.3, 123.2, 123.3, 146.8, 154.3, 158.8, 161.4, 162.0, 163.5, 163.9. Anal. Calcd. for $C_{14}H_{14}FN_3O_3S$: C, 52.00; H, 4.36; N, 13.00. Found: C, 52.33; H, 4.37; N, 13.21.

Phenyl (6-methyl-2,4-dioxo-1,2-dihydropyrimidin-3(4*H*)-yl)methylcarbamate (12). Yield 0.2 g (74%), mp 178-179 °C (ethanol); IR, ν, cm^{-1}: 1646, 1721 (C=O), 3268 (NH); ^{1}H NMR (DMSO-d_6), δ, ppm: 2.06 (s, 3H, CH_3), 5.18 (d, *J* = 4.8 Hz, 2H, NCH_2), 5.51 (s, 1H, CH) 7.10 (d, *J* = 8.1 Hz, 2H, ArH), 7.19-7.25 (m, 4H, ArH), 7.36-7.42 (m, 2H, ArH), 8.17 (br s, 1H, NH), 11.18 (s, 1H, NH); ^{13}C NMR (DMSO-d_6), δ, ppm: 18.8, 46.8, 99.0, 122.5, 125.8, 130.0, 151.6, 151.8, 152.7, 154.4, 163.0. Anal. Calcd. for $C_{13}H_{13}N_3O_4$: C, 56.72; H, 4.76; N, 15.27. Found: C, 56.43; H, 4.93; N, 15.46.

4-Chlorophenyl (6-methyl-2,4-dioxo-1,2-dihydropyrimidin-3(4*H*)-yl)methylcarbamate (13). Yield 0.195 g (63%), mp 210-211 °C (ethanol); IR, ν, cm^{-1}: 1638, 1725, 1741 (C=O), 3095, 3321 (NH); ^{1}H NMR (DMSO-d_6), δ, ppm: 2.06 (s, 3H, CH_3), 5.18 (d, *J* = 4.8 Hz, 2H, NCH_2), 5.51 (s, 1H, CH) 7.15 (d, *J* = 8.4 Hz, 2H, ArH), 7.44 (d, *J* = 8.4 Hz, 2H, ArH), 8.25 (br s, 1H, NH), 11.18 (br s, 1H, NH); ^{13}C NMR (DMSO-d_6), δ, ppm: 18.8, 46.8, 99.0, 124.4, 129.9, 141.6, 150.4, 151.8, 152.7, 154.1, 163.0. Anal. Calcd. for $C_{13}H_{12}ClN_3O_4$: C, 50.42; H, 3.91; N, 13.57. Found: C, 50.68; H, 4.27; N, 13.73.

4-Fluorophenyl (6-methyl-2,4-dioxo-1,2-dihydropyrimidin-3(4*H*)-yl)methylcarbamate (14). Yield 0.205 g (70%), mp 197-198 °C (ethanol); IR, ν, cm^{-1}: 1638, 1736, 1749 (C=O), 3086, 3271, 3442 (NH); ^{1}H NMR (DMSO-d_6), δ, ppm: 2.06 (s, 3H, CH_3), 5.18 (d, *J* = 4.8 Hz, 2H, NCH_2), 5.51 (s, 1H, CH) 7.11-7.24 (m, 4H, ArH), 8.21 (br s, 1H, NH), 11.18 (s, 1H, NH); ^{13}C NMR (DMSO-d_6), δ, ppm: 18.8, 46.8, 99.0, 116.3, 116.6, 124.2, 124.3, 147.7, 151.8, 152.7,

154.4, 158.3, 161.5, 163.0. Anal. Calcd. for $C_{13}H_{12}FN_3O_4$: C, 53.24; H, 4.12; N, 14.33. Found: C, 53.46; H, 4.45; N, 14.52.

***N*-Benzyl-2-(6-methyl-2-methylthiopyrimidin-4-yloxy)acetamide (10).** Benzylamine (0.107 g, 1 mmol) was added to a solution of azide **5** (0.24 g, 1 mmol) in dry benzene (5 mL). The reaction mixture was heated at reflux for 1 h, then cooled to room temperature. The resultant precipitate was collected by filtration, washed with methanol and crystallized from ethanol to yield **10**, 0.192 g (63%), mp 98-100 °C; IR, ν, cm^{-1}: 1654 (C=O), 3287 (NH); ^{1}H NMR ($CDCl_3$), δ, ppm: 2.40 (s, 3H, CH_3), 2.54 (s, 3H, SCH_3), 4.56 (d, *J* = 6 Hz, 2H, CH_2), 4.95 (s, 2H, OCH_2), 6.35 (s, 1H, CH) 6.60 (br s, 1H, NH), 7.27-7.42 (m, 5H, ArH); ^{13}C NMR ($CDCl_3$), δ, ppm: 14.3, 24.1, 43.3, 65.0, 101.9, 128.0, 129.1, 137.9, 167.8, 167.9, 169.0, 172.2. Anal. Calcd. for $C_{15}H_{17}N_3O_2S$: C, 59.38; H, 5.65; N, 13.85. Found: C, 59.63; H, 5.66; N, 13.97.

Methyl (6-methyl-2,4-dioxo-1,2-dihydropyrimidin-3(4*H*)-yl)methylcarbamate (11). The solution of azide **6** (0.21 g, 1 mmol) in abs. methanol (2 mL) was heated at reflux for 5 h and the reaction mixture was evaporated under reduced pressure to dryness. The residue was crystallized from 2-propanol to yield **11**, 0.12 g (56 %), mp 189-191 °C; IR, ν, cm^{-1}: 1642, 1734 (C=O), 3092, 3426 (NH); ^{1}H NMR (DMSO-d_6), δ, ppm: 2.04 (s, 3H, CH_3), 3.53 (s, 3H, OCH_3), 5.09 (d, *J* = 6 Hz, 2H, NCH_2), 5.46 (s, 1H, CH), 7.49 (br s, 1H, NH), 11.13 (s, 1H, NH); ^{13}C NMR (DMSO-d_6), δ, ppm: 18.8, 46.8, 52.2, 99.0, 151.8, 152.6, 156.5, 163.0. Anal. Calcd. for $C_8H_{11}N_3O_4$: C, 45.07; H, 5.20; N, 19.71. Found: C, 45.34; H, 5.49; N, 19.59.

General procedure for the synthesis of ureas (15-20)

To a solution of azide **6** (0.21 g, 1 mmol) in dry dioxane (7 mL) the corresponding aniline (1 mmol) was added. The reaction mixture was heated at reflux for 1 h and cooled to room temperature. The resultant precipitate was collected by filtration, washed with methanol and crystallized from ethanol.

***N*-[(6-Methyl-2,4-dioxo-1,2-dihydropyrimidin-3(4*H*)-yl)methyl]-*N'*-phenylurea (15).** Yield 0.24 g (88%), mp 227-229 °C; IR, ν, cm^{-1}: 1644, 1682, 1730 (C=O), 3204, 3263, 3318, 3419 (NH); ^{1}H NMR (DMSO-d_6), δ, ppm: 2.05 (s, 3H, CH_3), 5.24 (d, *J* = 6 Hz, 2H, NCH_2), 5.51 (s, 1H, CH) 6.78-7.04 (m, 2H, NH, ArH), 7.16-7.32 (m, 2H, ArH), 7.32-7.48 (m, 2H, ArH), 8.75 (s, 1H, NH), 11.21 (s, 1H, NH); ^{13}C NMR (DMSO-d_6), δ, ppm: 18.8, 45.8, 99.1, 118.3, 122.1, 129.4, 140.8, 151.9, 152.9, 154.7, 163.4. Anal. Calcd. for $C_{13}H_{14}N_4O_3$: C, 56.93; H, 5.14; N, 20.43. Found: C, 56.61; H, 5.38; N, 20.29.

***N*-[(6-Methyl-2,4-dioxo-1,2-dihydropyrimidin-3(4*H*)-yl)methyl]-*N'*-(2-methylphenyl)urea (16).** Yield 0.173 g (60%), mp 194-195 °C; IR, ν, cm^{-1}: 1648, 1677, 1729 (C=O), 3181, 3318, 3428 (NH); ^{1}H NMR (DMSO-d_6), δ, ppm: 2.06 (s, 3H, CH_3), 2.17 (s, 3H, CH_3), 5.25 (d, *J* = 5.4 Hz, 2H, NCH_2), 5.52 (s, 1H, CH) 6.82-6.95 (m, 1H, ArH), 7.02-7.21 (m, 2H, NH, ArH), 7.30-7.47 (m, 1H, ArH), 7.84 (d, *J* = 7.8 Hz, 1H, ArH), 7.94 (s, 1H, NH), 11.20 (s, 1H, NH); ^{13}C NMR (DMSO-d_6), δ, ppm: 18.6, 18.8, 45.7, 99.0, 121.0, 122.7, 126.7, 127.3 130.7, 138.5, 151.9, 152.8, 154.7, 163.3. Anal. Calcd. for $C_{14}H_{16}N_4O_3$: C, 58.32; H, 5.59; N, 19.43. Found: C, 58.03; H, 5.59; N, 19.27.

***N*-(4-Methoxyphenyl)-*N′*-[(6-methyl-2,4-dioxo-1,2-dihydropyrimidin-3(4*H*)-yl)methyl]urea (17).** Yield 0.21 g (69%), mp 230-231 °C; IR, ν, cm^{-1}: 1645, 1711, 1740 (C=O), 3104, 3171, 3312 (NH); ^{1}H NMR (DMSO-d_6), δ, ppm: 2.05 (s, 3H, CH_3), 2.52 (s, 3H, OCH_3), 5.22 (d, *J* = 6.6 Hz, 2H, NCH_2), 5.51 (s, 1H, CH) 6.78 (t, *J* = 6.6 Hz, 1H, NH), 6.83 (d, *J* = 8.7 Hz, 2H, ArH), 7.27 (d, *J* = 8.7 Hz, 2H, ArH), 8.56 (s, 1H, NH), 11.19 (s, 1H, NH); ^{13}C NMR (DMSO-d_6), δ, ppm: 18.8, 45.8, 55.8, 99.0, 114.6, 120.0, 133.9, 151.9, 152.2, 152.8, 154.8, 163.4. Anal. Calcd. for $C_{14}H_{16}N_4O_4$: C, 55.26; H, 5.30; N, 18.41. Found: C, 55.47; H, 5.53; N, 18.58.

***N*-(4-Fluorophenyl)-*N′*-[(6-methyl-2,4-dioxo-1,2-dihydropyrimidin-3(4*H*)-yl)methyl]urea (18).** Yield 0.254g (87%), mp 231-233 °C; IR, ν, cm^{-1}: 1638, 1682, 1732 (C=O), 3202, 3279, 3416 (NH); ^{1}H NMR (DMSO-d_6), δ, ppm: 2.05 (s, 3H, CH_3), 5.23 (d, *J* = 6 Hz, 2H, NCH_2), 5.51 (s, 1H, CH) 6.87 (t, *J* = 6 Hz, 1H, NH), 7.02-7.16 (m, 2H, ArH), 7.30-7.47 (m, 2H, ArH), 8.79 (s, 1H, NH), 11.21 (s, 1H, NH); ^{13}C NMR (DMSO-d_6), δ, ppm: 18.8, 45.8, 99.1, 115.7, 116.1, 119.9, 120.0, 137.1, 137.2, 151.9, 152.9, 154.7, 156.2, 159.3, 163.4. Anal. Calcd. for $C_{13}H_{13}FN_4O_3$: C, 53.42; H, 4.48; N, 19.17. Found: C, 53.71; H, 4.79; N, 19.31.

***N*-(2,4-Dichlorophenyl)-*N′*-[(6-methyl-2,4-dioxo-1,2-dihydropyrimidin-3(4*H*)-yl)methyl]urea (19).** Yield 0.2 g (59%), mp 223-225 °C; IR, ν, cm^{-1}: 1648, 1720 (C=O), 3117, 3177, 3339 (NH); ^{1}H NMR (DMSO-d_6), δ, ppm: 2.05 (s, 3H, CH_3), 5.24 (d, *J* = 6 Hz, 2H, NCH_2), 5.51 (s, 1H, CH) 7.33 (d, *J* = 9 Hz, 1H, ArH), 7.54 (s, 1H, ArH), 7.86 (t, *J* = 6 Hz, 1H, NH), 8.18 (d, *J* = 9 Hz, 1H, ArH), 8.45 (s, 1H, NH), 11.21 (s, 1H, NH); ^{13}C NMR (DMSO-d_6), δ, ppm: 18.8, 45.5, 99.0, 122.6, 122.8, 126.2, 128.1 129.1, 136.4, 151.9, 152.2, 154.4, 163.3. Anal. Calcd. for $C_{13}H_{12}Cl_2N_4O_3$: C, 45.50; H, 3.52; N, 16.33. Found: C, 45.55; H, 3.77; N, 16.45.

***N*-[(6-Methyl-2,4-dioxo-1,2-dihydropyrimidin-3(4*H*)-yl)methyl]-*N′*-[3-(trifluoromethyl)phenyl]urea (22).** Yield 0.23 g (67%), mp 235-237 °C; IR, ν, cm^{-1}: 1643, 1689, 1723 (C=O), 3121, 3166, 3393 (NH); ^{1}H NMR (DMSO-d_6), δ, ppm: 2.05 (s, 3H, CH_3), 5.25 (d, *J* = 6.3 Hz, 2H, NCH_2), 5.52 (s, 1H, CH), 7.01 (t, *J* = 6.3 Hz, 1H, NH), 7.26 (d, *J* = 6.9 Hz, 1H, ArH), 7.38-7.56 (m, 2H, ArH), 7.98 (s, 1H, ArH), 9.13 (s, 1H, NH), 11.23 (s, 1H, NH); ^{13}C NMR (DMSO-d_6), δ, ppm: 18.8, 45.6, 99.1, 114.2, 118.4, 121.9, 123.1 126.7, 130.0, 130.4, 130.6, 141.6, 151.9, 152.9, 154.6, 163.4. Anal. Calcd. for $C_{14}H_{13}F_3N_4O_3$: C, 49.13; H, 3.83; N, 16.37. Found: C, 49.39; H, 3.90; N, 16.58.

***N*,*N′*-Bis-[(6-methyl-2,4-dioxo-1,2-dihydropyrimidin-3(4*H*)-yl)methyl]urea (21).** Water (0.018 g, 1 mmol) was added to a solution of azide **6** (0.21 g, 1 mmol) in dioxane (7 mL). The reaction mixture was heated at reflux for 4 h and cooled to room temperature. The resultant precipitate was collected by filtration, washed with methanol and crystallized from a mixture of dimethyl sulfoxide-water to yield **21**, 0.2 g (59%), mp 312-314 °C; IR, ν, cm^{-1}: 1647, 1715 (C=O), 3112, 3187, 3250, 3383 (NH); ^{1}H NMR (DMSO-d_6), δ, ppm: 2.03 (s, 6H, $2CH_3$), 5.10 (d, *J* = 6.3 Hz, 4H, $2NCH_2$), 5.46 (s, 2H, 2CH) 6.96 (t, *J* = 6.3 Hz, 2H, 2NH), 11.12 (s, 2H, 2NH); ^{13}C NMR (DMSO-d_6), δ, ppm: 18.8, 45.9, 99.1, 151.8, 152.7, 156.2, 163.3. Anal. Calcd. for $C_{13}H_{16}N_6O_5$: C, 46.43; H, 4.80; N, 24.99. Found: C, 46.30; H, 5.09; N, 25.07.

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