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Ecofriendly regioselective one-pot synthesis of chromeno[4,3-*d*][1,2,4]triazolo[4,3-*a*]pyrimidine derivatives

Sobhi Mohamed Gomha [a,*] and Mohamed Gomaa Badrey [b]

[a] *Department of Chemistry, Faculty of Science, University of Cairo, Giza, 12613, Egypt*
[b] *Chemistry Department, Faculty of Science, Fayoum University, El-Fayoum, 63514, Egypt*

**Corresponding author at: Department of Chemistry, Faculty of Science, University of Cairo, Giza, 12613, Egypt. Tel.: +20.237.400304; fax: +2.025.685799. E-mail address: s.m.gomha@hotmail.com (S.M. Gomha).*

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ABSTRACT

The reaction between 2-mercapto-3*H*-chromeno[4,3-*d*]pyrimidine-4,5-dione (1) or its 2-methylthio derivative (7) with hydrazonoyl halides (2) in dioxane under ultrasound irradiation in the presence of chitosan yielded chromeno[4,3-*d*][1,2,4]triazolo[4,3-*a*]pyrimidine derivatives (5a-r). On the other hand, the reaction of compound 1 with the appropriate active chloromethylene compounds (9b, h and m) followed by coupling the products with benzenediazonium chloride afforded the azo coupling products which converted *in situ* to compound 5. The reaction mechanism was proposed and the structure of the newly synthesized compounds were established on the basis of spectral data (Mass, IR, ^{1}H and ^{13}C NMR) and elemental analyses.

1. Introduction

Benzopyranopyrimidine derivatives are reported to possess significant applications, as anticoagulant [1], antihrombotics [2], estrogenic activity on MCF-7 breast carcinoma cells [3] and antagonists as potential antipsychotic agents [4]. In view of these useful properties, it is not surprising that the development of synthetic approaches to these ring systems has attracted considerable interest over the years. Moreover, nitrogen-containing heterocycles are also of broad pharmaceutical interest and significance, which justifies our continuing efforts in exploring synthetic strategies which lead to structures formed from a combination of both types of heterocycles. This can also provide useful information regarding structural-activity relationship in this area. Furthermore, ultrasound irradiation has been established as an important technique in synthetic organic chemistry. It has been used as an efficient heating source for organic reactions. Shorter reaction time is the main advantage of ultrasound-assisted reactions; simple experimental procedure, very high yields, increased selectivity and clean reactions of many ultrasound-induced organic transformations offers additional conveniences in the field of synthetic organic chemistry [5-8]. The beneficial effects of ultrasound irradiation are playing an increasing role in process chemistry, especially in cases where classical methods require drastic conditions or prolonged reactions times.

The results found by Thoraya *et al.* [9] on their work on a starting material with somewhat related structure to ours were very promising to us although using normal heating procedures; this is because the prepared compounds showed promising activities against HCV, H1N1, and could also be used as antiandrogenic agents. Thus, in this paper, we aimed to improve the synthetic procedure for such type of compounds. This could be accomplished through the interaction of hydrazonyl halides with the title compound **1** under ultrasound irradiation as ecofriendly energy source and using the eco-friendly naturally occurring chitosan catalyst which has been previously used for similar synthesis [9-11].

2. Experimental

2.1. Instrumentation

Melting points were determined on a Gallenkamp apparatus and are uncorrected. IR spectra were recorded in potassium bromide using Pye-Unicam SP300 spectro-photometer. ^{1}H and ^{13}C NMR spectra were recorded in deuterated DMSO-d_6 using a Varian Gemini 300 NMR spectrometer (300 MHz for ^{1}H NMR and 75 MHz for ^{13}C NMR) and the chemical shifts were related to that of the solvent DMSO-d_6. Mass spectra were recorded on a GCMS-Q1000-EX Shimadzu and GCMS 5988-A HP spectrometers, the ionizing voltage was 70 eV. Irradiation was done in an ultrasonicator, (Electric supply: 230 V, A.C. 50 Hz, 1phase; Ultrasonic frequency: 36 KHz; Ultrasonic power: 100W). Elemental analyses of the products were carried out at the Microanalytical Centre of Cairo University, Giza, Egypt.

2.2. Synthesis

2-Mercapto-3*H*-chromeno[4,3-d]pyrimidine-4,5-dione (**2**) [12] and its 3-methylthio derivative (**7**) [13] and the hydrazonoyl halides **2** [14-17] were prepared as described in the literature.

2.2.1. Synthesis of 9,11-disubstituted 6H-chromeno[4,3-d][1,2,4]triazolo[4,3-a]pyrimidine-6,7(11H)-dione (5a-r)

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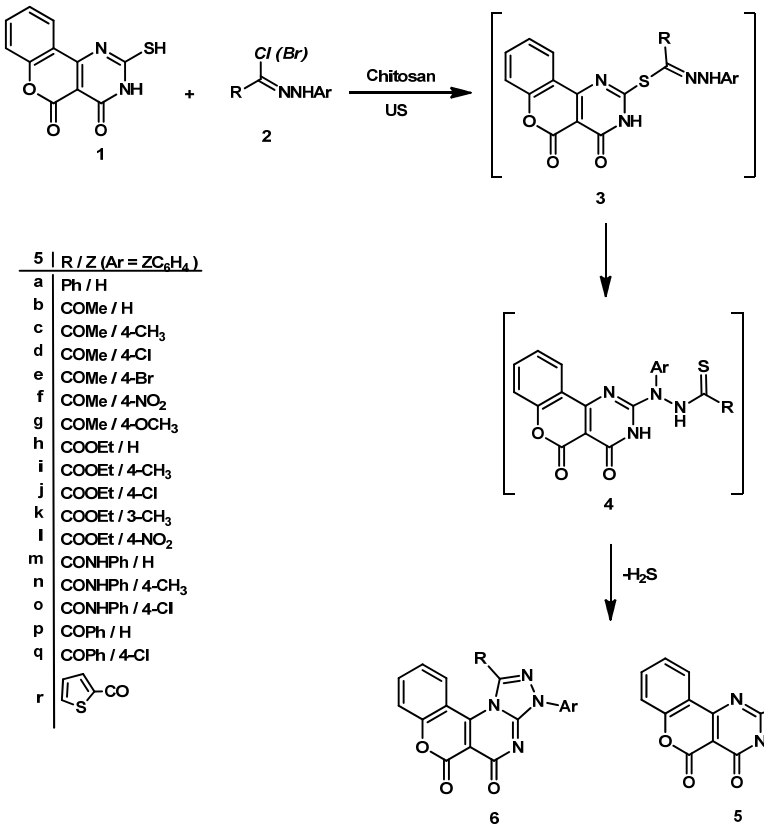
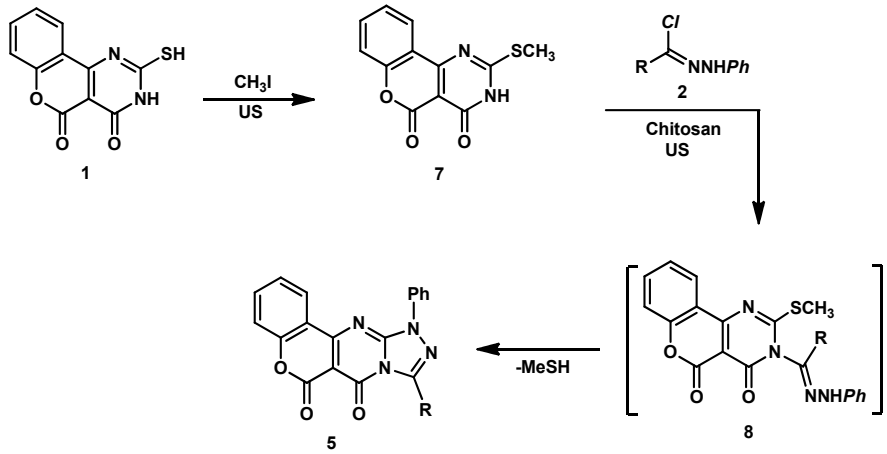


5	R / Z (Ar = ZC_6H_4)
a	Ph / H
b	COMe / H
c	COMe / 4-CH_3
d	COMe / 4-Cl
e	COMe / 4-Br
f	COMe / 4-NO_2
g	COMe / 4-OCH_3
h	COOEt / H
i	COOEt / 4-CH_3
j	COOEt / 4-Cl
k	COOEt / 3-CH_3
l	COOEt / 4-NO_2
m	CONHPh / H
n	CONHPh / 4-CH_3
o	CONHPh / 4-Cl
p	COPh / H
q	COPh / 4-Cl
r	

Scheme 1



Scheme 2

Method A: To a mixture of equimolar amounts of compound **1** and the appropriate hydrazonoyl halides **2** (10 mmol each) in dioxane (50 mL) was added chitosan (0.1 g). The reaction mixture was irradiated by an ultrasonic generator in a water-bath at 40-50 °C for 40 min. (irradiation was continued till all of the starting materials have been disappeared and hydrogen sulfide gas ceased to evolve, monitored by TLC). The hot solution was filtered to remove chitosan then the solvent was evaporated and the residue was triturated with methanol. The solid that formed was filtered and recrystallized from appropriate solvent to give compounds **5** (Scheme 1).

Method B: Treatment of the methylthio derivative **7** with hydrazonoyl halides **2** following the same procedure in method A led to formation of products which were found to be identical in all respects (M.p., mixed m.p. and IR) with products **5** (Scheme 2).

9,11-Diphenyl-6H-chromeno[4,3-d][1,2,4]triazolo[4,3-a] pyrimidine-6,7(11H)-dione (**5a**): Yield: 75%, crystallized from dioxane as white microcystals. M.p.: 324 °C. IR (KBr, ν, cm^{-1}): 1735 (δ-lactone), 1658 (CO amide). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 6.79-8.30 (m, 14H, Ar-H). ^{13}C NMR (75 MHz, DMSO-d_6, δ, ppm): 114.6, 119.2, 120.4, 123.4, 124.6, 128.6, 130.2,

130.7, 133.9, 134.7, 136.2, 138.9, 140.3, 140.9, 143.3, 148.0, 148.9, 151.6, 161.3 (C=O), 166.5 (C=O). MS (*m/z* (%)): 407 (M^++1, 14), 406 (M^+, 35), 190 (100), 116 (47), 77 (88). Anal. calcd. for $C_{24}H_{14}N_4O_3$ (406.11): C, 70.93; H, 3.47; N, 13.79. Found: C, 70.99; H, 3.36; N, 13.64%.

9-Acetyl-11-phenyl-6H-chromeno[4,3-d][1,2,4]triazolo[4,3-a] pyrimidine-6,7(11H)-dione (**5b**): Yield: 78%, crystallized from dioxane as pale yellow crystals. M.p.: 264 °C. IR (KBr, *ν*, cm^{-1}): 1734 (*δ*-lactone), 1682 ($COCH_3$), 1656 (CO amide). ^1H NMR (300 MHz, DMSO-d_6, *δ*, ppm): 2.44 (s, 3H, $COCH_3$), 7.20-8.39 (m, 9H, Ar-H). ^{13}C NMR (75 MHz, DMSO-d_6, *δ*, ppm): 22.6, 119.2, 120.4, 124.6, 128.6, 130.2, 130.7, 133.9, 136.2, 138.9, 140.3, 140.9, 143.3, 148.9, 151.6, 161.3 (C=O), 165.3 (C=O), 189.6 (C=O). MS (*m/z* (%)): 373 (M^++1, 15), 372 (M^+, 58), 343 (62), 289 (34), 213 (49),146 (14), 91 (100), 77 (8). Anal. calcd. for $C_{20}H_{12}N_4O_4$ (372.09): C, 64.52; H, 3.25; N, 15.05. Found: C, 64.43; H, 3.20; N, 14.89%.

9-Acetyl-11-p-tolyl-6H-chromeno[4,3-d][1,2,4]triazolo[4,3-a] pyrimidine-6,7(11H)-dione (**5c**): Yield: 78%, crystallized from ethanol as pale yellow crystals. M.p.: 234 °C. IR (KBr, *ν*, cm^{-1}): 1747 (*δ*-lactone), 1689 ($COCH_3$), 1649 (CO amide). ^1H NMR (300 MHz, DMSO-d_6, *δ*, ppm): 2.28 (s, 3H, $ArCH_3$), 2.43 (s, 3H, $COCH_3$), 7.20-8.39 (m, 8H, Ar-H). MS (*m/z* (%)): 386 (M^+, 2) 261 (89), 208 (21), 106 (100), 77 (44). Anal. calcd. for $C_{21}H_{14}N_4O_4$ (386.10): C, 65.28; H, 3.65; N, 14.50. Found: C, 65.17; H, 3.49; N, 14.38%.

9-Acetyl-11-(4-chlorophenyl)-6H-chromeno[4,3-d][1,2,4] triazolo[4,3-a]pyrimidine-6,7(11H)-dione (**5d**): Yield: 76%, crystallized from dioxane as pale yellow crystals. M.p.: 227 °C. IR (KBr, *ν*, cm^{-1}): 1745 (*δ*-lactone), 1679 ($COCH_3$), 1654 (CO amide). ^1H NMR (300 MHz, DMSO-d_6, *δ*, ppm): 2.49 (s, 3H, $COCH_3$), 7.16-8.25 (m, 8H, Ar-H). MS (*m/z* (%)): 407 (M^++1, 17), 406 (M^+, 14), 364 (100), 281 (43), 213 (69), 90 (95). Anal. calcd. for $C_{20}H_{11}ClN_4O_4$ (406.05): C, 59.05; H, 2.73; N, 13.77. Found: C, 59.00; H, 2.78; N, 13.65%.

9-Acetyl-11-(4-bromophenyl)-6H-chromeno[4,3-d][1,2,4] triazolo[4,3-a]pyrimidine-6,7(11H)-dione (**5e**): Yield: 73%, crystallized from dioxane as pale yellow crystals. M.p.: 268 °C. IR (KBr, *ν*, cm^{-1}): 1740 (*δ*-lactone), 1680 ($COCH_3$), 1664 (CO amide). ^1H NMR (300 MHz, DMSO-d_6, δ, ppm): 2.46 (s, 3H, $COCH_3$), 7.19-8.29 (m, 8H, Ar-H). MS (*m/z* (%)): 450 (M^+, 11), 384 (100), 302 (13), 152 (52), 77 (43). Anal. calcd. for $C_{20}H_{11}BrN_4O_4$ (450.00): C, 53.24; H, 2.46; N, 12.42. Found: C, 53.21; H, 2.40; N, 12.31%.

9-Acetyl-11-(4-nitrophenyl)-6H-chromeno[4,3-d][1,2,4] triazolo[4,3-a]pyrimidine-6,7(11H)-dione (**5f**): Yield: 72%, crystallized from ethanol as brown solid. M.p.: 254 °C. IR (KBr, *ν*, cm^{-1}): 1753 (*δ*-lactone), 1690 ($COCH_3$), 1667 (CO amide). ^1H NMR (300 MHz, DMSO-d_6, *δ*, ppm): 2.46 (s, 3H, $COCH_3$), 7.25-8.36 (m, 8H, Ar-H). MS (*m/z* (%)): 417 (M^+, 24), 374 (51), 349 (100), 213 (47), 90 (48). Anal. calcd. for $C_{20}H_{11}N_5O_6$ (417.07): C, 57.56; H, 2.66; N, 16.78. Found: C, 57.50; H, 2.61; N, 16.64%.

9-Acetyl-11-(4-methoxyphenyl)-6H-chromeno[4,3-d][1,2,4] triazolo[4,3-a]pyrimidine-6,7(11H)-dione (**5g**): Yield: 77%, crystallized from ethanol as yellow crystals. M.p.: 222 °C. IR (KBr, *ν*, cm^{-1}): 1749 (*δ*-lactone), 1683 ($COCH_3$), 1660 (CO amide) cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6, *δ*, ppm): 2.41 (s, 3H, $COCH_3$), 3.32 (s, 3H, OCH_3), 7.24-8.22 (m, 8H, Ar-H). MS (*m/z* (%)): 403 (M^++1, 6), 402 (M^+, 7), 335 (100), 320 (65), 213 (22), 77 (8). Anal. calcd. for $C_{21}H_{14}N_4O_5$ (402.10): C, 62.69; H, 3.51; N, 13.92. Found: C, 62.69; H, 3.51; N, 13.92%.

Ethyl 6,7-dioxo-11-phenyl-7,11-dihydro-6H-chromeno[4,3-d] [1,2,4]triazolo[4,3-a]pyrimidine-9-carboxylate (**5h**): Yield: 73%, crystallized from ethanol as white crystals. M.p.: 216 °C. IR (KBr, *ν*, cm^{-1}): 1753 (*δ*-lactone), 1682 (COOEt), 1648 (CO amide). ^1H NMR (300 MHz, DMSO-d_6, *δ*, ppm): 1.41 (t, *J* = 7 Hz, 3H, CH_2CH_3), 4.55 (q, *J* = 7 Hz, 2H, CH_2CH_3), 7.41-8.38 (m, 9H, Ar-H). ^{13}C NMR (75 MHz, DMSO-d_6, *δ*, ppm): 16.3, 48.4, 118.4, 120.8, 123.6, 127.3, 130.0, 130.7, 133.4, 136.6, 137.9, 140.3, 141.9, 143.3, 146.6, 150.6, 161.5 (C=O), 164.3 (C=O), 166.6 (C=O). MS (*m/z* (%)): 403 (M^++1, 21), 402 (M^+, 81), 329 (62), 289(42), 91 (100), 77 (65). Anal. calcd. for $C_{21}H_{14}N_4O_5$ (402.10): C, 62.69; H, 3.51; N, 13.92. Found: C, 62.52; H, 3.63; N, 13.72%.

Ethyl 6,7-dioxo-11-p-tolyl-7,11-dihydro-6H-chromeno[4,3-d] [1,2,4]triazolo[4,3-a]pyrimidine-9-carboxylate (**5i**): Yield: 72%, crystallized from ethanol as white crystals. M.p.: 225 °C. IR (KBr, *ν*, cm^{-1}): 1753 (*δ*-lactone), 1680 (COOEt), 1667 (CO amide). ^1H NMR (300 MHz, DMSO-d_6, *δ*, ppm): 1.40 (t, *J* = 7 Hz, 3H, CH_2CH_3), 2.38 (s, 3H, $ArCH_3$), 4.56 (q, *J* = 7 Hz, 2H, CH_2CH_3), 7.39-8.33 (m, 8H, Ar-H). MS (*m/z* (%)): 418 (M^++2, 5), 417 (M^++,26), 416 (M^+, 100), 343 (75), 303 (35), 105 (80), 77 (38). Anal. calcd. for $C_{22}H_{16}N_4O_5$ (416.11): C, 63.46; H, 3.87; N, 13.46; Found: C, 63.23; H, 3.84; N, 13.28%.

Ethyl 11-(4-chlorophenyl)-6,7-dioxo-7,11-dihydro-6H-chromeno[4,3-d][1,2,4]triazolo[4,3-a]pyrimidine-9-carboxylate (**5j**): Yield: 73%, crystallized from ethanol as white crystals. M.p.: 216 °C. IR (KBr, *ν*, cm^{-1}): 1754 (*δ*-lactone), 1682 (COOEt), 1664 (CO amide). ^1H NMR (300 MHz, DMSO-d_6, *δ*, ppm): 1.41 (t, *J* = 7 Hz, 3H, CH_2CH_3), 4.56 (q, *J* = 7 Hz, 2H, CH_2CH_3), 7.43-8.41 (m, 8H, Ar-H). MS (*m/z* (%)): 438 (M^++2, 38), 437 (M^++1, 28), 436 (M^+, 100), 363 (75), 213 (53), 125 (100), 90 (75). Anal. calcd. for $C_{21}H_{13}ClN_4O_5$ (436.06): C, 57.74; H, 3.00; N, 12.83. Found: C, 57.70; H, 3.04; N, 12.65%.

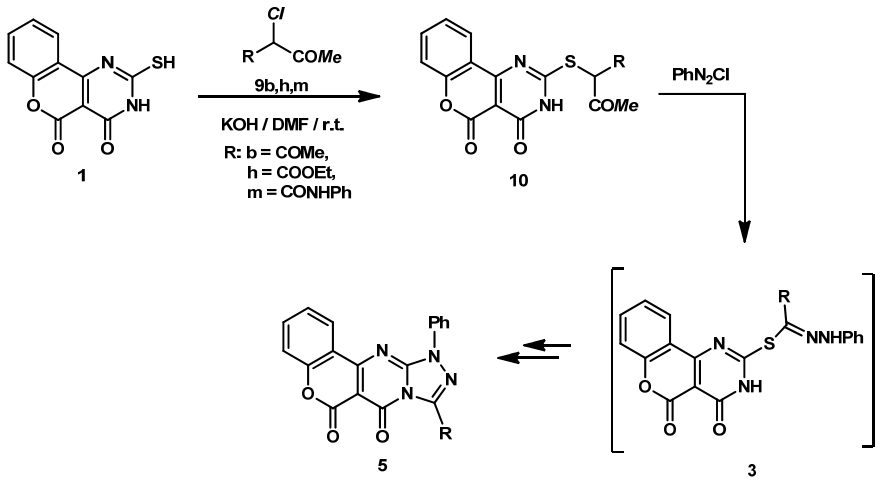
Ethyl 6,7-dioxo-11-m-tolyl-7,11-dihydro-6H-chromeno[4,3-d] [1,2,4]triazolo[4,3-a]pyrimidine-9-carboxylate (**5k**): Yield: 70%, crystallized from ethanol as white crystals. M.p.: 225 °C. IR (KBr, *ν*, cm^{-1}): 1745 (*δ*-lactone), 1680 (COOEt), 1661 (CO amide). ^1H NMR (300 MHz, DMSO-d_6, *δ*, ppm): 1.41 (t, *J* = 7 Hz, 3H, $CH_2C\mathit{H}_3$), 2.29 (s, 3H, $ArCH_3$), 4.50 (q, *J* = 7 Hz, 2H, $C\mathit{H}_2CH_3$), 7.31-8.37 (m, 8H, Ar-H). MS (*m/z* (%)): 417 (M^++1, 26), 416 (M^+, 100), 343 (95), 303 (35), 213 (16), 104 (85), 77(42). Anal. calcd. for $C_{22}H_{16}N_4O_5$ (416.11): C, 63.46; H, 3.87; N, 13.46. Found: C, 63.23; H, 3.84; N, 13.28%.

Ethyl 11-(4-nitrophenyl)-6,7-dioxo-7,11-dihydro-6H-chromeno[4,3-d][1,2,4]triazolo[4,3-a]pyrimidine-9-carboxylate (**5l**): Yield: 75%, crystallized from ethanol as white solid. M.p.: 245 °C. IR (KBr, *ν*, cm^{-1}): 1721 (*δ*-lactone), 1678 (COOEt), 1642 (CO amide). ^1H NMR (300 MHz, DMSO-d_6, *δ*, ppm): 1.44 (t, *J* = 7 Hz, 3H, CH_2CH_3), 4.58 (q, *J* = 7 Hz, 2H, CH_2CH_3), 7.45-8.42 (m, 8H, Ar-H). MS (*m/z* (%)): 448 (M^++1, 18), 447 (M^+, 49), 289 (38), 91 (100), 77(70). Anal. calcd. for $C_{21}H_{13}N_5O_7$ (447.08): C, 56.38; H, 2.93; N, 15.65. Found: C, 56.24; H, 2.75; N, 15.45%.

6,7-Dioxo-N,11-diphenyl-7,11-dihydro-6H-chromeno[4,3-d] [1,2,4]triazolo[4,3-a]pyrimidine-9-carboxamide (**5m**): Yield: 74%, crystallized from DMF as white crystals. M.p.: 258 °C. IR (KBr, *ν*, cm^{-1}): 4432 (NH), 1750 (*δ*-lactone), 1666, 1639 (2 CO amide). ^1H NMR (300 MHz, DMSO-d_6, *δ*, ppm): 6.78-8.34 (m, 14H, Ar-H), 11.12 (s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6, *δ*, ppm): 114.8, 118.4, 121.6, 121.8, 123.6, 123.9, 126.6, 130.2, 130.3, 133.4, 134.7, 137.2, 138.8, 140.6, 141.2, 143.9, 145.6, 151.4, 160.5 (C=O), 165.2 (C=O), 167.2 (C=O). MS (*m/z* (%)): 449 (M^+, 19), 329 (26), 276 (19), 202 (33), 128 (37), 111 (63), 77 (60), 55 (100). Anal. calcd. for $C_{25}H_{15}N_5O_4$ (449.11): C, 66.81; H, 3.36; N, 15.58. Found: C, 66.77; H, 3.26; N, 15.43%.

6,7-Dioxo-N-phenyl-11-p-tolyl-7,11-dihydro-6H-chromeno [4,3-d][1,2,4]triazolo[4,3-a]pyrimidine-9-carboxamide (**5n**): Yield: 76%, crystallized from DMF as white crystals. M.p.: 243 °C. IR (KBr, *ν*, cm^{-1}): 4441 (NH), 1754 (*δ*-lactone), 1688, 1646 (2 CO amide). ^1H NMR (300 MHz, DMSO-d_6, *δ*, ppm): 2.31 (s, 3H, Ar-CH_3), 6.74-8.21 (m, 13H, Ar-H), 11.18 (s, 1H, NH). MS (*m/z* (%)): 465 (M^++2, 2), 464 (M^++, 8), 463 (M^+, 13), 343 (100), 213 (17), 119 (97), 91 (81), 77 (26). Anal. calcd. for $C_{26}H_{17}N_5O_4$ (463.13): C, 67.38; H, 3.70; N, 15.11. Found: C, 67.30; H, 3.79; N, 15.00%.

11-(4-Chlorophenyl)-6,7-dioxo-N-phenyl-7,11-dihydro-6H-chromeno[4,3-d][1,2,4]triazolo[4,3-a]pyrimidine-9-carboxamide (**5o**): Yield: 74%, crystallized from DMF as yellow crystals. M.p.: 287 °C. IR (KBr, *ν*, cm^{-1}): 4448 (NH), 1755 (*δ*-lactone), 1673, 1642 (2 CO amide). ^1H NMR (300 MHz, DMSO-d_6, *δ*, ppm): 6.78-8.34 (m, 13H, Ar-H), 11.21 (s, 1H, NH).



Scheme 3

MS (*m/z* (%)): 485 (M^++2, 4), 484 (M^++1, 5) (M^+, 14), 363 (82), 213 (41), 152 (40), 119 (100), 77 (20). Anal. calcd. for $C_{25}H_{14}ClN_5O_4$ (483.07): C, 62.06; H, 2.92; N, 14.47. Found: C, 62.01; H, 2.87; N, 14.24%.

9-Benzoyl-11-phenyl-6H-chromeno[4,3-d][1,2,4]triazolo[4,3-a]pyrimidine-6,7(11H)-dione (**5p**): Yield: 83%, crystallized from DMF as yellow crystals. M.p.: 276 °C. IR (KBr, *ν*, cm^{-1}): 1750 (*δ*-lactone), 1680 (ArCO), 1643 (CO amide). ^{1}H NMR (300 MHz, DMSO-d_6, *δ*, ppm): 6.89-8.12 (m, 14H, Ar-H). ^{13}C NMR (75 MHz, DMSO-d_6, *δ*, ppm): 115.2, 118.0, 120.8, 121.4, 123.0, 124.3, 126.1, 130.0, 130.6, 131.3, 134.4, 134.7, 137.0, 141.2, 141.7, 142.9, 144.3, 153.4, 161.7 (C=O), 165.8 (C=O), 179.7 (C=O). MS (*m/z* (%)): 435 (M^++1, 6), 434 (M^+, 20), 405 (8), 105 (100), 77 (60). Anal. calcd. for $C_{25}H_{14}N_4O_4$ (434.10): C, 69.12; H, 3.25; N, 12.90. Found: C, 69.11; H, 3.13; N, 12.76%.

9-Benzoyl-11-(4-chlorophenyl)-6H-chromeno[4,3-d][1,2,4]triazolo[4,3-a]pyrimidine-6,7(11H)-dione (**5q**): Yield: 80%, crystallized from DMF as yellow crystals. M.p.: 259 °C. IR (KBr, *ν*, cm^{-1}): 1750 (*δ*-lactone), 1682 (ArCO), 1643 (CO amide). ^{1}H NMR (300 MHz, DMSO-d_6, *δ*, ppm): 6.80-8.24 (m, 13H, Ar-H). MS (*m/z* (%)): 469 (M^++1, 6), 468 (M^+, 20), 363 (34), 105 (100), 77 (53). Anal. calcd. for $C_{25}H_{13}ClN_4O_4$ (468.06): C, 64.04; H, 2.79; N, 11.95; Found: C, 64.01; H, 2.45; N, 11.67%.

11-Phenyl-9-(2-thienylcarbonyl)-6H-chromeno[4,3-d][1,2,4]triazolo[4,3-a]pyrimidine-6,7(11H)-dione (**5r**): Yield: 78%, crystallized from ethanol as yellow crystals. M.p.: 244 °C. IR (KBr, *ν*, cm^{-1}): 1747 (*δ*-lactone), 1688 (ArCO), 1645 (CO amide). ^{1}H NMR (300 MHz, DMSO-d_6, *δ*, ppm): 7.36-8.45 (m, 12H, Ar-H). MS (*m/z* (%)): 442 (M^++2, 3), 441 (M^++1, 7), 440 (M^+, 24), 304 (4), 111 (100), 77 (13). Anal. calcd. for $C_{23}H_{12}N_4O_4S$(440.06): C, 62.72; H, 2.75; N, 12.72. Found: C, 62.59; H, 2.70; N, 12.57%.

2.3.1. General procedure for the synthesis of compound 10b, h and m

To a solution of compound **1** (2.46 g, 0.01 mol) in ethanol was added an aqueous solution of potassium hydroxide (1 mL, 75%) and the mixture was warmed for 10 min. in a water bath at 80 °C and cooled. To the resulting clear solution was added the appropriate chloromethylene compounds **9b**, **h** and **m** (0.01 mol) dropwise while stirring the reaction mixture. After complete addition, the reaction mixture was stirred for further 18 h at room temperature. The solid that precipitated was filtered off, washed with water, dried and finally crystallized from DMF to give pure **10b**, **h** and **m** (Scheme 3) with the following physical and spectral data.

2-(2,4-Dioxopentan-3-ylthio)-3H-chromeno[4,3-d]pyrimidine-4,5-dione (**10b**): Yield: 82%, crystallized from ethanol as white solid. M.p.: 186 °C. IR (KBr, *ν*, cm^{-1}): 3444 (NH), 1735 (*δ*-lactone), 1714 ($COCH_3$), 1640 (CO amide). ^{1}H NMR (300 MHz, DMSO-d_6, *δ*, ppm): 2.16 (s, 6H, $COCH_3$), 5.18 (s, 1H, CH), 7.32-8.52 (m, 4H, Ar-H), 12.83 (s, 1H, NH). MS (*m/z* (%)): 344 (M^+, 15), 274 (100), 188 (51), 119 (34), 91 (23). Anal. calcd. for $C_{16}H_{12}N_2O_5S$ (344.05): C, 55.81; H, 3.51; N, 8.14. Found: C, 55.67; H, 3.43; N, 8.07%.

Ethyl 2-(4,5-dioxo-4,5-dihydro-3H-chromeno[4,3-d]pyrimidin-2-ylthio)-3-oxobutanoate (**10h**): Yield: 77%, crystallized from ethanol as white solid. M.p.: 162 °C. IR (KBr, *ν*, cm^{-1}): 3442 (NH), 1741 (*δ*-lactone), 1710 ($COCH_3$), 1692 (COOEt), 1648 (CO amide). ^{1}H NMR (300 MHz, DMSO-d_6, *δ*, ppm): 1.41 (t, *J* = 7 Hz, 3H, CH_2CH_3), 2.13 (s, 3H, $COCH_3$), 4.50 (q, *J* = 7 Hz, 2H, CH_2CH_3), 5.12 (s, 1H, CH), 7.20-8.44 (m, 4H, Ar-H), 12.78 (s, 1H, NH). MS (*m/z* (%)): 375 (M^++1, 7), 374 (M^+, 34), 326 (20), 302 (42), 259 (59), 231 (100), 145 (28), 114 (67), 77 (18). Anal. calcd. for $C_{17}H_{14}N_2O_6S$ (374.06): C, 54.54; H, 3.77; N, 7.48. Found: C, 54.67; H, 3.58; N, 7.34%.

2-(4,5-Dioxo-4,5-dihydro-3H-chromeno[4,3-d]pyrimidin-2-ylthio)-3-oxo-N-phenyl butanamide (**10m**): Yield: 71%, crystallized from ethanol as white solid. M.p.: 188 °C. IR (KBr, *ν*, cm^{-1}): 1743 (*δ*-lactone), 1710 ($COCH_3$), 1682, 1644 (2 CO amide). ^{1}H NMR (300 MHz, DMSO-d_6, *δ*, ppm): 1.90 (s, 3H, $COCH_3$), 5.10 (s, 1H, CH), 7.02-8.26 (m, 9H, Ar-H), 11.38 (s, 1H, NH), 13.12 (s, 1H, NH). MS (*m/z* (%)): 423 (M^++2, 2), 422 (M^++1, 8), 421 (M^+, 13), 343 (100), 213 (17), 119 (97), 91 (81), 77 (26). Anal. calcd. for $C_{21}H_{15}N_3O_5S$ (421.07): C, 59.85; H, 3.59; N, 9.97. Found: C, 59.70; H, 3.66; N, 9.68%.

2.3.2. Coupling of compound 10b, h and m

To a solution of the appropriate **10b**, **h** and **m** (10 mmol) in ethanol (40 mL) was added sodium acetate trihydrate (1.36 g, 10 mmol) and the mixture was cooled to 0-5 °C in an ice bath. To the resulting cold solution was added portionwise a cold solution of benzenediazonium chloride, prepared by diazotizing aniline (10 mmol) dissolved in hydrochloric acid (6 M, 6 mL) with a solution of sodium nitrite (0.7 g, 10 mmol) in water (10 mL). After complete addition of the diazonium salt, the reaction mixture was stirred for further 30 min in an ice bath. The solid precipitated was filtered off, washed with water, dried and crystallized from DMF to give the corresponding products, **5b**, **5h** and **5m** which were identical in all respects (M.p., mixed m.p. and IR spectra) with those obtained from reaction of compound **1** with **2b**, **2h** and **2m**, respectively.

3. Results and discussion

The thione derivative **1** which was prepared according to procedure reported in literature [12] through interaction between 3-ethoxycarbonylcoumarin and thiourea in ethanol and K_2CO_3 was found to be a good point to start. The thione group in combination with the two adjacent NH functions, provide a rich opportunity for heterocyclic construction. The homologation of the thione compound **1** by the interaction with various hydrazonyl halides **2a-r** in dioxane under ultrasound irradiation using the excellent cheap and eco-friendly chitosan catalyst delivered the triazole derivatives always as a single isomer (Scheme 1). All spectroscopic and analytical data were consistent with either the triazole **5** or its isomeric structure **6** in good to excellent yields. The identities of the products were concluded based on some spectroscopic data, although infrared carbonyl stretching data were inconclusive, there was a distinct pattern in the chemical shifts associated with the carbonyl resonance in the ^{13}C data. For example the two substituted products **5a** and **b** showed carbonyl carbons resonances around 166-167 ppm, These values were consistent with some appropriate data shown by similar compounds obtained by other researchers in literature [10-12,18-25]; hence, based on these, one can conclude that structure **5** is the correct structure for the reaction product rather than its isomer **6**. It is so clear to say that in structure **5** the carbonyl group is adjacent to sp^3-hybrisized nitrogen atom while in the isomer **6** it is adjacent to more electronegative sp^2-hybridized nitrogen atom in which the carbonyl carbon chemical shift should show more downfield values than those reported in literature. Unfortunately, other data (remaining ^1H and ^{13}C NMR data, IR) were closely similar and could not realistically be used for definitive assignments.

A more convenient alternative synthesis of the tetracyclic compound **5** is to use the methylthio derivative **7** of title compound **1**, itself prepared from alkylation of **1** with CH_3I in DMF containing potassium carbonate (its data consistent with those in literature) [13]. Reaction of compound **7** with hydrazonyl halides under same conditions used before in this article resulted in the formation of compound **5** with a concomitant evolution of methyl mercaptan (Scheme 2). All spectroscopic and physical data of these products are in a great accordance with those of the products obtained from reaction of compound **1** and **2**.

Another alternative two step non-heated synthesis for trizole **5** could be accomplished as followes: First, the alkylation of compound **1** with active chloromethylene compounds **9b**, **e** and **h** in KOH/DMF at room temperature furnished the alkylthio products **10** (Scheme 3). The structure proof of the latter products based on their microanalysis and spectroscopic data (Mass, IR, ^1H NMR). In the ^1H NMR, two characteristic singlet signals near δ 2.0 and 5.0 ppm are assignable to the CH_3CO and S–(CH)–R protons in addition to the characteristic signals of $COCH_3$, COOEt and CONHPh groups in the compounds **11b**, **e** and **h**, respectively. The formation of compound **11a-c** from reaction of compound **1** with **10b**, **e** and **h** is analogous to S-alkylation reactions reported for 2-thioxopyrimidines [26].

Second, coupling of compound **10** with benzenediazonium chloride in ethanol in the presence of sodium acetate at 0-5 °C yielded the corresponding thiohydrazonate esters **3b**, **e** and **h** which undergo *in situ* Smiles rearrangement [27,28] followed by cyclization to afford products identical in all respects (M.p., Mass and IR) with that obtained from reaction of each of compound **1** and **7** with hydrazonoyl halides **2**.

4. Conclusion

A new, efficient and regioselective method for preparation of chromeno[4,3-d][1,2,4]triazolo[4,3-a]pyrimidine by reaction of 2-mercapto-3*H*-chromeno[4,3-d]pyrimidine-4,5-dione or its 2-methylthio derivative with hydrazonoyl halides under ultrasound irradiation in the presence of chitosan at ambient temperature in a short time and high yields was developed and discussed.

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