http://www.e-journals.net

ISSN: 0973-4945; CODEN ECJHAO
E-Journal of Chemistry
2011, **8(4),** 1944-1950

Chemical Studies on 3,6-Dichloropyridazine (Part 2)

N.M. ABD EL-SALAM[*], Z.Y. AL SHOAIBI and G.A. AHMED[§]

[*]Department of Natural Sciences, Riyadh Community College
King Saud University, P.O.Box 28095, Riyadh-11437, Saudi Arabia
Organic Chemistry Department, Faculty of Pharmacy, Sana'a University, Egypt
[§]Chemistry Department, Faculty of Science, Zagazig University, Egypt
nelsalam@ksu.edu.sa

Received 30 November 2010; Accepted 22 January 2011

Abstarct: 3,6-Dichloropyridazine **(1)** reacted with 2-aminophenol, phenylalanine, acetophenone hydrazone derivatives, acid hydrazide derivatives and amino-aromatic acids (anthranilic acid and 5-bromoanthranilic acid) and yield the compounds **(2)**, (**3**), (**4a,b**), (**5a,b**) and (**6a,b**) respectively. Reaction of compounds (**5a,b**) with acid hydrazide gave (**8a,b**). Also, compounds (**6a,b**) reacted with aromatic amino acid and gave (**7a-c**).

Keywords: Ditriazolopyridazine, Triazolopyridazine, Benzoimidazolopyridazine, Imidazolopyridazine

Introduction

The present work is an extension to our studies on the preparation of some fused heterocyclic compounds using 3,6-dichloropyridazine as a starting material[1]. Many derivatives of pyridazine have been synthesized when compound (**1**) is allowed to react with oxygen[2,3], sulfur[4], nitroge[5,6] and halogen nucleophile[7-9]. It has been pointed out that they possess extremely excellent biological activity[10].

2-Chloro- and 2,6-dichloropyridazine are mainly found as medical and agricultural drug intermediate and pyridazine derivatives have been extensive therapeutic potential[11] and other medical and technological applications[12] as antibodies and antihypertensive agents[13,14].

Experimental

All melting points are uncorrected and were determined on Gallenkamp electric melting point apparatus. IR spectra (KBr disc) were recorded on a FT/IR-400 spectrophotometer (Perkin Elmer). ^{1}H NMR spectra were recorded on a varian-300 (DMS-d_6) solution. Chemicals shifts are reported as δ values relative to tetramethylsilane (TMS) as internal reference. The elemental analyses were carried out at micro analytical center, Cairo University.

*Reaction of compound (**1**) with 2-aminophenol; formation of compound (**2**)*

A mixture of compound (**1**) (0.01 mole) and 2-aminophenol (0.01 mole) or (0.02 mole) in DMF (20 mL) was heated under reflux for 7 h. The solid obtained upon dilution with water, filtered off and crystallized from ethanol to give compound (**2**) as brown crystals (Table 2).

*Reaction of compound (**1**) with L-phenylalanine; formation of compound (**3**)*

A mixture of compound (**1**) (0.01 mole) and *L*-phenylalanine (0.01 mole) or (0.02 mole) was heated in oil bath at 180-200 °C for 3 h. The reaction product was washed with water and crystallized from ethanol into (**3**) (Table 2).

*Reaction of compound (**1**) with acetophenonehydrazone derivatives; formation of compound (**4a,b**)*

A mixture of compound (**1**) (0.01 mole) and acetophenonehydrazone derivative (0.01 mol), was heated in oil bath at 160-180 °C for 4 h. The solid formed after cooling was collected and recrystallzien from the proper solvent into compounds (**4a,b**) (Table 2).

*Reaction of compound (**1**) with acid hydrazides; formation of compound (**5a,b**)*

A mixture of compound (**1**) (0.01 mole) and acid hydrazides, namely (benzoylhydrazine and 4-aminobenzoylhydrazine) (0.01 mole) in 20 mL *n*-butanol was heated under reflux for 8 h; the reaction mixture was left to cool, the solid produced was collected and recrystallized from the proper solvent into compounds (**5a,b**) (Table 2).

*Reaction of compounds (**5a,b**) with acid hydrazides; formation of compounds (**8a-b**)*

The above experiment was repeated replacing compound (**1**) by compounds (**5a,b**) (Table 2).

*Reaction of compound (**1**) with aromatic amino acids; formation of compounds (**6a,b**)*

Heat under reflux in 20 mL *n*-butanol a mixture of compound (**1**) (0.01 mole) and aromatic amino acids namely (anthranilic acid and 5-bromoanthranilc acid) (0.01 mole) for 7 h. The solid produced after cooling was collected, dried and recrystallized from the proper solvent into compounds (**6a,b**) (Table 2).

*Reaction of compounds (**6a,b**) with aromatic amino acids; formation of compounds (**7a,b**)*

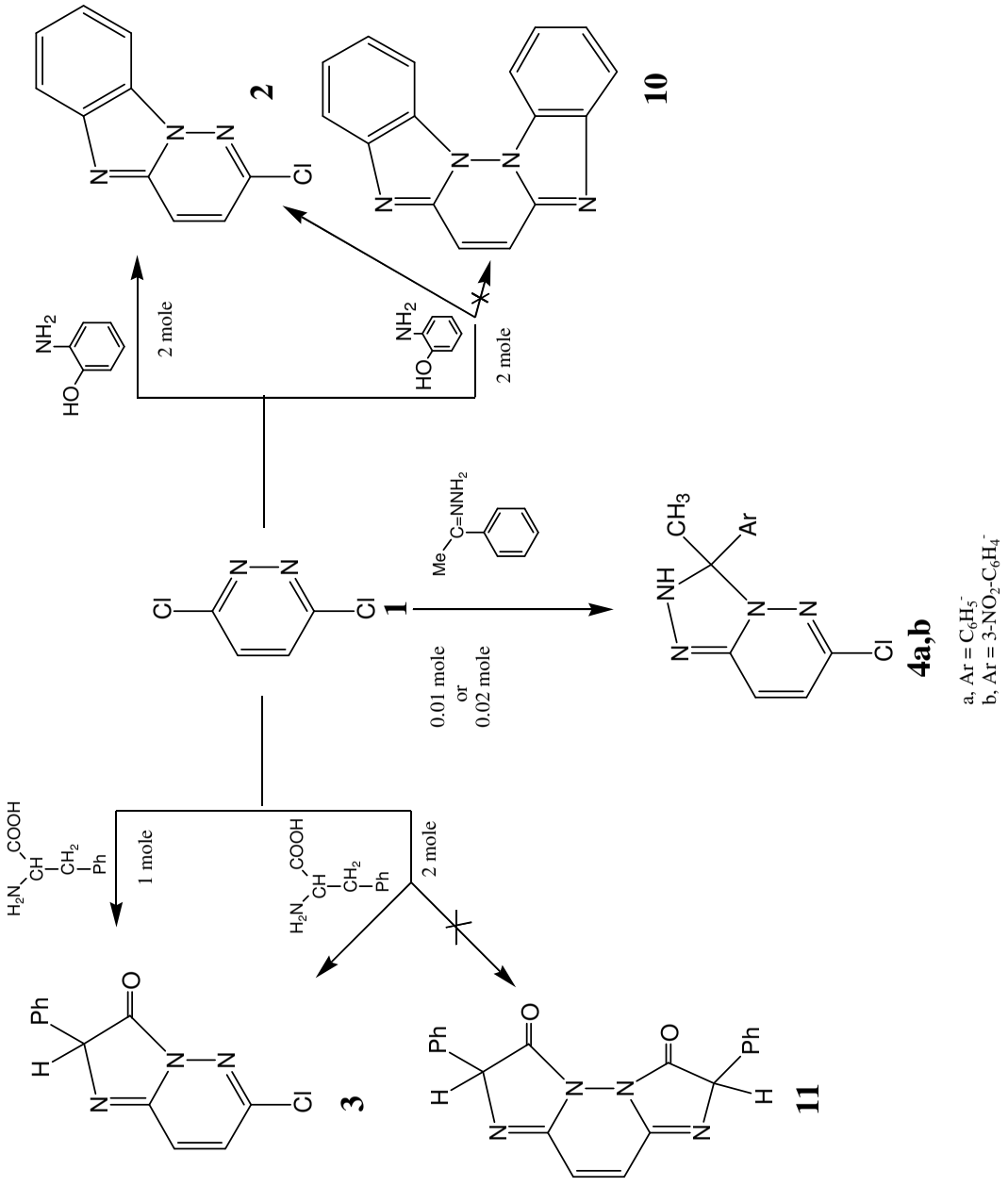
The above experiment was repeated replacing compound (**1**) by compounds (**6a,b**) (Table 2).

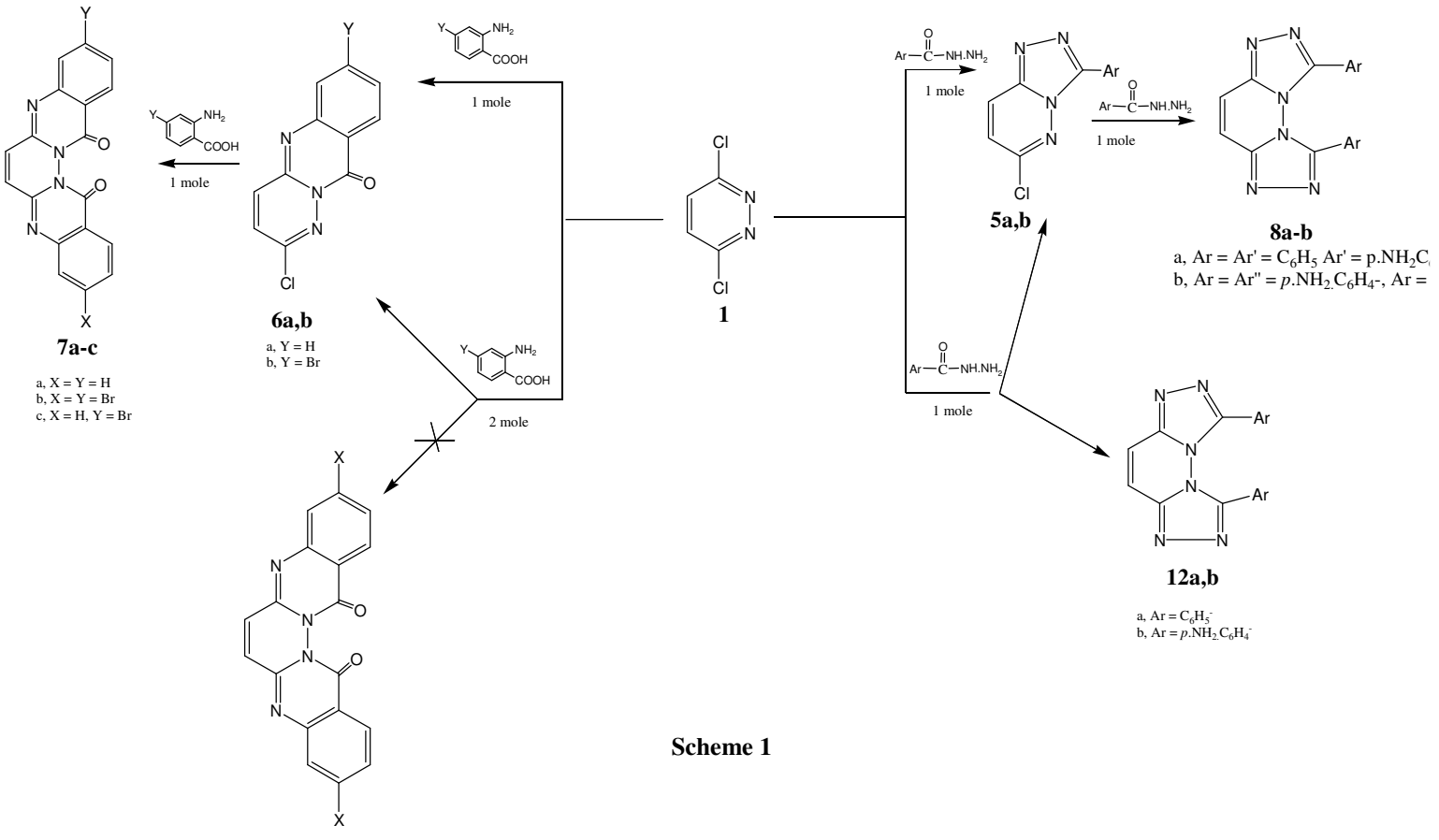
Results and Discussion

When compound (**1**) was allowed to react with orthoaminophenol in refluxing butanol it afforded the chlorobenzoimidazolopyridazine (**2**) (Scheme 1). The structure of compound (**2**) was confirmed from its correct analytical and spectral analysis (Table 1 and 2). Also, compound (**1**) reacted with phenylalanine by heating in oil bath at 160-180 °C it yield imidazolo pyridazine derivative (**3**) (Scheme 2). The chemical structure of compound (**3**) was elucidated from its correct analytical and spectral data (Table 1 & 2).

Heating a mixture of compound (**1**) and acetophenone hydrazone derivatives in an oil bath at 180-200 °C afforded the triazolopyridazine derivatives (**4a,b**) (Scheme 1).The structure of compounds (**4a,b**) was proved from their correct elemental and spectroscopic analysis (Table 1&2).

On the other hand, when compound (**1**) (0.01 mole) was allowed to react with aroylhydrazine (0.01 mole) it yields the triazolopyridazine derivatives (**5a,b**), which reacted with another molecule of aroylhydrazine afforded the compounds (**8a-c**) (Scheme 1). The structure of compounds (**5a,b**) and (**8a-c**) was confirmed from their correct elemental and spectral analysis (Table 1 and 2).


2
10
2 mole
2 mole
1
0.01 mole
or
0.02 mole
4a,b
a, Ar = C_6H_5
b, Ar = 3-NO_2-C_6H_4
1 mole
2 mole
3
11


7a-c
a, X = Y = H
b, X = Y = Br
c, X = H, Y = Br
1 mole
6a,b
a, Y = H
b, Y = Br
1 mole
2 mole
1
9a,b
a, X = H
b, X = Br
1 mole
5a,b
1 mole
8a-b
a, Ar = Ar' = C6H5 Ar' = p.NH2C
b, Ar = Ar'' = p.NH2.C6H4-, Ar =
1 mole
12a,b
a, Ar = C6H5-
b, Ar = p.NH2.C6H4-

Scheme 1

Reaction of compound (**1**) (0.01 mole) with aroylhydrazine (0.02 mole) afforded the triazolopyridazine derivatives (**5a,b**) and not the expected ditrazolopyridazine derivative (**12a-c**) (Scheme 1).

Furthermore, when (0.01 mole) of compound (**1**) was heated with (0.01 mole) or (0.02 mole) of acetophenonehydrazone derivatives in oil bath at 180-200 °C for 3 h, it from the triazolopyridazine derivatives (**4a,b**) (Scheme 1). The structure of compounds (**4a,b**) was elucidated by elemental and spectroscopic analysis (Table 1 and 2).

Also, compound (**1**), (0.01 mole reacted with aromatic amino acids (0.01 mole) and gave benzimidazolopyridazine derivatives (**6a,b**) (Scheme 1), which reacted with aromatic amino acids giving the polynuclear compounds (**7a-c**) (Scheme 1). The structure of (**5a,b**) and (**7a-c**) was confirmed from their correct analytical and spectral data (Tables 1 and 2), but when compound (**1**) (0.01 mole) was allowed to react with aromatic amino acids (0.02 mole) it produce the compounds (**6a,b**) and not the expected compounds (**9a-c**).

Table 1. Physical properties of the prepared compounds

Compd. No.	m.p. °C	Yield, %	Solvent of cryst.	Mol. formula (M.wt)	Elemental analysis calcd./found		
					C	H	N
1	69-70	60	Petroleum ether	$C_4H_2Cl_2N_2$ 148.98	32.25 32.21	1.35 1.33	18.80 18.79
2	130-132	70	Et-OH	$C_{10}H_6ClN_3$ 203.63	58.93 58.90	2.94 2.92	20.62 20.60
3	198-200	75	Et-OH	$C_{14}H_{12}ClN_3O$ 273.72	61.37 61.35	4.38 4.35	15.34 15.30
4a	200-202	70	Et-OH	$C_{13}H_{13}ClN_4O$ 276.08	56.50 56.48	4.70 4.68	20.28 20.26
4b	200-205	80	Et-OH	$C_{12}H_{10}ClN_5O_2$ 291.5	49.39 49.35	3.43 3.40	24.01 23.96
5a	230-231	60	Et-OH	$C_{11}H_7ClN_4$ 230.65	57.22 57.20	3.04 3.01	24.27 24.25
5b	235-237	80	Et-OH	$C_{11}H_8ClN_5$ 245.67	53.73 53.71	3.25 3.23	28.49 28.46
6a	238-240	60	Et-OH	$C_{11}H_6ClN_3O$ 231.64	56.98 56.95	2.59 2.57	18.13 18.10
6b	260-262	65	Et-OH	$C_{11}H_5BrClN_3O$ 310.53	42.50 42.48	1.61 1.60	13.52 13.50
7	265-267	65	Et-OH	$C_{18}H_9BrN_4O_2$ 393.19	54.93 54.92	2.28 2.28	14.24 14.22
8	180-181	60	Et-OH	$C_{18}H_{13}N_7$ 327.34	66.04 66.3	4.00 3.98	29.95 29.92

Table 2. Physical and spectral data of compounds (**2-8**)

Compound	IR cm^{-1}	^1H NMR, ppm
2	1560 (υ C=N) 1610 (υ C=N)	7.8 (d, 1H, CH), 7.6 (d, 1H, CH) 6.5-7.3 (m, 4H arom)
3	1690 (υ C=O) 1610 (υ C=N) 1580 (υ C=N)	7.9 (d, 1H, CH) 8.1 (d, 1H, CH) 6.6-7.5 (m, 5H arom) 7.2 (s, 1H imidazolone)
4a	1570 (υ C=N) 1530 (υ C=N) 3320 (υ NH)	7.7 (d, 1H, H), 7.8 (d, 1H, CH), 6.5-7.3 (m, 5H arom and 1H, Triazolyl)
4b	1550 (υ C=N) 1580 (υ C=N) 1460 (υ C=NO_2) 3320 (υ NH)	7.9 (d, 1H, CH), 8.1 (d, 1H, CH) 6.5-7.4 (m, 4H arom and 1H, Triazolyl)
5a	1560 (υ C=N) 1580 (υ C=N)	7.7 (d, 1H, CH) 7.9 (d, 1H, CH) 6.5-7.4 (m, 5H arom
5b	1675 (υ C=N) 1585 (υ C=N)	8.0 (d, 1H, CH),8.2 (d, 1H, CH)5.8 (broad, 2H, NH_2), 6.6-7.6 (m, 4H arom)
6a	1710 (υ C=O) 1615 (υ C=N) 1590 (υ C=N)	8.3 (d, 1H, CH) 8.1 (d, 1H, CH) 6.9-7.6 (m, 4H arom)
6b	1725 (υ C=O) 1610 (υ C=N) 1580 (υ C=N)	8.2 (d, 1H, CH) 8.0 (d, 1H, CH) 6.8-7.4 (m, 3H arom)
7a	1720 (υ C=O) 1580 (υ C=N) 1630 (υ C=N)	8.2 (d, 1H, CH) 7.9 (d, H, CH),7.6 (s, 1H, pyridyl)6.8-7.4 (m, 7H arom)
7b	1700 (υ C=O) 1610 (υ C=N) 1570 (υ C=N)	8.2 (d, 1H, CH) 8.1 (d, 1H, CH), 7.7 (s, 1H, pyridyl)6.5-7.3 (m, 7H arom)
7c	1690 (υ C=O) 1600 (υ C=N) 1575 (υ C=N)	7.8 (d, 1H, CH) 8.0 (d, 1H, CH) 6.8-7.6 (m, 7H arom)
8a	1610 (υ C=N) 1580 (υ C=N)	8.3 (d, 1H, CH), 5.5-6 (brand, 2H, NH_2)8.0 (d, H, CH) 6.4 – 7.0 (m, 9H arom)
8b	1590 (υ C=N) 1620 (υ C=N) 3310 (υ C=N)	7.9 (d, 1H, CH) 8.1 (d, 1H, CH) 5.4-6.0 (brand, 2H,NH_2) 6.7-7.3 (m, 8H arom)

References

1. Sherif M H, Ahmed G A, Elbahnasawy A A and Helal E O*, J Am Sci*., 2010, **6(11),** 570.
2. Parrot I, Rival Y and Wermuth C G, *Synthesis,* 1999, **7**, 1163-1168.
3. Huang J and Corey E J, *Org Lett.,* 2003, **5(19),** 3455-3458.
4. Parrot I, Wermuth C G and Hibert M, *Tetrahedron Lett.,* 1999, **40**, 7975-7978.
5. Rabisson P, Mekonnen B and Peet N P, *Tetrahedron Lett.,* 2003, **44**, 2919.
6. Ding S, Gray N S, Wu X, Ding Q and Schultz P G, *J Am Chem Soc.,* 2002, **124**, 1594.
7. Goodman A J, Stanforth S P and Tarbit B, *Tetrahedron,* 1999, **55**, 15067.
8. Yamada T, Nobuhara Y, Shimamura H, Yoshihara K, Yamaguch A and Ohki M, *Chem Pharm Bull.,* 1981, **29**, 3433-3439.
9. Easmon J, Purstinger G, Heinisch G, Roth T, Fiebig H H, Holzer W, Jager W, Jenny M and Hofmann J, *J Med Chem.,* 2001, **44(13),** 2164-2171.
10. Hamdouchi C, Sauchez Martinez C, Gruber J, Del Prado M, Lopez Rubio A and Heiz B A, *J Med Chem*., 2003, **46**, 4333-3341.
11. Tye S J, Wafford K A and Alack J R, *J Med Chem.*, 2006, **49**, 2660.
12. Luo S, MixWang B G and Cheng J P, *Tetrahedron Lett.*, 2004, **45**, 5171-5174.
13. Canmul and Hailes H C, *Tetrahedron Lett.*, 2005, **46(47)**, 8125-8127.
14. Al-Awadi N A, Abdelhamed I A, Al Etaibi A M and Elnagdi M H, *Synlett.*, 2007, **14**, 2205-2208.