CHEMICAL STUDIES ON 3,6-DICHLOROPYRIDAZINE

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ABSTRACT: Reaction of 3,6-dichloropyridazine **(1)** with acid hydrazides, p-toluene sulfonylhydrazine, anthranilic acid derivatives and ammonium hydroxide afforded the compounds **(2a,b), (3), (4a,b) and (5)** respectively. Compound **(5)** reacted with aromatic aldehydes yielded the Shiff's bases **(6)** and **(7).** Compound **(6)** reacted with anthranilic acid derivatives and gave **(8).** Also, compound **(1)** easily reacted with 2-chlorobenzylamine, sodium azide and thiosemicarbazide afforded the compounds **(9)**, **(10)** and **(11**) respectively.
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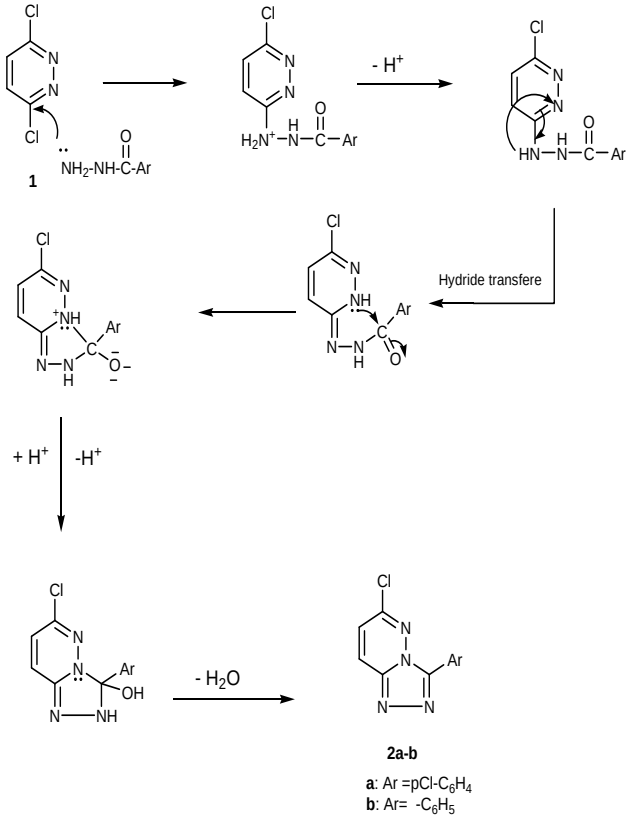
1. Introduction

Pyridazine derivatives continue to attract considerable attention due to the wide range of their biological activity (Yamada et al., 1981) and (Easmon et al., 2001). 3,6-disubstituted pyridazine (1) had a bioactive effect and was considered to be an appropriate starting material for pyridazine derivatives. It was well known that selective mono-substituted of single chlorine atom in (1) can be achieved when (1) was allowed to react with oxygen (Parrot et al., 1999) and (Huang et al., 2003), sulfur (Parrotm et al., 1999), nitrogen (Rabisson et al., 2003) and (Ding et al., 2002) and o-halogen nucleophiles (Goodman et al., 1999), (Hamdouchi et al., 2003) and (Tye et al., 2006). Hetrocyclic thiosemicarboxamide (pyridine and diazines) have shown an inhibitory effect on the acidity of gastric secretions (Van Hoeven et al., 1975), (Yamanoto et al., 1995) and (Pagni et al., 2000). The second important pharmaceutical property was an action against mycobacteria in particular against mycobacterium tuberculosis (Luo et al., 2004), (Caumul et al., 2005) and (Al-Awadi et al., 2007).

2. Results and discussion

When 3,6-dichloropyridazine (1) was allowed to react with acid hydrazides, namely (p-chlorobenzoylhydrazine and benzoylhydrazine) it gave the triazolopyridazine derivatives (2a,b) which were elucidated from their correct spectral data (Table 1).

The mechanism of reaction could be as:

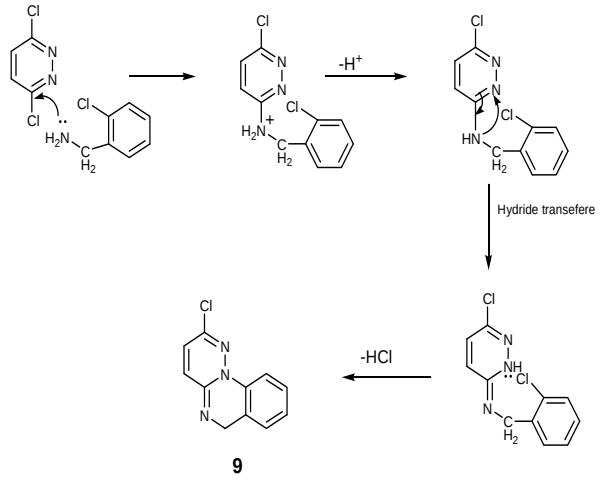


Also, compound (1) easily reacted with p-toluenesulfonylhydrazine afforded the compound (3). On the other hand, when compound (1) was reacted with anthranilic acid derivatives yielded the tricyclic compounds (4a,b).

Compound (1) easily reacted with ammonium hydroxide solution which formed the 3-amino-6-

chloropyridazine (5) which condensed with aromatic aldehydes, (namely, 3,4,5-trimethoxy benzaldehyde and m-nitrobenzaldehyde), and gave the Schiff's bases (6) and (7) respectively. Reaction of compounds (6) and (7) with anthranilic acid derivatives gave compounds (8a,b) (scheme 1).

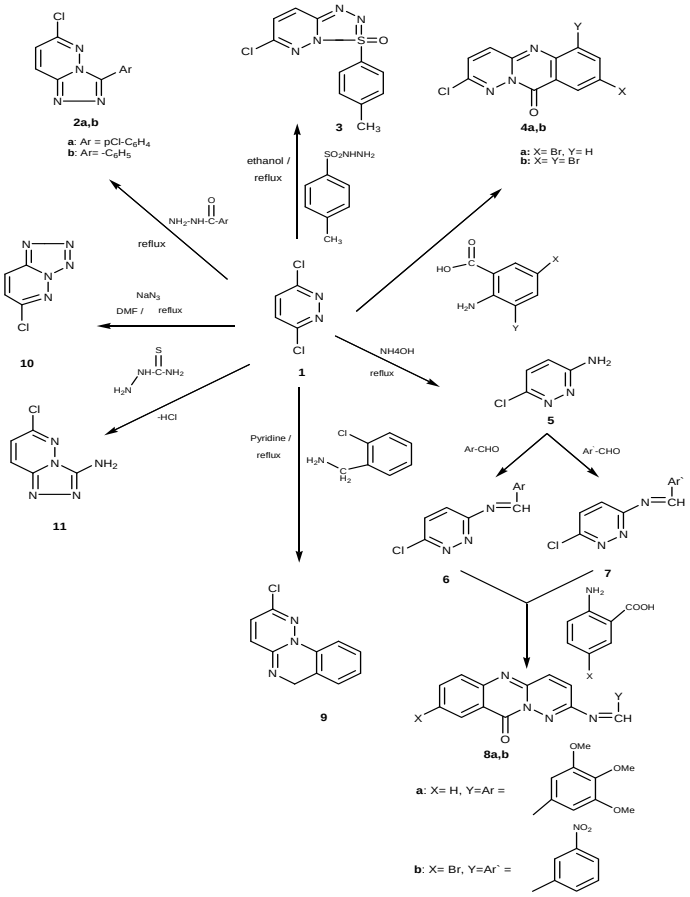
Reaction of compound (1) with o-chlorobenzylamine in pyridine afforded the tricyclic compound (9). The structure of (9) was confirmed from (1) of correct weight (M/e = 217) and ^{1}H NMR spectrum (Table 1). The mechanism of reaction could be as:



On the other hand, when compound (1) was allowed to react with sodium azide afforded the chlorotetrazolopyridazine derivative (10) (scheme 1). The structure of (10) was elucidated from the correct spectral data (table 1), and the mass spectrum showed a base peak at (M/e =151). Reaction of compound (1) with thiosemicarbazide in ethanol afforded compound (11). The chemical structure of compound (11) was confirmed from the correct spectral data (Table 1).

3. Experimental

All melting points were uncorrected and were determined on Gallenkamp electric melting point apparatus. IR spectra (KBr discs) were recorded on a FT/IR-400 spectrophotometer (Perkin Elmer). ^{1}H NMR spectra were recorded on a varian-300 (DMS-d6) solution. Chemical shifts were reported as δ values relative to tetramethylsilane (TMS) as internal reference. The mass specta were run at 70 ev on a varian MAT 711 mass spectrometer.



Scheme 1

1. Reaction of compound (1) with acid hydrazides; formation of compounds (2a,b).

A mixture of compound (**1**) (0.01 mole) and acid hydrazides, namely (p-chlorobenzoylhydrazine and benzoylhydrazine) in absolute ethanol (20 ml) was heated under reflux for 7 hours. The solid product obtained upon cooling, was filtered off, dried, and crystallized from ethanol to give compounds **(2a,b)** as white crystals **(Table 1).**

2. Reaction of compound (1) with p-toluenesulfonylhydrazine; formation of compound (3).

A mixture of compound **(1)** (0.01 mole) and p-toluenesulfonylhydrazine in absolute ethanol (20 ml) was heated under reflux for 7 hours. The solid product obtained upon cooling, was filtered off, dried, and crystallized from ethanol to give compound **(3)** as white crystals **(Table 1).**

Table (1): Physical and spectral data of the prepared compounds.

Compd. No.	m.p. °C	Yield (%)	Solvent of cryst.	IR cm^{-1}	^1H NMR ppm
2a	170	60	Et-OH	1593(C=N) 1557(C=N)	7.90(d,1H, CH-) 8.10(d,1H, CH-) 6.50-7.00(m, 4H ar)
2b	230	60	Et-OH	1569(C=N) 1584(C=N)	7.60(d,1H, CH-) 7.30(d,1H, CH-) 6.70-7.00(m,5H ar)
3	180	80	Et-OH	1572(C=N) 1340(S=O)	2.30(d,1H, CH-) 6.90(d, 1H, CH-) 7.40(d, 1H, CH-) 6.20-6.80(m,4H ar)
4a	260	76	Et-OH	1769(C=O) 1629(C=N)	8.12(d, 1H, CH-) 8.41(d, 1H, CH-) 7.39-7.72(m,3H ar)
4b	280	65	Et-OH	1740(C=O) 1641(C=N)	8.27(d, 1H, CH-) 8.51(d, 1H, CH-) 7.58-7.61(2H ar)
5	240	65	Et-OH	3320, 3214 (NH_2)	6.40-6.60(broad,2H, NH_2) 7.50(d,1H, CH-) 7.30(d, 1H, CH-)
6	>360	70	Et-OH	1587(C=N)	7.10(s,1H, CH=N-) 7.30(d, 1H, CH-) 7.50(d, 1H, CH-) 3.80-4.00(s, 9H, 3 OCH3)
7	>360	78	Et-OH	1590 (CH=N) 1450 (NO_2)	8.30(d,1H, CH-) 8.50(d, 1H, CH-) 7.50(s, 1H, CH=N-) 7.80-8.00(m, 4H ar)
8a	190	76	Et-OH	1688(C=O) 1586(C=N)	3.40-4.00(s,9H, 3 OCH_3) 7.40(d, 1H, CH-) 7.60(d, 1H, CH-) 7.50(s, CH=N) 6.30-7.20(m,6H ar)
8b	205	72	Et-OH	1690(C=O) 1560(C=N) 1460(NO_2)	7.80(d,1H, CH-) 7.60(d, 1H, CH-) 7.50(s, CH=N-) 6.50-7.40(m, 7H ar)
9	160	65	Et-OH	1600(C=N)	7.80(d,1H, CH-) 7.60(d, 1H, CH-) 4.62(s, 2H,CH_2-) 6.90-7.40(m, 4H ar)
10	130	65	Benzene	1564(C=N)	7.50(d,1H, CH-) 7.75(d, 1H, CH-)
11	235	65	Et-OH	1610(C=N) 1549(C=N) 3380,3290(NH_2)	7.40(d, 1H, CH-) 7.60(d, 1H, CH-) 5.60(broad,2H, NH_2)

3. Reaction of compound (1) with anthranilic acid derivatives; formation of compounds (4a,b).

A mixture of compound **(1)** (0.01 mole) and anthranilic acid derivatives (namely 5-bromoanthranilic acid and 3,5 dibromoanthranilic acid) (0.01 mole) in absolute ethanol (20 ml) was heated under reflux for 7 hours. The solid product obtained upon cooling, was filtered off, dried, and crystallized from ethanol to give compounds **(4a,b)** as white crystals **(Table 1).**

4. Reaction of compound (5) with aromatic aldehydes; formation of schiff's bases (6) and (7).

A mixture of compound **(5)** (0.01 mole) and aromatic aldehydes (namely, 3-Nitrobenzaldehyde and 3,4,5-trimethoxy benzaldehyde) (0.01 mole), in glacial acetic acid (20 ml) was heated under reflux for 7 hours. The solid product obtained upon cooling, poured on water, filtered off and crystallized from ethanol to give compounds **(6)** and **(7)** respectively as white crystals **(Table 1).**

5. Reaction of compound (6) with anthranilic acid derivatives; formation of compounds (8a,b).

A mixture of compound **(6** and / or **7)** (0.01 mole) and anthranilic acid derivatives in absolute ethanol (20 ml) was heated under reflux for 7 hours. The solid product obtained upon cooling, was filtered off, dried, and crystallized from ethanol to give compounds **(8a,b)** as white crystals **(Table 1).**

6. Reaction of compound (1) with o-chlorobenzylamine; formation of compound (9).

A mixture of compound **(1)** (0.01 mole) and o-chlorobenzylamine (0.01 mole) in pyridine (20 ml) was heated under reflux for 7 hours. The solid product obtained upon cooling, poured on ice , neutralized with HCl, and the precipitated solid was filtered off, washed with water, dried and crystallized from ethanol to give compounds **(9)** as brown crystals **(Table 1).**

7. Reaction of compound (1) with sodium azide; formation of compound (10).

A mixture of compound **(1)** (0.01 mole) and sodium azide (0.01 mole) in DMF (20 ml) was heated under reflux for 7 hours. The solid obtained upon dilution with water, filtered off and crystallized from benzene to give compounds **(10)** as white crystals **(Table 1).**

8. Reaction of compound (1) with thiosemicarbazide; formation of compound (11).

A mixture of compound **(1)** (0.01 mole) and thiosemicarbazide hydrochloride (0.01 mole) in absolute ethanol (20 ml) was heated under reflux for 7 hours. The solid product obtained upon cooling, was filtered off, dried, and crystallized from ethanol to give compounds **(11)** as white crystals **(Table 1).**

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