

Synthesis of Novel Fused Heterocycles Based on Pyrano[2,3-c]pyrazole

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Dedicated to Professor W. Zielinskei

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Abstract: 3-Substituted 1,2,4-triazole derivatives (**5**, **9**, **13**, **16b**, **19**), pyrimidinium salts (**21**), triazines (**24**), and aryl methylene hydrazono pyrazolopyrano-pyrimidine (**27a,b**) which are rearranged in basic medium to **30a,b**, were afforded via the reaction of 6-amino 1,4,5,6-tetrahydro-5-imino-3-methyl-1-phenyl-4 (p-chlorophenyl) pyrazolo [4', 3' : 5,6]-pyrano [2,3-d] pyrimidine (**3**) with different reagents.

Keywords: Condensed pyrazoles, cyclocondensation, Dimorth rearrangement.

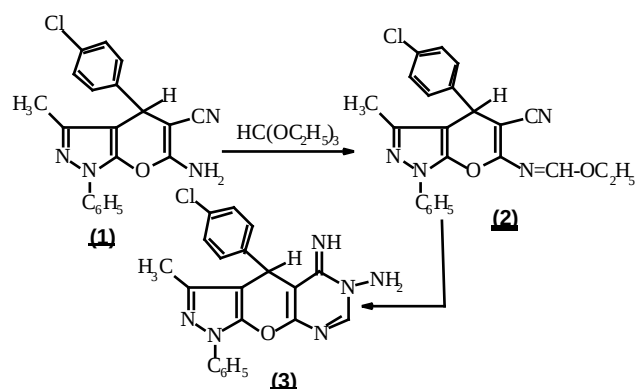
Introduction

Condensed pyrazoles are biologically interesting compounds and their chemistry has received considerable attention [1,2]. Several pyrano[2,3-c]pyrazoles are reported to have useful biological effects, such as analgesic and anti-inflammatory activities [3]. Moreover, the biological activity of fused azoles has led to intensive research on their synthesis [4-6].

Results and Discussion

In the present study, we report on the synthesis of pyrazolo [4', 3' : 5,6] pyrano [3,2-e] [1,2,4]-triazolo [1,5-c] pyrimidine and pyrazolo [4'', 3'' : 4',5'] pyrano [2' 3' : 4,5] pyrimido [1,6-b] [1,2,4]- triazine derivatives via the reaction of 6-amino-1,4,5,6- tetrahydro-5-imino-3-methyl-

1-phenyl-4-(p-chlorophenyl) pyrazolo [4', 3' : 5,6] pyrano [2,3-d] pyrimidine (**3**) with different reagents.



Scheme 1.

Compound **3**, considered as a key intermediate to prepare fused heterocycles as triazolo [1,5-c] pyrimidines which may possess pharmacological properties similar to theophylline [7,8], was prepared by treating ethyl N-(5-cyano-1,4-dihydro-3-methyl-1-phenyl-4-(p-chlorophenyl)-pyrano-[2,3-c] pyrazol-6-yl-methan-imidate (**2**) with hydrazine hydrate [9,10]. On the other hand, compound **2** was prepared by the reaction of 6-amino-5-cyano-1,4-dihydro-3-methyl-1-phenyl-4-(p-chlorophenyl) pyrano [2,3-c] pyrazole (**1**) [11,12] with an equimolar amount of triethyl orthoformate and acetic anhydride [9,10] (Scheme 1).

The cyclocondensation of compound **3** with the appropriate carboxylic acid derivatives was performed by heating compound **3** with an excess of neat formic acid **4** to afford 8,11-dihydro-10-methyl-8-phenyl-11-(p-chlorophenyl) [4',3' : 5',6'] pyrano [3,2-e] [1,2,4]-triazolo [1,5-c] pyrimidine (**5**) in a 65% combined yield. An improvement in the preparation of this compound was achieved using triethylorthoformate (**6**) by refluxing neat at 140°C, or by reacting of compound (**3**) with ethoxymethylene malononitrile (**7**) to afford 80-82% yield (Scheme 2).

When triethylorthoacetate (**8**) was used in the above cyclocondensation, 3,10-dimethyl-8,11-dihydro-11-(p-chlorophenyl)-8-phenyl pyrazolo [4',3' : 5,6] pyrano [3,2-e]-[1,2,4] triazolo [1,5-c] pyrimidine (**9**) was produced. Compound **9** was also produced via the reaction of **3** with acetic anhydride (**10**) as carboxylic acid anhydride and acetyl chloride (**11**) as acid chloride. The structure of **9** was based on the absence of NH and NH₂ absorption in the i.r. spectrum. (Scheme 2).

Moreover, the interaction of triethylorthopropionate (**12**) with **3** afforded 3-ethyl -10-methyl-8,11-dihydro-11-(p-chlorophenyl)-8-phenyl-pyrazolo [4', 3' : 5,6] pyrano [3,2-e] [1,2,4] triazolo [1,5-c] pyrimidine (**13**).

The subsequent incorporation of a one- carbon unit carrying an amino group into **3** to form the triazolo component was performed via two facile procedures. The first one consisted in applying cyanogen bromide (**14**) condensation to compound **3** and the second one involved refluxing the compound **3** and S-methyl isothiurea sulfate (**15**) [13] to afford 3-amino-10-methyl-8,11-dihydro-11-(p-chlorophenyl)-8-phenyl pyrazolo-[4', 3' : 5,6] pyrano [3,2-e] [1,2,4] triazolo [1,5-c] pyrimidine (**16b**). That compound **16b** exists in the 2-amino tautomeric form and not in the 2-iminoform was shown by the appearance of an intense absorption band at 3400 cm⁻¹ and a two proton singlet as broad band at 3.7 ppm due to NH₂ in the i.r. and 1H nmr spectra respectively. In the case involving the condensation of compound **3** with cyanogen bromide (**14**) and S-methyl isothiurea sulfate (**15**), the intermediates formed might

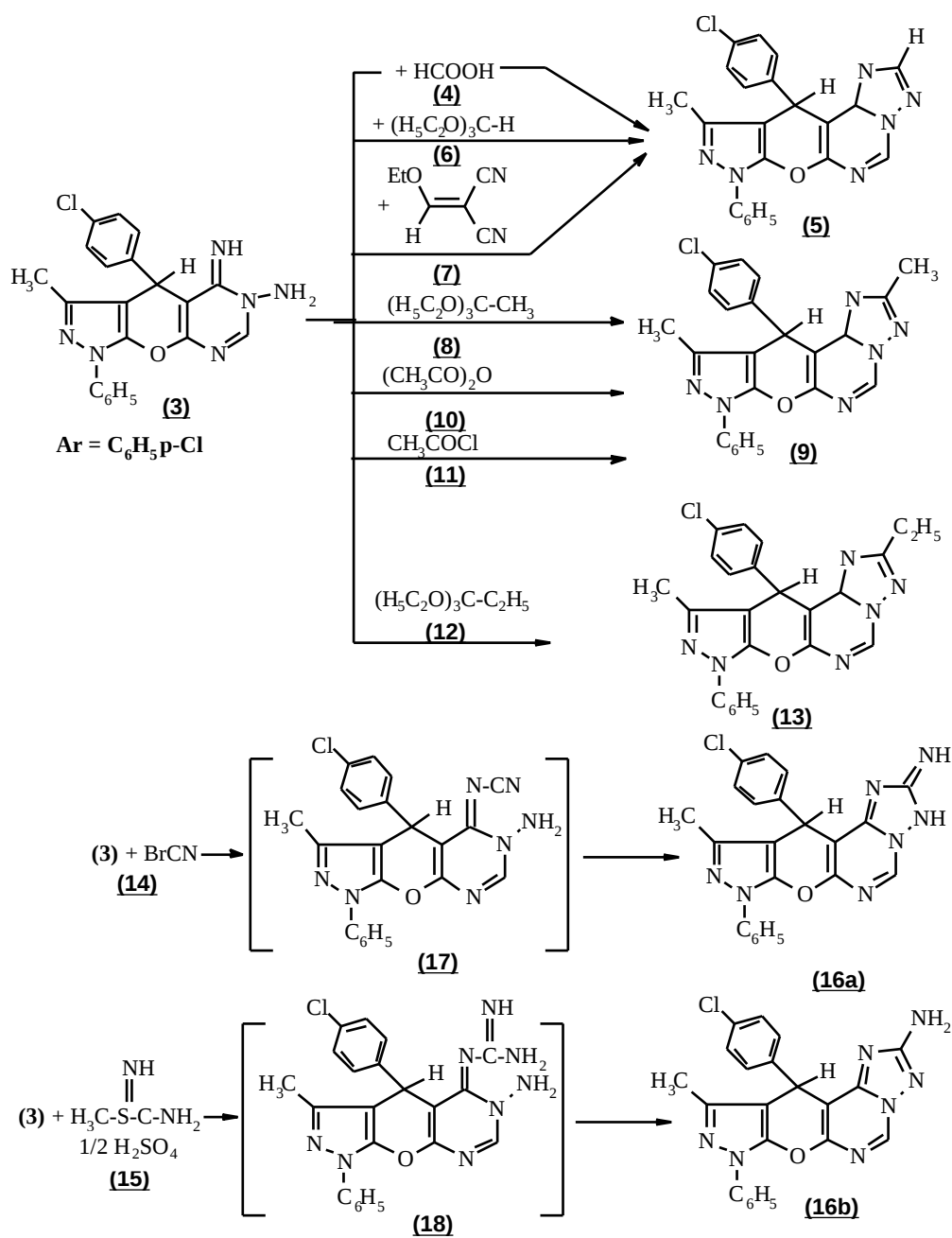
bear a cyanimino (**17**) or guanidino function (**18**). These intermediates (**17** and **18**) were cyclized) in an alkaline medium to give the target molecule **16b** as expected (Scheme 2). However because of the different electronic influence on each reaction centre, **16b** was obtained in different yields.

The formation of 3-trichloromethyl-10-methyl-8,11-dihydro-11-(p-chlorophenyl)-8-phenyl pyrazolo [4', 3' : 5,6] pyrano [3,2-e] [1,2,4] triazolo [1,5-c] pyrimidine (**19**) via the interaction of compound **3** with trichloroacetonitrile (**20**) in the absence of solvent under reflux according to a reported procedure for the construction of an allied heterocyclic system [14] was unsuccessful (Scheme 3). The pyrimidinium salt (**21**) was formed [15,16a,b], based on the presence of NH and NH₂ in its i.r. spectrum and the appearance of CN, its mass spectrum was (M⁺ - NH₂, 532.2, 30%). The trichloro methyl derivatives (**19**) were achieved using trichloroacetic acid (**22**) in the presence of phosphoryl chloride under reflux for 3 hours. The structure (**19**) was confirmed by the absence of NH and NH₂ absorption in its i.r. spectrum.

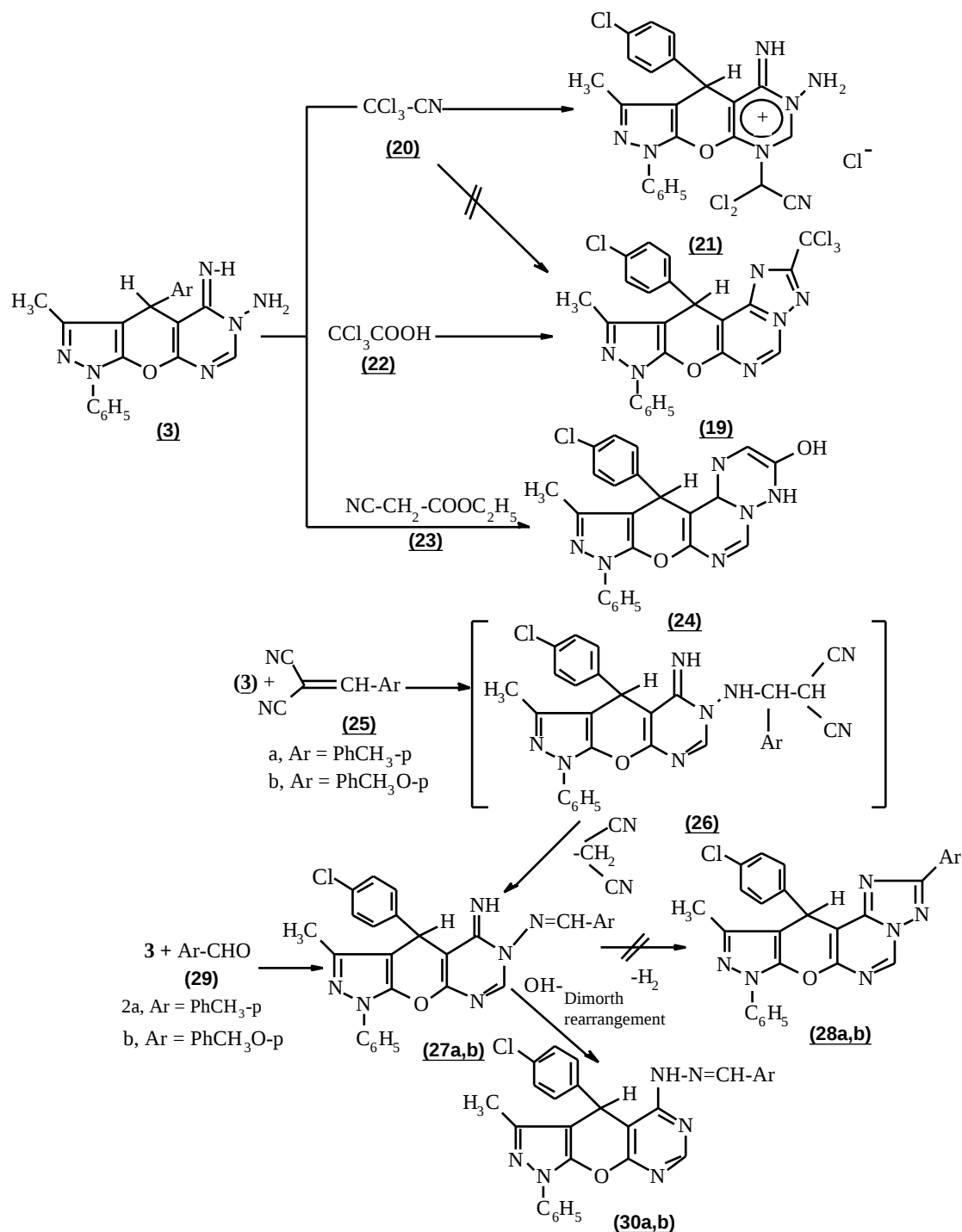
The activity of compound **3** towards the reaction product was active methylene was also tested [17]. Thus, with ethyl cyanoacetate (**23**), 9,12-dihydro-3-hydroxy-11-methyl-9-phenyl-12-(p-chlorophenyl) 2H-pyrazolo [4'', 3'' : 5',6'] pyrano [2',3':5,6] pyrimido [1,6-b] [1,2,4] triazine (**24**) as confirmed by its spectral data. (Scheme 3).

Compound **3**, when reacted with b-cyanocinnamionitrile derivatives, namely p-tolylmalononitrile and p-anisylmalononitrile (**25a,b**) respectively, in dioxane under reflux and in the presence of a catalytic amount of piperidine failed to afford 8,11-dihydro-11-(p-chlorophenyl)-3-aryl-8-methyl-10-phenylpyrazolo [4',3' : 5,6] pyrano [3,2-e] [1,2,4] triazolo [1,5-c] pyrimidine (**28a,b**). In addition p-tolylmalononitrile and p-anisylmalononitrile (**25a,b**) respectively reacted with compound **3** to give 6-aryl methylene hydrazono-1,4,5,6-tetrahydro-3-methyl-1-phenyl-4-(p-chlorophenyl) pyrazolo -[4', 3' : 5,6] pyrano [3,2-d] pyrimidine (**27a,b**) via the formation of 1,1 adduct (**26a,b**) followed by the loss of malononitrile [18]. Also the same product (**27b**) was isolated from the reaction of compound **3** with p-tolulaldehyde and p-anisaldehyde **29a,b** respectively. Based on their spectral data no cyclization took place (Scheme 3). From this experiment, it can be concluded that a Taylor-Löffler transformation has occurred [9]. Because the reaction was carried out in basic medium as catalyst which facilitates the Dimorth rearrangement, the formal structure **30a,b** is preferable (Scheme 3).

For convenience of the readers, the spectroscopic data are also collected in Table 1.



(Scheme 2)



(Scheme 3)

Experimental

General

Melting points are uncorrected and were taken on a Boetius melting point microscope. Microanalyses were performed by the Micro-analytical unit Cairo University I.R. spectra were recorded on a Mattson 5000 FIR

spectrometer ^1H NMR spectra were determined on a Varian EM NMR spectrometer using tetra-methylsilan as an internal standard. Mass spectra (MS) were recorded on a Finigan SSQ 7000 mass spectrometer.

Ethyl N-(5-cyano-1,4-dihydro-3-methyl-1-phenyl-4-(p-chlorophenyl) pyrano[2,3-c] [pyrazol-6-yl] methanimide (2):

A mixture of **1** (1.79 g, 0.005 mol) triethylorthoformate (0.741 g, 0.005 mol) and acetic anhydride (16 ml) was refluxed for 5 h. The solvent was removed under reduced pressure and the resulting solid product is crystallized from benzene to give 1.84 g (92%) of **2** as colourless needles. M.p. 166–168°C. ¹H NMR (DMSO-d₆): δ 1.5 (t, 3H, CH₃), 2.00 (s, 3H, CH₃), 4.41 (q, 2H, CH₂), 4.9 (s, 1H, H-4), 7.45–7.84 (m, 9H, arom.) 8.3 (s, 1H, CHOEt). IR (KBr) 2220 (CN). Anal. Calcd. for C₂₃H₁₉N₄OCl; C; 58.57; H, 4.75 Found: C; 68.44; H 4.59.

6-Amino-1,4,5,6-tetrahydro-5-imino-3-methyl-1-phenyl-4-(p-chlorophenyl) pyrazolo [4',3':5,6] pyrano [2,3-d] pyrimidine (3).

To a solution of **2** (2g, 0.005 mol) in methanol (25 ml) a solution of hydrazine hydrate (5 ml) was added and the mixture stirred for 1 hr. Then it is allowed to stand overnight. The precipitate formed is filtered, dried and crystallized from methanol to afford 55% of **3**. M.p. 213–214°C: ¹H NMR (DMSO-d₆): δ 1.95 (s, 3H, CH₃), 5.00 (s, 1H, H-4), 5.6 (s, 1H, NH), 7.45–7.84 (m, 9H, arom.), 8.3 (s, 1H, H-7). IR: 3370, 3340 (NH₂), 3150(NH). MS m/z (%), 404 (20) M⁺, 388 (60) 174(100), 77(65). Anal. Calcd. for C₂₁H₁₇N₆OCl; C, 62.30; H, 4.23, Found C, 62.19, H; 4.18.

8,11-Dihydro-10-methyl-8-phenyl-4-(p-chlorophenyl) pyrazolo [4',3':5,6] pyrano [3,2-e] [1,2,4] triazolo [1,5-c] pyrimidine (5).

Method A

A mixture of **3** (1.01g, 0.0025 mol) and (32 ml, 0.7 mol) of formic acid **4** was refluxed for 10 hrs. and then cooled poured onto ice-water to give a white precipitate which was filtered, washed several times by water, dried. and then crystallized from ethanol to afford 55% of **5**. M.p. 324–325°C. ¹H NMR (DMSO-d₆): δ 1.9 (s, 3H, CH₃) 5.7 (s, 1H, H-11), 7.4–7.8 (m, 9H, arom.), 8.65 (s, 1H, H-2), 9.7 (s, 1H, H-5). MS: m/z (%) 414 (47) M⁺, 303 (100), 278 (25), 77 (20). Anal. Calcd. for C₂₂H₁₅N₆OCl; C; 63.69, H; 3.64 Found C; 63.49, H; 3.49.

Method B

A solution of **3** (1.01 g; 0.0025 mol) and (2.2 g, 0.02 mole) of triethylorthoformate **6** neat was refluxed for 8 hrs. A precipitate was formed, filtered while and recrystallized from ethanol to give 0.83g (80%) of **5**.

Method C

To a solution of **3** (1.01g, 0.0025 mol) in absolute ethanol (30 ml) was added ethoxymethylene malononitrile

7 and the mixture was refluxed for 6 hr (TLC control). On cooling, a solid product separated, which was filtered and recrystallized from ethanol to give 0.85g (82%) of **5**.

3,10-dimethyl-8,11-dihydro-11-(p-chlorophenyl)-8-phenyl pyrazolo [4',3':5,6] pyrano [3,2-e] [1,2,4] triazolo [1,5-c] pyrimidine (9)

Method A

A solution of **3** (1.01g, 0.0025 mol) and (3.3g 0.2 mol) of triethylorthoacetate (**8**), neat was refluxed for 8 hrs, a precipitate was formed, filtered while hot, and recrystallized from ethanol to give 0.75g (70%) of **9**. M.p. 264–265°C. ¹H NMR (DMSO-d₆): δ 1.9(s, 3H, CH₃), 2.3 (s, 3H, CH₃) 5.6 (s, 1H, H-11), 7.4–7.8 (m, 9H, arom.) 9.6 (s, 1H, H-5). MS, m/z (%) 428 (25) M⁺, 317 (100) 77 (17). Anal. Calcd. for C₂₃H₁₇N₆OCl; C; 64.41, H; 3.99, Found C. 64.32 H, 3.79.

Method B

A solution of **3** (1.01g, .0025 mol) and 10 ml of acetic anhydride (**10**) was refluxed for 10 hrs. A precipitate was formed, filtered while hot, and recrystallized from ethanol to give 0.8g (75%) of **9**.

Method C

A mixture of **3** (1.01g, 0.0025 mol) and 7 ml of acetyl chloride (**11**) in 10 ml dimethylformamide was heated for 4 hrs on a water bath and after cooling, poured into 100 ml of ice water. The precipitate was collected on a filter, washed with water and recrystallized from ethanol to give 0.9g (84%) of **9**.

3-Ethyl 10-methyl-8,11-dihydro-11-(p-chlorophenyl)-8-phenyl pyrazolo [4',3':5,6]-pyrano[3,2-e][1,2,4]triazolo [1,5-c] pyrimidine (13).

A solution of **3** (1.01 g, 0.0025 mol) and (3.4 g, 0.02 mol) of triethy-lor-thopropionate **12** neat was refluxed for 8 hrs, and then worked out as described above to produce 0.83 g (75%) of **13**. M.p. 310–312°C. ¹H NMR (DMSO-d₆): δ 1.35 (t, 3H, CH₃), 1.95 (s, 3H, CH₃), 3.4 (q, 2H, CH₂), 5.6 (s, 1H, H-11) 7.4–7.8 (m, 9H, arom.), 9.5(s, 1H, H-5). MS: m/z (%) 428 (M⁺, 28), CH₃, 317 (100). Anal. Calcd. for C₂₄H₁₉N₆OCl, C: 65.08, H, 4.32, Found C: 64.89, H, 4.22.

3-amino-10-methyl-8,11-dihydro-11-(p-chlorophenyl)-8-phenyl pyrazolo [4',3':5,6] pyrano [3,2-e] [1,2,4] triazolo [1,5-c] pyrimidine(16b).

Table 1.

No.	Yield % (Meth.)	Mol. Form. Mol. Wt. M.p. (°C)	IR (KBr) (cm ⁻¹)	¹ H-NMR	m/z (%)
2	92	C ₂₃ H ₁₉ N ₄ O Cl (402.89) 166-168	2220 (CN)	1.5 (t, 3H, CH ₃), 2.00 (s, 3H, CH ₃), 4.41 (q, 2H, CH ₂), 4.9 (s, 1H, H-4) 7.45-7.84 (m, 9H, arom.), 8.3 (s, 1H, CHOEt)	
3	55	C ₂₁ H ₁₇ N ₆ O Cl (404.86) 213-214	3370, 3340 (NH ₂) 3150 (NH)	1.95 (s, 3H, CH ₃), 5.00 (s, 1H, H-4), 5.6 (s, 1H, NH), 7.45-7.84 (m, 9H, arom.), 8.3 (s, 1H, H-7)	404 (20%), M ⁺ , 388 (60%), 174 (100%), 77 (65%).
5	55 (A) 80 (B) 82 (C)	C ₂₂ H ₁₅ N ₆ O Cl (414.86) 324-325		1.9 (s, 3H, CH ₃), 5.7 (s, 1H, H-11), 7.4-7.8 (m, 9H, arom), 8.56 (s, 1H, H-2), 9.7 (s, 1H, H-5)	414 (47%), M ⁺ , 303 (100%), 278 (25%), 77 (20%).
9	70 (A) 75 (B) 84 (C)	C ₂₃ H ₁₇ N ₆ O Cl (428.88) 264-265		1.9 (s, 3H, CH ₃), 2.3 (s, 3H, CH ₃), 5.6 (s, 1H, H-11), 7.4-7.8 (m, 9H, arom), 9.6 (s, 1H, H-5)	428 (25%), M ⁺ , 317 (100%), 77 (17%)
13	75	C ₂₄ H ₁₉ N ₆ O Cl (442.91) 310-312		1.35 (t, 3H, CH ₃), 1.95 (s, 3H, CH ₃), 3.4 (q, 2H, CH ₂), 5.6 (s, 1H, H-11), 7.4-7.8 (m, 9H, arom), 9.5 (s, 1H, H-5)	428 (28%) M ⁺ -CH ₃ , 317 (100%)
16b	50 (A) 60 (B)	C ₂₂ H ₁₆ N ₇ O Cl (429.87) >330	3178, 3320 (NH ₂)	1.6 (s, 3H, CH ₃), 3.6 (broad, 2H, NH ₂ exchangeable with D ₂ O), 6.2 (s, 1H, H-11), 7.3-7.8 (m, 9H, arom), 9.3 (s, 1H, H-5)	429 (37%) M ⁺ , 388 (57%), 318 (60%), 278 (100%).
19	50	C ₂₃ H ₁₄ N ₆ O Cl ₄ (532.22) 270-271		1.8 (s, 3H, CH ₃), 4.6 (s, 1H, H-11) 7.2-7.7 (m, 9H, arom), 8.4 (s, 1H, H-pyrimidine)	

Table 1 Cont.

No.	Yield % (Meth.)	Mol. Form. Mol. Wt. M.p. (°C)	IR (KBr) (cm ⁻¹)	¹ H-NMR	m/z (%)
21	45	C ₂₃ H ₁₄ N ₇ OCl ₄ (532.22) 150-151	3455,3327 (NH ₂)3197 (NH),2199 (CN),1659 (C=NH)	1.78 (s, 3H, CH ₃), 4.7 (s, 1H, H-11), 7.2-7.8 (m, 13H, 9H arom + N-NH ₂ + 1-H pyrimidine).	532 (30%) (M ⁺ -NH ₃), 419 (100%), 385 (25%), 143 (4.98%) 77 (33%).
24	60	C ₂₃ H ₁₇ N ₆ O ₂ Cl (444.88) 276-277	3500 br (OHNH)	1.95 (s, 3H, CH ₃), 4.4 (s, 1H, NH), 5.6 (s, 1H, H ₁₂), 7.4-7.8 (m, 9H, arom.), 8.4 (1H, H-2), 9.5 (s, 1H, H-6).	414 (40%) (M ⁺ -CH ₃ , OH), 303 (100%).
30a	70 (A) 80 (B)	C ₂₉ H ₂₃ N ₆ OCl (506.99) 184-186	1600 (HC=N) 3450 (NH)	1.9 (s, 3H, CH ₃), 2.4 (s, 3H, CH ₃), 5.9 (s, 1H, H-11), 7.3-7.5 (m, 13H, arom.), 8.2 (s, 1H, N=CH), 8.5 (s, 1H, H pyrimidine), 10.6 (br, 1 H, NH, D ₂ O exchangeable)	M+506 (14%), 393 (40%), 386 (100%) 77 (15%)
30b	76 (A) 85 (B)	C ₂₉ H ₂₃ N ₆ O ₂ Cl (522.99) 196-197	1620 (HC=N) 3400 (NH)		

Method A

A solution of **3** (1.01 g, 0.0025 mol) in 50 ml dimethylformamide was kept at 0°C and treated with cyanogen bromide **14** (0.6 g, 0.005 mol). The mixture was refluxed for 5 hrs, then cooled and poured onto water to give a white precipitate, filtered, washed with water and crystallized from dimethylformamide to yield 0.54 g (50%) of **16b**. M.p.>300 C. ¹H NMR (DMSO-d₆): δ 1.6 (s, 3H, CH₃), 3.6 (br, 2H, NH₂ exchangeable with D₂O), 6.2 (s, 1H, H-11) 7.3-7.8 (m, 9H, arom.), 9.3(s, 1H, H-5), I.R.: 3178, 3320 (NH₂). MS: m/z (%) 429 (M⁺, 37), 388 (57), 318 (60), 278 (100). Anal. Calcd. for C₂₂H₁₆N₇OCl, C: 61.47, H: 3.75, Found C: 61.37, H: 3.66.

Method B

A solution of **3** (1.01 g, 0.0025 mol) and (0.28 g, 0.001 mol) of S-methylisothiurea sulfate **15** in alcoholic potassium hydroxide (0.5 N) was heated under reflux for 8 hours. After cooling, the mixture was poured on to water to give a white precipitate, which was collected, washed with water and recrystallized from dimethylformamide to yield 0.6 g (60%) of **16b**.

3-trichloromethyl-8,11-dihydro-11-(p-chlorophenyl)-8-phenyl pyrazolo [4',3':5.6] pyrano[3,2-e] [1,2,4] triazolo [1,5 -c] pyrimidine (19)

A mixture of **3** (1.01 g, 0.0025 mol) and 0.49 g (0.003 mol) of trichloroacetic acid (**22**) in 15 ml of freshly distilled phosphorus oxychloride, was refluxed on a water bath for 4 hrs, cooled then poured onto ice - water to give a precipitate which was filtered off, and washed with water. The solid that collected by filtration, was recrystallized in dioxane to afford 0.7 g (51%) of (**19**). m.p. 270-271°C. ¹H NMR (DMSO-d₆): 1.8 (s, 3H, CH₃), 4.6 (s, 1H, H-11), 7.2-7.7 (m, 9H, arom.) 8.4 (s, 1H, H-pyrimidine). Anal., Calcd. for C₂₃H₁₄N₆OCl₄ C: 51.91, H: 2.65, Found C: 51.81, H: 2.61.

Formation of pyrimidinium salt (**21**)

A mixture of **3** (1.01 g, 0.0025 mol) and 20 ml (0.2 mol) of trichloroacetonitrile (**20**) was heated under reflux for 15 hours. The precipitate formed, was filtered, washed with a small amount of benzene and recrystallized in anhydrous ethanol to afford 0.62 g (45%) of **21**. M.p. 150-151°C. ¹H NMR (DMSO-d₆): 1.78 (s, 3H, CH₃), 4.7 (s, 1H, H-11), 7.2-7.8 (m, 13H, arom. + NH₂ + 1H pyrimidine). I.R.: 3455, 3327 (NH₂), 3197 (NH), 2199 (CN), 1659 (C=NH). MS, m/z (%) 532 (M⁺ + NH₃), 419 (100), 385 (25) 143 (5), 77 (33). Anal., Calcd. for C₂₃H₁₄N₇OCl₄ C: 50.57, H: 2.58, Found C: 50.66, H: 2.51.

9,12-dihydro-3-hydroxy-11-methyl-9-phenyl-12-(p-chlorophenyl)-2H-pyrazolo [4'',3'':5',6'] pyrano [2',3':4.5] pyrimido [1,6-b] [1,2,4] triazine (**24**)

A mixture of (**3**) (1.01 g, 0.0025 mol) and ethylcyanoacetate (**23**) (0.1 ml, 0.001 mol) in absolute ethanol (50 ml) was refluxed for 10 hr. A precipitate was formed, filtered off washed with ethanol, and recrystallized from dioxane to afford 0.78 g (70%) of (**25**). m.p. 276-277° C. ¹H NMR (DMSO-d₆): 1.95 (s, 3H, CH₃), 4.4 (s, 1H, NH), 5.6 (s, 1H, H-12), 7.4-7.8 (m, 9H, arom.) 8.4 (s, 1H, H-2), 9.5 (s, 1H, H-6). IR: 3500 (OH, NH). MS m/z (%), 414 (40) (M⁺ - CH₃, OH), 303 (100). Anal., Calcd. for C₂₃H₁₇N₆O₂Cl C: 62.09, H: 3.85, Found C: 61.89, H: 3.66.

5-arylmethylene hydrazono-1,4,5,6-tetrahydro-3-methyl-1-phenyl-4-(p-chlorophenyl) pyrazolo [4',3':5.6] pyrano [2,3 d] pyrimidine (**30a,b**).

Method A

A mixture of **3** (1.01 g, 0.0025 mol) and p-tolylmalononitrile (**25a**) or p-anisylmalononitrile (**25b**) (0.0025 mol) in dioxane, in the presence of piperidine as a catalyst was refluxed for 8 hours. After cooling, the solid product formed was collected and crystallized from dioxane to yield 70% and 80% of **30a,b** respectively.

Method B

A mixture of **3** (1.01 g, 0.0025 mol) and p-tolulaldehyde (**29a**) or p-anisaldehyde (**29b**) (0.0025 mol) in dioxane in the presence of piperidine as a catalyst was refluxed for 8 hours and then worked out as described above to produce. 76%, 85% of (**30a,b**).

30a: m.p. 184-186°C. ¹H NMR: 1.9 (s, 3H, CH₃) 2.4 (s, 3H, CH₃), 5.9 (s, 1H, H-11), 7.3-7.5 (m, 13H, arom.) 8.2 (s, 1H, N=CH), 8.5 (s, 1H, H-pyrimidine), 10.6 (br, 1H, NH, D₂O exchangeable). IR: 1600 (C=N), 3450 (NH). MS m/z (%), 506 (M⁺, 14), 393 (40), 386, 100, 77 (15). Anal., Calcd. for C₂₉H₂₃N₆OCl; C: 68.70, H: 4.57, Found C: 68.60, H: 4.49.

30b: m.p. 196-197°C. ¹H NMR: 1.9 (s, 3H, CH₃), 3.4 (s, 3H, OCH₃), 5.9 (s, 1H, H-11), 7.3-7.8 (m, 13H, arom.) 8.4 (s, 1H, N=CH), 8.56 (s, 1H, H-pyrimidine), 10.8 (br, 1H, NH, D₂O exchangeable). IR: 1620 (C=N), 3450 (NH). Anal., Calcd. for C₂₉H₂₃N₆O₃Cl C: 66.60, H: 4.43, Found C: 66.49, H: 4.33.

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