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Studies on Vilsmeier-Haack Reaction: Preparation and Synthetic Applications of Synthones 4-Chloro-2-arylamino thiazole-5-carboxaldehydes

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2-Aryliminothiazolid-4-ones (**3b–h**) were formylated using Vilsmeier-Haack (V-H) reagent. The formylated synthones were used to synthesise various fused heterocyclic ring systems containing thiazole moiety and some heterocyclic Schiff bases to get some compounds of interesting biological activities. These synthones were also subjected to functional group interconversion followed by self-condensation to build linear furo-2-arylamino thiazolyl derivatives by a simple route.

Key Words: Synthesis, 4-Chloro-2-arylamino thiazoles-5-carboxaldehydes, Vilsmeier-Haack.

INTRODUCTION

We have reported the formylation of 2-phenylimino thiazolid-4-one, **3a** using Vilsmeier-Hack (V-H) reagent to 4-chloro-2-phenylaminothiazole-5-carboxaldehyde, **4a** in good yield. In continuation of our interest in Vilsmeier-Haack (V-H) reaction and its synthetic applications[1], it was planned to formylate 2-aryliminothiazolid-4-ones (**3b–h**) using V-H reagent to get 4-chloro-2-arylamino-thiazole-5-carboxaldehydes (**4b–h**). The resulting carboxaldehydes (**4b–h**) were used as synthones to prepare heterocyclic compounds, Schiff bases and furo-2-arylamino thiazolyl ethyl acetates which are rather difficult to synthesize[2].

The compounds 2-aryliminothiazolid-4-ones (**3b–h**) were synthesised by the known procedures[3] in which N-arylthioureas (**2b–h**) were refluxed with monochloro acetic acid and anhydrous sodium acetate in anhydrous ethanol, as shown in **Scheme-I.**

RESULTS AND DISCUSSION

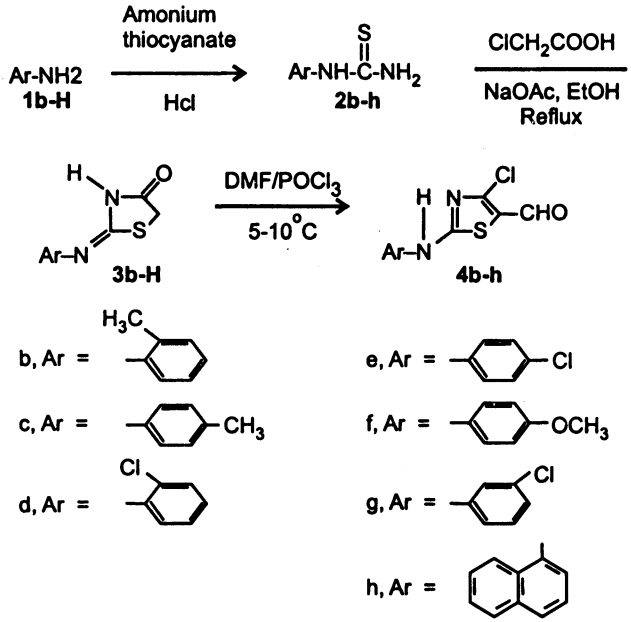
4-Chloro-2-arylaminothiazole-5-carboxaldehydes (4b–h)

The compounds (**3b–h**) were slowly added to cooled 1 mol of Vilsmeier reagent. This mixture was heated at 60°C for 6 h with constant stirring. The reaction mixture was kept overnight and it was then slowly added to crushed ice. The resulting yellow-coloured solution was then neutralized with NaOH solution (40%, 50 mL) maintaining the temperature below 50°C to get the formylated products: **4b** (59%), m.p. 142°C (found: N, 10.95; $C_{11}H_9N_2SOCl$ requires: N, 11.09%). PMR, 2.5 (s, 3H,

—CH$_3$), 7.5 (m, 4H, Ar—H), 10.3 (s, 1H, —CHO). **4c** (69%), m.p. 160–162°C (found: N, 11.30 $C_{11}H_9N_2SOCl$ requires: N, 11.09%) PMR: 2.6 (s, 3H, —CH$_3$), 7.4 (m, 4H, Ar—H), 10.3 (s, 1H, —CHO). **4d** (59%); 155–156°C (found: N, 10.40; $C_{10}H_6N_2SOCl_2$ requires: N, 10.26%); PMR: 7.5 (m, 4H, Ar—H), 10.0 (s, 1H-CHO). **4e** (70%), m.p. 156–158°C (Found: N, 10.35; $C_{10}H_6N_2SOCl_2$ requires: N, 10.26%); PMR 7.6 (m, 4H, Ar—H), 10.0 (s, 1H-CHO). **4f** (74%), m.p. 165°C (Found: N, 10.32; $C_{10}H_6N_2SO_2Cl$ requires: N, 10.43%); PMR 7.5 (m, 4H, Ar—H), 10.0 (s, 1H, —CHO), 4 g (64%), m.p. 170°C, (Found: N, 10.30; $C_{10}H_6N_2SOCl_2$ requires: N, 10.26); PMR 7.6 (m, 7H, Ar—H), 10.0 (s, 1H, —CHO). **4h** (64%), m.p. 185°C (Found: N, 9.73; $C_{14}H_9N_2SOCl$ requires: N, 9.70); PMR 7.5 (m, 7H, Ar—H), 10.0 (s, H, —CHO).

The structures of the compounds **(4b–h)** were established by elemental analysis, IR and PMR spectral data.

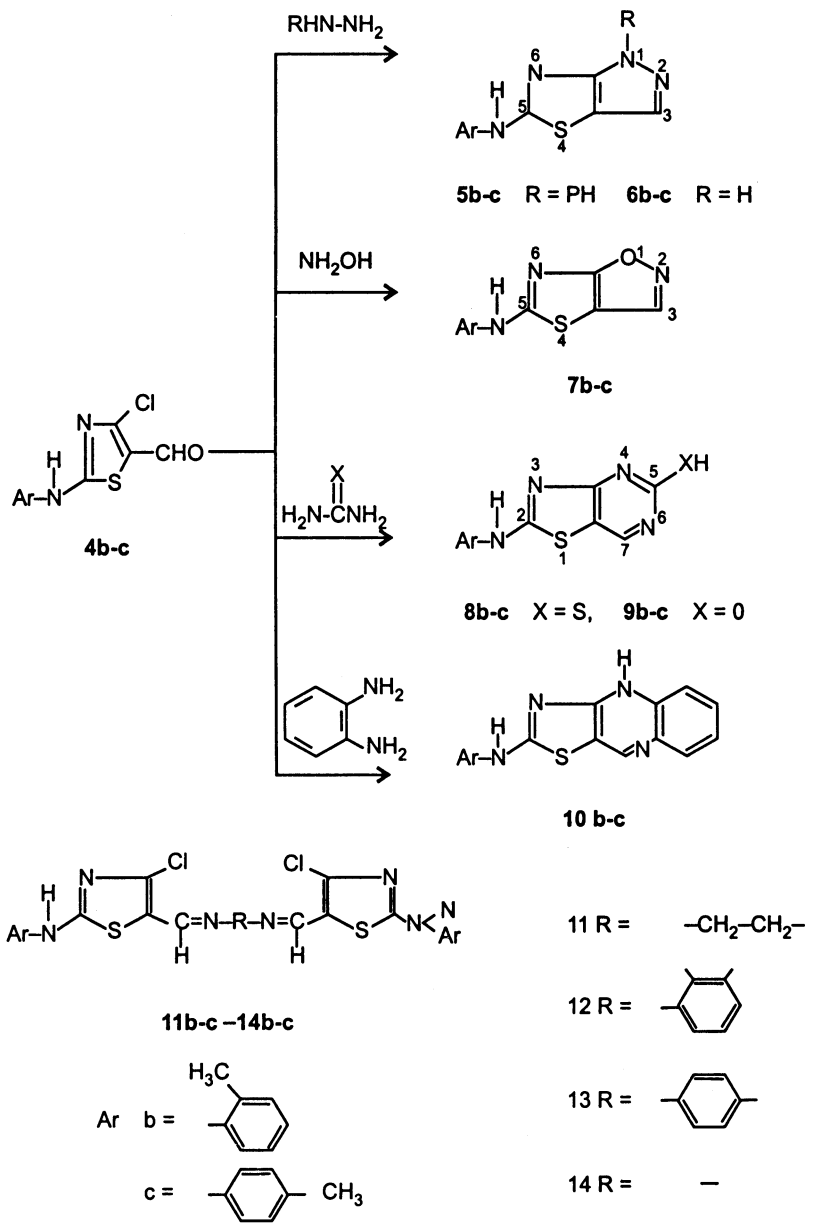
Many heterocyclic compounds containing thiazole, pyrazole moiety and Schiff bases possess antibacterial and antifungal activities[4]. The carboxaldehydes **(4b–c)** were used for the preparation of various heterocyclic systems of biological importance.



Scheme-I

Synthesis of fused heterocyclic ring systems containing thiazole moiety

The compound **(4b)**, on reaction with phenylhydrazine, hydrazine, hydroxylamine, thiourea and urea in 1 : 1 molar ratio yielded 1-phenyl-5-(2-methyl phenylamino) pyrazolo [4,3-d] thiazole **(5b)**, 5-(2-methyl phenylamino) pyrazolo [4,3-d] thiazole **(6b)**, 5-(2-methylphenylamino thiazolo [5, 4-d] isoxazole **(7b)**, 5-mercapto-2-(2-methylphenylammo) thiazolo [4,5-d] pyrimidine **(8b)** and 5-hydroxy-2-(2-methylphenylamino) thiazolo [4,5-d] pyrimidine **(9b)** respectively **(Scheme-II)**.



Scheme-II

A general synthetic method originally described by Thiele and Stemming[5] and modified by Mosher was used for the synthesis of 1,4-diazepine. A suspension of **(4b)** in *n*-propanol was added to the equimolar amount of *o*-phenylenediamine at pH-5 (maintained by adding formic acid). The product was identified as 2-(2-methylphenylimino) thiazole [4,5-e] (1,4) benzodiazepine **(10b)**. The compound **(4c)** on similar reaction sequence formed compounds **(5c–10c)** respectively.

Synthesis of heterocyclic Schiff bases

Condensation of compound **4b** with ethylenediamine, *o*-phenylenediamine, *p*-phenylenediamine and hydrazine in 2 : 1 molar ratio in refluxing ethanol yielded heterocyclic Schiff bases N,N′-bis-[4-chloro-2-(2-methylphenylimino thiazol-5-yl-methylene] ethylenediamine (**11b**), N,N′-bis-[4-chloro-2-(2-methyl-phenylimino thiazol-5-yl-methylene]-*o*-phenylenediamine (**12b**), N,N′-bis-[4-chloro-2-(2-methylphenyl-imino) thiazol-5-yl-methylene]-*p*-phenylenediamine (**13b**) and N,N′-bis-[4-chloro-2-(2-methylphenylimino) thiazol-5-yl-methylene] azine (**14b**) respectively. The compound **4c** on similar reaction sequence yielded products (**11c–14c**) respectively. Characterization data of the compounds (**5b,c–14b,c**) are given in Table-1. The IR data were in complete agreement with their structures.

TABLE-1
PHYSICAL PROPERTIES AND ANTIBACTERIAL ACTIVITY OF COMPOUNDS (**5b–c**) TO (**14b–c**)

Compd.	m.f.	m.p. (°C)	Yield (%)	N %*		Antibacterial screening	
				Calcd.	Found	*S. aureus*	*E. coli*
5b	$C_{17}H_{14}N_4S$	178	82	18.30	18.10	—	—
6b	$C_{11}H_{10}N_4S$	262	87	24.34	24.25	+(5 mm zone)	+(21 mm zone)
7b	$C_{11}H_9N_3OS$	212	87	18.18	18.05	—	+(7 mm zone)
8b	$C_{12}H_{10}N_4S_2$	175	73	20.44	20.30	—	—
9b	$C_{12}H_{10}N_4OS$	174	68	21.71	21.65	—	—
10b	$C_{17}H_{14}N_4S$	184	65	18.30	18.15	+(3 mm zone)	+(3 mm zone)
11b	$C_{24}H_{22}N_6S_2Cl$	298	66	15.88	15.75	—	—
12b	$C_{28}H_{22}N_6S_2Cl_2$	173	69	14.56	14.60	+(7 mm zone)	—
13b	$C_{28}H_{22}N_6S_2Cl_2$	250	76	14.56	14.65	—	+(9 mm zone)
14b	$C_{22}H_8N_6S_2Cl_2$	262	70	16.77	16.90	—	—
5c	$C_{17}H_{14}N_4S$	190	72	18.30	18.15	—	+(6 mm zone)
6c	$C_{11}H_{10}N_4S$	175	80	24.34	24.40	—	—
7c	$C_{11}H_9N_3OS$	248	78	18.18	17.95	—	+(6 mm zone)
8c	$C_{12}H_{10}N_4S_2$	238–240	69	20.44	20.25	—	+(5 mm zone)
9c	$C_{12}H_{10}N_4OS$	148	74	21.71	21.85	—	—
10c	$C_{17}H_{14}N_4S$	180	69	18.30	18.35	—	+(8 mm zone)
11c	$C_{24}H_{22}N_6S_2Cl_2$	294	72	15.88	15.70	—	—
12c	$C_{28}H_{22}N_6S_2Cl_2$	200	78	14.56	14.54	—	—
13c	$C_{28}H_{22}N_6S_2Cl_2$	210–212	80	14.56	14.60	—	—
14c	$C_{22}H_{18}N_6S_2Cl_2$	208	76	16.77	16.60	—	—

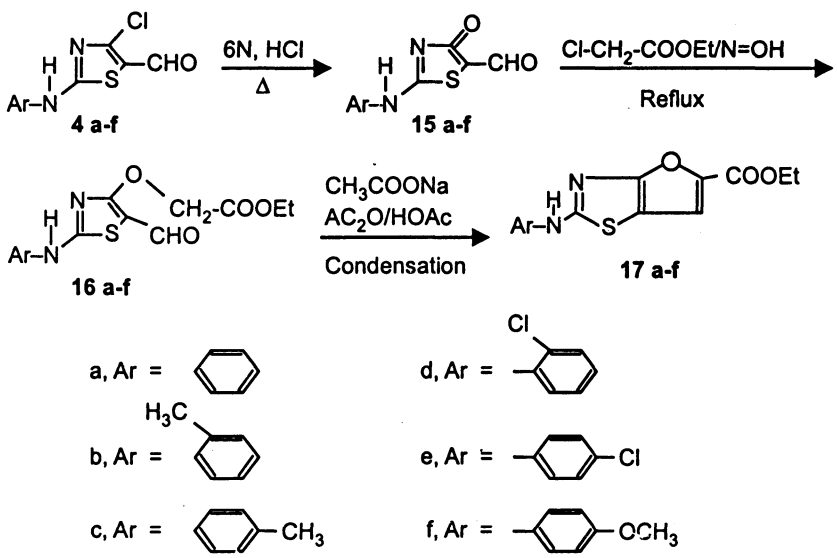
*Carbon and hydrogen analyses were satisfactory for all the compounds.
– Inactive, + Active

Antibacterial Activity

The compounds **(5b,c–14b,c)** were screened for their *in vitro* antibacterial activity against *S. aureus* and *E. coli* by paper disc method[6]. The discs were prepared from Whatmann filter paper No. I with 4 mm diameter and sterilized at 160°C for 30 min. The applied concentrations of compounds were saturated solutions in each case using suitable solvent. The suspension of the organisms *S. aureus* [gram (+)ve] and *E. coli* [gram (–)ve] was spread on nutrient agar plates by sterilized cotton swab and the disc containing compound was placed by sterilized forceps. The plates were incubated at 37°C for 24 h. The results were obtained in the form of clearing zone and noted after the period of incubation was over. The compounds showed moderate to good activity (Table-1).

Synthesis of furo-2-arylamino thiazolyl ethylacetates

In 4-chloro-2-arylamino thiazole-5-carboxaldehydes **(4a–f)** —CHO group and chlorine on adjacent carbons are versatile synthetic intermediates,[7] because chlorine can be displaced by reactive function for the construction of new heterocyclic rings bridged to thiazole moiety. We made use of versatile intermediates **(4a–f)** to build furo-2-arylamino thiazolyl ethyl acetates **(17a–f)** by a series of reactions as visualised in **Scheme-III.**



Scheme-III

The hydrolysis of **(4a–f)** was carried out with 6 N HCl to give 4-oxo-5-formyl-2-arylamino thiazoles **(15a–f)**. This type of functional group interconversion was also reported by Meth-Cohn *et al.*[8] The compounds **(15a–f)** on treatment with ethyl chloroacetate in the presence of NaOH formed the aryloxy esters **(16a–f)**. Identity of **(16a–f)** was based on elemental analysis and IR spectra. The compounds **(16a–f)** were condensed to furan ring systems **(17a–f)** by cyclisztion using sodium acetate in acetic anhydride. The structures **(17a–f)** were assigned on the basis of microanalysis and IR spectra[8].

EXPERIMENTAL

4-Oxo-5-formyl-2-arylamino thiazoles (15a–f)

4-Chloro-2-arylaminothiazole-5-carboxaldehydes (**4a–f**) (0.02 mol.) were heated on a water bath with 6 N HCl for 2 h. These were then poured into crushed ice with constant stirring. The resulting yellow solids were crystallized from acetic acid (70%) to afford the products: **15a** (82%), m.p. 148–150°C; **15b** (85%), 170°C; **15c** (81%), 195–196°C; **15d** (79%), 180°C; **15e** (83%), 209–211°C and **15f** (80%), 158°C.

Ethyl-5-formyl-2-arylamino-4-thiazolinyloxy acetates (16a–f)

To a mixture of (**15a–f**) (0.02 mol), ethyl chloroacetate (6 mL) and water (24 mL), NaOH (2.4 g in 60 mL water) was slowly added with stirring and the reaction mixture was refluxed on a sand bath for 3 h. The hot solution was kept overnight to yield the products: **16a** (65%), m.p. 204°C; **16b** (70%), 165–166°C; **16c** (72%), 200–201°C; **16d** (68%), 196–200°C; **16e** (72%), 205–206°C, **16f** (80%), 173–175°C. The compounds (**16a–f**) showed IR bands at 1725 ν(ester C=O), 1250 ν(O=C—OEt), 1700 ν(H—C=O).

Furo-2-arylamino thiazolyl ethylacetates (17a–f)

A mixture of ethyl-5-formyl-2-arylamino-4-thiazolyloxyacetates (**16a–f**) (0.01 mol), anhydrous sodium acetate (6 g), glacial acetic acid (15 mL) and acetic anhydride (15 mL) was refluxed for 8 h and then poured into ice-water (100 mL), stirred and allowed to stand for a few hours with occasional stirring. The products were extracted with ether. On work-up, the resulting solids were crystallized from methanol (50%) to afford: **17a** (69%), m.p. 270°C (found: N, 9.66; $C_{14}H_{12}SO_2$, requires: N, 9.72%). It showed IR bands (Nujol) at 1160, 1380 (substituted furan ring), 1600, 1050 ν(C=C of furan), 1260 ν(O=C—OEt), 1750 ν(C=O of ester). **17b** (66%), m.p. 220–221°C (found: N, 9.15; $C_{15}H_{14}N_2O_3S$ requires: N, 9.27%); IR bands at 1040, 1160, 1250, 1370, 1600, 1750 cm^{-1}. **17c** (73%), m.p. 193°C (found: N, 9.40; $C_{15}H_{14}N_2O_3S$ requires: N, 9.27%); IR bands at 1020, 1250, 1380, 1480, 1640, 1790 cm^{-1}. **17d** (68%), m.p. 217–218°C (found: N, 8.40; $C_{14}H_{11}N_2O_3SCl$ requires: N, 8.68%); IR bands at 1025, 1270, 1370, 1450, 1600, 1750 cm^{-1}; **17e** (74%), m.p. 228°C (found: N, 8.75; $C_{14}H_{11}N_2O_3SCl$ requires: N, 8.68%), IR bands at 1030, 1170, 1270, 1380, 1600, 1750 cm^{-1}. **17f** (79%), m.p. 298–305°C (found: N, 8.65; $C_{15}H_{14}N_2O_4S$ requires: N, 8.80%); IR 1020, 1160, 1250, 1380, 1630, 1700 cm^{-1}.

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