Reaction of Pyrimidinonethione Derivatives: Synthesis of N-methyl-2-hydrizinopyrimidine-4-one, thiazolo[3,4-b] N-methylpyrimidinone; 2-(1-pyrazolonyl) N-methylpyrimidine-4-one and 2-Hydrazino-N-methyl pyrimidine-4-one Derivatives

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6-Aryl-5-cyano-4-pyrimidinone-2-thion derivatives **1a-c** reacted with methyl iodide (1:2) to give the corresponding 2-S,N-dimethyl pyrimidine-4-one derivatives **2a-c**. Compounds **2a-c** were in turn, reacted with hydrazine hydrate to give the sulfur free reaction products **3a-c**. These reaction products were taken as the starting materials for the synthesis of several new heterocyclic derivatives. Reaction of **3a-c** with acetic anhydride and formic acid gave pyrimido triazines **4a-c** and **7a-c**, respectively. Their reactions with active methylene containing reagents gave the corresponding 2-(1-pyrazonyl)-N-methyl pyrimidine derivatives **9a-c** and **10a-c**, respectively. Their reactions with aromatic aldehydes afforded the corresponding 2-hydrazono pyrimidine derivatives **11a-c**. The structure of these reactions products were established based on both elemental analysis and spectral data studies.

Keywords: Pyrimidinethione; Pyrimidine; Triazine; Pyrazolopyrimidine and hydrazo pyrimidine.

INTRODUCTION

The reported biological activity of pyrimidine derivatives,[1-10] especially 2-hydrazinopyrimidines as antifungal antiviral and antibacterial[11-14] agents as well as the leishmanicidal activity[15,16] of the annelated pyrimidine derivatives, stimulated my interest in the synthesis of several new heterocyclic derivatives of these ring systems. The 6-aryl-5-cyano-4-pyrimidinone-2-thione derivatives **1a-c** were prepared according to literature procedures[17-19] and used as good starting material for the synthesis of the corresponding 2-hydrazinopyrimidine derivatives **3a-c** which were used, in turn, as the starting materials for the present study.

RESULTS AND DISCUSSION

Thus it has been found that compounds **1a-c** reacted with methyl iodide (1:2) in sodium methoxide to give 2-S,N-dimethyl-pyrimidine-4-one derivatives **2a-c**. The structure of **2a-c** was established based on the data of IR, ^{1}H-NMR spectra and elemental analysis (cf. Table 1 and 2). The IR spectra of these compounds showed a band of CN and imidic CO in each case. While their ^{1}H-NMR spectra revealed the signal of aromatic (or furyl) and the two CH_3 signals. Synthone **2a-c** reacted with hydrazine hydrate to give 6-aryl-5-cyano-N-methyl-2-hydrazino pyrimidine-4-one **3a-c** (cf. Equation 1). The structure of the reaction products **3a-c** was established based on the data of IR,^{1}H-NMR spectra and elemental analysis (cf. Tables 1 and 2). The IR spectra of these compounds showeda band of the CN and imidic CO as well as the band of $-NH_2$ and –NH– in each case. The ^{1}H-NMR spectra for compounds **3a-c** revealed the signals of aromatic (or furyl) and CH_3 as well as the signals of NH, NH_2 as hydrazine; moreover the mass spectrum of **3a** as typical example of the series gave *m/z* = 241 which corresponded to the exact molecular formula $C_{12}H_{11}N_5O$. Synthons **3a-c** are used as the starting material of synthesis of many pyrimidine derivatives. Thus it has been found that compound **3a-c** reacted with acetic anhydride to give the cyclized compounds triazolo[3,4-b]pyrimidinone derivatives **4a-c**. The structure of the reaction products **4a-c** were confirmed based on the data of IR, ^{1}H-NMR spectra and elemental analysis (cf. Table 1 and 2). The IR spectra of these compounds showed bands of CN and imidic CO in each case while the band of NH, NH_2 disappeared. The ^{1}H-NMR spectra for compounds **4a-c** revealed two $-CH_3$ bands as well as the signals of an aromatic (or furyl). The synthetic potential of **3a-c** was further directed toward the synthesis of tiazolo[3,4-b]pyrimidine derivative through their reactions with formic acid. Thus it has been found that **3a-c** reacted with formic acid to give the corresponding triazolo[3,4-b]pyrimidine derivatives **7a-c**. The

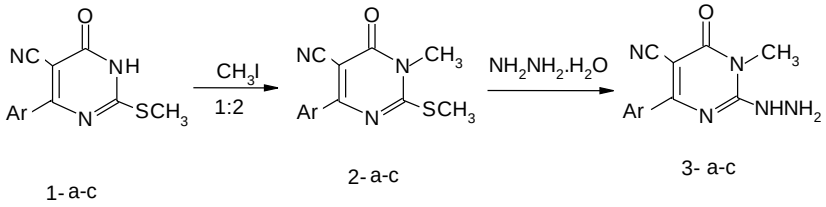
Table 1. Characterization Data of the Newly Synthesized Compounds

Comp.	M.P. (°C)	Yield (%)	Cryst. Solvent.	Molecular Formula	% of Analysis Calcd./Found				
					C	H	N	S	Cl
2a	272	74	Ethanol	$C_{13}H_{11}N_3SO$	60.70 60.60	4.28 4.30	16.34 16.40	12.45 12.60	– –
2b	> 300	78	DMF	$C_{13}H_{10}N_3SOCl$	53.52 53.70	3.43 3.30	14.40 14.50	10.98 11.00	12.18 12.20
2c	266-8	82	Ethanol	$C_{11}H_9N_3SO_2$	53.44 53.50	3.64 3.70	17.00 17.10	12.96 13.00	– –
3a	258	65	Ethanol	$C_{12}H_{11}N_5O$	59.75 59.70	4.56 4.50	29.05 29.10	– –	– –
3b	> 300	70	DMF	$C_{12}H_{10}N_5OCl$	52.27 52.30	3.63 3.61	25.41 25.32	– –	12.89 12.79
3c	278	84	Ethanol	$C_{10}H_9N_5O_2$	51.95 51.80	3.89 3.82	30.30 30.31	– –	– –
4a	286	80	Ethanol	$C_{14}H_{11}N_5O$	63.39 63.31	4.15 4.09	26.42 26.40	– –	– –
4b	293	78	DMF	$C_{14}H_{10}N_5ClO$	56.09 56.11	3.34 3.35	23.37 23.41	– –	11.85 11.78
4c	283	82	Ethanol	$C_{12}H_9N_5O_2$	56.47 56.44	3.53 3.41	27.45 27.42	– –	– –
7a	290	80	Ethanol	$C_{13}H_9N_5O$	62.15 62.00	3.59 3.48	27.90 27.82	– –	– –
7b	299	76	DMF	$C_{13}H_8N_5ClO$	54.64 54.65	2.80 2.74	24.52 24.52	– –	12.43 12.38
7c	288	82	Ethanol	$C_{11}H_7N_5O_2$	54.77 54.71	2.91 2.90	29.05 28.99	– –	– –
9a	296	70	DMF	$C_{15}H_{12}N_6O_2$	58.44 58.39	3.89 3.82	27.27 27.11	– –	– –
9b	260-2	65	Acetic Acid	$C_{15}H_{11}N_6O_2Cl$	52.55 52.51	3.21 3.20	24.53 24.41	– –	10.36 10.29
9c	220-2	66	DMF	$C_{13}H_{10}N_6O_3$	49.68 50.22	3.19 3.53	26.75 26.70	– –	– –
10a	210	76	Acetic Acid	$C_{17}H_{15}N_5O$	66.89 66.91	4.92 4.89	22.95 22.85	– –	– –
10b	286-8	62	Acetic Acid	$C_{17}H_{14}N_5OCl$	60.09 60.11	4.12 4.00	20.62 20.64	– –	10.46 10.43
10c	240-2	65	Acetic Acid	$C_{15}H_{13}N_5O_2$	61.02 61.10	4.41 4.45	23.73 23.63	– –	– –
11a	297-9	72	Acetic Acid	$C_{19}H_{15}N_5O$	69.30 69.20	4.56 4.60	21.28 21.31	– –	– –
11b	312	82	DMF	$C_{19}H_{14}N_5OCl$	62.79 62.70	3.85 3.91	19.26 19.31	– –	9.77 9.66
11c	295-7	82	Acetic Acid	$C_{17}H_{13}N_5O_2$	63.95 63.91	4.08 4.08	21.94 21.89	– –	– –

structure of the products **7a-c** was established based on the data given from elemental analysis, IR and ^{1}H-NMR studies (cf. Tables 1 and 2). The formation of triazolo[3,4-b]pyrimidine derivatives **7a-c** was most probably as shown in chart I via the non isolables **6a-c**. The synthetic potential of compounds **3a-c** was further investigated through their reaction with ethyl cyanoacetate as active methylene containing reagents. Thus it has been found that **3a-c** reacted with ethylcyanoacetate in glacial acetic acid to afford the corresponding 5-cyano-6-aryl-2-(1-pyrazolonyl) N-methyl pyrimidine-4-one derivatives **9a-c**. Compounds **9a-c** were most probably formed via elimination of ethanol to give the non isolable intermediates **8a-c**; the latter cyclized via addition of NH to the nitrile function and tautomerization (cf. chart 1).

Table 2. IR, ν (cm^{-1}) and ^{1}H-NMR δ (PPM)

Comp.	IR (kBr) ν (cm^{-1})	^{1}H-NMR, (DMSO-d_6) δ (PPM)
2a	3070 (aromatic, C-H); 2985, 2972 (aliphatic, C-H); 2214 (CN); 1690 (ring CO); 1620 (C=N); and 1600(C=C).	2.2 (s, 3H, N-CH_3); 1.3 (s, 3H, -S-CH_3); and 7.3-8.2 (m, 5H, ArH′ s).
2b	3070 (aromatic, C-H); 2982, 2968 (aliphatic, C-H); 1690 (ring, CO); 2214 (CN); 1618 (C=N); and 1603 (C=C).	2.3 (s, 3H, N-CH_3); 1.3 (s, 3H, -S-CH_3); and 7.1-7.9 (m, 4H, ArH′ s).
2c	3070 (aromatic, C-H); 2975 (aliphatic, C-H); 1690 (ring, CO); 1617 (C=N); 1600 (C=C); and 2214 (CN).	2.3 (s, 3H, N-CH_3); 1.3 (s, 3H-S-CH_3); and 6.4-7.2 (m, 3H, furyl).
3a	3359, 3332, 3270, 3180 (NH_2 and NH); 3079 (aromatic C-H); 2218 (CN); 1690 (ring CO); 1615 (C=N); and 1602 (C=C).	2.2 (s, 3H, N-CH_3); 6.2 (s, br, 1H, NH, hydrazino); 7.1-8.2 (m, 5H, ArH′ s); and 9.1 (s, br, 2H, NH_2, hydrazino).
3b	3390, 3325, 3280, 3182 (NH_2 and NH); 3074 (aromatic C-H); 2217 (CN); 1690 (ring CO); 1612 (C = N); and 1600 (C=C).	2.3 (s, 3H, N-CH_3); 6.4 (s, br, 1H, NH, hydrazin); 7.2-7.9 (m, 4H, ArH′s); and 9.3 (s, br, 2H, NH_2, hydrazino).
3c	3390, 3325, 3280, 3182 (NH_2 and NH); 3074 (aromatic, CH); 2217 (CN); 1690 (ring, CO); 1612 (C=N); and 1600 (C=C).	2.2 (s, 3H, NCH_3); 5.9 (s, br, 1H, NH, hydrazin); 6.4 - 7.0 (m, 3H, furyl, H′s); and 8.6 (s, br, 2H, NH_2, hydrazino).
4a	3070 (aromatic, C-H); 2985, 2972 (aliphatic, C-H); 2216 (CN); 1690 (ring, CO); 1620 (C=N); and 1600 (C=C).	2.3 (s, 3H, N-CH_3); 1.7 (s, 3H, CH_3); and 7.2-8.3 (m, 5H, ArH′ s).
4b	3070 (aromatic, C-H); 2981, 2968 (aliphatic, C-H); 1685 (ring CO); 2214 (CN); 1618 (C=N); and 1602 (C=C).	2.3 (s, 3H, N-CH_3); 1.6 (s, 3H, CH_3); and 7.1-7.9 (m, 4H, ArH′ s).
4c	3070 (aromatic C-H); 2975, (aliphatic C-H); 1690 (ring CO); 1618 (C=N); and 1600 (C=C); 2214 (CN).	2.2 (s, 3H, N-CH_3); 1.6 (s, 3H, CH_3); and 6.4-7.1 (m, 3H, furyl).
7a	3083 (aromatic, C-H); 2984, 2897 (aliphatic, C-H); 2218 (CN); 1693 (ring, CO); 1615 (C=N); and 1601 (C=C).	2.2 (s, 3H, N-CH_3); and 7.0-8.4 (m, 5H, aromatic and triazole, H-5 proton).
7b	3078 (aromatic C-H); 2980, (aliphatic C-H); 2213 (CN); 1685 (ring, CO); 1612 (C=N); and 1600 (C = C).	2.3 (s, 3H, N-CH_3); and 7.0-8.3 (m, 4H, aromatic and triazole H-5 proton).
7c	3080 (aromatic, C-H); 2979, 2873 (aliphatic, C-H); 2215 (CN); 1687 (ring, CO); 1613 (C=N); and 1600 (C=C).	2.2 (s, 3H, N-CH_3); and 6.4-7.2 (m, 3H, furyl and triazole, H-5).
9a	3087 (aromatic, C-H); 2216, (CN); 1685, 1690 (ring and amidic, CO); 1612 (C=N) and 1600 (C=C).	2.2 (s, 3H, N-CH_3); 3.6 (s, 1H, pyrazole H-4); 4.7 (s, 1H, N-H); 5.3 (s, br, 2H, NH_2); and 6.9-7.8 (m, 5H, ArH′ s).
9b	3094 (aromatic, C-H); 2220, (CN); 1699, 1690 (ring and amidic, CO); 1610 (C=N) and 1600 (C=C).	2.3 (s, 3H, N-CH_3); 3.2 (s, 1H, pyrazole H4); 4.5 (s, 1H, NH); 5.6 (s, br, 2H, NH_2); and 7.1-7.9 (m, 4H, ArH′ s).
9c	3085 (aromatic, C-H); 2222, (CN); 1687, 1690 (ring and amidic, CO); 1613 (C=N) and 1600 (C=C).	2.2 (s, 3H, N-CH_3); 3.0 (s, 1H, pyrazole H-4); 4.8 (s, 1H, N-H); 5.4 (s, br, 2H, NH_2); and 6.6-6.8 (m, 3H, furyl H′ s).
10a	3078 (aromatic, C-H); 2984, 2897 (aliphatic, C-H); 2218 (CN); 1693 (ring, CO); 1615 (C=N); and 1602 (C=C).	2.3 (s, 3H, N-CH_3); 1.5 (s, 6H, two CH_3); and 7.2-8.4 (m, 5H, aromatic and pyrazole H-4 protons).
10b	3078 (aromatic, C-H); 2980, 2890 (aliphatic, C-H); 2213 (CN); 1685 (ring, CO); 1610 (C=N); and 1600 (C=C).	2.2 (s, 3H, N-CH_3); 1.5 (s, 6H, two CH_3); and 7.1-8.5 (m, 5H, aromatic and pyrazole H-4 protons).
10c	3080 (aromatic C-H); 2979, 2873 (aliphatic C-H); 2215 (CN); 1687 (ring CO); 1612 (C=N); and 1600 (C=C).	2.2 (s, 3H, N-CH_3); 1.4 (s, 6H, two CH_3); 6.2-6.8 (m, 3H, furyl H s); and 8.6 (s, br, 1H, pyrazole H-4 protons).
11a	3232, 3198 (one, NH); 3070, (aromatic, C-H); 2980-2894 (aliphatic C-H); 2218 (CN); and 1690 (ring, CO).	2.3 (s, 3H, N-CH_3); 5.3 (s, 1H, -CH=N-); 7.1-8.2 (m, 10H, aromatic protons); and 9.7 (s, br, 1H, N-NH).
11b	3232, 3197 (one NH); 3084, (aromatic, C-H); 2980-2890 (aliphatic, C-H); 2222 (CN); 1612 (ring, CO); 1613 (C=N; and 1600 (C=C).	2.3 (s, 3H, N-CH_3); 5.5 (s, 1H, -CH=N-); 7.2-8.1 (m, 9H, aromatic protons); and 9.9 (s, br, 1H, N-NH-).
11c	3220, 3190 (one, NH); 3070, (aromatic, C-H); 2981-2873 (aliphatic, C-H); 2218 (CN); 1685 (ring, CO); 1610 (C=N; and 1600 (C=C).	2.3 (s, 3H, N-CH_3); 5.2 (s, 1H, -CH=N-); 6.3-6.8 (m, 5H, aromatic); and 9.7 (s, br, 1H, N-NH-).



1- a-c

2- a-c

3- a-c

Ar

a = C_6H_5

b = C_6H_4-Cl-p

c = C_4H_3-O-

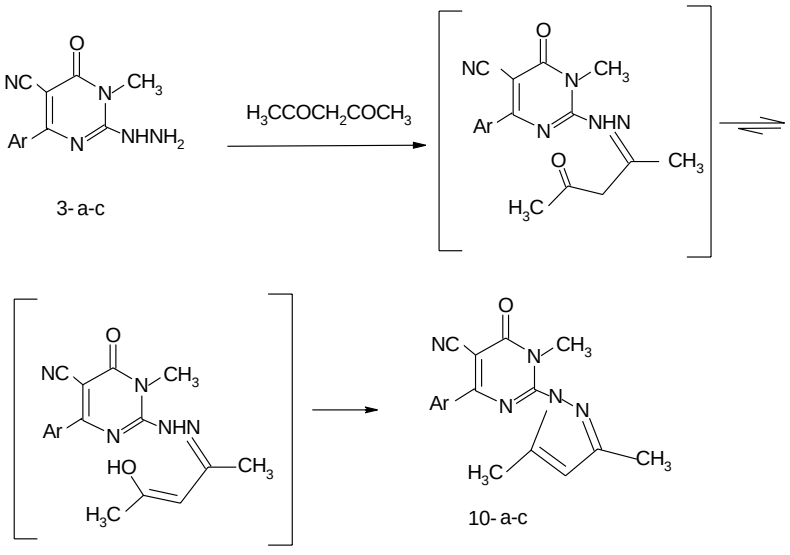
Equation-1

The proposed mechanism finds support by appearance of newly formed NH_2, NH bands in IR spectrum and by ^{1}H-NMR spectra as well as elemental analysis (cf Table 1 and 2). The compounds **3a-c** reacted in further investigation with acetylacetone to afford the corresponding 2-(1-pyrazolonyl) pyrimidine-4-one derivatives **10a-c**, respectively. These reaction products were most likely obtained via the elimination of water molecules followed by cyclization through enolization and dehydration (cf. Equation 2).

The structure of compounds **10a-c** were confirmed by elemental analysis, IR, and ^{1}H-NMR (cf. Tables 1 and 2). The IR spectra showed the signal of CN and imidic CO while the ^{1}H-NMR spectra revealed the signal for the CH_3 group as well as aromatic (furyl protons) and pyrazole H-4 protons. A further demonstration for the activity of compounds **3a-c** was achieved through their condensation with aromatic aldehyedes; thus it has been found that **3a-c** reacted with benzaldehyde in glacial acetic acid to give the Schiff's base **11a-c**. The products showed no bands of NH_2 function in IR spectra. Their mass spectra gave *m/z* = 327 and 362, respectively, which corresponded to the exact molecular weights of molecular formula $C_{19}H_{15}N_5O$ and $C_{19}H_{14}N_5OCl$ of the assigned structures (cf. chart I).

EXPERIMENTAL PROCEDURE

All melting points are uncorrected. The IR spectra in kBr discs were recorded on Perkin-Elmer FT-IR type 4 and Pye Unicam SP – 1100-Spectrophotometers. The ^{1}H-NMR spectra were recorded on Varian Em 390-90 MHZ, Gemini 200 and Bruker WP-80 Spectrometers using $CDCL_3$, DMSO-d_6 and $(CD_3)_2$ CO as solvents and TMS as an internal standard. Chemical shifs are expressed as δ ppm units. Mass



3- a-c

10- a-c

Equation-2

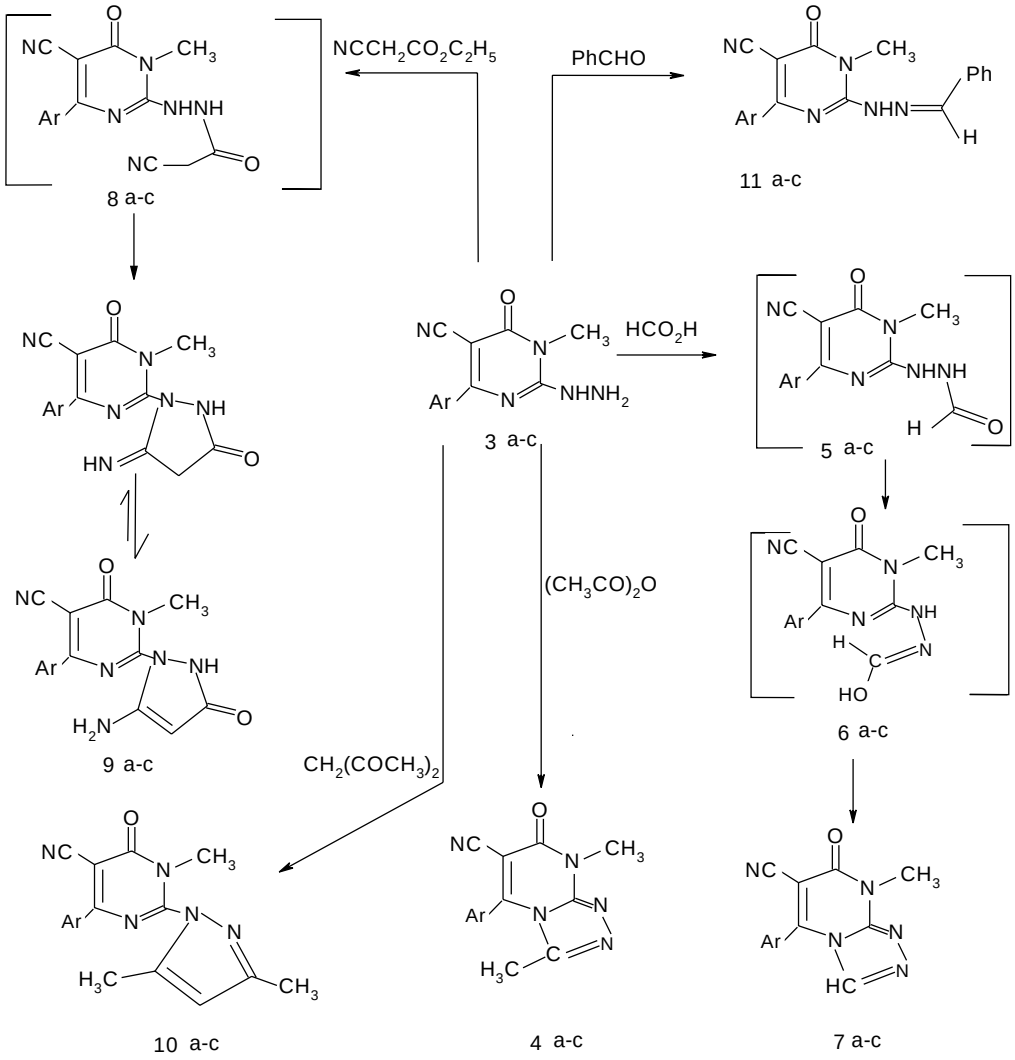


Chart 1

spectra were recorded on a Hewlett-Packard-GC-MS type 2988 series using DIP technique at 70 ev. Microanalyses were performed at the Microanalytical Center of Cairo University using a Perkin-Elmer 2400 CHN elemental analyzer. The compounds **1a,b** and **c** were prepared according to literature procedures.[17-19]

Reactions with alkyl iodide

Synthesis of 2-S-N-dimethyl pyridine 4-one derivatives 2a-c (General procedure)

A solution of each of **1a-c** (0.01 mole) in methanolic sodium methoxide (0.01 mole) prepared from 0.01 atom of sodium metal in 30 mL methanol was treated with methyl-iodide (0.02 mol) and heated under reflux for 10 hours. The solid product obtained on pouring onto cold water was filtered off, washed with water and recrystallized from the proper solvent (at boiling point of the solvent) and after concentration and cooling it gave **2a-c**, respectively (cf. Table 1 and 2).

2a as pale yellow crystals with m.p. 272 °C, yield 74%; **2b** as brown crystals with m.p. >300 °C, yield 78%; **2c** as pale yellow crystals with m.p. 266-268 °C, yield 82%.

Reactions with hydrazine hydrate

Synthesis of 6-aryl-5-cyano-N-methyl-2-hydrazino pyridines-4-one derivatives 3a-c (General procedure)

A mixture of each of **2a-c** (0.02 mole) in methanol (30 mL) was treated with excess hydrazine hydrate (5 mL) and then heated under reflux for 7 hours. The solid products obtained from hot solution after cooling were filtered off and recrystallized from the proper solvent (at boiling point of the solvent) and after concentration and cooling it gave **3a-c**, re-

spectively (cf. Table 1 and 2).

3a as pale yellow crystals with m.p. 258 °C, yield 65%; **3b** as brown crystals with m.p. >300 °C, yield 70%; **3c** as yellow crystals with m.p. 278 °C, yield 84%.

Reactions of 3a-c with formic acid and acetic anhydride

Synthesis of triazolo[3,4-b]pyrimidine derivatives 4a-c and 7a-c

A mixture of **3a-c** (0.01 mole) and each of formic acid (20 mL) or acetic anhydride (20 mL) was heated under reflux for 4 hours – the solid products obtained hot or after cooling were filtered off and recrystallized from the proper solvent (at boiling point of the solvent) and after concentration and cooling it gave **4a-c** and **7a-c**, respectively (cf. Table 1 and 2).

4a as pale yellow crystals with m.p. 286 °C, yield 80%; **4b** as pale brown crystals with m.p. 293 °C, yield 78%; **4c** as yellow crystals with m.p. 283 °C, yield 82%; **7a** as yellow crystals with m.p. 290 °C, yield 80%; **7b** as brown crystals with m.p. 299 °C, yield 76%; **7c** as yellow crystals with m.p. 288 °C, yield 82%.

Reaction of 3a-c with different active methylene containing reagents

Synthesis of 5-cyano-6-aryl-2-(1-pyrazolonyl) N-methyl pyrimidine-4-one derivatives 9a-c and 2-(1-pyrazolonyl) pyrimidine-4-one derivatives 10a-c (General procedure)

A solution of **3a-c** (0.01 mole) in glacial acetic acid was treated with ethylcyano acetate (0.01) and acetylacetone (0.01 mole), respectively. The reaction mixture was heated under reflux for 6 hours. The solid products obtained hot or after cooling were filtered off and recrystallized from the proper solvent (at boiling point of the solvent) and after concentration and cooling it give **9a-c** and **10a-c**, respectively (cf. Table 1 and 2).

9a as pale brown crystals with m.p. 296 °C, yield 70%; **9b** as yellow crystals with m.p. 260-2 °C, yield 65%; **9c** as brown crystals with m.p. 220-2 °C, yield 66%; **10a** as pale yellow crystals with m.p. 210 °C, yield 76%; **10b** as yellow crystals with m.p. 286-8 °C, yield 62%; **10c** as brown crystals with m.p. 240-2 °C, yield 65%.

Reactions of 3a-c with benzaldehyde

Synthesis of shifts 11a-c (General procedure)

A solution of each of **3a-c** (0.01 mol) in acetic acid (30 mL) was treated with benzaldehyde (0.01 mol). The reaction mixture was heated under reflux for 5 hours. The solid products obtained hot or after cooling were filtered off and recrystallized from the proper solvent (at boiling point of the solvent) and after concentration and cooling it gave **11a-c**, respectively (cf. Table 1 and 2).

11a as orange crystals with m.p. 297-9 °C, yield 72%; **11b** as yellow crystals with m.p. 312 °C, yield 82%; **11c** as brown crystals with m.p. 295-7 °C, yield 82%.

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