Some Reactions with α,β-unsaturated Acyl Isothiocyanates

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Summary: Nucleophilic addition reactions of α,β -unsaturated acyl isothiocyanates with aromatic and heteroaromatic amines have been studied. Compound **12** was also prepared which afforded pyrazolo [1,5-a]-s-triazine, coumarine and pyrazolo [1,5-c]-as-triazine derivatives on treatment with 5% potassium hydroxide, salicylaldehyde and diazotised aminopyrazole respectively.

Aroyl and acyl isothiocyanates are versatile reagents and their chemistry has received considerable recent interest [1-4]. These reagents can react with a vareity of polyfunctional molecules either via addition followed by cyclisation or via cycloaddition to yield a variety of heterocyclic derivatives. In the present study, we investigate additions of aromatic and heteroaromatic amines to α , β-unsaturated acyl isothiocyanates with the aim to obtain intermediates suitable for further cyclisation. Thus, treatment of **1a, b** with 4-aminoanti-pyrine has resulted in the formation of the corresponding thiourea derivatives 2a, b in high yield. Similarly, 4-aminopyridine and 2-aminopyridine reacted smoothly with 1c to afford the expected adducts **3** and **4**, respectively. On the other hand, 3-amino-1,2,4-triazole (**6**) and 2-aminothiazole (**5**) reacted with 1a, c to yield the acyl amino derivatives **7** and **8** respectively. The same products could be also obtained from the reaction of each of the amines **5** or **6** and the appropriate acid chloride in dry pyridine (Chart 1).

The formation of **8** from the reaction of **1** with **6** is assumed to proceed via intermediate formation of adduct **9**, which readily decompose to give **8** via. HCNS elimination. Also compound **7** may be formed under a similar mechanism (Chart 1).

In contrast, the experiments indicate that in the case of aromatic compounds carrying both a thiol and an amino group, a preferential attack occurs on the thiol group. Thus, by mixing acetone solution of **1a** and o-aminothiophenol in equimolecular proportions, a rapid exothermic reaction took place, and solid product of **10** separates which readily losses H_2S upon crystallization to afford 2-acylaminobenzothiazole (**11**), the latter product could be also obtained directly from the reaction of 2-aminobenzothiazole and p-methoxycinnamoyl chloride (Chart 1).

2-Cyanoethanoic acid hydrazide reacted with 1c to yield a product which may be formulated as **12** or isomeric **13**. Structure **12** could be established for the reaction product based on IR

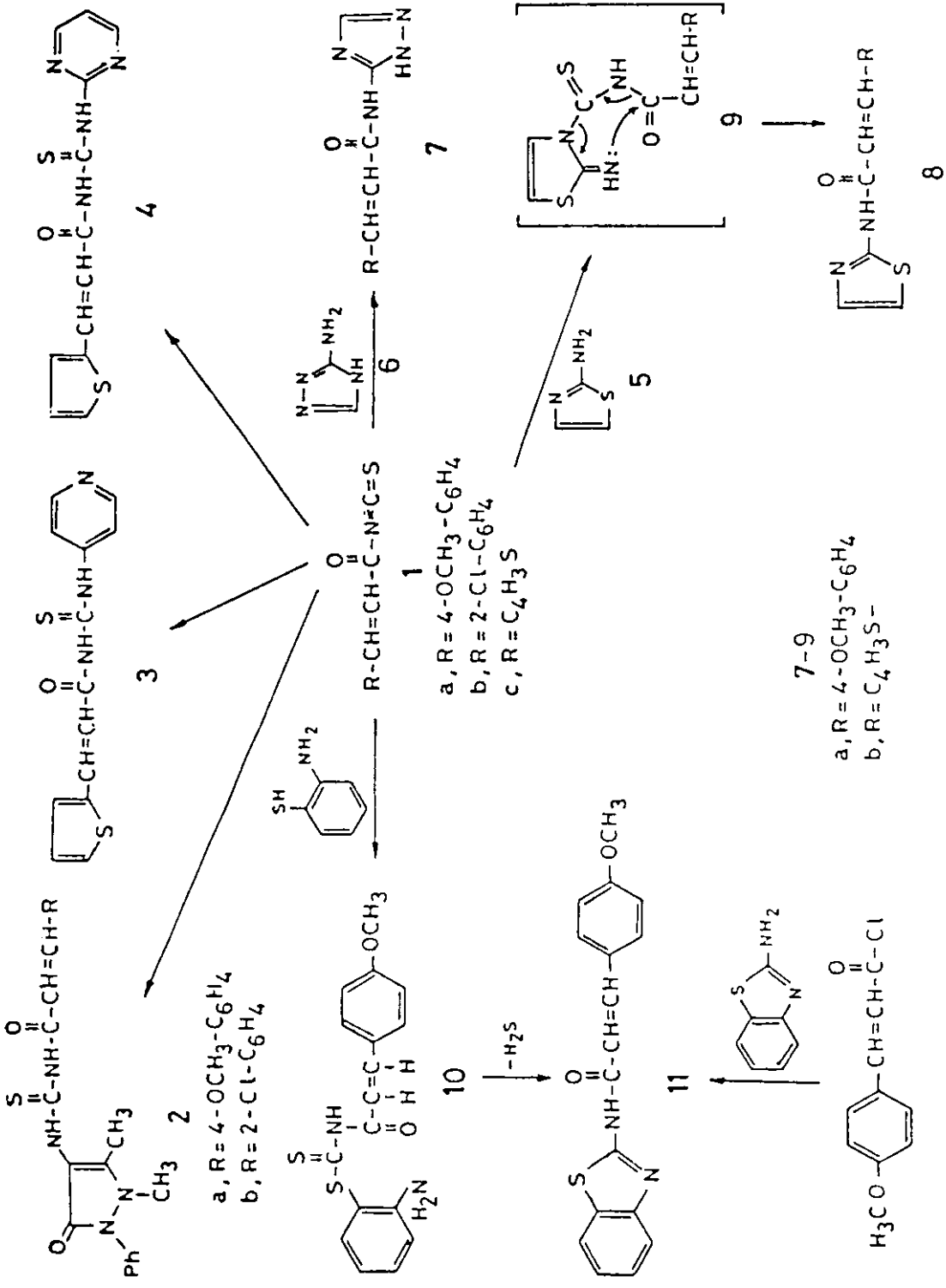

Chart 1

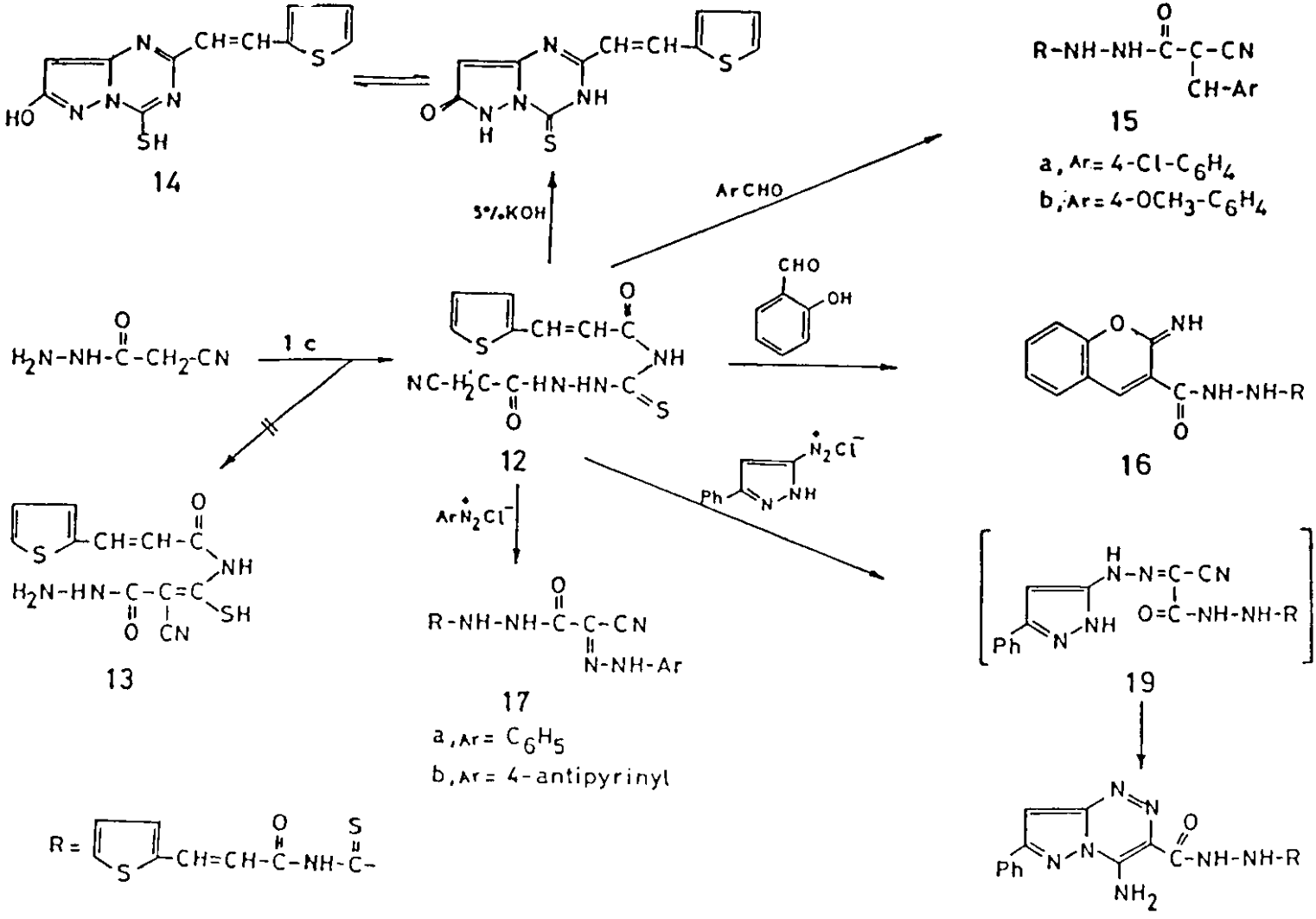
14
5%KOH
ArCHO
15
a, Ar= 4-Cl-C6H4
b, Ar= 4-OCH3-C6H4
1 c
12
16
13
ArN2Cl
17
a, Ar= C6H5
b, Ar= 4-antipyrinyl
19
18
R=

Chart 2

Table-1: Spectral data of compounds **2 -12**

Product No.	IR, (KBr), cm^{-1}	^{1}H-NMR ; δ ppm
2a	3310,3200(NH);1680 (CO); 1610 (C=C).	2.15(s,3H,CH_3); 3.25 (s, 3H, CH_3); 3.8 (s, 3H, CH_3); 6.75-7.7 (m, 11H, ethylenic and aromatic products); 11.5 (br, 2H, 2NH).
2b	3290,3230(NH);1690 (CO); 1620 (C=C).	2.3(s,3H,CH_3);3.3(s,3H,CH_3); 6.5 (d, ethylenic CH); 7.0-7.95 (m, 10H, aromatic and ethylenic protons).
3	3210,3100(NH);1690(CO), 1615 (C=C).	
4	3220,3150(NH);1675 (CO),1610(C=C)	
7a	3240,3290(NH);1700 (CO);1610(C=CO).	3.6(s,3H, CH_3); 7.0-7.95 (m,7H,ethylenic, aromatic and triazole H-5 protons).
7b	3400,3300 (NH);1700 (CO), 1610 (C=C)	
8b	3360,3210(NH);1700 (CO);1610(C=C).	
11	3450,3200(NH);1680 (CO);1620(C=C).	10H,aromatic and ethylenic protons
12	3450,3340,3210(NH,NH_2); 1690(CO);1620(C=C).	

spectrum. Since the obtained product is insufficiently soluble in the commonly used ^{1}H-NMR solvents ($CDCl_3$; $(CD_3)_2CO$; CF_3CO_2D and DMSO), other evidences for the structure could be inferared from its chemical behaviour.

Similar to the recently reported [5] compound **12** could be also cyclized into the pyrazolo [1,5-a] -s-triazine derivative **14** upon treatment with 5% aqueous potassium hydroxide solution (Chart 2).

Compound **12** condensed readily with aromatic aldehydes to afford the corresponding arylidene derivative **15a, b** and with salicylaldehyde to give the coumarine derivative **16**.

Compound **15** may exist in either the E or Z forms. However, we believe that the E conformer is the predominating form as previous work with similar systems [5] indicating that this is the sole existing form (conclusion was drown from observation of chemical shifts of both the ethylidene proton and the two o-phenylprotons).

Compund **12** also coupled with aromatic diazonium salts to yield coupling products for which the hydrozone structure **17** was established for the reaction product based on the presence of a conjugated -CN group in the IR spectra of the coupling products. Compound **17** is potentially tautomeric, predominating form will depend on both the solvent and temperature at which measurements are conducted. The tautomerism of arylhydrazononitriles of similar structure has been discussed [8].

Similarly, compound **12** coupled with diazotised aminopyrazole to afford the corresponding pyrazolo [1,5-c]-astriazine derivative **18**. The formation of the cyclic product **18** is assumed to proceed via formation of the acyclic hydrazones **19** which cyclize readily under the reaction condition.

Trials to isolate the acylic hydrazone **19** were unsuccessful. The direct isolation of tariazines on coupling **12** with heterocyclic diazonium salts find parralism to Tisler's finding as the reported isolation of triazines [6] on attempted coupling of diazotized aminoheterocycles with similar systems.

Experimental

All melting points are uncorrected IR spectra were recorded on Pye-Unicam SP-100 spectrophotometer. ^{1}H-NMR spectra were recorded on a Varian Em-390-spectrometer using TMS as the internal standard and chemical shifts are expressed in ppm as δ values. Analytical data were obtained from analytical Unit at Cairo University. No attempt has been made to optimize the yields of the described reactions.

The acyl isothiocyanates 1a-c used in the described reactions were prepared by literature methods [7].

Reactions of amines with isothiocyanates.

General procedures.

To a solution of **1** (0.12 mol) in 150 ml of dry acetone, a solution of the appropriate amine (0.1 mol) in dry acetone (50 ml) was added. The reaction mixture was refluxed for 3 hrs and then evaporated in vacuo. The remaining solid product was filtered off, washed with water and crystallized from the appropriate solvent (cf. Table II).

Reactions of amines with acid halides

To a solution of each 5,6 or 2-aminobenzothiazole (0.01 mol) in dry pyridine (20 ml) was added the equivalent quantity of the appropriate acid halide (Chart 1). The reaction mixture was heated on a water bath for 15 min., left to cool and the solid product, so formed, was collected by filtration to give **7,8** and **11**, respectively, which proved to be identical with those obtained from the above procedures.

6-Hydroxy-2-(thien-2-ylvinyl)-4-mercapto-pyrazolo[1,5-a]-1,3,5-triazine (14)

A solution of **12** (0.01 mol) in potassium hydroxide solution (30 ml, 5%), was refluxed for two hours, left to cool then acidified with dilute hydrochloric acid. The precipitated material was filtered off, washed with water and crystallized from DMF, compound **14** formed colourless crystals, m.p. > 300°C, yield 55%, IR : 3300 - 2400 (NH and OH dimer), 1680 (CO), 1640 (C=N), 1610 (C=C). $C_{11}H_8N_4OS_2$ (276.33) calcd. C, 47.12%; H, 2.90%, N, 20.28%, Found C, 47.27; H, 2.85; N, 20.42.

Condensation of compound 12 with aromatic aldhydes

A solution of **12** (0.01 mol) and (0.01 mol) of the appropriate aldehyde in 20 ml of absolute ethanol containing the catalytic amount of piperidine was

Table-2: Physical and analytical data of compounds **2 - 12**

Product No.	Cryst. Solvent	Yield [%]	M.P. [°C]	Fomrula (M.W.)	Calcd. Found C	H	Analysis N	S
2a	dioxane	78	204	$C_{22}H_{22}N_4O_3S$	62.54	5.24	13.27	7.59
				(422.51)	62.70	5.10	13.15	7.63
2b	ethanol	72	205	$C_{21}H_{19}N_4O_2SCl$	59.07	4.49	13.12	7.51
				(426.97)	59.20	4.20	12.91	7.49
3	ethanol/ chloforom	76	258	$C_{13}H_{11}N_3OS_2$	53.96	3.83	14.52	22.16
				(289.38)	54.27	3.59	14.23	22.31
4	ethanol/ chloroform	75	184	$C_{12}H_{10}N_4OS_2$	49.64	3.47	19.29	22.08
				(290.37)	49.91	3.50	19.10	22.19
7a*	dioxane	68	226	$C_{12}H_{12}N_4O_2$	59.00	4.95	22.95	
				(244.26)	58.80	4.76	22.81	
7b*	ethanol	65	213	$C_9H_8N_2OS$	49.08	3.66	25.44	14.56
				(220.26)	49.38	3.78	25.32	14.72
8a*	dioxane	70	212	$C_{13}H_{12}N_2OS$	59.98	4.65	10.76	12.31
				(260.32)	59.85	4.46	10.71	12.25
8b*	dioxane	65	236	$C_{10}H_8N_2OS_2$	50.83	3.41	11.85	27.13
				(236.32)	50.81	3.63	11.62	27.43
11*	dioxane	75	260	$C_{17}H_{14}N_2O_2S$	65.79	4.55	9.03	10.33
				(310.38)	66.01	4.42	9.23	10.51
12	DMF	80	210	$C_{11}H_{10}N_4O_2S_2$	44.85	3.53	18.79	21.56
				(294.36)	44.88	3.42	19.03	21.8

*Recorded yields corresponding to the products of the reaction of amines with acid chlorides.

heated at reflux for 3 hours. The solid product, so formed, on cooling was filtered off, washed with ethanol, dried and crystallized from DMF.

Compound **15a** formed brown crystals in 82% yield; m.p. 253°C, IR : 3300 - 3100 (NH); 2200 (conjugated CN), 1680 (C=O), 1610 (C=C).

$C_{18}H_{13}N_4O_2S_2Cl$ (416.88) calcd. C, 51.86%, H, 3.14%; N, 13.44%; S, 15.38%; Found, C, 52.21%; H, 2.95%; N, 13.35%; S, 15.36%.

Compound **15b** formed yellow crystals in 75% yield, m.p. 245°C; IR : 3400 - 3050 (NH); 2200 (conjugated CN); 1680 (C=O), 1620 (C=C). $C_{19}H_{16}N_4O_3S$ (412.5) calcd. C, 55.32%; H, 3.9%; N, 13.58%; Found C, 55.12%; H, 3.72%; N, 13.52%.

Compound **16** formed yellow crystals in 62% yield, m.p. 215°C IR : 3400, 3060 (NH); 1680 (CO); 1640 (C=N); 1610 (C=C). $C_{18}H_{14}N_4O_3S_2$ (398.4) calcd. C, 54.3%; H, 3.54%; N, 14.06%, Found C, 54.22%; H, 3.42%; N, 14.32%.

Coupling of diazotised amines with compound ***12***

A solution of the appropriate diazonium salt (0.01 mol) was added to a cold solution of compound **12** in ethanol (30 ml) and sodium acetate (3 gm) with stirring. The reaction mixture was left in a refrigerator for two hours. The precipitated product was filtered off, washed with water, dried and crystallized from the appropriate solvent.

Compound **17a** formed red crystals from DMF in 65% yield, m.p. 179°C, IR : 3500 - 3050 (NH); 2220 (conjugated CN); $C_{17}H_{14}N_6O_2S_2$ (398.47) calcd. C, 51.24%; H, 3.54%; N, 21.09%; Found C, 51.40%; H, 3.41%; N, 20.88%.

Compound **17b** formed brown crystals from acetic acid in 72% yield, m.p. 205°C; IR : 3450-3050 (NH); 2200 (CN); 1680 (exocyclic CO); 1660 (antipyrinyl CO); 1610 (C=C). $C_{22}H_{20}N_8O_3S_3$ (508.59) calcd. C, 51.95%; H, 3.96%; N, 22.03%; Found C, 52.13%; H, 4.22%; N, 22.34%.

Compound **18** formed brown crystals from DMF in 67% yield, m.p. 300°C, IR : 3450-3050 (NH); 1680 (C=O); 1610 (C=C). $C_{20}H_{16}N_8O_2S_2$ (464.52) calcd. C, 51.71%; H, 3.47%; N, 24.12%; Found C, 51.57%; H, 3.56%; N, 24.53%.

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