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

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Abstract: 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 material1. Many derivatives of pyridazine have been synthesized when compound (1) is allowed to react with oxygen2,3, sulfur4, nitrogen5,6 and halogen nucleophile7,9. It has been pointed out that they possess extremely excellent biological activity10.

2-Chloro- and 2,6-dichloropyridazine are mainly found as medical and agricultural drug intermediate and pyridazine derivatives have been extensive therapeutic potential11 and other medical and technological applications12 as antibodies and antihypertensive agents13,14.

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). 1H NMR spectra were recorded on a varian-300 (DMS-d6) 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 recrystallized 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 (benzylohydrazine 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-bromoanthranilic 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).

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 arolyhydrazine (0.01 mole) it yields the triazolopyridazine derivatives (5a,b), which reacted with another molecule of arolyhydrazine 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).
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\[ \text{3} \xrightarrow{1 \text{ mole}} \text{Cl} \xrightarrow{2 \text{ mole}} \text{1} \xrightarrow{0.01 \text{ mole} \text{ or } 0.02 \text{ mole}} \text{MeC=NNH}_2 \xrightarrow{2 \text{ mole}} \text{10} \]

\[ \text{4a, b} \]

a. \( \text{Ar} = \text{C}_6\text{H}_5^- \)
b. \( \text{Ar} = 3-\text{NO}_2\text{C}_6\text{H}_4^- \)
Scheme 1
Reaction of compound (1) (0.01 mole) with arylhydrazine (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) | C       | H       | N          |
|------------|--------|----------|-------------------|---------------------|---------|---------|------------|
| 1          | 69-70  | 60       | Petroleum ether   | C_{4}H_{2}Cl_{2}N_{2} 148.98 | 32.25   | 1.35    | 18.80      |
| 2          | 130-132| 70       | Et-OH             | C_{16}H_{12}ClN_{3} 203.63 | 58.93   | 2.94    | 20.62      |
| 3          | 198-200| 75       | Et-OH             | C_{14}H_{12}ClN_{3}O_{2} 273.72 | 61.37   | 4.38    | 15.34      |
| 4a         | 200-202| 70       | Et-OH             | C_{13}H_{13}ClN_{3}O_{4} 276.08 | 56.50   | 4.70    | 20.28      |
| 4b         | 200-205| 80       | Et-OH             | C_{12}H_{10}ClN_{3}O_{2} 291.5 | 49.39   | 3.43    | 24.01      |
| 5a         | 230-231| 60       | Et-OH             | C_{11}H_{2}ClN_{4} 230.65 | 57.22   | 3.04    | 24.27      |
| 5b         | 235-237| 80       | Et-OH             | C_{11}H_{2}ClN_{5} 245.67 | 53.73   | 3.25    | 28.49      |
| 6a         | 238-240| 60       | Et-OH             | C_{11}H_{6}ClN_{5}O_{2} 231.64 | 56.98   | 2.59    | 18.13      |
| 6b         | 260-262| 65       | Et-OH             | C_{11}H_{2}BrClN_{3}O 310.53 | 42.50   | 1.61    | 13.52      |
| 7          | 265-267| 65       | Et-OH             | C_{18}H_{8}BrN_{4}O_{2} 393.19 | 54.93   | 2.28    | 14.24      |
| 8          | 180-181| 60       | Et-OH             | C_{18}H_{13}N_{7} 327.34 | 66.04   | 4.00    | 29.95      |
Table 2. Physical and spectral data of compounds (2-8)

| Compound | IR cm⁻¹ | ¹H NMR, ppm |
|----------|---------|-------------|
| 2        | 1560 (v C=N) 1610 (v C=N) | 7.8 (d, 1H, CH), 7.6 (d, 1H, CH) 6.5-7.3 (m, 4H arom) |
| 3        | 1690 (v C=O) 1610 (v C=N) 1580 (v 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 (v C=N) 1530 (v C=N) 3320 (v NH) | 7.7 (d, 1H, CH), 7.8 (d, 1H, CH) 6.5-7.3 (m, 5H arom and 1H, Triazolyl) |
| 4b       | 1550 (v C=N) 1580 (v C=N) 1460 (v C=NO₂) 3320 (v NH) | 7.9 (d, 1H, CH), 8.1 (d, 1H, CH) 8.3 (d, 1H, CH), 7.7 (d, 1H, H), 6.5-7.4 (m, 4H arom and 1H, Triazolyl) |
| 5a       | 1560 (v C=N) 1580 (v C=N) | 7.7 (d, 1H, CH), 7.9 (d, 1H, CH) 6.5-7.4 (m, 5H arom) |
| 5b       | 1675 (v C=N) 1585 (v C=N) | 8.0 (d, 1H, CH), 8.2 (d, 1H, CH) 5.8 (broad, 2H, NH₂), 6.6-7.6 (m, 4H arom) |
| 6a       | 1710 (v C=O) 1615 (v C=N) 1590 (v C=N) | 8.3 (d, 1H, CH), 8.1 (d, 1H, CH) 6.9-7.6 (m, 4H arom) |
| 6b       | 1725 (v C=O) 1610 (v C=N) 1580 (v C=N) | 8.2 (d, 1H, CH), 8.0 (d, 1H, CH) 6.8-7.4 (m, 3H arom) |
| 7a       | 1720 (v C=O) 1580 (v C=N) | 8.2 (d, 1H, CH), 7.9 (d, 1H, CH), 7.6 (s, 1H, Triazolyl) 6.8-7.4 (m, 7H arom) |
| 7b       | 1700 (v C=O) 1610 (v C=N) 1570 (v 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 (v C=O) 1600 (v C=N) 1575 (v C=N) | 7.8 (d, 1H, CH), 8.0 (d, 1H, CH) 6.8-7.6 (m, 7H arom) |
| 8a       | 1610 (v C=N) 1580 (v C=N) | 8.3 (d, 1H, CH), 8.0 (d, 1H, CH) 2H, NH₂ 5.5-6 (broad, 2H, NH₂), 6.4 – 7.0 (m, 9H arom) |
| 8b       | 1590 (v C=N) 1620 (v C=N) 3310 (v C=N) | 7.9 (d, 1H, CH), 8.1 (d, 1H, CH) 5.4-6.0 (broad, 2H, NH₂) 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, Saechez 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.
