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Synthesis and studies of pyrazolo[3,4-*b*]piperidin-4-one derivatives

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ABSTRACT

A series of isolated/fused of pyrazole, isoxazolo, pyrimidine, pyrimidine thione, spiro thiazolodine and spiro β-lactam derivatives incorporating to 4-acetyl-5-amino-3-methyl-1-phenyl-2-pyrazoline have been synthesized by different methods of chemical reactions. The structure assignments of these compounds, based on chemical and spectroscopic evidence were deduced from their IR, ^{1}H NMR, elemental analysis and mass spectrometry.

1. Introduction

Mannich reaction is a versatile reaction and was studied used widely in the synthesis of biologically important molecules and natural products [1-5]. The reaction between benzaldehyde, aniline and cyclohexanone as a model reaction in water in the presence of various amounts of first generation dendrimer [6-14]. It was found that only 2 mol % of the catalyst was required to drive the reaction smoothly to completion. The scope of the dendrimer catalyzed Mannich reaction was extended to other aldehydes, ketones and anilines [15-25]. In a similar manner condensation between other substrates like 4-acetyl-5-imino-3-methyl-1-phenyl-2-pyrazoline (**1**) also a short period of time with excellent yield and high purity and non more purification was required. As literature search, it has found that Mannich bases had antimicrobial activities [26,27] besides various activities. The pyrazole nucleus is present in a wide variety of biologically interesting compounds, which exhibit ant hyperglycemic, analgesic, anti-inflammatory, antipyretic, antibacterial, hypoglycemic, sedative - hypnotic activity [28-31]. Pyrazoles and their derivatives are widely used as pharmaceutical [32,33] and agrochemical agents [34] and consequently a large number of synthetic routes to pyrazoles has been reported [35-38]. However, there is still great interest in finding milder and more efficient methods to these valuable compounds. Amino pyrazole derivative and imino pyrazole derivative undergo various reactions, and as such are excellent and general starting materials for the development of the organic synthesis.

2. Experimental

All melting points are uncorrected. IR spectra were recorded on a Pye Unicam SP-1100 Spectrophotometer KBr disc ^{1}H NMR spectra were recorded on a Varian EM-390 90M Hz spectrophotometer using DMSO d_6 as a solvent and TMS as an internal standard chemical shifts are expressed as ppm units. The microanalysis was performed by the micro analytical centers at Cairo University. Mass spectra were obtained on a Shimadzu GCMS QP 1000 EX mass spectrometer at 70 eV.

2.1. Synthesis of 4-acetyl-5-imino-3-methyl-1-phenyl-2-pyrazoline (1)

The compound (**1**) was carried out according to Mohanty *et al*., 1977 [39].

2.2. Synthesis of 4-acetyl-5-amino-3-methyl-1-phenyl-2-pyrazoline (2)

The compound **1** (2 g, 0.004 mol) was dissolved in 20 mL acetic acid with 1 g zinc dust, reflux for 2-3 hr. The hot mixture was filtrated to get off zinc dust residue. The filtrate was poured on ice/water with continuous stirring. The solid product was collected by filtration and crystallized from the diluted acetic acid (Scheme 1, Tables 1, 2).

2.3. Synthesis of 3-methyl-1-phenyl-5,6,7,7a-tetrahydro-1H-pyrazolo[3,4-b]pyridin-4(3aH)-one (3)

A solution of compound **2** (1.78 g, 0.008 mol) in dimethyl formamide was treated with paraformaldehyde (0.25 g, 0.008 mol) and piperidine (0.82 mL, 0.009 mol) and HCl (0.41 mL, 0.01 mol). The reaction mixture was heated under reflux for 3 hr, then left to cool and was poured into ice/water with the stirring. The solid product so formed was collected by filtration and crystallized from the diluted DMF (Scheme 1, Tables 1, 2).

2.4. Synthesis of 5-benzylidene-3-methyl-1-phenyl-5,6,7,7a-tetrahydro-1H-pyrazolo[3,4-b]pyridin-4(3aH)-one (4a), *5-(4-methoxybenzylidene)-3-methyl-1-phenyl-5,6,7,7a-tetrahydro-1H-pyrazolo[3,4-b]pyridin-4(3aH)-one* (4b), *5-(4-hydroxybenzylidene)-3-methyl-1-phenyl-5,6,7,7a-tetrahydro-1H-pyrazolo[3,4-b]pyridin-4(3aH)-one* (4c)

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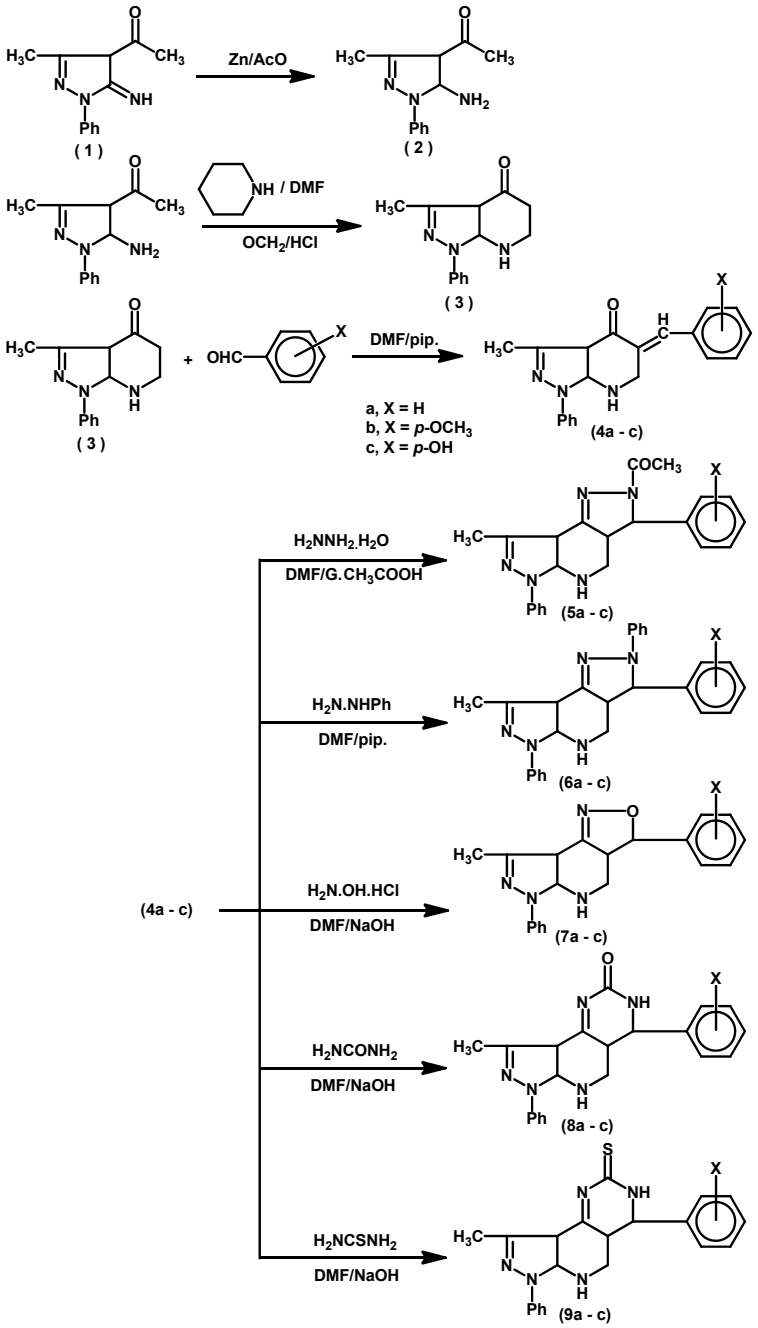


Scheme 1

A solution of compound **3** (1.17 g, 0.005 mol) was treated with aromatic aldehyde compounds (**4a**: 0.54 mL, 0.005 mol; **4b**: 0.68 mL, 0.005 mol; **4c**: 0.61 g, 0.005 mol) in the presence of 3 drops piperidine as a catalyst. The reaction mixture was heated under reflux for 4 hr, then left to cool and was poured on ice/water with stirring. The solid product so formed was collected by filtration and crystallized from the diluted DMF (Scheme 1, Tables 1, 2).

2.5. Synthesis of 1-(8-methyl-3,6-diphenyl-3,3a,4,5,5a,6-hexahydrodipyrazolo[3,4-b:3',4'-d]pyridin-2(8aH)-yl) ethanone (5a), *1-(3-(4-methoxyphenyl)-8-methyl-6-phenyl-3,3a,4,5,5a,6-hexahydrodipyrazolo[3,4-b:3',4'-d] pyridin-2 (8aH)-yl)ethanone* (5b), *1-(3-(4-hydroxyphenyl)-8-methyl-6-phenyl-3,3a,4,5,5a,6-hexahydrodipyrazolo[3,4-b:3',4'-d] pyridin-2(8aH)-yl)ethanone* (5c)

A solution of compounds **4a-c** (**4a**: 0.31 g, 0.001 mol; **4b**: 0.34 g, 0.001 mol; **4c**: 0.33 g, 0.001 mol) in dimethyl formamide was treated with hydrazine monohydrate (0.05 mL, 0.001 mol) in the presence of 4 drops of acetic acid. The reaction mixture was heated under reflux for 8 hr, then left to cool and was poured on ice/water. The solid product so formed was collected by filtration and crystallized from the diluted DMF (Scheme 1, Tables 1, 2).

Table 1. Characterization of compounds (**3-12**).

Comp. No.	Yield, %	M.P., °C	Color	Mol. Formula, (M.wt., g)	Elemental Analysis, % Calculated (Found)			Mass, *m/z*
					C	H	N	
3	66	208-210	Light yellow	C13H15N3O (229.28)	68.12 (68.15)	6.55 (6.57)	18.3 (18.5)	228
4a	59	166-168	Greenish yellow	C20H19N3O (317.39)	75.70 (75.72)	5.99 (6.00)	13.24 (13.25)	315
4b	98	130-132	Latency	$C_{21}H_{21}N_3O_2$ (347.42)	72.62 (72.64)	6.05 (6.06)	12.10 (12.12)	346
4c	92	138-140	Light beige	$C_{20}H_{19}N_3O_2$ (333.39)	72.07 (72.08)	5.70 (5.80)	12.61 (12.62)	331
5a	83	140-142	Brown	$C_{22}H_{23}N_5O$ (373.46)	70.77 (70.76)	6.16 (6.15)	18.76 (18.76)	374
5b	61	158-160-	Dark brown	$C_{23}H_{25}N_5O_2$ (403.48)	68.48 (68.47)	6.20 (6.10)	17.36 (17.35)	404
5c	75	160-162-	Light brown	$C_{22}H_{23}N_5O_2$ (389.46)	67.86 (67.84)	5.91 (5.90)	17.99 (17.97)	390
6a	50	166-168	Brown	$C_{26}H_{25}N_5$ (407.52)	76.65 (76.66)	6.14 (6.15)	17.19 (17.20)	408
6b	79	190-192	Brown	$C_{27}H_{23}N_5O$ (433.51)	74.82 (74.83)	5.31 (5.32)	16.16 (16.17)	433
6c	40	144-146	Dark beige	$C_{26}H_{25}N_5O$ (423.52)	73.75 (73.75)	5.91 (5.89)	16.54 (16.52)	423
7a	81	154-156	Light orange	$C_{20}H_{20}N_5O$ (346.41)	72.28 (72.30)	6.02 (6.02)	21.08 (21.08)	346
7b	66	100-102	Reddish brown	$C_{21}H_{22}N_4O_2$ (362.43)	69.61 (69.60)	6.07 (6.06)	15.46 (15.45)	362
7c	70	120-122	Dark beige	$C_{20}H_{20}N_4O_2$ (348.40)	68.96 (68.95)	5.74 (5.74)	16.09 (16.09)	349
8a	50	225-227	Reddish brown	$C_{21}H_{21}N_5O$ (359.43)	70.78 (70.77)	5.84 (5.83)	19.49 (19.48)	357
8b	84	150-152	Reddish brown	$C_{22}H_{23}N_5O_2$ (389.46)	67.86 (67.84)	5.90 (5.70)	17.99 (17.99)	389
8c	50	139-140	Dark beige	$C_{21}H_{21}N_5O_2$ (375.43)	67.20 (66.20)	5.60 (5.50)	18.66 (18.66)	375
9a	40	176-178	brown	$C_{21}H_{21}N_5S$ (375.49)	67.20 (67.20)	5.60 (5.70)	18.66 (18.67)	374
9b	80	141-143	Beige	$C_{22}H_{23}N_5OS$ (405.52)	65.16 (65.00)	5.72 (5.70)	17.27 (17.50)	405
9c	38	139-140	Yellow	$C_{21}H_{21}N_5OS$ (391.49)	64.45 (64.43)	5.37 (5.35)	17.90 (17.90)	391
10a	98	163-165	Beige	$C_{21}H_{23}N_5O$ (361.45)	69.80 (70.00)	6.37 (6.40)	19.39 (19.40)	360
10b	40	168-170	Brown	$C_{19}H_{18}N_4O_2$ (334.38)	68.26 (68.27)	5.38 (5.39)	16.76 (16.77)	334
10c	98	149-151	Brown	$C_{23}H_{20}N_4O_2$ (384.44)	71.87 (71.88)	5.20 (5.21)	14.58 (14.59)	384
11a	20	150-152	Brown	$C_{23}H_{25}N_5O_2S$ (435.54)	63.44 (63.45)	5.74 (5.75)	16.09 (16.09)	435
11b	30	120-122	Brown	$C_{21}H_{20}N_4O_3S$ (408.47)	61.76 (61.78)	4.90 (4.93)	13.72 (13.73)	406
11c	25	125-127	Light brown	$C_{25}H_{22}N_4O_3S$ (458.53)	65.50 (65.52)	4.80 (4.82)	12.22 (12.23)	458
12a	15	145-146	Brown	$C_{23}H_{24}N_5O_2Cl$ (437.93)	63.15 (63.16)	5.49 (5.50)	16.01 (16.03)	436
12b	18	200-202	Brown	$C_{21}H_{19}N_4O_3Cl$ (410.86)	61.46 (61.48)	4.63 (4.65)	13.60 (13.90)	412
12c	10	145-147	Brown	$C_{25}H_{21}N_4O_3Cl$ (460.92)	65.21 (65.22)	4.56 (4.57)	12.17 (12.18)	460

2.6. Synthesis of 8-methyl-2,3,6-triphenyl-2,3,3a,4,5,5a,6,8a-octahydrodipyrazolo[3,4-b:3',4'-d]pyridine (6a), *3-(4-methoxyphenyl)-8-methyl-2,6-diphenyl-2,3,3a,4,5,5a,6,8a-octahydrodipyrazolo[3,4-b:3',4'-d] pyridine* (6b), *3-(4-hydroxyphenyl)-8-methyl-2,6-diphenyl-2,3,3a,4,5,5a,6,8a-octahydrodipyrazolo[3,4-b:3',4'-d] pyridine* (6c)

A solution of compounds **4a-c** (**4a**: 0.31 g, 0.001 mol; **4b**: 0.34 g, 0.001 mol; **4c**: 0.33 g, 0.001 mol) in dimethyl formamide was treated with phenyl hydrazine (0.1 mL, 0.001 mol) in the presence of piperidine as catalyst. The reaction mixture was heated under reflux for 8 hr, then left to cool and was poured on ice/water. The solid product so formed was collected by filtration and crystallized from the diluted DMF (Scheme 1, Tables 1, 2).

2.7. Synthesis of 8-methyl-3,6-diphenyl-3a,4,5,5a,6,8a-hexahydro-3H-isoxazolo[3,4-d]pyrazolo[3,4-b]pyridine (7a), *3-(4-methoxyphenyl)-8-methyl-6-phenyl-3a,4,5,5a,6,8a-hexahydro-3H-isoxazolo[3,4-d]pyrazolo[3,4-b]pyridine* (7b), *3-(4-hydroxyphenyl)-8-methyl-6-phenyl-3a,4,5,5a,6,8a-hexahydro-3H-isoxazolo[3,4-d]pyrazolo[3,4-b]pyridine* (7c)

A solution of compounds **4a-c** (**4a**: 0.31 g, 0.001 mol; **4b**: 0.34 g, 0.001 mol; **4c**: 0.33 g, 0.001 mol) in dimethyl formamide was treated with hydroxyl amine hydrochloride (0.1 g, 0.001 mol) in the presence of sodium hydroxide as a catalyst. The reaction mixture was heated under reflux for 8 hr, then left to cool and was poured on ice/water. The solid product so formed was collected by filtration and crystallized from the diluted DMF (Scheme 1, Tables 1, 2).

Table 2. IR, ^{1}H NMR spectral data of compound (**3-12**).

Comp. No	IR (cm^{-1})	^{1}H NMR (δ, ppm)
3	3063 (NH), 1706 (C=O), 1596 (C=N)	0.86 (s, 3H, CH_3), 1.24 (d, *J* = 7.00 Hz, 1H, NCHN), 2.16 (t, *J* = 7.30 Hz, 2H, CH_2CO), 2.35 (d, *J* = 7.00, 1H, CHCO), 2.73 (t, *J* = 7.30 Hz, 2H, CH_2N), 3.37 (s, 1H, NH), 7.24-7.97 (m, 5H, Ar-H$^+$)
4c	3392 (OH), 3068-3063 (NH), 1640-1623 (C=O)	0.79 (s, 3H, CH_3), 1.23 (s, 1H, CHPh), 2.16 (d, *J* = 7.00 Hz, 1H, NCHN), 2.34 (d, *J* = 7.00 Hz, 1H, CHCO), 3.73 (s, 2H, CH_2N), 8.65 (s, 1H, NH), 6.7-8.1 (m, 9H, Ar-H$^+$), 9.8 (s, 1H, OH)
6c	3411-3150 (OH), 3064 (NH), 1707 (C=O), 1598 (C=N)	0.78 (s, 3H, CH_3), 2.3 (s, 1H, NH), 6.7-8.0 (m, 20H, Ar-H$^+$ + Heterocycle nuclei), 7.98 (s, 1H, OH)
7a	3064-3061 (NH), 1599-1598 (C=N)	0.77 (s, 3H, CH_3), 3.34 (s, 1H, NH), 7.42-7.82 (m, 16H, Ar-H$^+$ + Heterocycle nuclei)
7b	3391-3150 (NH), 1598 (C=N)	0.78 (s, 3H, CH_3), 2.14 (s, 1H, NH), 3.84 (s, 3H, OCH_3), 6.5-8.0 (m, 15H, Ar-H$^+$ + Heterocycle nuclei)
8b	3062 (NH), 1706 (C=O), 1601-1599 (C=N)	0.78 (s, 3H, CH_3), 1.17 (d, *J* = 7.00 Hz, 2H, NCHNH), 2.14 (q, *J* = 7.30 Hz, 1H, CHCH), 2.33 (d, *J* = 7.00 Hz, 1H, CHCN), 2.74 (d, *J* = 7.00 , 1H, CHN), 2.9 (s, 2H, NH), 3.35 (s, 3H, OCH_3), 3.69 (t, *J* = 7.30 Hz, 2H, CH_2N), 7.16-7.96 (m, 9H, Ar-H$^+$)
8c	3416-3150 (OH, NH), 1708 (C=O), 1598 (C=N)	0.78 (s, 3H, CH_3), 3.93 (s, 2H, NH), 6.0-7.97 (m, 16H, Ar-H$^+$ + Heterocycle nuclei)
9a	3061 (NH), 1599 (C=N)	0.78 (s, 3H, CH_3), 1.18 (q, *J* = 7.30 Hz, 1H, CHCH), 2.13 (d, *J* = 7.00 Hz, 1H, NCHN), 2.33 (d, *J* = 7.00 Hz, 1H, CHCN), 2.7 (d, *J* = 7.00 Hz, 1H, CHN), 2.9 (d, 2H, CH_2N), 3.31 (s, 2H, NH), 7.42-7.98 (m, 10H, Ar-H$^+$)
9b	3391-3150 (OH), 3068 (NH), 1597 (C=N)	0.75 (s, 3H, CH_3), 1.18 (q, *J* = 7.30 Hz, 1H, CHCH), 2.14 (d, *J* = 7.00 Hz, 1H, NCHN), 2.35 (d, *J* = 7.00 Hz, 1H, CHN), 2.68 (d, *J* = 7.00 Hz, 2H, CH_2N), 3.31 (br, 1H, NH), 3.33 (br, 1H, NHCS), 3.35 (s, 3H, OCH_3), 7.18-7.97 (m, 10H, Ar-H$^+$ + Heterocycle nuclei)
10c	3425-3150 (NH, OH), 1625-1614 (C=N)	0.75 (s, 3H, CH_3), 1.17 (d, *J* = 7.00 Hz, 1H, NCHN), 2.38 (d, *J* = 7.00 Hz, 1H, CHCO), 2.89 (s, 2H, CH_2N), 3.36 (s, 1H, NH), 6.89-7.48 (m, 11H, Ar-H$^+$), 7.96 (s, 1H, OH)
11b	3414-3150 (NH, OH), 1706 (C=O), 1601-1598 (C=N)	0.76 (s, 3H, CH_3), 3.35 (s, 1H, NH), 6.0-7.8 (m, 15H, Ar-H$^+$ + Heterocycle nuclei), 7.96 (s, 1H, OH)
11c	3411-3150 (OH), 3064-3061 (NH), 1751-1710 (C=O)	1.17 (s, 3H, CH_3), 3.34 (s, 1H, NH), 6.0-7.6 (m, 17H, Ar-H$^+$ + Heterocycle nuclei), 7.82 (s, 1H, OH)
12c	3428-3061 (NH), 1709-1706 (C=O)	0.78 (s, 3H, CH_3), 1.17 (d, *J* = 7.00 Hz, 1H, NCHN), 1.19 (d, *J* = 7.00 Hz, 1H, CHCO), 2.15 (s, 2H, CH_2N), 2.36 (s, 1H, NH), 3.38 (s, 1H, CHCl), 7.10-7.48 (m, 11H, Ar-H$^+$), 7.87 (s, 1H, OH)

2.8. Synthesis of 9-methyl-4,7-diphenyl-3,4,4a,5,6,6a,7,9a-octahydro-2H-pyrazolo[4',3':5,6]pyrido[4,3-d]pyrimidin-2-one (8a), *4-(4-methoxyphenyl)-9-methyl-7-phenyl-3,4,4a,5,6,6a,7,9a-octahydro-2H-pyrazolo[4',3':5,6] pyrido[4,3-d] pyrimidin-2-one* (8b), *4-(4-hydroxyphenyl)-9-methyl-7-phenyl-3,4,4a,5,6,6a,7,9a-octahydro-2H-pyrazolo[4',3':5,6] pyrido[4,3-d]pyrimidin-2-one* (8c)

A solution of compounds **4a-c** (**4a**: 0.31 g, 0.001 mol; **4b**: 0.34 g, 0.001 mol; **4c**: 0.33 g, 0.001 mol) in dimethyl formamide was treated with urea (0.06 g, 0.001 mol) in the presence of sodium hydroxide as a catalyst. The reaction mixture was heated under reflux for 8 hr, then left to cool and was poured on ice/water. The solid product so formed was collected by filtration and crystallized from the diluted DMF (Scheme 1, Tables 1, 2).

2.9. Synthesis of 9-methyl-4,7-diphenyl-3,4,4a,5,6,6a,7,9a-octahydro-2H-pyrazolo[4',3':5,6]pyrido[4,3-d]pyrimidine-2-thione (9a), *4-(4-methoxyphenyl)-9-methyl-7-phenyl-3,4,4a,5,6,6a,7,9a-octahydro-2H-pyrazolo[4',3':5,6]pyrido[4,3-d] pyrimidine-2-thione* (9b), *4-(4-hydroxyphenyl)-9-methyl-7-phenyl-3,4,4a,5,6,6a,7,9a-octahydro-2H-pyrazolo[4',3':5,6] pyrido[4,3-d]pyrimidine-2-thione* (9c)

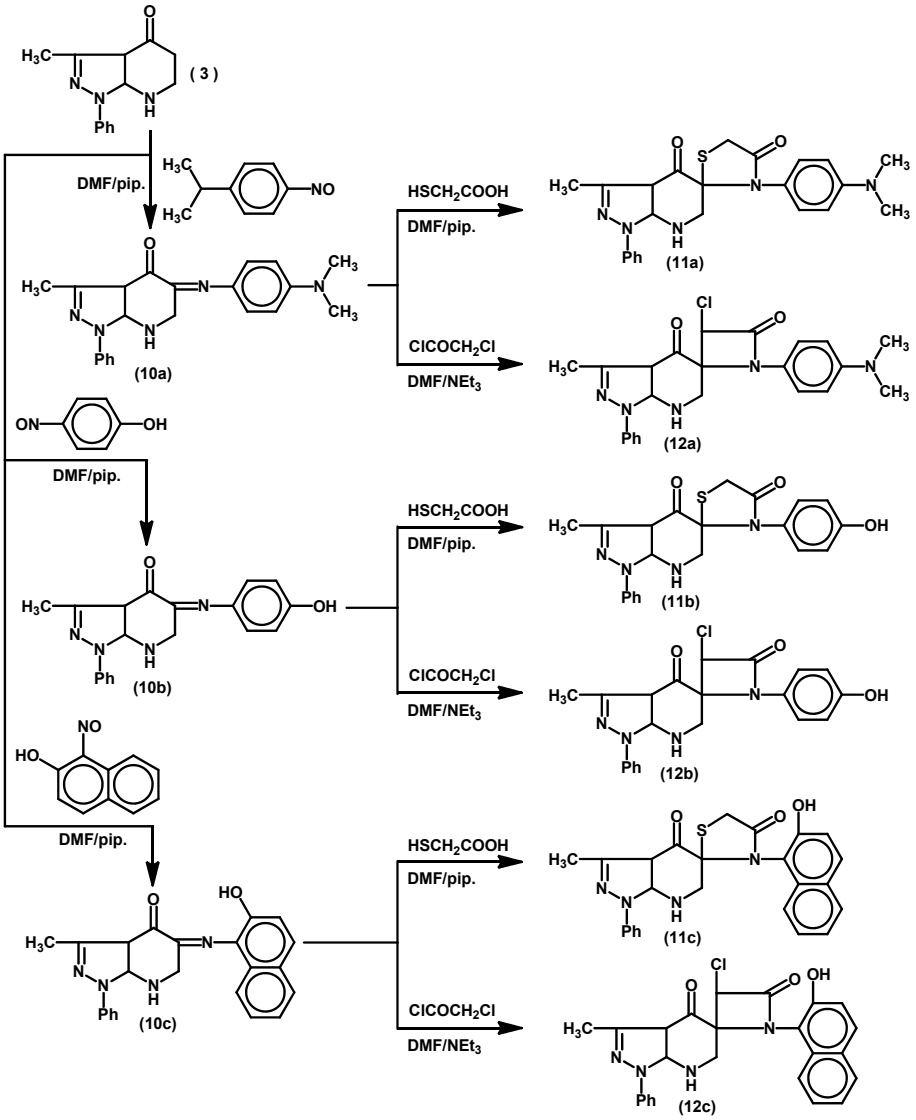
A solution of compounds **4a-c** (**4a**: 0.31 g, 0.001 mol; **4b**: 0.34 g, 0.001 mol; **4c**: 0.33 g, 0.001 mol) in dimethyl formamide was treated with thiourea (0.076 g, 0.001 mol) in the presence of sodium hydroxide as a catalyst. The reaction mixture was heated under reflux for 8 hr, then left to cool and was poured on ice/water. The solid product so formed was collected by filtration and crystallized from the diluted DMF (Scheme 1, Tables 1, 2).

2.10. Synthesis of 5-((4-(dimethylamino)phenyl)imino)-3-methyl-1-phenyl-5,6,7,7a-tetrahydro-1H-pyrazolo[3,4-b] pyridin-4(3aH)-one (10a), *5-((4-hydroxyphenyl)imino)-3-methyl-1-phenyl-5,6,7,7a-tetrahydro-1H-pyrazolo[3,4-b] pyridin-4(3aH)-one* (10b), *5-((2-hydroxynaphthalen-1-yl) imino)-3-methyl-1-phenyl-5,6,7,7a-tetrahydro-1H-pyrazolo [3,4-b]pyridin-4(3aH)-one* (10c)

A solution of compound **3** (0.5 g, 0.002 mol) in dimethyl formamide was treated with nitroso compounds (**10a**: 0.32 mL, 0.002 mol; **10b**: 0.24 g, 0.002 mol; **10c**: 0.34 mL, 0.002 mol) in presence of 2 drops of piperidine as a catalyst. The reaction mixture was heated under reflux for 8-10 hr, then left to cool and was poured on ice/water. The solid product so formed was collected by filtration and crystallized from the diluted DMF (Scheme 2, Tables 1, 2).

2.11. Synthesis of 3'-(4-(dimethylamino)phenyl)-3-methyl-1-phenyl-1,6,7,7a-tetrahydrospiro[pyrazolo[3,4-b]pyridine-5,2'-thiazolidine]-4,4'(3aH)-dione (11a), *3'-(4-hydroxy phenyl)-3-methyl-1-phenyl-1,6,7,7a-tetrahydrospiro [pyrazolo[3,4-b]pyridine-5,2'-thiazolidine]-4,4'(3aH)-dione* (11b), *3'-(2-hydroxynaphthalen-1-yl)-3-methyl-1-phenyl-1,6,7,7a-tetrahydrospiro[pyrazolo[3,4-b]pyridine-5,2'-thiazolidine]-4,4'(3aH)-dione* (11c)

A solution of compounds **10a-c** (**10a**: 0.73 g, 0.002 mol; **10b**: 0.66 g, 0.002 mol; **10c**: 0.77 g, 0.002 mol) in dimethyl formamide was treated with thioglycolic acid (0.18 mL, 0.002 mol) in presence of 2 drops of piperidine as a catalyst. The reaction mixture was heated under reflux for 8-10 hr, then left to cool and was poured on ice/water. The solid product so formed was collected by filtration and crystallized from the diluted DMF (Scheme 2, Tables 1, 2).



Scheme 2

***2.12. Synthesis of 3-chloro-1-(4-(dimethylamino)phenyl)-3'-methyl-1'-phenyl-1',6',7',7a'-tetrahydrospiro[azetidine-2,5'-pyrazolo[3,4-b]pyridine]-4,4'(3a'H)-dione* (12a), *3-chloro-1-(4-hydroxyphenyl)-3'-methyl-1'-phenyl-1',6',7',7a'-tetrahydrospiro[azetidine-2,5'-pyrazolo[3,4-b]pyridine]-4,4'(3a'H)-dione* (12b), *3-chloro-1-(2-hydroxynaphthalen-1-yl)-3'-methyl-1'-phenyl-1',6',7',7a'-tetrahydrospiro [azetidine-2,5'-pyrazolo[3,4-b]pyridine]-4,4'(3a'H)-dione* (12c)**

A solution of compounds **10a-c** (**10a**: 0.73 g, 0.002 mol; **10b**: 0.66 g, 0.002 mol; **10c**: 0.77 g, 0.002 mol) in dimethyl formamide was treated with chloroacetylchloride (0.23 mL, 0.002 mol) in presence of 2 drops of triethylamine as a catalyst. The reaction mixture was heated under reflux for 8-10 hr, then left to cool and was poured on ice/water. The solid product so formed was collected by filtration and crystallized from the diluted DMF Scheme 2, (Tables 1, 2).

3. Results and discussion

By using 4-acetyl-5-imino-3-methyl-1-phenyl-2-pyrazoline (**1**) [38], we could synthesize the new compound 4-acetyl-5-amino-3-methyl-1-phenyl-2-pyrazoline (**2**), Scheme 1 which has been considered as starting material for the synthesis of all newly compounds involved in this our research project. The structure of compound **2** was confirmed by IR spectra which revealed the presence of peaks at 3350 cm^{-1} (NH_2), at 1670 cm^{-1} (C=O), at 1600 cm^{-1} (C=N), also ^1H NMR spectra of compound **2** revealed the presence of signals peaks at 1.4 (s, 3H, CH_3), 2.25 (s, 3H, CH_3CO), 2.65 (s, 1H, CHN), 2.85(s, 1H, CHCO), 4.20 (br, 2NH, NH_2), and 7.00-8.00 (m, 5H, Ar-H^+) ppm, the mass spectrum showed the molecular ion peak at *m/z* = 229.28.

The structure of compound **3** was confirmed by IR spectra which revealed the presence of peaks at 3063 (NH), 1706 (C=O), 1596 (C=N) cm^{-1}, also ^1H NMR spectra of compound **3** revealed the presence of signals peaks at 0.86 (s, 3H, CH_3), 1.24 (d, *J* = 7.00 Hz, 1H, NCHN), 2.16 (t, *J* = 7.30 Hz, 2H, CH_2O), 2.35 (d, *J* = 7.00 Hz, H, CHCO), 2.73 (t, *J* = 7.30 Hz, 2H, CH_2N), 3.37 (s,

1H, NH), and 7.24-7.97 (m, 5H, Ar-H$^+$) ppm and the mass spectra showed the molecular ion peak at *m/z* 228.

The active methylene group in compound **3** condensed with different aromatic aldehydes (benzaldehyde, anisaldehyde and *p*-hydroxybenzaldehyde) in dimethylformamide under piperidine as catalyst to yield the corresponding 5-aryldino-4-piperidinone derivatives (**4a-c**), respectively (Scheme 1). The structure of compounds **4a-c** was confirmed by IR spectrum, ^{1}H NMR spectrum and mass spectra (Tables 1, 2). The activity of exocyclic C=C conjugated with the α-carbonyl group in compounds **4a-c** were determined by the reaction with hydrazines, hydroxylamine hydrochloride, urea and thiourea, to yield the compounds **5-9a-c**, (Scheme 1). The isoxazolo piperidino derivatives (**7a** and **7b**), the piperidine derivatives (**8b**, **c**) and the pyrimidine thione derivatives (**9a**, **9c**) were confirmed by micro-analytical and spectroscopic data.

The compounds (**10a-c**) were prepared by the condensation of 3-methyl-1-phenyl-5,6,7,7a-tetrahydro-1*H*-pyrazolo[3,4-*b*]pyridin-4(3*aH*)-one (**3**) with nitroso compounds such as (a) *p*-nitroso *N*,*N*-dimethyl aniline, (b) *p*-nitroso phenyl and (c) α-nitroso-*β*-naphthol in the presence of dimethylformamide as solvent under piperidine as catalyst (Scheme 2). When Schiff's base compounds (**10a-c**) reacted with thioglycolic acid in dimethylformamide under piperidine as catalyst yielded the corresponding *N*-thiazole derivatives (**11a-c**), (Scheme 2). By the reaction of Schiff's base compounds (**10a-c**) with chloroacetylchloride in dimethylformamide under triethylamine as catalyst yielded the corresponding *N*-β-lactam derivatives (**12a-c**) (Scheme 2).

4. Conclusion

The present study deals with the development of some synthetic applications of 3-methyl-1-phenyl-5-pyrazolone and is based on the generation of building blocks containing fused isolated and spiro heterocyclic compounds.

References

[1]. Heaney, H. In Comprehensive Organic Synthesis; Trost, B. M., Fleming, I. Eds.; Pergamon Press: New York, 1991; Vol. 2, pp. 953-973.
[2]. Arend, M.; Westermann, B.; Risch, N. *Angew. Chem., Int. Ed.* **1998**, *37*, 1044-1070.
[3]. Denmark, S. E.; Nicaise, O. J. C. In Comprehensive Asymmetric Catalysis*;* Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H. Springer, Heidelberg, 1999, Vol. 2, pp. 923-964.
[4]. Kobayashi, S.; Ishitani, H. *Chem. Rev.* **1999**, *99*, 1069-1094.
[5]. Cordova, A. *Acc. Chem. Res.* **2004**, *93*, 522-528.
[6]. Newkome, G. R.; Moorefield, C. N.; Vogtle, F. Dendrimers and Dendrons; Wiley-VCH: Verlag GmbH, 2002.
[7]. Dendrimers and Other Dendritic Polymers; Frechet, J. M. J.; Tomalia, D. A., Eds.; John Wiley & Sons: Chichester, 2001.
[8]. Dendrimers in Catalysis; Topics in Organometallic Chemistry; Gade, L. H., Eds.; Springer-Verlag: Heidelberg, 2006; Vol. 20, 1-42.
[9]. Mery, D.; Astruc, D. *Coord. Chem. Rev.* **2006**, *250(15-16)*, 1965-1979.
[10]. Helms, B.; Frechet, J. M. J. *Adv. Synth. Catal.* **2006**, *348*, 1125-1148
[11]. Astruc, D.; Heuze, K.; Gatard, S.; Mery, D.; Nlate, S.; Plault, L. *Adv. Synth. Catal.* **2005**, *347*, 329-338.
[12]. Astruc, D.; Chardac, F. *Chem. Rev.* **2001**, *101*, 2991-3023.
[13]. Ooosterom, G. E.; Reek, J. N. H.; Kamer, P. C. J.; VanLeeuwen, P. W. N. M. *Angew. Chem. Int. Ed.* **2001**, *40*, 1828-1849.
[14]. Scot, R. W. J.; Wilson, O. M.; Crooks, R. M. *J. Phys. Chem. B.* **2005**, *109*, 692-704.
[15]. Wu, H.; Chen, X.; Wan, Y.; Ye, L.; Xin, H.; Xu, H.; Yue, C.; Pang, L.; Ma, R. Shi, D. *Tetrahedron Lett.* **2009**, *50*, 1062-1065.
[16]. Dziedzic, V.; Ibrahem, I.; Cordova, A. *Tetrahedron Lett.* **2008**, *49*, 803-807.
[17]. Hayashi, Y.; Urushima, T.; Aratake, S.; Okano, T.; Obi, K. *Org. Lett.* **2008**, *10(1)*, 21-24.
[18]. Khan, A. T.; Pravin, T.; Choudhary, L. H. *Eur. J. Org. Chem.* **2008**, 834-839.
[19]. Bigdeli, M. A.; Nemati, F.; Mahdavinia, G. H. *Tetrahedron Lett.* **2007**, *48*, 6801-6804.
[20]. Guo, Q. X.; Liu, H.; Guo, C.; Luo, S. W.; Gu, Y.; Gong, L. Z. *J. Am. Chem. Soc.* **2007**, *129*, 3790-3791.
[21]. Wang, R.; Li, B. G.; Huang, T. K.; Shi, L.; Lu, X. X. *Tetrahedron Lett.* **2007**, *48*, 2071-2073.
[22]. Wu, H.; Shen, L. Y.; Fan, Y.; Zhang, P.; Chen, C. F.; Wang, W. X. *Tetrahedron* **2007**, *63*, 2404-2408.
[23]. Cheng, L.; Wu, X.; Lu, Y. *Org. Biomol. Chem.* **2007**, *5*, 1018-1020.
[24]. Azizi, N.; Torkiyan, L.; Saidi, M. R. *Org. Lett.* **2006**, *8*, 2079-2082.
[25]. Hayashi, Y.; Tsuboi, W.; Shoji, M.; Suzuki, N. *J. Am. Chem. Soc.* **2003**, *125*, 11208-11209.
[26]. Tomalia, D. A. In Polymer Chemistry A Practical Approach: Davis, F. J. Eds.; Oxford University Press: UK, 2004; pp. 188-194.
[27]. Tomalia, D. A.; Baker, H.; Dewald, J.; Hall, M.; Kallos, G.; Martin, S.; Roeck, J.; Ryder, J.; Smith, P. *Polym. J.* **1985**, *17*, 117-132.
[28]. Lee, K. Y.; Kim, J. M.; Kim, J. N. *Tetrahedron Lett.* **2003**, *44*, 6737-6740.
[29]. LeBlanc, R.; Dickson, J.; Brown, T.; Stewart, M.; Pati, H. N.; VanDerveer, D.; Arman, H.; Harris, J.; Pennington, W.; Holt, H. L. Jr.; Lee, M. *Bioorg. Med. Chem*. **2005**, *13*, 6025-6034.
[30]. Bhat, B. A.; Dhar, K. L.; Puri, S. C.; Saxena, A. K.; Shanmugavel, M.; Qazi, G. N. *Bioorg. Med. Chem. Lett*. **2005**, *15*, 3177-3180.
[31]. Bhat, B. A.; Puri, S. C.; Qurishi, M. A.; Dhar, K. L.; Qazi, G. N. *Synth. Commun*. **2005**, *35*, 1135-1142.
[32]. Abdon, I. M.; Saleh, A. M.; Zodhi, H. F. *Molecules* **2004**, *9*, 109-116.
[33]. Straub, A.; Stasch, J.; Alonso-Alija, C.; Benet-Buchholz, J.; Ducke, B.; Feurer, A.; Furstner, C. *Bioorg. Med. Chem.* **2001**, *11*, 781-784.
[34]. Ge, M.; Cline, E.; Yang, L. *Tetrahedron Lett.* **2006**, *47*, 5797-5799.
[35]. Martins, M. A. P.; Cunico, W.; Siqueira, G. M.; Leidens, V. L.; Zanatta, N.; Bonacorso, H. G.; Flores, A. F. C. *J. Braz. Chem. Soc.* **2005**, *16*, 275-279.
[36]. Martins, M. A. B.; Beck, P.; Machado, P.; Brondani, S.; Moura, S.; Zanatta, N.; Bonacorso, H. G. B.; Flores, A. F. C. *J. Braz. Chem. Soc.* **2006**, *17*, 408-410.
[37]. Atlan, V.; Buron, C.; Kaim, L. E. *Synlett* **2000**, *4*, 489-490.
[38]. Soleiman, H. A.; Khalafallah, A. K.; Abd-Ellatif, H. *Eur. J. Chem.* **2012**, *3(3)*, 316-321.
[39]. Mohanty, M. K.; Sridhar, R.; Padmanavan, S. Y. *Indian. J. Chem.* **1977**, *158*, 1146-1148.