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Utility of S-Benzylthiuronium Chloride in the Synthesis of Heterocyclic Systems

Mahmoud R. Mahmoud, Ahmed K. El-Ziaty and Ahmed M. Hussein

Department of Chemistry, Synthetic Organic Chemistry Laboratory,
Faculty of Science, Ain Shams University, Abbassia, Cairo, Egypt

Abstract: 4-Amino-2-(benzylthio)-6-(4-chlorophenyl)pyrimidine-5-carbonitrile 1 was prepared by treatment of s-benzylthiuronium chloride with 2-(4-chlorobenzylidene) malononitrile in ethanolic sodium hydroxide and subjected to react with hydrazine hydrate to afford the hydrazino derivative 2 which was allowed to react with different electrophilic reagents to give the pyrimidine derivatives 3-16. IR, ^{1}H-NMR and mass spectra for all the synthesized compounds were discussed.

Key words: Activated nitriles · Pyrimidines and triazolopyrimidine derivatives

INTRODUCTION

The recent wide applications of pyrimidine derivatives as anti-tumer [1], anti-HIV-1 [2], analgesic [3], anti-depressive [4], anti-convulsant [5], anti-microbial [6], anti-inflammatory and antioxidant [3,7], beside their uses as precursors in the synthesis of fused ring compounds like, triazolopyrimidines as antibacterial agents [8] and anti-tumer agents [9], imidazolopyrimidines as antimycobacterial and pyridopyrimidines as antibacterial agents [10] make them worthy to be synthesized and evaluated as drugs.

RESULTS AND DISCUSSION

The utility of activated nitriles in the synthesis of a wide variety of heterocyclic systems [11-20] encouraged us to synthesize pyrimidine derivatives from relatively simple starting materials. The title compound 1 was prepared by reaction of 2-(4-chlorobenzylidene)malononitrile with s-benzylthiuronium chloride in refluxing ethanolic sodium hydroxide according to the following suggested mechanism (cf. Scheme 1).

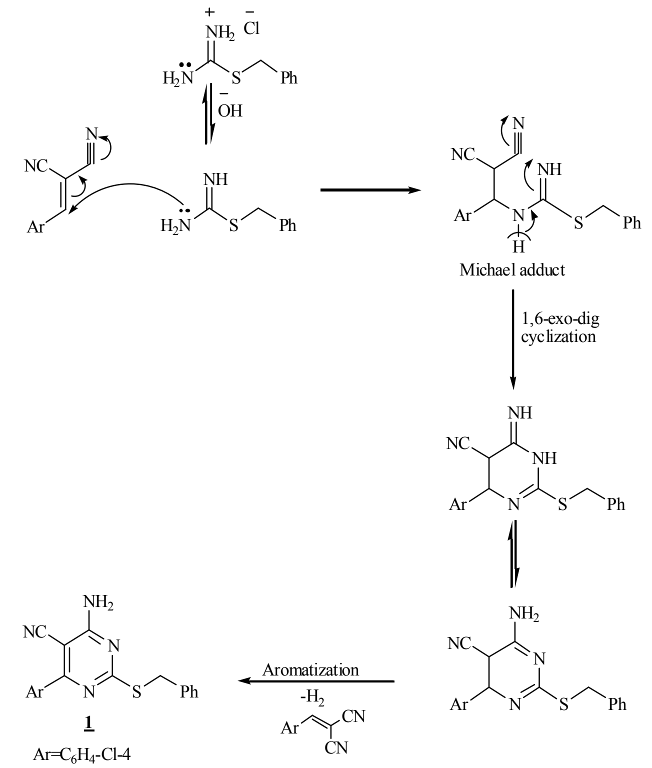
Hydrazinolysis of 1 afforded the sulfur free compound which was identified as 4-amino-6-(4-chlorophenyl)-hydrazinyl pyrimidine-5-carbonitrile 2[6] (Scheme 2).

Recently, it has been reported [21] that the hydrazino pyrimidines can be considered as key starting materials for the synthesis of diverse nitrogen bridgehead compounds. This prompted us to reinvestigate the proclivity of compound 2 with electrophilic reagents such as, β-diketones, β-ketoesters, carbon disulphide, phenyl isothiocyanate, phenyl isocyanate, arylidinemalononitrile, ethoxymethylenemalono ester, anhydrides, ethyl chloroformate, ethyl cyanoacetate, ethyl chloroacetate and triethyl orthoformate with the aim of preparing new pyrimidine derivatives which might have chemotherapeutic and biological evaluation. Thus, treatment of the 2-hydrazino derivative 2 with acetyl acetone and/or benzoyl acetone in refluxing ethanol afforded pyrimido[2,1-*c*]triazepine derivatives 3 (Scheme 2).

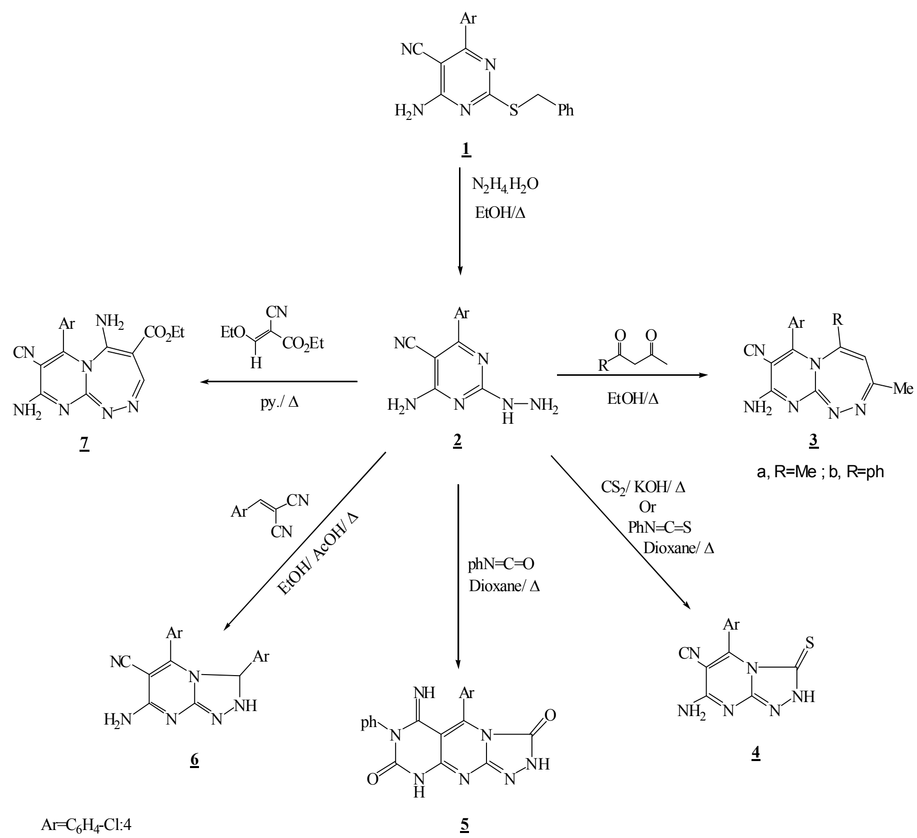
It has been reported that heterocyclic o-aminocarbonitriles including furans, pyrimidines and quinazolines reacted with carbon disulphide under different conditions to afford biologically interest fused thiazines and pyrimidinedithione [22]. However, compound 2 was treated with carbon disulphide in ethanolic potassium hydroxide to yield 7-amino-5-(4-chloroyphenyl)-3-thioxo-2,3-dihydro-[1,2,4]-triazolo[4,3-*a*]pyrimidine-6-carbonitrile 4 (Scheme 2). The same compound 4 was further obtained by treatment of compound 2 with phenyl isothiocyanate in refluxing dioxane. The formation of 4 could be visualized as shown in (Scheme 3).

Treatment of hydrazinopyrimidine derivative 2 with phenylisocyanate in boiling dioxane afforded the pyrimidotriazolopyrimidine derivative 5 (Scheme 2).

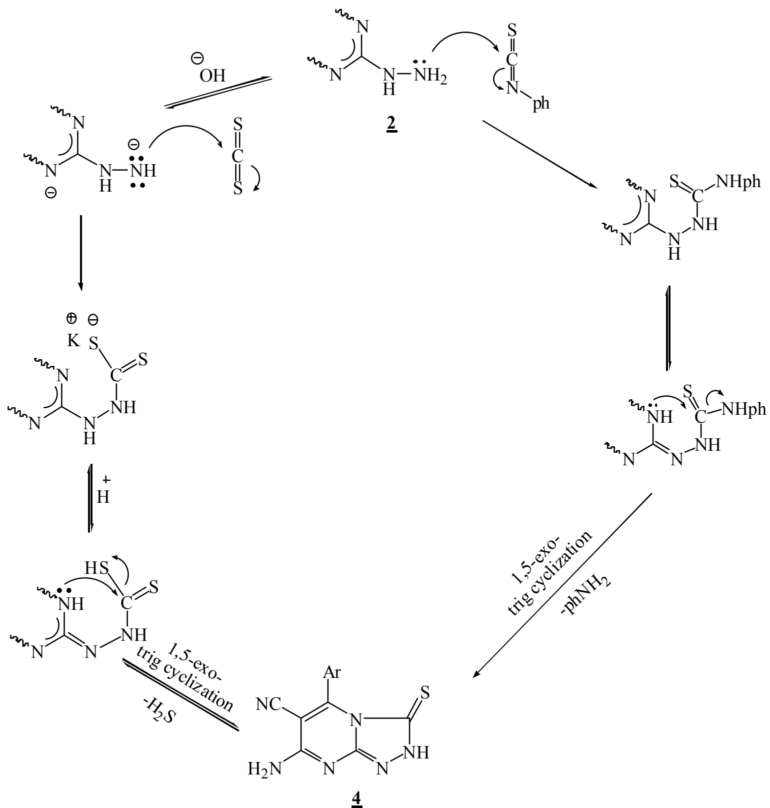
Corresponding Author: Ahmed K. El-Ziaty, Department of Chemistry, Synthetic Organic Chemistry Laboratory, Faculty of Science, Ain Shams University, Abbassia, Cairo, Egypt.
Post Code: 11566.



Scheme 1:



Scheme 2:

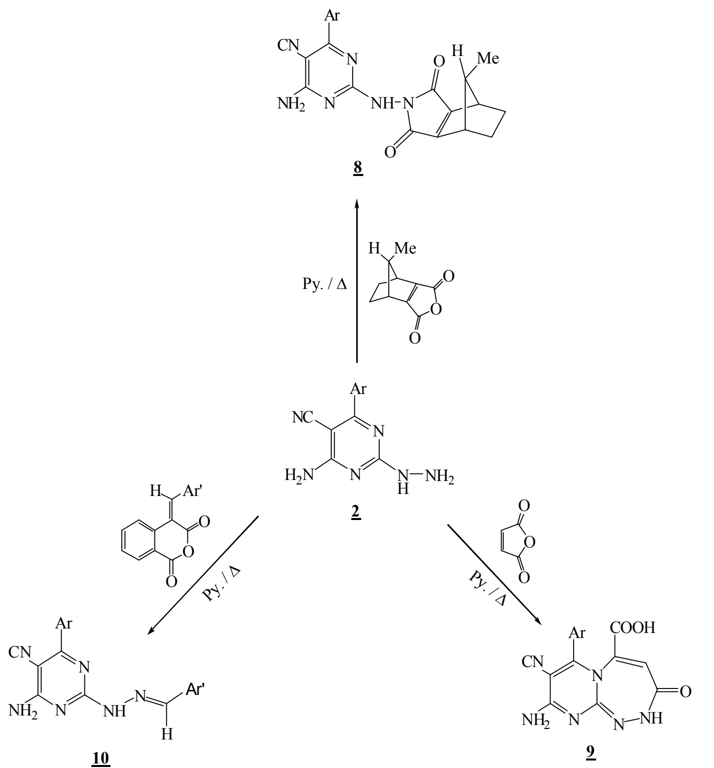


Scheme 3:

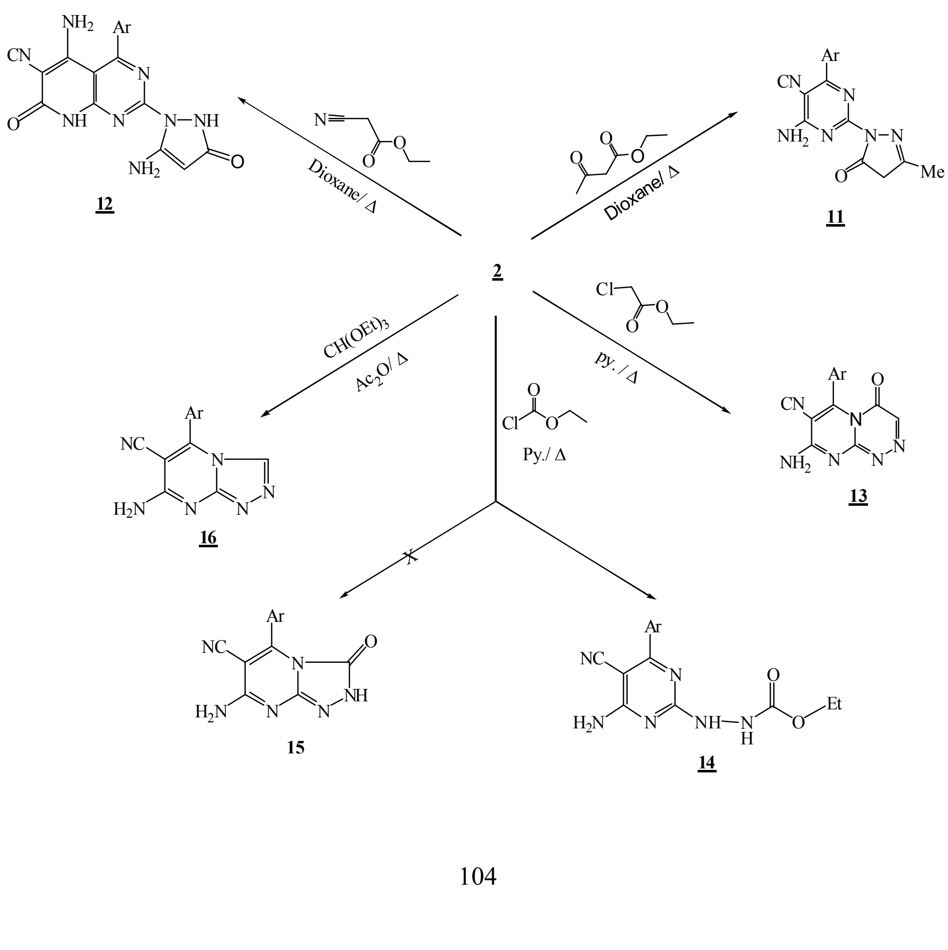
7-Amino-3,5-bis(4-chloroyphenyl)-2,3-dihydro-[1,2,4] triazolo [4,3-*a*] pyrimidine-6-carbonitrile 6 was obtained in fairly good yield upon treatment of compound 2 with 2-(4-chlorobenzylidene)malononitrile in boiling ethanol in the presence of few drops of acetic acid (Scheme 2). Ethyl-5,9-diamino-7-(4-chlorophenyl)-8-cyano-pyrimido [2,1-*c*] [1,2,4] triazepine-4-carboxylate 7 was obtained in fairly good yield (68%) upon treatment of compound 2 with ethyl ethoxymethylenecyanoacetate in refluxing pyridine (Scheme 2). The assigned structure was confirmed from analytical and spectroscopic data. Full analysis of the mass spectrum show the correct molecular ion peak at m/z= 383 which in the base peak. ^{1}H-NMR spectrum of (DMSO-d_6) revealed the presence of ethyl protons as triplet at δ 1.15 ppm (J= 7.4Hz) and quartet at δ = 4.2 ppm (J= 7.4Hz) together with aromatic protons as multiplet at δ 7.7-7.6 ppm integrated for 4H. Furthermore the IR spectrum displayed the stretching absorption bands characteristic for NH_2, C=N and chelated carbonyl ester group (cf. Exp.).

It has been reported that the hydrazine derivatives were reacted with phthalic anhydride and yielded the phthalazin-1,4-dione and N-substituted amino phthalimide derivative [23] this promoted us to reinvestigate the reaction of the hydrazine derivative 2 with some anhydrides such as methylnorbornene 3,4-dicarboxylic acid anhydride, 4-(3,4-dimethoxybenzylidine)-4H-isochromen-1,3-dione and maleic anhydride. Thus refluxing 2 with methylnorbornene 3,4 dicarboxylic acid anhydride in pyridine afforded the N-substituted amino methylnorbornene 3,4-dicarboxylic acid imide 8 (Scheme 4). While 2 behaved differently when reacted with maleic anhydride, it yielded 9-amino-7-(4-chlorophenyl)-8-cyano-3-oxo-2,3-dihydropyrimido [2,1-*c*] [1,2,4] -triazepine-5-carboxylic acid 9 and with 4-(3,4-dimethoxybenzylidine)-4 H-isochromen-1,3-dione it gave the corresponding 2-(3,4-dimethoxybenzylidene)hydrazinyl derivative 10 (Scheme 4).

The proclivity of the hydrazine derivative 2 towards the active methylene compounds such as ethyl acetate, ethyl cyanoacetate and ethyl chloroacetate have been investigated. Thus, refluxing compound 2 with ethyl acetoacetate in dioxane yielded 4-amino-6-(4-chlorophenyl)-2-(3-methyl-5-oxo-4,5-dihydropyrazol-1-yl) pyrimidin-5-carbonitrile 11 (Scheme 5). The highest recorded peak at m/z= 326 (40.6) in the EI spectrum of 11 represent the molecular ion peak which upon loss of acetonitrile molecule afforded the base peak at m/z= 285.



Scheme 4: $Ar' = -C_6H_3(OMe)_2$3:4 ; $Ar = -C_6H_4$-Cl:4



Scheme 5:

^{1}H-NMR spectrum of 11 (DMSO-d_6) revealed signals at δ (ppm) 10.03 (s, 2H, NH_2 exchangeable with D_2O), 7.84 (d, $2H_{arom.}$ J= 7.8 Hz), 7.6-7.5 (d, $2H_{arom.}$, J= 7.5 Hz), 4.1 (brs, 2H, $COCH_2$), 3.1 (s, 3H, Me) which is in accord with the assigned structure.

Treatment of compound 2 with ethyl cyanoacetate in boiling dioxane yielded the pyrido[2,3-d]pyrimidine derivative 12 (Scheme 5). The IR spectrum of 12 indicates the presence of stretching absorption bands characteristic for NH_2, C=N and C=O $_{(enolic)}$. The mass spectrum of compound 12 revealed the incorporation of two molecules of ethyl cyanoacetate in the reaction product (cf. Exp).

he reaction of compound 2 with ethyl chloroacetate in refluxing pyridine afforded 8-amino-6-(4-chlorophenyl)-4-oxo-4H-pyrimido [2,1-*c*] [1,2,4] triazine-7-carbonitrile 13 (Scheme 5). Full analysis of the mass spectrum of 13 showed the correct molecular ion peak at m/z= 299 which is the base peak together with peaks at m/z= 300 (18.6%) and m/z= 301 (27.1%) attributable to M+1 and M+2 (cf. Exp.).

Ethyl N-[4-amino-6-(4-chlorophenyl)-5-cyano-pyimidin-2-yl] carbazate 14 was obtained upon treatment of compound 2 with ethyl chloroformate in refluxing pyridine (Scheme 5). The structure of compound 14 was substantiated from the IR, ^{1}H-NMR and mass spectrum. Thus, the IR spectrum of 14 displayed the stretching absorption bands characteristic for NH_2, NH, C=N and CO $_{(ester)}$ at 3420, 3326, 3218,2209 and 1720 cm^{-1}, respectively. The ^{1}H-NMR spectra revealed the existence of ethyl protons as triplet and quartet which reject the cyclized product 15.

Compelling evidence for the structure of 14 was forthcoming from the full analysis of the mass spectrum of 14 which show the correct molecular ion peak at m/z= 332 (21.2%). Loss of ethanol molecule yielded the radical cation at m/z= 286 (51.6%). The later radical cation when loss N_2 and CO molecules afforded the base peak at m/z= 230.

When the hydrazino derivative 2 was subjected to react with triethyl orthoformate in freshly distilled acetic anhydride, it afforded 7-amino-5-(4-chlorophenyl) [1,2,4] triazolo [4,3-*a*] pyrimidine-6-carbonitrile 16 (Scheme 5).

Experimental: Melting points are uncorrected and were measured by an electric melting point apparatus (G-K). The IR spectra were recorded on a Pye-Unicam SP1200 spectrophotometer using KBr Wafer technique. The ^{1}H-NMR spectra were determined on a Varian GEMINI 300 MHz NMR spectrophotometer using $CDCl_3$ or DMSO-d_6 as solvent and TMS as an internal standard. All chemical shifts are in ppm downfield from TMS. The elemental analysis was carried out in faculty of Science, Ain Shams University. MS were recorded on Shimadzu GC-MS QP1000EX instrument in microanalytical lab, Cairo University. The monitoring of the progress of all reactions and homogeneity of the synthesized compound were carried out by TLC, S-benzylthiuronium chloride was prepared by following the method in literature [24].

4-Amino-2-Benzylthio-6-(4-Chlorophenyl) Pyrimidine-5-Carbonate 1: To a solution of s-benzylthiuronium chloride (2.03 g , 0.01 mole) in water (10 ml), sodium hydroxide (1N, 10 ml) was added dropwise with shaking, the pale green ppt so formed, was dissolved in warmed ethanol (10 ml), then a solution of 4-chlorobenzylidene malononitrile (1.80 g, 0.01 mole) in ethanol (20 ml) was added and the whole mixture was heated under reflux for 5 hrs. The solid formed after cooling was collected by filtration and recrystallized from ethanol to give 1 as pale yellow crystals; m.p: 152-3°C, yield 83%. Anal. calcd. for $C_{18}H_{13}ClN_4S$ (352.5): C, 61.27; H, 3.68; Cl, 10.07; N, 15.88; S, 9.07. Found C, 61.55; H, 3.89; Cl, 9.86; N, 15.70; S, 9.34

IR (ν cm^{-1}): 3413, 3343 cm^{-1} (NH_2), 2214 cm^{-1}(C=N), 1658 cm^{-1}(C=N). MS m/z (%): 352 (M^+, 939), 353 (M+1, 2.9), 354(30.1); 229(29), 91(100), 65(36). ^{1}HNMR ($CDCl_3$) δ (ppm): 7.94 (d,$2H_{arom.}$, J= 8.1 Hz) 7.5-7.2 (m, $5H_{arom.}$), 7.918-7.916 (d, $2H_{arom.}$, J= 8.4 Hz), 5.8 (s, 2H, CH_2) and 4.43 (br.s, 2H, NH_2), exchangeable with D_2O).

4-Amino-6-(4-Chlorophenyl)-2-Hydrazinopyrimidine-5-Carbonitrile 2: A mixture of 1 (3.52 g , 0.01 mole) and hydrazine hydrate 98% (0.015 mole) in ethanol (50 ml) was heated under reflux for 6 hrs. The colourless solid separated on hot was collected by filtration and then recrystallized from dioxane to give 2 as white crystals; m.p: 248-3°C, Yield 55%. Anal. calcd. for $C_{11}H_9ClN_6$ (260.5): C, 50.67; H, 3.45; Cl, 13.62; N, 32.24. Found C, 50.88; H, 3.62; Cl, 13.31; N, 32.48. IR (νcm^{-1}): 3413,3343 cm^{-1} (NH_2, NH), 2214 cm^{-1}(C=N), 1658 cm^{-1}(C=N). MS m/z (%): 260 (M^+, 22), 261 (M+1, 1.2), 262 (M+2, 7.4), 231(54), 229(31), 234(13), 102(11.5).

9-Amino-7-(4-Chlorophenyl)-3,5-Dimethyl Pyrimido [2,1-c] [1,2,4]-Triazepine-8-Carbonitrile 3a: A mixture of compound 2 (1g , 3.9 mmole) and pentane-2,4-dione (0.4 ml , 3.9 m mole) in absolute ethanol (25 ml) was heated under reflux for 6 hrs., the solid deposited while hot was collected by filtration and crystallized from dioxane to give

3a as pale yellow crystals; m.p: 270-2°C, Yield 66%. Anal. calcd. for $C_{16}H_{13}ClN_6$ (324.5): C, 59.16; H, 4.01; N, 25.88. Found C, 59.35; H, 4.23; N, 25.92. IR (ν cm^{-1}): 3474, 3269, 3133 cm^{-1} (NH_2), 2204 cm^{-1} (C=N), 1647 cm^{-1} (C=N). MS m/z (%): 324 (M^+, 100), 305(24.9), 225(24.3). ^{1}HNMR (DMSO-d_6) δ (ppm): 7.9-7.6 (d,2H $_{arom.}$ J= 9 Hz), 7.3 (d,2$H_{arom.}$, J= 8.8 Hz), 6.1 (s, 1H, C_4-H), 3.2 (br.s, 2H, NH_2) exchangeable with D_2O, 2.1 (s, 6H, 2Me).

9-Amino-7-(4-Chlorophenyl)-3-Methyl-5-Phenyl-Pyrimido [2,1-C] [1,2,4]-Triazepine-8-Carbonitrile 3b: A mixture of compound 2 (1 g , 3.9 mmole) and benzoyl acetone (0.63g, 3.9mmole) in ethanol (25 ml) was heated under reflux for 6 hrs. the solid deposited while hot was collected by filtration and crystallized from dioxane to give 3b as yellow crystals, m.p: 230-3°C, Yield 72%. Anal. calcd. for $C_{21}H_{15}ClN_6$ (386.5): C, 65.20; H, 3.88; N, 21.67. Found C, 65.42; H, 3.69; N, 21.70. IR (ν cm^{-1}): 3446, 3379, 3305, 3145 cm^{-1} (NH_2), 2206 cm^{-1} (C=N), 1624 cm^{-1} (C=N). MS m/z (%): 387 (24.1), 388 (M+1, 8.4), 389 (M^++2, 17.6), 105(100). ^{1}HNMR (DMSO-d_6) δ (ppm): 7.8-7.3 (m,9$H_{arom.}$), 6.4 (br.s, 1H, C_4-H), 2.1 (br.s, 3H, C_3-Me) the NH_2 protons are hidden under DMSO.

7-Amino-5-(4-Chlorophenyl)-3-Thioxo-2,3-Dihydro1,2,4-triazolo [4,3-a] Pyrimidin-6-Carbonitrile 4

Method 1 Reaction of 2 with CS_2/Ethanolic KOH: A mixture of 2 (1g, 3.9 mmole) and carbon disulphide (5 ml) in ethanolic KOH 10% (1.0 g KOH dissolved in one ml water and 9 ml ethanol) was heated under reflux on water bath for 6 hrs. After cooling the reaction mixture was acidified with ice cold hydrochloric acid (10ml) and the crude solid that separated out was filtered off, washed several times with cold water and crystallized from ethanol to give 4 as yellow crystals; m.p: 220-2°C, yield 42%. Anal. calcd. for $C_{12}H_7ClN_6S$ (302.5): C, 47.60; H, 2.31; Cl, 11.37; N, 27.76; S, 10.57. Found C, 47.61; H, 2.32; Cl, 11.75; N, 27.78; S, 10.59, IR ($\upsilon$$cm^{-1}$): 3290, 3251, 3190 cm^{-1} (NH_2, NH), 2215 cm^{-1} (C=N), 1644 cm^{-1} (C=N), 1223 cm^{-1} (C=S). MS m/z (%): 302 (M^+, 100), 229 (13.6), 187 (13), 111 (11.9), 75 (21.5).

Method 2 Reaction of 2 with Phenyl Isothiocyanate: A mixture of 2 (1g, 3.9 m mole) and phenyl isothiocyanate (0.53 ml, 3.9 m mole) in dioxane (25 ml) was heated under reflux for 6 hrs. The excess solvent was evaporated and the crude solid that separated out was filtered off, washed several times with ethanol and crystallized from ethanol to give 4 yield 56% (identity m.p, mixed m.p, IR, MS and T.L.C comparison).

5-(4-chlorophenyl)-6-imino-7-phenyl-2,6,7,9-tetrahydro Pyrimido[4,5-d][1,2,4]triazolo[4.3-a] Pyrimidine 3,8 Dione 5: A mixture of 2 (1g, 3.9 mmole) and phenyl isocyanate (0.46 ml, 3.9 m mole) in dioxane 25 ml was heated under reflux for 3h. The solid deposited after cooling was filtered off, washed several times with ether and recrystallized from dioxane to give 5 as colourless crystals; m.p: 170-2°C, yield 61%. Anal. Calcd. for $C_{19}H_{12}ClN_7O_2$ (405.5): C, 56.22; H, 2.55; N, 24.16. Found C, 56.24; H, 2.98; N, 24.26. IR (cm^{-1}): 3407, 3325, 3282, 3181, 3130 cm^{-1} (NH_2), 1719, 1650 cm^{-1} (C=O). MS m/z (%): 289 (M^+-PhNCO+2H, 14.3), 245 (17), 119 (100%) ,93 (65.7).

7-amino-3,5-bis(4-chlorophenyl)2,3-dihydro-[1,2,4]-Triazolo[4,3-a]pyrimidin-6-carbonitril 6: A mixture of 2 (1g, 3.9 mmole) and 2-(4-chlorobenzylidene)malononitrile (0.73 gm, 3.9 m mole) in ethanol (25 ml) and drops of glacial acetic acid was heated under reflux for 6h. The colourless solid separated on hot was collected by filtration and then recrystallized from dioxane to give 6 as pale yellow crystals; m.p: 290-2°C, yield 53%. Anal. Calcd. for $C_{18}H_{12}Cl_2N_6$ (384): C, 56.39; H, 3.38; N, 21.87. Found C, 56.27; H, 3.40; N, 21.89. IR ($\upsilon$$cm^{-1}$): 3462, 3292 cm^{-1} (NH_2), 2207 cm^{-1} (C=N), 1645 cm^{-1} (C=N). MS m/z (%):383 (24.5), 385 (M+1, 2), 386 (M+2, 15.6), 244 (58.6), 203 (48), 138 (44.8), 111 (100). ^{1}HNMR (DMSO-d_6) δ (ppm): 11.5 (s, 1H,

NH, exchangeable with D_2O), 8.7 (s, 1H, C_3-H), 7.9-7.6 (m, 8H_{arom}), NH_2 protons are hidden under DMSO.

Ethyl-5,9-diamino-7-(4-chlorophenyl)8-cyano-pyrimido[2,1-c][1,2,4]triazepine-4-carboxylate 7: A mixture of 2 (1g, 3.9 mmole) in pyridine and ethyl ethoxymethylene cyanoacetate (0.66 g 3.9mmol) in 25ml pyridine was heated under reflux for 7h. After cooling the reaction mixture was acidified with cold dilute hydrochloric acid, the yellow solid was filtered off, washed several times with ether and recrystallized from ethanol to give 7 as yellow crystals; m.p: 270-2°C, yield 65%. Anal. Calcd. for $C_{17}H_{14}ClN_7O_2$ (383.5): C, 53.19; H, 3.68; N, 25.55. Found C, 53.26; H, 3.68; N, 25.87. IR ($\upsilon$$cm^{-1}$): 3478, 3406, 3299, 3154 cm^{-1} (NH_2, NH), 2211 cm^{-1} (C=N), 1675 cm^{-1} (C=O). MS m/z (%):383 (M^+, 100), 337 (56.7), 271 (21.6), 229 (30.9), 187 (23.7). ^{1}HNMR (DMSO-d_6) δ (ppm): 1.5 (t, 3H, J=7.4Hz), 2.67 (s, 1HC_3-H), 3.6 (br.s, 4H exchangeable with D_2O), 4.2 (q, 2H, J=7.4Hz), 7.6-7.7 (m, 4Harom.)

4-amino-6-(4-chlorophenyl)-2-{[10-methyl-3,5-dioxo-4-azatricyclo[5.2.2.0^{2,6}]dec-2(6)-en-4-yl]amino}pyrimidine-5-carbonitrile 8: A mixture of 2 (1.2 g, 3.9 mmole) and methyl norbornen 3,4 dicarboxylic anhydride (0.7 g, 3.9 mmole) in pyridine (25 ml) was heated under reflux for 6h. The white solid crystals appears after the addition of ice cold acidified hydrochloric acid, was collected by filtration and then recrystallized from ethanol. m.p: 170-3°C, yield 75%. Anal. Calcd. for $C_{21}H_{17}ClN_6O_2$ (420.5): C, 59.92; H, 4.04; N, 19.9. Found C, 59.72; H, 4.06; N, 19.98. IR (υcm^{-1}): 3438, 3331, 3194 cm^{-1} (NH_2, NH), 2210 cm^{-1} (C=N), 1791, 1726 cm^{-1} (C=O). MS m/z (%):420 (7.2), 341 (100), 295 (19.3), 229 (11.7), 80 (84.8). ^{1}H-NMR (DMSO-d_6) δ (ppm): 10.1-9.9 (s, 2H, NH_2, exchangeable with D_2O), 7.8-7.5 (m, $4H_{arom}$), 7.3 (s, 1H, NH, exchangeable with D_2O), 3.3-1.02 (m, 10H, norbornyl and methyl protons).

9-amino-7-(4-chlorophenyl)-8-cyano-3-oxo-2,3-dihydropyrimido[2,1-c][1,2,4]triazepine-5-carboxylic Acid 9: A mixture of 2 (1g, 3.9 mmole) and maleic anhydride (0.38 g, 3.9 mmole) in dioxane (20 ml) was heated under reflux for 3h. The pale yellow solid deposited after cooling was collected by filtration and then recrystallized from ethanol to give 9 as pale yellow crystals; m.p: 212-215°C, yield 50%. Anal. Calcd. for $C_{15}H_9ClN_6O_3$ (356.5): C, 50.49; H, 2.52; N, 23.56. Found C, 50.51; H, 2.54; N, 23.58. IR (υcm^{-1}): 3325, 3219cm^{-1} (NH_2,NH), br. 3600-3400 (OH), 2210 cm^{-1} (C=N), 1703, 1663 cm^{-1} (C=O). MS m/z (%):355 (M-2; 10.2), 260 (27.0), 245 (62.9), 203 (39.8), 68(100).

2-[2-(3,4-dimethoxybenzylidene)hydrazinyl]-4-amino-6-(4-chlorophenyl)pyrimidine-5-carbonitrile 10: A mixture of 2 (1g, 3.9 mmole) and chromene-1,3-dione derivatives (1.2g, 3.9 mmole) in dioxane or pyridine (15 ml) was heated under reflux for 6h. After evaporation of the solvent in vaccuo, the solid obtained was collected by filtration and recrystallized from ethanol to give 10 as dark yellow crystals; m.p: 280-282°C, yield 85%. Anal. Calcd. for $C_{20}H_{17}ClN_6O_2$ (408.5): C, 58.75; H, 4.16; N, 20.56. Found C, 58.75; H, 4.18; N, 20.58. IR (υcm^{-1}): 3484, 3322, 3234 cm^{-1} (NH_2), 2198 cm^{-1} (C=N), 1637 cm^{-1} (C=N). MS m/z (%):408 (M^+; 13.8), 245 (100), 203 (38.6), 163 (59.1), 92 (67). ^{1}H-NMR (DMSO-d_6) δ (ppm): 11.3 (s, 1H, NH, exchangeable with D_2O), 8.1 (s, 1H, N=CH), 7.87-7.2 (m, $7H_{arom.}$), 6,99 (s,2H, NH_2 exchangeable with D_2O), 3.8 (s, 6H, OMe).

4-amino-6-(4-chlorophenyl)-2-[3-methyl-5-oxo-4,5-dihydropyrazol-1-yl)pyrimidin-5-carbonitrile 11: A mixture of 2 (1.0 g, 3.9 mmole) and ethyl acetoacetate (0.4 ml, 3.9 m mole) in dioxane (20 ml) was heated under reflux for 6 hrs. The reaction mixture was concentrated and the solid deposited was collected by filtration and recrystallized from ethanol to give 11 as yellow crystals, m.p: 280-2°C. Yield 60%. Anal. calcd. for $C_{15}H_{11}ClN_6O$ (326.5): C, 55.13; H, 3.36; N, 25.72. Found C, 55.22; H, 3.57; N, 25.74. IR (υ cm^{-1}): 3429, 3355, 3286, 3154 cm^{-1} (NH_2), 2204 cm^{-1} (C=N), 1716 cm^{-1} ($C=O_{ester}$), 1631 cm^{-1} (C=N). MS m/z (%): 326 (M^+, 40.6), 285 (100), 229 (32.2), 187 (21.2). ^{1}HNMR (DMSO-d_6) δ (ppm): 10.03(s, 2H, NH_2 exchangeable with D_2O), 7.84 (d, $2H_{arom.}$, *J*= 7.8 Hz), 7.5-7.6 (d, $2H_{arom}$, *J*= 7.5 Hz), 4.1 (br.s, 2H, $COCH_2$), 3.1 (s, 3H, Me).

5-amino-2-(5-amino-3-oxo-2,3-dihydropyrazol-1-yl)-4-(4-chlorophenyl)-7-oxo-7,8-dihydropyrido[2,3-d]pyrimidine-6-carbonitrile 12: A mixture of 2 (1g, 3.9 mmole) and ethyl cyanoacetate (0.45 ml, 3.9 mmole) in dioxane (25 ml) was heated under reflux for 6h. The reaction mixture was concentrated. The solid separated out was filtered off and recrystallized from ethanol to give 12 as yellow crystals; m.p: 190-192°C, yield 50%. Anal. Calcd. for $C_{17}H_{11}ClN_8O_2$ (394.5): C, 51.71; H, 2.78; N, 28.39. Found C, 51.52; H, 2.83; N, 28.66. IR (υcm^{-1}): 3413, 3343, 3251 cm^{-1} (NH_2), 2211 cm^{-1} (C=N), 1656 cm^{-1} (C=O). MS m/z (%):394 (3.3), 331 (100), 314 (7.1), 288 (11.4), 258 (52.9), 77 (88.6).

8-amino-6-(4-chlorophenyl)-4-oxo-4h-pyrimido[2,1-c][1,2,4]triazine-7-carbonitrile 13: A mixture of 2 (1g, 3.9 mmole) and ethyl chloroacetate (0.5 ml, 3.9 mmole) in pyridine (25 ml) was refluxed for 8h. The reaction mixture was concentrated and acidified with cold dilute acetic acid. The solid separated out was filtered off, washed several times with cold water and recrystallized from ethanol to give 13 as white crystals; m.p: 250-253°C, yield 60%. Anal. Calcd. for $C_{13}H_7ClN_6O$ (298.5): C, 52.26; H, 2.34; N, 28.14. Found C, 52.44; H, 2.6; N, 27.07. IR (υcm^{-1}): 3484, 3375, 3288 cm^{-1}(NH_2), 2202 cm^{-1} (C=N), 1650 cm^{-1} (C=O). MS m/z (%):301 (M+2; 7.1), 300 (M+1;18.6), 299 (M^+, 100), 213 (18.3), 77 (36.5).

Ethyl N-[4-amino-5-cyano-6-(4-chlorophenyl)pyrimidin-2-yl]carbazate 14: A mixture of 2 (1g, 3.9 mmole) and ethyl chloroformate (0.42 ml, 3.9 mmole) in pyridine (20 ml) was heated under reflux for 6h. The reaction mixture was concentrated and acidified with cold dilute acetic acid.

The solid separated out was filtered off, washed several times with cold water and recrystallized from ethanol to give 14 as colourless crystals; m.p: 255-258°C, yield 54%. Anal. Calcd. for $C_{14}H_{13}ClN_6O_2$ (332.5): C, 50.52; H, 3.90; N, 25.26. Found C, 50.43; H, 4.09; N, 25.28. IR (υcm^{-1}): 3420, 3326, 3218 cm^{-1} (NH_2), 2209 cm^{-1} (C=N), 1720 cm^{-1} (C=O). MS m/z (%):332 (21.2), 286 (57.6), 230 (100), 195 (17.3). ^{1}H-NMR (DMSO-d_6) δ (ppm): 9.3-9.1 (m, 4H, 2NH, NH_2, exchangeable with D_2O), 7.5-7.4 (d, $2H_{arom}$, *J*= 8.6 Hz), 7.4 (d, $2H_{arom}$, *J*= 8.6 Hz), 4.3(q, 2H, $COOCH_2CH_3$), 1.26-1.05 (t, 3H, $COOCH_2CH_3$ *J*= 7.6 Hz).

7-amino-5-(4-chlorophenyl) [1,2,4]triazolo[4,3-a]pyrimidine-6-carbonitrile 16: A mixture of 2 (1g, 3.9 mmole) and triethyl orthoformate in freshly distilled acetic anhydride (10 ml) was heated under reflux for 5h. After cooling the reaction mixture was poured on ice cold water. The crude deposited was collected and recrystallized from dioxane to give 16 as yellow crystals; m.p: 270-274°C, yield 70%. Anal. Calcd. for $C_{12}H_7ClN_6$ (270.5): C, 53.23; H, 2.59; N, 31.05. Found C, 53.35; H, 2.57; N, 31.12. IR (υcm-1): 3321, 3320 cm-1 (NH2), 2214 cm-1 (C?N), 1719 cm-1 (C=N). MS m/z (%):272 (M+2, 32.5), 271 (M+1, 24.7), 270 (M+, 100), 205 (12.7), 84 (25.8). ^{1}H-NMR (DMSO-d6) δ (ppm): 9.3 (br.s, 3H, NH_2, C_3-H), 7.8 (d, $2H_{arom}$. *J*= 8.6 Hz), 7.6 (d, $2H_{arom}$. *J*= 8.6 Hz).

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